Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

Preparation of Highly Functionalized Aryl and Heteroaryl Organometallics by C-H Activation of Aromatics and Heterocycles Using new Hindered TMP-Amide Bases of Zn, Al, Mn, Fe and La

Stefan Wunderlich

aus

Rosenheim

München 2010

Erklärung
Diese Dissertation wurde im Sinne von § 13 Abs. 3 der Promotionsordnung vom 29. Januar 1998 von Professor Dr. Paul Knochel betreut.

Ehrenwörtliche Versicherung
Diese Dissertation wurde selbstständig, ohne unerlaubte Hilfe erarbeitet.

München, den 13.01.2010

……..
Stefan Wunderlich

Dissertation eingereicht am	13.01.2010
1. Gutachter:	Prof. Dr. Paul Knochel
2. Gutachter:	Prof. Dr. Thomas Carell
Mündliche Prüfung am	19.02.2010

This work was carried out from October 2006 to November 2009 under the guidance of Prof. Knochel at the Fakultät für Chemie und Pharmazie der Ludwig-Maximilians-Universität, Munich.

I would like to thank Prof. Dr. Paul Knochel, for giving me the opportunity to do my Ph. D. in his group, for his generous support and for his guidance in the course of my scientific research.

I am also very grateful to Prof. Dr. Thomas Carell for agreeing to be my "Zweitgutachter", as well as Prof. Dr. M. Heuschmann, Prof. Dr. H. Langhals, Prof. Dr. K. Karaghiosoff and Prof. Dr. H. R. Pfaendler for the interest shown in this manuscript by accepting to be referees.

I thank Christoph Rohbogner, Andreas Wagner, Silvia Zimdars, Sebastian Bernhardt and Matthias Schade for the careful correction of this manuscript.

I thank all past and present co-workers I have met in the Knochel's group for their kindness and their help. Special thanks to my actual and former lab mates Nadège Boudet, Cora Dunst, Sylvie Perrone, Giuliano Clososki, Wenwei Lin, Marcel Kienle, Andreas Unsinn, Andreas Wagner and Jeganmohan Masilamani.

I would like to thank Andreas Unsinn, Christoph Rohbogner and Giuliano Clososki for the fruitful collaboration in the field of directed metalations.

I would also like to thank Renate Schröder, Beatrix Cammelade, Vladimir Malakov, Simon Matthe and Yulia Tsvik for their help in organizing everyday life in the lab and in the office, as well as the analytical team of the LMU for their invaluable help.

I thank Cora Dunst, Andreas Unsinn and Johannes Heppegkausen for their help doing their Diploma or Master thesis as well as Marie Médoc, Leonhard Kade and Pascal Patschinski for their contributions to this work in course of their ''F-Praktika'' and bachelor thesis.

I thank Fabian Piller, Laurin Melzig and Anne Kramer for having a great time at the "Chemiker-WG" as well as all my friends for having wonderful days and nights inside and outside the laboratory.

Finally, I would like to thank my family and my darling Anna for the great support throughout my studies and my Ph. D. and for all the love.

Parts of this Ph. D. thesis have been published:

1 S. H. Wunderlich, P. Knochel. **$(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$: A Chemoselective Base for the Directed Zincation of Sensitive Arenes and Heteroarenes.** *Angew. Chem. Int. Ed.* **2007**, *46*, 7685-7688.

2 S. H. Wunderlich, P. Knochel. **High Temperature Metalation of Functionalized Aromatics and Heteroaromatics Using $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ and Microwave Irradiation**. *Org. Lett.* **2008**, *10*, 4705-4707.

3 S. H. Wunderlich, P. Knochel. **Efficient Mono- and bis-Functionalization of 3,6-Dichloropyridazine using $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.** *Chem. Commun.* **2008,** *47*, 6387-6389.

4 Z. Dong, G. C. Clososki, S. H. Wunderlich, A. Unsinn, J. Li, P. Knochel. **Direct Zincation of Functionalized Aromatics and Heterocycles by Using a Magnesium Base in the Presence of $ZnCl_2$.** *Chem. Eur. J.* **2009**, *15*, 457-468.

5 S. H. Wunderlich, P. Knochel. **Aluminum Bases for the Highly Chemoselective Preparation of Aryl and Heteroaryl Aluminum Compounds.** *Angew. Chem. Int. Ed.* **2009**, *48*, 1501-1504.

6 C. J. Rohbogner, S. H. Wunderlich, G. C. Clososki, P. Knochel. **New Mixed Li/Mg- and Li/Mg/Zn-Amides for the chemoselective Metalation of Arenes and Heteroarenes**. *Eur. J. Org. Chem.* **2009**, 1781-1795.

7 S. H. Wunderlich, M. Kienle, P. Knochel. **Directed Manganation of Functionalized Arenes and Heterocycles Using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$.** *Angew. Chem. Int. Ed.* **2009**, *48*, 7256-7260.

8 S. H. Wunderlich, P. Knochel. **Preparation of Functionalized Aryl-Fe(II)-Compounds and a Ni-Catalyzed Cross-Coupling with Alkyl Halides.** *Angew. Chem. Int. Ed.* **2009**, *48*, 9717-9720.

9 S. H. Wunderlich, P. Knochel. **Atom-Economical Preparation of Aryl and Heteroaryl- Lanthanum Reagents by Directed ortho-Metalation using TMP_3[La]**. *Chem. Eur. J.* **2010**, *manuscript accepted.*

10 S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel. **Large Scale Preparation of Functionalized Organometallics *via* Directed *ortho*-Metalation Using Mg- and Zn-Amide Bases.** *Org. Pro. Res. & Dev., manuscript accepted.*

11 S. H. Wunderlich, T. Bresser, C. Dunst, G. Monzon, P. Knochel. **Efficient Preparation of Functionalized Organometallics *via* Directed *ortho*-Metalation**. *Synthesis, manuscript in preparation.*

12 A. Unsinn, S. H. Wunderlich, P. Knochel. **Unusual Regioselectivities in the Metalation using Aluminium Bases**. *Org. Lett., manuscript in preparation.*

13 A. Unsinn, S. H. Wunderlich, B. Haag, P. Knochel. **Accelerated Zincations Mediated by TMPMgCl·LiCl for an Efficient and Mild Functionalization of Aromatics and Heterocycles.** *Chem. Eur. J., manuscript in preparation.*

14 S. H. Wunderlich, M. Kienle, S. Matthe, P. Knochel. **Convenient Preparation of Transition Metal Organometallics *via* Directed Metalation.** *Chem. Eur. J., manuscript in preparation.*

15 S. H. Wunderlich, A. Unsinn, P. Knochel. **Aluminum Bases for the Highly Chemoselective Preparation of Aryl and Heteroaryl Aluminum Compounds.** *Eur. J. Org. Chem., manuscript in preparation.*

Table of Contents

Abbreviations:

Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
DA	*N*,*N*-diisopropylamide
dba	*trans*,*trans*-dibenzyledenacetone
DMSO	dimethyl sulfoxide
equiv	equivalent
EI	electron-impact
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
HMDS	hexamethyldisilazane
hex	hexyl
HRMS	high resolution mass spectrospcopy
*i*Pr	isopropyl
IR	infra-red
J	coupling constant (NMR)
LDA	Lithium *N*,*N*-diisopropylamide
M	molarity
m	meta
Me	methyl
min	minute
mp.	melting point
MS	mass spectroscopy
NMP	*N*-methyl-2-pyrrolidine
NMR	nuclear magnetic resonance
o	ortho
Oct	octyl

p	para
Pent	pentyl
PEPPSI	[1,3-*bis*(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)-palladium(II) dichloride
Ph	phenyl
R	organic substituent
sat.	saturated
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
*t*Bu	*tert*-butyl
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetrametyhlethylendiamine
TMP-H	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TP	typical procedure
Ts	4-toluenesulfonyl
X	halogen (Cl, Br, I)

1 Introduction

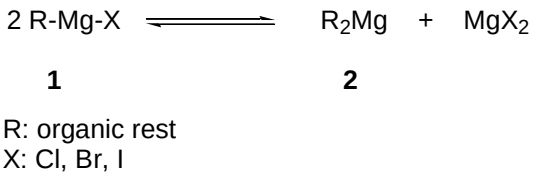
1.1 General Overview

The regioselective and chemoselective functionalization of arenes and heterocycles *via* organometallic intermediates has been proven to be an important synthetic tool since such resulting molecules have found numerous applications for their biological properties (pharmaceuticals, agrochemicals)[1] or for their physical properties (new materials).[2] Based on the pioneering work of *Frankland*[3] (preparation of Et_2Zn) and *Grignard*[4] (preparation of organomagnesium reagents), various methods for the preparation of organometallics have been reported (a short overview is discussed in the subsequent paragraph).[5] Thus, these reaction pathways can be considered as a toolbox for the efficient transformation for all kind of substrates with unique chemo-, regio- and enantioselectivity. Almost every metal of the periodic system has found useful applications in organometallic chemistry, either as catalyst or as reagent.[5]

Certainly, the choice of the metallic reagent is of fundamental importance since the chemo-, regio- and enantioselectivity of the reactions involving organometallic intermediates depends on the nature of the metal. In general, the reactivity of a carbon-metal bond increases with the ionic character of this bond due to the difference of the electronegativity. For instance, extensively investigated organolithium compounds react with most functional groups and electrophiles at temperatures above –20 °C.[6] These in general clustered reagents (depending on the solvent and additives such as TMEDA) are compatible with a cyano- or a nitro-group only at very low temperatures (–80 to –100 °C) and are able to react with esters even at –100 °C.[7] For comparison, organomagnesium reagents which display a more covalent carbon-magnesium bond are much more tolerant towards various organic functionalities and very low temperatures are usually not required for preparing polyfunctional aryl- or

[1] For examples, see: a) K. C. Nicolaou, J. S. Chen, D. J. Edmonds, A. A. Estrada, *Angew. Chem. Int. Ed.* **2009**, *48*, 660; b) R. Chinchilla, C. Nájera, M. Yus, *Tetrahedron* **2005**, *61*, 3139; c) *Classics in Total Synthesis* (Eds.: K. C. Nicolaou, E. J. Sorensen), Wiley-VCH: Weinheim, Germany, **1996**; d) *Classics in Total Synthesis II* (Eds.:K. C. Nicolaou, S. A. Snyder), Wiley-VCH: Weinheim, Germany, **2003**.
[2] a) J. Y. Kim, K. Lee, N. E. Coates, D. Moses, T.-C. Nguyen, M. Dante, A. J. Heeger, *Science*, **2007**, *317*, 222; b) T. Clarke, A. Ballantyne, F. Jamieson, C. Brabec, J. Nelson, J. Durrant, *Chem. Commun*. **2009**, 89.
[3] a) E. Frankland, *Liebigs Ann. Chem.* **1848-9**, *71*, 171; b) E. Frankland, *J. Chem. Soc.* **1848-9**, *2*, 263.
[4] a) V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322; b) V. Grignard, *Ann. Chim.* **1901**, *24*, 433.
[5] For an overview, see: *Handbook of Functionalized Organometallics Vol 1 and 2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, Germany, **2005**.
[6] P. Stanetty, M. D. Mihovilovic, *J. Org. Chem*. **1997**, *62*, 1514.
[7] a) P. Buck, G. Köbrich, *Chem Ber.* **1970**, *103*, 1420; b) H. A. Brune, B. Stapp, G. Schmidtberg, *Chem. Ber.* **1986**, *119*, 1845; c) W. E. Parham, R. M. Piccirilli, *J. Org. Chem*. **1976**, *41*, 1976.

heteroaryl-magnesium reagents.[8] Furthermore, organomagnesium reagents of the type RMg-X are in equilibrium with their *bis*-organometallic species (Scheme 1) depending on the solvent and the dilution.[9]



Scheme 1: The Schlenk-equilibrium of organomagnesium halides.

Moreover, organometallics possessing an even more covalent carbon-metal bond like organozinc- or organoboron reagents may tolerate most functional groups even at higher temperature and react with electrophiles in the presence of an appropriate catalyst (Cu, Ni or Pd) in the desired way.[10] In general, three major pathways exist allowing the preparation of numerous organometallics: oxidative insertion of elementary metal into a halogen-carbon-bond, halogen-metal exchange and directed metalation. Due to the uncountable numbers of reported results for preparing organometallics, just a few milestones in chemical history will be pointed out and summarized.

1.2 Preparation of Organometallic Reagents

1.2.1 Oxidative Insertion

As mentioned above, *Frankland* and *Grignard* pioneered the preparation of organometallic substrates *via* direct insertion of a metal (Zn or Mg) into a carbon-halogen bond. Furthermore, outstanding results on the field of lithium organometallics were obtained by *Gilman, Wittig* and *Ziegler*, for instance. They established the reaction of lithium metal with numerous organic halides and showed the synthetic use of those reagents.[11] As a drawback of lithium reagents remains the insufficient tolerance *versus* functional groups and

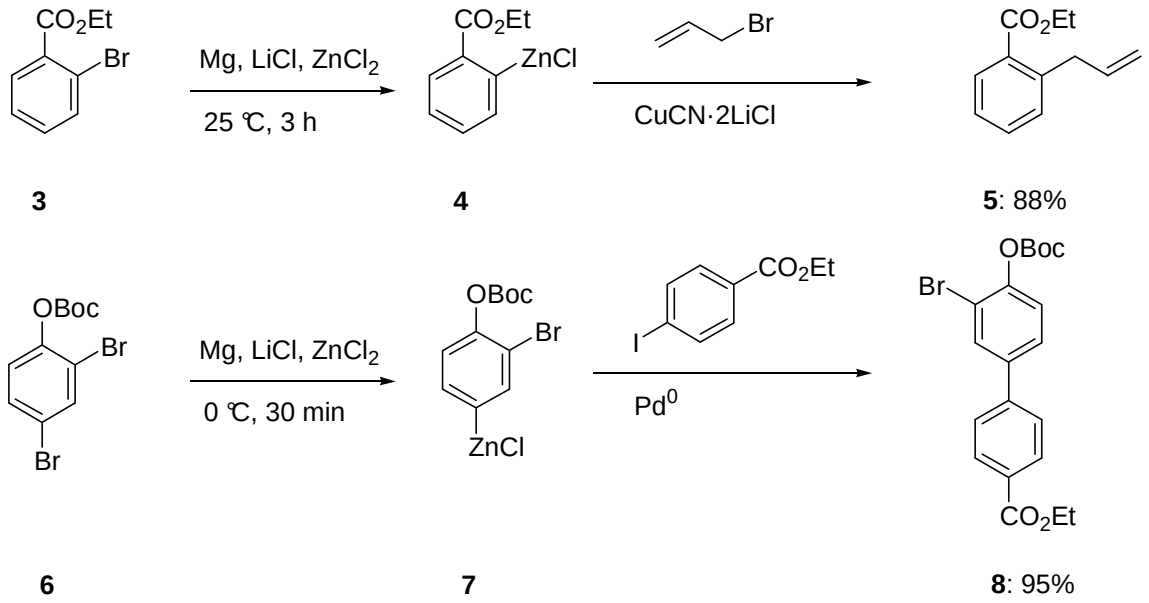
[8] a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; b) *Handbook of Grignard Reagents* (Eds.: G. S. Silverman, P. E. Rakita) CRC Press, New York, **1996**; c) *Grignard Reagents, New Developments* (Ed.: H. G. Richey, Jr.), Wiley-VCH, Weinheim, **2000**, p. 185.

[9] T. Holm, I. Crossland in *Grignard Reagents-New Developments*; (Eds.: H. G. Richey, Jr.), Wiley, New York, **2000**.

[10] a) *Metal-Catalyzed Cross-Coupling Reactions* 2nd ed. (Eds.: A. de Meijere, F. Diederich) Wiley-VCH, Weinheim, **2004**; b) J. Tsuji, *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, **1995**; c) *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH: Weinheim, Germany, **2002**.

[11] For an early review about the preparation of organometallics, see: R. G. Jones, H. Gilman, *Chem. Rev.* **1954**, *54*, 835 and references therein.

their low stability in ethereal solvents. Additionally, *Rieke* and co-workers performed those insertion reaction using highly active, so-called *Rieke*-metals which have to be freshly prepared by the reduction of metal halides with lithium-naphthalenide or elemental sodium or potassium.[12] These in general pyrophoric metals perform the insertion even at low temperatures (–78 °C). In general, the mechanism of those insertions is considered to proceed over a radical pathway.[13] Recently, *Knochel* and co-workers demonstrated the convenient insertion of elemental Mg,[14] In[15] or Zn[16] into carbon-halogen bonds in the presence of LiCl in THF. The cheap, commercially available metals are just activated with a few drops DIBAL-H, TMSCl and/or 1,2-dibromoethane. Remarkably, these insertions proceed highly regioselective tolerating a number of functional groups like esters, cyano-groups, ketones and aldehydes (Schemes 2 and 3).



Scheme 2: Preparation and reactions of organomagnesium reagents.

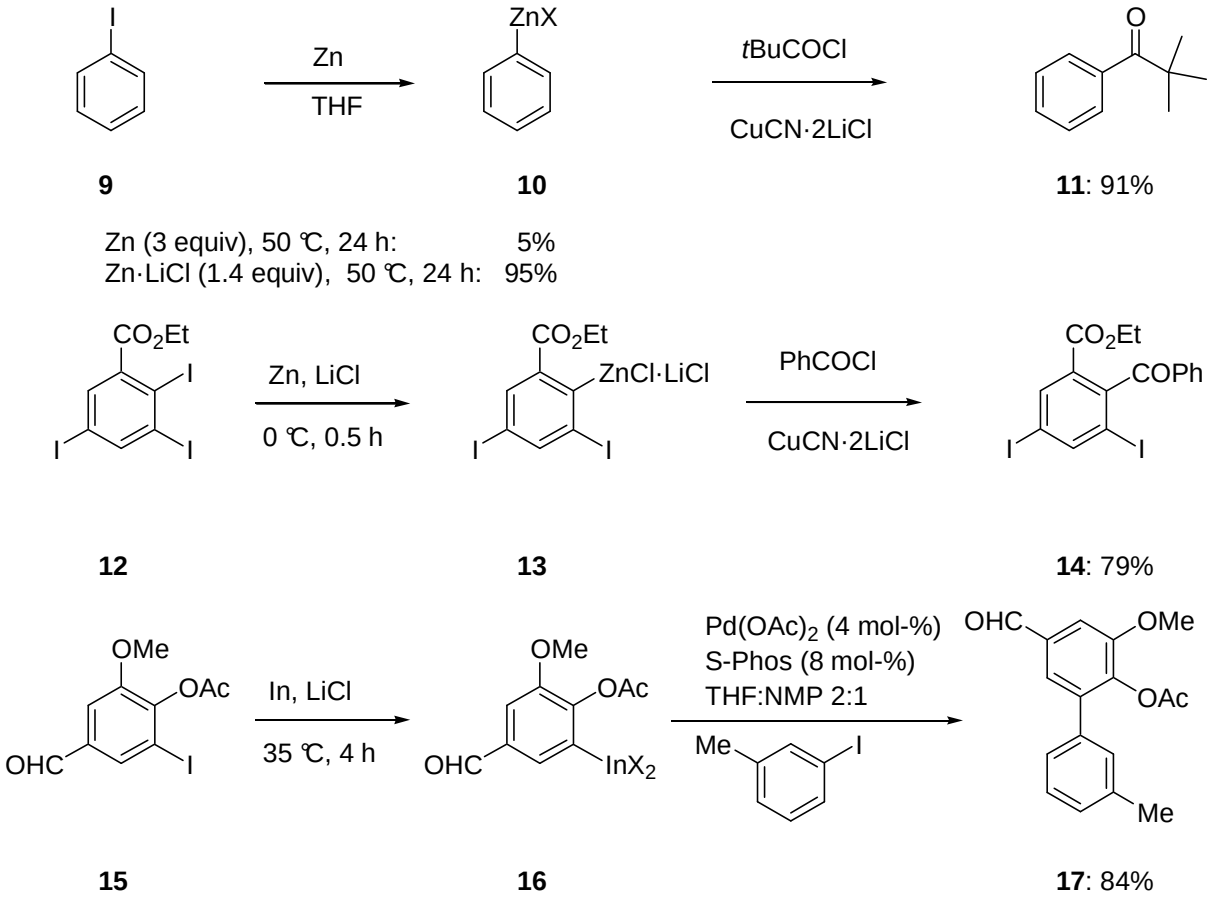
[12] a) R. D. Rieke, *Science* **1989**, *246*, 1260; b) R. D. Rieke, *Aldrichim. Acta* **2000**, *33*, 52; c) T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 3674; d) R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323; e) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428; f) S.-H. Kim, M. V. Hanson, R. D. Rieke, *Tetrahedron Lett.* **1996**, *37*, 2197; g) S.-H. Kim, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 2322; h) R. D. Rieke, L. D. Rhyne, *J. Org. Chem.* **1979**, *44*, 3445; i) G. Ebert, R. D. Rieke, *J. Org. Chem.* **1984**, *49*, 5280; j) T. C. Wu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 5057.

[13] M. S. Kharasch, O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice Hall, New York, **1954**.

[14] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192; c) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun*. **2008**, 5824.

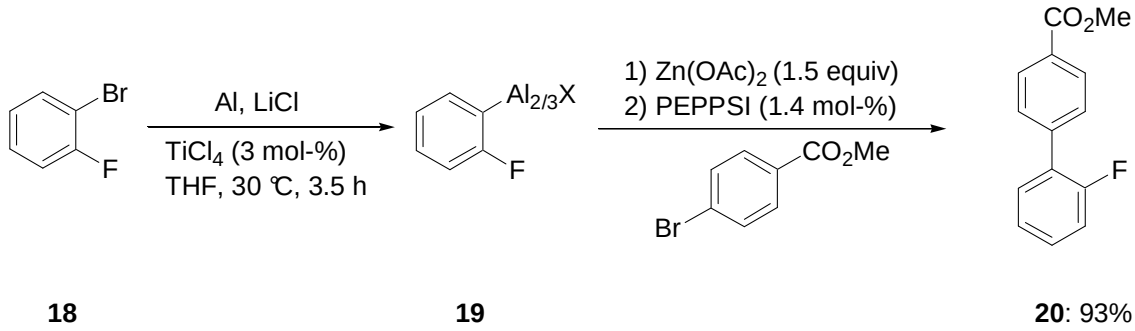
[15] a) Y.-H. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648; b) Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed*. **2009**, *48*, 2236.

[16] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; c) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.



Scheme 3: Preparation and reactions of organozinc and organoindium reagents.

Just recently, a new LiCl-mediated and $TiCl_4$ or $PbCl_2$ catalyzed direct insertion of commercial available Al-powder to aryl iodides or bromides allows a direct access to polyfunctional aryl or heteroaryl aluminum reagents such as **19** which display a good reactivity toward aryl bromides after a transmetalation to the corresponding Zn-compound with $Zn(OAc)_2$ and Pd-catalyzed cross-coupling using PEPPSI as catalytic system (Scheme 4).[17]

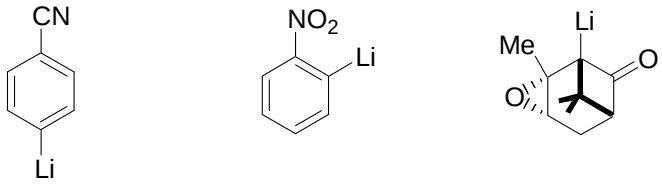


Scheme 4: Preparation and reaction of an arylaluminum reagent.

[17] T. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nature Chem.***2010**, *in press.*

1.2.2 Halogen-Metal Exchange

Beside this well-known insertion of metals into carbon-halogen bonds, the halogen-metal exchange triggered by an appropriate exchange reagent was developed in the first half of the 20th century.[18] The driving force of this reaction is the formation of the most stable organometallic compound. In general, sp^2-carbon atoms offer the possibility for a much more stabilized carbon-metal bond due to electronic effects than sp^3-carbon atoms. A first example is the reaction reported by *Prévost* of cinnamyl bromide (**21**) with EtMgBr to give cinnamylmagnesium bromide (**22**) in 14% yield.[19] This concept has been studied extensively and remarkable achievements have been made. Hence, it was possible to generate the lithium species **23-25** at very low temperatures bearing a cyano function, a nitro-group and even a ketone (Figure 1).[20] These generated organometallics have to be reacted immediately with electrophiles since rapid polymerization reactions occur due to the high reactivity of the carbon-lithium bond.



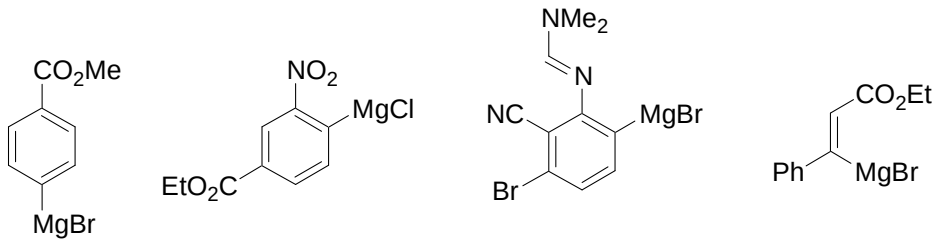
23 **24** **25**

Figure 1: Functionalized organolithium reagents.

So far, the mechanism of the halogene-metal exchange reactions still remains not completely elucidated although it is assumed that a halogen ate complex can be considered as an intermediate.[21] However, *Knochel* and *Cahiez* reported in 1998 the first general approach to polyfunctional organomagnesium reagents prepared *via* an iodine/magnesium exchange using *i*PrMgBr.[22] The exchange usually is carried at moderate temperature (–20 to –50 °C) and a number of functionalities can be present. Extensions of this concept led to various applications in organic synthesis as shown for the reagents **26-29** in Figure 2. Sensitive

[18] "Halogen Metal Interconversion Reactions with Organolithium Compounds": R. G. Jones, H. Gilman, in *Organic Reactions*, (Ed.: R. Adams) Vol. 6, John Wiley and Sons, Inc New York, **1951**.
[19] C. Prévost, *Bull. Soc. Chem. Fr.* **1931**, *49*, 1372.
[20] a) C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983; b) P. A. Wender, L. A. Wessjohann, B. Peschke, D. B. Rawlins, *Tetrahedron Lett.* **1995**, *36*, 7181.
[21] a) R. W. Hoffmann, M. Bönstrup, M. Müller, *Org. Lett.* **2003**, *5*, 313; b) V. P. W. Böhm, V. Schulze, M. Bönstrup, M. Müller, R. W. Hoffmann, *Organometallics* **2003**, *22*, 2925; c) W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1; d) H. J. Reich, N. H. Phillips, I. L. Reich, *J. Am. Chem. Soc.* **1985**, *107*, 4101; e) W. B. Farnham, J. C. Calabrese, *J. Am. Chem. Soc.* **1986**, *108*, 2449.
[22] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.

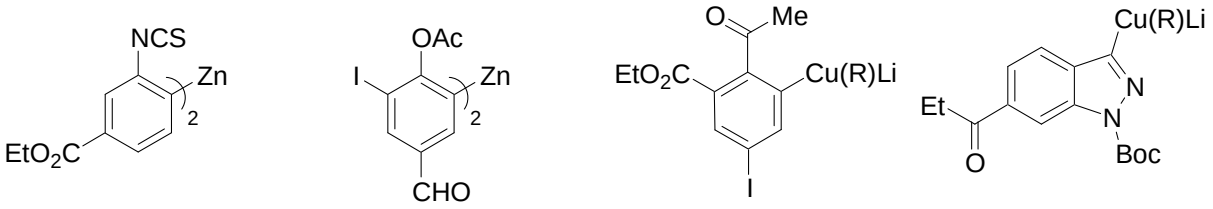
functional groups like esters and nitro-groups can be tolerated as well as cyano-groups or vinylic esters.[23]



26 **27** **28** **29**

Figure 2: Functionalized organomagnesium reagents.

More recently, *Knochel* and co-workers extended this concept to a Li(acac)-catalyzed I/Zn-exchange[24] using freshly prepared *i*Pr_2Zn and a copper-iodine exchange reaction.[25] Remarkably, molecules bearing very sensitive functional groups like aldehydes, ketones or isothiocyanates as well as sensitive heterocycles can be converted into the corresponding organometallics (Figure 3). These reagents can be reacted with various electrophiles leading to the desired products in good to excellent yields.



30 **31** **32** **33**

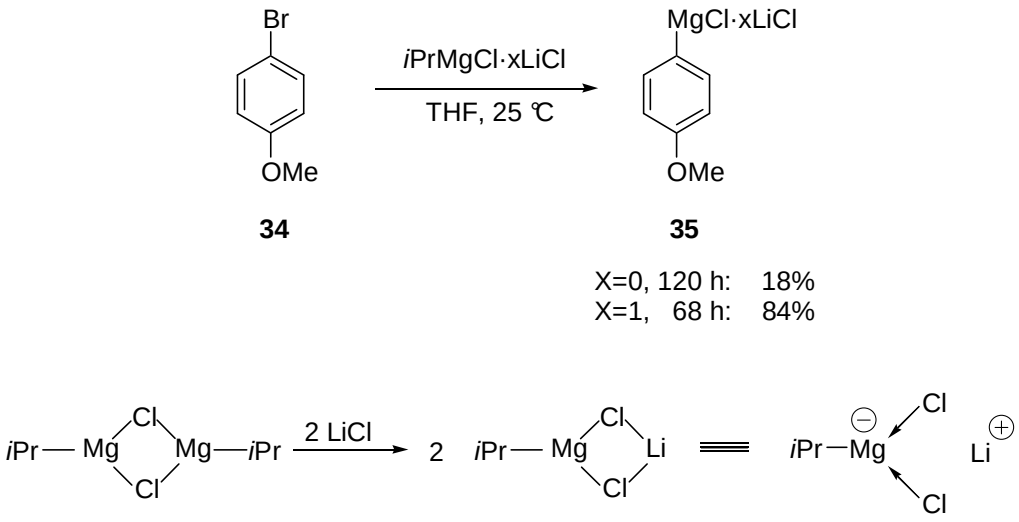
Figure 3: Functionalized organozinc and organocopper reagents prepared *via* exchange reactions.

[23] a) A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu, P. Knochel, *Synthesis* **2002**, 565; b) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 1610; c) G. Varchi, A. E. Jensen, W. Dohle, A. Ricci, G. Cahiez, P. Knochel, *Synlett* **2001**, 477; d) I. Sapountzis, W. Dohle, P. Knochel, *Chem. Commun.* **2001**, 2068; for heterocyclic reagents, see: e) L. Bérrillon, A. Leprêtre, A. Turck, N. Plé, G. Quéguiner, P. Knochel, *Synlett* **1998**, 1359; f) M. Abarbri, J. Thibonnet, L. Bérrillon, F. Dehmel, M. Rottländer, P. Knochel, *J. Org. Chem.* **2000**, *65*, 4618; g) M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 7449; h) M. Abarbri, P. Knochel, *Synlett* **1999**, 1577; i) F. Dehmel, M. Abarbri, P. Knochel, *Synlett* **2000**, 345.

[24] a) F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017; b) L.-Z. Gong, P. Knochel, *Synlett* **2005**, 267.

[25] a) X. Yang, P. Knochel, *Org. Lett.* **2006**, *8*, 1941; b) X. Yang, T. Rotter, C. Piazza, P. Knochel, *Org. Lett.* **2003**, *5*, 1229; c) X. Yang, P. Knochel, *Synlett* **2004**, 2303; d) N. Harrington-Frost, H. Leuser, M. I. Calaza, F. F. Kneisel, P. Knochel, *Org. Lett.* **2003**, *5*, 2111; e) C. Piazza, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 3263.

A breakthrough in the halogen/magnesium exchange was achieved in 2004.[26] By complexing the exchange reagent *i*PrMgCl with one equivalent of LiCl, a dramatically enhanced rate of these reactions is observed. Thus, the reaction of 4-bromoanisole (**34**) with *i*PrMgCl gives the desired organometallic species **35** in only 18% yield after 5 days, whereas the highly reactive reagent *i*PrMgCl·LiCl leads to the magnesiated anisole **35** in 84% yield within 3 d (Scheme 5). From the mechanistic point of view, LiCl coordinates to the exchange reaction reagent *i*PrMgCl·LiCl giving an intermediate ate-species.[27] Therefore, the aggregation of the exchange reagent is decreased and on the other hand the reactivity is increased.

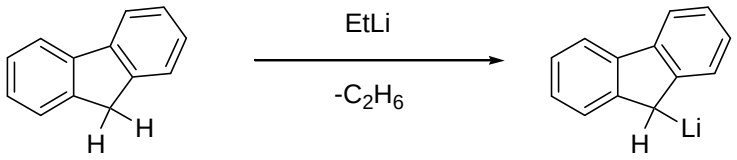


Scheme 5: Bromine/magnesium exchange using the reagent *i*PrMgCl·LiCl.

1.2.3 Directed Metalation

The third major way to generate organometallics is the directed metalation using amide bases or alkyl organometallics. In contrast to the previously presented methods (insertion and exchange reaction), there is no need for a halogen-carbon bond, whereas a more or less activated hydrogen-carbon bond is directly transformed into the corresponding metal species. The research for metalation strategies and their properties started with the reaction of EtLi with fluorene (**36**) giving fluorenyllithium (**37**) and ethane reported by *Schlenk* (Scheme 6).[28] From that point on, this method was extensively investigated.[29]

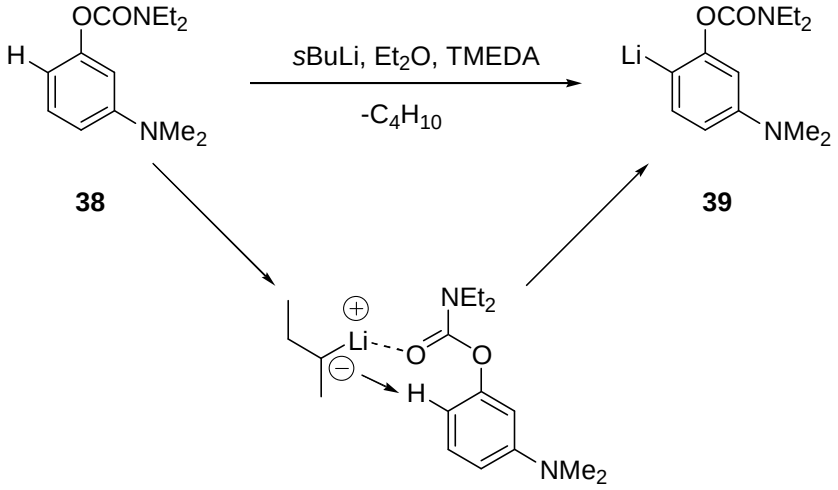
[26] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[27] A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 159.
[28] W. Schlenk, E. Bergmann, *Ann.* **1928**, *463*, 98.
[29] For an early overview about metalation using organolithium compounds, see: J. M. Mallan, R. L. Bebb, *Chem. Rev.* **1969**, *69*, 693 and references therein.



36 **37**

Scheme 6: First performed deprotonation (lithiation) of fluorene (**36**) using EtLi.

Moreover, numerous results have been published making this methodology more and more attractive. For example, noteworthy are the investigations of the lithiation of halogenated substrates carried out by *Schlosser* and co-workers.[30] Especially *Beak* and *Snieckus* explored intensively the directed *ortho*-metalation using lithium bases and the complex-induced proximity effect.[31] The concept "directed *ortho*-metalation" (DoM) describes the regioselective functionalization of aromatics if a directing group is present in the molecule. For example, amides, carbamides, sulfonamides, esters, cyanides or phosphorous-containing substituents are considered to be efficient directing groups in contrast to ethers or amines. In the presence of such a group, the metalating agent is complexed and therefore the corresponding base is conducted to the next activated proton, in general in *ortho*-position to the directing group (Scheme 7). In some cases, the directing effect of one group can overrule the effect of the other one or the presence of two groups with equal properties lead to a decreased regioselectivity of the metalation process.



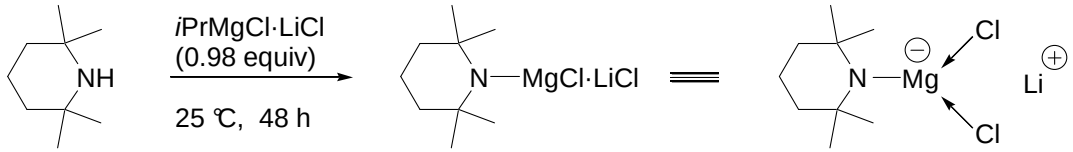
38 **39**

Scheme 7: Regioselective lithiation of the carbamate **38**.[32]

[30] a) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376; b) M. Schlosser, *Angew. Chem. Int. Ed.* **2006**, *45*, 5432; c) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827.
[31] For an overview, see: a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667; c) M. C. Whisler, S. MacNeil, P. Beak, V. Snieckus, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; d) P. Beak, A. I. Meyers, *Acc. Chem. Res*. **1986**, *19*, 356.
[32] M. Skowronska-Ptasinska, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1985**, *50*, 2690.

The drawbacks of these metalations are the low tolerance towards functional groups and the low temperatures required for the deprotonations (mostly –78 °C or even below). Beside these lithiations, magnesium bases have also been investigated pioneered by *Hauser*.[33] Moreover, *Eaton* reported the use of the *bis*-amide TMP_2Mg (TMP = 2,2,6,6-tetramethylpiperidyl) and related reagents for the functionalization of aromatic substrates.[34] Due to the higher aggregation and lower ionic character of the amide-metal bond, a big excess of the metalation reagent is necessary to obtain good magnesiation rates. Similarly, *Mulzer* investigated the use of TMPMgCl (up to 12 equivalents) allowing the functionalization of activated heterocycles.[35]

A remarkable improvement of the reagent TMPMgCl was obtained by complexing this amide with LiCl.[36] Thus, the reaction of *i*PrMgCl·LiCl with TMPH at 25 °C leads to the new complex TMPMgCl·LiCl (**40**; Scheme 8) possessing an excellent solubility in THF (up to 1.3 M). The presence of LiCl is certainly responsible for disaggregating this reagent by generating an intermediate ate complex.[37] Therefore, the solubility is improved and similar to the exchange reagent *i*PrMgCl·LiCl, the reactivity is outstandingly increased. Remarkably in contrast to lithium amides, this reagent can be stored at 25 °C for at least 6 months.



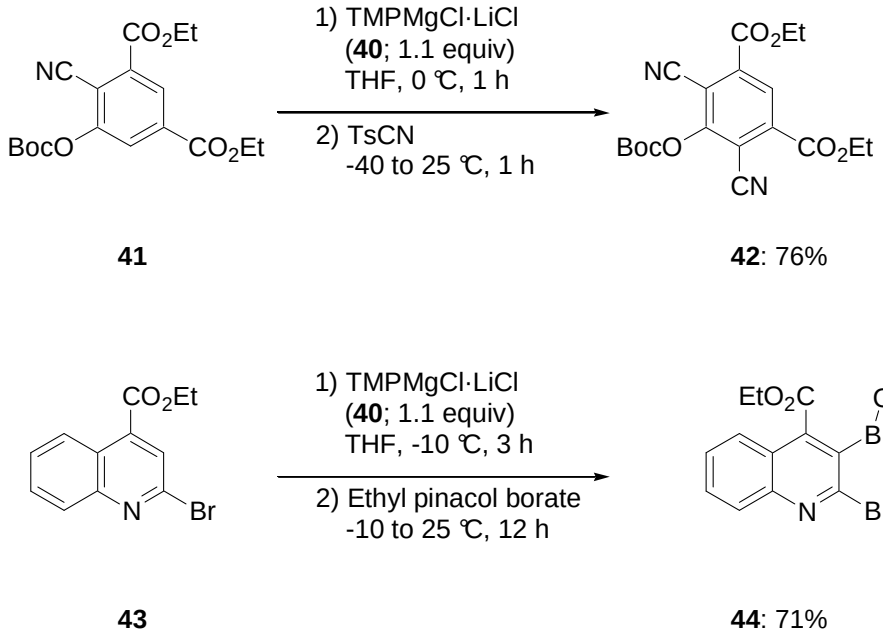
40: >95 %
c = 1.30 M in THF

Scheme 8: Preparation of the reagent TMPMgCl·LiCl (**40**).

Moreover, this reagent accomplishes the smooth functionalization of aromatics as shown exemplarily in Scheme 9. Thus, the benzoate **41** is deprotonated with TMPMgCl·LiCl (**40**) to give the desired metal species in good yield.[38] The resulting organometallic reagent is reacted with TsCN providing the desired product in 76% yield. Furthermore, a smooth

[33] a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295; b) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350.
[34] a) P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016; b) M.-X. Zhang, P. E. Eaton, *Angew. Chem. Int. Ed.* **2002**, *41*, 2169; c) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc.* **1993**, *115*, 11375; d) Y. Kondo, A. Yoshida, T. Sakamoto, *J. Chem. Soc., Perkin Trans 1*, **1996**, 2331.
[35] a) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414; b) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Liebigs Ann.* **1995**, 1441; c) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Synthesis* **1995**, 1225.
[36] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
[37] P. García-Alvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, S.; *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.
[38] a) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; b) A. H. Stoll, P. Knochel, *Org. Lett.* **2008**, *10*, 113.

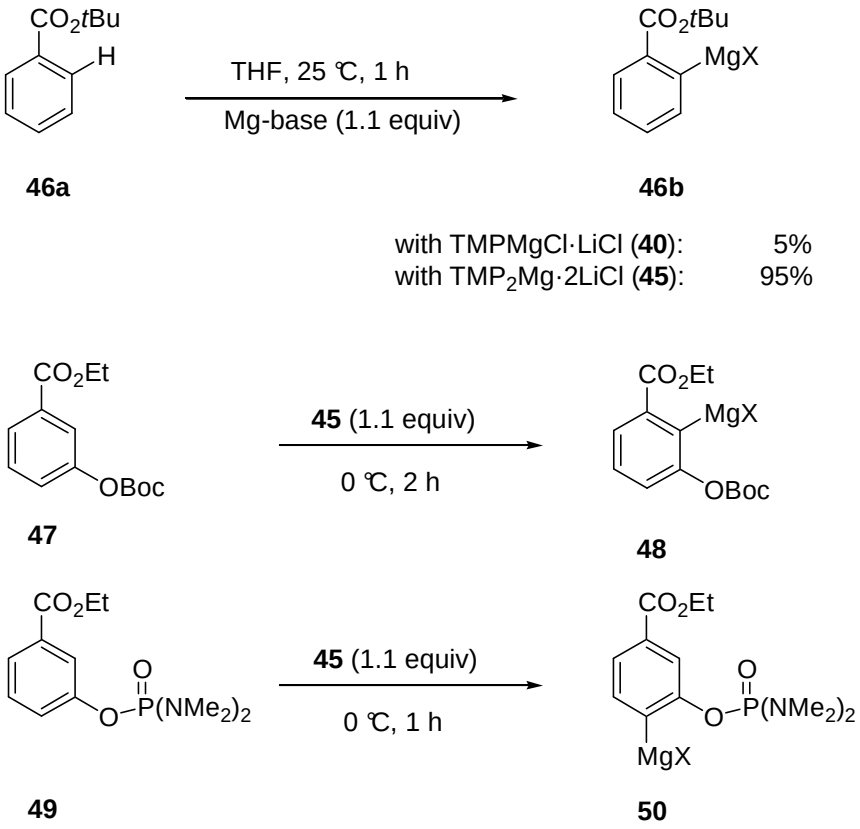
magnesiation of various heterocycles can also be achieved by using this metalation protocol.[39] Hence, the treatment of the quinoline **43** and the subsequent reaction of the metalated heterocycle with ethyl pinacol borate gives the functionalized boronic ester **44** in 71% yield.



Scheme 9: Functionalization of the benzoate **41** and the heterocycle **43**.

Recently, an extension of the directed magnesiation concept led to the more kinetically active base $TMP_2Mg·2LiCl$ (**45**) allowing the efficient functionalization of medium-activated arenes and heteroarenes.[40] Hence, ethyl benzoate (**46a**) which could not be magnesiated with TMPMgCl·LiCl (**40**; 1.2 equiv), gives the fully magnesiated species **46b** by using $TMP_2Mg·2LiCl$ (**45**; 1.1 equiv) within 1 h at 25 °C (Scheme 10). Moreover, the combination of magnesiation with $TMP_2Mg·2LiCl$ (**45**) and the use of the directing group $-OP(O)(NMe_2)_2$ provides unusual regioselectivities since this phosphorous group can overrule the effects of many other directing groups. Thus, the metalation of the benzoate **47** bearing a Boc-protected hydroxy group leads regioselectively to the metalated species **48.** Alternatively, the benzoate **49** is regioselectively metalated in position 4 giving the intermediate **50** (Scheme 10).

[39] a) N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525; b) N. Boudet, S. R. Dubbaka, P. Knochel, *Org. Lett.* **2008**, *10*, 1715; c) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497.
[40] a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681; b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503; c) C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel, *Org. Synth.* **2009**, 86, 374.

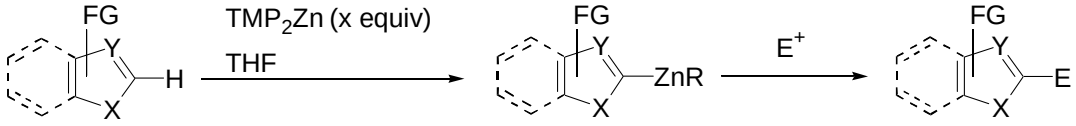


Scheme 10: Magnesiation of the benzoates **46a**, **47** and **49** using Mg-amides.

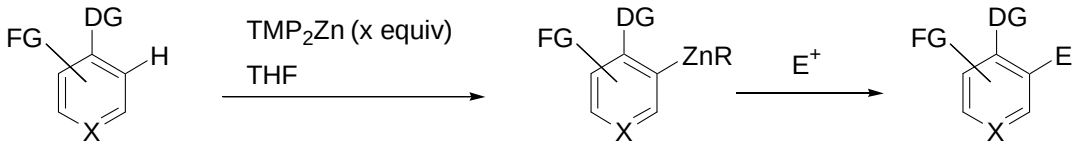
Beside this great progress in generating organometallic reagents under convenient conditions, there is still a need for more chemoselective metalation reagents. For example, molecules bearing aldehydes or nitro groups did not undergo directed magnesiations. Similarly, sensitive heterocycles which are subject to fragmentation could also not efficiently be converted into the corresponding magnesium reagents.

2 Objectives

As previously described, the directed metalation using lithium or magnesium bases has been studied in detail. In contrast, Zn-amides are sparely described due to their low reactivity. Therefore, the development of a selective Zn amide base for the directed zincation would be desirable since the use of zinc organometallics allows the presence of most organic functional groups and should provide stable metalated heterocycles (Scheme 11). The smooth preparation (e.g. the most convenient amine) of the metalating reagent, the properties and the kinetic basicity should be studied and, if needed, the use of additives and/or elevated temperatures should be investigated.



FG: functional group; X: heteroatom
Y: CH or heteroatom



DG: directing group; FG: functional group; X: CH or heteroatom

Scheme 11: General pathway leading to functionalized organozinc species and subsequent reaction with electrophile.

Accordingly, this metalation concept should be extended to different metals, since this may lead to unique reactivity and selectivity. Thereby, the attention should be turned to cheap and non-toxic metals. Due to the strong Lewis-acidity of the aluminum ion and the resulting potential suitable attachment to directing groups, the alumination seems to be promising. Similarly, the use of lanthanum as metal center should allow performing reactions (e.g. additions to carbonyl groups) with high chemoselectivity.

Furthermore, a continuative project should grant access to so far unknown functionalized organometallics of transition metals. Since manganese and iron can be considered as non-toxic and cheap metals, the preparation should be accomplished similar to the zinc base. The reaction with functionalized aromatics and heteroaromatics should provide organometallics with unique reactivity not accessible for main group metals.

3 Directed Zincation of Functionalized Aromatics and Heteroaromatics Using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$

3.1 Introduction

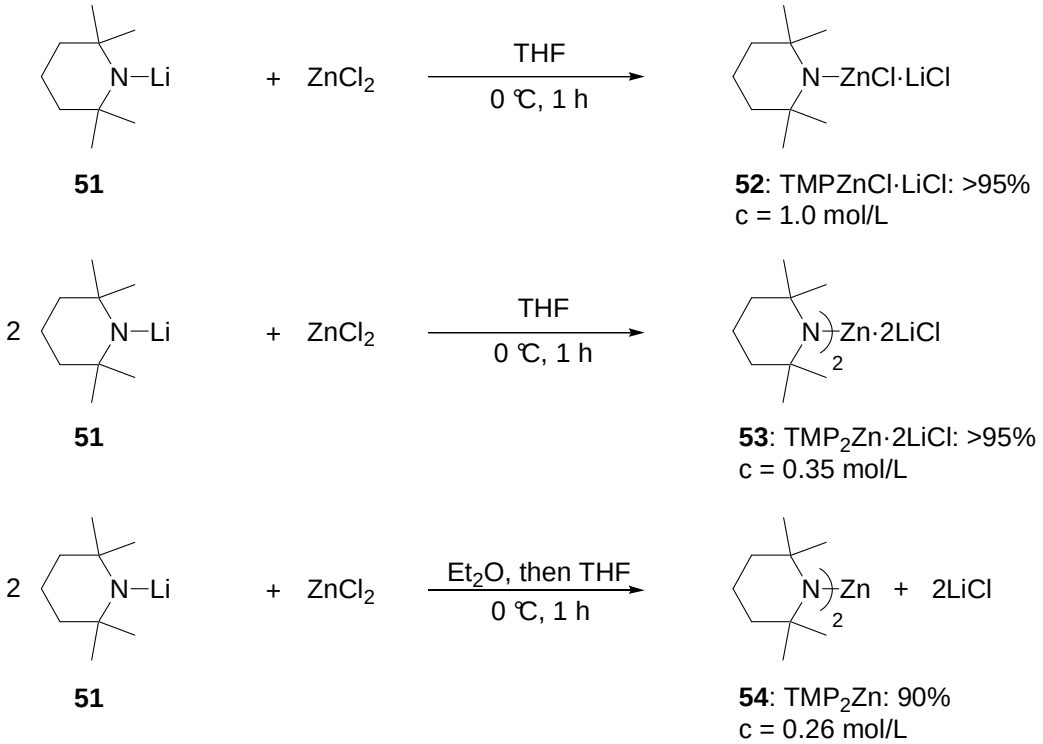
The research for new chemoselective amide bases for the efficient preparation of new organometallics *via* directed metalation started with the development of a new zinc base. Due to the high covalent character of the carbon-zinc bond, organozinc compounds can be considered as one of the most stable group of organometallics[41] and are able to react in the desired way even in the presence of acidic protons.[42] Although zinc reagents are known for more than 160 years and some reactions soon have found useful applications (e. g. Reformatsky reactions[43] or Simmons-Smith reactions[44]), their synthetic benefit has been extensively explored with the availability of new Pd-catalysts [45] or copper-mediated reactions.[46] Beside the already mentioned direct insertion of Zn dust into carbon-halogen-bonds and iodine-zinc exchange reaction, *Kondo* reported the use of Li*t*Bu_2ZnTMP allowing the efficient preparation of arylzinc species due to the ate-character of this reagent (the structures of the metalated intermediates were extensively studied by *Mulvey*).[47] A major drawback of this method is the high excess of electrophile necessary for the complete consumption of the metalated species (low atom-economy) and the non-compatibility with sensitive functional groups like aldehydes or nitro groups. Recently, the neutral reagent TMP_2Zn without any additive was reported to allow the preparation of Zn-enolates and the zincation of extremely electron-poor substrates like pyridine *N*-oxides or

[41] a) *Organozinc Reagents* (Eds.: P. Knochel, P. Jones), Oxford University Press, New York, **1999**; b) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.
[42] a) G. Manolikakes, M. Schade, C. Muñoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765; b) G. Manolikakes, Z. Dong, H. Mayr, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 1324.
[43] A) S. Reformatsky, *Chem. Ber.* **1887**, *20*, 1210; b) S. Reformatsky, *Chem. Ber.* **1895**, *28*, 2842.
[44] H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 4256.
[45] For examples, see: a) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; b) E. Negishi, H. Matsushita, M. Kobayashi, C. L. Raud, *Tetrahedron Lett.* **1983**, *24*, 3823; c) E. Negishi, T. Takahashi, S. Baba, D. E. Van Horn, N. Okukado, *J. Am. Chem. Soc.* **1987**, *109*, 2393; d) E. Negishi, Z. Ouczarczyka, *Tetrahedron Lett.* **1991**, *32*, 6683.
[46] For examples, see: P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; b) P. Knochel, S. A. Rao, *J. Am. Chem. Soc.* **1990**, *112*, 6146.
[47] a) Y. Kondo, H. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539; b) T. Imahori, M. Uchiyama, Y. Kondo, *Chem. Comm.* **2001**, 2450; c) P. F. H. Schwab, F. Fleischer, J. Michl, *J. Org. Chem.* **2002**, *67*, 443; d) M. Uchiyama, T. Miyoshi, Y. Kajihana, T. Sakamoto, Y. Otami, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514; e) D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2006**, *45*, 3775; f) M. Uchiyama, Y. Kobayashi, T. Furuyama, S. Nakamura, Z. Kajihara, T. Miyoshi, T. Sakamoto, Y. Kondo, K. Morokuma, *J. Am. Chem. Soc.* **2008**, *130*, 472; g) R. E. Mulvey, *Acc. Chem. Res.* **2009**, *42*, 743; h) W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, C. T. O'Hara, L. Russo, *Angew. Chem. Int. Ed.* **2008**, *47*, 731; i) W. Clegg, B. Conway, E. Hevia, M. D. McCall, L. Russo, R. E. Mulvey, *J. Am. Chem. Soc.* **2009**, *131*, 2375.

DMSO.[48] Based on our experience on LiCl-accelerated reactions (see chapter 1) we envisioned the development of a new neutral, highly active zinc amide base.

3.2 Preparation of the Zn-Reagent 60

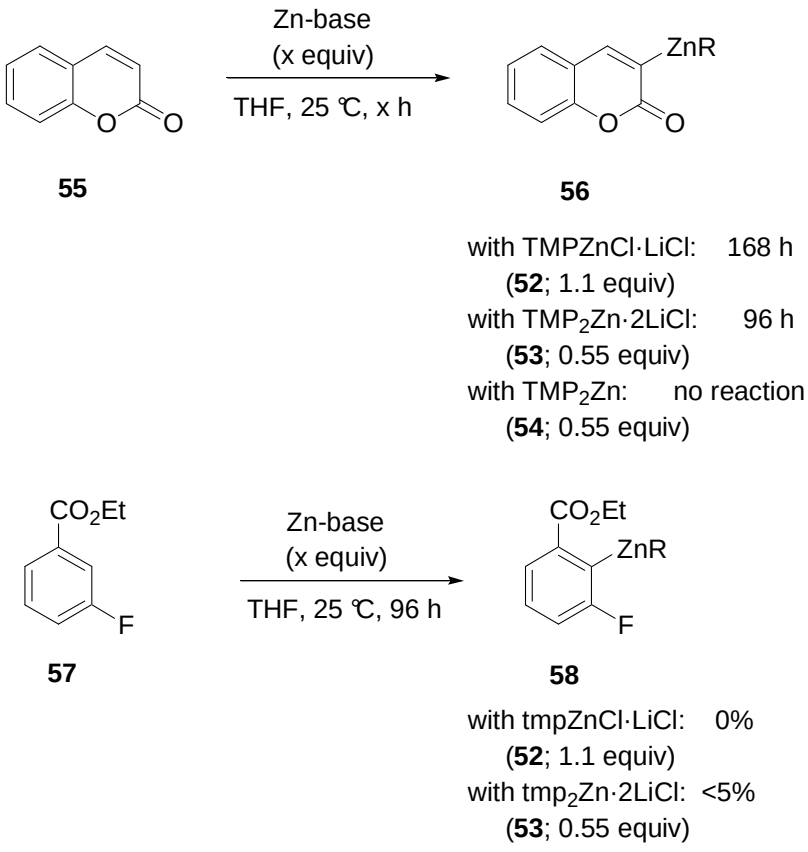
For the first attempts, freshly prepared TMPLi (**51**)[49] was transmetalated to the corresponding zinc amides TMPZnCl·LiCl (**52**) and $TMP_2Zn \cdot 2LiCl$ (**53**) using $ZnCl_2$ (1.0 equiv or 0.50 equiv, respectively). After stirring these mixtures for 1 h at 0 °C, the solvents were removed *in vacuo* and the resulting residues were redissolved in THF (Scheme 12). Both bases could be obtained as orange solutions in THF in nearly quantitative yield. Interestingly, the *mono* amide base TMPZnCl·LiCl (**52**) displays a higher concentration than the *bis*-amide **53** (1.0 M compared to 0.35 M). Additionally, TMP_2Zn (**54**) was prepared by reacting freshly prepared TMPLi with $ZnCl_2$ (0.5 equiv) in Et_2O for 1 h at 0 °C. The generated precipitate was filtered off, the solvents removed *in vacuo* and the resulting residue was redissolved in THF. The amide base TMP_2Zn was obtained as a yellowish solution in 90% yield and displays a decreased concentration (0.26 M) compared to $TMP_2Zn \cdot 2LiCl$ (**53**) due to the absence of LiCl.



Scheme 12: Preparation of the zinc amide bases **52**-**54**.

[48] a) M. L. Hlavinka and J. R. Hagadorn, *Organometallics* **2007**, *26*, 4105; b) M. L. Hlavinka, J. F. Greco J. R. Hagadorn, *Chem .Comm.* **2005**, 5304; c) M. L. Hlavinka and J. R. Hagadorn, *Tetrahedron Lett.* **2006**, *47*, 5049; d) W. Rees, O. Just. H. Schumann, R. Weimann, *Polyhedron* **1998**, *17*, 1001.
[49] I. E. Kopka, Z. A. Fataftah, M. W. Rathke, *J. Org. Chem.* **1987**, 52, 448.

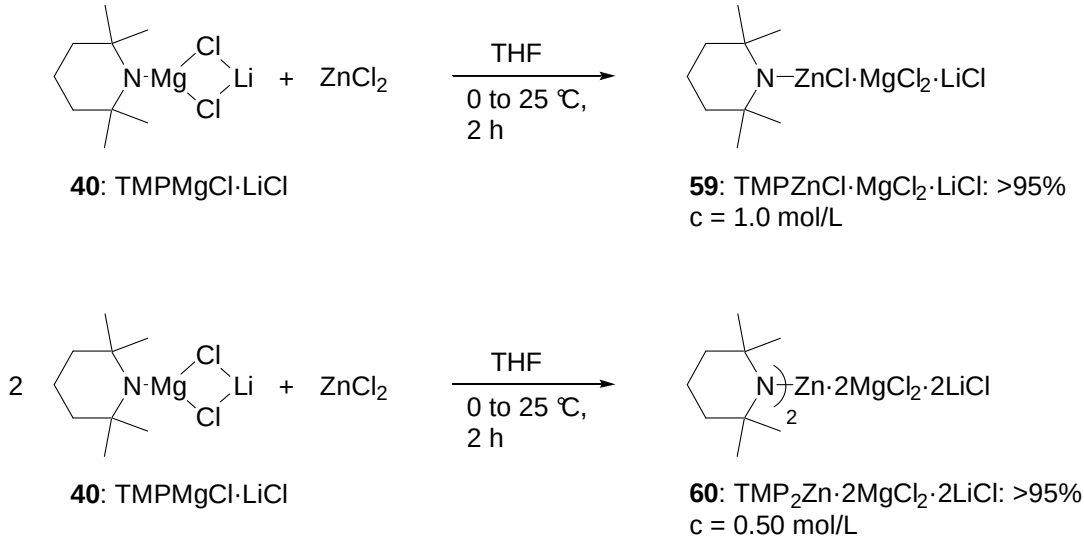
Then, the reactivity of these bases was investigated. Thus, the reaction of coumarin (**55**) with TMPZnCl·LiCl (**52**; 1.1 equiv) provides the fully metalated species **56** after a reaction time of 7 d, whereas ethyl 3-fluorobenzoate (**57**) can not be metalated at all under these conditions (25 °C; 1.1 equiv; Scheme 13). Furthermore, the metalation of coumarin is accomplished within 96 h at 25 °C using $TMP_2Zn \cdot 2LiCl$ (**53**; 0.55 equiv), but the reaction of ethyl 3-fluorobenzoate (**57**) with $TMP_2Zn \cdot 2LiCl$ (**53**; 0.55 equiv) furnishes the desired metalated species **58** in less than 5% after 96 h at 25 °C (Scheme 13). Interestingly, the attempts to zincate coumarin (**55**) with TMP_2Zn (**54**) does not lead to the corresponding zinc species **56**. Moreover, the use of an excess of the amides **52** and **53** does not improve the metalation rates leading to zincated ethyl 3-fluorobenzoate (**57**).



Scheme 13: Metalation of coumarin (**55**) and ethyl 3-fluorobenzoate (**57**) using the amide bases **52**-**54**. The conversion to the corresponding metal species **56** and **58** was monitored by GC-analysis of aliquots of the reaction mixture quenched with a solution of I_2 in THF using tetradecane as internal standard.

Alternatively, two more reagents for achieving zincations have been prepared *via* the transmetalation of TMPMgCl·LiCl (**40**). Thus, the reaction of freshly titrated TMPMgCl·LiCl (**40**) with $ZnCl_2$ (1.0 equiv or 0.50 equiv, respectively) in THF for 2 h at

0 °C affords the $MgCl_2$-containing amides $TMPZnCl \cdot MgCl_2 \cdot LiCl$ (**59**) and $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) as green-brown solutions in THF in nearly quantitative yield (Scheme 14). Whereas $TMPZnCl \cdot MgCl_2 \cdot LiCl$ (**59**) displayed a comparable concentration like the related base $TMPZnCl \cdot LiCl$ (1.0 M each), the *bis*-amide base **60** possesses an increased concentration (max. 0.50 M) compared to $TMP_2Zn \cdot 2LiCl$ (**53**; just 0.35 M). Certainly, the formed $MgCl_2$ leads to a better solubility in THF. Remarkably, all five zinc bases (**52**-**54**, **59** and **60**) are stable at 25 °C for at least 3 months without noticeable loss of reactivity. (Note: The preparation of zinc amides using other (cheaper) amines is discussed in chapt. 6.)

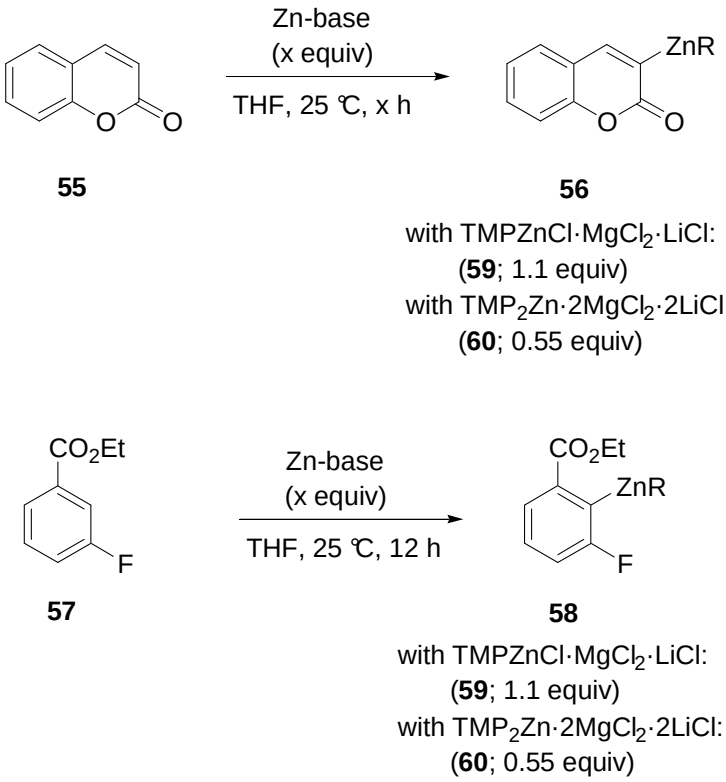


Scheme 14: Preparation of the amide bases $TMPZnCl \cdot MgCl_2 \cdot LiCl$ (**59**) and $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**).

Subsequently, the zincation of coumarin (**55**) and ethyl 3-fluorobenzoate (**57**) is now carried out using the new zinc amides **59** and **60** (Scheme 15). It clearly turns out, that these $MgCl_2$-containing amides $TMPZnCl \cdot MgCl_2 \cdot LiCl$ (**59**) and $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) display a much higher kinetic basicity. Thus, the zincation of coumarin (**55**) using $TMPZnCl \cdot MgCl_2 \cdot LiCl$ (**59**; 1.1 equiv) gives the zincated intermediate **56** within 72 h instead of 168 h using $TMPZnCl \cdot LiCl$ (**52**). Moreover, coumarin (**55**) is completely converted to **56** within only 4 h at 25 °C using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv). Additionally, this powerful base achieves the zincation of ethyl 3-fluorobenzoate (**57**) within 12 h at 25 °C whereas the *mono*-amide base **59** (1.1 equiv) affords the zincated species **58** in only 11% after 12 h at 25 °C. These preliminary experimental results lead to two conclusions:

1. *Bis*-amide bases display an enhanced kinetic basicity compared to the corresponding *mono*-amide bases.

2. The combination of TMP_2Zn with the Lewis-acids[50] LiCl and $MgCl_2$ leads to an enormously accelerated metalation progress of aromatics and heteroaromatics. Furthermore, $MgCl_2$ as well as LiCl (for remarkable enhanced solubility due to LiCl see chap. 1) are responsible for an increased solubility of $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) in THF compared to TMP_2Zn (**54**) and $TMP_2Zn \cdot 2LiCl$ (**53**).

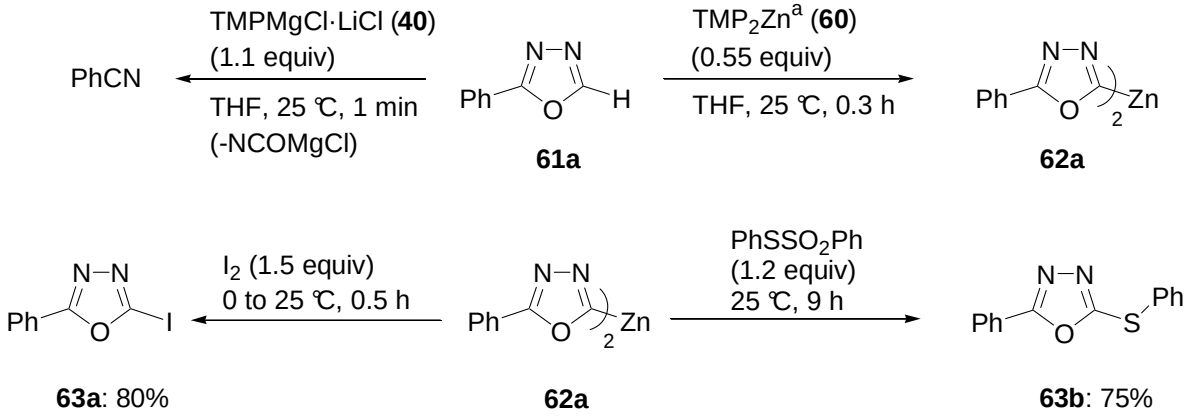


Scheme 15: Metalation of coumarin (**55**) and ethyl 3-fluorobenzoate (**57**) using the amide bases $TMPZnCl \cdot MgCl_2 \cdot LiCl$ (**59**) and $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**). The conversion to the corresponding metal species **56** and **58** was monitored *via* GC-analysis of aliquots of the reaction mixture quenched wtih a solution of I_2 in THF using tetradecane as internal standard.

[50] a) E. Negishi, *Chem. Eur. J.* **1999**, 411; b) *Lewis Acids in Organic Synthesis*; (Ed.: H. Yamamoto), Wiley-VCH: Weinheim, **2000**; Vols. 1 and 2; c) *Lewis Acid Reagents: A Practical Approach*; (Ed.: H. Yamamoto), Oxford University Press: Oxford, **1999**; d) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570; e) Y. Zhang, K. Shibatomi, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 15038; f) G. Xia, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 2554.

3.3 Metalation of Heteroaromatics

The mixed-metal complex base $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) has a high activity for the zincation of sensitive heterocycles such as 2-phenyl-1,3,4-oxadiazole (**61a**). The lithiated or magnesiated species as well as related metalated heterocycles are subject to fragmentation.[51] However, its reaction with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv) provides the zincated heterocycle **62a** after 20 min at 25 °C without any formation of benzonitrile (product of ring fragmentation). After quenching the diheteroarylzinc with iodine or $PhSSO_2Ph$, the expected substituted oxadiazoles **63a-b** are isolated in 75-85% yield (Scheme 16).



Scheme 16: Reactivity of TMP_2Zn (**60**)[a] compared to TMPMgCl·LiCl (**40**). [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

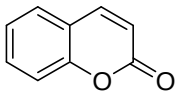
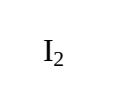
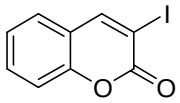
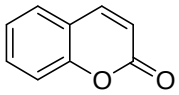
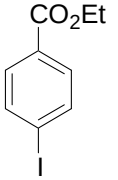
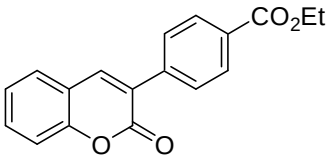
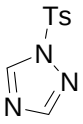
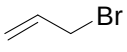
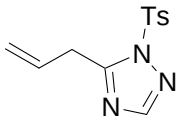
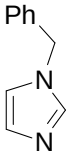
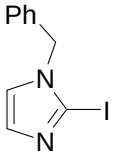
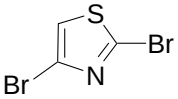
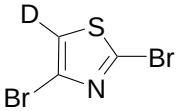
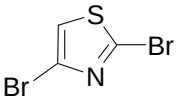
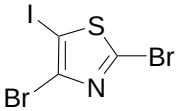
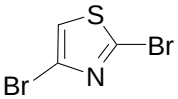
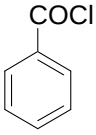
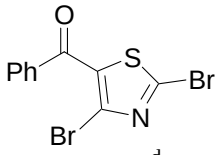
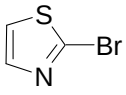
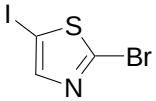
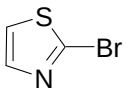
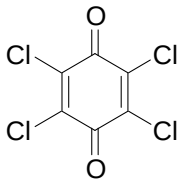
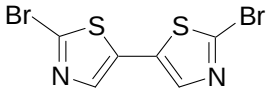
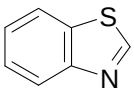
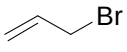
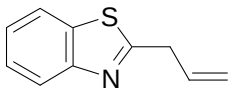
As already noted above, the metalation of coumarin (**55**) is finished within 4 h at 25 °C using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv). After the reaction with I_2 or a Pd-catalyzed cross-coupling reaction[45] with ethyl 4-iodobenzoate, the desired functionalized coumarins **63c-d** are provided in 85-87% yield (Table 1, entries 1-2). Moreover, this metalation concept can easily be extended to various unsubstituted heterocycles. Thus, the zincation of *N*-tosyl-1,2,4-triazole (**61b**) proceeds within 40 min at –25 °C and the subsequent reaction with allyl bromide in the presence of $CuCN \cdot 2LiCl$[46] (5 mol-%) leads to the heterocycle **63e** in 85% yield (entry 3). Additionally, the iodinated imidazole **63f** is

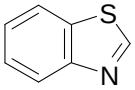
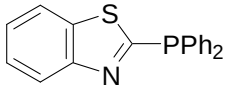
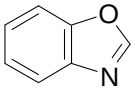
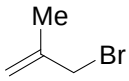
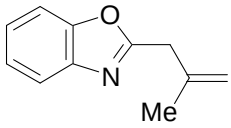
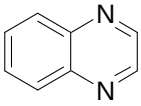
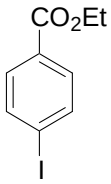
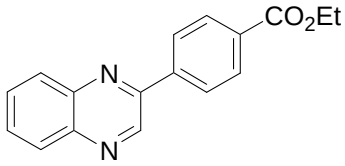
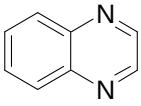
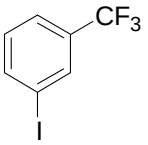
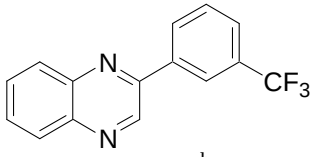
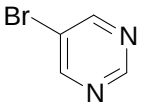
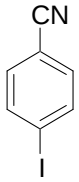
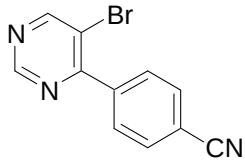
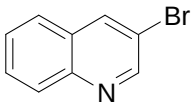
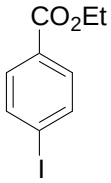
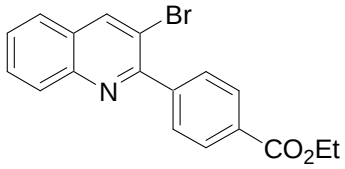
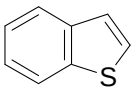
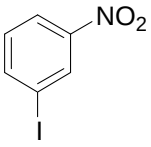
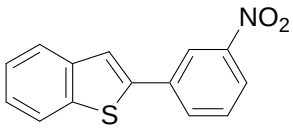
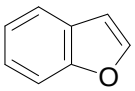
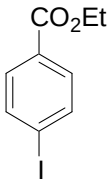
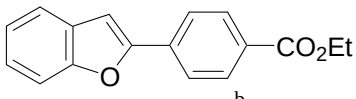
[51] a) R. G. Micetich, *Can. J. Chem.* **1970**, *48*, 2006; b) A. I. Meyers, G. N. Knaus, *J. Am. Chem. Soc.* **1974**, *95*, 3408; c) G. N. Knaus, A. I. Meyers, *J. Org. Chem.* **1974**, *39*, 1189; d) R. A. Miller, M. R. Smith, B. Marcune, *J. Org. Chem.* **2005**, *70*, 9074; e) *Heterocyclic Compounds* (Ed. I. J. Turchi) J. Wiley and Sons: New York, **1986**; f) *Heterocyclic Compounds*; (Ed. D. Palmer), J. Wiley and Sons: New York, **2003**, **2004**; Vol. 60, Parts A and B; g) C. Hilf, F. Bosold, K. Harms, M. Marsch, G. Boche, *Chem. Ber. Rec.* **1997**, *130*, 1213.

obtained in 81% yield after the smooth metalation of 1-benzyl-1*H*-imidazole (**61c**) with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv, 25 °C, 30 min) followed by the reaction with I_2 (1.5 equiv; entry 4). Continuously, 2,4-dibromothiazole (**61d**) undergoes a fast zincation within 15 min at 25 °C. Subsequent reactions with either D_2O, iodine or benzoyl chloride mediated by CuCN·2LiCl furnish the thiazoles **63g-i** in 84-91% yield (entries 5-7). Accordingly, the zincation of 2-bromothiazole (**61e**) is accomplished within 20 min and the reaction with I_2 (1.5 equiv) gives the heterocycle **63j** in 84% yield (entry 8). Interestingly, the treatment of the metalated 2-bromothiazole (**62e**) with chloranil [52] (0.6 equiv) affords the dimeric thiazole [53] **63k** in 91% yield (entry 9). Moreover, unsusbtituted benzothiazole (**61f**) is fully zincated within 30 min at 25 °C using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv). After the reaction with allyl bromide in the presence of catalytic amounts of CuCN·2LiCl (5 mol-%) or the quenching with Ph_2PCl,[54] the desired products **63l-m** are obtained in 77-79% yield (entries 10-11). Similarly, the allylated benzoxazole **63n** is provided in 57% yield after the metalation of benzoxazole (**61g**) with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv, 0 °C, 1 h) and a Cu(I)-catalyzed reaction with methallyl bromide (entry 12). Interestingly, quinoxaline (**61h**) is readily converted into the metalated species within 5 h at 25 °C without the formation of dimeric quinoxaline (see chapt. 7.2). Adjacent cross-couplings[45] with ethyl 4-iodobenzoate or 1-iodo-3-trifluoromethylbenzene using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%) as catalytic system afford the expected substituted quinoxalines **63o-p** in 82-88% yield (entries 13-14). Accordingly, 5-bromopyrimidine (**61i**) and 3-bromoquinoline (**61j**) are readily zincated at 25 °C within 5 h and 2 h, respectively. The desired heterocycles **63q-r** are isolated in 75-93% yield after Negishi cross-couplings with 4-iodobenzonitrile or ethyl 4-iodobenzoate (entries 15-16). Finally, the less activated heterocycles benzothiophene (**61k**) and benzofuran (**61l**) undergo also zincation reactions. After 144 h and 168 h, respectively, the metalations using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv) are complete and subsequent Pd-catalyzed cross-couplings with different aryl iodides give the products **63s-t** in 65-82% yield (entries 17-18).

[52] A. Krasovskiy, A. Tishkov, V. del Amo, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 5010.
[53] H. Iwanaga, U.S. Pat. Appl. US 20040062950, **2004**; *Chem. Abstr.* 140: 312117.
[54] a) A. Longeau, F. Langer, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 2209; b) A. Longeau, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 6099; c) F. Langer, K. Püntener, R. Stürmer, P. Knochel, *Tetrahedron: Assymetry* **1997**, *8*, 715.

Table 1: Products of type **63** obtained by zincation of coumarin and heteroaromatics using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv) and subsequent reactions with electrophiles.

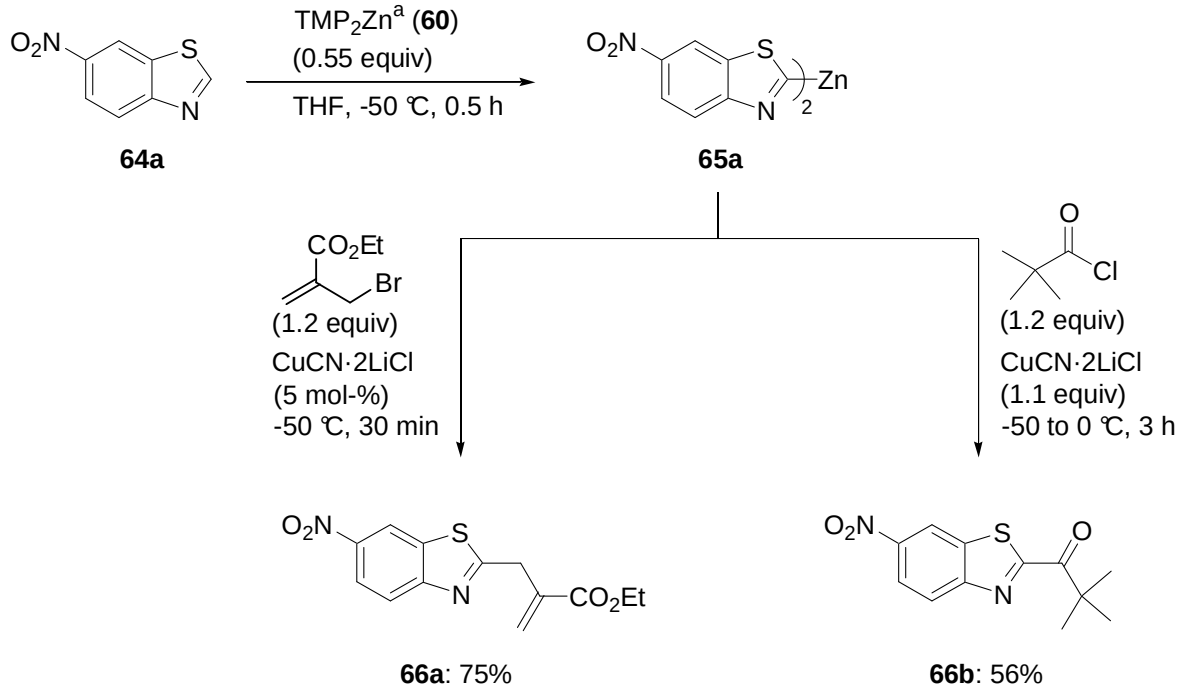
Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
1	 **55**	25, 4		 **63c**: 87
2	 **55**	25, 4		 **63d**: 85[b]
3	 **61b**	–25, 0.6		 **63e**: 85[c]
4	 **61c**	25, 0.5	I_2	 **63f**: 81
5	 **61d**	25, 0.25	D_2O	 **63g**: 91
6	 **61d**	25, 0.25	I_2	 **63h**: 88
7	 **61d**	25, 0.25		 **63i**: 84[d]
8	 **61e**	25, 0.3	I_2	 **63j**: 84
9	 **61e**	25, 0.3		 **63k**: 91
10	 **61f**	25, 0.5		 **63l**: 77[c]

Entry	Substrate	T[°C], t[h]	Electrophile	Product/Yield [%][a]
11	 **61f**	25, 0.5	Ph_2PCl	 **63m**: 79
12	 **61g**	0, 1		 **63n**: 57[c]
13	 **61h**	25, 5		 **63o**: 82[b]
14	 **61h**	25, 5		 **63p**: 88[b]
15	 **61i**	25, 5		 **63q**: 75[b]
16	 **61j**	25, 2		 **63r**: 93[b]
17	 **61k**	25, 144		 **63s**: 82[b]
18	 **61l**	25, 168		 **63t**: 65[b]

[a] Isolated yield of analytically pure product. [b] A transmetalation with CuCN·2LiCl (5 mol-%) was performed. [c] Obtained by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%). [d] A transmetalation with CuCN·2LiCl (1.1 equiv) was performed.

3.4 Metalation of Heterocycles Bearing Sensitive Functionalities

Interestingly, heterocycles bearing nitro groups are also readily zincated using the new base $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv). Thus, the metalation of 6-nitrobenzothiazole (**64a**) proceeds smoothly within 30 min at –50 °C giving the zinc species **65a**. Subsequent Cu-mediated reactions[46] with ethyl 2-(bromomethyl)acrylate[55] or pivaloyl chloride afford the allylated thiazole **66a** in 75% and the ketone **66b** in 56% yield (Scheme 17).

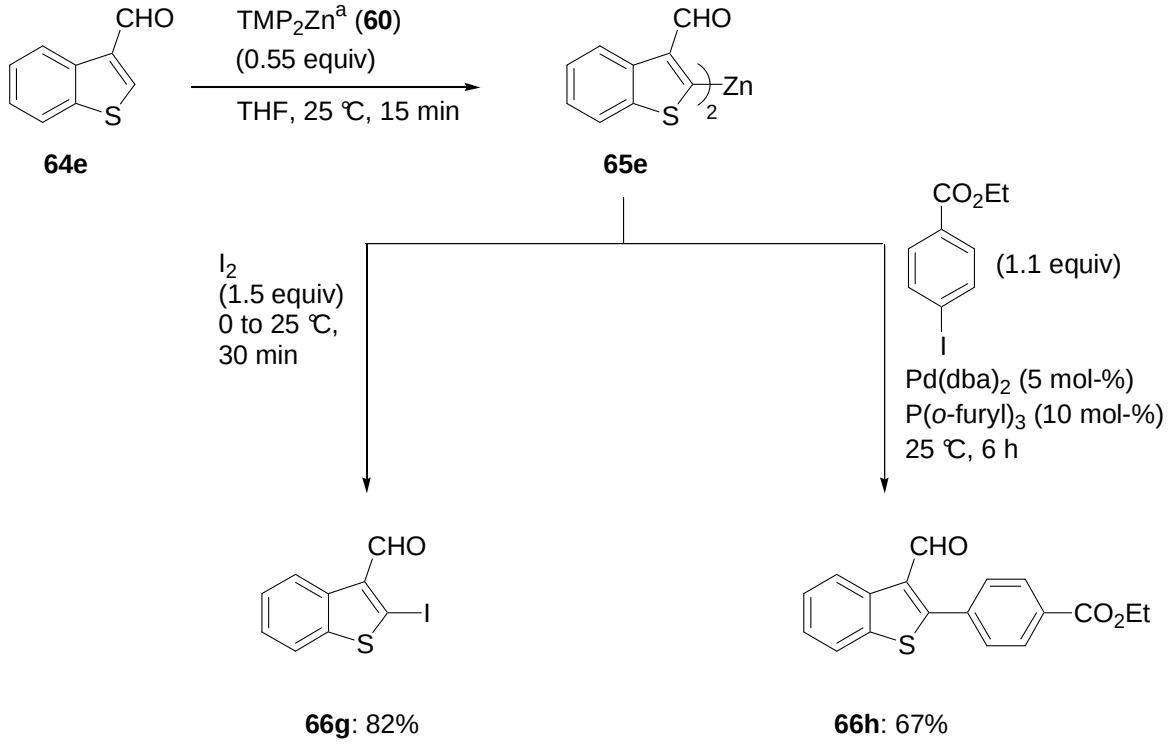


Scheme 17: Functionalization of 6-nitrobenzothiazole (**64a**). [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

Moreover, 2-nitrobenzofuran (**64b**) undergoes a smooth zincation within 1.5 h at –25 °C. The adjacent reactions of **65b** with either D_2O or 3-cyclohexenyl bromide in the presence of CuCN·2LiCl (5 mol-%) lead to the substituted benzofurans **66c-d** in 80-82% yield (Table 2, entries 1-2). Furthermore, the protected 4-nitroimidazole **64c** is converted into the corresponding zinc species **65c** within 45 min at –40 °C and the subsequent allylation catalyzed by CuCN·2LiCl (5 mol-%) provides the functionalized imidazole **66e** in 59% yield (entry 3). Accordingly, 2-chloro-3-nitropyridine (**64d**) is regioselectively metalated within 1.5 h at –40 °C in position 4 and the highly functionalized pyridine **66f** is isolated in 80% yield after a Cu(I)-catalyzed reaction with 3-cyclohexenyl bromide (entry 4). Remarkably, substrates

[55] J. Villieras, M. Rambaud, *Org. Synth.* **1988**, *66*, 220.

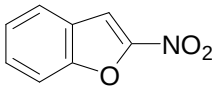
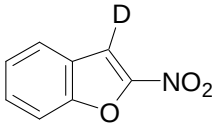
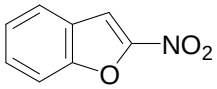
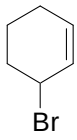
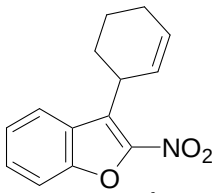
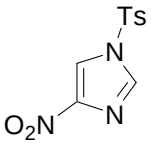
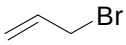
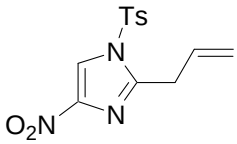
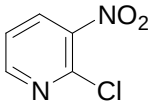
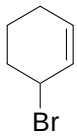
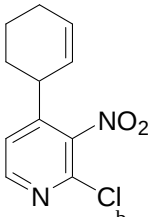
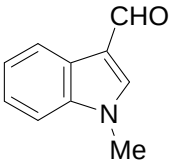
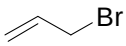
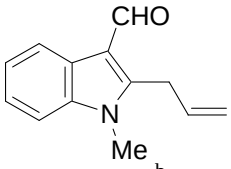
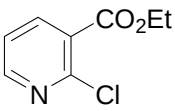
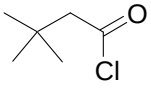
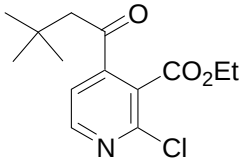
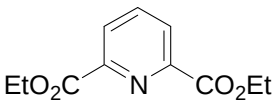
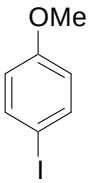
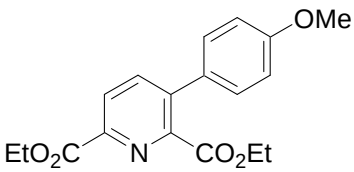
bearing aldehyde groups can also be readily zincated. Thus, benzothiophene-3-carbaldehyde (**64e**) undergoes a fast zincation using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv, 25 °C, 15 min). Iodolysis or a Pd-catalyzed cross-coupling[45] with ethyl 4-iodobenzoate of the metalated benzothiophene furnish the substituted aldehydes **66g-h** in 67-82% yield (Scheme 18).



Scheme 18: Functionalization of benzothiophene-3-carbaldehyde (**64e**). [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

Similarly, the related aldehyde **64f** is zincated within 45 min and the subsequent allylation catalyzed by CuCN·2LiCl (5 mol-%) leads to the substituted indole **66i** in 71% yield (Table 2, entry 5). Finally, ester-bearing pyridines are further functionalized using this new metalation method. Thus, the nicotinate **64g** is regioselectively metalated in position 4 within 5.5 h at 25 °C. A CuCN·2LiCl-mediated acylation with 3,3-dimethylbutyryl chloride affords the ketone **66j** in 75% yield (entry 6). The metalation of the diester **64h** proceeds regioselectively in position 3 and the fully zincated species is obtained after 24 h at 25 °C. The biaryl **66k** is then isolated in 65% yield after a Pd-catalyzed cross-coupling with 4-iodoanisole (entry 7). These results clearly show that the new base $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) combines excellent selectivity and tolerance of functional groups with high kinetic basicity. Since both TMP-moieties are used for the directed metalations, this procedure can also be considered as atom-economical, too.

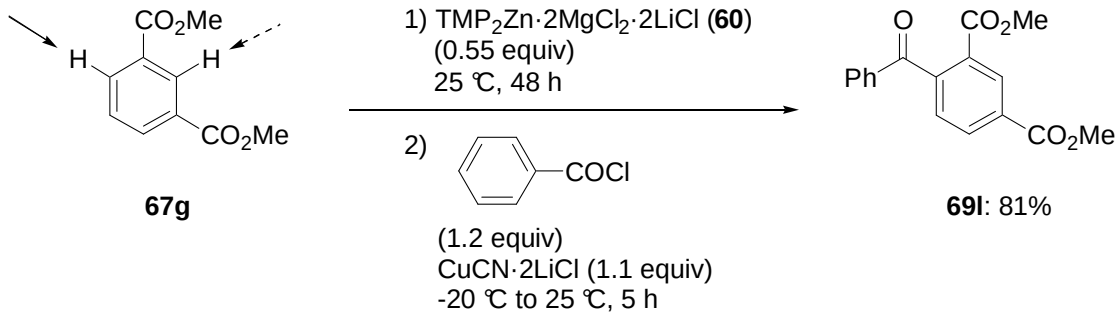
Table 2: Products of type **66** obtained by zincation of functionalized heteroaromatics using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv) and subsequent reactions with electrophiles.

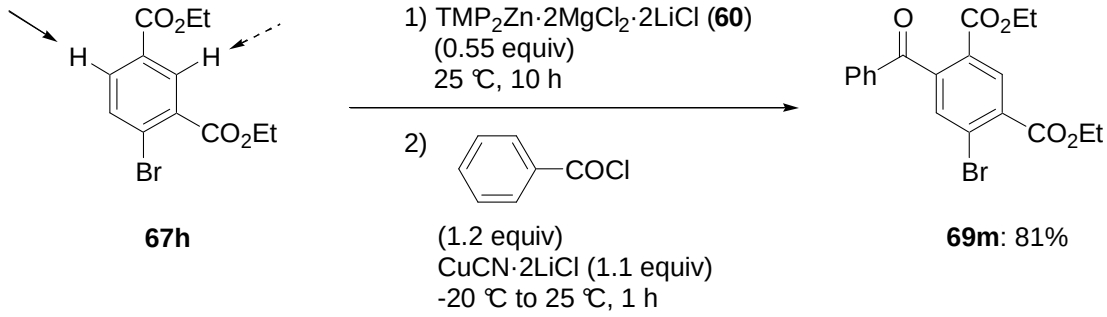
Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
1	 **64b**	–25, 1.5	D_2O	 **66c**: 82
2	 **64b**	–25, 1.5		 **66d**: 80[b]
3	 **64c**	–40, 0.75		 **66e**: 59[b]
4	 **64d**	–40, 1.5		 **66f**: 80[b]
5	 **64f**	25, 0.75		 **66i**: 71[b]
6	 **64g**	25, 5.5		 **66j**: 75[c]
7	 **64h**	25, 20		 **66k**: 63[d]

[a] Isolated yield of analytically pure product. [b] A transmetalation with $CuCN \cdot 2LiCl$ (5 mol-%) was performed. [c] A transmetalation with $CuCN \cdot 2LiCl$ (1.1 equiv) was performed. [d] Obtained by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%).

3.5 Metalation of Functionalized Aromatics

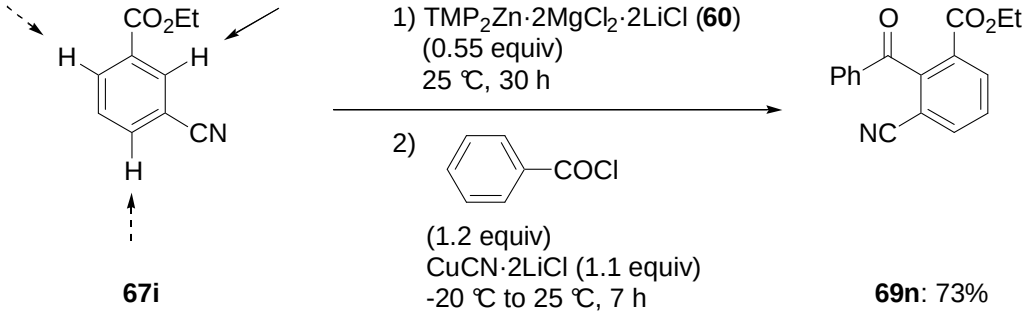
This metalation concept can be extended to numerous functionalized aromatics bearing various functionalities. As already noted above, the metalation of ethyl 3-fluorobenzoate (**57**) is completed within 12 h at 25 °C using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv). A subsequent acylation with 3,3-dimethylbutyryl chloride mediated by $CuCN \cdot 2LiCl$[46] (1.1 equiv) or a Pd-catalyzed cross-coupling[45] with 4-iodobenzonitrile afford the desired products **69a-b** in 69-76% yield (Table 3, entries 1-2). Surprisingly, the related ethyl 4-fluorobenzoate (**67a**) needs 336 h for a full metalation using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv) giving the zinc species **68a**. The biphenyl **69c** is isolated in 72% after the reaction with 4-iodotoluene in the presence of $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%; entry 3). Moreover, the zincation of ethyl 3-chlorobenzoate (**67b**) to the corresponding diaryl zinc species **68b** is accomplished within 25 h at 25 °C and deuterolysis gives the benzoate **69d** in 84% yield (entry 4). Whereas ethyl 4-chlorobenzoate (**67c**) is converted to its zincated species within 110 h, *tert*-butyl 4-chlorobenzoate (**67d**) is completely metalated within 134 h at 25 °C. Adjacent benzoylations of the three zincated benzoates **68b-d** in the presence of $CuCN \cdot 2LiCl$ (1.1 equiv each) provide the benzophenones **69e-g** in 69-83% yield (entries 5-7). Additionally, the metalation of the more sensitive methyl 4-chlorobenzoate (**67e**) proceeds smoothly within 110 h at 25 °C without noteworthy side reactions and after a Negishi cross-coupling with 1-iodo-3-trifluoromethylbenzene the biphenyl **69h** is obtained in 75% yield (entry 8). Similarly, the full metalation of ethyl 4-bromobenzoate (**67f**) is achieved within 110 h at 25 °C and subsequent Pd-catalyzed cross-couplings with different aryl iodides give the desired biphenyls **69i-j** in 78-83% yield (entries 9-10). Interestingly, dimethyl isophthalate (**67g**) is regioselectively zincated in position 4 within 48 h at 25 °C using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv). The quenching reactions of the metalated species **68g** like an acylation with benzoyl chloride mediated by $CuCN \cdot 2LiCl$ (1.1 equiv) or a Pd-catalyzed cross-coupling with 1-chloro-4-iodo-benzene give the expected products **69k-l** in 75-81% yield (Table 2, entry 11 and Scheme 19). Surprisingly, the presence of a bromo atom like in the phthalate **67h** leads to an enhanced metalation rate compared to dimethyl isophthalate (**67g**). Thus, the metalation of the phthalate **67h** proceeds readily within 10 h at 25 °C exclusively in position 6 and the benzophenone **69m** is provided in 83% yield after the reaction with benzoyl chloride mediated by $CuCN \cdot 2LiCl$ (1.1 equiv; Scheme 19).





Scheme 19: Regioselective functionalization of the phthalates **67g-h**.

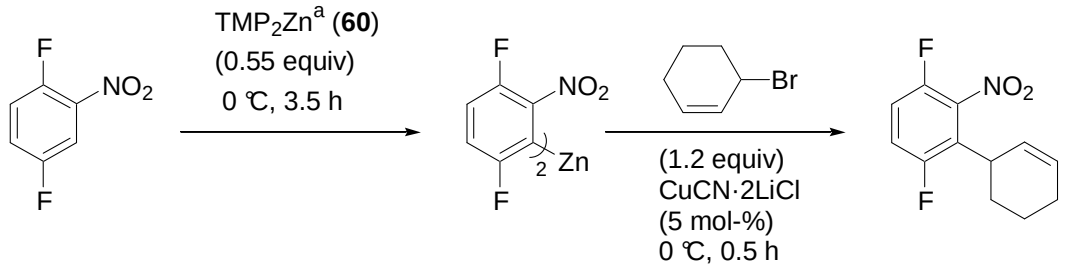
Molecules bearing cyano-groups undergo smooth zincations as well. Hence, the metalation of ethyl 3-cyanobenzoate (**67i**) bearing three different activated protons is finished after 30 h at 25 °C. In contrast to the phthalates **67g-h**, the zincation occurs regioselectively in position 2. A subsequent benzoylation in the presence of CuCN·2LiCl (1.1 equiv) furnishes the ketone **69n** in 73% yield (Scheme 20).



Scheme 20: Regioselective functionalization of ethyl 3-cyanobenzoate (**67i**).

Similarly, ethyl 4-cyanobenzoate (**67j**) is regioselectively converted into the corresponding diarylzinc species **68j** within 24 h at 25 °C using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**) and an adjacent cross-coupling with iodobenzene in the presence of $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%) gives the biphenyl **69o** in 85% yield (Table 3, entry 12). Moreover, the fluorinated benzonitriles **67k-l** are smoothly zincated at 25 °C within 48 h and 20 h,

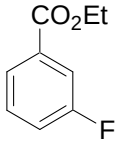
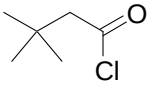
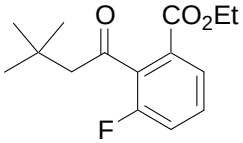
respectively. The Negishi cross-couplings with either 4-iodotoluene or ethyl 3-iodobenzoate afford the functionalized biaryls **69p-q** in 72-88% yield (entries 13-14). In contrast, the zincation of the related 2-fluorobenzonitrile (**67m**) takes 144 h at 25 °C using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv). The subsequent acylation with 4-chlorobenzoyl chloride mediated by CuCN·2LiCl (1.1 equiv) gives the ketone **69r** in 63% yield (entry 15). The metalation of the halogenated benzonitrile **67n** is complete within 5.5 h at 25 °C. Surprisingly, a Cu(I)-catalyzed reaction with 1-bromo-3-methyl-but-2-ene furnish the formal S_N2-product **69s** in 85% yield and does not lead to the S_N2`-product as it would be expected for copper-catalyzed reaction of organozinc reagents with allylic bromides (entry 16). Remarkably, the fluorinated nitrobenzene **67o** is converted into the *bis*-aryl zinc species **68o** within 3.5 h at 0 °C. After a copper-catalyzed allylation with 3-bromocyclohexene, the highly substituted arene **69t** is obtained in 69% yield (Scheme 21).

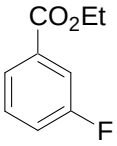
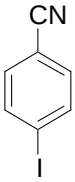
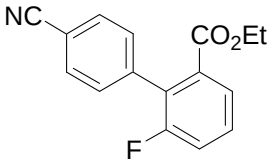
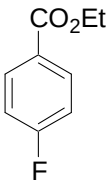
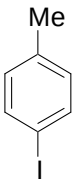
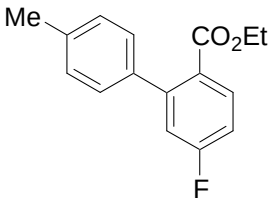
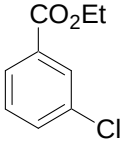
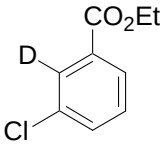
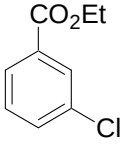
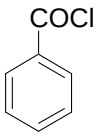
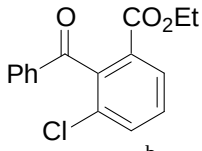
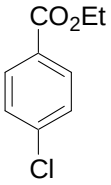
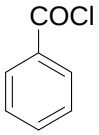
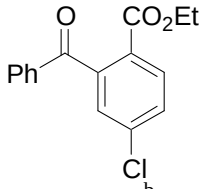
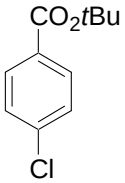
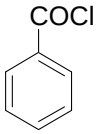
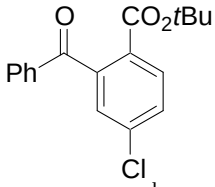
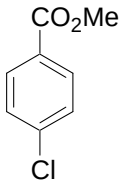
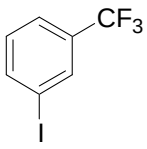
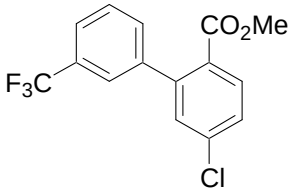
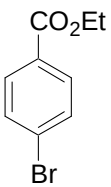
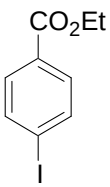
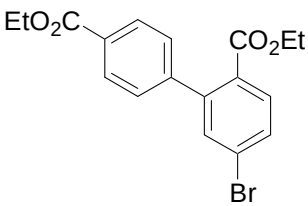


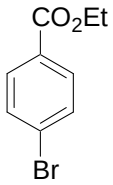
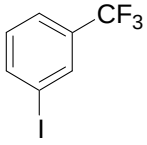
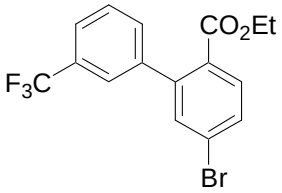
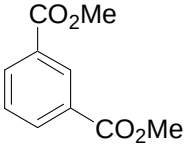
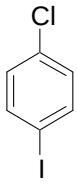
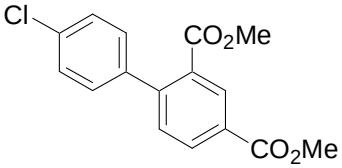
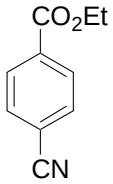
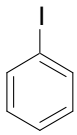
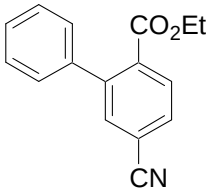
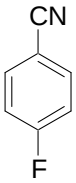
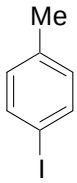
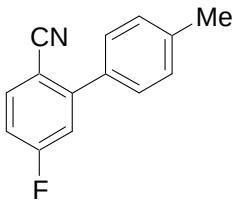
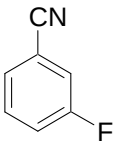
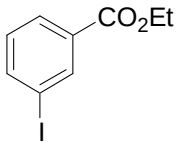
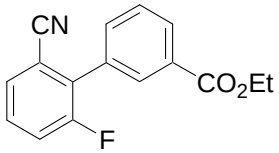
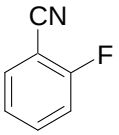
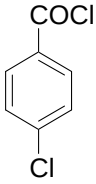
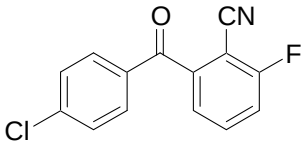
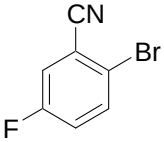
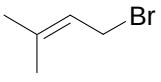
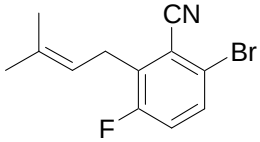
Scheme 21: Functionalization of the benzene **67o**. [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

In conclusion, the use of $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) allows the smooth zincation at very convenient temperature (0 to 25 °C) of numerous aromatics bearing sensitive functionalities like methyl or ethyl esters, cyano groups as well as nitro groups.

Table 3: Products of type **69** obtained by zincation of functionalized aromatics using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.55 equiv) and subsequent reactions with electrophiles.

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
1	 **57**	25, 12		 **69a**: 76[b]

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
				
2	**57**	25, 12		**69b**: 69[c]
				
3	**67a**	25, 336		**69c**: 72[c]
			D_2O	
4	**67b**	25, 25		**69d**: 84
				
5	**67b**	25, 25		**69e**: 79[b]
				
6	**67c**	25, 110		**69f**: 83[b]
				
7	**67d**	25, 134		**69g**: 69[b]
				
8	**67e**	25, 110		**69h**: 75[c]
				
9	**67f**	25, 110		**69i**: 78[c]

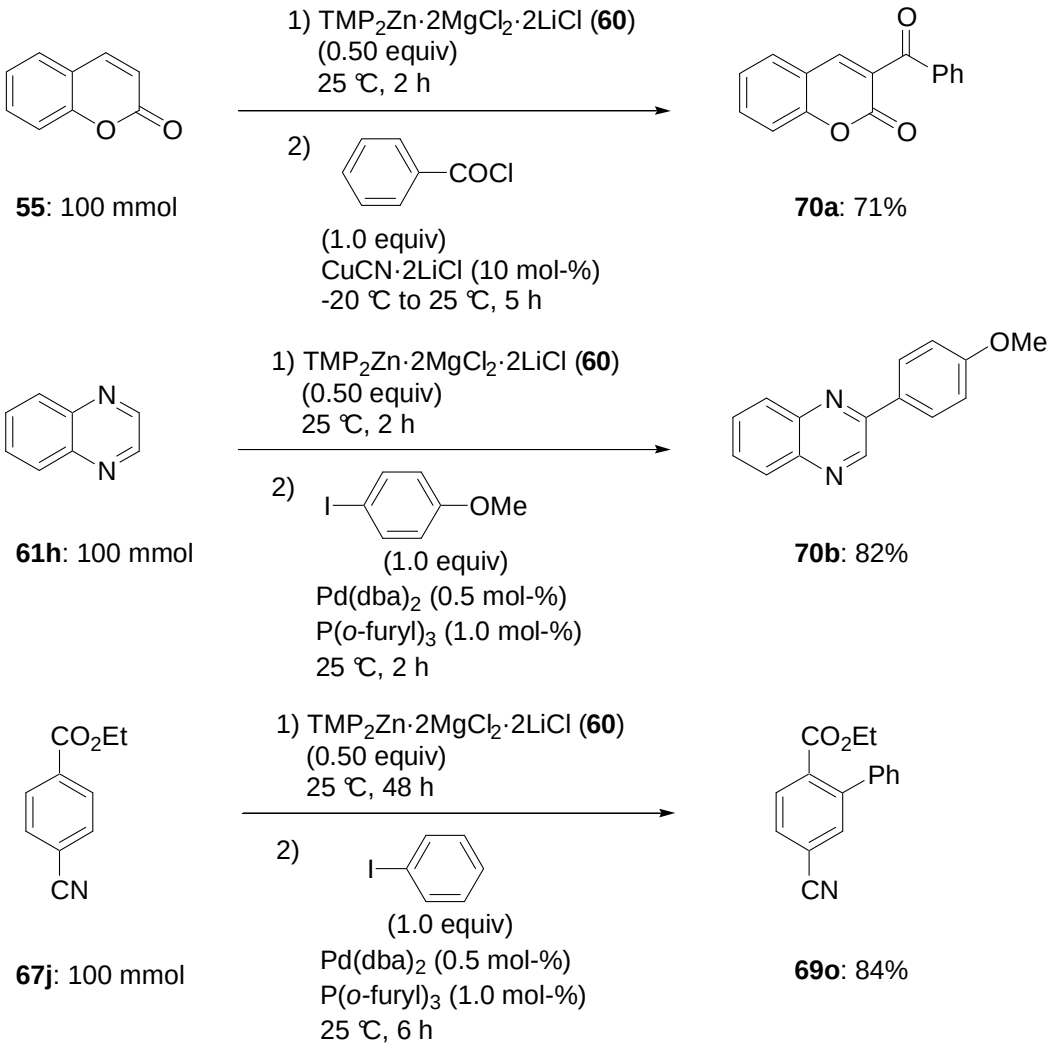
Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
10	 **67f**	25, 110		 **69j**: 83[c]
11	 **67g**	25, 48		 **69k**: 75[c]
12	 **67j**	25, 24		 **69o**: 85[c]
13	 **67k**	25, 48		 **69p**: 88[c]
14	 **67l**	25, 20		 **69q**: 72[c]
15	 **67m**	25, 144		 **69r**: 63[b]
16	 **67n**	25, 5.5		 **69s**: 85

[a] Isolated yield of analytically pure product. [b] A transmetalation with CuCN·2LiCl (1.1 equiv) was performed. [c] Obtained by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%). [d] A transmetalation with CuCN·2LiCl (5 mol-%) was performed.

3.6 Larger Scale Experiments

Finally, larger scale zincations are carried out (Scheme 22). Thus, a 250 mL Schlenk-flask is charged with a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 50 mmol) and coumarin (**55**; 100 mmol) is added to the zinc base **60** in one portion at 25 °C. After 2 h (compared to 4 h for the 2 mmol scale reaction), the metalation of coumarin is complete and the resulting mixture is cooled to –20 °C. Then, CuCN·2LiCl (10 mL, 10 mmol, 10 mol-%) is added, followed by benzoyl chloride (100 mmol, 1.0 equiv). The acylation reaction proceeds while the reaction mixture is slowly warmed to reach 25 °C over 5 h. The desired benzoylated coumarin **70a** is obtained in 69% yield (compared to 75% in 2 mmol scale). Accordingly, the metalation of quinoxaline (**61h**; 100 mmol) is achieved within 3 h (compared to 5 h for the 2 mmol scale reaction) using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 50 mmol). Subsequently, a Pd-catalyzed cross-coupling reaction with 4-iodoanisole (1.0 equiv) using $Pd(dba)_2$ (0.5 mol-%) and P(*o*-furyl)$_3$ (1 mol-%) as catalytic system furnishes the arylated quinoxaline **70b** in 82% yield (compared to 85% for 2 mmol scale reaction). Interestingly, the metalation of coumarin (**55**) and quinoxaline (**61h**) proceeds twice faster when carried out in 100 mmol scale. In contrast, the metalation of ethyl 4-cyanobenzoate (**67j**; 100 mmol) using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 50 mmol) takes 48 h at 25 °C (compared to 24 h for the 2 mmol scale reaction). A subsequent Pd-catalyzed cross-coupling with iodobenzene (1.0 equiv) using $Pd(dba)_2$ (0.5 mol-%) and P(*o*-furyl)$_3$ (1 mol-%) as catalytic system leads to the biaryl **69o** in 84% yield (compared to 85% for the 2 mmol scale reaction).

To regenerate 2,2,6,6-tetramethylpiperidine (TMPH), the aqueous layers of the above described reaction mixtures are collected and treated with NaOH (pH = 12-13) until TMP-H separates from the aqueous phase. Then, TMP-H can easily be separated and is recovered after distillation from CaH_2 in up to 75% yield. Remarkably, acylation reactions can be carried out with only 10 mol-% CuCN·2LiCl (in general 20-100% CuCN·2LiCl for small scales) and the catalyst loading of cross-coupling reactions can be decreased to 0.5% of Pd.

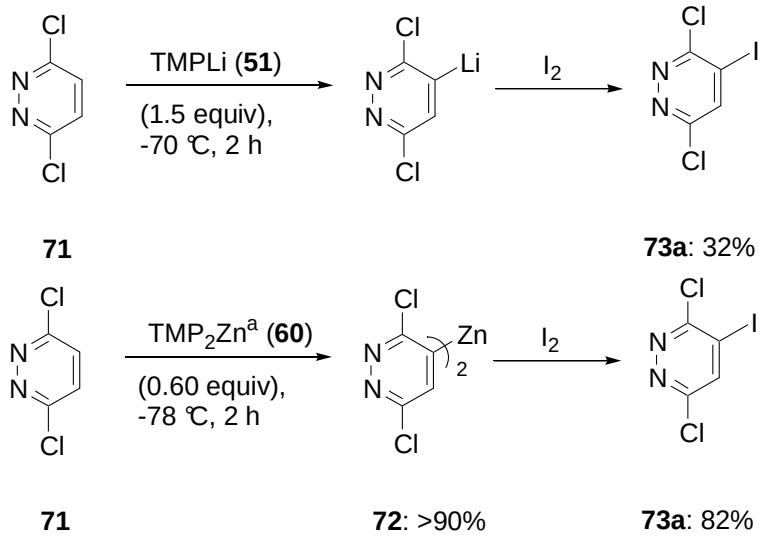


Scheme 22: Metalation of coumarin (**55**), quinoxaline (**61h**) and ethyl 4-cyanobenzoate (**67j**) using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) and subsequent reactions with electrophiles.

4 Functionalization of 3,6-Dichloropyridazine (71)

4.1 Introduction

As already mentioned, the directed metalation of aromatics and heteroaromatics is known to be an important tool to functionalize these scaffolds.[30, 31] Especially, the metalation of nitrogen-containing heterocycles like pyridazines or pyrazines is of great interest and challenging.[56] Using TMPLi or related methods, the metalation and successive reactions with electrophiles often lead to low yields due to the instability of lithiated heterocycles.[57] Thus, the reaction of 3,6-dichloropyridazine (**71**) with TMPLi (**51**; 1.5 equiv, –70 °C, 1.5 h) followed by the addition of I_2 gives the iodinated pyridazine **73a** in only 32% yield[58] (Scheme 23). In contrast, by using the zinc amide $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**), the zincated intermediate **72** is obtained in over 90% yield within 2 h at –78 °C (Scheme 23). The subsequent reaction with I_2 affords the 4-iodo-3,6-dichloropyridazine (**73a**) in 82% yield. An alternative to these metal amides is the use of P4-bases reported by *Kondo*.[59]



Scheme 23: Comparison of the isolated yields of 4-iodo-3,6-dichloropyridazine (**73a**) prepared by using either TMPLi (**51**) or $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**). [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

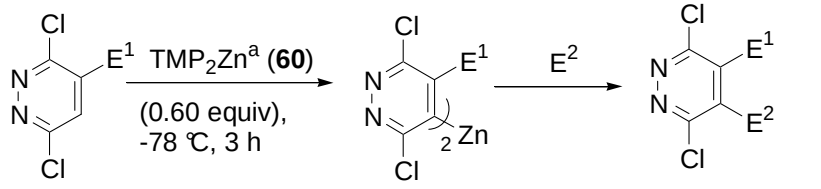
[56] a) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489; b) F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4059; c) F. Buron, N. Plé, A. Turck, G. Quéguiner, *J. Org. Chem.* **2005**, *70*, 2616; d) C. Fruit, A. Turck, N. Plé, L. Mojovic, G. Quéguiner, *Tetrahedron* **2001**, *57*, 9429; e) M. R. Grimmett, B. Iddon, *Heterocycles* **1995**, *41*, 1525; f) D. K. Anderson, J. A. Sikorski, D. B. Reitz, L. T. Pilla, *J. Heterocycl. Chem.* **1986**, *23*, 1257.
[57] A. Turck, N. Plé, L. Mojovic, G. Quéguiner, *J. Heterocycl. Chem.* **1990**, *27*, 1377.
[58] L. Mojovic, A. Turck, N. Plé, M. Dorsy, B. Ndzi, *Tetrahedron* **1996**, *52*, 10417.
[59] T. Imahori, Y. Kondo, *J. Am. Chem. Soc.* **2003**, *125*, 8082.

4.2 *Mono*- and *Bis*-Functionalization of 3,6-Dichloropyridazine (71)

Moreover, this new zinc reagent **72** can be reacted with various electrophiles (see Table 4). Thus, the reaction with ethyl 2-(bromomethyl)acrylate[55] in the presence of CuCN·2LiCl[46] (25 mol-%) furnishes the allylated product **73b** in 85% yield (entry 1). Furthermore, the zincated pyridazine derivate **72** can also be transmetalated with CuCN·2LiCl[46] to promote the reaction of **72** with acid chlorides. The subsequent addition of various acid chlorides such as benzoyl chloride, 2-furoyl chloride or 2-thiophene carbonyl chloride provides the ketones **73c-e** in 66-73% yield within 16 h at -20 °C (entries 2-4). Additionally, after the addition of chloranil (0.60 equiv)[52] to **72**, the dimeric pyridazine **73f** is obtained in 88% yield (entry 5).

Remarkably, low-temperature Pd-catalyzed cross-coupling reactions[45] can also be performed using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%) as a catalyst system with simultaneous warming of the reaction mixture from -78 °C to –20 °C within 4 h. The cross-couplings of **72** with electron-rich electrophiles like 4-iodoanisole as well as electron-poor ones such as ethyl 4-iodobenzoate or 3-iodo-nitrobenzene are leading to the functionalized biaryls **73g-i** in 76-81% yield (entries 6-8).

Various substituted 3,6-dichloropyridazines can be further functionalized using $TMP_2Zn·2MgCl_2·2LiCl$ (**60**) leading to the new zincated pyridazine of type **75** within 3 h at –78 °C (Scheme 24).

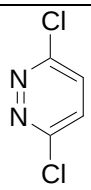
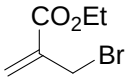
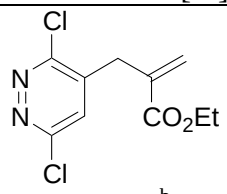
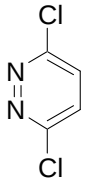
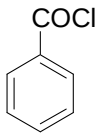
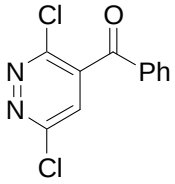
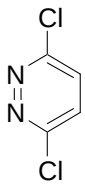
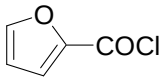
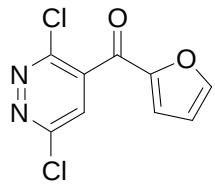
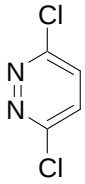
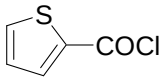
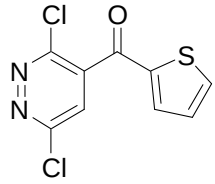
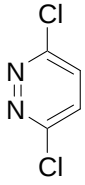
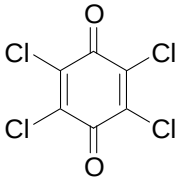
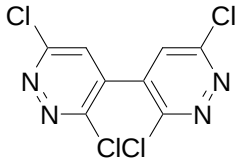
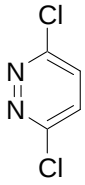
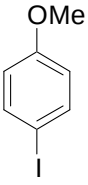
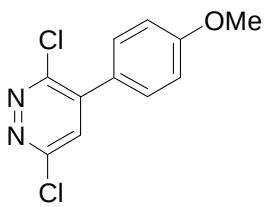


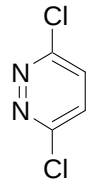
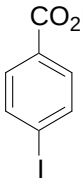
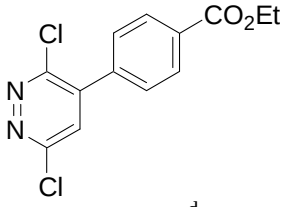
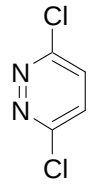
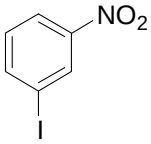
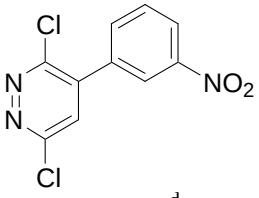
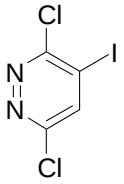
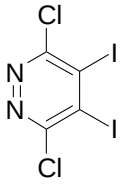
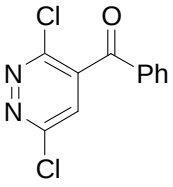
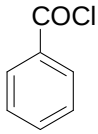
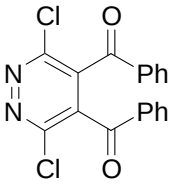
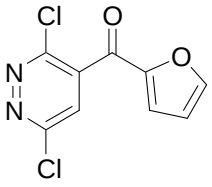
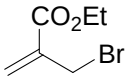
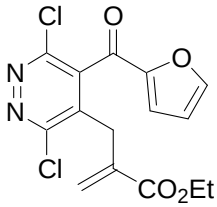
Scheme 24: Preparation of *bis*-functionalized 3,6-dichloropyridazines of type **75**. [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

Therefore, the iodolysis of the metalated 3,6-dichloro-4-iodopyridazine (**73a**) gives the diiodide **75a** in 56% yield (entry 9). The zincation of **73c** and subsequent reaction with benzoyl chloride in the presence of CuCN·2LiCl[46] provides the symmetrical *bis*-

ketosubstituted pyridazine **75b** in 77% yield (entry 10). The ketone **73d** is also further functionalized by the reaction with ethyl 2-(bromomethyl)acrylate in the presence of CuCN·2LiCl (25 mol-%)[46] furnishing the substituted pyridazine derivative **75c** in 75% yield (entry 11).

Table 4: Products of type **73** and **75** obtained by *mono* or *bis*-zincation of the dichloropyridazine **71** using $TMP_2Zn·2MgCl_2·2LiCl$ (**60**) and subsequent reactions with electrophiles.

Entry	Substrate	Electrophile	Product/Yield [%][a]
1	 **71**		 **73b**: 85[b]
2	 **71**		 **73c**: 73[c]
3	 **71**		 **73d**: 68[c]
4	 **71**		 **73e**: 66[c]
5	 **71**		 **73f**: 88
6	 **71**		 **73g**: 76[d]

Entry	Substrate	Electrophile	Product/Yield [%][a]
7	 **71**		 **73h**: 81[d]
8	 **71**		 **73i**: 77[d]
9	 **73a**	I_2	 **75a**: 56
10	 **73c**		 **75b**: 77[c]
11	 **73d**		 **75c**: 75[b]

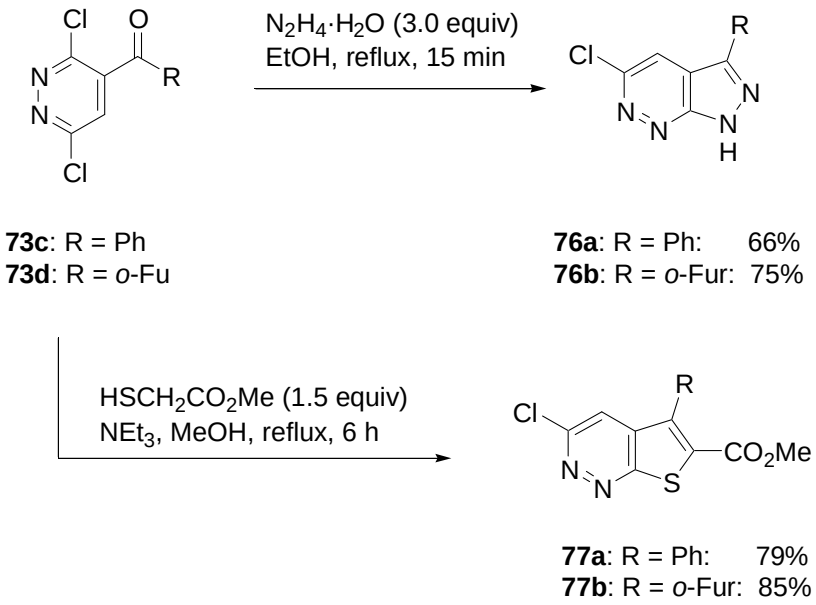
[a] Isolated yield of analytically pure product. [b] CuCN·2LiCl (25 mol-%) was used. [c] CuCN·2LiCl (1.1 equiv) was used. [d] Obtained by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%).

4.3 Synthesis of Annelated Heterocycles

The ketones **73c** and **73d** can also be converted into the annelated heterocyclic system of type **76** using hydrazine-hydrate as ring-closing agent [60] within 15 min giving the corresponding pyrazolo[3,4-*c*]pyridazines **76a** and **76b** in 66-75% yield (Scheme 25). Additionally, the related thiopheno[2,3-*c*]pyridazines 7**7a** and **77b** are prepared by the reaction of **73c** and **73d** with $HSCH_2CO_2Me$ in the presence of NEt_3.[61] After 6 h reaction time

[60] T. A. Eichhorn, S. Piesch, W. Ried, *Helv. Chim. Acta* **1988**, *71*, 988.
[61] L. K. A. Rahman, R. M. Scrowston, *J. Chem. Soc., Perk. Trans 1* **1984**, 385.

in refluxing MeOH, the annelated compounds **77a** and **77b** are isolated in 79-85% yield (Scheme 25). Those ring systems are of high interest for their potential pharmaceutical properties.[62]



Scheme 25: Preparation of the annelated heterocycles **76a-b** and **77a-b**.

[62] a) J. Witherington, R. W. Ward, PCT Int. Appl. **2003**, WO 2003080616; b) J. Witherington, V. Bordas, S. L. Garland, M. B. Deirdre, D. Smith, *J. Bioorg. Med. Chem. Lett*. **2003**, 1577; c) D. S. Patel, P. V. Bharatam, *Eur. J. Med. Chem.* **2008**, *43*, 949; d) M. O. Taha, Y. Bustanji, M. A. S. Al-Ghussein, M. Mohammad, H. Zalloum, I. M. Al-Masri, N. Atallah, *J. Med. Chem.* **2008**, *51*, 2062.

5 Directed Zincation of Functionalized Aromatics and Heteroaromatics Using $TMP_2Zn·2MgCl_2·2LiCl$ (60) and Microwave Irradiation

5.1 Introduction

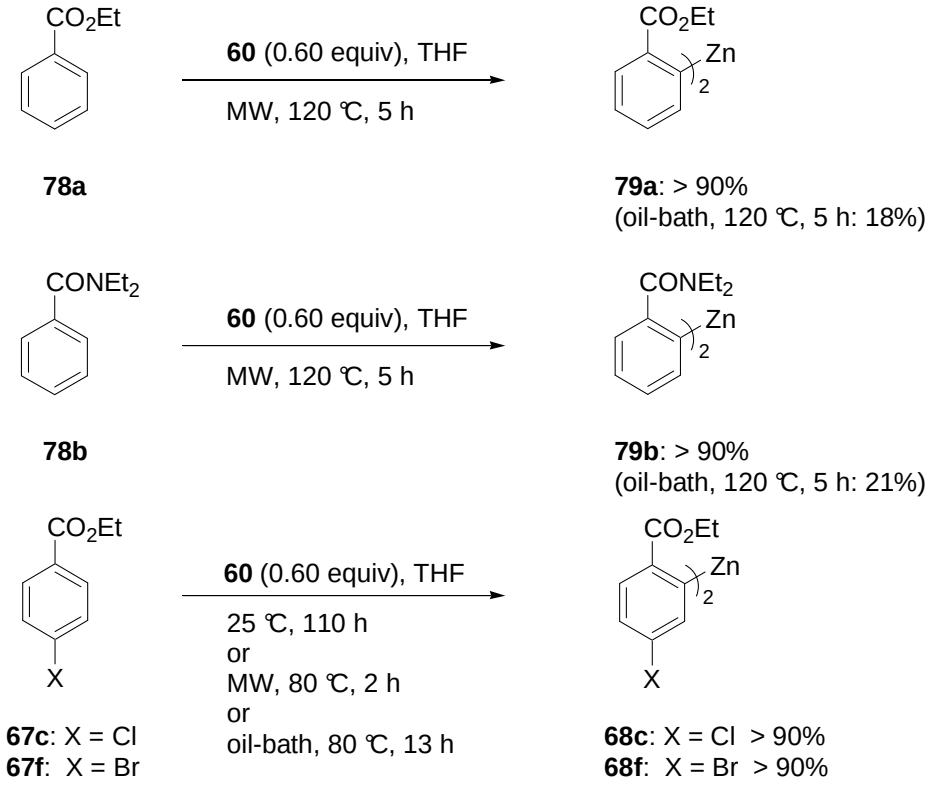
A significant drawback of the base **60** is the relatively long reaction times required for the zincation reactions of unactivated substrates (for examples, see: Table 3, entries 3-10). Over the last decades, microwave irradiation has been used to accelerate numerous organic reactions,[63] including organometallic reactions.[64] Since organozinc reagents of the type RZnX are thermally quite stable and tolerate functional groups even at elevated temperature, [65] we have envisioned accelerating TMP_2Zn-performed zincations using microwave irradiation. This mode of heating proved to be essential since it delivers the thermal energy very efficiently to the reaction partners. Thus, ethyl benzoate (**78a**) and *N*,*N*-diethylbenzamide (**78b**), which both can not be metalated to an appreciable extent at 25 °C, react with $TMP_2Zn·2MgCl_2·2LiCl$ (**60**; 0.6 equiv) under microwave irradiation (120 °C, 5 h) leading to the corresponding zinc reagent **79a-b** in > 90% yield (Scheme 26). When these metalations are carried at 120 °C using an oil-bath, the metalated arenes **79a-b** are provided in only 18-20% yield after 5 h using $TMP_2Zn·2MgCl_2·2LiCl$ (**60**; 0.60 equiv). Additionally, the direct zincation of ethyl 4-chlorobenzoate (**67c**) or ethyl 4-bromobenzoate (**67f**) with $TMP_2Zn·2MgCl_2·2LiCl$ (**60**; 0.60 equiv) at 25 °C requires 110 h for a complete reaction. By applying microwave irradiation, a complete zincation was achieved within 2 h (80 °C) leading to the expected *bis*-arylzinc species **67c** and **67f** in

[63] a) R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, R. Rousell, *Tetrahedron Lett.* **1986**, *27*, 279; b) R. J. Giguere, T. L. Bray, S. M. Duncan, G. Majetich, *Tetrahedron Lett.* **1986**, *27*, 4945; c) *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation and Applications* (Eds.: H. Kingston, S. J. Haswell), American Chemical Society, Washington, DC, **1997**; d) B. L. Hayes, *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, **2002**; e) *Microwave-Assisted Organic Synthesis*; (Eds.: P. Lidström, J. P. Tierney), Blackwell Publishing: Oxford, **2005**; f) C. O. Kappe, A. Stadler, *Microwaves in Organic and Medicinal Chemistry;* Wiley-VCH: Weinheim, **2005**; g) *Microwaves in Organic Synthesis*, 2nd ed.; (Ed.: A. Loupy), Wiley-VCH, Weinheim, **2006**; h) *Microwave Methods in Organic Synthesis*; (Eds: M. Larhed, K. Olofsson), Springer: Berlin, **2006**.

[64] a) D. Dallinger, C. O. Kappe, *Chem. Rev.* **2007**, *107* , 2563; b) C. O. Kappe, *Angew. Chem. Int. Ed.* **2004**, *43*, 6250; c) H. Tsukamoto, T. Matsumoto, Y. Kondo, *J. Am. Chem. Soc*. **2008,** *130*, 388; d) G. Shore, S. Morin, M. G. Organ, *Angew. Chem. Int. Ed.* **2006**, *45*, 2761; e) J. C. Lewis, J. Y. Wu, R. G. Bergman, J. A. Ellman, *Angew. Chem. Int. Ed.* **2006**, *45*, 1589; f) S. Fustero, D. Jimenez, M. Sanchez-Rosello, C. del Pozo, *J. Am. Chem. Soc.* **2007**, *129*, 6700; g) S. Constant, S. Tortoioli, J. Müller, D. Linder, F. Buron, J. Lacour, *Angew. Chem. Int. Ed.* **2007**, *46*, 8979.

[65] a) P. Walla, C. O. Kappe, *Chem. Commun.* **2004**, 564; b) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.*, **1991**, *56*, 1445.

>90% yield (Scheme 26). In contrast, using an oil-bath at the same elevated temperature, the desired diarylzinc compounds **68c** and **68f** are obtained after 13 h reaction time using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.60 equiv). The remarkable acceleration of these metalations can be explained by the efficient absorption of the microwave irradiation. Since THF is one of the worst solvents for microwave chemistry due to the low polarity, the presence of LiCl and $MgCl_2$ certainly causes this effect. Carefully spoken, these salts may lead to "microwave effects" like so called hot-spots (local area with higher temperature than indicated) or a superheated solvent, which can be the actual reason for the observed dramatically enhanced metalation rates.



Scheme 26: Metalation of ethyl benzoate (**78a**), *N*,*N*-diethylbenzamide (**78b**), ethyl 4-chlorobenzoate (**67c**) and ethyl 4-bromobenzoate (**67f**), using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) under various conditions. The conversion to the corresponding metal species was monitored *via* GC-analysis of aliquots of the reaction mixture quenched with a solution of I_2 in THF using tetradecane as internal standard.

5.2 Preparation of Functionalized Aromatics

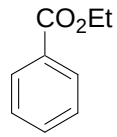
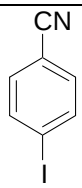
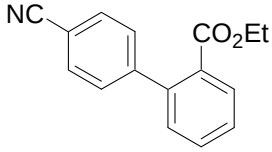
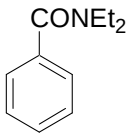
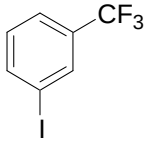
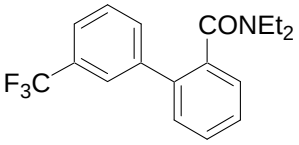
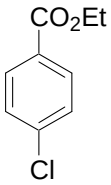
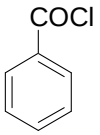
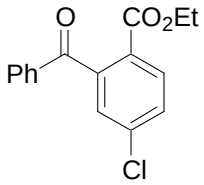
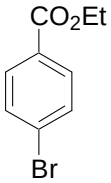
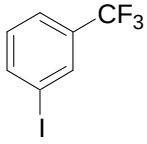
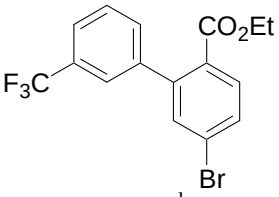
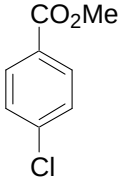
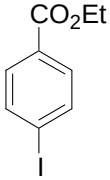
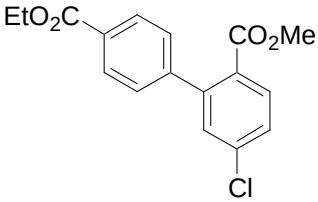
Subsequently, the reactions of the metalated arenes **79a-b** with either 4-iodobenzonitrile or 1-iodo-3-trifluoromethylbenzene in the presence of $Pd(dba)_2$ (5 mol-%)

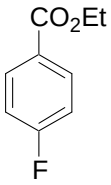
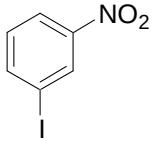
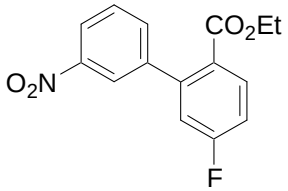
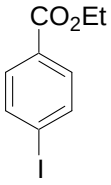
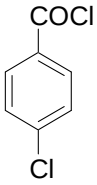
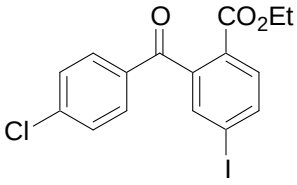
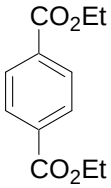
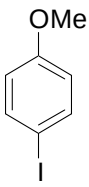
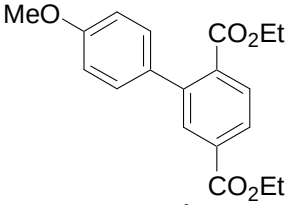
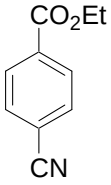
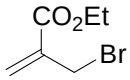
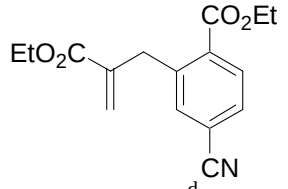
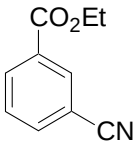
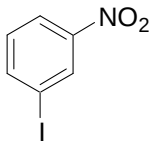
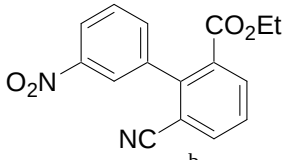
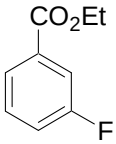
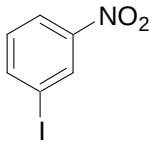
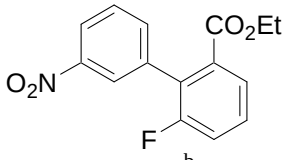
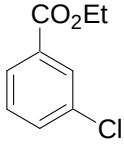
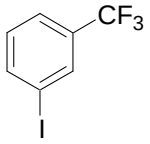
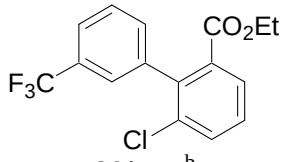
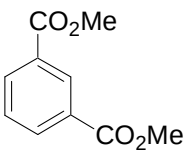
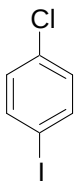
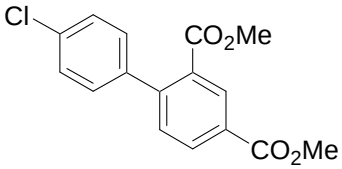
and P(*o*-furyl)$_3$ (10 mol-%) afford the functionalized biphenyls **80a-b** in 82-85% yield (Table 5, entries 1-2). Similarly, the zincated species **68c** and **68f** can either undergo a copper-mediated acylation[46] or a Pd-catalyzed cross-coupling reaction.[45] The desired products **69f** and **69i** are isolated in 83-86% yield (entries 3-4). Interestingly, the related methyl 4-chlorobenzoate (**67e**) is also converted into the corresponding zinc species **68e** showing the tolerance of the more sensitive methyl ester even at higher temperature. After a Negishi cross-coupling with ethyl 4-iodobenzoate, the diester **80c** is obtained in 73% yield (entry 5). Furthermore, the zincation of ethyl 4-fluorobenzoate (**67a**) takes 336 h at 25 °C, whereas the microwave-accelerated metalation proceeds smoothly within 1.25 h at 80 °C. An adjacent cross-coupling with 3-iodo-nitrobenzene gives the biphenyl **80d** in 87% yield (entry 6). Moreover, ethyl 4-iodobenzoate (**78c**) and diethyl therephthalate (**78d**) which can not be metalated at 25 °C using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.60 equiv) are now readily zincated within 3-4 h at 80-90 °C. Subsequent reactions with either 4-chlorobenzoyl chloride in the presence of CuCN·2LiCl (1.1 equiv) or a Pd-catalyzed cross-coupling reaction with 4-iodoanisole furnish the expected products **80e-f** in 72-74% yield (entries 7-8). Surprisingly, ethyl 4-cyanobenzoate (**67j**) is regioselectively zincated in position 2 within 1 h at 80 °C and a Cu(I)-catalyzed allylation[46] with ethyl 2-(bromomethyl)acrylate[55] gives the functionalized arene **80g** in 76% (entry 9). In contrast, the metalation of ethyl 3-cyanobenzoate (**67i**) at 80 °C (1 h) leads to a decreased regioselectivity (3:1 ration between position 2 and position 6; see Scheme 20) and therefore the biphenyl **80h** is isolated in only 62% after a Negishi cross-coupling with 3-iodo-nitrobenzene (entry 10). Furthermore, ethyl 3-fluorobenzoate (**57**) and ethyl 3-chlorobenzoate (**67b**) are readily zincated within 1-2 h at 80 °C using this microwave-zincation. After Pd-catalyzed cross-coupling with several aryl iodides, the functionalized benzoates **80i-j** are obtained in 77-92% yield (entries 11-12). Also dimethyl isophthalate (**67g**) undergoes a smooth zincation in position 4 within 1.5 h and a Pd-catalyzed cross-coupling reaction affords the diester **69e** in 79% yield (entry 13). Remarkably, ethyl 2-fluorobenzoate (**78e**) and diethyl phthalate (**78f**) require a larger metalation time (3-4 h at 90-95 °C) but both subtrates show no conversion to the corresponidng zinc reagents **79e-f** at 25 °C using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.60 equiv). After Pd-catalyzed cross-coupling reactions the functionalized arenes **80k**-l are isolated in 71-74% yield (entries 14-15).

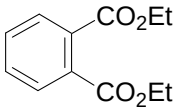
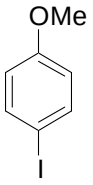
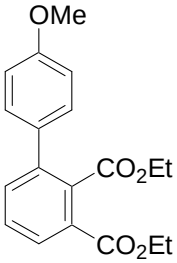
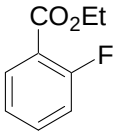
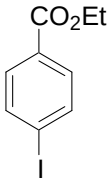
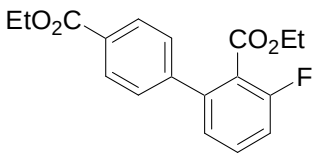
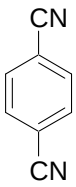
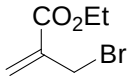
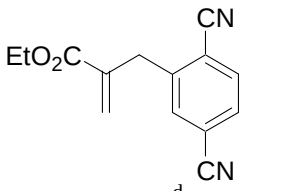
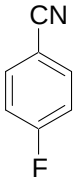
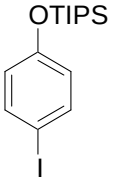
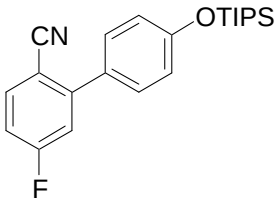
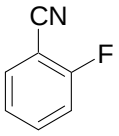
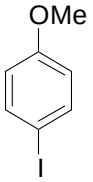
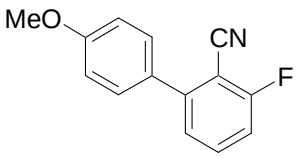
Accordingly, benzonitriles are also converted into their zinc reagents by using this metalation procedure. Thus, 1,4-dicyanobenzene (**78g**) is zincated within 3 h at 80 °C using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.60 equiv). A subsequent Cu-mediated reaction with

ethyl 2-(bromomethyl)acrylate[55] affords the substituted benzonitrile **80m** in 67% yield (entry 16). Additionally, 4-fluorobenzonitrile (**67k**) and 2-fluorobenzonitrile (**67m**) are treated with the base **60** using microwave irradiation (entries 17-18) leading to the zincated species within 3 h (80-85 °C). The adjacent Pd-catalyzed cross-coupling reactions with elctron-rich aryl iodides lead to the biaryls **80o-n** in 88-89% yields. Remarkably, beside the enormously enhanced metalation rate, this metalation concept still offers a great tolerance towards functional groups like methyl and ethyl ester as well as cyano-groups.

Table 5: Products obtained by zincation of functionalized aromatics using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.60 equiv), microwave irradiation and subsequent reactions with electrophiles.

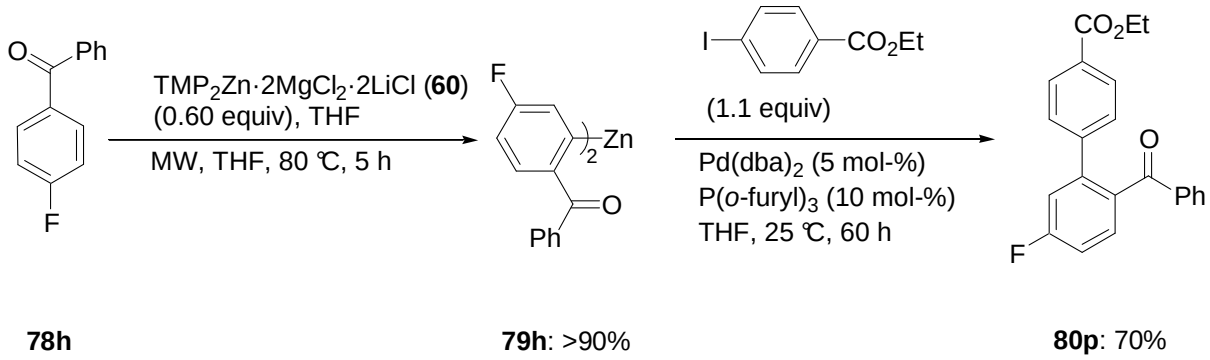
Entry	Substrate	*T*[°C], *t*[h]	E^+	Product/Yield [%][a]
1	 **78a**	120, 5		 **80a**: 82[b]
2	 **78b**	120, 5		 **80b**: 85[b]
3	 **67c**	80, 2		 **69f**: 86[c]
4	 **67f**	80, 2		 **69i**: 83[b]
5	 **67e**	80, 2		 **80c**: 73[b]

Entry	Substrate	*T*[°C], *t*[h]	E^+	Product/Yield [%][a]
6	 **67a**	80, 1.25		 **80d**: 87[b]
7	 **78c**	80, 3		 **80e**: 72[c]
8	 **78d**	90, 4		 **80f**: 74[b]
9	 **67j**	80, 1		 **80g**: 76[d]
10	 **67i**	80, 1		 **80h**: 62[b]
11	 **57**	80, 1		 **80i**: 92[b]
12	 **67b**	80, 2		 **80j**: 77[b]
13	 **67g**	90, 2		 **69e**: 79[b]

Entry	Substrate	*T*[°C], *t*[h]	E^+	Product/Yield [%][a]
				
14	**78e**	90, 4		**80k**: 71[b]
				
15	**78f**	95, 3		**80l**: 74[b]
				
16	**78g**	80, 3		**80m**: 67[d]
				
17	**67k**	85, 3		**80n**: 89[b]
				
18	**67m**	80, 3		**80o**: 88[b]

[a] Isolated yield of analytically pure product. [b] Obtained by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%). [c] A transmetalation with CuCN·2LiCl (1.1 equiv) was performed. [d] A transmetalation with CuCN·2LiCl (5 mol-%) was performed.

Finally 4-fluorobenzophenone (**78j**) provides a zinc reagent bearing a keto group (**78j**) within 5 h (80 °C). After a Pd-catalyzed cross-coupling reaction, the functionalized benzophenone **80p** is isolated in 70% yield showing the compatibility of a ketone for at least 5 h at 80 °C using microwave irradiation (Scheme 27).



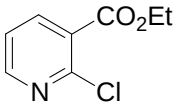
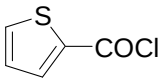
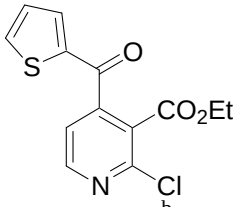
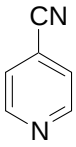
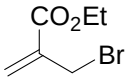
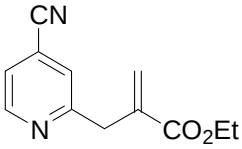
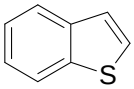
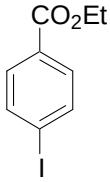
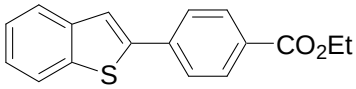
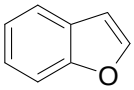
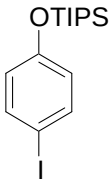
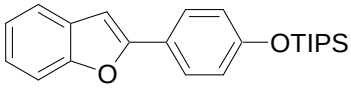
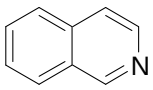
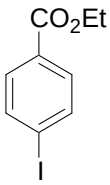
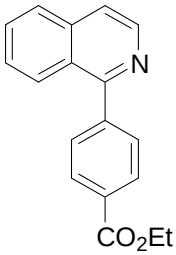
78h **79h**: >90% **80p**: 70%

Scheme 27: Functionalization of 4-fluorobenzophenone (**78h**) using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) and microwave irradiation.

5.3 Preparation of Functionalized Heteroaromatics

Moreover, this zincation procedure is applied to heterocyclic systems. Thus, ethyl 2-chloro nicotinate (**64g**) is smoothly zincated within 1 h and a copper-mediated acylation[46] furnishes the ketone **80q** in 80% yield (Table 6, entry 1). Furthermore, 4-cyanopyridine (**78i**) undergoes a regioselective zincation in position 2 (entry 2). The reaction with ethyl 2-(bromomethyl)acrylate[55] in the presence of CuCN·2LiCl (25 mol%)[46] leads to the acrylate derivate **80r** in 68% yield. Substrates such as benzothiophene (**61k**) and benzofuran (**61l**) can only slowly be zincated with the base **60** at 25 °C (144-168 h, see Table 1, entries 17-18). However, microwave irradiation allows a smooth zincation at 120 °C. Trapping of the resulting zincated heterocycles with various aryl iodides in the presence of a Pd-catalyst,[45] afford the heterocycles **80s-t** 95% yield (entries 3-4). Finally, isoquinoline (**78j**) is also reacted with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) (entry 5). After 1 h at 120 °C, a full zincation is achieved and the zincated isoquinoline undergoes a Pd-catalyzed cross-coupling reaction providing the isoquinoline derivate **80u** in 82% yield.

Table 6: Products obtained by zincation of functionalized heteroaromatics using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.60 equiv), microwave irradiation and subsequent reactions with electrophiles.

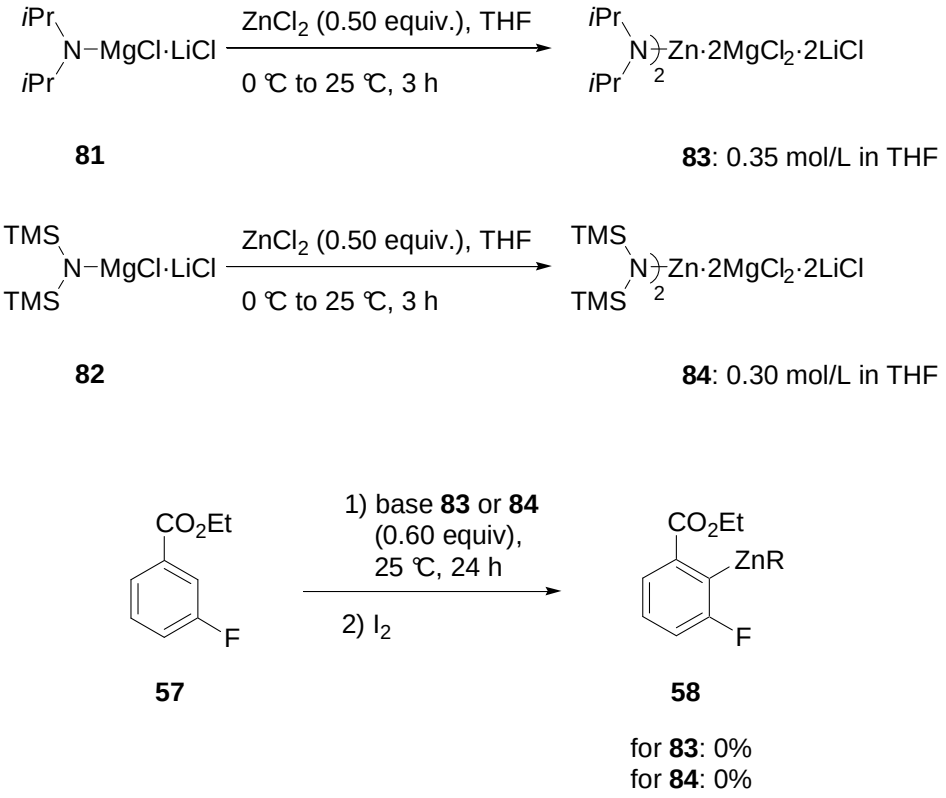
Entry	Substrate	T[°C], t[h]	E^+	Product/Yield [12][a]
1	 **64g**	80, 1		 **80q**: 80[b]
2	 **78i**	60, 1		 **80r**: 68[c]
3	 **61k**	120, 1		 **80s**: 95[d]
4	 **61l**	120, 1		 **80t**: 95[d]
5	 **78j**	120, 1		 **80u**: 82[d]

[a] Isolated yield of analytically pure product. [b] A transmetalation with $CuCN \cdot 2LiCl$ (1.1 equiv) was performed. [c] A transmetalation with $CuCN \cdot 2LiCl$ (5 mol-%) was performed. [d] Obtained by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%).

6 Directed Zincation of Functionalized Aromatics and Heteroaromatics Using [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl

6.1 Preparation of Alternative Bases

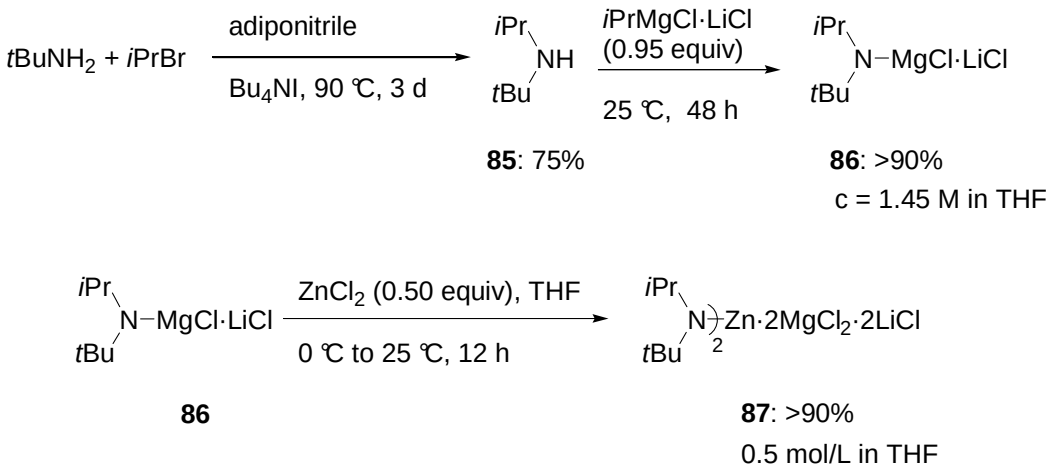
Despite the constantly decreasing price for 2,2,6,6-tetramethylpiperidine, a more economical (cheaper) amine would be desirable for metalation reactions, especially for large-scale applications. Unfortunately, the reaction of *i*PrMgCl·LiCl with *i*Pr$_2$NH resulted in the only 0.60 M amide base **81** (approx. half the concentration of TMPMgCl·LiCl). Additionally, the use of HMDS affords the even less concentrated base **82** (0.55 M). Accordingly, the resulting zinc amides **83** and **84** display a lower concentration than TMP$_2$Zn·2MgCl$_2$·2LiCl (**60**; Scheme 28). Furthermore, the reactivity of theses zinc amides is also not comparable to the one of TMP$_2$Zn·2MgCl$_2$·2LiCl (**60**) since ethyl 3-fluorobenzoate (**57**) can not be metalated using either (*i*Pr$_2$N)$_2$Zn·2MgCl$_2$·2LiCl (**83**) or HMDS$_2$Zn·2MgCl$_2$·2LiCl (**84**).



Scheme 28: Preparation of (*i*Pr$_2$N)$_2$Zn·2MgCl$_2$·2LiCl (**83**) and hmds$_2$·Zn·2MgCl$_2$·2LiCl (**84**). The conversion to the corresponding metal species **58** was monitored *via* GC-analysis of aliquots of the reaction mixture quenched with a solution of I$_2$ in THF using tetradecane as internal standard.

6.2 Preparation of [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl

Sterically hindered non-cyclic amides can be used in principle for directed metalations. Since neither *i*Pr$_2$NH nor HMDS gave satisfactory zinc amide bases, an additional sterically hindered amine has been prepared. Thus, *tert*-butyl(*iso*-propyl)amine (**85**) is readily obtained by the reaction of cheap bulk chemicals such as *iso*-propyl bromide, *tert*-butylamine and adiponitrile.[66] After treatment of the amine **85** with *i*PrMgCl·LiCl, the resulting base **86** is provided as a 1.45 M solution in THF. This concentration is comparable to TMPMgCl·LiCl and the subsequent transmetalation with $ZnCl_2$ (0.50 equiv) affords the corresponding zinc amide base [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl (**87**) as a max. 0.50 M solution in THF and can be stored under argon at 25 °C for at least two months (Scheme 29).



Scheme 29: Preparation of [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl (**87**).

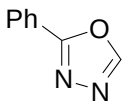
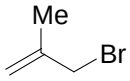
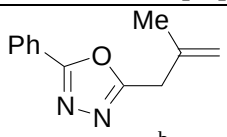
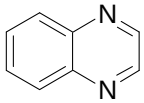
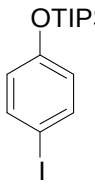
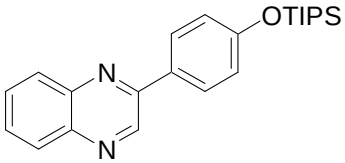
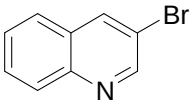
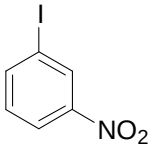
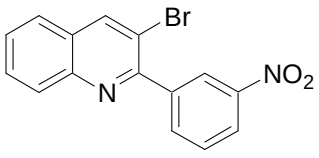
6.3 Metalation of Aromatics and Heteroaromatics

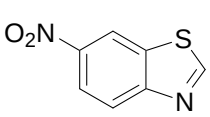
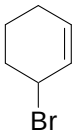
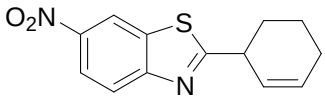
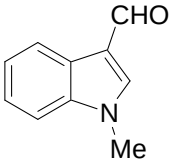
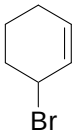
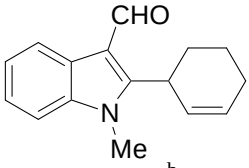
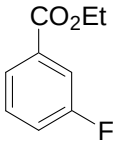
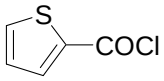
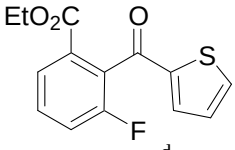
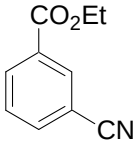
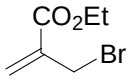
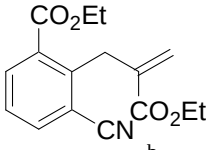
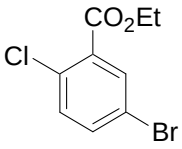
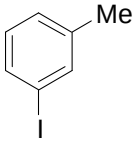
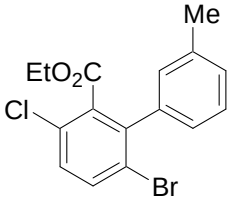
The metalation ability of this base proves to be comparable to TMP$_2$Zn·2MgCl$_2$·2LiCl (**60**). Hence, 2-phenyl-1,3,4-oxadiazole (**61a**) is metalated within 45 min at 25 °C using the zinc base **87** (0.60 equiv) giving exclusively the desired zincated species. The resulting diorganozinc reagent undergoes a copper-catalyzed allylation[46] reaction leading to the allylated product **89a** in 88% yield (Table 7, entry 1). Furthermore, quinoxaline (**61h**) is readily zincated within 9 h at 25 °C. After a Pd-catalyzed cross-coupling reaction,[45] the quinoxaline derivative **89b** is isolated in 81% yield (entry 2). During this reaction, no dimerization of quinoxaline (**56**) is observed. Accordingly, 3-bromoquinoline (**21**) is smoothly zincated at

[66] H. C. Brown, J. V. B. Kanth, P. V. Dalvi, M. Zaidlewicz, *J. Org. Chem.* **1999**, *64*, 6263.

25 °C within 4 h. After a Pd-catalyzed cross-coupling reaction with 3-iodo-nitrobenzene, the quinoline **89c** is provided in 86% yield (entry 3). Nitro-groups are also tolerated as shown for the zincation of 6-nitrobenzothiazole (**64a**). Thus, this metalation occurs at –50 °C within 1 h selectively at position 2. After a copper(I)-mediated allylation reaction with 3-bromocyclohexene, the 2-allylated benzothiazole **89d** is obtained in 79% yield (entry 4). The presence of an aldehyde does not affect this metalation procedure and the 3-formylated indole **64f** is smoothly converted to the corresponding diorganozinc species. A subsequent copper-catalyzed allylation affords the expected allylated aldehyde **89e** in 50% yield (entry 5). Aromatic esters bearing halogen or cyano substituents are also smoothly zincated. Thus, ethyl 3-fluorobenzoate (**57**) is converted at 25 °C within 20 h to the corresponding zinc reagent. No side reactions (e.g. dimerization, transformation of the ester into an amide) were observed during the metalation. After a copper-mediated acylation[46] with thiophene-2-carbonyl chloride, the polyfunctional ketone **89f** is obtained in 75% yield (entry 6). Ethyl 3-cyanobenzoate (**67i**) is regioselectively zincated between both substituents and the adjacent allylation reaction with ethyl (2-bromomethyl)acrylate[55] affords the 1,2,3-trisubstituted benzene **89g** in 72% yield (entry 7). Finally, ethyl 3-bromo-5-chlorobenzoate (**88)** is metalated within 60 h between the bromo substituent and the ester group using [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl (**87**; 0.60 equiv). The resulting biphenyl **89h** is isolated in 67% yield after a Pd-catalyzed cross-coupling with 3-iodotoluene (entry 8).

Table 7: Products of type **89** obtained by zincation using the zinc *bis*-amide **87** and quenching with electrophiles.

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
1	 **61a**	25, 0.75		 **89a**: 88[b]
2	 **61h**	25, 9		 **89b**: 81[c]
3	 **61j**	25, 4		 **89c**: 86[c]

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
4	 **64a**	–50, 1		 **89d**: 79[b]
5	 **64f**	25, 1.25		 **89e**: 50[b]
6	 **57**	25, 20		 **89f**: 75[d]
7	 **67i**	25, 36		 **89g**: 72[b]
8	 **88**	25, 60		 **89h**: 67[c]

[a] Isolated yield of analytically pure product. [b] Obtained after transmetalation with CuCN·2LiCl (5 mol-%). [c] Obtained via Pd-catalyzed cross-coupling with Pd(dba)$_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%). [d] Obtained after transmetalation with CuCN·2LiCl (5 mol-%).

7 Directed Metalation of Aromatics and Heteroaromatics Using *in situ* Protocols

7.1 Introduction

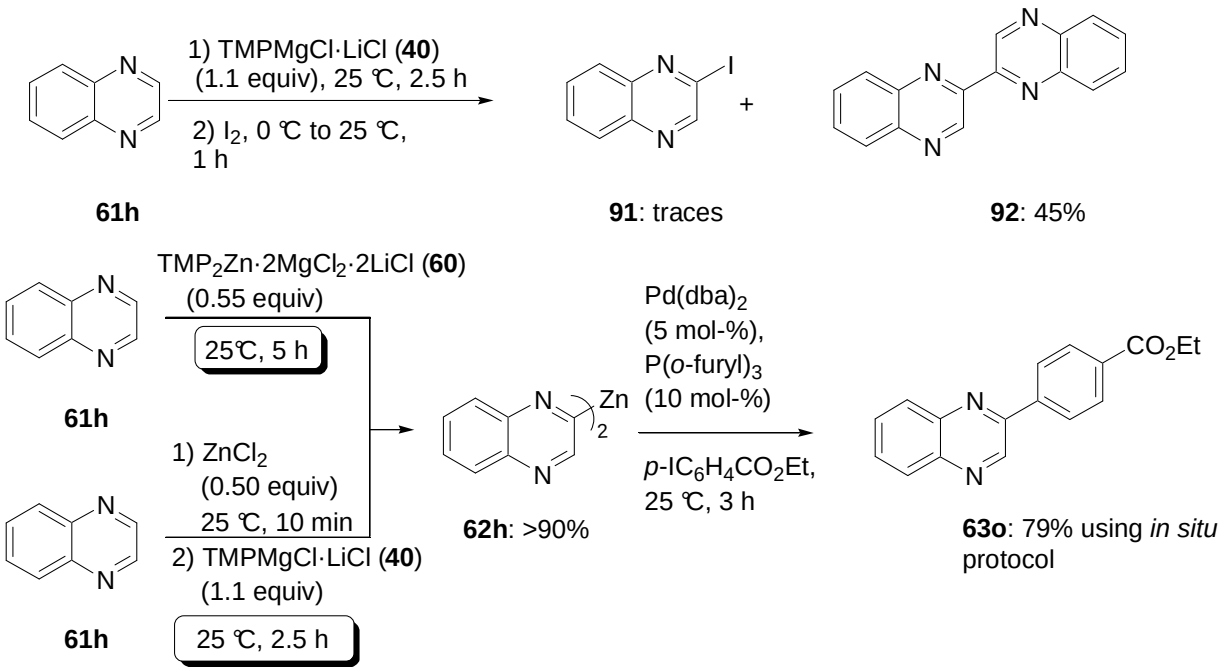
Eaton and coworkers have already performed direct lithiations with TMPLi (**51**) in the presence of mercury salts in 1987.[67] The *in situ* generated organo mercurials can be further converted to corresponding halides or transmetalated with organomagnesium or organolithium reagents in a process called *reverse transmetalation*.[68] Two decades later, *Mongin* and coworkers adapted this concept and investigated metalation procedures using *in situ* formed zincates or cadmates.[69] In 2008, it was shown that the direct insertion of magnesium turnings into C-Br bonds in the presence of LiCl using substituted methyl or ethyl benzoates as substrates is best carried out in the presence of $ZnCl_2$.[14a] The primary formed unstable Mg-intermediate is immediately transmetalated to the corresponding Zn-compound. Recently, we reported the deprotonation and functionalization of some sensitive aromatic and heteroaromatic substrates by using $TMP_2Mg{\cdot}2LiCl$ (**45**) in the presence of $ZnCl_2$.[70] The methodology allows sensitive aromatics and heterocycles to be metalated at 25 °C, giving after reaction with electrophiles the expected functionalized products in good yields. We have found that the addition of $ZnCl_2$ to the substrate, *prior to the addition of the base* lead to excellent results. However, this last method had several drawbacks: (i) the stability of $TMP_2Mg{\cdot}2LiCl$ (**45**) was limited due to its high kinetic basicity;[40a] (ii) the tolerance of functional groups and sensitive heterocycles was also moderate. Therefore, the metalation of aromatics and heteroaromatics using TMPMgCl·LiCl (**40**) in the presence of $ZnCl_2$ was investigated.

7.2 Optimization Process and Mechanistic Aspects

First, the metalation of quinoxaline (**61h**) was investigated since this heterocycle is prone to undergo dimerization during metalation processes. Hence, its metalation using TMPMgCl·LiCl (**40**) or $TMP_2Mg{\cdot}2LiCl$ (**45**) just affords the dimeric quinoxaline **92**. In contrast, the metalation of this diazine using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.55 equiv) is accomplished within 5 h at 25 °C. Alternatively, by dissolving quinoxaline (**61h**) in a $ZnCl_2$

[67] P. E. Eaton, G. T. Cunkle, G. Marchioro, R. M. Martin, *J. Am. Chem. Soc.* **1987**, 109, 948; for an early example of a lithiation-zincation procedure see: P. Gros, Y. Fort, *Synthesis* **1999**, 754.
[68] a) P. E. Eaton, R. M. Martin, *J. Org. Chem.* **1988**, 53, 2728; b) P. E. Eaton, R. G. Daniels, D. Casucci, G. T. Cunkle, *J. Org. Chem.* **1987**, 52, 2100.
[69] a) F. Chevallier, F. Mongin, *Chem. Soc. Rev.* **2008**, *37*, 595; b) A. Seggio, F. Chevallier, M. Vaultier, F. Mongin, *J. Org. Chem.* **2007**, 72, 6602; c) J-M. L'Helgoual'ch, A. Seggio, F. Chevallier, M. Yonehara, E. Jeanneau, M. Uchiyama, F. Mongin, *J. Org. Chem.* **2008**, *73*, 177.
[70] Z. Dong, G. C. Clososki, S. H. Wunderlich, A. Unsinn, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 457.

solution (1.0 M in THF; 0.50 equiv) and further treatment of this solution with TMPMgCl·LiCl (**40**), the fully metalated quinoxaline **62h** is obtained after 2.5 h. Interestingly, using the *in situ* protocol, no formation of the dimer **92** is observed (Scheme 30). A subsequent Pd-catalyzed cross-coupling[45] with ethyl 4-iodobenzoate furnishes the substituted quinoxaline **63o** in 79% yield (82% yield if metalation performed with **60**). By using the monomeric complexes $ZnCl_2$·LiCl or $ZnCl_2$·2LiCl, a further acceleration of the metalation rates can be achieved (Figure 4). The use of $ZnBr_2$ leads to a dramatically decreased metalation rate.



Scheme 30: Metalation of quinoxaline (**61h**) using different metalation methods.

Several reaction pathways leading to this result are conceivable (Scheme 31). In *pathway a*, the base TMPMgCl·LiCl (**40**) reacts first with quinoxaline (**61h**) affording the magnesiated heterocycle **93**. After a fast transmetalation with $ZnCl_2$ (0.50 equiv) the quinoxalylzinc reagent **62h** is formed (Scheme 31, *pathway a*). Alternatively in *pathway b*, TMPMgCl·LiCl (**40**) reacts rapidly with $ZnCl_2$ to provide $TMP_2Zn·MgCl_2·2LiCl$ (**60**, Scheme 31, *pathway b*) which subsequently reacts with quinoxaline (**61h**) leading to the zinc reagent **62h**. This second pathway can be excluded since the reaction times of the *in situ* procedure are considerably shorter (25 °C, 2.5 h) than the metalation using $TMP_2Zn·2MgCl_2·2LiCl$ (**60**) generated separately (25 °C, 5 h, Scheme 30). Moreover, a third pathway has to be considered (Scheme 31, *pathway c*): the heterocycle **61h** coordinates $ZnCl_2$ affording the tentative Zn-complex[71] **94** which reacts with TMPMgCl·LiCl (**40**) leading to the zinc species **62h** after fast transmetalation.

[71] B. M. E. Markowitz, M. M. Turnbull, F. F. Awwadi, *Acta Cryst.* **2006**, *E62*, 1278.

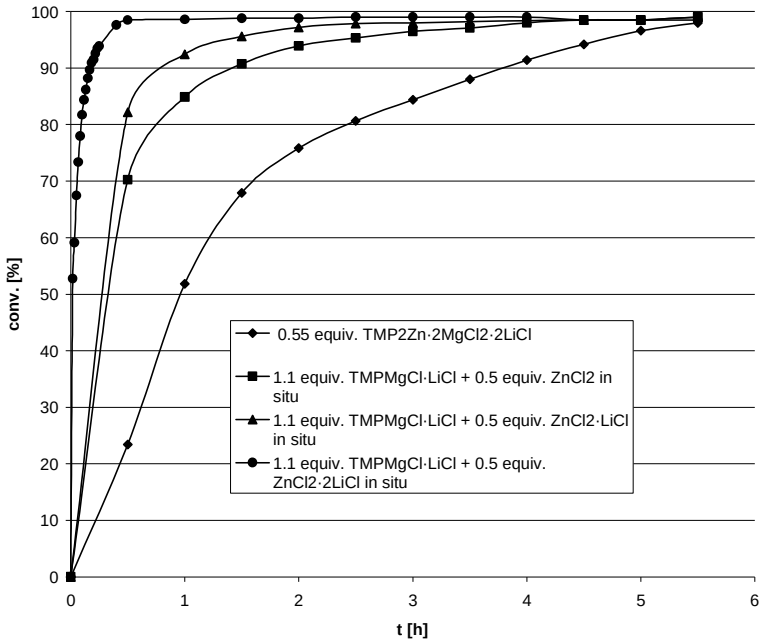
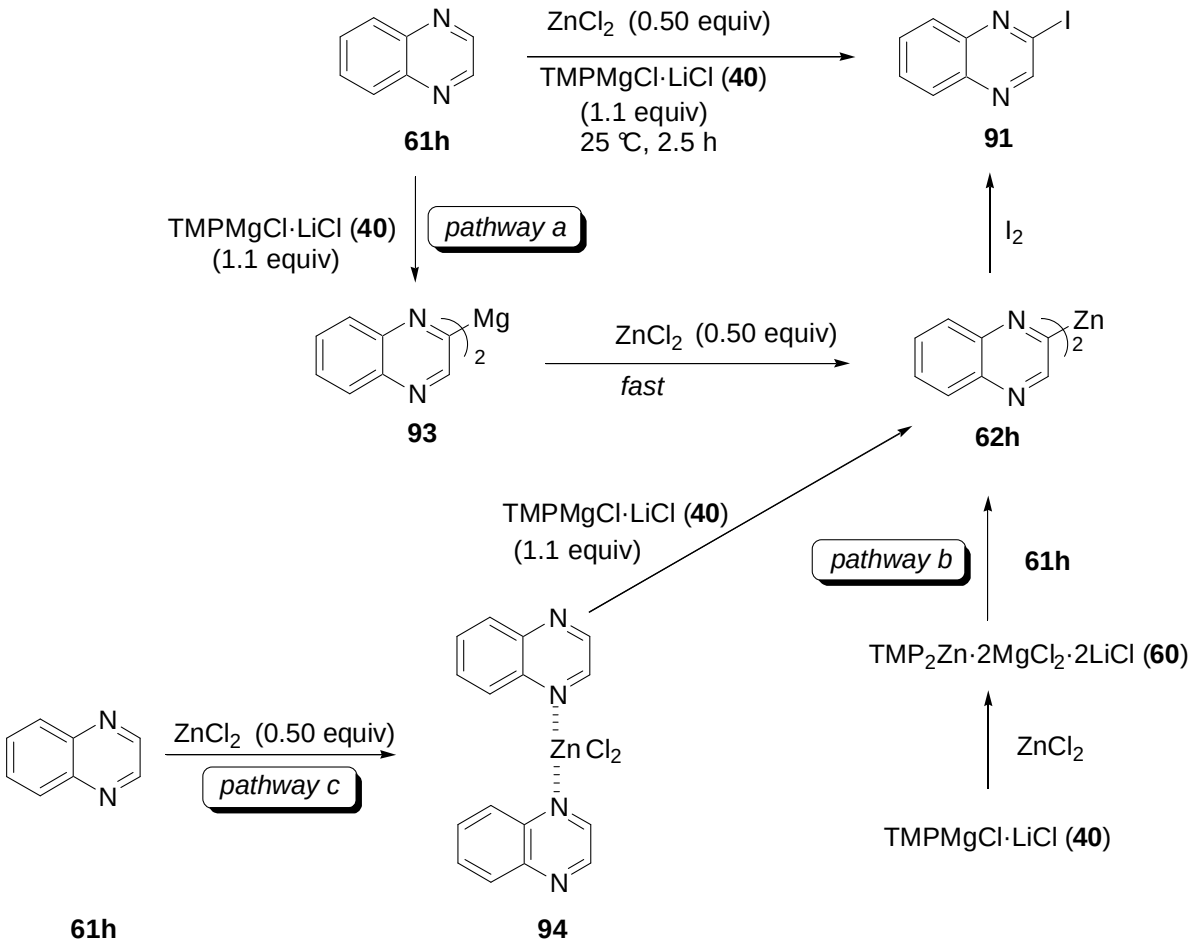
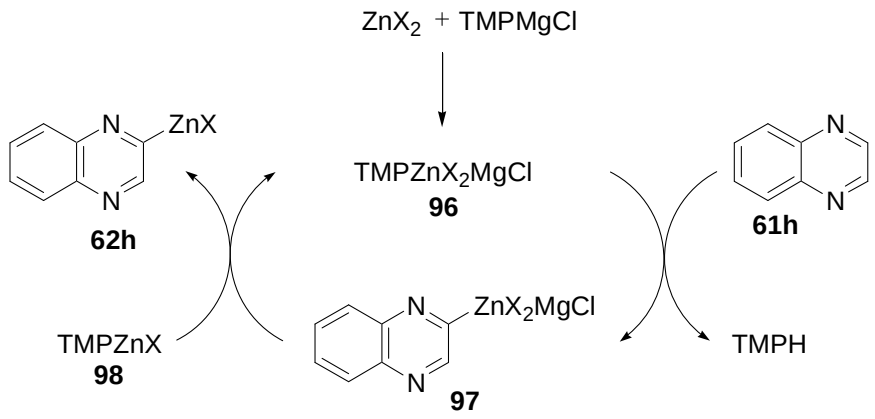


Figure 4: Metalation progress of quinoxaline.



Scheme 31: Possible pathways leading to the zincated quinoxaline **62h**.

Since preliminary experiments have shown that a formal ate-species like $TMP_3ZnMgCl \cdot 0.5MgCl_2 \cdot 3LiCl$ (**94**) or $TMP_4Zn(MgCl)_2 \cdot 4LiCl$ (**95**) can be considered to be active intermediates during the *in situ* zincation using $TMP_2Mg \cdot 2LiCl$ (**45**),[70] a different pathway leading to the metalated species is thinkable. The reaction of $ZnCl_2$ with TMPMgCl·LiCl (**40**) affords the highly reactive zincate base (**96**) which deprotonates rapidly quinoxaline (**61h**) providing the magnesium arylzincate **97**. An exchange reaction with TMPZnX (**98**) regenerates the magnesium zincate **96** and releases the diheteroarylzinc **62h** as final product (Scheme 32). However, a zincate species such as TMP_3ZnLi (**99**) has been calculated to be thermodynamically unstable, and therefore a similar energetic situation may well be applicable to $TMP_3ZnMgCl \cdot LiCl$ (**96**). Unfortunately, the attempts to prepare this highly reactive base **96** in the absence of a substrate failed and led to rapid decomposition. Since kinetic measurements of numerous metalation progresses have shown that neither TMPMgCl·LiCl (**40**) nor $TMP_2Zn \cdot MgCl_2 \cdot 2LiCl$ (**60**) are exclusively responsible for the observed conversions, this last tentative mechanism explains best the achieved metalation rates.



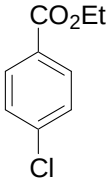
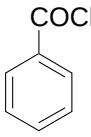
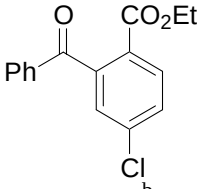
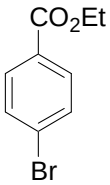
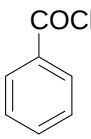
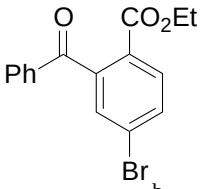
Scheme 32: Proposed metalation cycle involving catalytic amounts of a highly active ate-base.

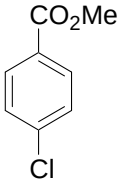
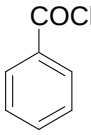
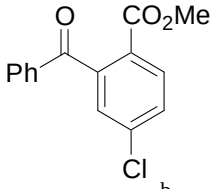
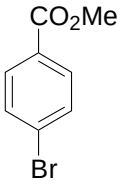
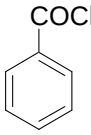
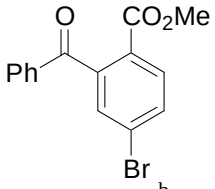
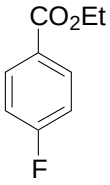
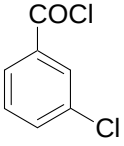
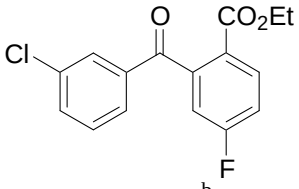
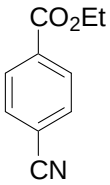
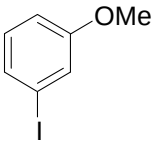
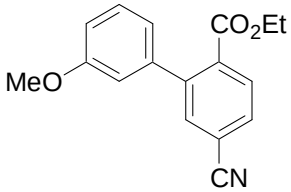
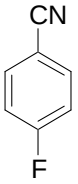
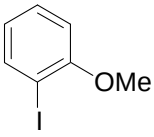
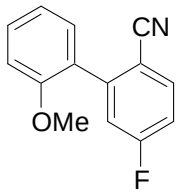
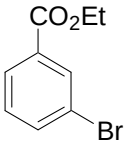
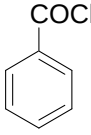
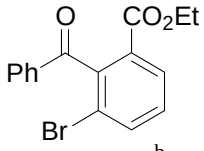
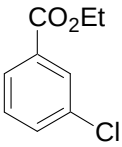
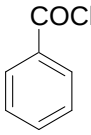
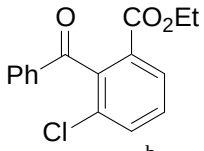
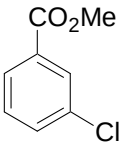
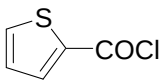
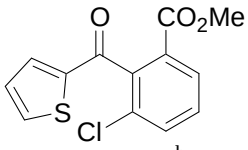
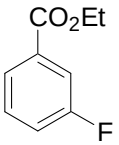
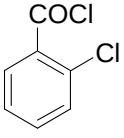
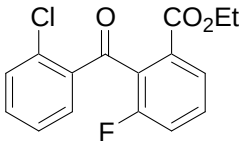
7.3 Zincation of Aromatics and Heteroaromatics

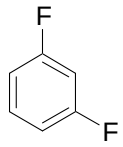
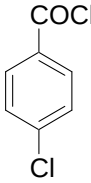
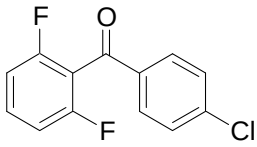
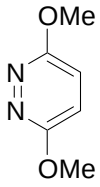
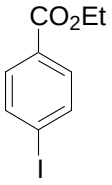
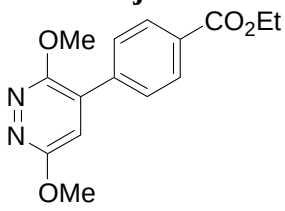
Nevertheless, this *in situ* zincation protocol using TMPMgCl·LiCl (**40**) at 25 °C proves to be quite general. Thus, the 4-halogenated ethyl benzoates **67c,f** are readily converted into the corresponding diaryl reagents within 20 h. After CuCN·2LiCl-mediated benzoylations[46] with PhCOCl (1.1 equiv), the expected benzophenones **69f** and **101a** are isolated in 79-83% yield (Table 8, entries 1-2). Interestingly, the related methyl benzoates **67e** and **100a** can also be converted to the desired organometallics. The ketones **101b-c** are obtained in 85-86% yield

after the reaction with PhCOCl (1.1 equiv) in the presence of CuCN·2LiCl (1.1 equiv; entries 3-4). Additionally, ethyl 4-fluorobenzoate is smoothly zincated within 11 h and a subsequent copper(I)-mediated acylation furnishes the substituted benzoate **101d** in 85% yield (entry 5). Furthermore, ethyl 4-cyanobenzoate (**67j**) is readily metalated within 3 h at 25 °C, whereas the zincation of 4-fluorobenzonitrile (**67k**) is accomplished within 8 h using TMPMgCl·LiCl (**40**; 1.1 equiv). The subsequent Pd-catalyzed cross-coupling reactions with different iodoanisoles using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%) as catalytic system provide the biaryls **101e-f** in 80-87% yield (entries 6-7). Additionally, ethyl 3-bromobenzoate (**100b**) and ethyl 3-chlorobenzoate (**67b**) are smoothly zincated within 4 h and 3 h, respectively. The desired benzophenones **101g** and **69e** are isolated in 84-91% yield after the reactions with benzoyl chloride mediated by CuCN·2LiCl (entries 8-9). Similarly, the metalation of methyl 3-chlorobenzoate (**100c**) is finished within 5 h and the subsequent reaction with thiophene-2-carbonyl chloride in the presence of CuCN·2LiCl (1.1 equiv) gives the expected ketone **101h** in 82% yield (entry 10). Moreover, ethyl 3-fluorobenzoate (**57**) is readily converted into the corresponding diary zinc species within 2 h and the adjacent acylation with 2-chlorobenzoyl chloride affords the benzophenone **101i** in 94% yield (entry 11). Interestingly, the zincation of 1,3-difluorobenzene (**100d**) proceeds well in position 2 within 6 h. The ketone **101k** is obtained in 80% after the CuCN·2LiCl-mediated reaction with 4-chlorobenzoyl chloride (entry 12). Finally, 3,6-dimethoxy-pyridazine (**100e**) is smoothly metalated within 5 h and the subsequent Pd-catalyzed cross-coupling reaction[45] with ethyl 4-iodobenzoate using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%) as catalytic system leads to the biaryl **101k** in 65% yield (entry 13).

Table 8: Products obtained by the zincation of aromatics and heteroaromatics at *25 °C* using the *in situ* protocol and subsequent reactions with electrophiles.

Entry	Substrate	Time [h]	Electrophile	Product/Yield [%][a]
1	 **67c**	20		 **69f**: 83[b]
2	 **67f**	20		 **101a**: 79[b]

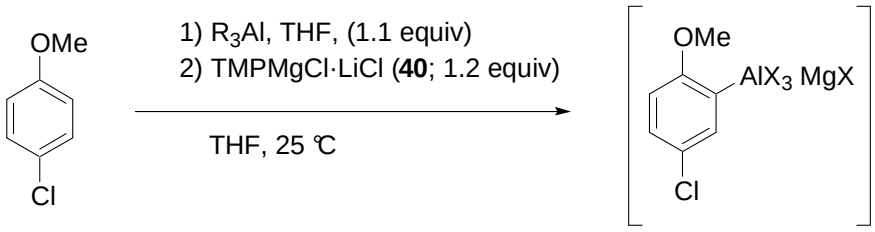
Entry	Substrate	Time [h]	Electrophile	Product/Yield [%][a]
3	 **67e**	20		 **101b**: 86[b]
4	 **100a**	20		 **101c**: 85[b]
5	 **67a**	11		 **101d**: 85[b]
6	 **67j**	3		 **101e**: 87[c]
7	 **67k**	8		 **101f**: 80[c]
8	 **100b**	4		 **101g**: 91[b]
9	 **67b**	3		 **69e**: 84[b]
10	 **100c**	5		 **101h**: 82[b]
11	 **57**	2		 **101i**: 94[b]

Entry	Substrate	Time [h]	Electrophile	Product/Yield [%][a]
12	 **100d**	6		 **101j**: 80[b]
13	 **100e**	5		 **101k**: 65[c]

[a] Isolated yield of analytically pure product. [b] Obtained after transmetalation with CuCN·2LiCl (1.1 equiv); [c] Obtained via Pd-catalyzed cross-coupling with $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%).

7.4 Metalation of Aromatics Using *in situ* Aluminations

Furthermore, this *in situ* metalation concept was extended to directed alumination reactions since aluminum possesses a high Lewis-acidity giving the opportunity to complex appropriately directing groups like esters, amides and even ethers. First, an applicable aluminum source had to be found. 4-Chloroanisole (**102a**) was chosen as a model substrate and reacted with various aluminum reagents followed by TMPMgCl·LiCl (**40**) giving the tentative aluminated anisole of the type **103** (Scheme 33).



102a **103**

Scheme 33: Optimization of the *in situ* alumination using TMPMgCl·LiCl (**40**) and different Al-sources.

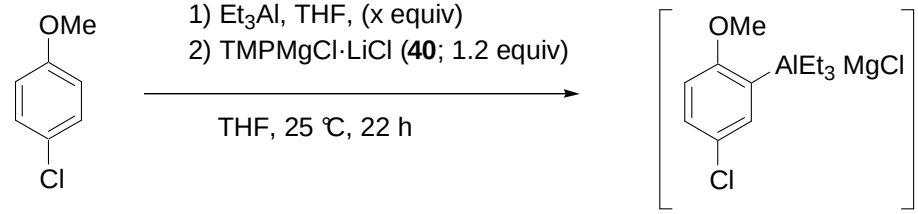
Interestingly, the use of $AlCl_3$, $MeAlCl_2$ and Me_2AlCl (1.1 equiv in each case) did not lead to improved metalation rates of 4-chloroanisole (**102a**) compared to the metalation using just TMPMgCl·LiCl (**40**; 1.2 equiv; Table 9, entry 1-4). The trialkyl aluminum reagents Me_3Al, Et_3Al and *i*Bu_3Al displayed a comparable effect on the formation of the aluminated anisole of type **103** (entries 5-19), whereas Et_3Al proved to be the most effective aluminum reagent for this *in situ* protocol.

Table 9: Metalation progress of 4-chloroanisole (**102a**) using different aluminum sources.

entry	R_3Al	Time [h]	Conversion to **103** [%][a]
1	----	22	30
2	$AlCl_3$	7	<5
3	$MeAlCl_2$	7	<5
4	Me_2AlCl	7	<5
5	Me_3Al	2	44
6	Me_3Al	4	58
7	Me_3Al	7	69
8	Me_3Al	10	74
9	Me_3Al	22	76
10	Et_3Al	2	48
11	Et_3Al	4	66
12	Et_3Al	7	78
13	Et_3Al	10	82
14	**Et_3Al**	**22**	**90**
15	*i*Bu_3Al	2	35
16	*i*Bu_3Al	4	53
17	*i*Bu_3Al	7	69
18	*i*Bu_3Al	10	76
19	*i*Bu_3Al	22	81

[a] The conversion to the corresponding metal species **103** was monitored *via* GC-analysis of aliquots of the reaction mixture quenched with allyl bromide in the presence of CuCN·2LiCl using tetradecane as internal standard.

Continuously, the necessary amount of Et_3Al was determined. Therefore, 4-chloroanisole (**102a**) is first treated with Et_3Al (0.33-2.00 equiv) and subsequently reacted with TMPMgCl·LiCl (**40**) at 25 °C for 22 h (Scheme 34). In contrast to the previous described *in situ* zincation, the aluminum additive had to be used in stoichiometric amounts. Thus, the use of less than 1 equiv of Et_3Al leads to decreased metalation rates (51-65% instead of 90%), whereas more than 1 equiv of the Lewis acid reagent does not deeply influence the metalation rate.

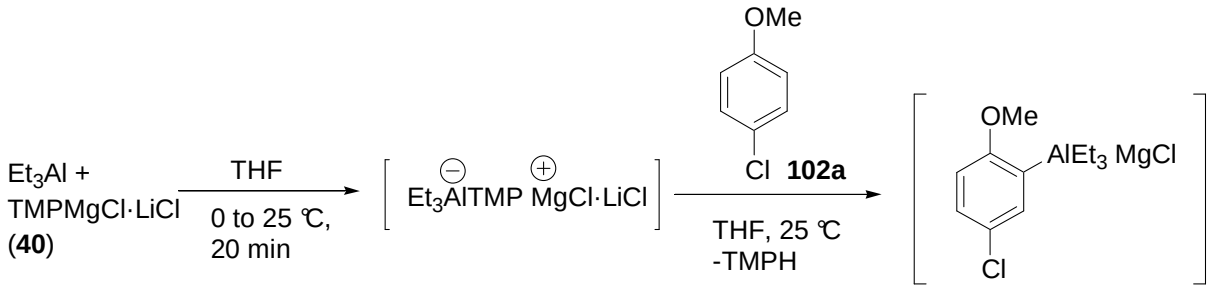


102a **103a**

for x = 0.33: 51%
for x = 0.67: 65%
for x = 1.00: 90%
for x = 2.00: 95%

Scheme 34: Metalation of 4-chloroanisole (**102a**) using different amounts of Et_3Al.

To obtain more mechanistic insights of this *in situ* alumination, TMPMgCl·LiCl (**40**) is treated with Et_3Al (1.0 equiv) to give the concievable ate-species $Et_3AlTMPMgCl·LiCl$ (**104**; Scheme 35). Then, this freshly prepared reagent is reacted with 4-chloroanisole (**102a**) at 25 °C. In contrast to the above described *in situ* zincation with $ZnCl_2$ (0.50 equiv), it turned out that the formation of the ate-species $Et_3AlTMPMgCl·LiCl$ (**104**) is thoroughly responsible for the observed metalation rates since the aluminations using either $Et_3AlTMPMgCl·LiCl$ (**104**) or the *in situ* protocol proceeds with comparable rates.



104 **103a**

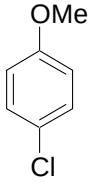
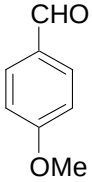
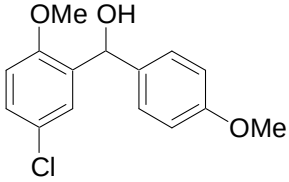
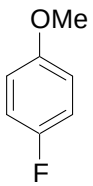
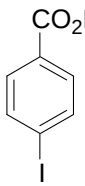
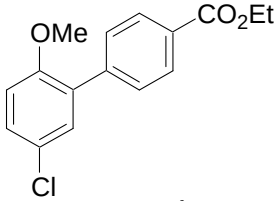
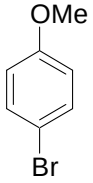
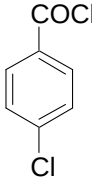
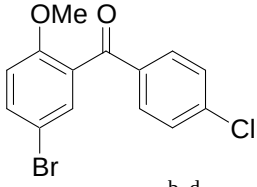
2 h: 39%
5 h: 62%
7 h: 69%
10 h: 75%
24 h: 88%

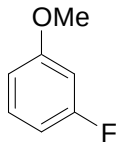
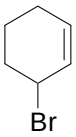
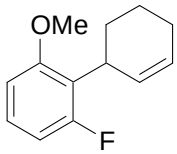
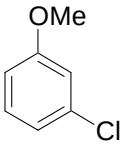
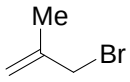
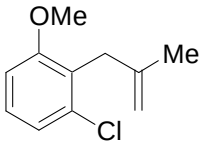
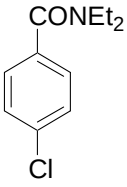
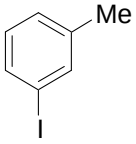
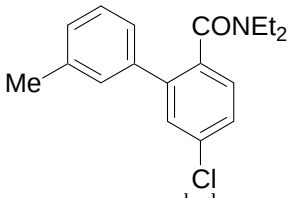
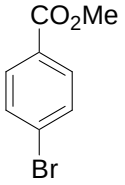
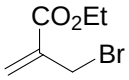
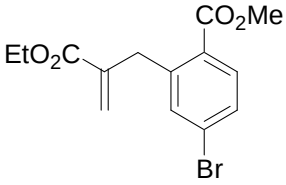
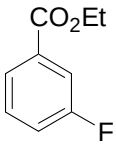
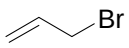
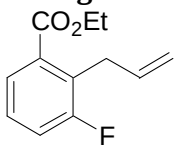
Scheme 35: Formation of the tentative ate-species $Et_3AlTMPMgCl·LiCl$ (**104**) and its reaction with 4-chloroanisole (**102a**). The conversion to the corresponding metal species **103a** was monitored *via* GC-analysis of aliquots of the reaction mixture quenched with allyl bromide in the presence of CuCN·2LiCl using tetradecane as internal standard.

This *in situ* alumination procedure seems to work best with halogenated anisoles. Thus, the reaction of the fully metalated 4-chloroanisole **103a** with 4-methoxy benzaldehyde

provides the alcohol **105a** in 75% yield (Table 10, entry 1). Moreover, the alumination of 4-fluoroanisole (**102b**) is accomplished within 15 h at 25 °C. After transmetalation to zinc and a subsequent Pd-catalyzed cross-coupling reaction[45] with ethyl 4-iodobenzoate using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%) as catalytic system, the biaryl **105b** is obtained in 77% yield (entry 2). Additionally, 4-bromoanisole (**102c**) is converted into the corresponding Al-species within 28 h. After transmetalation to zinc and the reaction with 4-chlorobenzoyl chloride mediated by CuCN·2LiCl (1.1 equiv),[46] the expected benzophenone **105c** is isolated in 79% yield (entry 3). Furthermore, 3-fluoroanisole (**102d**) is smoothly aluminated within 20 min at –5 °C, whereas the metalation of 3-chloroanisole (**102e**) proceeds within 1 h at 25 °C. Adjacent copper-catalyzed allylation reactions[46] afford the substituted anisoles **105d-e** in 85-87% yield (entries 4-5). 4-Chloro-*N*,*N*-diethylbenzamide (**102f**) is smoothly aluminated within 3 h at 0 °C and the biphenyl **105f** is obtained in 73% yield after transmetalation to zinc and a subsequent Pd-catalyzed cross-coupling reaction with 3-iodotoluene using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%) as catalytic system (entry 6). Finally, methyl 4-bromobenzoate (**100a**) is fully metalated within 2 h at 0 °C, whereas the alumination of ethyl 3-fluorobenzoate (**57**) readily proceeds within 1 h at 0 °C. Subsequent copper-catalyzed allylation reactions lead the 1,2,3-trisubstituted arenes **105g-h** in 51-81% yield (entries 7-8).

Table 10: Products obtained using *in situ* alumination and subsequent reactions with electrophiles.

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
1	 **102a**	25, 24		 **105a**: 75
2	 **102b**	25, 15		 **105b**: 77[b, c]
3	 **102c**	25, 28		 **105c**: 79[b, d]

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
4	 **102d**	–5, 0.3		 **105d**: 87[e]
5	 **102e**	25, 1		 **105e**: 85[e]
6	 **102f**	0, 3		 **105f**: 73[b, d]
7	 **100a**	0, 2		 **105g**: 51[e]
8	 **57**	0, 1		 **105h**: 81[e]

[a] Isolated yield of analytically pure product. [b] A transmetalation with $ZnCl_2$ (2.0 equiv) was performed. [c] Obtained via Pd-catalyzed cross-coupling with $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%). [d] Obtained after transmetalation with CuCN·2LiCl (1.1 equiv). [e] Obtained after transmetalation with CuCN·2LiCl (5 mol-%).

8 Directed Metalation of Aromatics and Heteroaromatics Using Aluminum-Bases

8.1 Introduction

Remarkably, organoaluminum reagents have found numerous applications in synthetic organic chemistry, such as carbo- and hydroalumination reactions.[72] The Lewis-acidic character of the aluminum metal center allows performing reactions with unique chemo-, regio- and enantio-selectivity.[73] Moreover, aluminum amides are not an invention of nowadays. In 1974, *Yamamoto* reported the use of Et_2AlTMP for the selective deprotonative opening of epoxides.[74] Later, this reagent was used for the opening of oxetanes and the formation of Al-enolates.[75] Furthermore, Et_2AlTMP promotes a regioselective Fischer indole synthesis.[76] In general, arylaluminum species are generated by transmetalation of aryllithium reagents using various aluminum(III) sources[77] or in some cases through aluminum-tin or -boron exchange reactions.[78] More recently, *Uchiyama* and co-workers reported the directed deprotonation using the ate-base $(i\text{Bu})_3\text{AlTMPLi}$.[79] Due to the ate-character of this base, several aromatics and heteroaromatics were readily metalated. A major drawback of this method is the atom-economy since 2 equivalents of the base and up to 9 equivalents of the corresponding electrophile are needed for the complete functionalization of the used aromatic and

[72] "Aluminum in Organic Synthesis": S. Saito, *Main Group Metals in Organic Synthesis*, Vol. 1 (Eds.: H. Yamamoto, K. Oshima), Wiley-VCH, Weinheim, **2004**, chap. 6.

[73] a) S. Baba, E. Negishi, *J. Am. Chem. Soc.* **1976**, *98*, 6729; b) B. Liang, T. Novak, Z. Tan, E. Negishi, *J. Am. Chem. Soc.* **2006**, *128*, 2770; c) J. P. Abell, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 10521; d) N. Takenaka, J. P. Abell, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 742; e) T. Ooi, K. Ohmatsu, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 2410; f) K. Ohmatsu, T. Tanaka, T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2008**, *47*, 5203; g) E. Negishi, *Chem. Eur. J.* **1999**, 411; h) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313; i) L. C. Wieland, H. Deng, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 15453; j) S. Saito, T. Sone, M. Murase, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 10216; k); X. Zhou, X. Liu, X. Yang, D. Shang, J. Xin, X. Feng, *Angew. Chem. Int. Ed.* **2008**, *47*, 392; l) T. Ooi, M. Takahashi, M. Yamada, E. Tayama, K. Omoto, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 1150; m) M. d´Augustin, L. Palais, A. Alexakis, *Angew. Chem. Int. Ed.* **2005**, *44*, 1376.

[74] A) A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc.* **1974**, *96*, 6513; b) H. Yamamoto, H. Nozaki, *Angew. Chem, Int. Ed. Engl.* **1978**, *3*, 169.

[75] K. Maruoka, M. Oishi, H. Yamamoto, *J. Org. Chem.* **1993**, *58*, 7638.

[76] K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc.* **1977**, *99*, 7705.

[77] a) J. J. Eisch, *Comprehensive Organometallic Chemistry*; (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon Press: Oxford, **1982**; Vol 6; b) T. Ishikawa, A. Ogawa, T. Hirao, *J. Am. Chem. Soc.* **1998**, *120*, 5124; c) C. Hawner, K. Li, V. Cirriez, A. Alexakis, *Angew. Chem. Int. Ed.* **2008**, *47*, 8211.

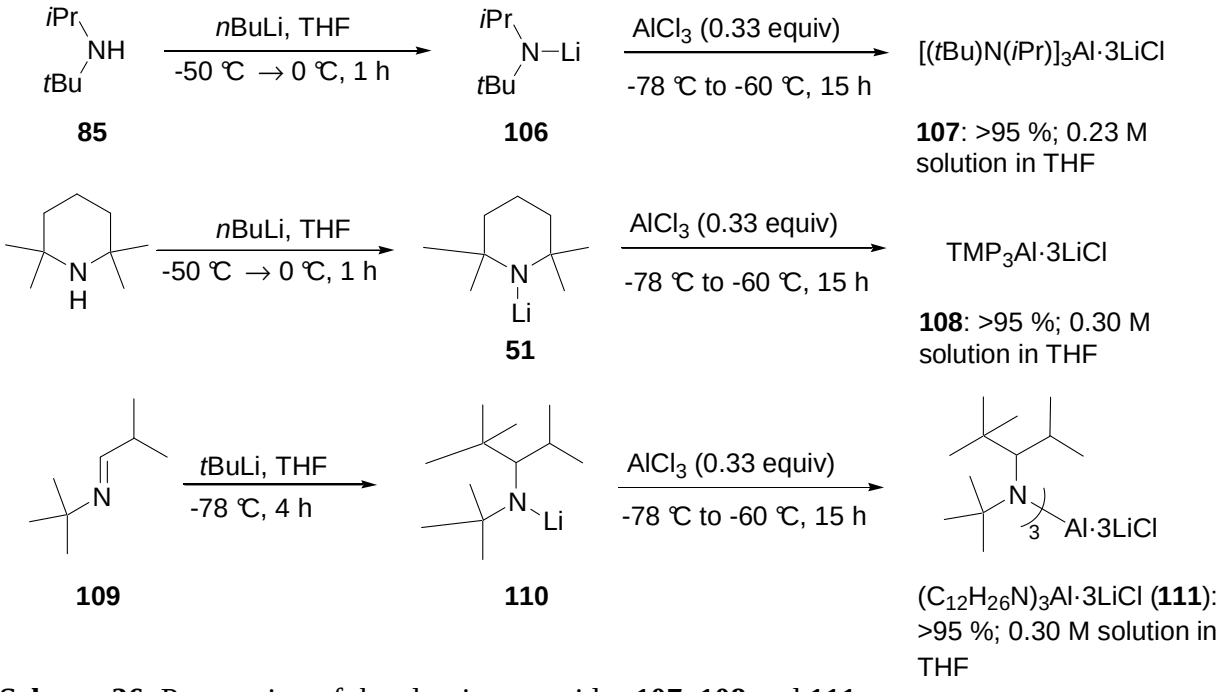
[78] a) J. J. Eisch, K. Mackenzie, H. Windisch, C. Krüger, *Eur. J. Inorg. Chem.* **1999**, 153; b) M. Tschinkl, R. E. Bachmann, F. P. Gabbaï, *Chem. Comm.* **1999**, 1367; c) M. Bochmann, M. J. Sarfield, *Organometallics* **1998**, *17*, 4684.

[79] a) M. Uchiyama, H. Naka, Y. Matsumoto, T. Ohwada, *J. Am. Chem. Soc.* **2004**, *126*, 10526; b) H. Naka, M. Uchiyama, Y. Matsumoto, A. E. H. Wheatley, M. McPartlin, J. V. Morey, Y. Kondo, *J. Am. Chem. Soc.* **2007**, *129*, 1921; c) H. Naka, J. V. Morey, J. Haywood, D. J. Eisler, M. McPartlin, F. Garcia, H. Kudo, Y. Kondo, M. Uchiyama, A. E. H. Wheatley, *J. Am. Chem. Soc.* **2008**, *130*, 16193.

heteroaromatics. Therefore, the development of new *neutral* aluminum *tris*-amide bases for highly regioselective metalations was carried out. Supported by pioneering structural investigations,[80] the reaction of TMPLi (**51**) or related Li-amides with $AlCl_3$ has been considered to be promising.

8.2 Preparation of the Al-Bases

Starting from (*t*Bu)(*i*Pr)NH (**85**), the formation of the corresponding Li-amide **106** proceeds smoothly within 1 h and the subsequent reaction with a THF solution of $AlCl_3$ (0.33 equiv)[81] at –78 °C affords the aluminum amide **107** as a 0.23 M solution in THF. Similarly, the treatment of freshly prepared TMPLi (**51**) with a THF solution of $AlCl_3$ (0.33 equiv) at –78 °C (15 h) leads to a solution of $TMP_3Al{\cdot}3LiCl$ (**108**) (Scheme 36). Furthermore, an additional hindered aluminum base has been prepared. Thus, the imine **109**[82] readily adds *t*BuLi (1.0 equiv) in THF at –78 °C leading to the lithium amide **110**. After transmetalation with a THF solution of $AlCl_3$ (0.33 equiv.) the corresponding aluminum *tris*-amide base **111** is obtained in quantitative yield (Scheme 36). These bases **108** and **111** display both an enhanced solubility (0.30 M in THF) compared to $[(t\text{Bu})N(i\text{Pr})]_3Al{\cdot}3LiCl$ (**107**).



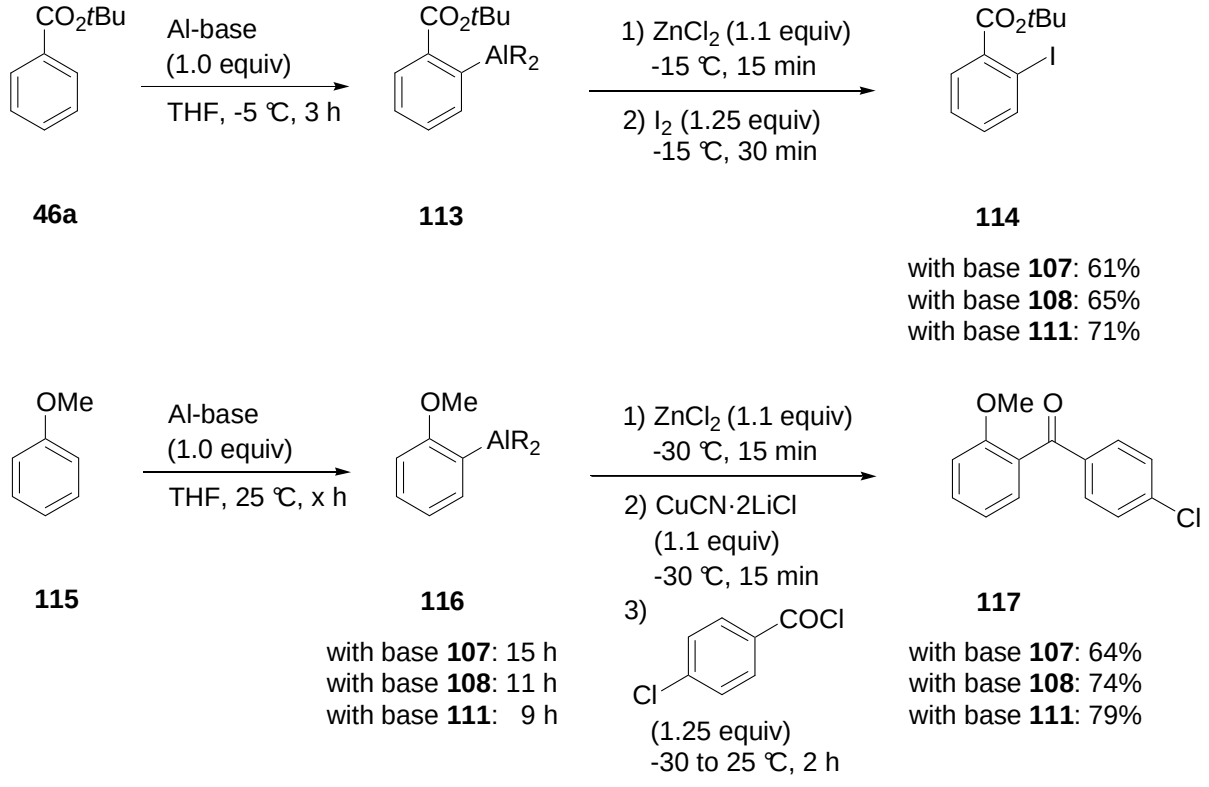
Scheme 36: Preparation of the aluminum amides **107**, **108** and **111**.

[80] a) B. Conway, E. Hevia, J. García-Álvarez, D. V. Graham, A. R. Kennedy, R. E. Mulvey, *Chem. Comm.* **2007**, 5241; b) J. García-Álvarez, D. V. Graham, A. R. Kennedy, R. E. Mulvey, S. Weatherstone, *Chem. Comm.* **2006**, 3208; c) W. Clegg, S. T. Liddle, K. W., Henderson, F. E. Keenan, A. R. Kennedy, A. E. Mckeown, R. E. Mulvey, *J. Organomet. Chem.* **1999**, 283; d) D. Rutherford, D. A. Atwood, *J. Am. Chem. Soc.* **1996**, *118*, 11535; e) I. Krossing, H. Nöth, H. Schwenk-Kirchner, *Eur. J. Inorg. Chem.* **1998**, 927; f) C. Klein, H. Nöth, M. Tacke, M. Thomann, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 886.

[81] H. Nöth, R. Rurländer, P. Wolfgardt, *Z. Naturforschung, Part B* **1982**, 37, 29.

[82] N. de Kimpe, D. Smaele, A. Hofkens, Y Dejaegher, B. Kesteleyn, *Tetrahedron* **1997**, *53*, 10803.

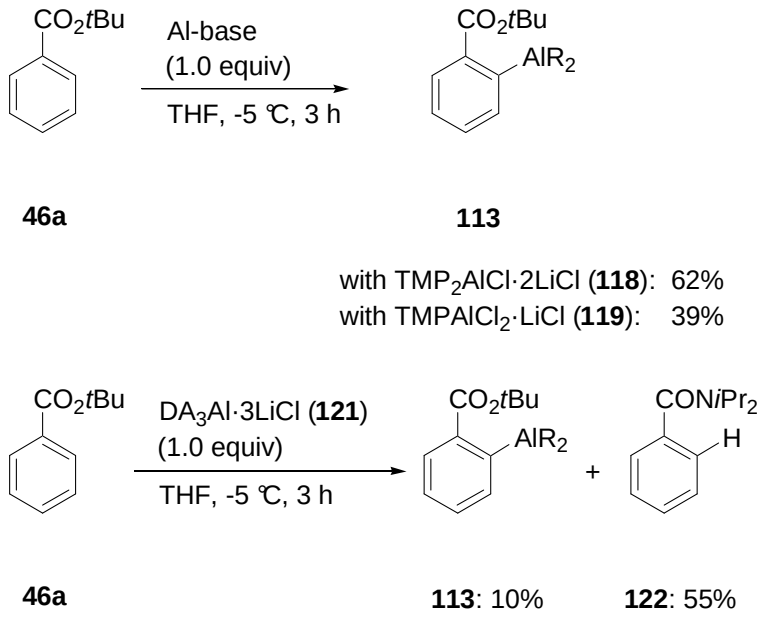
Thereafter, these bases were reacted with *tert*-butyl benzoate (**46a**; unfortunately, the alumanition of ethyl benzoate (**78a**) and isopropyl benzoate (**112**) could not be achieved). The reactions are carried out using 1.0 equiv of the corresponding base at –5 °C (Scheme 37) and after 3 h, each of the alumination reactions is accomplished.[83] Subsequently, the aluminated benzoates are transmetalated to the more stable Zn-species which then are treated with iodine giving the iodinated benzoate **114**. It turned out, that by using the most sterically hindered amide **111**, the highest isolated yield could be obtained (71% compared to 65% and 61%, respectively). The use of less than 1.0 equiv of aluminum amides led to decreased metalation rates and significantly lower yields of the *tert*-butyl 2-iodobenzoate (**114**). Additionally, the alumination of anisole (**115**) using the less soluble amide base [(*t*Bu)N(*i*Pr)]$_3$Al·3LiCl (**107**) proceeds within 15 h at 25 °C, whereas the metalation using TMPAl$_3$·3LiCl (**108**) is already finished within 11 h. Moreover, the most sterically hindered Al-amide **111** performs this metalation within 9 h. After transmetalation to the corresponding Zn-compounds, an acylation with 4-chlorobenzoyl chloride in the presence of CuCN·2LiCl is carried out. The benzophenone **117** is isolated in 64% yield using the base [(*t*Bu)N(*i*Pr)]$_3$Al·3LiCl (**107**), whereas the reaction sequences carried out by the Al-bases **108** and **111** lead to this ketone **117** in significantly higher yields (74-79%; Scheme 37).



Scheme 37: Comparison of the metalation ability of the Al-bases **107**, **108** and **111**.

[83] If the aluminum bases **107**, **108** and **111** are prepared in Et_2O to precipitate LiCl, the kinetic basicity droped dramatically leading to no desired metalated species. Similar to the previousely discussed Zn-base **60**, LiCl increases the solubility in THF of such bases.

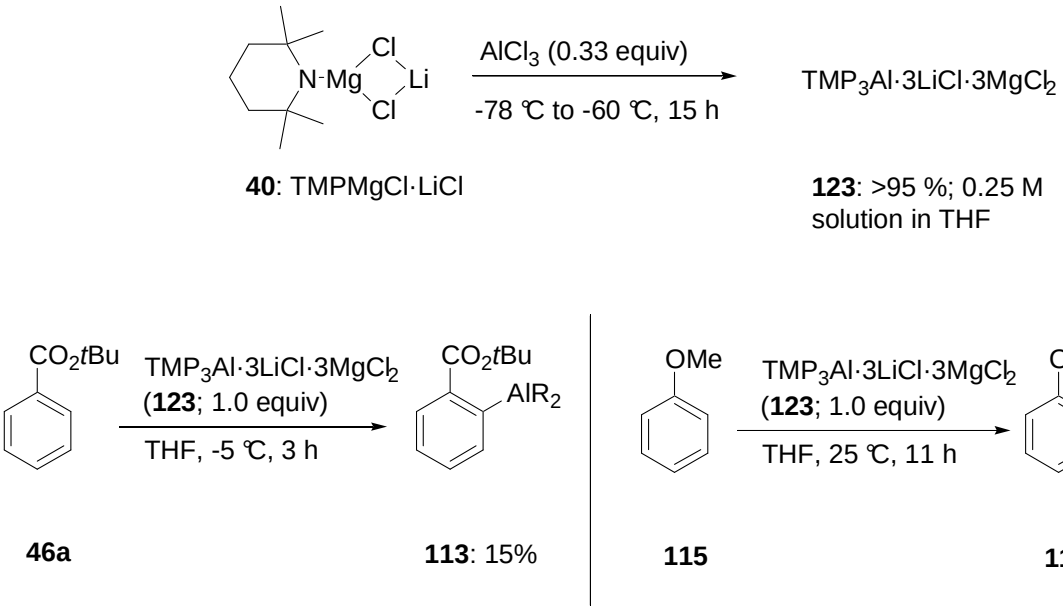
Additionally, several other aluminum amides bases have been prepared to study their metalation properties. Similar to $TMP_3Al·3LiCl$ (**108**), the reaction of freshly prepared TMPLi (**51**) with a THF solution of $AlCl_3$ (0.50 or 1.0 equiv) at –78 °C (15 h) furnishes Al-amides $TMP_2AlCl·2LiCl$ (**118**) and $TMPAlCl_2·LiCl$ (**119**). Both amide bases display a lower solubility in THF than the *tris*-amide $TMP_3Al·3LiCl$ (**108**). Accordingly, the transmetalation of freshly prepared LDA (**120**) with a THF solution of $AlCl_3$ (0.33 equiv) at –78 °C (15 h) affords the *tris*-amide **121** as a 0.20 M solution in THF. Subsequently, the metalation progress of *tert*-butyl benzoate (**46a**) is investigated using these Al-bases (Scheme 38). After 3 h at –5 °C, the desired Al-species is obtained in 39-62% yield using either $TMP_2AlCl·2LiCl$ (**118**; 1.0 equiv) or $TMPAlCl_2·LiCl$ (**119**; 1.0 equiv). Interestingly, the use of $DA_3Al·3LiCl$ (**121**; 1.0 equiv) as metalation agent leads mainly to the benzamide **122** (Scheme 38). Running this reaction at lower temperatures (e.g. –30 °C) avoids the formation of the benzamide **122**, but also leads to no alumination reaction giving the desired aluminum reagent **113**.



Scheme 38: Reactivity of the Al-bases **118**, **119** and **121**. The conversion to the corresponding metal species **113** was monitored *via* GC-analysis of aliquots of the reaction mixture quenched with allyl bromide in the presence of CuCN·2LiCl using tetradecane as internal standard.

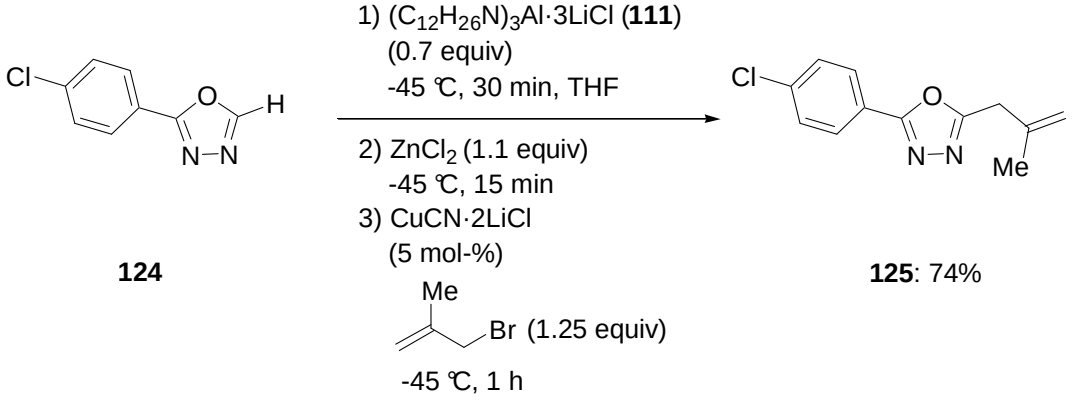
Moreover, an aluminum amide starting from TMPMgCl·LiCl (**40**) has been prepared. Thus, the reaction of TMPMgCl·LiCl (**40**) with a THF solution of $AlCl_3$ (0.33 equiv) at –78 °C (15 h) resulted in a base with the stoichiometry $TMP_3Al·3LiCl·3MgCl_2$ (**123**; Scheme 39). This reagent is quantitatively obtained as a 0.25 M solution in THF. Unfortunately, neither of

tert-butyl benzoate (**46a**) nor anisole (**115**) are metalated with comparable rates under similar conditions using $TMP_3Al·3LiCl$ (**108**; 1.0 equiv).



Scheme 39: Preparation and reactivity of $TMP_3Al·3LiCl·3MgCl_2$ (**123**). The conversion to the corresponding metal species **113** and **116** was monitored *via* GC-analysis of aliquots of the reaction mixture quenched with allyl bromide in the presence of CuCN·2LiCl using tetradecane as internal standard.

Furthermore, the oxadiazole **124** was aluminated using the Al-amide **111**. This metalation is accomplished within 30 min at –45 °C without ring fragmentation of the fragile metalated oxadiazole system. This indicates clearly the formation of an aluminum species since the magnesiated and especially the lithiated oxadiazoles are prone to easily undergo ring opening. Interestingly, only 0.7 equiv of the base **111** is needed for the complete metalation. After transmetalation to Zn and a copper(I)-catalyzed allylation,[46] the expected oxadiazole **125** is isolated in 74% (Scheme 40).



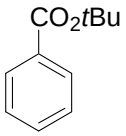
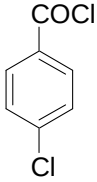
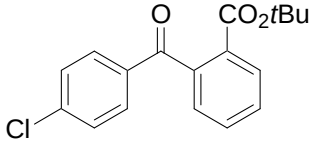
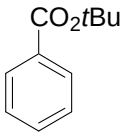
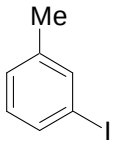
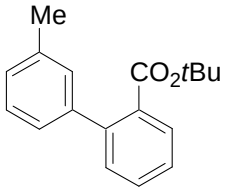
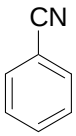
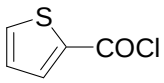
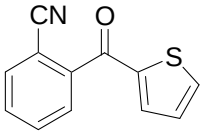
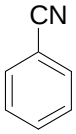
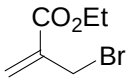
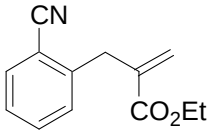
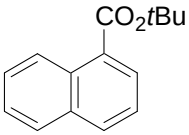
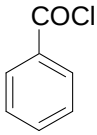
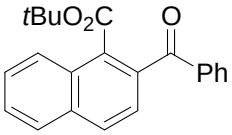
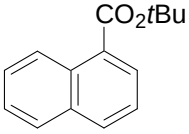
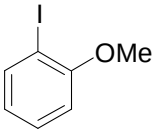
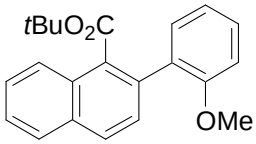
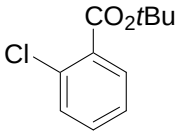
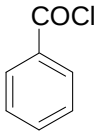
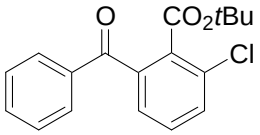
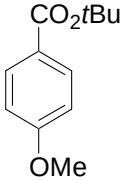
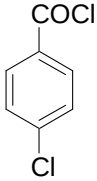
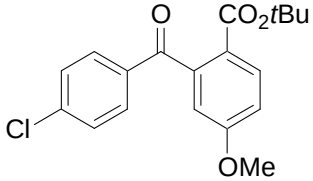
Scheme 40: Alumination and functionalization of the oxadiazole **124**.

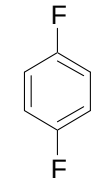
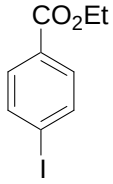
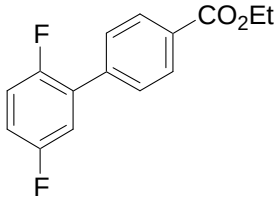
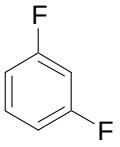
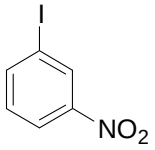
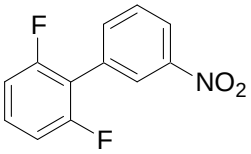
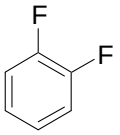
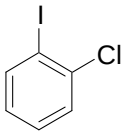
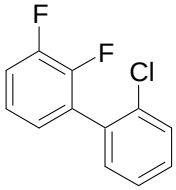
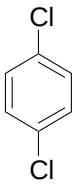
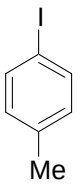
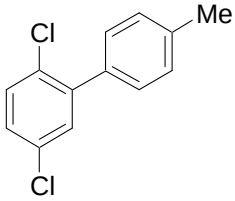
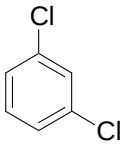
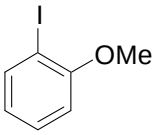
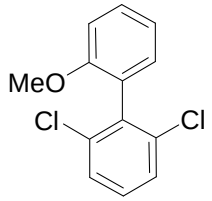
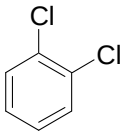
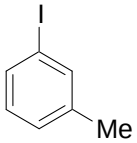
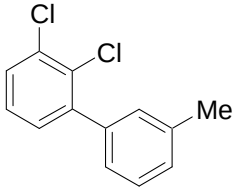
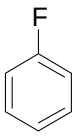
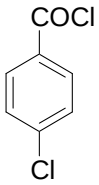
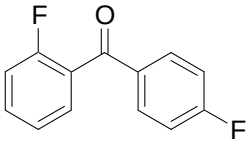
8.3 Alumination of Aromatics Bearing Efficient Directing Groups

In general, esters and nitriles are considered to be efficient substituents for directed *ortho* metalation.[31a] Thus, the alumination of various functionalized aromatics like *tert*-butyl benzoate (**46a**), benzonitrile (**126a**) and *tert*-butyl 1-naphthoate (**126b**) was investigated. These substrates all underwent complete formation of the aluminum reagent with $TMP_3Al{\cdot}3LiCl$ (**107**; 1.0 equiv) within 3-6 h at –5 to –10 °C. The resulting arylaluminum compounds were transmetalated with $ZnCl_2$ to the corresponding zinc reagents and after Cu-mediated acylations[46] or a Pd-catalyzed cross-coupling reaction[45] using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%), the products **127a-c** and **127e** were obtained in 70-79% yield (Table 11, entries 1-3, 5). Similarly, by using the aluminum *tris*-amide **111** (1.0 equiv) a full alumination was observed within 3-5 h at –5 to –10 °C and the products **127a-f** were isolated in 71-77% yield (entries 1-6). These results again indicate that both bases (**107** and **111**) show similar metalation rates. However, the practical and economical synthesis of the aluminum *tris*-amide **111** led us to use this base for further experiments. Thus, the alumination of *tert*-butyl 2-chlorobenzoate (**126c**) is accomplished within 7 h at –40 °C. After transmetalation to Zn and a Cu-mediated acylation with benzoyl chloride, the ketone **127g** is isolated in 75% yield (entry 7). Interestingly, the benzoate **126d** is fully metalated within 10 h at –5 °C, but the metalation occurs just with a 3:1 regioselectivity in *ortho*-position to the ester. Therefore, the benzophenone **127h** is obtained only in 55% yield after a transmetalation to Zn and a subsequent Cu-mediated acylation with 4-chlorobenzoyl chloride (entry 8). Whereas the metalation of difluorobenzenes (**126e**, **100d**, **126f**) is especially challenging and requires low reaction temperature,[84] a smooth regioselective alumination proceeds at –40 °C within 1.5-3 h using the aluminum base **111** (1.0 equiv). After transmetalation to the corresponding zinc derivatives and Negishi cross-couplings, the polyfunctional biphenyls **127i-k** are provided in 79-89% yield (entries 9-11). Moreover, the metalation of the corresponding *bis*-chlorinated benzenes **126g-i** proceed within 3-4.5 h under similar conditions at –60 °C leading after transmetalation and cross-couplings to the functionalized aromatics **127l-n** in 78-85% yield (entries 12-14). Additionally, the benzophenone **127o** is isolated in 67% yield after a smooth alumination of fluorobenzene (**126j**; 2 h, –10 °C) followed by a transmetalation to the corresponding Zn compound and a Cu-mediated acylation with 4-chlorobenzoyl chloride (entry 15).

[84] E. Masson, M. Schlosser, *Eur. J. Org. Chem*. **2005**, 4401.

Table 11: Products of type **6** obtained by the alumination of aromatics with the aluminum bases **108** and **111** and reactions with electrophiles.

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
				
1	**46a**	–5, 3		**127a**: 81 (75)[b, c, d]
				
2	**46a**	–5, 3		**127b**: 77 (79)[b, c, e]
				
3	**126a**	–10, 4 (4)[b]		**127c**: 71 (70)[b, c, d]
				
4	**126a**	–10, 4		**127d**: 69%[c, f]
				
5	**126b**	–5, 5 (6)		**127e**: 76 (78)[b, c, d]
				
6	**126b**	–5, 5		**127f**: 79[c, e]
				
7	**126c**	–40, 7		**127g**: 75[c, d]
				
8	**126d**	–5, 10		**127h**: 55[c, d]

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
9	 **126e**	–30, 2		 **127i**: 79[c, e]
10	 **100d**	–40, 1.5		 **127j**: 88[c, e]
11	 **126f**	–45, 3		 **127k**: 89[c, f]
12	 **126g**	–60, 3		 **127l**: 85[c, e]
13	 **126h**	–60, 4.5		 **127m**: 78[c, e]
14	 **126i**	–60, 4.5		 **127n**: 81[c, e]
15	 **126j**	–10, 3		 **127o**: 67[c, d]

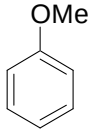
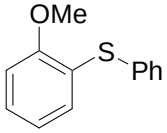
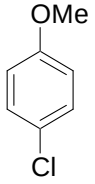
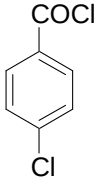
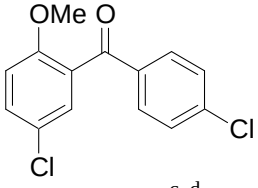
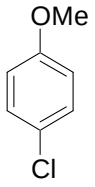
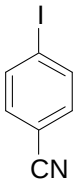
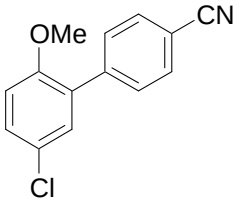
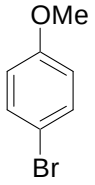
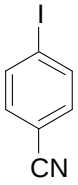
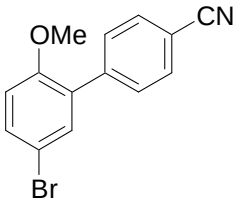
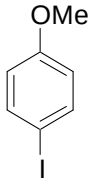
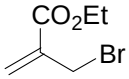
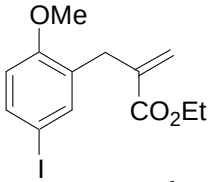
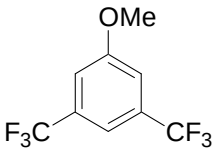
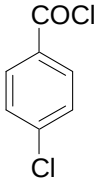
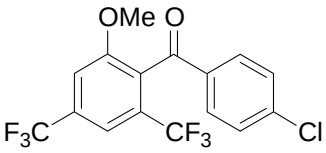
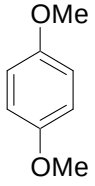
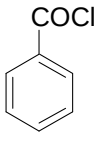
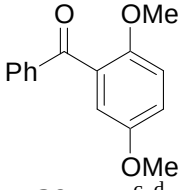
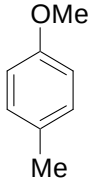
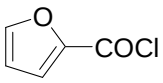
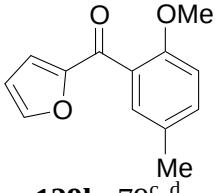
[a] Isolated yield of analytically pure product. [b] In parentheses the metalation times and isolated yields using $TMP_3Al{\cdot}3LiCl$ (**108**) are given. [c] A transmetalation with $ZnCl_2$ (1.1 equiv) was performed. [d] A transmetalation with CuCN·2LiCl (1.1 equiv) was performed. [e] Obtained by Pd-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%). [f] A transmetalation with CuCN·2LiCl (5 mol-%) was performed.

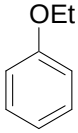
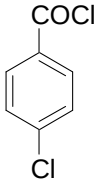
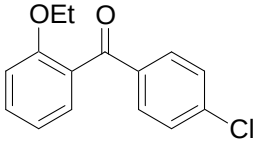
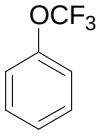
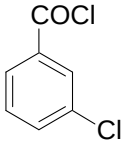
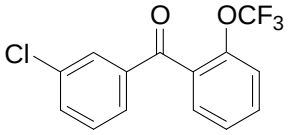
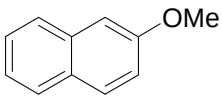
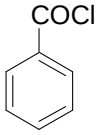
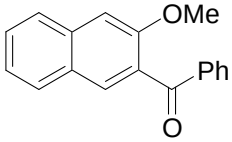
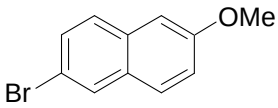
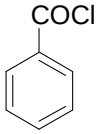
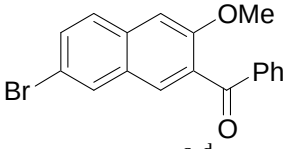
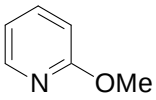
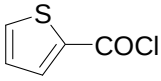
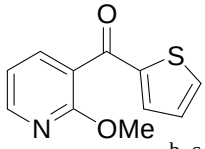
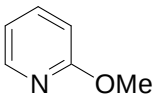
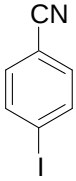
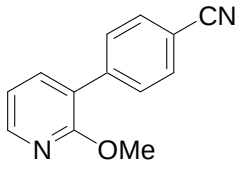
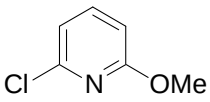
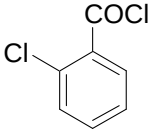
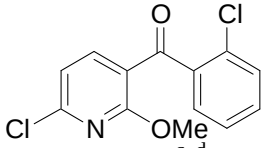
8.4 Metalation of Aromatic and Heterocyclic Ethers

Electron-rich aromatics are generally reluctant to undergo metalation reactions. Thus, aromatic ethers are poor *ortho*-directing groups for lithiations.[31a] Monometal Mg- and Zn-amides are unable to metalate such substrates at all. However, aluminum amides display a high metalation power, probably triggered by the strong complexiation of the aluminum to the ether oxygen. As noted above, the metalation of anisole (**115**) using **111** is completed within 9 h at 25 °C.[85] The reaction of the aluminated anisole **116** with $PhSSO_2Ph$ affords the thioether **129a** in 65% yield (Table 12, entry 1). Interestingly, the halogenated anisoles **102a,c** and **128a** are also regioselectively metalated at the *ortho* position next to the methoxy group within 4-8 h at 25 °C. An adjacent transmetalation to Zn followed by Cu-mediated trapping reactions[46] or Pd-catalyzed cross-coupling reactions[45] furnish the expected products **129b-e** in 73-85% yield (entries 2-5). Furthermore, the substituted anisoles **128b-d** are smoothly metalated within 2-15 h at 25 °C using **111** (1.0 equiv) without significant decomposition of the formed aryl-aluminum compound. The ketones **129f-h** are isolated in 77-83% yield after Cu-mediated acylations with different acid chlorides (entries 6-8). Additionally, phenetole (1**28e**) is aluminated within 10 h at 25 °C, whereas the metalation of *tri*-fluoro-methoxybenzene (**128f**) proceeds within 3 h at 0 °C. The subsequent reactions with various chlorobenzoyl chlorides in the presence of CuCN·2LiCl (1.1 equiv) lead to the benzophenones **129i-j** in 81-85% yield (entries 9-10). Alternatively, the naphthalene derivatives **128g-h** are readily converted into the corresponding aluminum reagents within 8-9 h at 25 °C. Subsequent acylations with benzoyl chloride in the presence of CuCN·2LiCl afford the ketones **129k-l** in 77-78% yield (entries 11-12). Moreover, 2-methoxypyridine (**128i**) and 6-chloro-2-methoxypyridine (**128j**) are aluminated within 3 h at 25 °C and 0 °C, respectively. After CuCN·2LiCl mediated acylations or Pd-catalyzed cross-coupling reaction using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol), the desired pyridines **129m-o** are obtained in 82-90% yield (entries 13-15). Interestingly, the use of aromatic or heteroaromatic ethers as metalating substrates allows performing the alumination reactions at *very convenient temperature* (0 °C or 25 °C). This may be a consequence of the complexiation of the aluminum center with the ether oxygen.

[85] $TMP_2Mg·2LiCl$ did not allow an efficient metalation of anisole and its derivatives. Unfortunately, *N*,*N*-dimethylaniline did not undergo an alumination using **111** at 25 °C.

Table 12: Products of type **129** obtained by the alumination of aromatics and heteroaromatics with **111** and subsequent reactions with electrophiles.

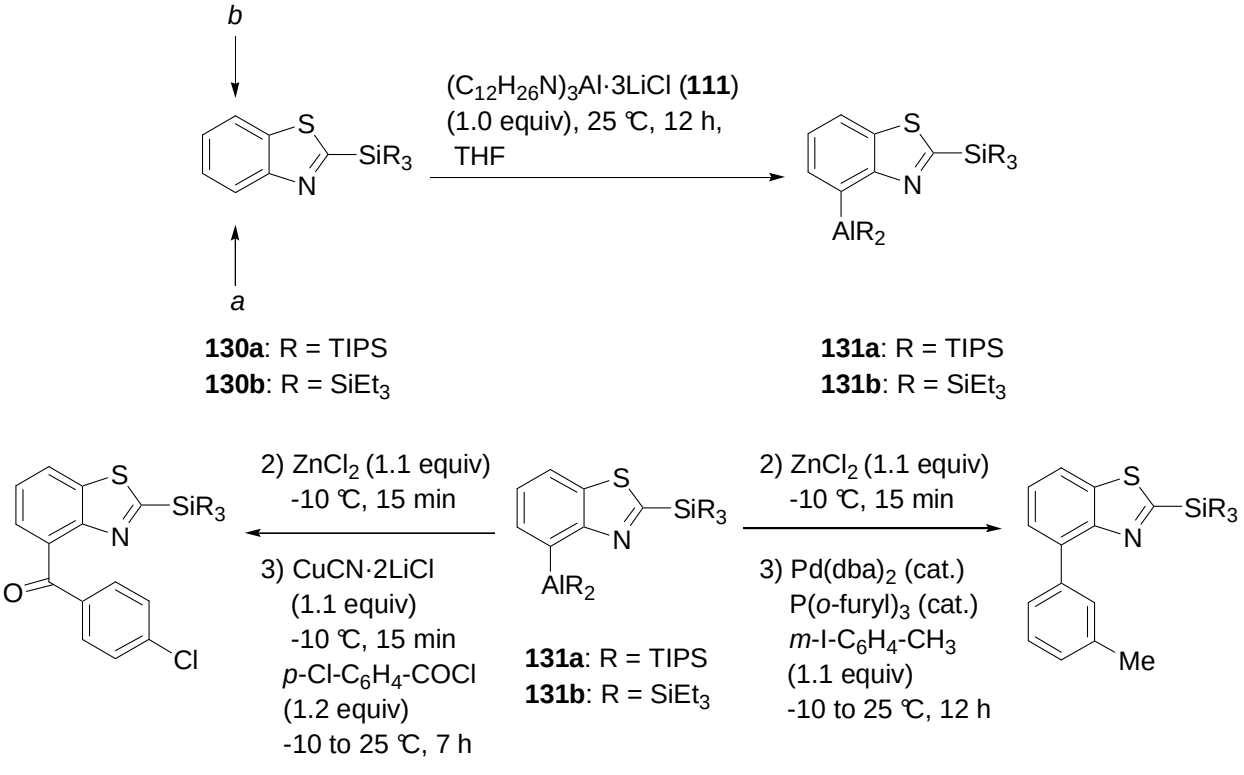
Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
			$PhSSO_2Ph$	
1	**115**	25, 9		**129a**: 65
				
2	**102a**	25, 4		**129b**: 85[c, d]
				
3	**102a**	25, 4		**129c**: 78[c, e]
				
4	**102c**	25, 5		**129d**: 77[c, e]
				
5	**128a**	25, 8		**129e**: 73[c, f]
				
6	**128b**	25, 2		**129f**: 83[c, e]
				
7	**128c**	25, 15		**129g**: 77[c, d]
				
8	**128d**	25, 6		**129h**: 79[c, d]

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
9	 **128e**	25, 10		 **129i**: 85[c, d]
10	 **128f**	0, 3		 **129j**: 81[c, d]
11	 **128g**	25, 9		 **129k**: 78[c, d]
12	 **128h**	25, 8		 **129l**: 77[c, d]
13	 **128i**	25, 3 (3.5)[b]		 **129m**: 85 (81)[b, c, d]
14	 **128i**	25, 3		 **129n**: 82[c, e]
15	 **128j**	3, 0		 **129o**: 90[c, d]

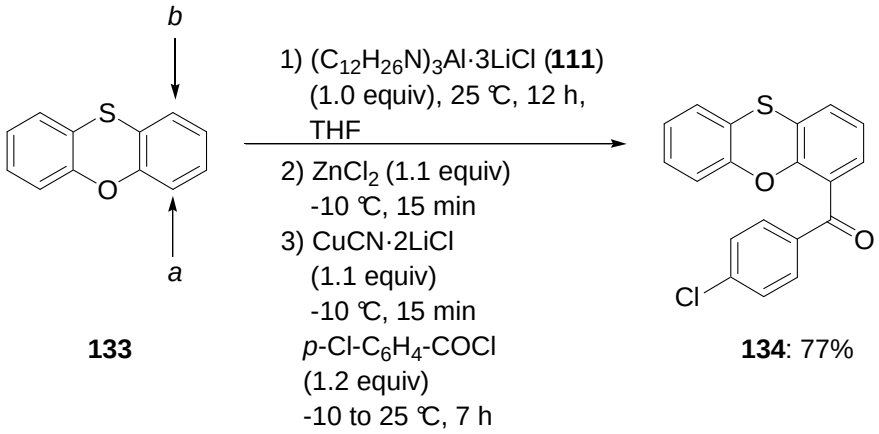
[a] Isolated yield of analytically pure product. [b] In parentheses the metalation times and isolated yields using $TMP_3Al \cdot 3LiCl$ (**108**) are given. [c] A transmetalation with $ZnCl_2$ (1.1 equiv) was performed. [d] A transmetalation with CuCN·2LiCl (1.1 equiv) was performed. [e] Obtained by Pd-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol-%) and P(*o*-furyl)$_3$ (10 mol-%). [f] A transmetalation with CuCN·2LiCl (5 mol-%) was performed.

8.5 Unusual Substitution Patterns

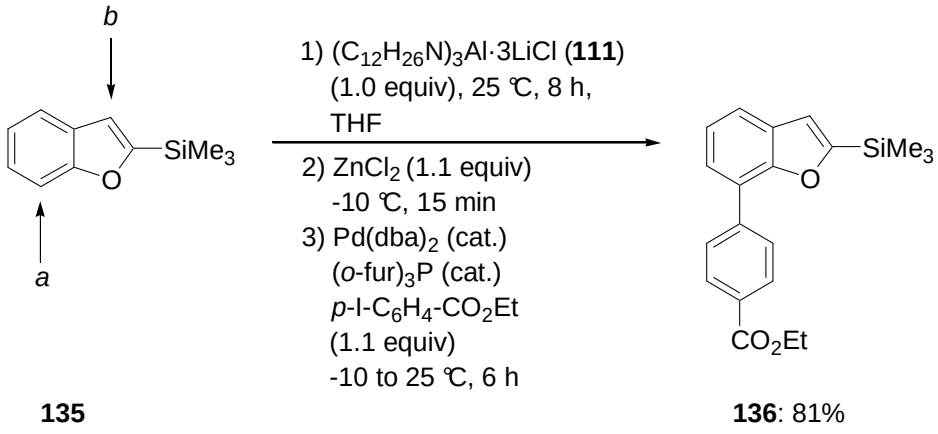
The highly regioselective alumination can be applied to create unusual substitution patterns on heteroaromatics. Thus, 2-TIPS-benzothiazole (**130a**) and 2-TES-benzothiazole (**130b**) may be either metalated in *ortho* position to nitrogen (position *a*) or in *ortho* position to sulphur (position *b*) (Scheme 41). Interestingly, both substrates are exclusively metalated in *ortho* position to nitrogen (position *a*) after 12 h at 25 °C using the base **111** (1.0 equiv) giving the corresponding aluminum reagents **131a-b**. After transmetalation to the zinc compounds and a Cu-mediated acylation[46] or Pd-catalyzed cross-coupling reaction[45] the functionalized benzothiazoles **132a** and **132b** are isolated in 81-83% yield. A related regioselectivity is observed when there is a competition between a metalation alpha to oxygen or sulphur. Thus, phenoxathiine (**133**) undergoes a smooth regioselective metalation within 12 h at 25 °C at the *ortho* position to oxygen leading after transmetalation and a Cu-mediated acylation to the ketone **134** in 77% yield (Scheme 42). Additionally, 2-TMS-benzofuran (**135**) is also efficiently converted to the aluminated species within 8 h at 25 °C using the highly regioselective base **111**. After transmetalation to zinc and a Pd-catalyzed cross-coupling with ethyl 4-iodobenzoate, the desired benzofuran derivative **136** is isolated in 79% yield (Scheme 43).



Scheme 41: Regioselective alumination of the benzothiazoles **130a** and **130b** using the aluminum base **111**.



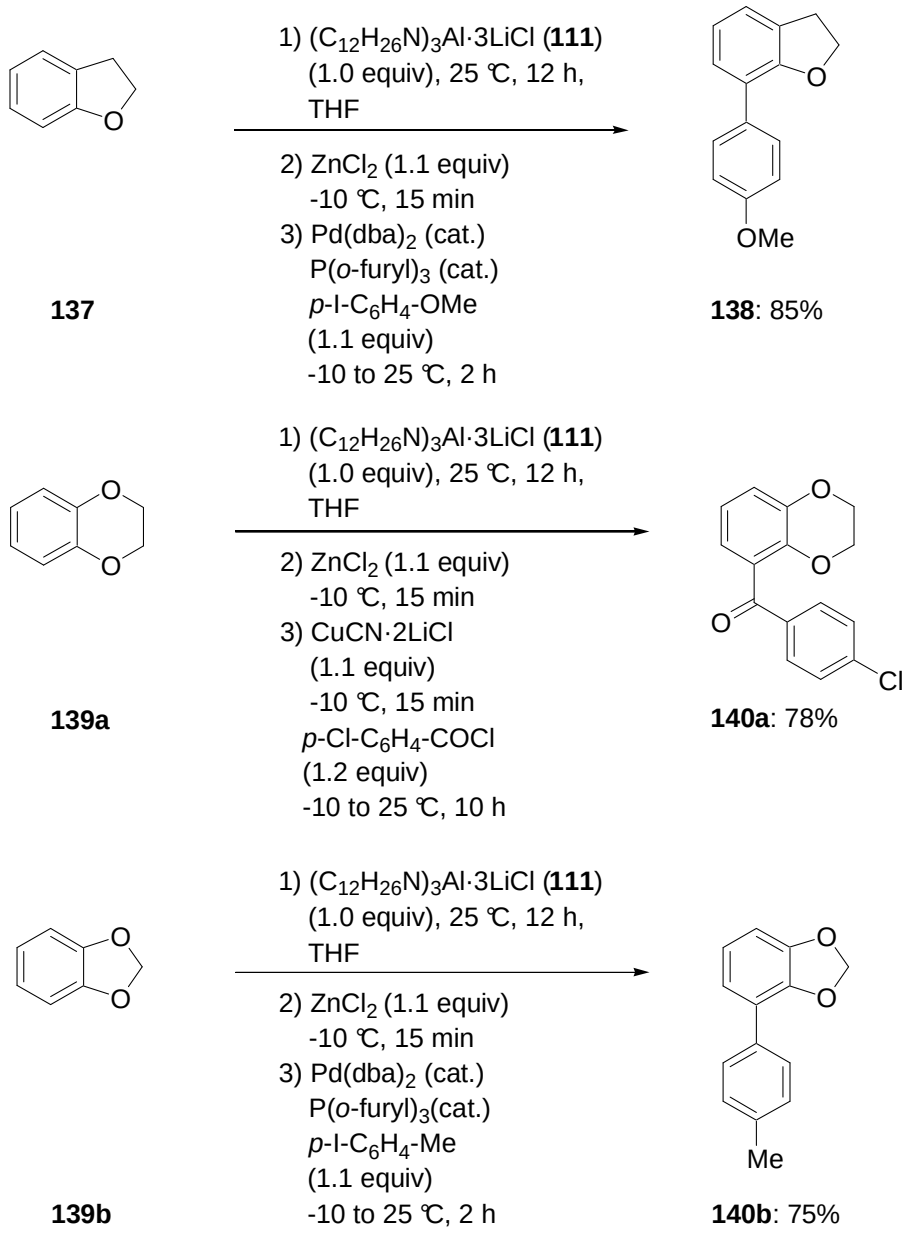
Scheme 42: Regioselective alumination of phenoxathiine (**133**) using the aluminum base **111**.



Scheme 43: Regioselective alumination of 2-TMS-benzofuran (**135**) using the aluminum base **111**.

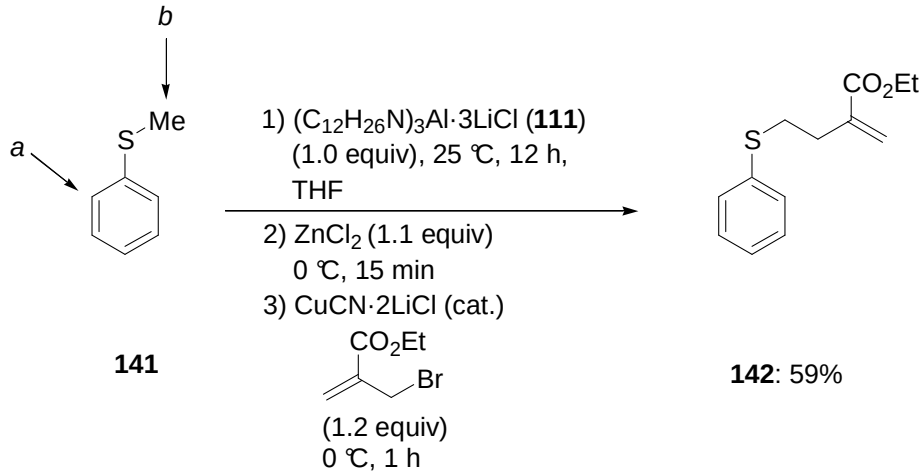
The metalation of substrates bearing partly saturated rings is sparely described.[86] However, the metalation of 2,3-dihydrobenzofuran (**137**) proceeds smoothly within 12 h at 25 °C and a Pd-catalyzed cross-coupling reaction furnishes the compound **138** in 85% yield (Scheme 44). Furthermore, the treatment of benzo[1,3]dioxole (**139a**) or benzo[1,4]dioxane (**139b**) with **4** (1.0 equiv) leads to an aluminated intermediate within 12 h at 25 °C. A subsequent transmetalation using $ZnCl_2$ and successive Cu-mediated acylation or Pd-catalyzed cross-coupling reaction provides the products **140a** and **140b** in 75-78% yield (Scheme 44).

[86] No directed metalation of substrates like **137** and **139a-b** were reported. Using Mg- or Zn-bases, no metalation was observed, neither for the substrates **131a-b** and **133**. For an alternative Br/Mg exchange, see: S. Ravi Kanth, G. Venkat Reddy, T. Yakaiah, B. Narsaiah, P. Shanthan Rao, *Synth. Commun.* **2006**, *36*, 3079.



Scheme 44: Alumination on substrates bearing annelated oxygen-containing rings.

Finally, the metalation of thioanisole (**141**) is accomplished within 15 h at 25 °C using the aluminum amide **111** (Scheme 45). Unfortunately, the metalation proceeds not regioselectively and lead to a 9:1 ratio of aluminated thioanisoles. Interestingly, the alumination mainly occurs at the methyl group outside of the aromatic system (position *b*). A transmetalation to Zn and a Cu(I)-catalyzed allylation[46] with ethyl 2-(bromomethyl)acrylate[55] affords the thioether **142** in 59% yield.



Scheme 45: Alumination of thioanisole (**141**) using the aluminum base **111**.

9 Directed Metalation of Aromatics and Heteroaromatics Using $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$

9.1 Introduction

Organolanthanum derivatives are relatively inexpensive and low-toxic organometallic intermediates.[87] They are usually prepared by transmetalation reactions starting from lithium or magnesium reagents as has been pioneered by Imamoto and continued by various researchers.[88] One drawback of this method is the insufficient solubility of the used lanthanide chlorides in THF. Recently, THF-soluble complexes such as $LaCl_3{\cdot}2LiCl$ or $CeCl_3{\cdot}2LiCl$ for the highly selective addition of Grignard reagents to hindered ketones and aldehydes has been reported.[89] The use of these additives dramatically reduces side reactions such as deprotonation of the acidic proton next to the carbonyl group or reduction of the carbonyl group. Moreover, these additions reactions of organomagnesium reagents can be carried out even with catalytic amounts of $LaCl_3{\cdot}2LiCl$.[90] Additionally, several lanthanum amides have been reported mainly for the performance of hydroamination reactions[91] or for structural studies.[92] Therefore, the preparation of a convenient (e. g. atom-economical, sufficient solubility, good tolerance towards functional groups) lanthanation reagent has been envisioned starting from TMPMgCl·LiCl (**40**).

---

[87] a) G. A. Molander, *Chem. Rev.* **1992**, *92*, 29; b) G. A. Molander, *Chem. Rev.* **1996**, *96*, 307; c) A. Knief, A. M. Laval, G. A. Molander, *Chem. Rev.* **1999**, *99*, 745; d) *Lanthanides: Chemistry and uses in Organic Synthesis*, (Ed.: S. Kobayashi), Springer-Verlag Berlin, Germany, **1999**; e) P. G. Steel, *J. Chem. Soc., Perkin Trans 1*, **2001**, 2727; f) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W. L. Lam, *Chem. Rev.* **2002**, *102*, 2227; g) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209.

[88] a) T. Imamoto, Y. Sugiyura, N. Takiyama, *Tetrahedron Lett.* **1984**, *25*, 4233; b) T. Imamoto, N. Takiyama, K. Nakamura, *Tetrahedron Lett.* **1985**, *26*, 4763; c) T. Imamoto, Y. Sugiyura, N. Takiyama, T. Hatojima, Y. Kamiya, *J. Am. Chem. Soc.* **1989**, *111*, 4392; d) H. Schumann, M. Glanz, J. Gottfriedsen, S. Dechert, D. Wolff, *Pure Appl. Chem.* **2001**, *73*, 279; e) V. Dimitrov, K. Koslova, M. Genov, *Tetrahedron Lett.* **1996**, *37*, 6787; f) C. Alcaraz, U. Groth, *Angew. Chem. Int. Ed.* **1997**, *36*, 2480; g) U. Groth, M. Jeske, *Angew. Chem. Int. Ed.* **2000**, *39*, 574; h) U. Groth, M. Jeske, *Synlett* **2001**, 129; i) S. Fischer, U. Groth, M. Jeske, T. Schutz, *Synlett* **2002**, 1922; j) W.-D. Z. Li, J.-H. Yang, *Org. Lett.* **2004**, *6*, 1849; k) D. Tsvelikhovsky, D. Gelman, G. A. Molander, J. Blum, *Org. Lett.* **2004**, *6*, 1995; l) M. Shenglof, D. Gelman, G. A. Molander, J. Blum, *Tetrahedron Lett.* **2003**, **44**, 8593; m) P. Eckenberg, U. Groth, T. Köhler, *Liebigs Ann. Chem.* **1994**, 673; n) M. Hatano, T. Matsuma, K. Ishkihara, *Org. Lett.* **2005**, *7*, 573; o) S. Fukuzawa, T. Fujinami, S. Yamauchi, S. Sakai, *J. Chem. Soc. Perkin Trans. 1* **1986**, 1929; p) F. T. Edelmann, D. M. M. Freckmann, H. Schumann, *Chem. Rev.* **2002**, *102*, 1851.

[89] A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497.

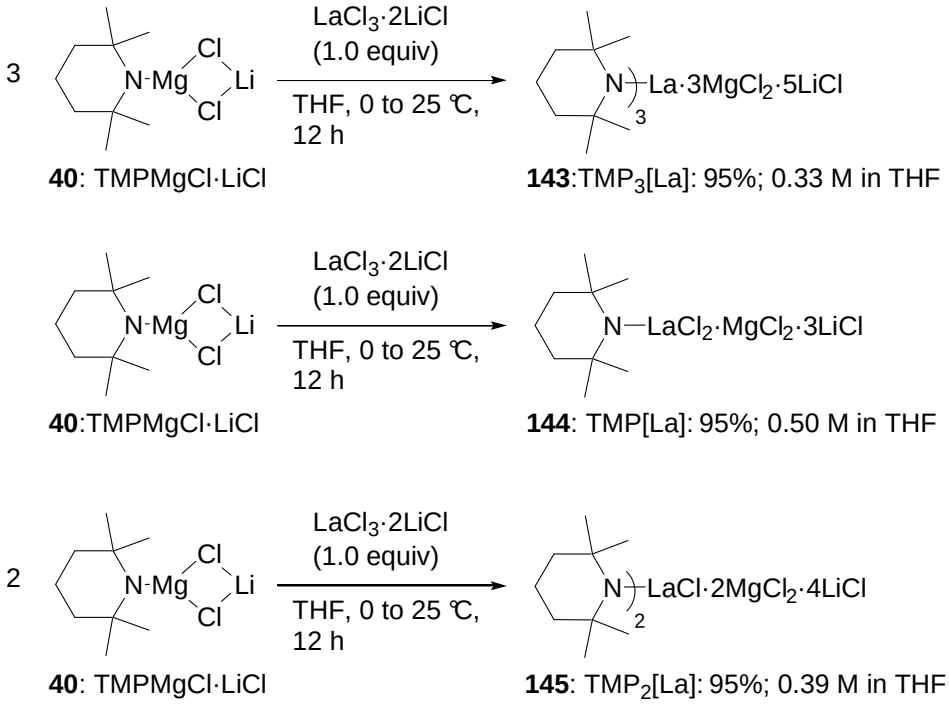
[90] A. Metzger, A. Gavryushin, P. Knochel, *Synlett* **2009**, 1433.

[91] a) J.-S. Ryu, G. Y. Li, T. J. Marks, *J. Am. Chem. Soc.* **2003**, *125*, 12584; b) I. Aillaud, J. Collin, C. Duhayon, R. Guillot, D. Lyubov, E. Schulz, A. Trifonov, *Chem. Eur. J.* **2008**, *14*, 2189; c) R. Liu, C. Zhang, Z. Zhu, J. Luo, X. Zhou, L. Weng, *Chem. Eur. J.* **2006**, *12*, 6940; d) Q. Shen, W. Huang, J. Wang, X. Zhou, *Organometallics* **2008**, *27*, 301.

[92] A) P. B. Hitchcock, Q.-G. Huang, M. F. Lappert, X.-H. Wei, *J. Mater. Chem.* **2004,** *14*, 3266; b) L. Ma, J. Zhang, R. Cai, Z. Chen, L. Wenig, X. Zhou, *J. Organomet. Chem.* **2005**, 4926; c) D. Cui, M. Nishiura, Z. Hou, *Angew. Chem. Int. Ed.* **2005**, *44*, 959; d) W. J. Evans, D. B. Rego, J. W. Ziller. *Inorg. Chem.* **2006**, *45*, 3437; e) Y. Wu, S. Wang, X. Zhu, G. Yang, Y. Wei, L. Zhang, H.-B. Song, *Inorg. Chem.* **2008**, *47*, 5503; f) C. Döhring, R. Kempe, *Eur. J. Inorg. Chem.* **2009**, 412.

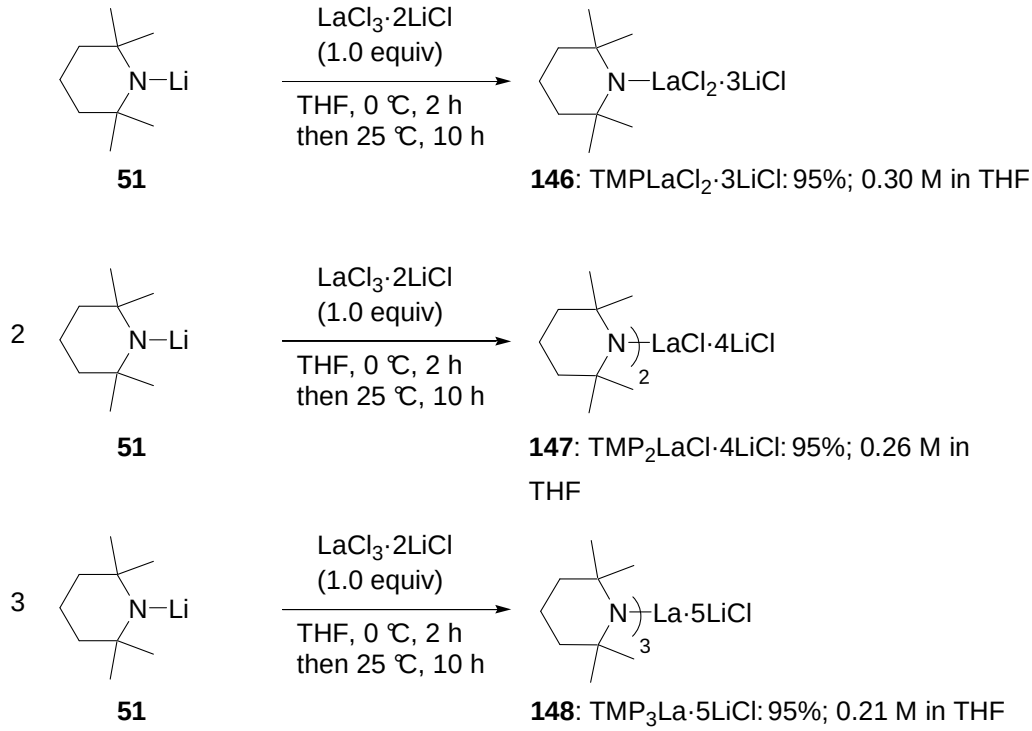
9.2 Preparation of the La-Bases

The probably most powerful base $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**) is readily prepared by the reaction of TMPMgCl·LiCl (**40**; 3.0 equiv) with the THF soluble complex $LaCl_3 \cdot 2LiCl$ in THF for 12 h. The resulting dark brown solution (0.33 M in THF; 95% yield as determined by titration) is stable under argon for at least 2 months without decomposition (Scheme 46). Additionally, the corresponding *mono*- and *bis*-amide lanthanum bases $TMPLaCl_2 \cdot MgCl_2 \cdot 3LiCl$ (**144**) and $TMP_2LaCl \cdot 2MgCl_2 \cdot 4LiCl$ (**145**) have been prepared *via* the same reaction sequence. These room temperature stable reagents appear as dark brown solutions with a concentration of 0.50 M and 0.39 M, respectively.



Scheme 46: Preparation of lanthanum-bases **143-145** derived from TMPMgCl·LiCl (**40**).

Alternatively, the *mono*-, *bis*- and *tris*-amide lanthanum bases are prepared by the reaction of freshly prepared TMPLi (**51**; 1-3 equiv) with $LaCl_3 \cdot 2LiCl$ (Scheme 47). After 2 h stirring at 0 °C followed by 10 h at 25 °C, the desired lanthanum amides **146-148** are quantitatively obtained as brown solutions in THF. These bases display a significant lower concentration than the corresponding lanthanum amides derived from TMPMgCl·LiCl (**40**). Hence, the presence of $MgCl_2$ in solution of lanthanum amides leads to better solubility.

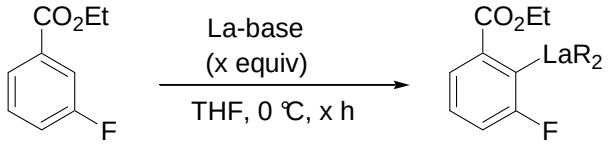


Scheme 47: Preparation of lanthanum-bases **146-148** derived from TMPLi (**51**).

First, the reactivity of the $MgCl_2$-containing La-amides **143-145** was investigated. Therefore, ethyl 3-fluorobenzoate (**57**) is reacted at 0 °C with $TMPLaCl_2 \cdot MgCl_2 \cdot 3LiCl$ (**145**; 1.1 equiv), $TMP_2LaCl \cdot 2MgCl_2 \cdot 4LiCl$ (**144**; 0.55 equiv) and $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.35 equiv). Interestingly, all three amide bases are able to deprotonate completely ethyl 3-fluorobenzoate (**57**) within 0.5-1 h without decomposition neither of the starting material nor the metalated species (Table 13, entries 1-3). The use of the $MgCl_2$-free amides **146-148** did not display fair metalation rates at all since none of theses bases lead to the desired metalated species **58** in significant amounts even if a large excess of the amide bases **147** and **148** was used (entries 4-9). When the metalation of **57** is carried out using the La-amides **146-148** at 25 °C, no starting material was left after 30 min, but no expected metalated species **58** could be identified due to possible polymerization reactions (entries 10-12). In conclusion, the presence of $MgCl_2$ is responsible for a better solubility in THF and therefore enormously enhanced metalation abilities of the amides **143-145** are obtained. Moreover, $MgCl_2$ certainly stabilizes the corresponding metalated arenes, since in the presence of $MgCl_2$ no significant disappearance of the metalated species **58** is observed within 2 h even at 25 °C. The new base **143** displays a good atom economy[93] since *all three TMP moieties* are consumed in the metalation progress.

[93] B. M. Trost, *Science* **1991**, 1471.

Table 13: Comparison of the reactivity of the amide bases **143-148**.



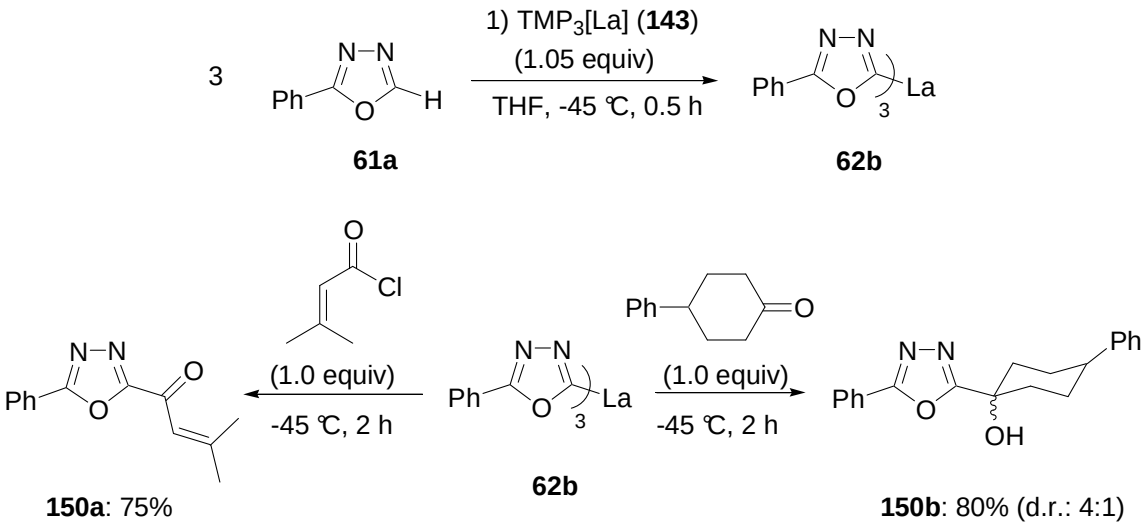
57 **149**

Entry	Base	Equiv	Time (h)	Conversion to **149** [%][a]
1	**143**	0.35	0.5	>95
2	**144**	0.55	0.75	>95
3	**145**	1.1	1	>95
4	**146**	1.1	1	<5
5	**147**	0.55	1	<5
6	**147**	1.1	1	<5
7	**148**	0.35	1	<5
8	**148**	0.55	1	<5
9	**148**	1.1	1	<5
10	**146**	1.1	0.5	0[b]
11	**147**	0.55	0.5	0[b]
12	**148**	0.35	0.5	0[b]

[a] The conversion to the corresponding metal species **149** was monitored *via* GC-analysis of aliquots of the reaction mixture quenched with allyl bromide in the presence of CuCN·2LiCl using tetradecane as internal standard. [b] The reaction was carried out at 25 °C.

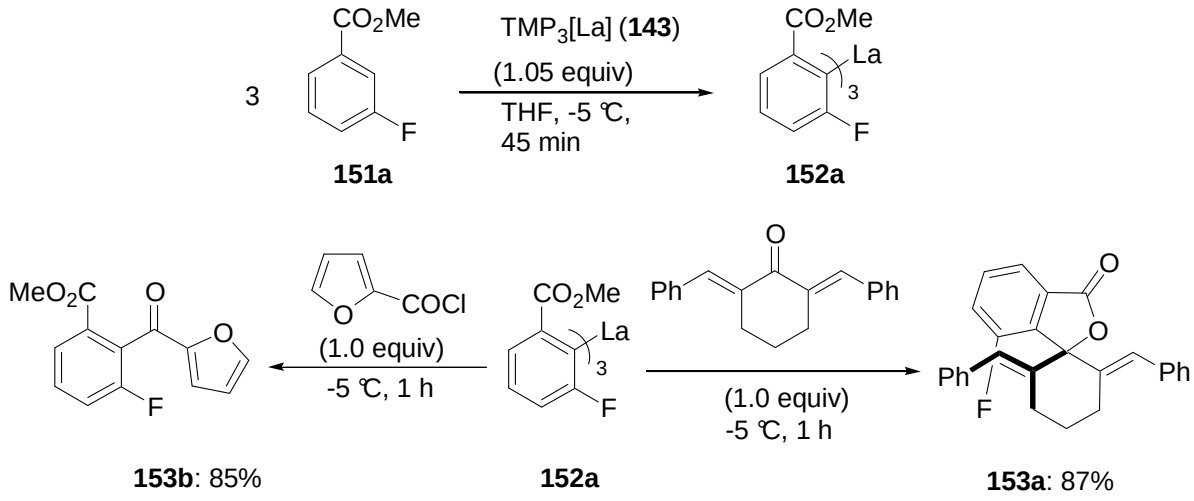
9.3 Preparation of Functionalized Organolanthanum Reagents

Starting from 2-phenyl-1,3,4-oxadiazole (**61a**), its reaction with TMP_3[La] (**143**; 0.35 equiv) in THF (–45 °C, 30 min) gives the desired metalated species **62b**. In contrast to the corresponding magnesiated or lithiated heterocycle, no fragmentation of this sensitive heterocycle resulting in the formation of benzonitrile is observed. Its quenching with 3,3-dimethyl acryloyl chloride (1.1 equiv, –45 °C, 1 h) provides the ketone **150a** in 75% yield (Scheme 48). Remarkably, no further addition of **62b** to **150a** has been observed. Alternatively, the reaction of **62b** with 4-phenylcyclohexanone (1.0 equiv, –45 °C, 1 h) leads to the desired tertiary alcohol **150b** in 80% yield.



Scheme 48: Metalation of 2-phenyl-1,3,4-oxadiazole (**61a**) with $TMP_3[La]$ (**143**) and its reaction with a ketone and an acid chloride.

Aromatic methyl ester can also used for this metalation procedure without special precautions. Thus, the reaction of methyl 3-fluorobenzoate (**151a**) with $TMP_3[La]$ (**143**, 0.35 equiv) in THF at –5 °C (45 min) affords the triaryllanthanum species **152a**. This lanthanum reagent readily reacts with hindered carbonyl derivatives such as 2,6-dibenzylidenecyclohexanone (1.0 equiv, –5 °C, 1 h) giving the spirolactone **153d** in 87% yield (Scheme 49). Similarly, the reaction of **152a** with 2-furoyl chloride (1.1 equiv, –5 °C, 1 h) smoothly leads to the ketone **153e** in 85% yield.

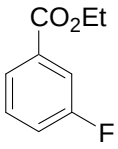
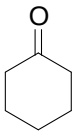
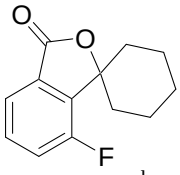
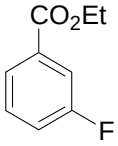
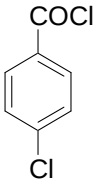
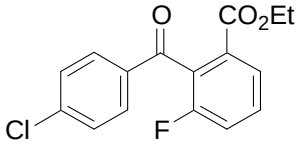
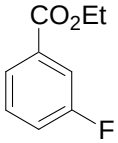
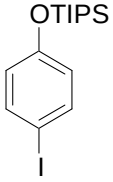
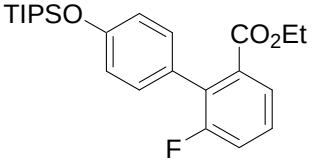
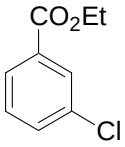
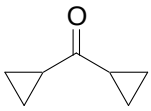
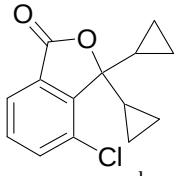
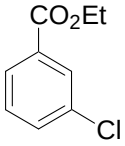
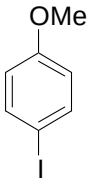
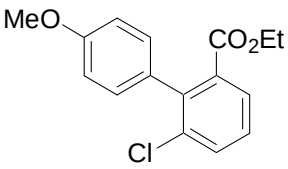
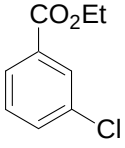
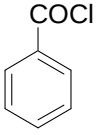
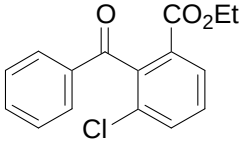
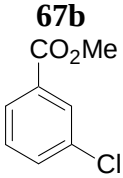
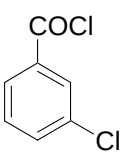
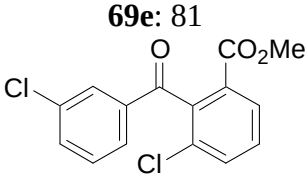


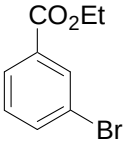
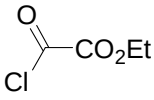
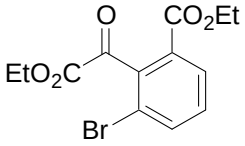
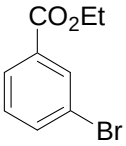
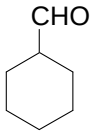
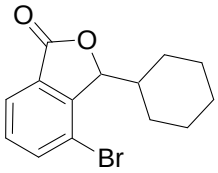
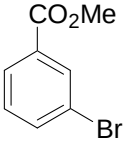
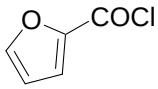
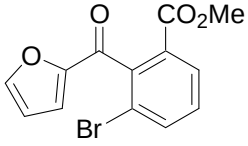
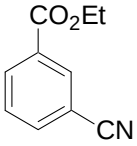
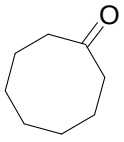
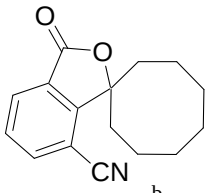
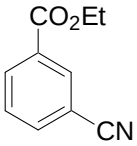
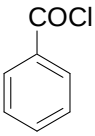
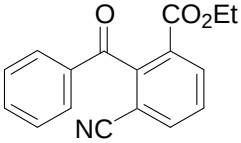
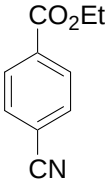
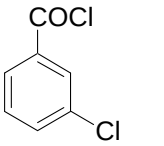
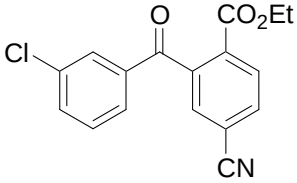
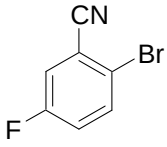
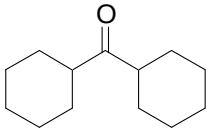
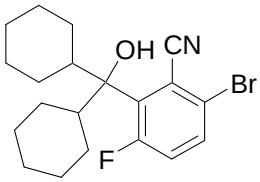
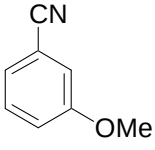
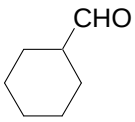
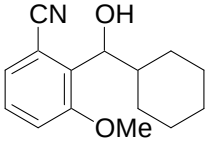
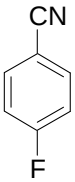
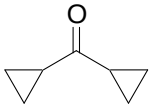
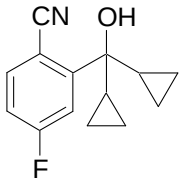
Scheme 49: Typical metalation conditions of a functionalized arene such as **151a** with $TMP_3[La]$ (**143**) and its reaction with a hindered ketone or an acid chloride.

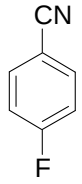
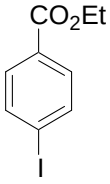
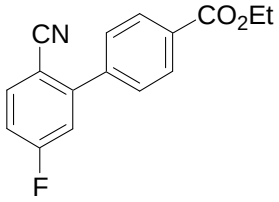
As already noted above, the metalation of ethyl 3-fluorobenzoate (**57**) using TMP_3[La] (**143**; 0.35 equiv) is finished within 30 min at 0 °C giving the corresponding lanthanum reagent **149**. Its reaction with cyclohexanone (activated prior to the addition with $LaCl_3{\cdot}2LiCl$ (0.25 equiv) gives the spiro compound **153a** in 82% yield, whereas the reactions with 4-chlorobenzoyl chloride provides the benzophenone **153b** in 88% yield (Table 14, entries 1-2). Interestingly, triaryllanthanum species undergo Pd-catalyzed cross-coupling reactions without the need of any additional transmetalation. Thus, the lanthanum species **149** reacts directly with (4-iodo-phenoxy)-triisopropyl-silane in the presence of $Pd(PPh_3)_4$ (2.5 mol-%) giving the biphenyl **153c** in 79% yield (entry 3). Furthermore, the metalation of ethyl 3-chlorobenzoate (**67b**) proceeds within 3.5 h at 0 °C, and the reaction with dicyclopropyl ketone (activated prior to the addition with $LaCl_3{\cdot}2LiCl$ (0.25 equiv)) leads to the lactone **153f** in 69% yield (entry 4). Alternatively, a cross-coupling of lanthanated ethyl 3-chlorobenzoate (**67b**) with 4-iodoanisole using $Pd(PPh_3)_4$ (2.5 mol-%) affords the biphenyl **153g** in 75% yield, whereas the benzophenone **69e** is isolated in 81% yield after the reaction with benzoyl chloride (entries 5-6). Additionally, the metalation of methyl 3-chlorobenzoate (**100c**) is accomplished within 3.5 h at 0 °C and the benzophenone **153h** is obtained in 84% yield after the acylation with 3-chlorobenzoyl chloride (entry 7). Moreover, ethyl 3-bromobenzoate (**100b**) can be converted into the lanthanted species **152d** within 2.5 h at 25 °C and the subsequent reactions with either ethyl oxalyl chloride or cyclohexane carbaldehyde furnish the products **153i-j** in 67-79% yield (entries 8-9). Similarly, methyl 3-bromobenzoate (**151b**) is also fully metalated within 2.5 h at 25 °C using TMP_3[La] (**143**; 0.35 equiv) and the following reaction with 2-furoyl chloride (1.1 equiv, –5 °C, 1 h) provides the ketone **153k** in 58% yield (entry 10). Furthermore, ethyl 3-cyanobenzoate (**67i**) is regioselectively metalated at position 2 within 1.25 h at 0 °C. After the reaction with cyclooctanone (activated prior to the addition with $LaCl_3{\cdot}2LiCl$ (0.25 equiv)), the spirolactone **153l** is isolated in 74% yield (entry 11), whereas the reaction with benzoyl chloride afford the expected ketone **69h** in 85% yield (entry 12). Additionally, the lanthanation of ethyl 4-cyanobenzoate (**67j**) proceeds smoothly within 3 h at –25 °C and the reaction with 3-chlorobenzoyl chloride provides the ketone **153m** in 68% yield (entry 13). Furthermore, 2-bromo-5-fluorobenzonitrile (**67o**) is converted into the lanthanum species **152h** within 30 min at –35 °C. Its reaction with dicyclohexyl ketone leads to the tertiary alcohol **153n** in 66% yield (entry 14). 3-Methoxybenzonitrile (**151c**) is readily lanthanated at position 2 within 1.5 h at 25 °C and the reaction with cyclohexane carbaldehyde furnishes the product **153o** in 74% yield (entry 15). Additionally, the metalation of 4-fluorobenzonitrile (**67k**) is accomplished within 1 h at 0 °C giving the triaryllanthanum species **152j**. The alcohol **153p** is obtained in

77% yield after the addition of **152j** to dicyclopropyl ketone whereas the cross-coupling product **153q** is isolated in 73 % yield using $Pd(PPh_3)_4$ (2.5 mol-%) and ethyl 4-iodobenzoate (entries 16-17).

Table 14: Lanthanation of aromatics using TMP_3[La] (**143**) and reactions with electrophiles.

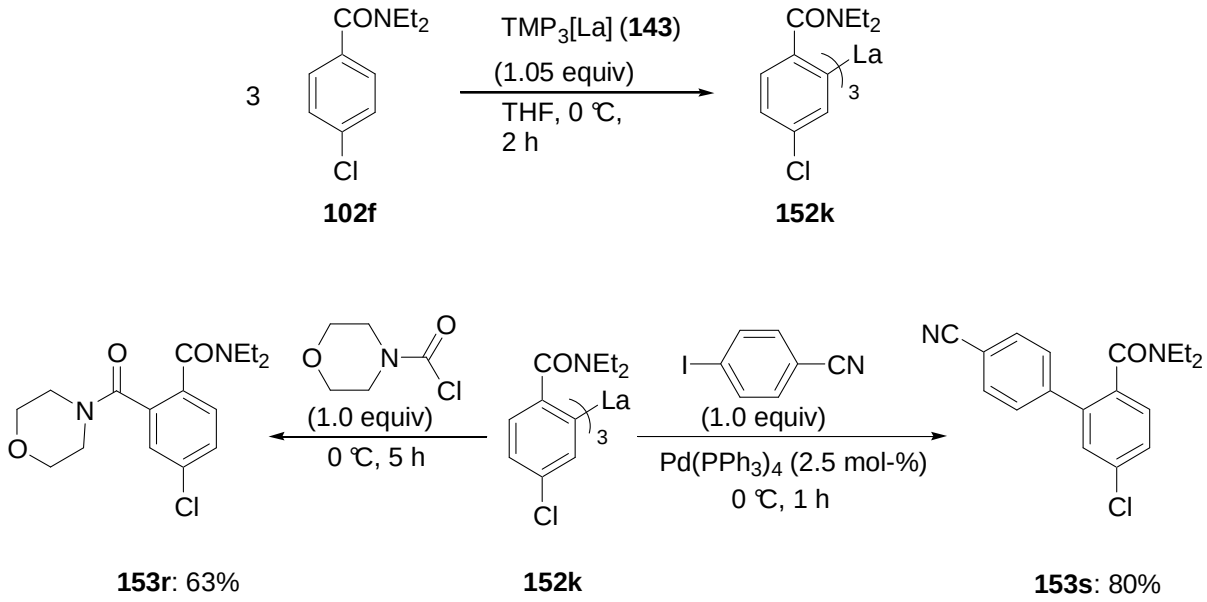
Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
1	 **57**	0, 0.5		 **153a**: 82[b]
2	 **57**	0, 0.5		 **153b**: 88
3	 **57**	0, 0.5		 **153c**: 79[c]
4	 **67b**	0, 3.5		 **153f**: 69[b]
5	 **67b**	0, 3.5		 **153g**: 75[c]
6	 **67b**	0, 3.5		 **69e**: 81
7	 **100c**	0, 3.5		 **153h**: 84

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
8	 **100b**	25, 2.5		 **153i**: 67
9	 **100b**	25, 2.5		 **153j**: 79
10	 **151b**	25, 2		 **153k**: 58
11	 **67i**	0, 1.25		 **153l**: 74[b]
12	 **67i**	0, 1.25		 **69h**: 85
13	 **67j**	–25, 3		 **153m**: 68
14	 **67o**	–35, 0.5		 **153n**: 66
15	 **151c**	25, 1.5		 **153o**: 74
16	 **67k**	0, 1		 **153p**: 77

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
17	 **67k**	0, 1		 **153q**: 73[c]

[a] Isolated yield of analytically pure product. [b] $LaCl_3 \cdot 2LiCl$ (0.25 equiv) was used. [c] $Pd(PPh_3)_4$ (2.5 mol-%) was used.

Finally, the lanthanation of 4-chloro-*N*,*N*-diethylbenzamide (**102f**) proceeds smoothly within 2 h at 0 °C and the subsequent reactions like an acylation using morpholine-4-carbonyl chloride or a Pd-catalyzed cross-coupling with 4-iodobenzonitrile afford substituted benzamides **153r-s** in 63-80% yield (Scheme 50).

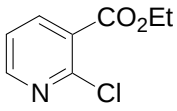
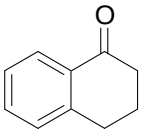
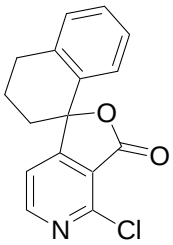
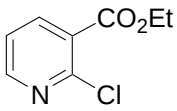
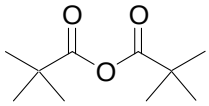
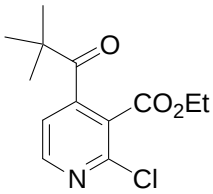
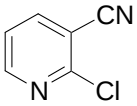
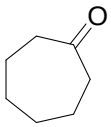
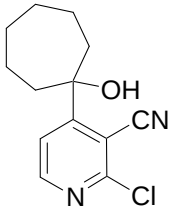
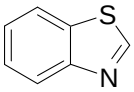
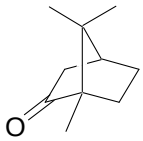
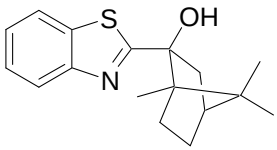
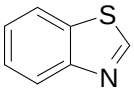
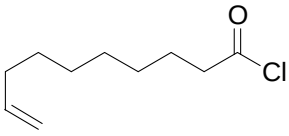
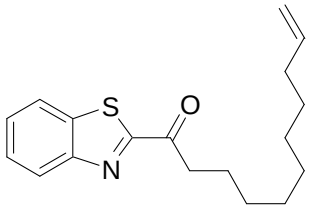


Scheme 50: Lanthanation of **102f** with TMP_3[La] (**143**) and its reaction with an acid chloride or an aryl iodide in the presence of $Pd(PPh_3)_4$.

The metalation of both electron-rich and electron-poor heterocycles can also be performed. Thus, the reaction of ethyl 2-chloronicotinate (**64g**) with TMP_3[La] (**143**) gives the fully metalated species **152l** within 45 min at –20 °C. The lactone **154t** is obtained in 74% yield after quenching with α-tetralone (Table 15, entry 1). Surprisingly, the addition of **152l** to the sterically hindered anhydride leads to the *tert*-butyl ketone **154u** in 85% yield (entry 2). Additionally, 2-chloro-3-cyanopyridine (**151d**) undergoes a smooth metalation at –30 °C within 45 min and the adjacent reaction with cycloheptanone furnishes the tertiary alcohol

154v in 71% yield (entry 3). Thus, the metalation of benzothiazole (**61f**) proceeds smoothly within 30 min at 0 °C. The subsequent reactions with camphor or an acid chloride furnish the products **154w-x** in 77-83% yield (entries 4-5).

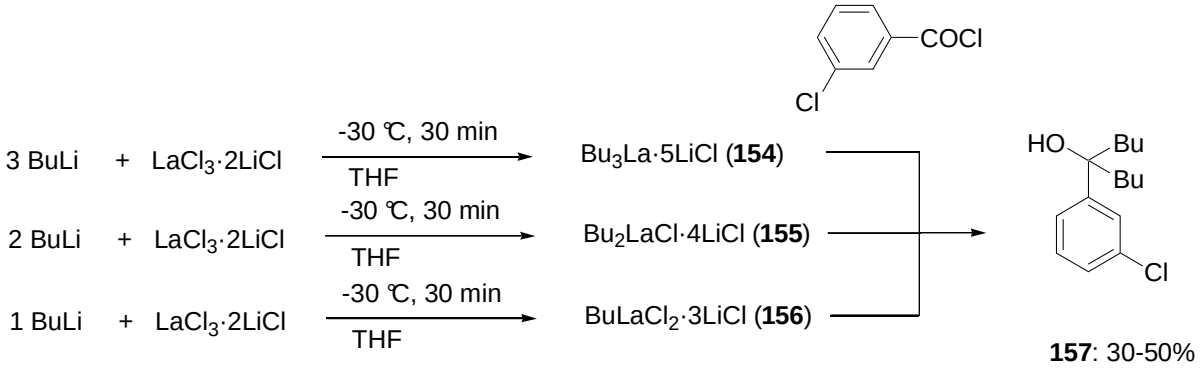
Table 15: Lanthanation of heteroaromatics using $TMP_3[La]$ (**143**) and reactions with electrophiles.

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
1	 **64g**	–20, 0.75		 **153t**: 74
2	 **64g**	–20, 0.75		 **153u**: 85
3	 **151d**	–30, 0.75		 **153v**: 71
4	 **61f**	0, 0.5		 **153w**: 83
5	 **61f**	0, 0.5		 **153x**: 77

[a] Isolated yield of analytically pure product.

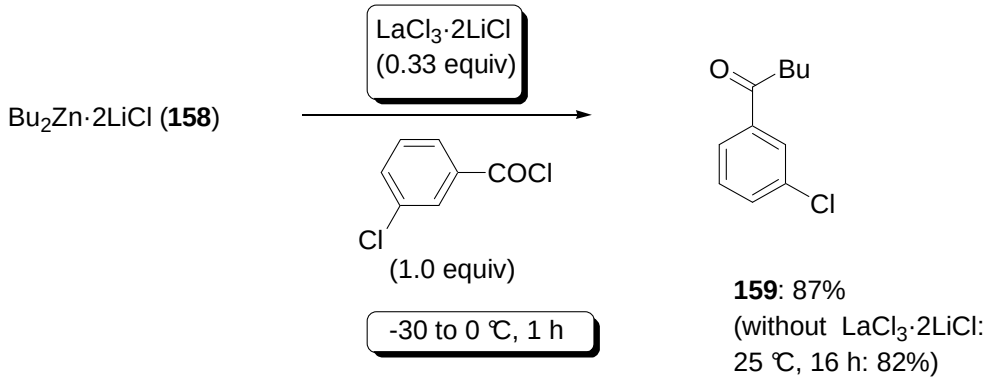
9.4 Preliminary Experiments for the La-Catalyzed Acylation of Organozinc Reagents

Although there are numerous methods reported for the preparation of ketones derived from organometallics,[94] a general procedure involving lanthanum reagents and/or catalysis has not been described so far. Based on the convenient direct acylation of lanthanum reagents, the preparation of ketones catalyzed by $LaCl_3 \cdot 2LiCl$ has been investigated. Thus, the reaction of *n*BuLi with $LaCl_3 \cdot 2LiCl$ (0.33; 0.50; 1.0 equiv) leads to the tentative lanthanum reagents **154-156** within 30 min at –30 °C (Scheme 51). Their reaction with 3-chlorobenzoyl chloride only ends in the formation of the tertiary alcohol **157** in 30-50% yield within 30 min at –30 °C.



Scheme 51: Reaction of the lanthanum reagents **154-156** with 3-chlorobenzoyl chloride.

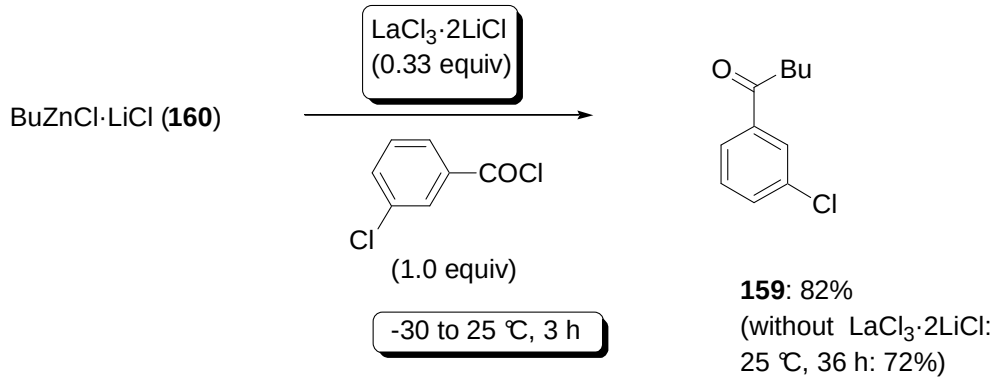
In contrast, by using the zinc reagent $Bu_2Zn \cdot 2LiCl$ (**158**; obtained by the reaction of *n*BuLi with 0.5 equiv $ZnCl_2$, see Experimental Part) the desired ketone **159** is provided in 87% yield after a smooth $LaCl_3 \cdot 2LiCl$ (33 mol-%) catalyzed acylation reaction with 3-chlorobenzoyl chloride within 1 h at –30 °C. Interestingly, in the absence of $LaCl_3 \cdot 2LiCl$, this product **159** is isolated in 82% yield after 16 h at 25 °C (Scheme 52).



Scheme 52: Preparation of the ketone **159** derived from $Bu_2Zn \cdot 2LiCl$ (**158**).

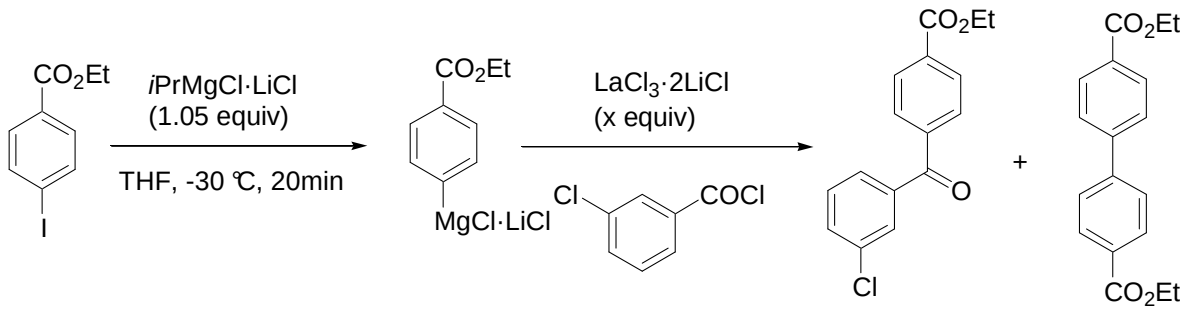
[94] For an excellent overview, see: R. K. Dieter, *Tetrahedron* **1999**, *55*, 4177.

Moreover, the use of the related zinc reagent BuZnCl·LiCl (**160**; obtained by the reaction of *n*BuLi with 1.0 equiv $ZnCl_2$, see Experimental Part) displays a considerably longer reaction time for the formation of **159**. Thus, the $LaCl_3 \cdot 2LiCl$ (33 mol-%) catalyzed acylation with 3-chlorobenzoyl chloride proceeds within 3 h with simultaneous warming the reaction mixture from –30 °C to 25 °C and gives the ketone **159** in 82% yield. The absence of $LaCl_3 \cdot 2LiCl$ leads to this product **159** within 36 h at 25 °C in only 72% yield (Scheme 53).



Scheme 53: Preparation of the ketone **159** derived from BuZnCl·LiCl (**160**).

Furthermore, the reaction of the Grignard reagent **161** (prepared *via* iodine/magnesium exchange reaction at –30 °C within 20 min, see Experimental Part) with 3-chlorobenzoyl chloride in the absence of $LaCl_3 \cdot 2LiCl$ affords the expected benzophenone **162** in 52% yield within 2 h at –30 °C, whereas the $LaCl_3 \cdot 2LiCl$ (33 mol-%) catalyzed reaction leads under similar conditions only to 25% of the desired product **162** and 57% of the biphenyl **163** obtained by a homo-coupling reaction of the magnesiated species **161** (Scheme 54).

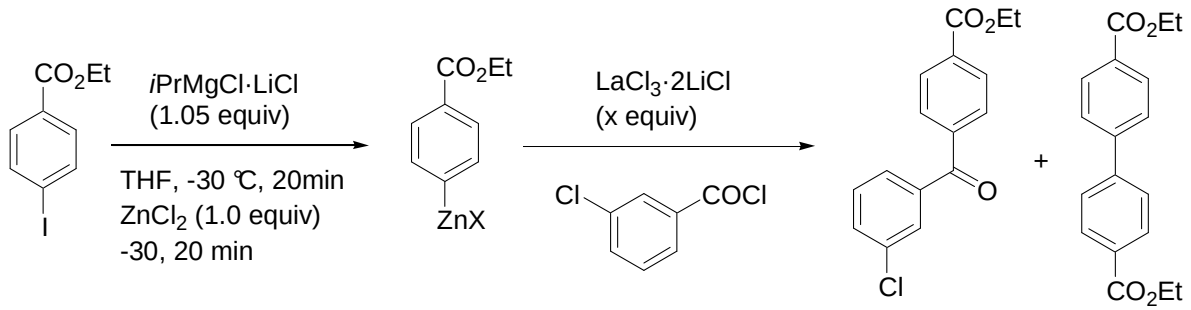


161

	162	**163**
0 equiv $LaCl_3 \cdot 2LiCl$:	52%	21%
0.33 equiv $LaCl_3 \cdot 2LiCl$:	25%	57%

Scheme 54: Reaction of the Grignard reagent **161** with 3-chlorobenzoyl chloride.

The transmetalation of the Grignard reagent **161** to the corresponding Zn species **164** now allows the access to the desired benzophenone in good yield. Whereas the reaction of the zinc reagent **164** with 3-chlorobenzoyl chloride in the absence of $LaCl_3 \cdot 2LiCl$ gives only 20% of the desired product **162**, the benzophenone **162** is obtained in 85% yield in the presence of $LaCl_3 \cdot 2LiCl$ (33 mol-%) without significant amounts of the homo-coupling product **163** (Scheme 55).



	162	**163**
0 equiv $LaCl_3 \cdot 2LiCl$:	20%	5%
0.33 equiv $LaCl_3 \cdot 2LiCl$:	85%	>3%

Scheme 55: $LaCl_3 \cdot 2LiCl$-catalyzed preparation of the benzophenone **162**.

10 Directed Manganation of Functionalized Aromatics and Heterocycles Using $TMP_2Mn·2MgCl_2·4LiCl$

10.1 Introduction

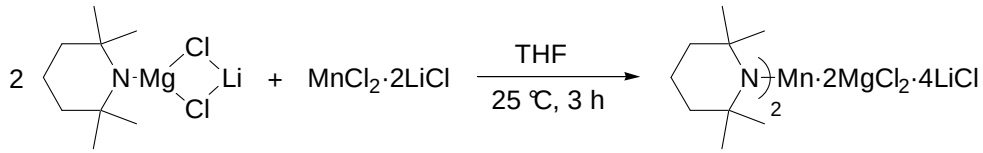
The preparation of metalated arenes and heteroarenes using transition metal amides has been sparely described although transition metals display reactivity pattern not accessible for main-group elements.[95] Especially manganese due to its low price, moderate toxicity and versatile reactivity ("soft Grignard reagents") is of synthetic interest.[96] *Cahiez* reported the use of manganese amides for the selective preparation of enolates and highly diastereoselective aldol-reactions.[97] Moreover, the transmetalation of Li- or Mg-reagents with $MnCl_2·2LiCl$ allows performing the reactions with acid chlorides with enhanced rates.[98] Additionally, manganese reagents are especially interesting since manganese reagents undergo various Pd- or Cu-catalyzed cross-coupling reactions and manganese itself can catalyze cross-coupling reaction.[96] Recently, *Mulvey* showed the smooth deprotonation of aromatics using a tmeda-stabilized manganate base.[99] Therefore, the development of a convenient (e.g. neutral) manganese amide base for the efficient deprotonation of aromatics and heteroaromatics has been started

10.2 Preparation of the Base

According to previously discussed zinc and lanthanum amide bases, the preparation of the desired Mn-base has been started using TMPMgCl·LiCl (**40**). Thus, the addition of freshly prepared TMPMgCl·LiCl (**40**; 2.0 equiv) to $MnCl_2·2LiCl$ (1.0 equiv) at 0 °C followed by 3 h of stirring at 25 °C, furnishes the manganese amide **165** as a 0.50 M dark red solution in THF

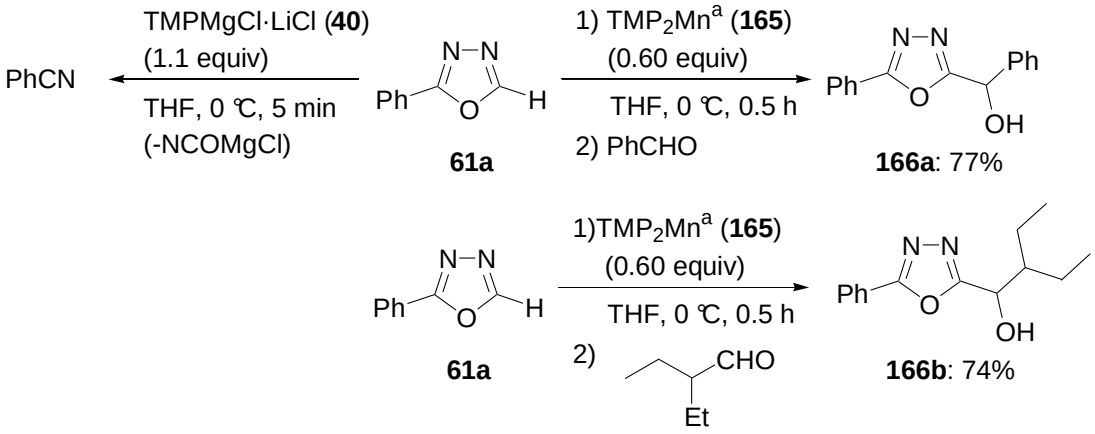
[95] B. Weidmann, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31.
[96] For reviews see: a) J. F. Normant, G. Cahiez, *Modern Synthetic Methods* (Ed.: R. Scheffold), John Wiley and Sons, Inc.: Chichester, U.K., **1983**; Vol. 3, p 173; b) K. Oshima, *J. Organomet. Chem.* **1999**, *575*, 1; c) H. Shinokubo, K. Oshima, *Eur. J. Org. Chem.* **2004**, 2081; d) J. M. Concellón, H. Rodríguez-Solla, V. del Amo, *Chem. Eur. J.* **2008**, *14*, 10184; e) G. Cahiez, C. Duplais, J. Buendia, *Chem. Rev.* **2009**, *109*, 1434.
[97] a) G. Cahiez, B. Figadère, P. Tozzolino, Eur. Patent 373993, **1990**; b) G. Cahiez, B. Figadère, P. Tozzolino, *Chem. Abstr.* **1991**, *114*, 61550; c) G. Cahiez, P. Cléry, J. A. Lafitte, Int. Patent 9306071, **1993**; d) G. Cahiez, P. Cléry, J. A. Lafitte, *Chem. Abstr.* **1993**, *118*, 169340.
[98] G. Cahiez, A. Masuda, D. Bernard, J. F. Normant, *Tetrahedron Lett.* **1976**, *36*, 3155.
[99] a) L. M. Carrella, W. Clegg, D. V. Graham, L. M. Hogg, A. R. Kennedy, J. Klett, R. E. Mulvey, E. Rentschler, L. Russo, *Angew. Chem. Int. Ed.* **2007**, *46*, 4662; b) V. L. Blair, W. Clegg, B. Conway, E. Hevia, A. Kennedy, J. Klett, R. E. Mulvey, L. Russo, *Chem. Eur. J.* **2008**, *14*, 65; c) V. L. Blair, L. M. Carrella, W. Clegg, B. Conway, R. W. Harrington, L. M. Hogg, J. Klett, R. E. Mulvey, E. Rentschler, L. Russo, *Angew. Chem. Int. Ed.* **2008**, *47*, 6208; d) V. L. Blair, L. M. Carrella, W. Clegg, J. Klett, R. E. Mulvey, E. Rentschler, L. Russo, *Chem. Eur. J.* **2009**, *15*, 856.

(Scheme 56).[100] The base **165** has an excellent thermal stability and can be stored at 25 °C for more than 4 months without appreciable decomposition. Preliminary experiments show immediately that the new Mn-base has a very different reactivity compared to TMPMgCl·LiCl (**40**). Thus, the reaction of TMPMgCl·LiCl (**40**) with 2-phenyl-1,3,4-oxadiazole (**61a**) at 0 °C leads only to ring fragmentation products (PhCN and NCOMgCl). Similar to the described Zn- and La-base, the metalation of **61a** using $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**165**) furnishes cleanly the corresponding diheteroarylmanganese reagent which smoothly reacts with an aromatic aldehyde (benzaldehyde) or an aliphatic aldehyde bearing an acidic proton (2-ethyl butanal) giving the alcohols **166a-b** in 74-77% yield (Scheme 56).[101]



40: TMPMgCl·LiCl

165: $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$: >95%
c = 0.50 mol/L

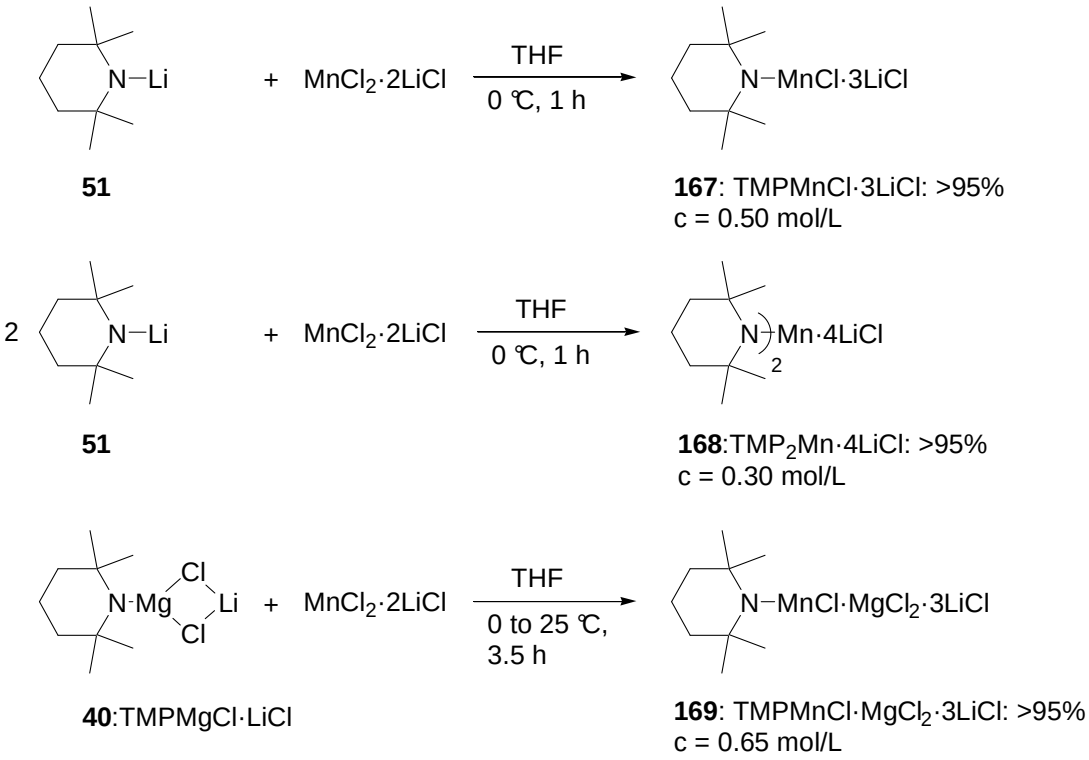


Scheme 56: Preparation and reactivity of TMP_2Mn (**165**)[a] compared to TMPMgCl·LiCl (**40**). [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

To confirm the composition of the reagent $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**165**), 3 additional Mn-bases have been prepared. Thus, the reaction of freshly prepared TMPLi (**51**) with either $MnCl_2 \cdot 2LiCl$ (1.0 equiv) or $MnCl_2 \cdot 2LiCl$ (0.50 equiv) at 0 °C furnishes the amide bases TMPMnCl·3LiCl (**167**) and $TMP_2Mn \cdot 4LiCl$ (**168**), respectively within 1 h (Scheme 507). Additionally, the reaction of TMPMgCl·LiCl (**40**) with $MnCl_2 \cdot 2LiCl$ (1.0 equiv) at 0 °C

[100] The preparation of this base without LiCl as additive is not convenient, since it is already necessary to provide a THF-soluble manganese source.
[101] a) G. Cahiez, B. Figadère, *Tetrahedron Lett.* **1986**, *27*, 4445.

followed by 3 h of stirring at 25 °C leads to the reagent $TMPMnCl{\cdot}MgCl_2{\cdot}3LiCl$ (**169**; Scheme 57). All 3 bases could be obtained in >95% yield.



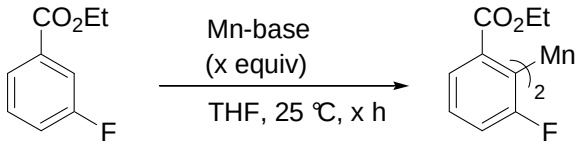
Scheme 57: Preparation of the Mn-bases **167-169**.

As shown in Scheme 56 and Scheme 57, the concentration of the $MgCl_2$-containing amide bases **165** and **169** is significantly higher than the concentration of the bases derived *via* transmetalation of TMPLi (**51**). Although the solvents of the bases **167-168** were completely removed, the concentration of the redissolved residue (in THF) was determined to be 0.50 M for the base **167** and 0.30 M for the base **168**, respectively. Subsequently, the metalation ability of all four bases has been investigated using ethyl 3-fluorobenzoate (**57**) a model substrate.

Thus, the amide base **167** displays the worst metalation ability since only 50% conversion to **170a** is observed after 5 h at 25 °C (Table 16, entry 1). In contrast, the use of $TMPMnCl{\cdot}MgCl_2{\cdot}3LiCl$ (**169**) leads to the fully metalated species **170a** within 5 h at 25 °C (entry 2). Under similar conditions, the manganation of **57** using the *bis*-TMP base **168** (0.6 equiv) furnishes the desired organometallic **170a** in 70% yield after 5 h at 25 °C (entry 3). Alternatively, a full metalation of ethyl 3-fluorobenzoate (**57**) is observed after 2.5 h at 25 °C using 1.1 equiv of $TMP_2Mn{\cdot}4LiCl$ (**168**; entry 4). Finally, the complete metalation of **57** is achieved within 1 h and 0.5 h using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.6 equiv and 1.1 equiv, respectively; entries 5-6). Similar to the previously discussed zinc amide **60** and the lanthanum base **143**, the presence of $MgCl_2$ leads to an enhanced reactivity. Also, the *bis*-TMP amide

bases **165** and **168** posses higher metalation ability than the corresponding *mono*-TMP amide bases **167** and **169**. This excellent kinetic basicity allows the use of both TMP-moieties for directed metalations.

Table 16: Comparison of the reactivity of the amide bases **165** and **167**-**169**.



57 **170a**

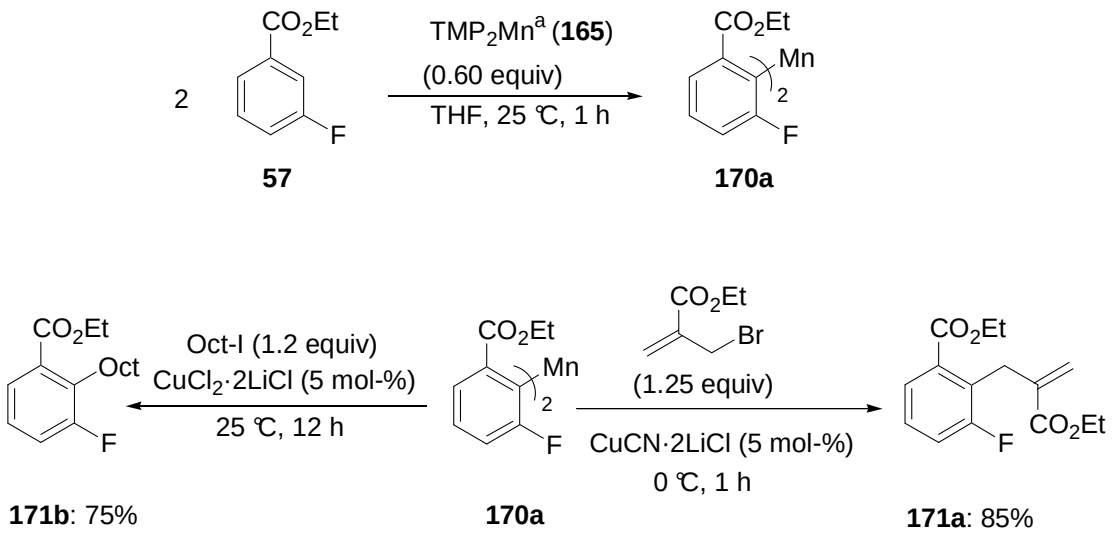
Entry	Base	Equiv	Time [h]	Conversion to **170a** [%][a]
1	**167**	1.1	5	50%
2	**169**	1.1	5	>95%
3	**168**	0.6	5	70%
4	**168**	1.1	2.5	>95%
5	**165**	0.6	1	>95%
6	**165**	1.1	0.5	>95%

[a] The metalation progress was monitored via GC-analysis of aliquots of the reaction mixture reacted with allyl bromide in the presence of $CuCN \cdot 2LiCl$ using tetradecane as internal standard.

10.3 Preparation of Functionalized Aryl-Manganese Species

Various halogenated benzoates are efficiently manganated using $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**165**; 0.60 equiv) at 25 °C. Starting from fully metalated ethyl 3-fluorobenzoate (**57**), its reaction with either ethyl 2-(bromomethyl)acrylate[55] in the presence of $CuCN \cdot 2LiCl$[102] or with Oct-I in the presence of $CuCl_2 \cdot 2LiCl$[103] furnishes the desired products **171a-b** in 75-85% yield (Scheme 58).

[102] For related reactions of Zn-reagents, see ref. 46.
[103] G. Cahiez, S. Marquais, *Synlett* **1993**, 45.



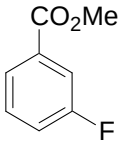
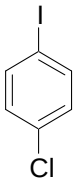
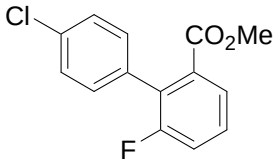
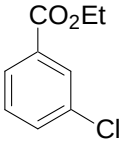
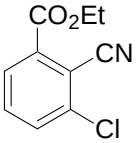
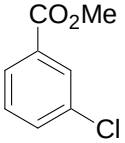
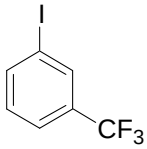
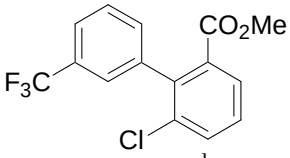
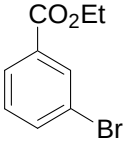
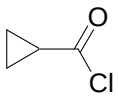
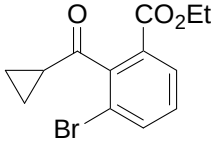
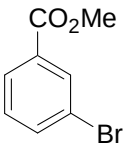
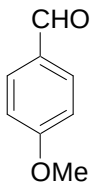
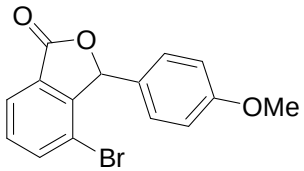
Scheme 58: Typical metalation conditions of a functionalized arene such as **57** using TMP_2Mn (**165**)[a]. [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

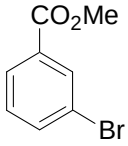
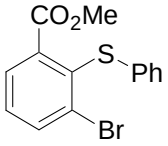
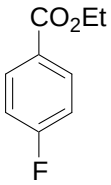
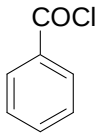
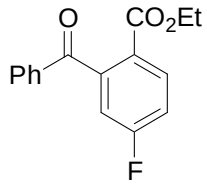
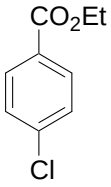
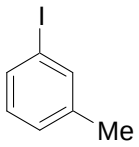
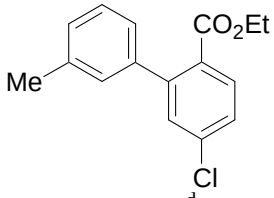
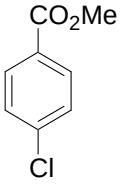
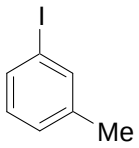
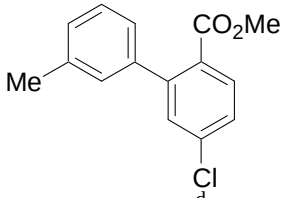
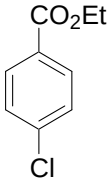
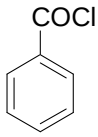
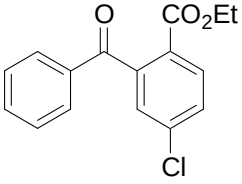
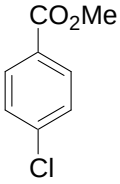
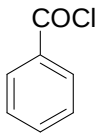
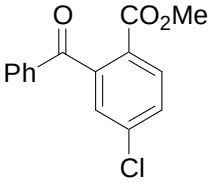
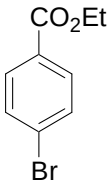
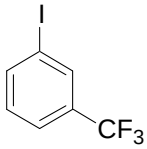
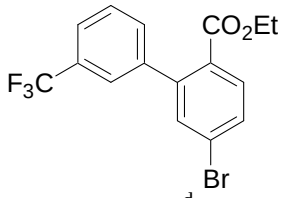
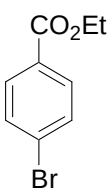
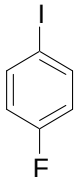
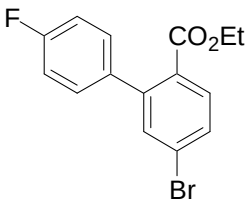
Additionally, the metalation of methyl 3-fluorobenzoate (**151a**) proceeds well within 1.25 h and a subsequent Pd-catalyzed cross-coupling with 1-iodo-4-chlorobenzene and $Pd(PPh_3)_4$ (2.5 mol-%) gives the biaryl **171c** in 82% yield (Table 17, entry 1).[104] Moreover, the chloro-substituted benzoates **67b** and **100c** are converted into the fully metalated reagents **170b-c** within 2 h using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.60 equiv). Adjacent reactions with either TosCN or a Pd-catalyzed cross-coupling with 1-iodo-3-trifluoromethylbenzene and $Pd(PPh_3)_4$ (2.5 mol-%) leads to the desired products **171d-e** in 77-85% yield (entries 2-3). Similarly, ethyl 3-bromobenzoate (**100b**) is manganated within 2 h and a CuCN·2LiCl mediated acylation with cyclopropanecarbonyl chloride affords the ketone **171f** in 86% yield (entry 4). Similarly, the metalation of methyl 3-bromobenzoate (**151b**) is also accomplished within 2 h. The lactone **171g** is obtained in 81 % after the addition to 4-methoxybenzaldehyde (entry 5), whereas the reaction with $PhSSO_2Ph$ leads to the thioether **171h** in 79% yield (entry 6). Furthermore, the metalation of 4-halogenated benzoates can be achieved by using this metalation protocol. Thus, ethyl 4-fluorobenzoate (**67a**) is manganated within 1.25 h and the benzophenone **171i** is isolated in 78% yield after a CuCN·2LiCl mediated acylation with benzoyl chloride (entry 7). Subsequently, ethyl 4-chlorobenzoate (**67c**) and methyl 4-chlorobenzoate (**67e**) are smoothly converted into the fully metalated arenes **170h-i** within 3 h. Then, Pd-catalyzed cross-couplings with 3-iodotoluone and $Pd(PPh_3)_4$ (2.5 mol-%) furnish the

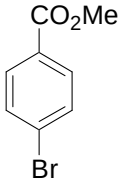
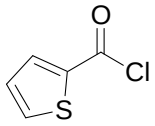
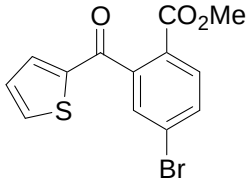
[104] E. Riguet, M. Alami, G. Cahiez, *Tetrahedron Lett.* **1997**, *38*, 4397.

biaryls **171j-k** in 75-80% yield (entries 8-9). Moreover, the reaction of manganese reagents **170h-i** with benzoyl chloride in the presence of CuCN·2LiCl afford the ketones **69f** and **101b** in 79-83% yield (entries 10-11). Ethyl 4-bromobenzoate (**67f**) is manganated within 3.5 h and the desired products **69i** and **171l** are obtained in 72-78% yield after Pd-catalyzed cross-couplings using $Pd(PPh_3)_4$ (2.5 mol-%) as catalytic system (entries 12-13). Accordingly, the reaction of methyl 4-bromobenzoate (**100a**) with $TMP_2Mn\cdot 2MgCl_2\cdot 4LiCl$ (**165**; 0.60 equiv) furnishes the organometallic derivative **170k** within 3.5 h. A subsequent CuCN·2LiCl mediated acylation with 2-thiophene acid chloride gives the ketone **171m** in 79% yield (entry 14). These results clearly display that both methyl and ethyl ester can be efficiently functionalized using $TMP_2Mn\cdot 2MgCl_2\cdot 4LiCl$ (**165**).

Table 17: Products obtained by metalation using $TMP_2Mn\cdot 2MgCl_2\cdot 4LiCl$ (**165**; 0.60 equiv) and subsequent reactions with electrophiles.

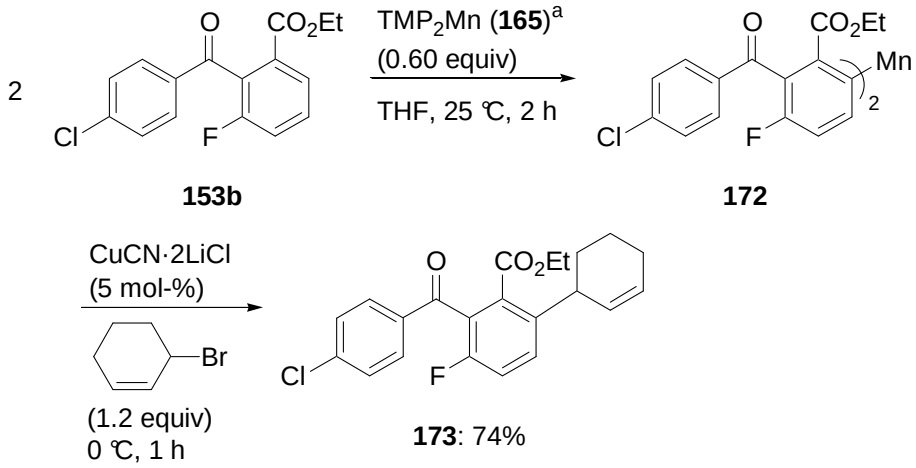
Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
1	 **151a**	25, 1.25		 **171c**: 82[d]
2	 **67b**	25, 2	TsCN	 **171d**: 85
3	 **100c**	25, 2		 **171e**: 77[d]
4	 **100b**	25, 2		 **171f**: 86[e]
5	 **151b**	25, 2		 **171g**: 81

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
			$PhSSO_2Ph$	
6	**151b**	25, 2		**171h**: 79
				
7	**67a**	25, 1.5		**171i**: 78[e]
				
8	**67c**	25, 3		**171i**: 75[d]
				
9	**67e**	25, 3		**171k**: 80[d]
				
10	**67c**	25, 3		**69b**: 83[e]
				
11	**67e**	25, 3		**101b**: 79[e]
				
12	**67f**	25, 3.5		**69i**: 78[d]
				
13	**67f**	25, 3.5		**171l**: 72[d]

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
14	 **100a**	25, 3.5		 **171m**: 79[e]

[a] Isolated yield of analytically pure product. [b] CuCN·2LiCl (5 mol-%) was used. [c] $CuCl_2{\cdot}2LiCl$ (5 mol-%) was used. [d] $Pd(PPh_3)_4$ (2.5 mol-%) was used. [e] CuCN·2LiCl (20 mol-%) was used.

Remarkably, the highly functionalized benzophenone **153b** is converted to the corresponding manganese species **172** by the reaction with **165** (0.60 equiv, 25 °C, 2 h). Cu(I)-catalyzed allylation with 3-bromocyclohexene (1.2 equiv) provides the polyfunctional benzophenone **173** in 74% yield (Scheme 59).[105] In conclusion, the manganation using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.60 equiv) combines high kinetic basicity (metalations usually occur at least 10 times faster than by using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.55 equiv) with excellent tolerance of functional groups since molecules bearing sensitive functionalities (methyl esters, a ketone) can cleanly be converted into the corresponding organomanganese reagents.

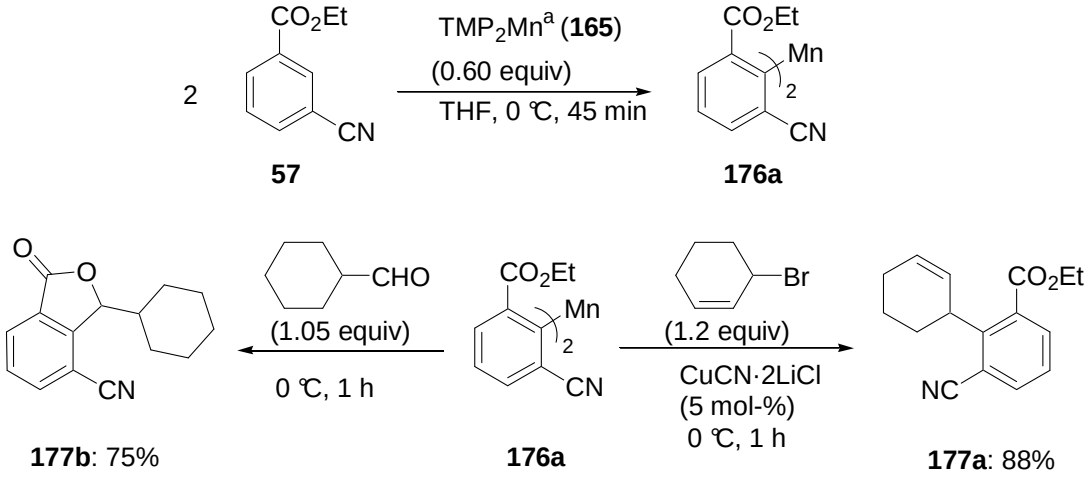


Scheme 59: Manganation of the functionalized aromatic **153b** with TMP_2Mn (**165**)[a] followed by an allylation. [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

Furthermore, aromatics bearing cyano-groups can also be further functionalized using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.60 equiv). Thus, the reaction of ethyl 3-cyanobenzoate (**67i**) with **165** (0.60 equiv) affords regioselectively the metalated species **176a** within 45 min at

[105] Unfortunately, benzophenone (**174**) and 4-fluorobenzophenone (**78h**) could not be efficiently metalated using **165** (0.6 equiv)

0 °C. An allylation with 3-bromocyclohexene in the presence of CuCN·2LiCl gives the 1,2,3-trisubstitued arene **177a** in 88% yield (Scheme 60). Moreover, the addition of **177a** to cyclohexane carbaldehyde bearing an acidic proton leads to the lactone **177b** in 76% yield.

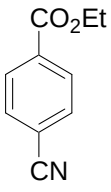
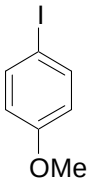
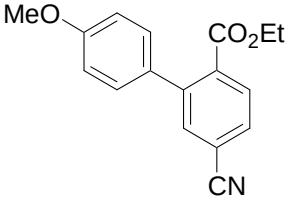
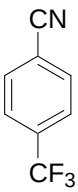
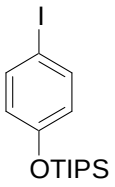
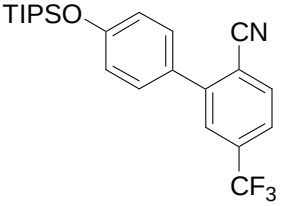
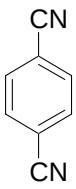
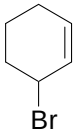
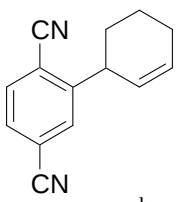


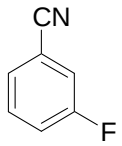
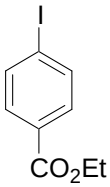
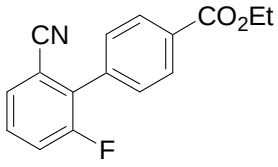
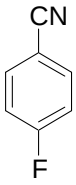
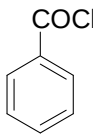
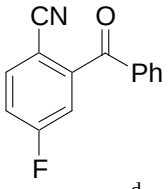
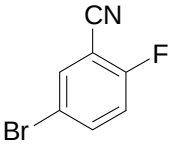
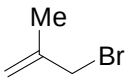
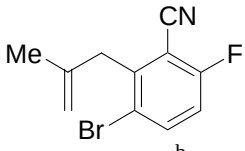
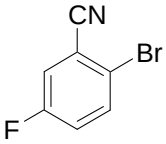
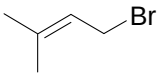
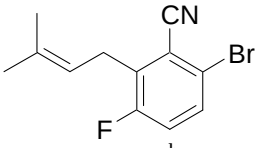
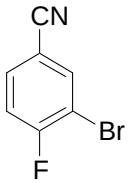
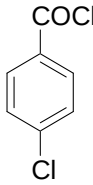
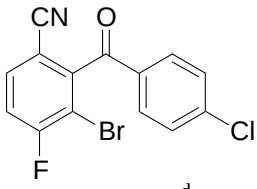
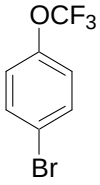
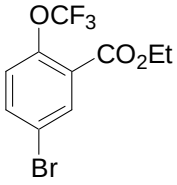
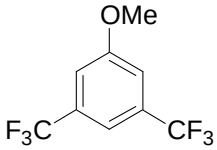
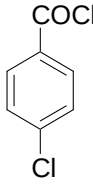
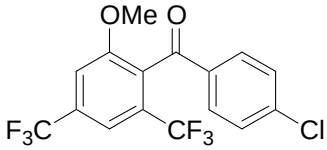
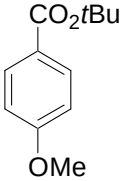
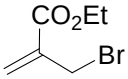
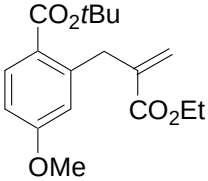
Scheme 60: Manganation of ethyl 3-cyanobenzoate (**67i**) with TMP_2Mn (**165**)[a] followed by an allylation or a reaction with an aldehyde. [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

Similarly, ethyl 4-cyanobenzoate (**67j**) is also regioselectively metalated in position 2 within 1.25 h at 0 °C giving the reagent **176b**. The subsequent Pd-catalyzed cross-coupling[104] with 4-iodoanisole in the presence of $Pd(PPh_3)_4$ (2.5 mol-%) at 0 °C provides the functionalized biaryl **177c** in 77% yield (Table 18, entry 1). Furthermore, the 4-substituted benzonitrile **175a** is fully metalated within 5 h at 25 °C and the expected product **177d** is obtained in 59 % yield after a $Pd(PPh_3)_4$ (2.5 mol-%) catalyzed cross-coupling (entry 2). Accordingly, the manganation of 1,4-dicyanobenzene (**78g**) is accomplished within 3.5 h at 0 °C and a Cu(I)-catalyzed reaction with 3-bromocyclohexene leads to the allylated benzonitrile **177e** in 78% yield (entry 3). Halogenated benzonitriles can also undergo smooth deprotonations. Thus, 3-fluorobenzonitrile (**67c**) is reacted with $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**165**; 0.60 equiv) for 1.5 h at 0 °C and the adjacent reaction with ethyl 4-iodobenzoate catalyzed by $Pd(PPh_3)_4$ (2.5 mol-%) provides the biaryl **69a** in 78% yield (entry 4). Furthermore, the diorganomanganese reagent **176g** obtained within 2 h at 25 °C by the deprotonation of 4-fluorobenzonitrile (**67k**) using $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**165**; 0.60 equiv) smoothly reacts with benzoyl chloride in the presence of CuCN·2LiCl (20 mol-%) giving the ketone **177f** in 82% yield (entry 5). The dihalogenated benzonitriles **175b** and **67o** are converted to the manganated species **176g-h** within 30 min at 0 °C. The reaction of **176g** with methallyl bromide catalyzed by CuCN·2LiCl (5 mol-%) furnishes the expected allylated product **177g** in 83% yield

(entry 6). Surprisingly, the quenching of **176h** with 1-bromo-3-methyl-but-2-ene in the presence of CuCN·2LiCl (5 mol-%) gives the formal S_N2-product **177h** in 92% yield (entry 7). Additionally, the metalation of the benzonitrile **175c** is complete within 30 min at 0 °C and a subsequent CuCN·2LiCl mediated acylation with 4-chlorobenzoyl chloride leads to the benzophenone **177h** in 81% yield (entry 8). Interestingly, aromatics bearing methoxy groups also undergo efficient metalations using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.60 equiv). Thus, the manganation of 1-bromo-4-trifluoromethoxybenzene (**175d**) proceeds smoothly within 10 h at 25 °C and the subsequent acylation with NC-CO_2Et provides the disubstituted ethyl benzoate **177i** in 77% yield (entry 9). Moreover, the anisole **128b** is metalated within 2 h at 25 °C and the benzophenone **129f** is obtained in 84% yield after the reaction with 4-chlorobenzoyl chloride in the presence of CuCN·2LiCl (entry 10). Finally, the metal species of the benzoate **126d** is formed within 30 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.60 equiv). The quenching the diaryl manganaes species with ethyl 2-(bromomethyl)acrylate[55] in the presence of CuCN·2LiCl (5 mol-%) leads to the highly functionalized benzoate **177k** in 73% yield (entry 11).

Table 18: Products obtained by metalation using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.60 equiv) and subsequent reactions with electrophiles.

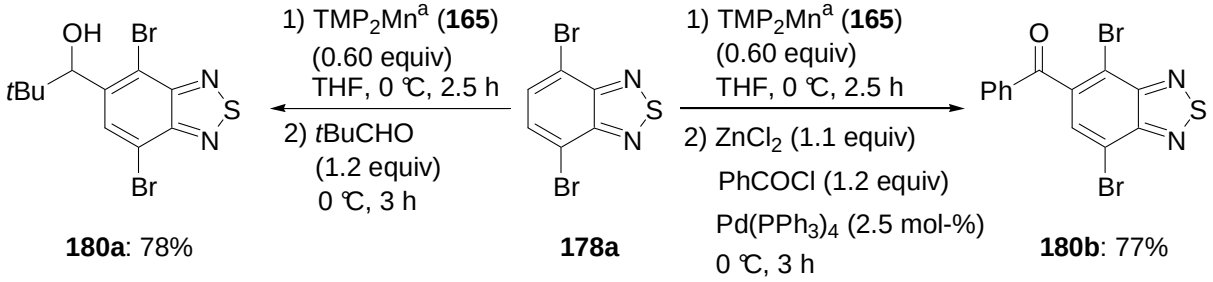
Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
1	 **67j**	0, 1.25		 **177c**: 77[c]
2	 **175a**	25, 5		 **177d**: 59[c]
3	 **78g**	0, 3.5		 **177e**: 78[b]

Entry	Substrate	T[°C], t[h]	Electrophile	Product/Yield [%][a]
				
4	**67c**	0, 1.5		**69a**: 78[b]
				
5	**67k**	25, 2		**177f**: 82[d]
				
6	**175b**	0, 0.5		**177g**: 83[b]
				
7	**67o**	0, 0.5		**69t**: 92[b]
				
8	**175c**	0, 0.5		**177h**: 81[d]
			CN-CO_2Et	
9	**175d**	25, 10		**177i**: 77
				
10	**128b**	25, 2		**129f**: 84[d]
				
11	**126d**	25, 30		**177k**: 73[b]

[a] Isolated yield of analytically pure product. [b] CuCN·2LiCl (5 mol-%) was used. [c] $Pd(PPh_3)_4$ (2.5 mol-%) was used. [d] CuCN·2LiCl (20 mol-%) was used.

10.4 Preparation of Functionalized Heteroaryl-Manganese Reagents

Moreover, this metalation concept was successfully extended to various heteroaromatics. Thus, a novel functionalization of 3,6-dibromobenzothiadiazole (**178a**) in position 4 is readily achieved by treating **178a** with $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**, 0.60 equiv; 0 °C, 2.5 h). The resulting diheteroarylmanganese reagent **179a** is then reacted with pivaldehyde to give the alcohol **180** in 78% yield. Alternatively, a Pd-catalyzed benzoylation gives the ketone **180b** in 77% yield (Scheme 61).[106]



180a: 78% **178a** **180b**: 77%

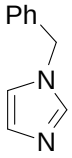
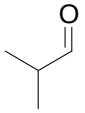
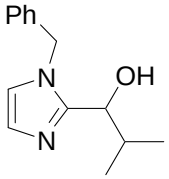
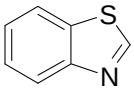
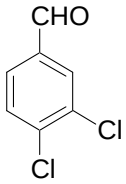
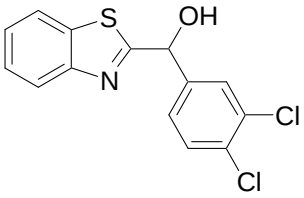
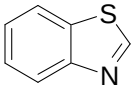
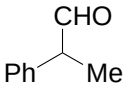
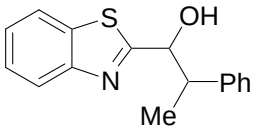
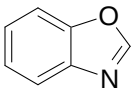
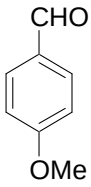
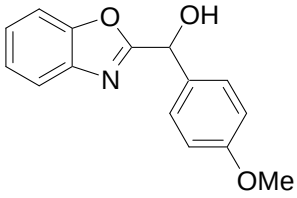
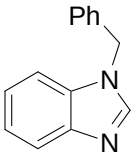
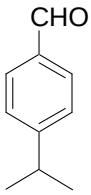
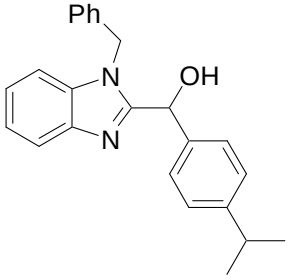
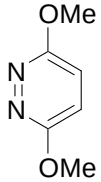
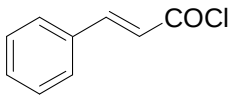
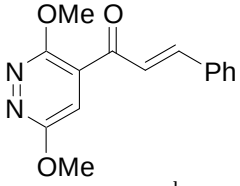
Scheme 61: Manganation of 3,6-dibromobenzothiadiazole (**178a**) with TMP_2Mn^a (**165**) and reactions with electrophiles. [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

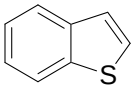
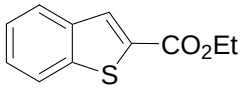
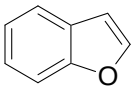
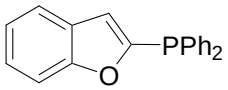
Additionally, the metalation of 1-benzyl-1*H*-imidazole (**61c**) is finished within 20 min at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**, 0.60 equiv). The addition of the metalated species **179b** to isobutyraldehyde gives the alcohol **180c** in 85% yield (Table 19, entry 1). Moreover, benzothiazole (**61f**) is readily converted to the diheteroarylmanganese species **179c** within 30 min at 25 °C and the subsequent reactions with either 3,4-dichlorobenzyldehyde or 2-phenylpropanal furnish the expected products **180d-e** in 82-87% yield (entries 2-3). Furthermore, the metalation of benzoxazole (**61g**) proceeds smoothly within 1 h at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**, 0.60 equiv) and the addition of the manganated species **179d** to 4-methoxy-benzaldehyde gives the alcohol **180f** in 74% yield (entry 4). Similarly, the manganation of 1-benzyl-1*H*-benzimidazole (**178b**) is achieved within 45 min at 0 °C and the desired product **180g** is obtained in 84% after the reaction of the manganated heterocycle **179e** with 4-*i*Pr-benzaldehyde (entry 5). Remarkably, the pyridazine **100e** is reacted with $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**, 0.60 equiv) to give the fully metalated species **179f** within 30 min at 0 °C. The subsequent acylation of **179f** with 3-phenyl-acryloyl chloride in the presence of CuCN·2LiCl (20 mol-%) provides the ketone **180h** in 88% yield (entry 6).

[106] a) E. Negishi, V. Bagheri, S. Chatterjee, F. T. Luo, *Tetrahedron Lett.* **1983**, *24*, 5181; b) R. A. Grey, *J. Org. Chem.* **1984**, *49*, 2288.

Additionally, benzothiophene (**61k**) and benzofuran (**61l**) are readily metalated within 2 h at 25 °C (in contrast to several days for a full metalation of both substrates using the zinc amide **60**, see Table 1, entries 17-18). After an acylation using ethyl cyanoformate or the reaction with $ClPPh_2$, the products **180i-j** are isolated in 82-95% yield (entries 7-8).

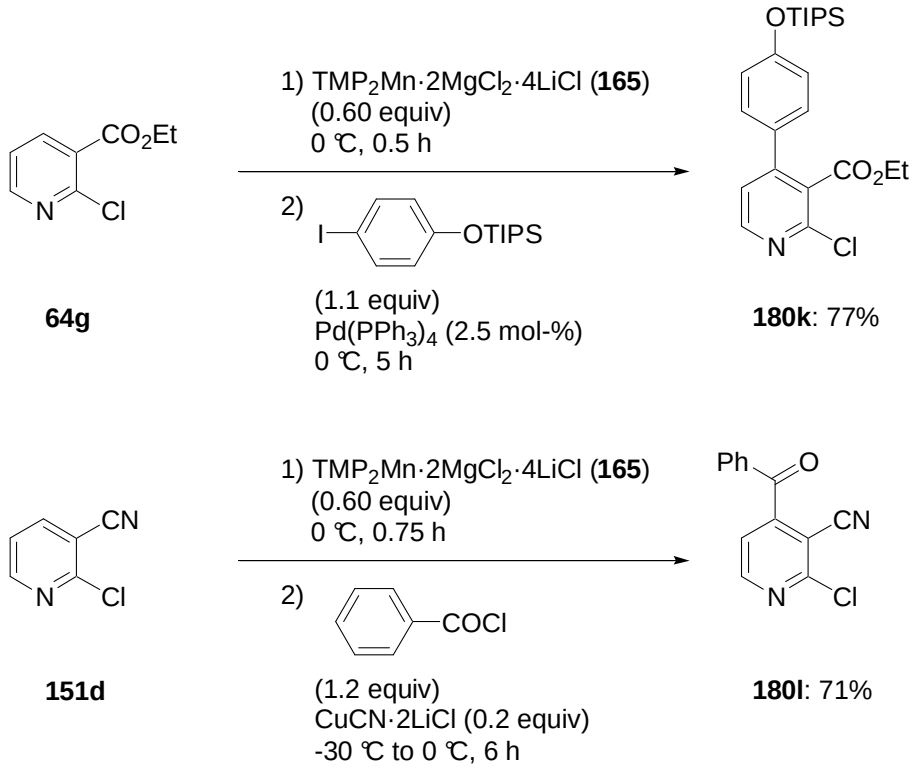
Table 19: Products obtained by metalation using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**1**; 0.60 equiv) and subsequent reactions with electrophiles.

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
1	 **61c**	0, 0.3		 **180c**: 82
2	 **61f**	25, 0.5		 **180d**: 87
3	 **61f**	25, 0.5		 **180e**: 82 (d.r.: 1:1)
4	 **61g**	0, 1		 **180f**: 74
5	 **178b**	0, 0.75		 **180g**: 84
6	 **100e**	0, 0.5		 **180h**: 88[b]

Entry	Substrate	*T*[°C], *t*[h]	Electrophile	Product/Yield [%][a]
7	 **61k**	25, 2	NC-CO_2Et	 **180i**: 95
8	 **61l**	25, 2	$ClPPh_2$	 **180j**: 82

[a] Isolated yield of analytically pure product. [b] CuCN·2LiCl (20 mol-%) was used. [c] $Pd(PPh_3)_4$ (2.5 mol-%) was used.

Moreover, the nicotinate **64g** is converted to its manganated species within 30 min at 0 °C. The subsequent cross-coupling with (4-iodo-phenoxy)-triisopropyl-silane catalyzed by $Pd(PPh_3)_4$ (2.5 mol-%) provides the biaryl **180k** in 77% yield (Scheme 62). Additionally, the pyridine **151d** is smoothly metalated with $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**, 0.60 equiv) within 45 min at 0 °C. The ketone **180l** is obtained in 71% yield after a Cu(I)-mediated acylation with benzoyl chloride (Scheme 62).



Scheme 62: Functionalization of the pyridines **64g** and **151d** using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**).

11 Directed Ferration of Functionalized Aromatics Using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$

11.1 Introduction

Iron is considered to be one of the most existing and non-toxic metals found on earth.[107] Therefore, Fe-organometallic chemistry is highly desirable and various iron-catalyzed cross-coupling reactions of organometallic reagents have already found numerous applications in organic synthesis.[108] Beside the wide acceptance,[109] the mechanism of these reactions still needs to be further investigated since the single steps of the mechanism remains not completely elucidated.[110] Therefore, the preparation of Fe-organometallics in a stoichiometric way could help to learn more about the reactivity of those intermediates.[111] Only a few aryl-Fe compounds are described since aryl-Fe(II)-derivatives could only be sparingly prepared by transmetalation[112] or by direct ferration using a TMEDA-stabilized mixed sodium-, iron-ate-base reported by *Mulvey* and co-workers.[113] Therefore, we have envisioned the general preparation of aryliron compounds *via* directed metalation according to the previously developed amide bases.

---

[107] *Elements and their Compounds in the Environment*; (Eds.: E. Merian, M. Anke, M. Ihnat, M. Stoeppler) Vol. 1-3, Wiley-VCH: Weinheim, Germany, **2004**.

[108] For reviews, see: a) C. Bolm, J. Legros, J. LePiah, L. Zani, *Chem. Rev.* **2004**, 6217; b) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500.

[109] a) A. Fürstner, M. Méndez, *Angew. Chem. Int. Ed.* **2003**, *42*, 5355; b) A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc*. **2002**, *124*, 13856; c) A. Fürstner, R. Martin, H. Krause, G. Seidel, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc*. **2008**, *130*, 8773; d) J. Norinder, A. Matsumoto, N. Yoshikai, E. Nakamura, *J. Am. Chem. Soc*. **2008**, *130*, 5858; e) M. Nakamura, K. Matsu, S. Ito, E. Nakamura, *J. Am. Chem. Soc*. **2004**, *126*, 3686; f) G. Cahiez, L. Foulgoc, A. Moyeux, *Angew. Chem. Int. Ed.* **2009**, *48*, 2969; g) G. Cahiez, V. Habiak, C. Duplais, A. Moyeux, *Angew. Chem. Int. Ed.* **2007**, *46*, 4364; h) I. Sapountzis, W. Lin, C. C. Kofink, C. Despotopoulou, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 1654; i) C. Duplais, F. Bures, I. Sapountzis, T. J. Korn, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 2968; j) M. Carril, A. Correa, C. Bolm, *Angew. Chem. Int. Ed.* **2008**, *47*, 4862; k) O. Bistri, A. Correa, C. Bolm, *Angew. Chem. Int. Ed.* **2008**, *47*, 586; l) A. Correa, M. Carril, C. Bolm, *Angew. Chem. Int. Ed.* **2008**, *47*, 2880; m) A. Correa, C. Bolm, *Angew. Chem. Int. Ed.* **2007**, *46*, 8862; n) R. B. Bedford, M. Huwe, C. M. Wilkinson, *Chem. Commun.* **2009**, 600; o) R. B. Bedford, M. Betham, D. W. Bruce, A. A. Danopoulos, R. M. Frost, M. Hird, *J. Org. Chem.* **2006**, *71*, 1104; p) A. Guérinot, S. Reymond, J. Cossy, *Angew. Chem. Int. Ed.* **2007**, *46*, 6521.

[110] Fürstner, K. Majima, R. Martin, H. Krause, E. Kattnig, R. Goddard, C. W. Lehman, *J. Am. Chem. Soc*. **2008**, *130*, 1992; c) A. Fürstner, H. Krause, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 440; d) R. Martin, A. Fürstner, *Angew. Chem. Int. Ed.* **2004**, *43*, 3955.

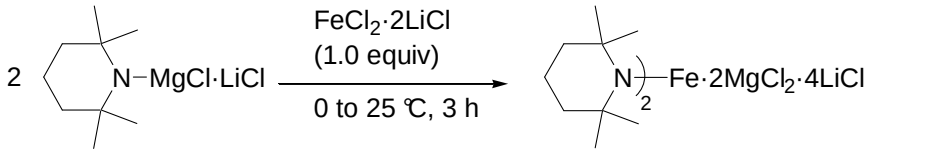
[111] C. Kishan Reddy, P. Knochel, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1700.

[112] a) T. Kauffmann, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 386; b) H. Bürger, U. Wannagat, *Mh. Chemie* **1963**, *94*, 1007.

[113] P. Alborés, L. M. Carrella, W. Clegg, P. Garcí-Álvares, A. R. Kennedy, J. Klett, R. E. Mulvey, E. Rentschler, L. Russo, *Angew. Chem. Int. Ed.* **2009**, *48*, 3317.

11.2 Preparation of the Hindered Fe-TMP Base 181

Based on the experience on the preparation of lanthanum and manganese amides, the development of an iron base started with the reaction of $FeCl_2{\cdot}2LiCl$ with freshly prepared TMPMgCl·LiCl (**40**). To obtain $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**) in quantitative yield, TMPMgCl·LiCl (**40**; 2.0 equiv) was reacted with $FeCl_2{\cdot}2LiCl$ (1.0 equiv) at 0 °C and the resulting solution was further stirred at 25 °C for 3 h (Scheme 63). This dark brown base has an excellent solubility in THF (0.50 M) and can be stored without decomposition for at least 3 month at 25 °C. Similarly to the above mentioned amide-bases, LiCl is certainly responsible for the solubility in THF since LiCl can break aggregates of organometallics by complexing the metallic center.[114]

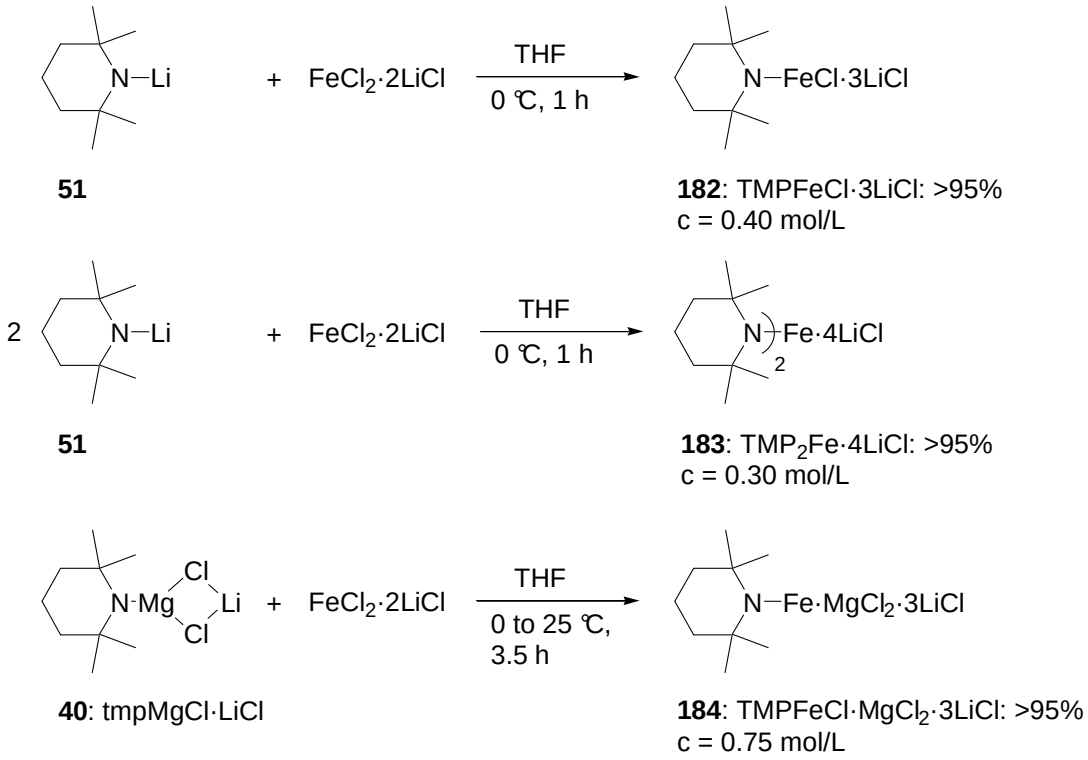


40 **161**: TMP_2Fe:[a] 95%; 0.50 M in THF

Scheme 63: Preparation and reactions of TMP_2Fe (**161**). [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

To verify again the importance of the components of the base $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**), 3 additional Fe-bases have been prepared. Thus, the reaction of freshly prepared TMPLi (**51**) with either $FeCl_2{\cdot}2LiCl$ (1.0 equiv) or $FeCl_2{\cdot}2LiCl$ (0.50 equiv) at 0 °C furnishes the amide bases TMPFeCl·3LiCl (**182**) and $TMP_2Fe{\cdot}4LiCl$ (**183**), respectively within 1 h (Scheme 64). Additionally, the reaction of TMPMgCl·LiCl (**40**) with $FeCl_2{\cdot}2LiCl$ (1 equiv) at 0 °C followed by 3 h of stirring at 25 °C leads to the reagent $TMPFeCl{\cdot}MgCl_2{\cdot}3LiCl$ (**184**; Scheme 64). All 3 bases were prepared in >95% yield.

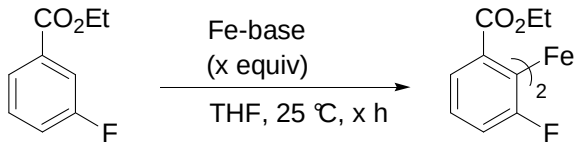
[114] Similar to the previousely discussed manganese base **165**, the preparation of this base without LiCl as additive is not convenient, since it is already necessary to provide a THF-soluble iron source.



Scheme 64: Preparation of the Fe-bases **182-184**.

The concentration of the $MgCl_2$-containing amide bases **181** and **184** is again (see chapter 3, 9 and 10) significantly higher than the concentration of the bases **182** and **183** derived *via* transmetalation of TMPLi (**51**). Although the solvents of the bases **182-183** were completely removed, the concentration of the redissolved residue (in THF) was determined to be 0.40 M for the base **182** and 0.30 M for the base **183**, respectively. Subsequently, the metalation progress of ethyl 3-fluorobenzoate (**57**) using the amide bases **181-184** has been investigated.

Table 20: Comparison of the reactivity of the amide bases **181-184**.



57 **185a**

Entry	Base	Equiv	Time [h]	Conversion to **185a** [%][a]
1	**182**	1.5	5	<5
2	**184**	1.5	5	39
3	**183**	0.75	5	55

Entry	Base	Equiv	Time [h]	Conversion to **185a** [%][a]
4	**183**	1.5	5	78
5	**181**	1.5	1.5	>95
6	**181**	0.75	3	>95

[a] The conversion to the corresponding metal species **185a** was monitored *via* GC-analysis of aliquots of the reaction mixture quenched with allyl bromide in the presence of CuCN·2LiCl using tetradecane as internal standard.

As already noted for related amide bases, the *mono*-amide base **182** displays the worst metalation ability since almost no formation of **185a** is observed after 5 h at 25 °C (Table 20, entry 1). In contrast, the use of $TMPFeCl \cdot MgCl_2 \cdot 3LiCl$ (**184**) furnishes 39% of the metalated species **185a** within 5 h at 25 °C (entry 2). Additionally, the metalation using $TMP_2Fe \cdot 4LiCl$ (**183**; 0.75 equiv) leads only to 55% of **185a** after 5 h (entry 3). Moreover, the use of a huge excess of **183** (1.5 equiv) also does not result in a complete formation of **185a** after 5 h at 25 °C (entry 4). Under similar conditions, the ferration of **57** using the *bis*-TMP base **181** (1.5 equiv) affords the desired organometallic **185a** in 95% yield after 3 h at 25 °C (entry 5). Finally, by using 0.75 equiv of $TMP_2Fe \cdot 2MgCl_2 \cdot 4LiCl$ (**185**), a complete metalation of ethyl 3-fluorobenzoate (**57**) was achieved within 3 h at 25 °C. As already observed, $MgCl_2$ enhances dramatically the kinetic basicity of the corresponding Fe-bases and additionally increases the solubility of the Fe-base **181** and **184** derived from TMPMgCl·LiCl (**40**).

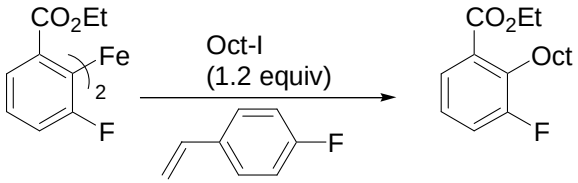
11.3 Alkylation Reactions Catalyzed by Impurities

As noted above, the metalation of ethyl 3-fluorobenzoate (**57**) with TMP_2Fe (**181**; 25 °C, 3 h) affords the corresponding diaryl-Fe(II) species **185a** which reacted smoothly with 1-iodooctane (1.2 equiv) providing the 1,2,3-trisubstituted benzoate **171b** in 86% yield. The cross-coupling lasted 14 h, but by adding 4-fluorostyrene (**186**; 10 mol-%), this reaction was accomplished within 7 h at 25 °C (88% yield; Table 21, entry 1). 4-Fluorostyrene (**186**) is known to promote Ni-catalyzed cross-coupling reactions.[115] It is assumed that it accelerates the reductive elimination step through a coordination of the electron-poor olefin to the metal center. Although, the purity of $FeCl_2$ did not influence the metalation rate leading to **185a**, it considerably changes the formation rate of the desired product **171b**. Thus, we have observed that the use of 99.998% pure $FeCl_2$ leads to a cross-coupling conversion to **171b** of 25% after

[115] a) A. Devasagayaraj, T. Stüdemann, P. Knochel, *Angew. Chem. Int. Ed.* **1995**, *34*, 2723; b) R. Giovannini, T. Stüdemann, G. Dussin, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 2387; c) R. Giovannini, T. Stüdemann, A. Devasagayaraj, G. Dussin, P. Knochel, *J. Org. Chem.* **1999**, *64*, 3544; d) A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, *67*, 79; e) T. J. Korn, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 2947.

a reaction time of 8 h instead of 95% by using $FeCl_2$ having a purity of 98% (Table 21, entries 1 and 2). Since atomic absorption analysis revealed that the commercial sample of 98% pure $FeCl_2$ contains traces of Mn, Ni, Co and Cu, small amounts (0.5%) of the corresponding chlorides were intentionally added to $FeCl_2$ (99.998%).

Table 21: Influence of the purity of $FeCl_2$ and additives on the cross-coupling yield.



185a **186** (10 mol-%) additive 25 °C, 8 h **171b**

Entry	Additive[a]	Yield [%][b]	Entry	Additive[a]	Yield [%]
1	---	95[c] (88)	10	$NiCl_2$, $MnCl_2$	88[d]
2	---	25[d]	11	$MnCl_2$, $FeCl_3$	18[d]
3	$MnCl_2$	20[d]	12	$NiCl_2$, $MnCl_2$, $FeCl_3$	74[d]
4	$CoCl_2$	34[d]	13	$CuCl_2$, $FeCl_3$	18[d]
5	$CuCl_2$	27[d]	14	$CuCl_2$, $NiCl_2$	85[d]
6	CuCl	23[d]	15	$CuCl_2$, $MnCl_2$	26[d]
7	$FeCl_3$	12[d]	16	$CuCl_2$, $NiCl_2$, $FeCl_3$	65[d]
8	**$NiCl_2$**	**94[d] (86)**	17	$CuCl_2$, $MnCl_2$, $FeCl_3$	17[d]
9	$NiCl_2$, $FeCl_3$	69[d]			

[a] 0.5% of the additive was used. In the case of several additives, equimolar amounts were used. [b] Yields in brackets refer to isolated yield of analytically pure product. [c] $FeCl_2$ with a purity grade of 98% was used. [d] $FeCl_2$ with a purity grade of 99.998% was used.

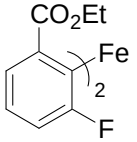
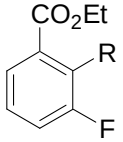
Whereas the addition of either $CoCl_2$, $MnCl_2$, $CuCl_2$ or CuCl changes only moderately the cross-coupling rate (entries 3-6), the use of $FeCl_3$ not only furnishes the worst cross-coupling rate to **171b**, but also causes homo-coupling of **185a** in considerable amounts (entry 7). Remarkably, the addition of 0.5% of $NiCl_2$ restores the full cross-coupling rate observed with $FeCl_2$ having a purity of 98% (entry 8). Interestingly, combinations of two or three metallic chlorides afford intermediate cross-coupling rates (entries 9-17). In conclusion, the presence of 0.25% Ni in commercial $FeCl_2$ is certainly responsible for the observed cross-

coupling reaction rate. From a practical point of view, $FeCl_2$ (98% pure) has been used for preparing TMP_2Fe (**181**) since this Fe-(II)-source already contains the catalytic system.

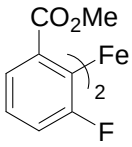
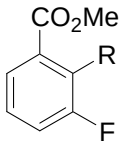
11.4 Reactivity versus Electrophiles

Starting from ethyl 3-fluorobenzoate (**57**), the cross-coupling of **185a** proceeds well with octyl iodide (Table 22, entry 1). Octyl bromide reacts slower, giving after 20 h at 25 °C the alkylated benzoate **171b** in 74% yield (entry 2). Moreover, the reaction of the metalated species **185a** with secondary iodides and bromides such as *i*Pr-Br, *c*Hex-I and *c*Hex-Br provides the corresponding cross-coupling products **187a-b** in 60-83% yield (entries 3-5) in the presence of **186** (10 mol-%). Remarkably, when no 4-fluorostyrene was added to the reaction mixtures, the isolated yields of the products **187a-b** were considerable lower (51-76%). In the absence of 4-fluorostyrene (**186**), a smooth reaction with benzyl chloride was observed, furnishing the benzylated arene **187c** in 88% yield (entry 6). Additionally, various functionalized alkyl iodides undergo smooth cross-coupling reactions. Thus, the reaction of **185a** with ethyl 4-iodobutyrate (1.2 equiv) affords the desired diester **187d** in 80% yield (entry 7). Accordingly, diethyl iodomethyl phosphonate readily reacts at –10 °C in the absence of 4-fluorostyrene (**186**) with **185a** giving the phosphonate **187e** in 68% yield (entry 8). Interestingly, the dihalide 1-chloro-6-iodohexane undergoes only a substitution of the carbon-iodine bond providing the benzoate **187f** in 85% yield (entry 9). Surprisingly, the reaction of **185a** with 6-iodo-hex-1-ene provided only the alkenylated product **187g** in 77% yield without any cyclization product (entry 10).[116] Methyl ester can also be used as substrates. Thus, methyl 3-fluorobenzoate (**151a**) is smoothly converted to the corresponding (Fe)-derivative using TMP_2Fe (**181**; 0.75 equiv, 25 °C, 3 h). The subsequent allylation with 1-chloro-6-iodohexane furnishes the desired benzoate **187h** in 79% yield (entry 11).

Table 23: Cross-coupling of **185a-b** with organic halides in the presence of 4-fluorostyrene (**186**) leading to the corresponding substitution products.

Entry	Substrate	Organic halide	Product of type **5**	Yield [%][a]
				
1	**185a**	Oct-I	**171b**: R = Oct	88 (86)[b]

[116] a) V. B. Phapale, D. J. Cardenas, *Chem. Soc. Rev.* **2009**, *38*, 1598; b) V. B. Phapale, D. J. Cardenas, *Angew. Chem. Int. Ed.* **2007**, *46*, 8790.

Entry	Substrate	Organic halide	Product of type **5**	Yield [%][a]
2	**185a**	Oct-Br	**171b**: R = Oct	74 (65)[b]
3	**185a**	*i*Pr-Br	**187a**: R = *i*Pr	70 (54)[b]
4	**185a**	*c*Hex-I	**187b**: R = *c*Hex	83 (76)[b]
5	**185a**	*c*Hex-Br	**187b**: R = *c*Hex	60 (51)[b]
6	**185a**	$PhCH_2Cl$	**187c**: R = Bn	88[b]
7	**185a**	$I(CH_2)_3CO_2Et$	**187d**: R = $(CH_2)_3CO_2Et$	80 (54)[b]
8	**185a**	$ICH_2P(O)(OEt)_2$	**187e**: R = $CH_2P(O)(OEt)_2$	68[b]
9	**185a**	$I(CH_2)_6Cl$	**187f**: R = $(CH_2)_6Cl$	85
10	**185a**	$I(CH_2)_4CH=CH_2$	**187g**: R = $(CH_2)_4CH=CH_2$	77
				
11	**185b**	$I(CH_2)_6Cl$	**187h**: R = $(CH_2)_6Cl$	79

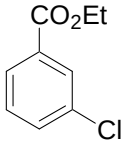
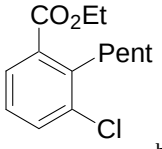
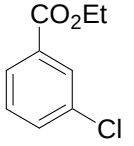
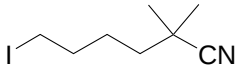
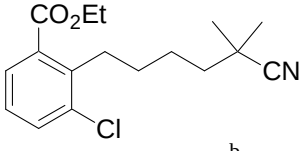
[a] Isolated yield of analytically pure product. [b] No 4-fluorostyrene (**186**) was added.

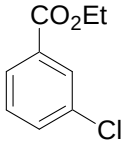
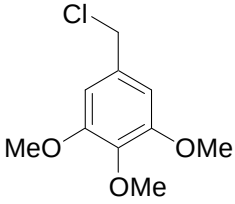
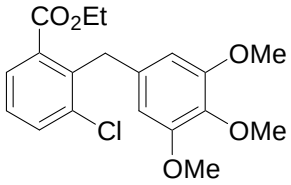
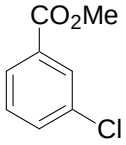
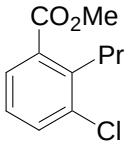
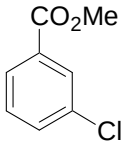
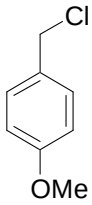
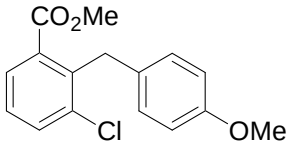
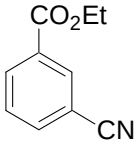
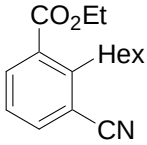
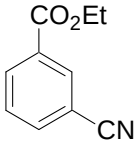
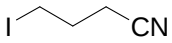
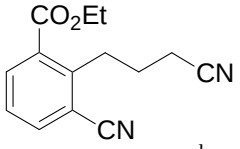
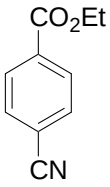
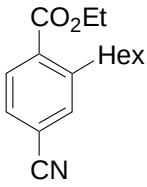
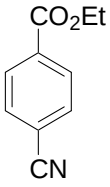
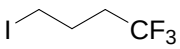
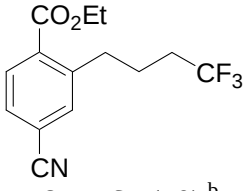
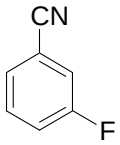
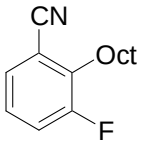
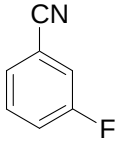
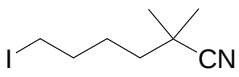
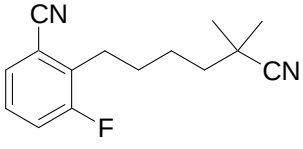
11.5 Preparation of Functionalized Aryl-(Fe) Compounds

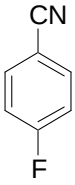
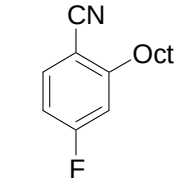
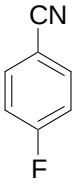
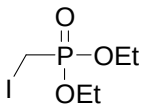
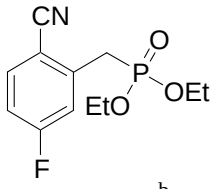
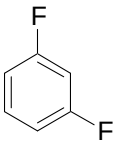
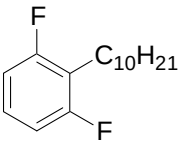
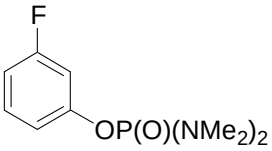
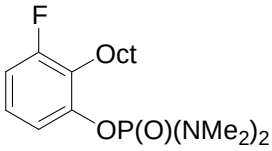
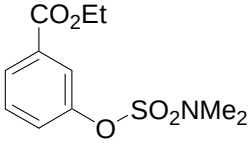
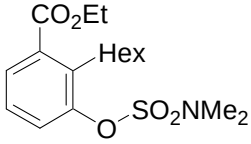
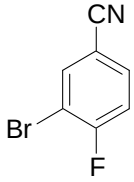
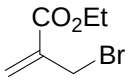
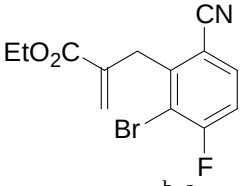
Subsequently, this tandem metalation/cross-coupling procedure could be extended to various organic halides. Thus, the ferration of ethyl 3-chlorobenzoate (**67b**) using TMP_2Fe (**181**) proceeds within 36 h at 25 °C and the adjacent couplings with either pentyl iodide or 6-iodo-2,2-dimethyl-hexanenitrile in the presence of **186** (10 mol-%) provide the desired alkylated benzoates **187i-j** in 71-81% yield (Table 23, entries 1-2). Additionally, the metalated species **185c** readily reacts with 5-chloromethyl-1,2,3-trimethoxybenzene giving the benzylated arene **187k** in 69% yield (entry 3). Similarly, methyl 3-chlorobenzoate (**100c**) is converted into the ferrated species **185d** within 36 h at 25 °C using TMP_2Fe (**181**; 0.75 equiv) and the subsequent couplings with respectively an alkyl iodide in the presence of 4-fluorstyrene (**186**; 10 mol-%) and a benzylic chloride leads to the desired products **187l-m** in 65-66% yield (entries 4-5). Additionally, the cyano-substituted ethyl benzoates **67i-j** are smoothly metalated at 25 °C within 18 h and 48 h, respectively. After cross-coupling reactions with various primary aliphatic iodides the alkylated products **187n-q** are obtained in 65-81% yield (entries 6-9). It should be noted, that the isolated yields for the above mentioned cross-couplings using aliphatic iodides are significantly decreased when no 4-fluorstyrene (**186**;

10 mol-%) is used. Furthermore, fluoro-substituted benzonitriles are also excellent substrates. Thus, the metalation of 3-fluorobenzonitrile (**67l**) with TMP_2Fe (**186**; 0.75 equiv, 25 °C) is completed within 9 h, and the alkylation with either octyl iodide or 6-iodo-2,2-dimethyl-hexanenitrile furnish the substituted benzonitriles **187r-s** in 70-80% yield (entries 10-11). Moreover, the metalation of 4-fluorobenzonitrile (**67k**) requires 18 h using TMP_2Fe (**186**; 0.75 equiv) and the desired benzonitriles **187t-u** are isolated 72-83% yield after the reaction with octyl iodide and diethyl iodomethyl phosphonate, respectively (entries 12-13). Interestingly, the ferration of 1,3-difluorobenzene (**100d**) is accomplished within 10 h and the reaction with 1-iododecane leads to the alkylated benzene **187v** in 77% yield (entry 14). Additionally, the protected phenols **188a** and **188b** are deprotonated by TMP_2Fe (**181**) at 25 °C within 30 h and 60 h, respectively. After alkylation reactions with 1-iodooctane or 1-iodohexane in the presence of 4-fluorstyrene (**186**; 10 mol-%), the 1,2-disubstituted phenols **189a-b** are obtained in 66-85% yield (entries 15-16). Furthermore, the halogenated benzonitrile **175c** is converted into the corresponding metal derivative **3l** within 2 h at 25 °C using TMP_2Fe (**186**; 0.75 equiv, 25 °C). Interestingly, the subsequent Cu-(I) catalyzed reaction with ethyl 2-(bromomethyl)acrylate[55] furnishes the allylated benzonitrile **189c** (entry 17). In the absence of copper, low conversions to the corresponding products have been observed. It should be pointed out, when $FeCl_2$ with a purity 99.998 % was used, the metalation rate giving the ferrated species **185a-d** remained equally compared to preparing the organoiron derivatives using 98% pure $FeCl_2$. Hence, iron is certainly responsible for the metalation process.

Table 23: Preparation of diaryl-Fe(II) derivatives and cross-coupling with various organic halides in the presence of **186** (10 mol-%).

Entry	Substrate	Time [h]	Organic halide	Product/Yield [%][a]
1	 **67b**	36	I-Pent	 **187i**: 81 (70)[b]
2	 **67b**	36		 **187j**: 71 (55)[b]

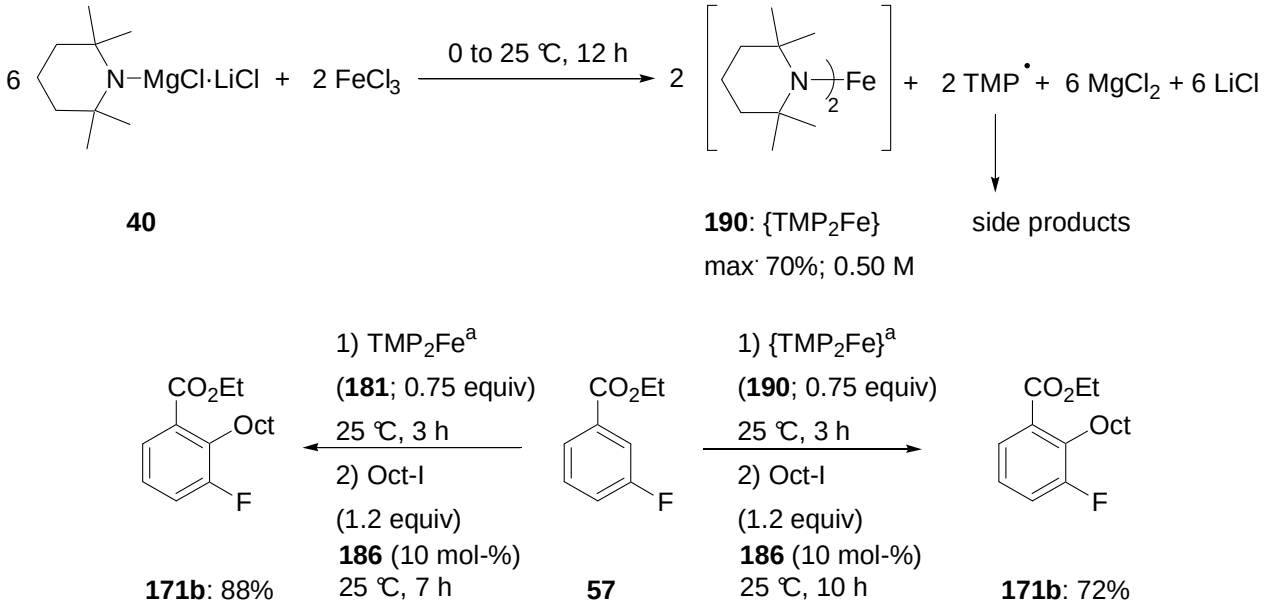
Entry	Substrate	Time [h]	Organic halide	Product/Yield [%][a]
				
3	**67b**	36		**187k**: 69[b]
			I-Pr	
4	**100c**	36		**187l**: 65 (58)[b]
				
5	**100c**	36		**187m**: 66[b]
			I-Hex	
6	**67i**	18		**187n**: 81 (75)[b]
				
7	**67i**	18		**187o**: 75 (66)[b]
			I-Hex	
8	**67j**	48		**187p**: 70 (58)[b]
				
9	**67j**	48		**187q**: 65 (50)[b]
			I-Oct	
10	**67l**	9		**187r**: 80
				
11	**67l**	9		**187s**: 70

Entry	Substrate	Time [h]	Organic halide	Product/Yield [%][a]
12	 **67k**	18		 **187t**: 83
13	 **67k**	18		 **187u**: 72[b]
14	 **100d**	10		**187v**: 77
15	 **188a**	30		**189a**: 85
16	 **188b**	60		**189b**: 66
17	 **175c**	2		 **189c**: 75[b, c]

[a] Isolated yield of analytically pure product. [b] No 4-fluorostyrene (**186**) was added. [c] CuCN·2LiCl (5 mol-%) was used.

In order to get some mechanistic insight on the structure and behavior of organometallic Fe-intermediates, TMPMgCl·LiCl (**40**; 3.0 equiv) is reacted with $FeCl_3$ (1.0 equiv) in THF (Scheme 65). Surprisingly, Mössbauer-spectroscopy (see Experimental Part) indicated that the product is mainly a Fe(II) TMP-amide (**190**; max. 70% yield compared to 95% yield for the preparation of **181** starting from $FeCl_2{\cdot}2LiCl$). The decreased yield can be best explained by the tentative, formal reduction of $FeCl_3$ caused by the electron-rich amide TMPMgCl·LiCl (**40**) resulting in the formation of **190** and TMP-radicals. These radicals can further cause side reactions. This reagent **190** has a comparable stability as **181** and undergoes a smooth deprotonation (0.75 equiv, 25 °C, 3 h) of ethyl 3-fluorobenzoate (**57**) leading to the

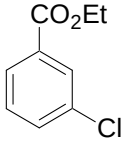
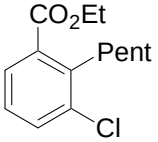
corresponding Fe(II)-derivative. Its cross-coupling with octyl iodide in the presence of 4-fluorostyrene (**186**) proceeds with similar rate as by using the Fe(II)-base **181**. It provides the corresponding cross-coupling product **171b** in 72% yield (compared to 88% obtained with the base **1**, Table 22, entry 1).

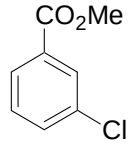
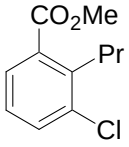
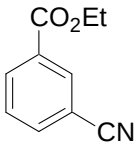
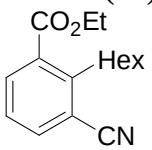
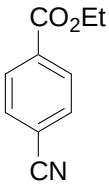
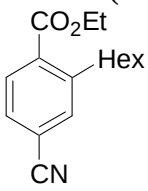


Scheme 65: Preparation and reactivity of the Fe-(II)-base **190**. [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

Furthermore, the benzoates **67b**, **100c** and **67i-j** are converted to the corresponding Fe-derivatives using the reagent **190** (25 °C, 0.75 equiv). All four substrates could be metalated with the same rate observed for the reagent **181** (Table 24) additionally indicating the existence of a Fe(II)-species. The subsequent cross-couplings under similar conditions with primary aliphatic iodides in the presence of 4-fluorostyrene (**186**; 10 mol-%) furnish the expected substituted benzoates **187i**, **187l**, **187n** and **187p** in 58-78% yield. Compared to the obtained results using TMP_2Fe (**181**), these isolated yields are significantly lower due to possible side reactions.

Table 24: Preparation of diaryl-Fe(II) derivatives using the Fe-base **190** and subsequent reactions with aliphatic iodides.

Entry	Substrate	Time [h]	Organic halide	Product/Yield [%][a]
1	 **67b**	36	I-Pent	 **187i**: 73 (81)

Entry	Substrate	Time [h]	Organic halide	Product/Yield [%][a]
2	 **100c**	36	I-Pr	 **187l**: 58 (65)
3	 **67i**	18	I-Hex	 **187n**: 74 (81)
4	 **67j**	48	I-Hex	 **187p**: 59 (70)

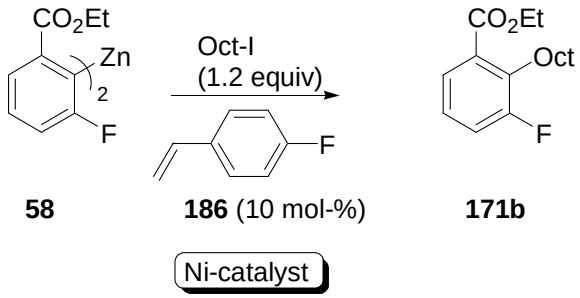
[a] Isolated yield of analytically pure product. The yields in brackets refer to the ones obtained by using TMP_2Fe (**181**; 0.75 equiv).

11.6 Preliminary Experiments about a Ni-catalyzed Alkylation of Organozinc Reagents

Although the Ni-catalyzed alkylation of organozinc reagents has been already reported,[117] the new results (especially the low catalyst loading) are worth investigating this reaction once again. Hence, the reaction of the diarylzinc species **58** (for the preparation, see chapt. 3) with Oct-I is carried under different conditions, but in the presence of 4-fluorostyrene (**186**), since first experiments have shown the necessity of this additive. Thus, the use of $NiCl_2$ in small quantities (0.5 and 1.0 mol-%) gives only traces of the desired alkylated benzoate **171b** after 12 h at 25 °C (Table 25, entries 1-2). Under similar conditions, 2.5 mol-% of the Ni-catalyst provides 39% of desired product (entry 3), whereas a catalyst loading of 5 mol-% accounts a full conversion to **171b** (entry 4). Subsequently, these reactions are carried out at 55 °C for 8 h. Now, the progress to **171b** is significantly increased, since the use of $NiCl_2$ (0.5 mol-%) affords 33% of the substituted arene **171b** (entry 5). Moreover, the use of 1.0 mol-% of the Ni-catalyst gives the alkylated benzoate in 69% yield (entry 6). Accordingly, the complete formation of **171b** is accomplished within 8 h using $NiCl_2$ (2.5 mol-%; entry 7). Interestingly, if 1 mol-% of either $NiBr_2$ or $Ni(acac)_2$ is used as catalyst, a decreased rate leading to the benzoate **171b** is observed (entries 8-9).

[117] R. Giovannini, P. Knochel, *J. Am. Chem. Soc.*, **1998**, *120*, 11186.

Table 25: Cross-coupling of **58** with Oct-I in the presence of 4-fluorostyrene (**186**) leading to the substitution product **171b**.



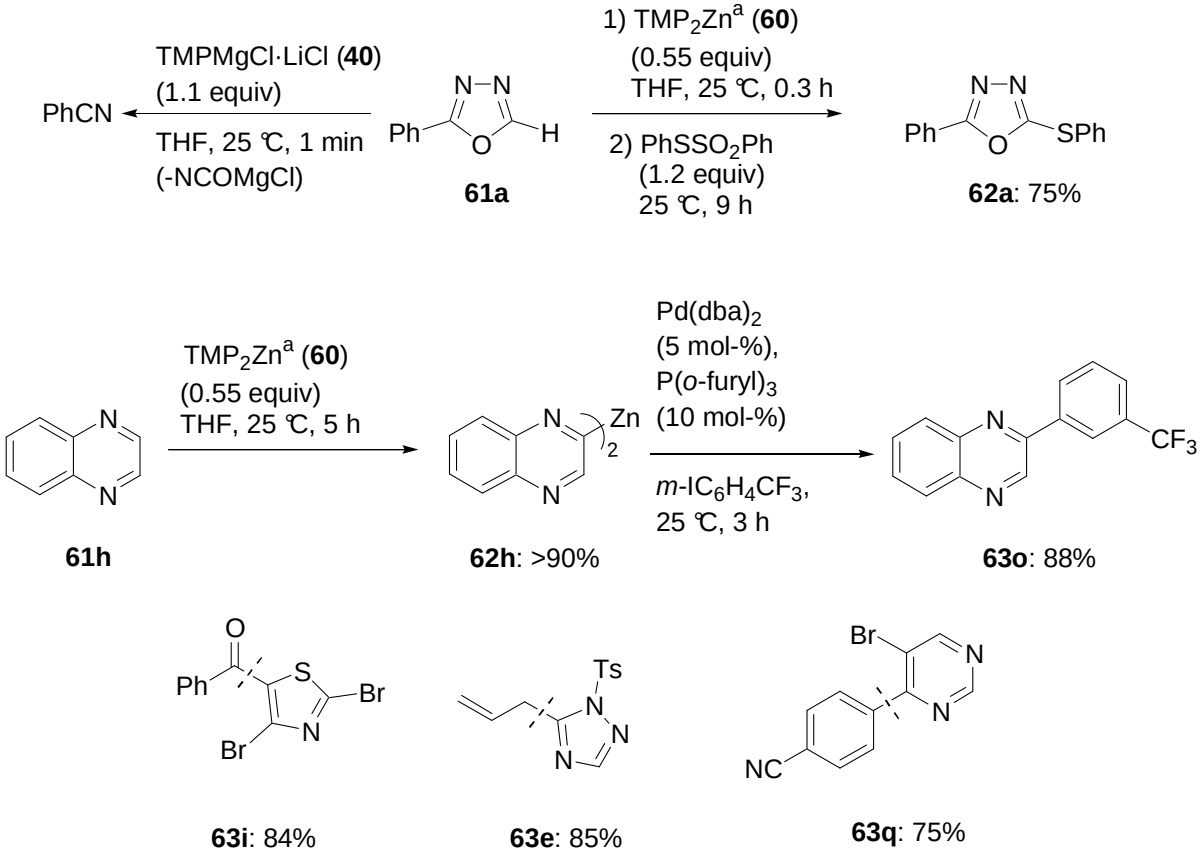
Entry	Ni-catalyst	*T* [°C], *t* [h]	Conversion to **171b** [%]
1	$NiCl_2$ (0.5 mol-%)	25, 12	<5
2	$NiCl_2$ (1.0 mol-%)	25, 12	<5
3	$NiCl_2$ (2.5 mol-%)	25, 12	39
4	**$NiCl_2$ (5.0 mol-%)**	**25, 12**	**94**
5	$NiCl_2$ (0.5 mol-%)	55, 8	33
6	$NiCl_2$ (1.0 mol-%)	55, 8	69
7	**$NiCl_2$ (2.5 mol-%)**	**55, 8**	**95**
8	$NiBr_2$ (1.0 mol-%)	55, 8	41
9	$Ni(acac)_2$ (1.0 mol-%)	55, 8	56

12 Summary and Outlook

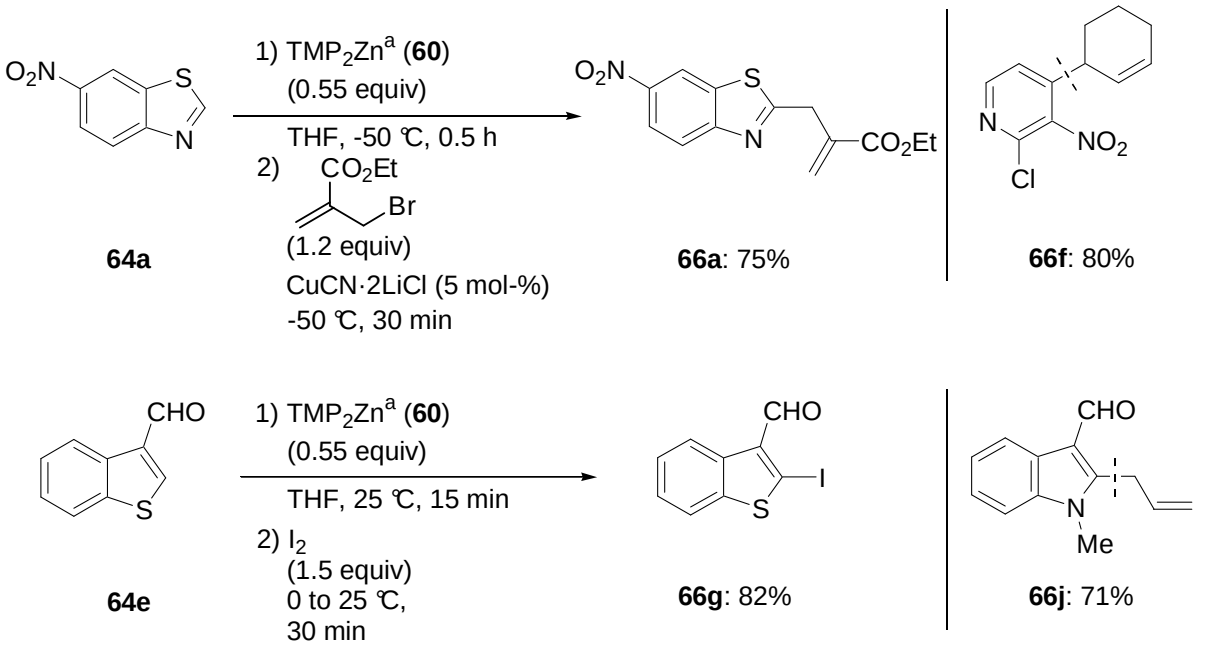
This work was focused on the formation of functionalized organometallics *via* directed metalation using new hindered TMP-amide bases. After the convenient preparation of the respective amide bases, the transformations of organic substrates into new organometallics could be readily accomplished in an atom-economical way and opens new pathways in organic synthesis. The resulting organometallics have been reacted with various electrophiles giving the desired products in moderate to excellent yields.

12.1 Directed Zincations

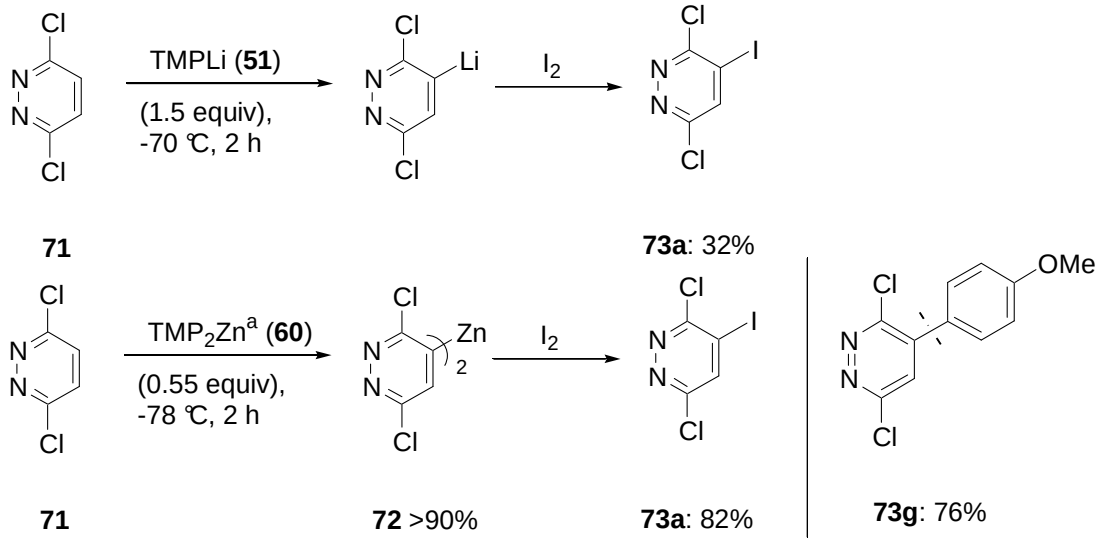
By using the new reagent $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**), the metalation of various sensitive heterocycles like 2-phenyl-1,3,4-oxadiazole (**61a**) or quinoxaline (**61h**) could be successfully achieved which easily undergo ring-fragmentation or dimerization (Scheme 66). Usually, the zincations can be carried out at very convenient temperatures with high regioselectivity. Remarkably, the outstanding tolerance towards functional groups was demonstrated by the smooth zincation of substrates bearing sensitive functionalities such as aldehydes or nitro-groups (Scheme 67). The corresponding Mg- or Li-organometallics of these substrates could not be prepared by using directed metalations. Moreover, an efficient functionalization of 3,6-dichloropyridazine (**71**) was achieved (Scheme 68). Naturally, aromatics and heteroaromatics bearing esters and cyano-groups could also be successfully zincated (Scheme 69). The generated diorganozinc reagents underwent smooth copper-mediated acylations or Pd-catalyzed cross-couplings. The alternadtive base $[(t\text{Bu})(i\text{Pr})N]_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**87**) proved to be an alternative to the zinc base **60**.



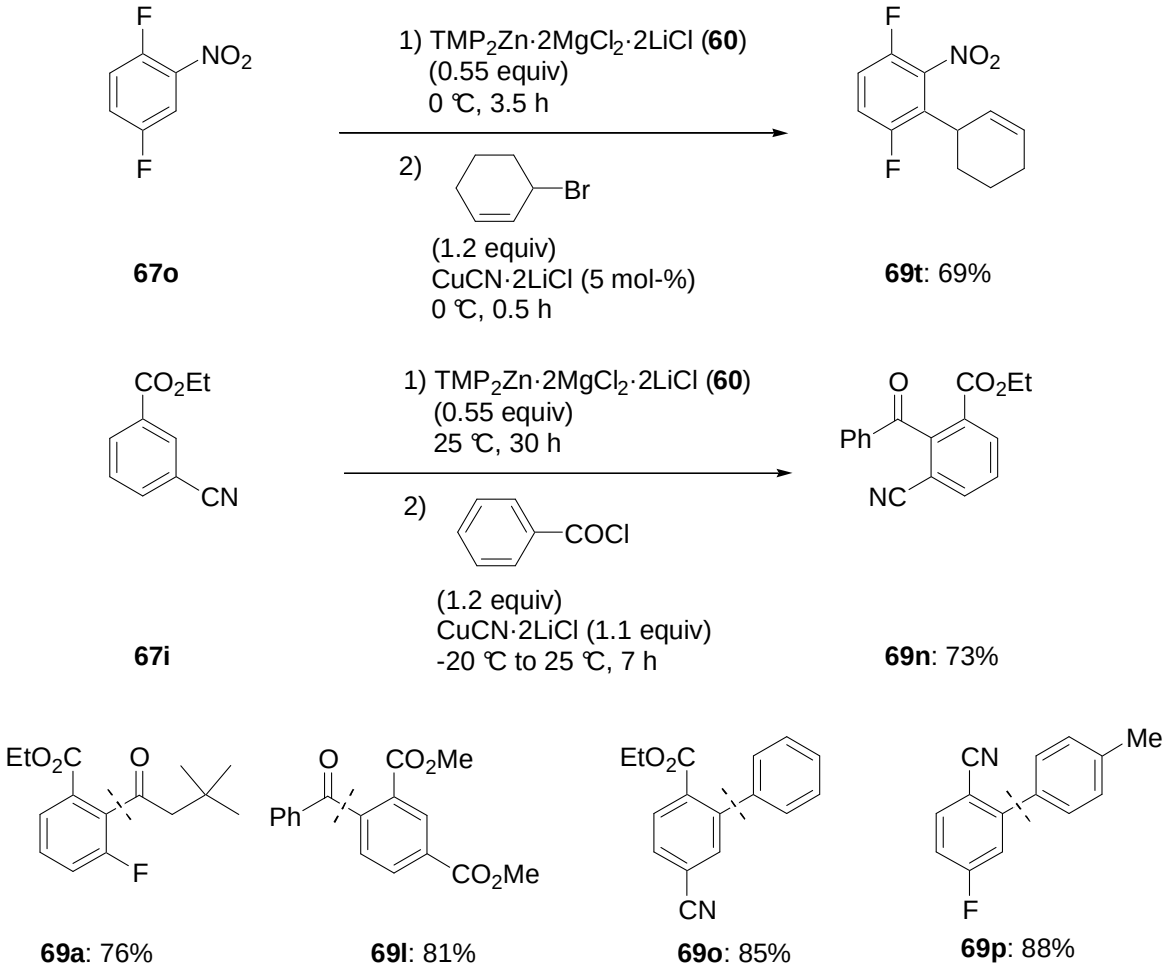
Scheme 66: Functionalization of heterocycles with TMP_2Zn^a (**60**). [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.



Scheme 67: Functionalization of heterocycles bearing sensitive functionalities with TMP_2Zn^a (**60**). [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

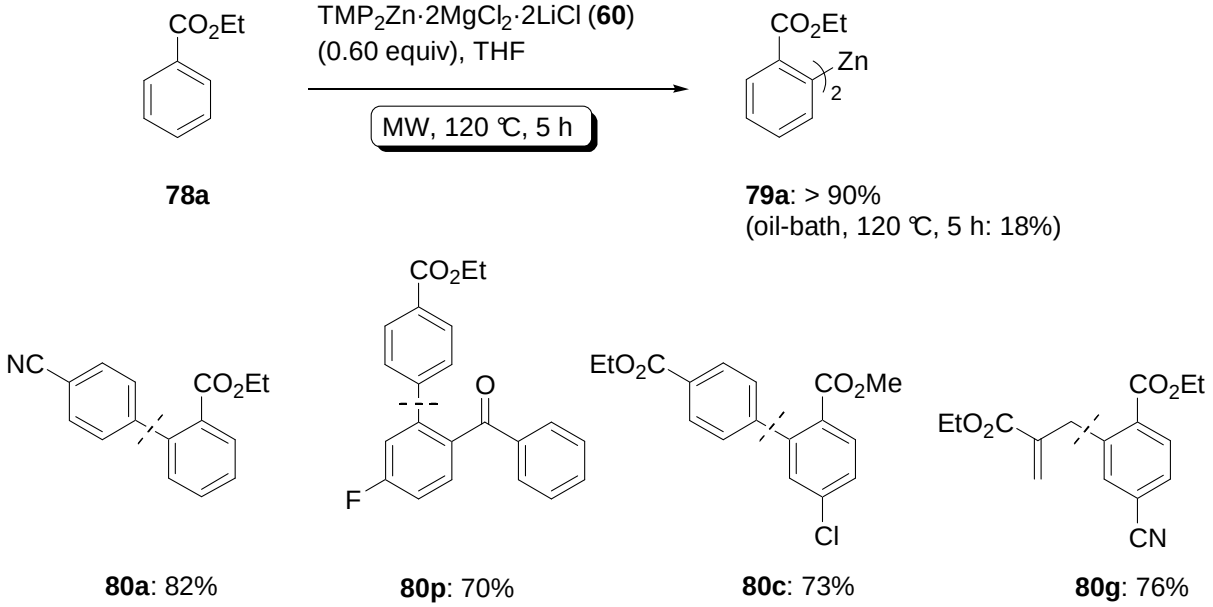


Scheme 68: Functionalization of 3,6-dichloropyridazine (**71**) with TMP_2Zn[a] (**60**). [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.



Scheme 69: Products obtained by directed zincation using $TMP_2Zn·2MgCl_2·2LiCl$ (**60**).

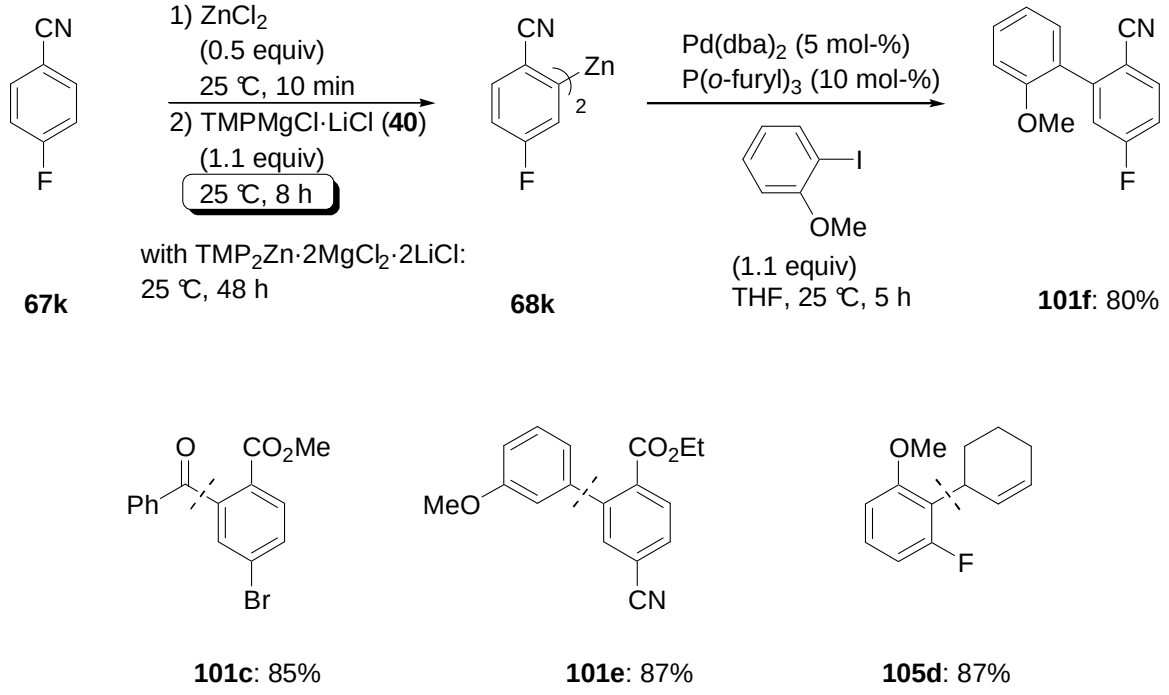
Furthermore, the zincation of medium-activated substrates was successfully carried out using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) and microwave irradiation. Thereby, we could show that the tolerance towards functional groups still remains extraordinary (e. g. tolerance of a ketone and of methyl esters). The metalation times can be reduced from several days to a few hours and in some cases the metalation can just be carried out under microwave conditions. This mode of heating is essential for the dramatically accelerated formation of diorganozinc species since the thermic energy is efficiently absorbed by the present salts (Scheme 70).



Scheme 70: Products obtained by directed zincation using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) and microwave irradiation.

12.2 Directed Metalation Using *in situ* Protocols

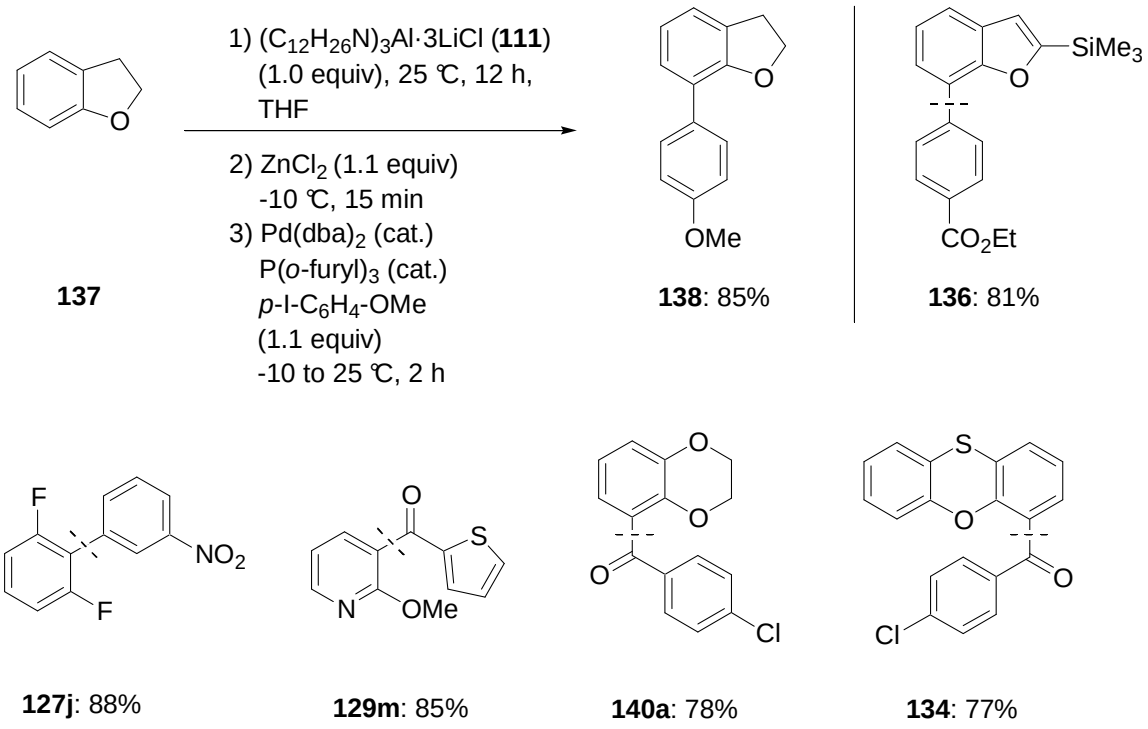
Additionally, we could show that the treatment of an aromatic or heteroaromatic substrate with a Lewis-acid like $ZnCl_2$ or Et_3Al *prior* to the addition of the base TMPMgCl·LiCl (**40**) furnished highly regioselective and fast metalations combined with good tolerance of functional groups like esters or cyano-groups (Scheme 71). Usually, these metalations are carried at –5 to 25 °C. Interestingly, mechanistic studies revealed that the *in situ* metalation using $ZnCl_2$ proceeds over a different pathway than by using Et_3Al.



Scheme 71: Products obtained by directed metalations using *in situ* protocols.

12.3 Directed Metalation Using Aluminum Bases

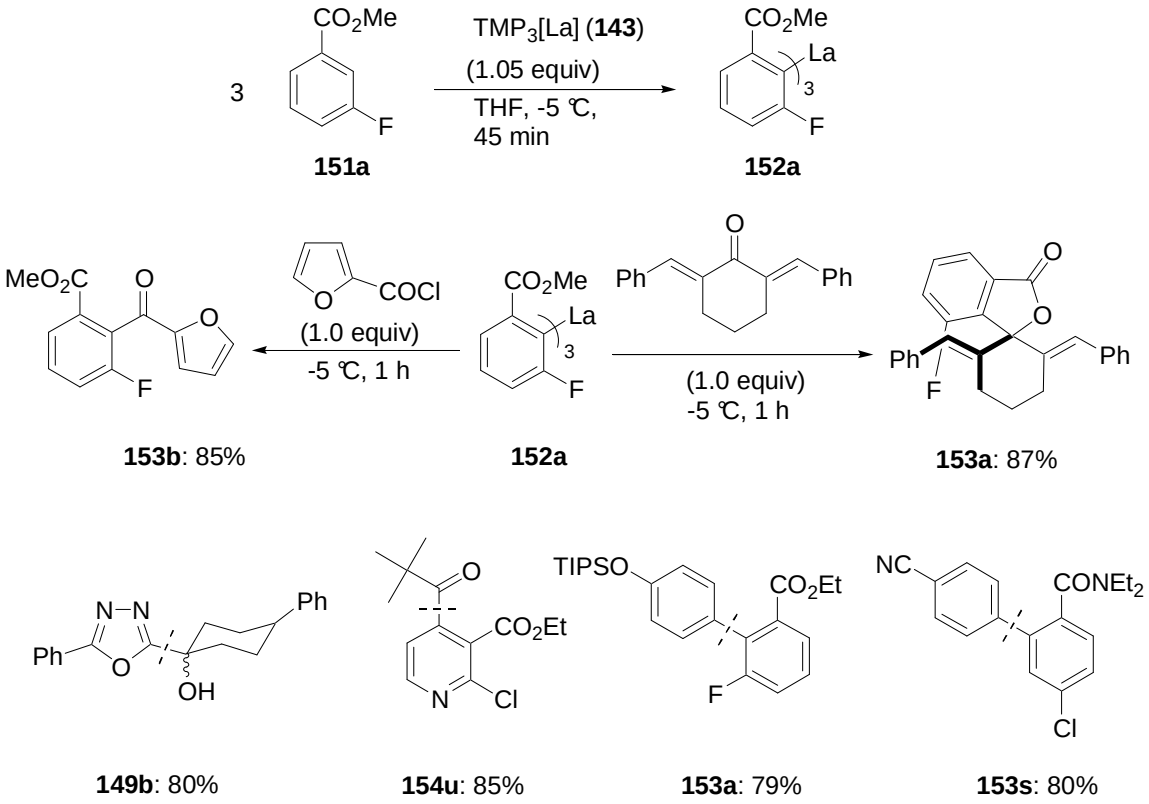
In this project, we have shown that the new aluminum amide **111** readily transforms a number of aromatics and heteroaromatics into the corresponding aryl aluminum species tolerating *tert*-butyl esters and cyano-groups. Molecules bearing halogen atoms (e.g. *bis*-halogenated benzenes) undergo smooth alumination reactions. Remarkably, these aluminations proceed with unique regioselectivity especially at aromatics and heteroaromatics bearing ether-groups (The use of Zn- or Mg-amides did not lead to satisfactory metalation rates). Therefore, various organic substrates could be efficiently metalated for the first time allowing the creation of unusual substitution patterns (Scheme 72). Moreover, the alumination of those ethers can be mostly carried out at 25 °C.



Scheme 72: Products obtained by directed metalations using the aluminum amide **111**.

12.4 Directed Metalation Using $TMP_3La\cdot3MgCl_2\cdot5LiCl$ (143)

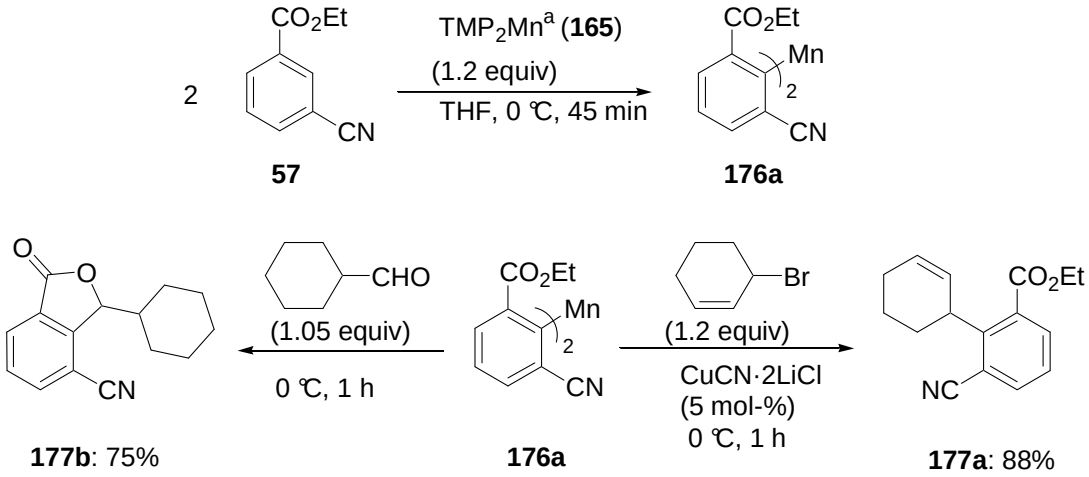
Accordingly, the high affinity to carbonyl groups was used to generate efficiently the *tris*-organo lanthanum reagents using $TMP_3La\cdot3MgCl_2\cdot5LiCl$ (**143**) with enhanced progress compared to the Zn amide **60**. Noteworthy, ethyl and methyl ester are tolerated as well as cyano-groups and the lanthanation of sensitive heteroaromatics could also be accomplished. Remarkably, Pd-catalyzed cross coupling reactions can be carried out without transmetalation to Zn. Moreover, the organolanthanum reagents can be directly acylated by the reaction with acid chlorides or an acid anhydride and add conveniently to aldehydes and ketones (Scheme 73).



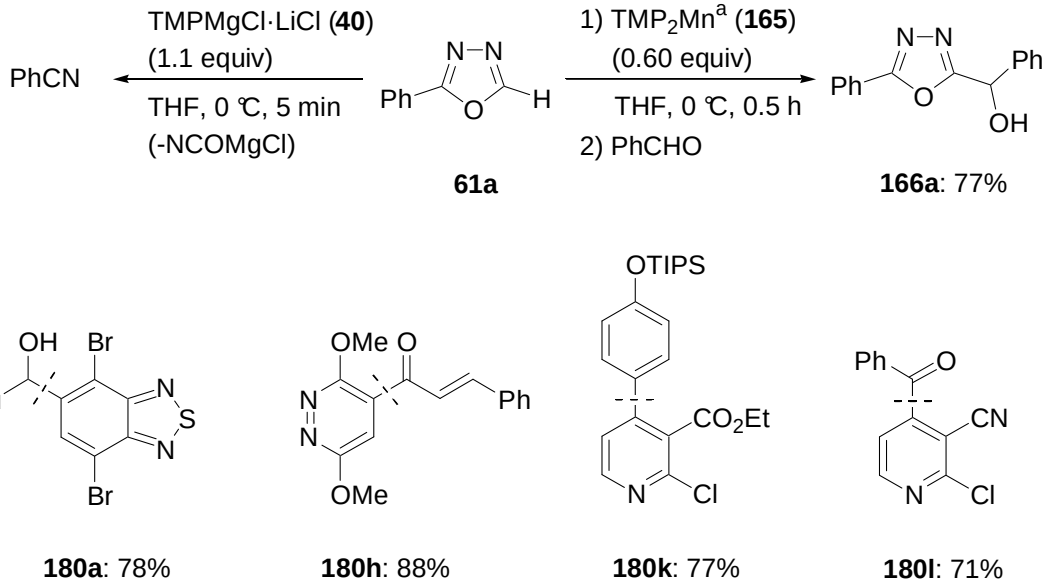
Scheme 73: Products obtained by directed metalations using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**).

12.5 Directed Metalation Using $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (165)

The metalation using the highly kinetic active base $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**165**) proved to be quite general. This reagent combines high metalation rates (approx. ten times faster than the Zn amide **60**) with excellent tolerance of functional groups (esters, cyano-groups or a ketone) and good regioselectivity (Scheme 74). Additionally, the metalation of sensitive heterocycles proceeded well (Scheme 75) showing the existence of Mn-species. The resulting diorgano manganese reagents added efficiently to aldehydes and heteroatom electrophiles. These highly reactive organometallics also underwent smooth Cu-catalyzed allylations and acylations as well as Pd-catalyzed cross-couplings.



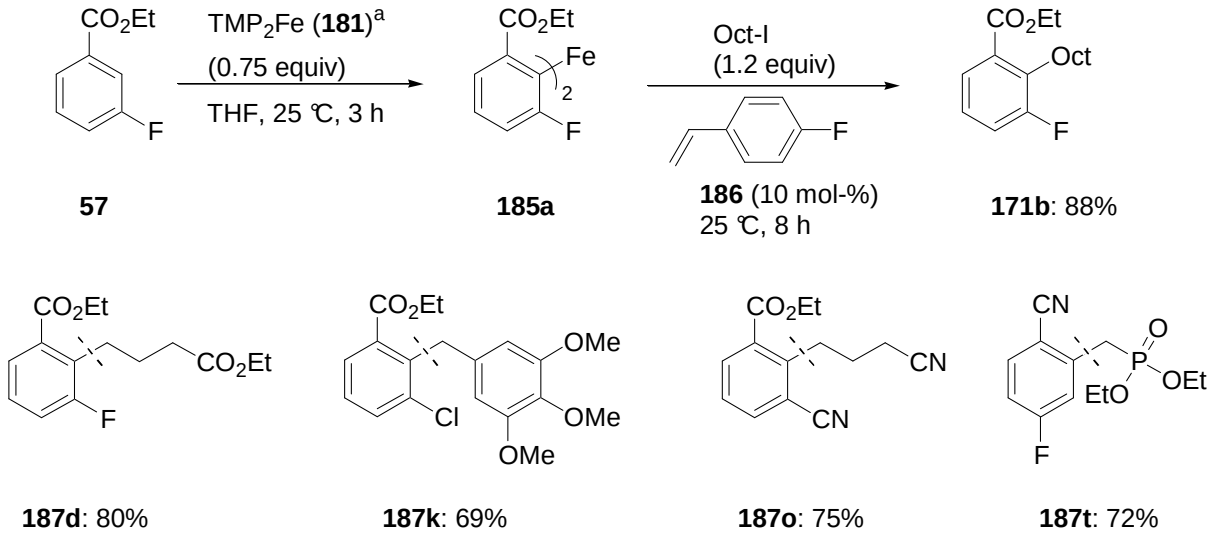
Scheme 74: Products obtained by directed metalations of aromatics using $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**165**). [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.



Scheme 75: Products obtained by directed metalations of heteroaromatics using $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**165**). [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

12.6 Directed Metalation Using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (181)

Finally, the preparation of aryl-Fe(II)-derivatives starting from various aromatics was successfully achieved with the new reagent $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**). The resulting organometallics underwent smooth cross-couplings with various alkyl iodides and bromides in the presence of 4-fluorostyrene (**186**) as well as benzylic chlorides (Scheme 76). Interestingly, the Ni-impurities of commercial available $FeCl_2$ were found to be responsible for the observed cross-coupling rate.



Scheme 76: Products obtained directed metalations using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**). [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

12.7 Outlook

Although various new amide bases have been presented, a few more metals for the preparation of such reagents are conceivable. Especially the low-toxic, cheap and high Lewis-acidic metals Zr and Ti can lead to an unique reactivity due to the high positive charge and oxophily of the metal centers. Since the reactivity of the developed amide bases has been compared for the transformation of aromatics and heteroaromatics into the corresponding organometallics, these methodologies could be now adapted to the deprotonation of benzylic, allylic and vinylic systems. Furthermore, the selective formation of enolates and the subsequent reaction with aldehydes could be investigated in detail to give highly diastereoselective aldol products.

13 Experimental Part

13.1 General Considerations

All reactions were carried out with magnetic stirring and, if air or moisture sensitive, in flame dried glassware under argon. Syringes were used to transfer solvents and reagents, and were purged with argon prior to use.

Solvents

Solvents were dried according to standard methods by distillation over drying agents as stated below and were stored under argon.

Dichloromethane was predried over CaH_2 and distilled from CaH_2.

Diethyl ether was predried over calcium hydride and dried with the solvent purification system by INNOVATIVE TECHNOLOGIES INC (SPS-400-2; Al_2O_3, 1-3 mm, ICN, Eschwege, Germany).

DMF was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

Methanol was treated with magnesium turnings (10 g/L), heated to reflux and distilled.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

Triethylamine was dried over KOH and distilled.

Chromatography

Thin layer chromatography (TLC) was performed using aluminium plates coated with SiO_2 (Merck 60, F-254). The spots were visualized by UV light or by staining of the TLC plate with the solution below followed by heating if necessary:

- Phosphomolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12.0 mL) in water (230 mL)
- Iodine absorbed on silica gel
- $KMnO_4$ (0.3 g), K_2CO_3 (20 g) and KOH (0.3 g), in water (300 mL).

Flash column chromatography was performed using SiO_2 60 (0.04-0.063 mm, 230-400 mesh) from Merck.

Analytical data

NMR spectra were recorded on *Bruker* ARX 200, AC 300 WH 400 or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the solvent peak. NMR spectra were recorded on solutions in $CDCl_3$ (residual chloroform: δ 7.25 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR), d_6-DMSO (residual DMSO: δ 2.49 ppm for ^{1}H NMR and δ 39.5 ppm for ^{13}C NMR), d_8-THF (residual THF: δ 1.73, 3.58 for ^{1}H NMR and δ 25.3 and 67.4 ppm for ^{13}C NMR) or d_6-benzene (residual benzene: δ 7.27 ppm for ^{1}H NMR and δ 128.0 ppm for ^{13}C NMR).
For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), q (quartet), qn (quintet), m (multiplet), as well as br (broad).

Melting points are uncorrected and were measured on a *Büchi* B.540 apparatus.

Infrared spectra were recorded from 4000-400 cm^{-1} on a Perkin 281 IR spectrometer. Samples were measured neat (ATR, Smiths Detection DuraSampl IR II Diamond ATR). The absorption bands were reported in wave numbers (cm^{-1}).

Gas chromatography was performed with machines of type *Hewlett-Packard* 6890 or 5890 series II, using a column of type HP 5 (*Hewlett-Packard*, 5% phenylmethylpolysiloxane; length: 15 m, diameter: 0.25 mm; film thickness 0.25 µm). The detection was accomplished by using a flame ionization detector. The carrier gas was air; alkanes like decane or tetradecane were used as internal standards.

Mass Spectra were recorded on Finnigan MAT 95Q or Finnigan MAT 90 instrument for electron impact ionization (EI). High resolution mass spectra (HRMS) were recorded on the same instrument.

13.2 Reagents

As not otherwise stated, all reagents were obtained from commercial sources. Reagents of >97% purity were used without purification, except technical grade tosyl cyanide (purity

95%). Liquid acid chlorides and aldehydes were distilled prior to use. TMPH was distilled from CaH_2 and stored under argon.

The following substances were prepared according to literature procedures:

2-Phenyl-1,3,4-oxadiazole, [118] 2-(4-chloro-phenyl)-1,3,4-oxadiazole,[118] 1-tosyl-1*H*-1,2,4-triazole,[119] 1-tosyl-1*H*-4-nitro-imidazole,[119] 2,4-dibromo-thiazole,[120] 2-nitrobenzofuran,[121] 3,6-dibromo-2,1,3-benzothiadiazole,[122] 3,6-dimethoxy-pyridazine,[123] *tert*-butyl benzoate,[124] *tert*-butyl 2-chlorobenzoate,[124] of *tert*-butyl 4-methoxybenzoate,[124] *tert*-butyl 1-naphthanoate,[124] 2-trimethylsilanylbenzofuran,[125] 3-fluoro-phenyl-*N*,*N*,*N'*,*N'*-tetramethyl-diamidophosphate,[40] 3-dimethylsulfamoyloxybenzoic acid ethyl ester,[40] cyclohexenyl bromide, [126] 2-bromomethylacrylic acid ethyl ester,[55] (4-iodophenoxy)-triisopropylsilane,[127] 4-iodobutyric acid ethyl ester, [128] 6-iodohex-1-ene,[128] 6-iodo-2,2-di-methyl-hexanenitrile,[128] 4-iodobutyronitrile.[128]

Preparation of *tert*-butyl-isobutylidene-amine (109):

A 500 mL round-bottom flask was charged with isobutyraldehyde (500 mmol, 36 g), *tert*-butylamine (750 mmol, 55 g), $MgSO_4$ (50 g) and CH_2Cl_2 (250 mL). The mixture was refluxed for 2 h, the $MgSO_4$ was filtered off and the solvent was then removed *in vacuo*. Distillation under ambient pressure afforded *tert*-butylisobutylidene-amine as a colourless liquid (47 g, 74%).

*i*PrMgCl·LiCl in THF (approx. 1.3 M) was purchased from Chemetall.

*n*BuLi in hexane (approx. 2.5 M) was purchased from Chemetall.

*t*BuLi in pentane (approx. 1.6 M) was purchased from Chemetall.

$LaCl_3$·2LiCl in THF (approx. 0.5 M) was purchased from Chemetall.

[118] C. Ainsworth, *J. Am. Chem. Soc.* **1955**, *77*, 1148.
[119] H. Law, I. Baussanne, J. M. García Fernandéz, Jaques Defaye, *Carbohydr. Res.* **2003**, 451.
[120] P. Reynaud, M. Robba, R. C. Moreau, *Bull. Chim. Fr.* **1962**, 1735.
[121] A. Tromelin, P. Demerseman, R. Royer, *Synthesis* **1985**, *11*, 1074.
[122] F. S. Mancilha, B. A. Da Silveira Neto, A. S. Lopes, P. F. Moreira, F. H. Quina, R. S. Goncalves, J. Dupont, *Eur. J. Org. Chem*. **2006**, 4924.
[123] J. Druey, Kd. Meier, Kd.; K. Eichenberger, *Helv. Chim. Acta* **1954**, *37*, 121.
[124] E. C. Taylor, P. S. Ray, *J. Org. Chem*. **1988**, *53*, 35.
[125] D. Crich, D. Daniel, *J. Org. Chem.* **1005**, *70*, 2384.
[126] S. Fuchs, V. Berl, Valerie; J.-P. Lepoittevin, *Eur. J. Org. Chem*. **2007**, 1145.
[127] D. J. Aitken, S. Faure, S. Roche, *Tetrahedron Lett.* **2003**, *44*, 8827.
[128] C. M. Thompson, J. A. Frick, *J. Org. Chem*. **1989**, *54*, 890.

The metal chlorides for the preparation of the corresponding amide bases were purchased as follows:

$ZnCl_2$ (>99% purity):	Merck
$AlCl_3$ (>99% purity):	Merck
$MnCl_2$ (>99% purity):	Acros
$FeCl_2$ (98% purity and 99.998% purity):	Aldrich

$ZnCl_2$ (1.0 M in THF):

This solution was prepared by drying $ZnCl_2$ (68.2 g, 500 mmol) under high vacuum (1 mbar) for 6 h at 150 °C. After cooling to 25 °C, dry THF (500 mL) was added and stirring was continued until the salt was completely dissolved.

$AlCl_3$ (0.33 M in THF):

In a dry and argon-flushed 100 mL Schlenk-flask, THF (60 mL) was cooled to -78 °C and dry $AlCl_3$ (20 mmol, 2.67 g) was added in small portions over a period of 20 min. The resulting mixture was stirred at -78 °C for 1 h and then slowly warmed to 0 °C within 4 h.

CuCN·2LiCl (1.0 M in THF):

A dry and argon-flushed 250 mL Schlenk-tube, equipped with a magnetic stirring bar and a glass stopper, was charged with LiCl (6.8 g, 160 mmol) and heated up to 150 °C under high vacuum for 3 h. After cooling to room temperature under argon, CuCN (7.2 g, 80 mmol, 99% pure) was added and the Schlenk-flask was further heated to 130 °C for 3 h under high vacuum, cooled to room temperature, charged with freshly distilled THF (80 mL) under argon with vigorous stirring. The mixture was stirred for at least 24 h at 25 °C. The reagent CuCN·2LiCl (1.0 M in THF) appears as a pale yellow solution.

$MnCl_2$·2LiCl (1.0 M in THF):

A dry and argon-flushed 250 mL Schlenk-tube, equipped with a magnetic stirring bar and a glass stopper, was charged with LiCl (6.8 g, 160 mmol) and heated up to 150 °C under high vacuum for 3 h. After cooling to room temperature under argon, $MnCl_2$ (10.1 g, 80 mmol, 99% pure) was added under inert atmosphere inside a glove-box. The Schlenk-flask was further heated to 130 °C for 3 h under high vacuum, cooled to room temperature, charged with freshly distilled THF (80 mL) under argon with vigorous stirring. The mixture was

stirred for at least 24 h at 25 °C. The reagent $MnCl_2 \cdot 2LiCl$ (1.0 M in THF) appears as a yellow solution.

$FeCl_2 \cdot 2LiCl$ (1.0 M in THF):

A dry and argon-flushed 250 mL Schlenk-tube, equipped with a magnetic stirring bar and a glass stopper, was charged with LiCl (4.7 g, 110 mmol) and heated up to 150 °C under high vacuum for 3 h. After cooling to room temperature under argon, $FeCl_2$ (6.34 g, 50 mmol, 98% pure) was added under inert atmosphere inside a glove-box. The Schlenk-flask was further heated to 130 °C for 5 h under high vacuum, cooled to room temperature, charged with freshly distilled THF (50 mL) under argon and wrapped in an aluminium foil to protect it from light. The mixture was vigorously stirred until all solid goes in solution (ca. 6 h). The reagent $FeCl_2 \cdot 2LiCl$ (1.0 M in THF) appears as a brown solution.

Preparation of TMPMgCl·LiCl (40):

A dried and argon-flushed 2 L Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, was charged with *i*PrMgCl·LiCl (1.31 M in THF, 850 mL, 1.11 mol). Then, 2,2,6,6-tetramethylpiperidine (161 g, 194 mL, 1.14 mol, 1.02 equiv) was added at once and the mixture was stirred until gas evolution ceases (48 h). Titration with benzoic acid using 4-(phenylazo)diphenylamine as indicator prior to use showed a concentration of about 1.15 M.

Preparation of $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (60):

A flame-dried and nitrogen-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, was charged with a solution of TMPMgCl·LiCl (**1**; 348 mL, 400 mmol) and cooled to 0 °C. Then, $ZnCl_2$ (1.0 M in THF, 200 mL, 200 mmol, 0.5 equiv) was added over a period of 15 min. After stirring this mixture for 2 h at 0 °C, the solution of $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**) was concentrated *in vacuo*. Titration with benzoic acid using 4-(phenylazo)diphenylamine as indicator prior to use showed a concentration of 0.40-0.50 M.

Preparation of $[(t\text{Bu})N(i\text{Pr})]_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (87):

A dried, argon flushed 250 mL Schlenk-flask equipped with magnetic stirring bar and rubber septum was charged with $ZnCl_2$ (4.09 g, 30 mmol). The flask was heated to 150 °C under high vacuum for at least 6 h under vigorous stirring. After cooling to 25 °C, dry THF (10 mL) was added and the resulting slurry was cooled to 0 °C with an ice bath. Then (*t*Bu)(*i*Pr)NMgCl·LiCl (**86**; 41.4 mL, 1.45 M in THF, 60 mmol) was added via syringe. The

mixture was stirred for 12 h until complete dissolution of the salts. Precipitates of the base **54** can easily be redissolved by adding a few mL of dry THF. The freshly prepared $[(t\text{Bu})(i\text{Pr})\text{N}]_2\text{Zn}\cdot 2\text{MgCl}_2\cdot 2\text{LiCl}$ solution was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.50 M in THF was obtained.

Preparation of $[(t\text{Bu})\text{N}(i\text{Pr})]_3\text{Al}\cdot 3\text{LiCl}$ (107):

In an argon flushed Schlenk-flask, [(*t*Bu)N(*i*Pr)] (**85**; 6.9 g, 60.0 mmol) was dissolved in THF (60 mL). This solution was cooled to –40 °C and *n*BuLi (2.40 M in hexane, 25 mL, 60.0 mmol) was added dropwise. After the addition was complete, the reaction mixture was warmed to 0 °C and stirred at this temperature for 30 min. Then, the solution was cooled to –78 °C and the freshly prepared solution of $AlCl_3$ (20 mmol, 2.67 g) in THF was added. The mixture was stirred at –60 °C for 15 h. The solvents were then removed *in vacuo* without heating, affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring, until a complete dissolution of the salts was observed. The fresh $[(t\text{Bu})\text{N}(i\text{Pr})]_3\text{Al}\cdot 3\text{LiCl}$ (**107**) solution was titrated prior to use at 0 °C with menthol or 2-propanol using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.23 M in THF was obtained.

Preparation of the Reagent $TMP_3Al\cdot 3LiCl$ (108):

In an argon flushed Schlenk-flask, 2,2,6,6-tetramethylpiperidine (8.5 g, 60.0 mmol) was dissolved in THF (60 mL). This solution was cooled to –40 °C and *n*BuLi (2.40 M in hexane, 25 mL, 60.0 mmol) was added dropwise. After the addition was complete, the reaction mixture was warmed to 0 °C and stirred at this temperature for 30 min. Then, the solution was cooled to –78 °C and the freshly prepared solution of $AlCl_3$ (20 mmol, 2.67 g) in THF was added. The mixture was stirred at –60 °C for 15 h. The solvents were then removed *in vacuo* without heating, affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring, until a complete dissolution of the salts was observed. The fresh $TMP_3Al\cdot 3LiCl$ (108) solution was titrated prior to use at 0 °C with menthol or 2-propanol using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.30 M in THF was obtained.

Preparation of the reagent tris-(*tert*-butyl-(1-isopropyl-2,2-dimethyl-propyl)-amide)aluminum-tris(lithium chloride) ($(C_{12}H_{26}N)_3Al\cdot3LiCl$; 111):

In a dry and argon flushed Schlenk-flask, *tert*-butyl-isobutylidene-amine (**109**; 7.63 g, 60.0 mmol) was dissolved in THF (60 mL). This solution was cooled to –78 °C and *t*BuLi (1.50 M in pentane, 40 mL, 60.0 mmol) was added dropwise and stirred at this temperature for 4 h. Then, a freshly prepared solution of $AlCl_3$ (20 mmol, 2.67 g) in THF was added. The mixture was stirred at –60 °C for 15 h. The solvents were then reduced *in vacuo*. The freshly prepared *tris*-(*tert*-butyl-(1-isopropyl-2,2-dimethyl-propyl)-amide)aluminum-*tris*(lithium chloride) ($(C_{12}H_{26}N)_3Al\cdot3LiCl$; **111**) solution was titrated prior to use at 0 °C with menthol or 2-propanol using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.30 M in THF was obtained.

Preparation of the reagent $TMP_3La\cdot3MgCl_2\cdot5LiCl$ (143):

In a dry and argon-flushed 250 mL Schlenk-flask, freshly titrated TMPMgCl·LiCl (**1**; 100 mmol, 1.18 M, 85 mL) was purged and cooled to 0 °C. Then, freshly titrated $LaCl_3\cdot2LiCl$ (0.50 M in THF, 66 mL, 33 mmol) was added over 5 min. The resulting mixture was stirred for 30 min at 0 °C, warmed to 25 °C and stirred for another 12 h. The resulting solution of $TMP_3La\cdot3MgCl_2\cdot5LiCl$ (**143**) was concentrated *in vacuo* and was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.33 M in THF was obtained.

Preparation of the reagent $TMP_2Mn\cdot2MgCl_2\cdot4LiCl$ (165):

In a dry and argon-flushed 250 mL Schlenk-flask, freshly titrated TMPMgCl·LiCl (**40**; 200 mmol, 1.18 M, 170 mL) was purged and cooled to 0 °C. Then, $MnCl_2\cdot2LiCl$ (1.0 M in THF, 100 ml, 100 mmol) was added over a period of 5 min. The resulting mixture was stirred for 30 min at 0 °C, warmed to 25 °C and stirred for another 3 h. The resulting solution of $TMP_2Mn\cdot2MgCl_2\cdot4LiCl$ (**165**) was concentrated *in vacuo* and was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.50 M in THF was obtained.

Preparation of the reagent $TMP_2Fe\cdot2MgCl_2\cdot4LiCl$ (181):

In a dry and argon-flushed 250 mL Schlenk-flask, freshly titrated TMPMgCl·LiCl (**40**; 100 mmol, 1.18 M, 85 mL) was purged and cooled to 0 °C. Then, $FeCl_2\cdot2LiCl$ (1.0 M in THF, 50 ml, 50 mmol) was added over 5 min. The resulting mixture was stirred for 30 min at 0 °C,

warmed to 25 °C and stirred for another 3 h. The resulting solution of $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**) was concentrated *in vacuo* and was titrated prior to use at 0 °C with benzoic acid (0.2 M in THF) using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.50 M in THF was obtained.

Preparation of the reagent {TMP_2Fe} (190):

In a dry and argon-flushed 250 mL Schlenk-flask, freshly titrated TMPMgCl·LiCl (30 mmol, 1.18 M, 25 mL) and THF (50 mL) was purged and cooled to –5 °C. Then, $FeCl_3$ (1.63 g, 10 mmol) was added in small portions. The resulting mixture was stirred for 30 min at –5 °C, slowly warmed to 25 °C and stirred for another 5 h. The resulting solution of {TMP_2Fe} (**190**) was concentrated *in vacuo* and was titrated prior to use at 0 °C with benzoic acid (0.2 M in THF) using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.50 M in THF was obtained (yield: 70%).

Mössbauer spectroscopy was recorded at 90 K with v_{max} = 5.99294 mm/s using a conventional Mössbauer spectrometer operating in the constant acceleration mode. The sample was placed in an Oxford bath cryostat.

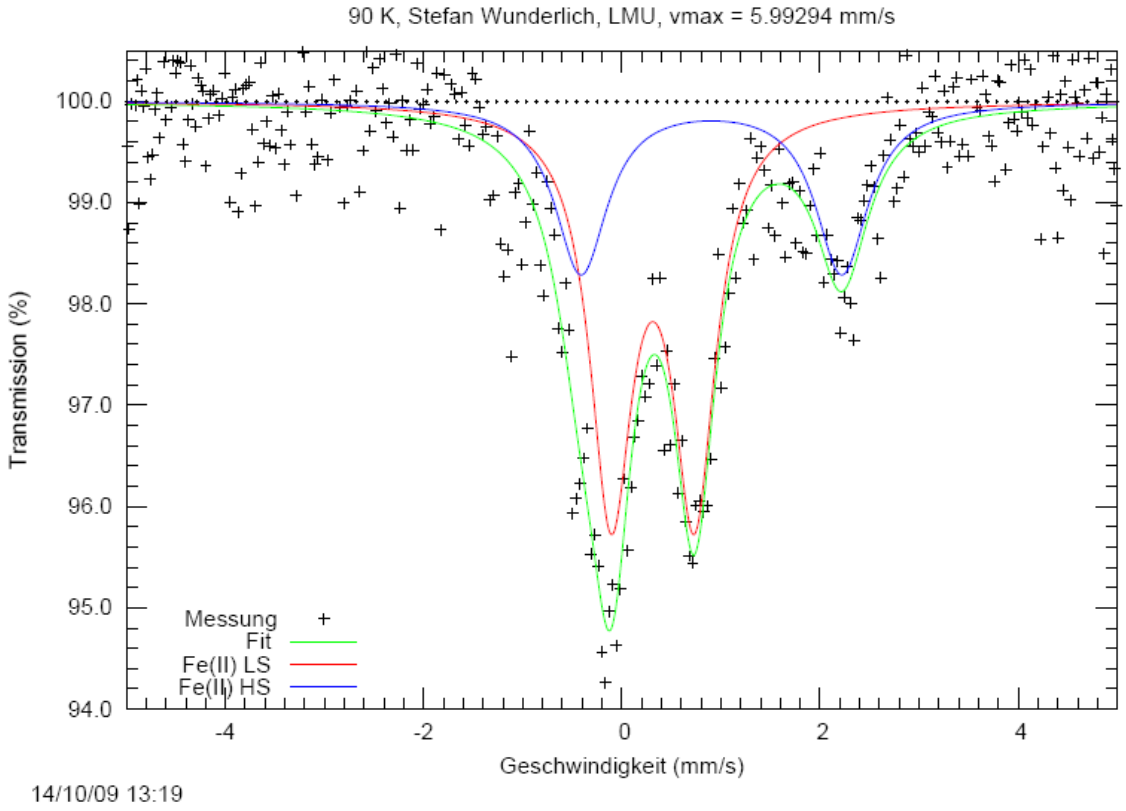


Figure 5: Mössbauer-spectrum of {TMP_2Fe} (**190**).

13.3 Typical Procedures

Typical procedure for the zincation of polyfunctionalized aromatics and heterocycles using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (60) or $[(tBu)N(iPr)]_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (87) (TP 1):

A dry and argon flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding arene (2.0 mmol) in dry THF (2 mL). After setting the desired temperature, the indicated Zn-base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**) or $[(t\text{Bu})N(i\text{Pr})]_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**87**) was added dropwise and stirred at the same temperature. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

Typical procedure for the preparation of the zincated 3,6-dichloropyridazine (72) using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (60) (TP 2):

A dry and argon flushed 25-mL Schlenk-tube, equipped with a magnetic stirring bar was charged with a solution of 3,6-dichloropyridazine (**71**, 298 mg, 2.0 mmol) in dry THF (5 mL). The solution was cooled to –78 °C and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol) was added dropwise. The resulting mixture was stirred for 2 h at –78 °C. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with an I_2 solution in dry THF. Compound **72** was obtained in >90% yield as determined by titration with I_2.

Typical procedure for the zincation of polyfunctionalized aromatics and heterocycles with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (60) using microwave irradiation (TP 3):

A dry and argon flushed 10-mL pressurized vial, equipped with a magnetic stirring bar was charged with a solution of the corresponding arene (2.0 mmol) in dry THF (1 mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 1.2 mmol) was added and the reaction mixture was heated in a 10-mL pressurized vial, by using a Discover BenchMate® Microwave system under the indicated conditions (maximum magnetron power output 120 W). The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF. After complete metalation und cooling to room temperature, the resulting reaction mixture was put into a dry and argon flushed 25 mL Schlenk-flask, equipped with a magnetic

stirring bar and a septum. The subsequent reactions with electrophiles were carried out with the indicated conditions.

Typical procedure for the zincation of polyfunctionalized aromatics and heterocycles with TMPMgCl·LiCl (40) using $ZnCl_2$ (TP 4):

In a dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum the given starting material (2.0 mmol) was dissolved in THF (1 mL), $ZnCl_2$ (1.0 M solution in THF, 1.0 mL, 1.0 mmol) was added und the mixture was stirred for 10 min. TMPMgCl·LiCl (**40**; 1.2 M in THF, 1.85 mL, 2.2 mmol) was added dropwise at 25 °C and the reaction mixture was stirred at 25 °C for the indicated time. Complete metalation was detected by GC-analysis of reaction aliquots quenched with I_2 in dry THF using tetradecane as internal standard.

Typical procedure for the zincation of polyfunctionalized aromatics with TMPMgCl·LiCl (40) using Et_3Al (TP 5):

In a dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum the given starting material (2.0 mmol) was dissolved in THF (2 mL) and cooled to 0 °C. Et_3Al (300 mg, 2.6 mmol, 1.3 equiv) was added at 0 °C und the mixture was stirred for 10 min. TMPMgCl·LiCl (**40**; 1.2 M in THF, 1.85 mL, 2.2 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at the given temperature for the indicated time. Complete metalation was detected by GC-analysis of reaction aliquots quenched with allyl bromide in the presence of CuCN·2LiCl in dry THF using tetradecane as internal standard.

Typical procedure for the alumination of functionalized aromatics and heteroaromatics using aluminum bases (TP 6):

A dry and argon flushed 50-mL Schlenk-Tube, equipped with a magnetic stirring bar was charged with a solution of the corresponding arene (2.0 mmol) in dry THF (2 mL) and then brought to the indicated temperature. The corresponding aluminum-base **107**, **108** or **111** was added dropwise and the mixture was stirred at the indicated temperature. Complete metalation was detected by GC-analysis of reaction aliquots quenched with allyl bromide in the presence of CuCN·2LiCl using tetradecane as internal standard.

Typical procedure for the lanthanation of functionalized aromatics and heteroaromatics using $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (143) (TP 7):

In a dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum the given starting material (2.0 mmol) was dissolved in THF (2 mL). This solution was brought to the given temperature, then $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) was added dropwise and stirred at this temperature for the indicated time. The metalation progress was monitored by GC-analysis of reaction aliquots quenched with allyl bromide in the presence of CuCN·2LiCl in dry THF using tetradecane as internal standard.

Typical procedure for the manganation of functionalized aromatics and heteroaromatics using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (165) (TP 8):

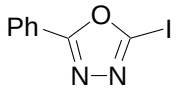
In a dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum the given starting material (2.0 mmol) was dissolved in THF (2 mL). This solution was brought to the given temperature, then $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol) was added dropwise and stirred at this temperature for the indicated time. Complete metalation was monitored by GC-analysis of reaction aliquots quenched with allyl bromide in the presence of CuCN·2LiCl in dry THF using tetradecane as internal standard.

Typical procedure for the ferration of functionalized aromatics using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (181) or {TMP_2Fe} (190) (TP 9):

In a dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum the given starting material (2.0 mmol) was dissolved in THF (1 mL). Then $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) or {TMP_2Fe} (**190**) was added dropwise at 25 °C and stirred at this temperature for the indicated time. The metalation progress was monitored by GC-analysis of reaction aliquots quenched with allyl bromide in the presence of CuCN·2LiCl in dry THF using tetradecane as internal standard.

13.4 Zincation of Arenes and Heteroarenes using $TMP_2Zn·2MgCl_2·2LiCl$ (60)

Synthesis of 5-iodo-2-phenyl-1,3,4-oxadiazole (63a)



According to **TP 1**, the metalation of 2-phenyl-1,3,4-oxadiazole (**61a**; 292 mg, 2.0 mmol) was finished within 20 min at 25 °C using a solution of $TMP_2Zn·2MgCl_2·2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). I_2 (762 mg, 3.0 mmol) dissolved in dry THF (4 mL) was then added dropwise at 0 °C, the resulting mixture was warmed to 25 °C and stirred for 0.5 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/CH_2Cl_2 = 1:1) to give **63a** (440 mg, 80%) as a colourless solid.

m.p.: 166.4-167.9 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.01-8.05 (m, 2 H), 7.50-7.60 (m, 3 H).

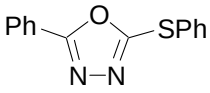
^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 169.63, 132.55, 129.39, 127.16, 123.09, 107.16.

MS (EI, 70 eV) *m/z* (%): 272 (48) [M^+], 146 (18), 145 (100), 105 (22), 103 (26), 89 (14), 77 (73).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1604, 1552, 1446, 1139, 1065, 1028, 979, 958, 775, 703.

HRMS (EI) for **$C_8H_5N_2OI$** (271.9447): 271.9459.

Synthesis of 2-phenyl-5-phenylsulfanyl-1,3,4-oxadiazole (63b):



According to **TP 1**, the metalation of 2-phenyl-1,3,4-oxadiazole (**61a**; 292 mg, 2.0 mmol) was finished within 20 min at 25 °C using a solution of $TMP_2Zn·2MgCl_2·2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $PhSSO_2Ph$ (300 mg, 2.4 mmol) dissolved in dry THF (4 mL) was then added dropwise at 25 °C, the resulting mixture was stirred for 9 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2) to give **63b** (382 mg, 75%) as a colourless solid.

m.p.: 62.4-63.1°C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.96 (d, *J*=7.5 Hz, 2 H), 7.65-7.71 (m, 2 H), 7.51 (t, *J*=7.3 Hz, 1 H), 7.41-7.51 (m, 5 H).

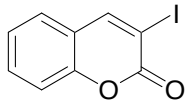
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 166.60, 163.13, 133.85, 132.07, 130.05, 129.99, 129.27, 127.36, 127.01, 123.77.

MS (70 eV, EI) *m/z* (%): 255 (7), 254 (68) [M^+], 198 (8), 145 (100), 121 (17), 109 (21), 105 (21), 103 (22), 77 (81), 65 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1465, 1439, 1171, 1062, 1000, 770, 745, 703, 682.

HRMS (EI) for **$C_{14}H_{10}N_2OS$** (254.0514): 254.0493.

Synthesis of 3-iodocoumarin (13c):



According to **TP 1**, the metalation of coumarin (**55**; 292 mg, 2.0 mmol) was finished within 4 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). I_2 (762 mg, 3.0 mmol) dissolved in dry THF (4 mL) was then added dropwise at 0 °C, the resulting mixture was warmed to 25 °C and stirred for 0.5 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 1:1) furnished **63c** (473 mg, 87%) as a colourless solid.

m.p.: 89.3-90.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.37 (s, 1 H), 7.55-7.59 (m, 1 H), 7.42–7.45 (m, 1 H), 7.27-7.35 (m, 2 H).

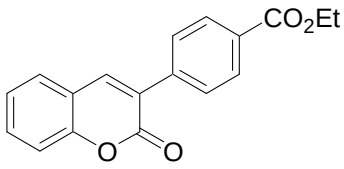
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.76, 154.21, 152.41, 132.55, 127.04, 125.01, 120.40, 117.11, 86.52.

MS (70 eV, EI) *m/z* (%): 272 (36) [M^+], 145 (20), 89 (100), 63 (41), 62 (22).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1718, 1706, 1688, 1670, 1602, 1554, 1508, 1486, 1450, 1440, 1350, 1330, 1274, 1246, 1214, 1158, 1132, 1120, 1104, 1026, 1016, 948, 934, 914, 860, 802, 762, 750, 724, 616.

HRMS (EI) for **$C_9H_5IO_2$** (271.9334): 271.9356.

Synthesis of 4-(2-oxo-2*H*-chromen-3-yl)-benzoic acid ethyl ester (63d):



According to **TP 1**, the metalation of coumarin (**55**; 292 mg, 2.0 mmol) was finished within 4 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (3 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (607 mg, 2.4 mmol) dissolved in THF (1 mL). The reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 3:1) furnished the compound **63d** (488 mg, 83%) as a colorless solid.

m.p.: 193.3-194.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, *J*=8.5 Hz, 2 H), 7.89 (s, 1 H), 7.79 (d, *J*=8.7 Hz, 2 H), 7.54-7.58 (m, 2 H), 7.30-7.40 (m, 2 H), 4.40 (d, *J*=7.2 Hz, 2 H), 1.41 (t, *J*=7.0 Hz, 3 H).

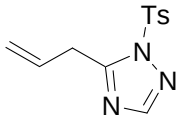
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.42, 160.41, 153.93, 141.00, 139.23, 132.18, 130.86, 129.89, 128.72, 128.37, 127.61, 124.91, 119.65, 116.81, 61.37, 14.57.

MS (70 eV, EI) *m/z* (%): 295 (17), 294 (81) [M^+], 266 (23), 250 (22), 249 (100), 238 (16), 222 (11), 221 (39), 165 (45), 163 (10), 44 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1710, 1606, 1560, 1478, 1366, 1292, 1272, 1234, 1104, 954, 864, 856, 784, 766, 752, 738, 730, 698, 640, 622.

HRMS (EI) for **$C_{18}H_{14}O_4$** (294.0892): 294.0915.

Synthesis of 5-allyl-1-tosyl 1*H*-1,2,4-triazole (63e):



According to **TP 1**, the metalation of 1-tosyl 1*H*-1,2,4-triazole (**61b**; 446 mg, 2.0 mmol) was finished within 40 min at –25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). Allyl bromide (290 mg, 2.4 mmol) and CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) was added at –25 °C and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent

was evaporated *in vacuo*. Purification by column chromatography (CH_2Cl_2) furnished **63e** (448 mg, 85%) as a colourless solid.

m.p.: 54.0-54.7 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.93 (dd, *J*=8.0, 0.7 Hz, 2 H), 7.83 (s, 1 H), 7.35 (dd, *J*=8.0, =0.7 Hz, 2 H), 5.98-6.06 (m, 1 H), 5.18-5.23 (m, 2 H), 3.93 (dt, *J*=6.5, 1.5 Hz, 2 H), 2.44 (s, 3 H).

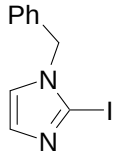
^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 157.64, 152.12, 147.12, 133.84, 131.48, 130.64, 130.45, 128.96, 128.84, 119.06, 32.29, 22.08.

MS (EI, 70 eV) *m/z* (%): 264 (15), 263 (54) [M^+], 262 (24), 108 (67), 92 (13), 91 (100), 65 (23), 53 (11).

IR (ATR) $\tilde{\nu}$ **(**cm^{-1}**)**: 1718, 1706, 1601, 1350, 1274, 1119, 947, 913, 762, 724, 615.

HRMS (EI) for $\mathbf{C_{12}H_{13}N_3O_2S}$ (263.0728): 263.0741.

Synthesis of 1-benzyl-2-iodo-1*H*-imidazole (63f):



According to **TP 1**, the metalation of 1-benzyl-1*H*-imidazole (**61c**; 316 mg, 2.0 mmol) was finished within 30 min at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol).). I_2 (762 mg, 3.0 mmol) dissolved in dry THF (4 mL) was then added dropwise at 0 °C, the resulting mixture was warmed to 25 °C and stirred for 0.5 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (30 mL), extracted with diethyl ether (5 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2) to give **63f** (460 mg, 81%) as a colourless solid.

m.p.: 110.6-111.3 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.33-7.41 (m, 3 H), 7.13-7.17 (m, 2 H), 7.12 (d, *J*=1.5 Hz, 1 H), 7.02 (d, *J*=1.5 Hz, 1 H), 5.11 (s, 2 H).

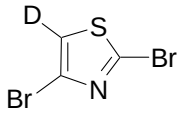
^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 135.86, 133.21, 129.22, 128.51, 127.50, 123.58, 90.92, 53.33.

MS (EI, 70 eV) *m/z* (%): 284 (100) [M^+], 158 (9), 157 (97), 92 (19), 91 (36), 65 (26).

IR (ATR) $\tilde{\nu}$ **(**cm^{-1}**)**: 3108, 3028, 1695, 1596, 1495, 1146, 1420, 1356, 1278, 1196, 1127, 1095, 1056, 1028, 915, 747, 725, 693, 664, 632.

HRMS (EI) for $\mathbf{C_{10}H_9IN_2}$ (283.9810): 283.9797.

Synthesis of 2,4-dibromo-5-deuterothiazole (61d):



According to **TP 1**, the metalation of 2,4-dibromothiazole (**63g**; 486 mg, 2.0 mmol) was finished within 15 min at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). D_2O (0.2 mL, 10 mmol) was added dropwise at 5 °C and the resulting mixture was warmed to 25 °C and stirred for 20 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 5:1) furnished **61d** (446 mg, 91%) as a colourless solid.

m.p.: 81.8-82.8 °C.

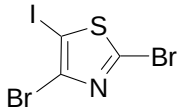
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 136.56, 124.42, 120.99.

MS (70 eV, EI) *m/z*: 246 (52), 245 (28), 244 (100), 243 (49), 242 (53) [M^+], 241 (27), 139 (33), 138 (17), 137 (28), 136 (14), 125 (13), 123 (13), 84 (10), 58 (25), 57 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1726, 1528, 1434, 1352, 1336, 1276, 1236, 1196, 1168, 1142, 1120, 1028, 978, 968, 956, 924, 888, 826, 812, 800, 766, 740, 692.

HRMS (EI) for **C_3Br_2DNS** (241.8259): 241.8262.

Synthesis of 2,4-dibromo-5-iodothiazole (63h):



According to **TP 1**, the metalation of 2,4-dibromothiazole (**61d**; 486 mg, 2.0 mmol) was finished within 15 min at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). I_2 (762 mg, 3.0 mmol) dissolved in dry THF (4 mL) was then added dropwise at 0 °C, the resulting mixture was warmed to 25 °C and stirred for 0.5 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 4:1) furnished **63h** (650 mg, 88%) as a colourless solid.

m.p.: 100.0-101.2 °C.

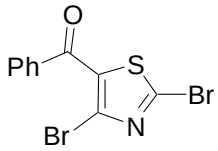
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 140.39, 134.15, 74.80.

MS (70 eV, EI) *m/z*: 371 (44), 369 (85), 367 (41) [M^+], 293 (14), 281 (12), 244 (41), 242 (78), 240 (39), 231 (17), 219 (14), 181 (31), 169(24), 137 (30), 135 (31), 131 (44), 127 (22), 119 (35), 82 (20), 69 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1442, 1390, 1382, 1234, 1184, 1128, 1020, 1006, 962, 898, 816, 740, 724, 680, 666, 634, 616.

HRMS (EI) for **C_3Br_2INS** (366.7163): 366.7158.

Synthesis of 5-benzoyl-2,4-dibromothiazole (63i):



According to **TP 1**, the metalation of 2,4-dibromothiazole (**61d**; 486 mg, 2.0 mmol) was finished within 15 min at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The reaction mixture was cooled to –20 °C, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 15 min. Then, benzoyl chloride (353 mg, 2.5 mmol) was added at –20 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 8 h. Then the reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (CH_2Cl_2) furnished **63i** (578 mg, 84%) as a colourless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.82 (d, *J*=8.2 Hz, 2 H), 7.65 (t, *J*=7.4 Hz, 1 H), 7.51 (t, *J*=7.5 Hz, 2 H).

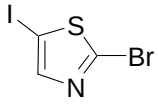
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 185.99, 141.11, 136.88, 135.72, 134.15, 129.80, 128.99, 128.09.

MS (70 eV, EI) *m/z* (%): 349 (20), 347 (38), 345 (18) [M^+], 270 (7), 251 (19), 106 (7), 105 (100), 77 (35), 51 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1654, 1594, 1460, 1375, 1279, 1248, 1207, 1026, 920, 874, 851, 827, 716, 696.

HRMS (EI) for **$C_{10}H_5Br_2NOS$** (344.8459): 344.8444.

Synthesis of 2-bromo-5-iodo-thiazole (63j)



According to **TP 1**, the metalation of 2-bromothiazole (**61e**; 326 mg, 2.0 mmol) was finished within 20 min at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). I_2 (762 mg, 3.0 mmol) dissolved in dry THF (4 mL) was then added dropwise at 0 °C, the resulting mixture was warmed to 25 °C and stirred for 0.5 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 1:1) furnished **63j** (490 mg, 84%) as a colourless solid.

m.p.: 112.5-113.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.65 (s, 1 H).

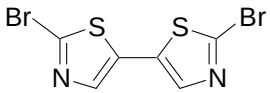
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 150.78, 139.65, 72.56.

MS (70 eV, EI) *m/z* (%): 291 (96), 289 [M^+] (100), 164 (91), 162 (99), 127 (21), 83 (38), 57 (76).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1692, 1478, 1378, 1250, 1136, 1004, 978, 958, 848, 734, 698, 676, 666.

HRMS (EI) for **$C_3HBrINS$** (288.8058): 288.8044.

Synthesis of 2,2'-dibromo-5,5'-bithiazolyl (63k):



According to **TP 1**, the metalation of 2-bromothiazole (**61e**; 326 mg, 2.0 mmol) was finished within 20 min at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). Chloranil (292 mg, 1.2 mmol) dissolved in dry THF (7 mL) was then added dropwise at –40 °C, the resulting mixture was slowly warmed to 0 °C and stirred for 5 h. Then the reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (CH_2Cl_2) furnished **63k** (285 mg, 91%) as a yellow solid.

m.p.: 122.2-124.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.63 (s, 2 H).

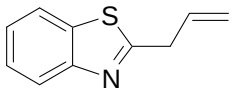
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 140.80, 136.49, 130.98.

MS (70 eV, EI) *m/z* (%): 328 (53), 327 (7), 326 (100), 324 (47) [M^+], 247 (17), 245 (15), 221 (11), 219 (8), 166 (8), 140 (24), 96 (12), 69 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1682, 1477, 1375, 1153, 1000, 893, 850, 829, 735.

HRMS (EI) for **$C_6H_2Br_2N_2S_2$** (323.8026): 323.8023.

Synthesis of 2-allylbenzothiazole (63l):



According to **TP 1**, the metalation of benzothiazole (**61f**; 270 mg, 2.0 mmol) was finished within 20 min at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The mixture was then cooled to 0 °C, allyl bromide (290 mg, 2.4 mmol) and CuCN 2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) were added and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 9:1) furnished **63l** (270 mg, 77%) as a pale yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.83-8.02 (m, 2 H), 7.29-7.49 (m, 2 H), 6.05-6.16 (m, 1 H), 5.28-5.34 (m, 2 H), 3.89 (dt, *J*=6.8, 1.4 Hz, 2 H).

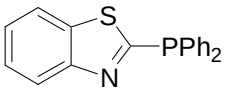
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.53, 153.84, 137.11, 134.28, 126.26, 125.28, 123.02, 121.73, 121.61, 38.81.

MS (70 eV, EI) *m/z* (%): 176 (25), 175 (100) [M^+], 174 (63), 173 (11), 149 (47), 75 (10) 44 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1490, 1456, 1434, 1314, 1284, 1218, 1202, 1126, 954, 938, 926, 756, 726, 708, 696, 650, 610.

HRMS (EI) for **$C_{10}H_9NS$** (175.0456): 175.0471.

Synthesis of 2-diphenylphosphanylbenzothiazole (63m):



According to **TP 1**, the metalation of benzothiazole (**61f**; 270 mg, 2.0 mmol) was finished within 20 min at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The mixture was then cooled to 0 °C and PPh_2Cl (530 mg, 2.4 mmol) was then added dropwise at 0 °C. The resulting mixture was warmed to 25 °C and stirred for 5 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 4:1) furnished **63m** (504 mg, 79%) as a pale yellow solid.

m.p.: 79.9-80.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.25 (d, *J*=7.9 Hz, 1 H), 7.84 (d, *J*=7.9 Hz, 1 H), 7.51-7.63 (m, 5 H), 7.38-7.47 (m, 7 H).

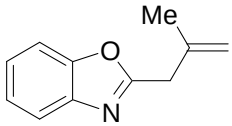
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 174.33 (d, $^1J_{CP}$=22 Hz), 156.05 (d, $^1J_{CP}$=12 Hz), 137.30, 135.69 (d, $^1J_{CP}$=10 Hz), 134.40, 134.13, 132.60, 132.16, 130.16, 129.14, 128.85, 126.47, 125.51, 125.05, 123.71, 121.65.

MS (70 eV, EI) *m/z* (%): 320 (25), 319 (100) [M^+], 318 (63), 242 (15), 241 (13), 183 (45), 152 (6), 107 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1452, 1435, 1414, 1312, 1236, 1089, 1000, 988, 767, 742, 734, 690.

HRMS (EI) for **$C_{19}H_{14}NPS$** (319.0585): 319.0569.

Synthesis of 2-(2-methylallyl)benzoxazole (63n):



According to **TP 1**, the metalation of benzoxazole (**61g**; 238 mg, 2.0 mmol) was finished within 1 h at 0 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The mixture was then cooled to 0 °C and 2-methyl allyl bromide (325 g, 2.4 mmol) and CuCN 2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) were added and the reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 15:1) furnished **63n** (270 mg, 77%) as a pale yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.66-7.69 (m, 1 H), 7.46-7.51 (m, 2 H), 7.27-7.33 (m, 2 H), 4.97 (d, *J*=11.2 Hz, 1 H), 3.65 (s, 2 H), 1.84 (s, 3 H).

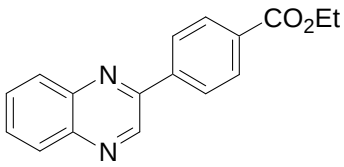
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 164.81, 150.96, 141.36, 139.22, 124.66, 124.18, 119.77, 114.76, 110.42, 37.49, 22.27.

MS (70 eV, EI) *m/z* (%): 174 (10), 173 (80) [M^+], 172 (47), 158 (48), 133 (100), 63 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3080, 2976, 2916, 1724, 1678, 1656, 1614, 1568, 1540, 1518, 1506, 1474, 1454, 1428, 1378, 1348, 1272, 1240, 1192, 1178, 1142, 1104, 1066, 1024, 1002, 974, 948, 930, 898, 876, 862, 844, 824, 798, 764, 742, 708, 668, 656, 634, 624, 606, 588, 572.

HRMS (EI) for **$C_{11}H_{11}NO$** (173.0841): 173.0841.

Synthesis of 4-quinoxalin-2-ylbenzoic acid ethyl ester (63o):



According to **TP 1**, the metalation of quinoxaline (**61h**, 230 mg, 2.0 mmol) was completed within 5 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). A solution of $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (615 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 3:1) furnished **63o** (455 mg, 82%) as a colourless solid.

m.p.: 88.8-90.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.39 (s, 1 H), 8.16-8.33 (m, 6 H), 7.80-7.85 (m, 2 H), 4.46 (q, *J*=7.2 Hz, 2 H), 1.47 (t, *J*=7.2 Hz, 3 H).

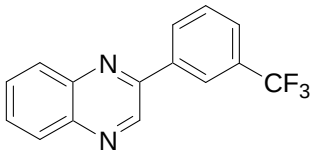
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.14, 150.69, 143.11, 142.29, 141.80, 140.68, 131.83, 130.55, 130.29, 130.10, 129.76, 129.15, 127.42, 61.26, 14.34.

MS (70 eV, EI) *m/z* (%): 279 (15), 278 (74) [M^+], 250 (32), 233 (100), 206 (12), 205 (32), 102 (12), 76 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2923, 1713, 1607, 1363, 1271, 1183, 1126, 1099, 1048, 1017, 958, 861, 772, 758, 752, 698, 668, 615.

HRMS (EI) for **$C_{17}H_{14}O_2N_2$** (278.1055): 278.1030.

Synthesis of 2-(3-trifluoromethylphenyl)quinoxaline (63p):



According to **TP 1**, the metalation of quinoxaline (**61h**, 230 mg, 2.0 mmol) was completed within 5 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). A solution of $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) in THF (2 mL) was added, followed by 1-iodo-3-trifluoromethylbenzene (598 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by

column chromatography (pentane/diethyl ether = 3:1) furnished **63p** (482 mg, 88%) as a colourless solid.

m.p.: 119.0-121.8 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 9.33 (s, 1 H), 8.50 (s, 1 H) 8.36 (d, *J*=7.9 Hz, 1 H), 8.13-8.18 (m, 2 H), 7.75-7.82 (m, 3 H), 7.68 (t, *J*=7.7 Hz, 1 H).

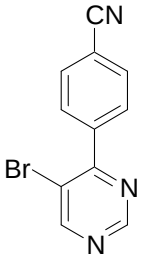
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 150.13, 142.70, 142.18, 141.81, 137.51, 131.69 (q, $^2J_{CF}$=32 Hz), 130.61, 130.53 (q, $^4J_{CF}$=1 Hz), 130.11, 129.68, 129.61, 129.15, 126.68 (q, $^3J_{CF}$=3.7 Hz), 124.85 (q, $^1J_{CF}$=272 Hz), 124.42 (q, $^3J_{CF}$=4.0 Hz).

MS (70 eV, EI) *m/z* (%): 275 (14), 278 (100) [M^+], 247 (30), 178 (5), 76 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1546, 1487, 1366, 1338, 1327, 1309, 1279, 1263, 1231, 1223, 1209, 1187, 1179, 1160, 1140, 1130, 1110, 1096, 1076, 1048, 1013, 973, 961, 952, 937, 919, 889, 885, 877, 838, 809, 795, 763, 706, 690, 651, 637, 632, 624, 615, 591, 561.

HRMS (EI) for **$C_{15}H_9F_3N_2$** (274.0718): 274.0703.

Synthesis of 4-(5-bromopyrimidin-4-yl-benzonitrile (63q):



According to **TP 1**, the metalation of 5-bromopyrimidine (**61i**; 318 mg, 2.0 mmol) was completed within 5 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). A solution of $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) in THF (2 mL) was added, followed by 4-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 4:1) furnished **63q** (390 mg, 75%) as a colourless solid.

m.p.: 158.9-160.9 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 9.19 (s, 1 H), 8.97 (s, 1 H), 7.93 (d, *J*=8.8 Hz, 2 H), 7.80 (d, *J*=8.6 Hz, 2 H).

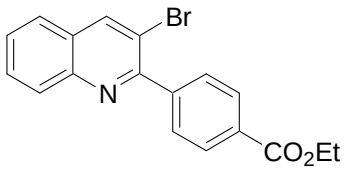
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 162.34, 160.55, 157.05, 140.82, 132.06, 130.03, 119.06, 118.15, 114.02.

MS (70 eV, EI) *m/z* (%): 261 (30), 259 (30) [M^+], 181 (14), 180 (100), 153 (25), 126 (10), 74 (11), 59 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2231, 1558, 1498, 1438, 1405, 1392, 1283, 1228, 1172, 1152, 1058, 1025, 1017, 926, 842, 815, 774, 746, 724, 668, 664, 643, 579, 572, 568, 559.

HRMS (EI) for **$C_{11}H_6BrN_3$** (258.9745): 258.9735.

Synthesis of 4-(3-bromo-quinolin-2-yl)benzoic acid ethyl ester (63r):



According to **TP 1**, the metalation of 3-bromoquinoline (**61j**; 416 mg, 2.0 mmol) was completed within 2.5 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). A solution of $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (615 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 5:1) furnished **63r** (662 mg, 93%) as a colourless solid.

m.p.: 130.4-132.0 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.51 (s, 1 H), 8.16-8.19 (m, 2 H), 8.14 (d, *J*=8.3 Hz, 1 H), 7.74-7.82 (m, 4 H), 7.60 (td, *J*=7.5, 1.2 Hz, 1 H), 4.42 (q, *J*=7.2 Hz, 2 H), 1.42 (t, *J*=7.2 Hz, 3 H).

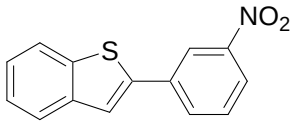
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 166.28, 157.13, 146.42, 143.88, 140.20, 130.71, 130.34, 129.54, 129.48, 129.27, 128.37, 127.83, 126.51, 116.42, 61.11, 14.33.

MS (70 eV, EI) *m/z* (%): 357 (38), 356 (12) 355 (40) [M^+], 312 (38), 310 (34), 281 (21), 277 (20), 276 (100) 248 (32), 203 (35), 101 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3064, 2988, 2973, 1712, 1673, 1651, 1612, 1586, 1571, 1546, 1484, 1475, 1457, 1411, 1397, 1387, 1365, 1309, 1289, 1274, 1262, 1242, 1201, 1180, 1153, 1145, 1121, 1106, 1098, 1072, 1023, 971, 954, 913, 884, 878, 857, 850, 824, 791, 780, 767, 748, 714, 697, 636, 630, 622, 613, 606, 597, 581, 576, 570, 565, 560, 552.

HRMS (EI) for **$C_{18}H_{14}BrNO_2$** (355.0208): 355.0194.

Synthesis of 2-(3-nitrophenyl)benzothiophene (63s)



According to **TP 1**, the metalation of benzothiophene (**61k**; 268 mg, 2.0 mmol) was finished within 144 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (3 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 3-iodonitrobenzene (548 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 30:1) furnished the compound **63s** (417 mg, 82%) as a yellowish solid.

m.p.: 155.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.53 (t, *J*=1.9 Hz, 1 H), 8.15 (ddd, *J*=8.3, 2.2, 1.0 Hz, 1 H), 7.96-8.02 (m, 1 H), 7.81-7.88 (m, 2 H), 7.65 (s, 1 H), 7.57 (t, *J*=8.0 Hz, 1 H), 7.37-7.45 (m, 2 H).

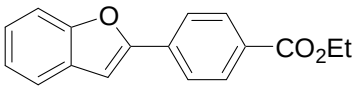
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 148.70, 141.08, 140.26, 139.69, 136.00, 131.98, 129.88, 125.20, 124.92, 124.05, 122.56, 122.35, 121.36, 120.95.

MS (70 eV, EI) *m/z* (%): 256 (14), 255 (100) [M^+], 209 (25), 208 (36), 164 (29), 104 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3080, 3060, 29v22, 2856, 1574, 1528, 1512, 1480, 1456, 1434, 1346, 1316, 1292, 1278, 1250, 1232, 1192, 1168, 1156, 1130, 1094, 1072, 1014, 996, 988, 978, 944, 920, 890, 878, 862, 832, 804, 748, 734, 724, 710, 688, 668, 648, 622, 606, 586, 562.

HRMS (EI) for **$C_{14}H_9NO_2S$** (255.0354): 255.0344.

Synthesis of 4-benzofuran-2-ylbenzoic acid ethyl ester (63t)



According to **TP 1**, the metalation of benzofuran (**61l**; 236 mg, 2.0 mmol) was finished within 168 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (3 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (607 g, 2.4 mmol). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was

evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 30:1) furnished the compound **63t** (330 mg, 65%) as a colorless solid.

m.p.: 115.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.11 (dt, *J*=8.6, 1.9 Hz, 2 H), 7.93 (dt, *J*=8.6, 1.9 Hz, 2 H), 7.62-7.65 (m, 1 H), 7.53-7.58 (m, 1 H), 7.24-7.37 (m, 2 H), 7.14 (d, *J*=0.97 Hz, 1 H), 4.40 (q, *J*=7.1 Hz, 2 H), 1.41 (t, *J*=7.2 Hz, 3 H).

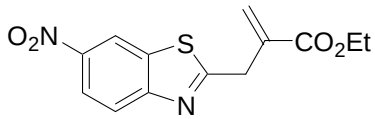
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.19, 155.17, 154.71, 134.39, 130.08, 130.07, 128.92, 125.03, 124.58, 123.20, 121.27, 111.34, 103.38, 61.09, 14.36.

MS (70 eV, EI) *m/z* (%): 267 (14), 266 (100) [M^+], 238 (36), 221 (52), 165 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2980, 2934, 2904, 2874, 1704, 1668, 1634, 1626, 1610, 1562, 1504, 1466, 1450, 1410, 1392, 1366, 1352, 1310, 1268, 1208, 1178, 1168, 1148, 1128, 1096, 1032, 1014, 938, 920, 884, 864, 854, 804, 780, 768, 744, 694, 668, 654, 632, 612, 596, 578, 570, 556.

HRMS (EI) for **$C_{17}H_{14}O_3$** (266.0943): 266.0945.

Synthesis of 2-(6-nitrobenzothiazol-2-ylmethyl)acrylic acid ethyl ester (66a):



According to **TP 1**, the metalation of 6-nitrobenzothiazole (**64a**; 512 mg, 2.0 mmol) was finished within 30 min at –50 °C using a solution of $TMP_2Zn·2MgCl_2·2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). Ethyl 2-(bromomethyl)acrylate (460 mg, 2.4 mmol) and CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) were added at –50 °C and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 2:1) furnished **66a** (442 mg, 76%) as a pale yellow solid.

m.p.: 74.7-75.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.79 (d, *J*=2.2 Hz, 1 H), 8.34 (dd, *J*=8.9, 2.3 Hz, 1 H), 8.08 (d, *J*=9.0 Hz, 1 H), 6.49 (s, 1 H), 5.93 (s, 1 H), 4.25 (q, *J*=7.2 Hz, 2 H), 4.20 (d, *J*=0.9 Hz, 2 H), 1.29 (t, *J*=7.2 Hz, 3 H).

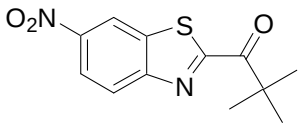
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 175.48, 166.01, 159.64, 157.19, 145.14, 136.17, 129.49, 124.35, 121.88, 118.35, 61.62, 37.62, 14.37.

MS (70 eV, EI) *m/z* (%): 293 (14), 292 (91) [M^+], 263 (22), 247 (28), 246 (61), 220 (28), 219 (49), 218 (100), 201 (12), 174 (12), 173 (48), 172 (39), 63 (22).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3111, 1698, 1269, 1601, 1570, 1517, 1478, 1439, 1425, 1409, 1371, 1321, 1298, 1273, 1219, 1173, 1123, 1092, 1040, 1022, 969, 902, 830, 754, 721.

HRMS (EI) for **$C_{13}H_{12}N_2O_4S$** (292.0518): 292.0511.

Synthesis of 2,2-dimethyl-1-(6-nitrobenzothiazol-2-yl)propan-1-one (66b):



According to **TP 1**, the metalation of 6-nitrobenzothiazole (**64ab**; 512 mg, 2.0 mmol) was finished within 30 min at –50 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added at -50 °C and the resulting mixture was stirred for 20 min. Pivaloyl chloride (305 mg, 2.5 mmol) was added and the reaction mixture was slowly warmed to 0 °C within 3 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 2:1) furnished **66b** (274 mg, 56%) as a pale yellow solid.

m.p.: 84.9-86.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.89 (d, *J*=1.8 Hz, 1 H), 8.39 (dd, *J*=9.3, 2.2 Hz, 1 H), 8.27 (d, *J*=9.7 Hz, 1 H), 1.53 (s, 9 H).

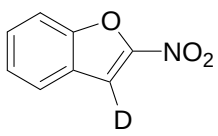
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 199.21, 171.18, 157.17, 146.42, 136.76, 125.98, 121.75, 118.71, 44.38, 26.84.

MS (70 eV, EI) *m/z* (%): 264 (23) [M^+], 236 (13), 221 (12), 207 (15), 180 (64), 57 (100), 41 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3092, 3067, 2968, 2955, 2927, 2870, 1760, 1677, 1564, 1515, 1481, 1461, 1435, 1394, 1345, 1332, 1305, 1282, 1222, 1179, 1122, 1103, 1043, 970, 944, 914, 885, 874, 836, 812, 795, 756, 749, 721, 660.

HRMS (EI) for **$C_{12}H_{12}N_2O_3S$** (264.0569): 264.0570.

Synthesis of 3-deutero-2-nitrobenzofuran (66c):



According to **TP 1**, the metalation of 2-nitrobenzofuran (**64b**; 326 mg, 2.0 mmol) was finished within 1.5 h at –25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF,

2.8 mL, 1.1 mmol). D_2O (0.2 mL, 10 mmol) was added dropwise at –25 °C, the resulting mixture was warmed to –10 °C and stirred for 20 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 3:1) furnished **66c** (268 mg, 82%) as a pale yellow solid.

m.p.: 134.8-135.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.89 (d, *J*=7.9 Hz, 1 H), 7.59-7.67 (m, 2 H), 7.4-7.49 (m, 1 H).

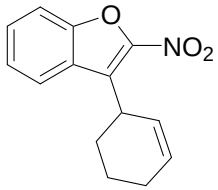
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 153.62, 130.25, 126.02, 125.59, 124.26, 124.26, 112.97, 107.47.

MS (70 eV, EI) *m/z* (%): 165 (10), 164 (100) [M^+], 163 (39), 134 (56), 133 (23), 106 (24), 105 (11), 90 (48), 78 (22), 77 (9), 64 (22), 63 (28), 62 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1611, 1559, 1544, 1508, 1476, 1441, 1366, 1308, 1241, 1177, 1111, 1091, 1007, 920, 885, 866, 790, 765, 753, 661.

HRMS (ESI) for **$C_8H_4DNO_3$** (164.0331): 164.0345.

Synthesis of 3-cyclohex-2-enyl-2-nitrobenzofuran (66d):



According to **TP 1**, the metalation of 2-nitrobenzofuran (**64b**; 326 mg, 2.0 mmol) was finished within 1.5 h at –25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). 3-Bromo-cyclohexene (400 mg, 2.5 mmol) and CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) were added at –25 °C and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 2:1) furnished **66d** (390 mg, 80%) as a pale yellow solid.

m.p.: 104.4-107.6 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.96 (d, *J*=8.2 Hz, 1 H), 7.52-7.59 (m, 2 H), 7.31-7.38 (m, 1 H), 6.00-6.07 (m, 1 H), 5.77 (d, *J*=10.1 Hz, 1 H), 4.60 (d, *J*=2.2 Hz, 1 H), 2.23 (d, *J*=1.8 Hz, 2 H), 2.08-2.26 (m, 1 H), 1.93 (s, 1 H), 1.80 (t, *J*=8.0 Hz, 2 H).

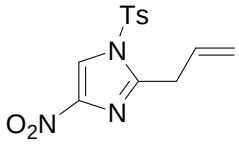
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 152.07, 149.30, 130.08, 129.72, 127.80, 127.52, 126.95, 124.82, 124.47, 112.78, 33.74, 29.43, 25.04, 22.24.

MS (70 eV, EI) *m/z* (%): 243 (13) [M^+], 227 (17), 226 (100), 225 (42), 209 (37), 208 (32), 196 (22), 183 (13), 182 (16), 181 (17), 170 (49), 169 (23), 165 (22), 156 (14), 153 (16), 152 (18), 141 (13), 139 (14), 133 (24), 128 (15), 121 (52), 120 (29), 115 (25), 105 (14), 101 (22), 92 (19), 89 (23), 81 (17), 77 (22), 76 (13), 65 (16), 63 (26), 59 (36), 58 (23), 51 (13), 43 (94), 41 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1564, 1507, 1478, 1444, 1366, 1322, 1280, 1244, 1187, 978, 921, 874, 860, 832, 779, 766, 754, 744, 728, 644.

HRMS (EI) for **$C_{14}H_{13}NO_3$** (243.0895): 243.0890.

Synthesis of 2-allyl-1-tosyl-4-nitro-1*H*-imidazole (66e):



According to **TP 1**, the metalation of 1-tosyl-4-nitro-1*H*-imidazole (**64c**; 535 mg, 2.0 mmol) was finished within 45 min at –40 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). Allyl bromide (290 mg, 2.4 mmol) and CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) were added at –40 °C and the resulting reaction mixture was stirred for 30 min at –40 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 1:1) furnished **66e** (356 mg, 58%) as a pale yellow solid.

m.p.: 118.2-119.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.21 (s, 1 H), 7.88 (d, *J*=9.0 Hz, 2 H), 7.46 (d, *J*=9.0 Hz, 2 H), 5.92-5.98 (m, 1 H), 5.10-5.18 (m, 2 H), 3.71 (dt, *J*=6.5, 1.5 Hz, 2 H), 2.50 (s, 3 H).

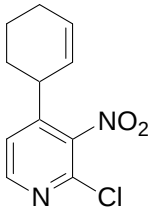
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 148.15, 147.24, 133.45, 131.13, 130.94, 128.36, 119.27, 119.02, 32.80, 22.11.

MS (70 eV, EI) *m/z* (%): 307 (100) [M^+], 306 (20), 156 (23), 155 (61), 152 (94), 92 (46), 91 (39), 65 (55), 41 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3146, 2922, 1644, 1595, 1552, 1512, 1372, 1240, 1192, 1171, 1055, 988, 918, 832, 818, 794, 700, 673, 569.

HRMS (EI) for **$C_{13}H_{13}N_3O_4S$** (307.0627): 307.0623.

Synthesis of 2-chloro-4-cyclohex-2-enyl-3-nitropyridine (66f):



According to **TP 1**, the metalation of 2-chloro-3-nitropyridine (**64d**; 320 mg, 2.0 mmol) was finished within 1.5 h at –40 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). 3-Bromocyclohexene (400 mg, 2.5 mmol) and CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) were added at –40 °C and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (4 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 1:1) furnished **66f** (392 mg, 82%) as a yellow solid.

m.p.: 54.5-55.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44 (d, *J*=5.1 Hz, 1 H), 7.32 (d, *J*=5.1 Hz, 1 H), 6.07 (ddd, *J*=10.0, 6.1, 3.7 Hz, 1 H), 5.54 (dd, *J*=10.0, 1.9 Hz, 1 H), 3.41-3.49 (m, 1 H), 2.02-2.17 (m, 3 H), 1.47-1.76 (m, 3 H).

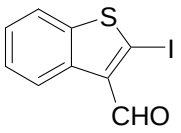
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.21, 150.09, 146.51, 141.84, 131.88, 125.94, 123.31, 37.41, 31.25, 24.70, 20.85.

MS (70 eV, EI) *m/z* (%): 237 (3) [M^+-H], 223 (31), 221 (100), 105 (19), 204 (14), 203 (48), 195 (18), 193 (48), 191 (14), 185 (20), 184 (14), 183 (18), 182 (15), 181 (45), 167 (32), 165 (31), 157 (21), 155 (18), 154 (14), 142 (15), 140 (18), 130 (17), 129 (29), 128 (31), 127 (19), 117 (15), 116 (17), 115 (21), 102 (17), 89 (14), 77 (35), 63 (16), 51 (22), 41 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2939, 1589, 1539, 1446, 1361, 1347, 1231, 1137, 1041, 973, 918, 890, 855, 845, 757, 723, 691, 616.

HRMS (EI) for $\mathbf{C_{11}H_{11}ClN_2O_2}$ (237.0431 [M^+-H]): 237.0424 [M^+-H].

Synthesis of 2-iodo-benzothiophene-3-carbaldehyde (66g):



According to **TP 1**, the metalation of benzothiophene-3-carbaldehyde (**64e**; 324 mg, 2.0 mmol) was finished within 15 min at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol), I_2 (762 mg, 3.0 mmol) dissolved in dry THF (4 mL) was then added

dropwise at 0 °C, the resulting mixture was warmed to 25 °C and stirred for 0.5 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 2:1) furnished **16b** (472 mg, 82%) as a yellow solid.

m.p.: 97.6-99.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.02 (s, 1 H), 8.73-8.77 (m, 1 H), 7.74-7.78 (m, 1 H), 7.39-7.49 (m, 2 H).

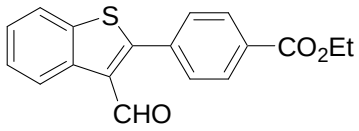
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 188.92, 143.33, 135.84, 134.37, 126.38, 126.33, 123.30, 121.31, 99.99.

MS (70 eV, EI) *m/z* (%): 289, (12), 288 (100) [M^+], 287 (55), 259 (9), 160 (14), 132 (24), 89 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1655, 1482, 1455, 1416, 1374, 1342, 1256, 1102, 1048, 929, 745, 727, 694.

HRMS (EI) for **C_9H_5IOS** (287.9106): 287.9108.

Synthesis of 4-(3-formylbenzothiophen-2-yl)benzoic acid ethyl ester (66h):



According to **TP 1**, the metalation of benzothiophene-3-carbaldehyde (**64e**; 324 mg, 2.0 mmol) was finished within 15 min at 25 °C using a solution of $TMP_2Zn·2MgCl_2·2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (2 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (607 g, 2.2 mmol) dissolved in THF (1 mL). The reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 3:1) furnished **66h** (416 mg, 67%) as a yellow solid.

m.p.: 104.9-107.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.10 (s, 1 H), 8.82 (d, *J*=7.9 Hz, 1 H), 8.22 (d, *J*=8.4 Hz, 2 H), 7.89 (d, *J*=7.9 Hz, 1 H), 7.69 (d, *J*=8.4 Hz, 2 H), 7.52 (m, 2 H), 4.47 (q, *J*=7.1 Hz, 2 H), 1.46 (t, *J*=7.1 Hz, 3 H).

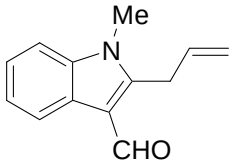
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 186.47, 166.03, 159.02, 143.56, 138.41, 137.26, 136.11, 132.09, 130.80, 130.24, 129.22, 128.65, 126.76, 121.39, 61.69, 14.58.

MS (70 eV, EI) *m/z* (%): 311 (20), 310 (100) [M^+], 309 (26), 282 (12), 281 (57), 265 (18), 238 (14), 237 (76), 236 (11), 209 (8), 208 (25), 165 (16), 104 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1714, 1675, 1606, 1459, 1431, 1409, 1348, 1284, 1224, 1181, 1104, 1091, 1050, 1022, 757, 748, 724, 699.

HRMS (EI) for **$C_{18}H_{14}O_3S$** (310.0664): 310.0664.

Synthesis of 2-allyl-1-methyl-1*H*-indole-3-carbaldehyde (66i):



According to **TP 1**, the metalation of 1-methyl-1*H*-indole-3-carbaldehyde (**64f**; 318 mg, 2.0 mmol) was finished within 45 min at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The mixture was then cooled to 0 °C and allyl bromide (290 mg, 2.4 mmol) and CuCN 2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) were added and the reaction mixture was stirred for 10 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 2:1) furnished **66i** (282 mg, 71%) as a red solid.

m.p.: 65.9-68.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.10 (s, 1 H), 8.31-8.36 (m, 1 H), 7.29-7.37 (m, 3 H), 5.95-6.02 (m, 1 H), 5.19-5.23 (m, 1 H), 4.98-5.04 (m, 1 H), 3.87 (dt, *J*= 5.8, 1.4 Hz, 2 H), 3.71 (s, 3 H).

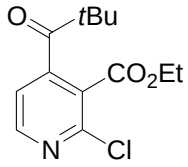
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 184.39, 148.37, 137.41, 133.28, 125.91, 123.56, 123.14, 121.33, 118.06, 114.58, 109.62, 30.08, 28.77.

MS (70 eV, EI) *m/z* (%): 199 (48) [M^+], 185 (36), 184 (100), 167 (11), 154 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1640, 1580, 1470, 1434, 1392, 1376, 1324, 1260, 1186, 1128, 1044, 1010, 992, 922, 884, 756, 742, 728.

HRMS (EI) for **$C_{13}H_{13}NO$** (199.0997): 199.1005.

Synthesis of 2-chloro-4-(3,3-dimethylbutyryl)nicotinic acid ethyl ester (66j):



According to **TP 1**, the metalation of ethyl 2-chloronicotinate (**64g**; 372 mg, 2.0 mmol) was finished within 5 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The reaction mixture was cooled to –20 °C, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 15 min. Thereafter, tBuCH$_2$COCl (336 mg, 2.5 mmol) was added at –20 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 2 h. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (CH_2Cl_2) furnished **66j** (424 mg, 75%) as a colourless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.66 (d, J=5.1 Hz, 1 H), 7.51 (d, J=5.1 Hz, 1 H), 4.45 (q, J=7.3 Hz, 2 H), 2.78 (s, 2 H), 1.40 (t, J=7.2 Hz, 3 H), 1.04 (s, 9 H).

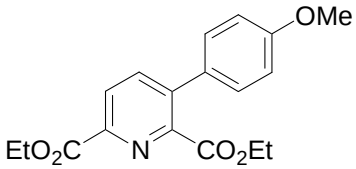
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 199.06, 165.66, 150.95, 149.76, 146.62, 128.17, 120.45, 62.69, 51.94, 32.35, 29.93, 14.07.

MS (70 eV, EI) *m/z* (%): 283 [M^+] (2), 237 (13), 222 (23), 214 (14), 212 (19), 212 (46), 210 (56), 186 (40), 185 (11), 184 (100), 183 (32), 182 (34), 181 (93), 57 (29), 41 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2951, 1731, 1690, 1571, 1540, 1362, 1261, 1186, 1119, 1055, 876, 732, 677.

HRMS (EI) for **$C_{14}H_{18}ClNO_3$** (283.0975): 283.0969.

Synthesis of 3-(4-methoxyphenyl)pyridine-2,6-dicarboxylic acid diethyl ester (66k):



According to **TP 1**, the metalation of pyridine-2,6-dicarboxylic acid diethyl ester (**64h**; 446 mg, 2.0 mmol) was finished within 24 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(o-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (3 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 4-iodoanisole (515 mg, 2.2 mmol) dissolved in THF (1 mL). The resulting solution was stirred for 12 at 25 °C. Then, the

reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 1:1) furnished **66k** (424 mg, 75%) as a brownish solid.

m.p.: 68.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.21 (d, *J*=8.0 Hz, 1 H), 7.86 (d, *J*=8.0 Hz, 1 H), 7.27-7.34 (m, 2 H), 6.92-6.99 (m, 2 H), 4.48 (q, *J*=7.0 Hz, 2 H), 4.23 (q, *J*=7.2 Hz, 2 H), 3.84 (s, 3 H), 1.44 (t, *J*=7.2 Hz, 3 H), 1.13 (t, *J*=7.2 Hz, 3 H).

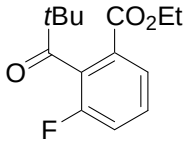
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.59, 164.61, 160.14, 149.83, 146.23, 139.26, 138.90, 129.57, 129.44, 126.07, 114.19, 62.17, 61.86, 55.38, 14.30, 13.82.

MS (70 eV, EI) *m/z* (%):= 329 (15) [M^+], 258 (13), 257 (95), 212 (14), 211 (100), 183 (23), 140 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3070, 2996, 2980, 2936, 2900, 2872, 2842, 1732, 1606, 1578, 1554, 1540, 1512, 1472, 1442, 1398, 1386, 1368, 1310, 1286, 1274, 1244, 1220, 1176, 1146, 1134, 1110, 1034, 1014, 996, 986, 942, 928, 868, 852, 818, 806, 784, 738, 716, 660, 636, 606, 592, 570.

HRMS (EI) for **$C_{18}H_{19}NO_5$** (329.1263): 329.1255.

Synthesis of 2-(3,3-dimethylbutyryl)-3-fluorobenzoic acid ethyl ester (69a):



According to **TP 1**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was finished within 12 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The reaction mixture was cooled to –20 °C, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 15 min. Then, *t*$BuCH_2COCl$ (0.335 g, 2.2 mmol) was added at –20 °C. The reaction mixture was slowly warmed to 0 °C and stirred at this temperature for 3 h. Then, the reaction was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 2:1) furnished **69a** (404 mg, 76%) as a colourless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.74 (d, *J*=7.9 Hz, 1 H), 7.37-7.41 (m, 1 H), 7.24 (t, *J*=8.6 Hz, 1 H), 4.34 (q, *J*=7.1 Hz, 2 H), 2.77 (s, 2 H), 1.35 (t, *J*=7.2 Hz, 3 H), 1.13 (s, 9 H).

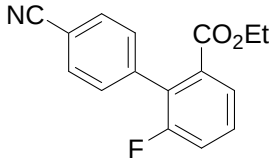
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 201.06, 165.31, 158.78 (d, $^1J_{CF}$=247 Hz), 132.61 (d, $^2J_{CF}$=20 Hz), 130.28 (d, $^3J_{CF}$=8 Hz), 130.12 (d, $^3J_{CF}$=4 Hz), 126.21, 120.23 (d, $^2J_{CF}$=22 Hz), 61.99, 56.53, 31.01, 29.65, 14.35.

MS (70 eV, EI) *m/z* (%): 266 (2) [M^+], 210 (19), 195 (29), 167 (100), 165 (11), 164 (30), 94 (7), 41 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1713, 1604, 1450, 1365, 1277, 1135, 1021, 1008, 956, 907, 760, 747, 675.

HRMS (EI) for **$C_{15}H_{19}FO_3$** (266.1318): 266.1318.

Synthesis of 4'-cyano-6-fluorobiphenyl-2-carboxylic acid ethyl ester (69b):



According to **TP 1**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was finished within 12 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (3 mL) were then transferred *via* cannula to the reaction mixture, followed by 4-iodobenzonitrile (550 g, 2.4 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 3:1) furnished **69b** (370 mg, 69%) as a colorless solid.

m.p.: 94.5-95.3 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.76 (d, *J*=7.7 Hz, 1 H), 7.70 (d, *J*=8.2 Hz, 2 H), 7.45-7.51 (m, 1 H), 7.40 (d, *J*=8.2 Hz, 2 H), 7.32 (t, *J*=8.7 Hz, 1 H), 4.08 (q, *J*=7.1 Hz, 2 H), 1.02 (t, *J*=7.2 Hz, 3 H).

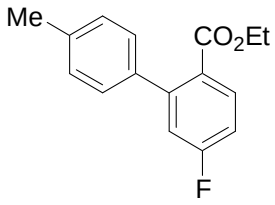
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 166.55, 159.63 (d, $^1J_{CF}$=247 Hz,) 139.69, 133.00, 131.91, 130.44, 130.08 (d, $^3J_{CF}$=8.0 Hz), 128.55, (d, $^2J_{CF}$=17 Hz), 126.28 (d, $^3J_{CF}$=4.1 Hz), 119.47 (d, $^2J_{CF}$=23 Hz,), 118.97, 111.86, 61.59, 13.91.

MS (70 eV, EI) *m/z* (%): 270 (9), 269 (51) [M^+], 241 (23), 225 (17), 224 (100), 196 (17), 195 (16), 169 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2228, 1709, 1612, 1450, 1362, 1279, 1262, 1183, 1147, 1028, 1007, 953, 840, 825, 815, 760.

HRMS (EI) for **$C_{16}H_{12}FNO_2$** (269.0852): 269.0851.

Synthesis of 5-fluoro-4'-methylbiphenyl-2-carboxylic acid ethyl ester (69c):



According to **TP 1**, the metalation of ethyl 4-fluorbenzoate (**67a**; 336 mg, 2.0 mmol) was completed within 336 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.00 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 4-iodotoluene (480 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 6:1) furnished the compound **69c** (371 mg, 72%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.80-7.86 (m, 1 H), 7.16-7.21 (m, 4 H), 7.01-7.09 (m, 2 H), 4.09 (q, *J*=7.0 Hz, 2 H), 2.39 (s, 3 H) 1.03 (t, *J*=7.0 Hz, 3 H).

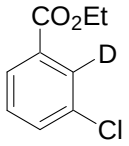
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.74, 163.88 (d, $^1J_{CF}$=252.6 Hz), 145.44 (d, $^3J_{CF}$=8.6 Hz), 137.50 (d, $^4J_{CF}$=1.5 Hz), 137.36, 132.28, 132.18, 128.74, 128.11, 128.05, 127.23 (d, $^3J_{CF}$=2.9 Hz), 117.59 (d, $^2J_{CF}$=22 Hz), 113.86 (d, $^2J_{CF}$=22 Hz), 60.94, 21.16, 13.68.

MS (70 eV, EI) *m/z* (%): 258 (48) [M^+], 230 (19), 229 (12), 214 (17), 213 (100), 199 (10), 192 (14). 185 (11), 184 (10), 183 (30), 170 (28), 165 (31), 74 (17), 59 (27), 45 (20), 44 (14), 43 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2928, 2904, 2872, 1710, 1654, 1608, 1592, 1580, 1568, 1518, 1506, 1480, 1466, 1450, 1412, 1390, 1366, 1274, 1238, 1182, 1154, 1094, 1034, 1016, 938, 932, 920, 900, 876, 854, 832, 816, 778, 770, 746, 708, 692, 668, 648, 634, 618, 608, 586, 574, 560.

HRMS (EI) for **$C_{16}H_{15}FO_2$** (258.1056): 258.1041.

Synthesis of 2-deutero-3-chlorobenzoic acid ethyl ester (69d):



According to **TP 1**, the metalation of ethyl 3-chlorobenzoate (**67b**; 370 mg, 2.0 mmol) was finished within 25 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF,

2.8 mL, 1.1 mmol). D_2O (0.2 mL, 10 mmol) was added dropwise at 5 °C and the resulting mixture was warmed to 25 °C and stirred for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 4:1) furnished **69d** (310 mg, 84%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.92-7.95 (m, 1 H), 7.35-7.54 (m, 2 H), 4.38 (q, *J*=7.5 Hz, 2 H), 1.40 (t, *J*=7.1 Hz, 3 H).

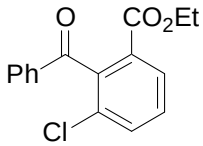
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.57, 134.66, 134.56, 133.03, 132.43, 129.84, 127.87, 61.58, 14.48.

MS (70 eV, EI) *m/z* (%): 185 (19) [M^+], 159 (10), 157 (33), 156 (10), 142 (28), 141 (16), 140 (100), 139 (29), 112 (24).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1718, 1572, 1418, 1366, 1274, 1256, 1210, 1196, 1122, 1080, 768, 748, 728, 626.

HRMS (EI) for **$C_9H_8DClO_2$** (185.0354): 185.0374.

Synthesis of 2-benzoyl-3-chlorobenzoic acid ethyl ester (69e):



According to **TP 1**, the metalation of ethyl 3-chlorobenzoate (**67b**; 370 mg, 2.0 mmol) was finished within 25 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The reaction mixture was cooled to –20 °C, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 15 min. Then, benzoyl chloride (353 mg, 2.5 mmol) was added at –20 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 4 h. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 5:1) furnished **69e** (456 mg, 79%) as a colourless solid.

m.p.: 108.6-109.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.04-8.10 (m, 1 H), 7.76-7.81 (m, 2 H), 7.44-7.68 (m, 5 H), 4.17 (q, *J*=7.1 Hz, 2 H), 1.10 (t, *J*=7.1 Hz, 3 H).

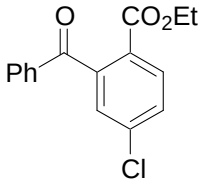
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 194.26, 164.56, 140.39, 136.65, 133.89, 133.38, 131.71, 130.63, 129.85, 128.98, 128.67, 61.84, 13.59.

MS (70 eV, EI) *m/z* (%): 290 (19), 288 (43) [M^+], 242 (32), 211 (73), 211 (26), 185 (32), 183 (100), 152 (10), 151 (13), 105 (87), 77 (31)

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1706, 1672, 1584, 1564, 1430, 1366, 1284, 1202, 1152, 1074, 1028, 928, 866, 764, 744, 734, 702, 652, 618.

HRMS (EI) for **$C_{16}H_{13}ClO_3$** (288.0553): 288.0569.

Synthesis of 2-benzoyl-4-chlorobenzoic acid ethyl ester (69f):



According to **TP 1**, the metalation of ethyl 4-chlorobenzoate (**67c**; 370 mg, 2.0 mmol) was completed within 110 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The reaction mixture was cooled to –30 °C, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, benzoyl chloride (353 mg, 2.5 mmol) was added at –30 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 6:1) furnished the compound **69f** (500 mg, 86%) as a colourless solid.

m.p.: 78.9-80.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J*=8.4 Hz, 1 H), 7.73-7.77 (m, 2 H), 7.52-7.57 (m, 2H), 7.41–7.46 (m, 2 H), 7.36 (d, *J*=8.4 Hz, 1 H), 4.07 (q, *J*=7.1 Hz, 2 H), 1.04 (t, *J*=7.1 Hz, 3 H).

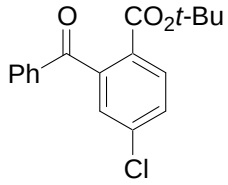
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 195.54, 165.22, 143.44, 139.24, 136.85, 133.69, 131.93, 129.89, 129.61, 128.89, 127.96, 127.82, 61.98, 13.82.

MS (70 eV, EI) *m/z* (%): 288 (24) [M^+], 245 (16), 244 (15), 243 (35), 213 (11), 211 (36), 183 (56), 152 (21), 105 (100), 77 (45), 57 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 2909, 1712, 1677, 1619, 1590, 1583, 1560, 1490, 1473, 1450, 1445, 1385, 1363, 1319, 1311, 1283, 1267, 1243, 1177, 1153, 1134, 1105, 1089, 1074, 1021, 1001, 979, 966, 954, 942, 899, 875, 860, 843, 815, 808, 780, 770, 712, 698, 690, 643, 619, 609, 591, 585.

HRMS (EI) for **$C_{16}H_{13}ClO_3$** (288.0553): 288.0550.

Synthesis of 2-benzoyl-4-chlorobenzoic acid *tert*-butyl ester (69g):



According to **TP 1**, the metalation of *tert*-butyl 4-chlorobenzoate (**67d**; 425 mg, 2.0 mmol) was completed within 134 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The reaction mixture was cooled to –30 °C, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, benzoyl chloride (353 mg, 2.5 mmol) was added at –30 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 9 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 25:1) furnished the compound **69g** (438 mg, 69%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J*=8.0 Hz, 1 H), 7.75 (ddd, *J*=6.8, 1.6, 1.3 Hz, 2 H), 7.44-7.49 (m, 2 H), 7.51-7.55 (m, 2 H), 7.33 (d, *J*=2.2 Hz, 1 H), 1.20 (s, 9 H).

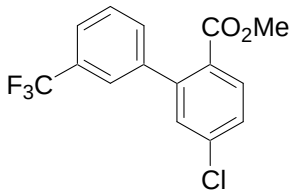
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 195.04, 164.29, 142.51, 138.48, 136.71, 133.44, 131.56, 129.64, 129.61, 129.43, 128.58, 127.64, 83.11, 27.44.

MS (70 eV, EI) *m/z* (%): 316 (1) [M^+], 261 (14), 261 (40), 245 (31), 244 (16), 243 (100), 183 (12), 182 (15), 181 (90), 152 (48), 151 (14), 105 (91), 78 (10), 77 (53), 75 (10), 57 (66), 56 (12), 51 (14), 43 (11), 41 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3064, 2980, 2934, 1714, 1674, 1592, 1562, 1512, 1472, 1450, 1394, 1368, 1346, 1300, 1288, 1264, 1250, 1170, 1128, 1106, 1074, 1038, 1026, 1000, 988, 976, 952, 886, 848, 840, 808, 788, 774, 748, 718, 690, 668, 644, 608, 586, 574.

HRMS (EI) for **$C_{18}H_{17}ClO_3$** (316.0866): 316.0869.

Synthesis of 5-chloro-3'-trifluoromethylbiphenyl-2-carboxylic acid methyl ester (69h):



According to **TP 1**, the metalation of methyl 4-chlorobenzoate (**67e**; 340 mg, 2.0 mmol) was completed within 110 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-3-trifluoromethylbenzene (598 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 10 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 20:1) furnished the compound **69h** (619 mg, 83%) as a yellowish oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.87 (d, *J*=8.6 Hz, 1 H), 7.63 (d, *J*=7.6 Hz, 1 H), 7.50-7.55 (m, 2 H), 7.42-7.48 (m, 2 H), 7.35 (d, *J*=2.1 Hz, 1 H), 3.63 (s, 3 H).

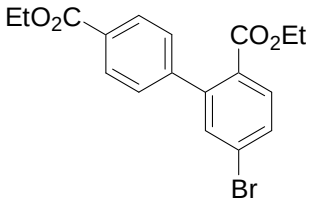
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 167.31, 143.00, 140.87, 137.80, 131.81, 131.61, 130.81, 130.54 (q, $^2J_{CF}$=32 Hz), 130.43, 128.70, 128.51, 128.04, 125.12 (q, $^3J_{CF}$=3.7 Hz), 124.42 (q, $^3J_{CF}$=3.7 Hz), 123.90 (q, $^1J_{CF}$=272 Hz), 52.11.

MS (70 eV, EI) *m/z* (%): 316 (12), 314 (36) [M^+], 285 (32), 284 (15), 283 (100), 235 (10), 220 (28), 219 (11), 74 (17), 59 (29).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 1723, 1614, 1590, 1561, 1474, 1433, 1385, 1329, 1284, 1275, 1240, 1178, 1164, 1122, 1104, 1097, 1072, 1038, 1001, 962, 907, 885, 862, 838, 815, 803, 779, 761, 701, 697, 657, 627, 615, 612, 608, 597, 573, 567, 554.

HRMS (EI) for **$C_{15}H_{10}ClF_3O_2$** (314.0321): 314.0316.

Synthesis of 5-bromobiphenyl-2,4'-dicarboxylic acid diethyl ester (69i):



According to **TP 1**, the metalation of ethyl 4-bromobenzoate (**67f**; 458 mg, 2.0 mmol) was completed within 110 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**1**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (615 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 10 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over

anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 15:1) furnished the compound **69ib** (586 mg, 78%) as a yellowish oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.04-8.08 (m, 2 H), 7.76 (d, *J*=8.1 Hz, 1 H), 7.57 (dd, *J*=8.2, 2.0 Hz, 1 H), 7.50 (d, *J*=1.9 Hz, 1 H), 7.33-7.36 (m, 2 H), 4.40 (q, *J*=7.2 Hz, 2 H), 4.07 (q, *J*=7.2 Hz, 2 H), 1.40 (t, *J*=7.2 Hz, 3 H), 1.00 (t, *J*=7.2 Hz, 3 H).

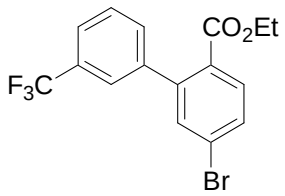
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 167.25, 166.29, 144.78, 143.52, 133.37, 131.63, 130.86, 129.65, 129.30, 128.30, 127.17, 125.88, 61.23, 61.04, 14.32, 13.67.

MS (70 eV, EI) *m/z* (%): 378 (74), 376 (70) [M^+], 350 (12), 348 (13), 334 (21), 333 (100), 332 (26), 331 (99), 322 (11), 320 (11), 305 (34), 304 (17), 303 (39), 298 (11), 261 (39), 259 (43), 253 (19), 180 (29), 152 (42), 151 (42), 144 (12), 139 (11), 89 (17) 75 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2979, 1710, 1609, 1585, 1552, 1464, 1445, 1408, 1385, 1365, 1309, 1266, 1241, 1178, 1132, 1096, 1029, 1013, 887, 858, 835, 798, 771, 760, 700, 649, 642, 635, 623, 614, 608, 602, 583, 576, 573.

HRMS (EI) for **$C_{18}H_{17}BrO_4$** (376.0310): 376.0309.

Synthesis of 5-bromo-3'-trifluoromethylbiphenyl-2-carboxylic acid ethyl ester (69j):



According to **TP 1**, the metalation of ethyl 4-bromobenzoate (**67f**; 458 mg, 2.0 mmol) was completed within 110 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-3-trifluoromethylbenzene (598 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 10 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 20:1) furnished the compound **69j** (586 mg, 78%) as a yellowish oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.79 (d, *J*=8.3 Hz, 1 H), 7.63 (d, *J*=7.6 Hz, 1 H), 7.59 (dd, *J*=8.3, 1.9 Hz, 1 H) 7.46–7.54 (m, 4 H), 4.06 (q, *J*=7.2 Hz, 2 H), 0.98 (t, *J*=7.2 Hz, 3 H).

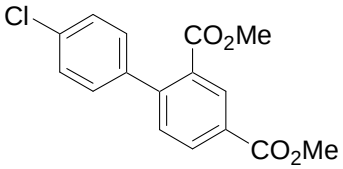
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 167.10, 142.94, 141.05, 133.56, 131.84, 131.63 (q, $^4J_{CF}$=1.3 Hz), 131.03, 130.43 (q, $^2J_{CF}$=32 Hz), 129.66, 128.51, 126.03, 125.22 (q, $^3J_{CF}$=3.9 Hz), 124.35 (q, $^3J_{CF}$=3.9 Hz), 123.82 (q, $^1J_{CF}$=272 Hz), 61.23, 13.51.

MS (70 eV, EI) *m/z* (%): 374 (42), 372 (38) [M^+], 346 (26), 345 (11), 344 (25), 330 (17), 329 (94), 328 (16), 327 (100), 248 (38), 221 (11), 220 (68), 219 (28), 201 (18), 170 (10), 43 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 1715, 1585, 1557, 1492, 1444, 1432, 1384, 1365, 1328, 1272, 1238, 1164, 1122, 1094, 1072, 1035, 1016, 905, 885, 860, 834, 803, 778, 753, 701, 688, 657, 626, 615, 608, 591, 568, 560, 554.

HRMS (EI) for **$C_{16}H_{12}BrF_3O_2$** (371.9973): 371.9955.

Synthesis of 4'-chlorobiphenyl-2,4-dicarboxylic acid dimethyl ester (69k):



According to **TP 1**, the metalation of isophthalic acid dimethyl ester (**67g**; 388 mg, 2.0 mmol) was completed within 48 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-chloro-4-iodobenzene (524 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 15 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 6:1) furnished the compound **69k** (455 mg, 75%) as a yellowish solid.

m.p.: 54.8-56.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.53 (d, *J*=1.8 Hz, 1 H), 8.20 (dd, *J*=7.5, 1.8 Hz, 1 H), 7.38-7.45 (m, 2 H), 7.24-7.29 (m, 3 H), 3.98 (s, 3 H), 3.73 (s, 3 H).

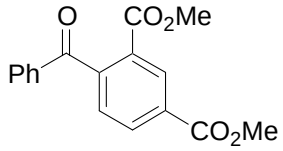
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.78, 165.97, 145.68, 138.76, 134.11, 132.22, 131.36, 130.98, 129.54, 129.54, 128.42, 52.42, 52.27.

MS (70 eV, EI) *m/z* (%): 306 (16), 304 (61) [M^+], 275 (27), 274 (12), 273 (100), 151 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950, 1711, 1608, 1595, 1576, 1557, 1504, 1476, 1458, 1444, 1437, 1409, 1391, 1306, 1297, 1283, 1273, 1240, 1196, 1182, 1140, 1116, 1106, 1096, 1087, 1018, 1005, 988, 963, 948, 929, 877, 863, 834, 820, 811, 789, 769, 738, 712, 702, 662, 642, 631, 612, 605, 601, 583, 576, 569, 564, 558.

HRMS (EI) for **$C_{16}H_{13}ClO_4$** (304.0502): 304.0499.

Synthesis of 4-benzoylisophthalic acid dimethyl ester (69l):



According to **TP 1**, the metalation of dimethyl isophthalate (**67g**; 388 mg, 2.0 mmol) was completed within 48 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The reaction mixture was cooled to –20 °C, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 15 min. Then, benzoyl chloride (353 mg, 2.5 mmol) was added at –20 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 5 h. Then the reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 2:1) furnished **69l** (481 mg, 81%) as a colourless solid.

m.p.: 120.2-121.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.70 (d, *J*=1.3 Hz, 1 H), 8.29 (dd, *J*=7.9, 1.8 Hz, 1 H), 7.70-7.74 (m, 2 H), 7.56 (dt, *J*=7.5, 1.8 Hz, 1 H), 7.40-7.48 (m, 3 H), 3.98 (s, 3 H), 3.67 (s, 3 H).

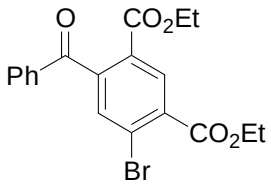
^{13}C-NMR ($CDCl_3$, 75 MHz) δ**:** 196.18, 165.53, 165.44, 145.75, 136.60, 133.41, 133.29, 131.42, 131.37, 129.49, 129.21, 128.63, 127.94, 52.60, 52.44.

MS (EI, 70 eV) *m/z* (%): 298 (16) [M^+], 267 (15), 221 (100), 105 (61), 77 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3042, 2954, 1716, 1674, 1598, 1582, 1492, 1436, 1396, 1312, 1280, 1264, 1242, 1188, 1144, 1112, 1076, 1024, 1000, 976, 932, 882, 856, 812, 806, 792, 768, 742, 722, 712, 702, 688, 656, 616 .

HRMS (EI) for **$C_{17}H_{14}O_5$** (298.0841): 298.0853.

Synthesis of 4-benzoyl-6-bromoisophthalic acid diethyl ester (69m):



According to **TP 1**, the metalation of 6-bromoisophthalic acid diethyl ester (**67h**; 602 mg, 2.0 mmol) was finished within 10 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The reaction mixture was cooled to –20 °C, CuCN·2LiCl

(1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 15 min. Then, benzoyl chloride (353 mg, 2.5 mmol) was added at –20 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 1 h. Then the reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 3:1) furnished **69m** (672 mg, 83%) as a colourless solid.

m.p.: 66.9-68.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.43 (s, 1 H), 7.70-7.77 (m, 2 H), 7.66 (s, 1 H), 7.58-7.64 (m, 1 H), 7.42-7.48 (m , 2 H), 4.46 (q, *J*=7.1 Hz, 2 H), 4.09 (q, *J*=7.1 Hz, 2 H), 1.44 (t, *J*= 7.5 Hz, 3 H), 1.04 (t, *J*=7.1 Hz, 3 H).

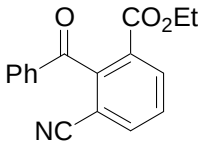
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 194.58, 165.22, 164.64, 145.01, 136.54, 133.93, 133.90, 133.60, 133.10, 129.62, 128.96, 128.356, 126.67, 62.52, 62.31, 14.45, 13.82.

MS (70 eV, ESI) *m/z* (%): 406 (10), 404 (11) [M^+], 361 (17), 359 (16), 329 (21), 327 (21), 301 (30), 299 (30), 151 (12), 105 (100), 77 (32).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1734, 1710, 1670, 1578, 1470, 1448, 1322, 1278, 1238, 1226, 1100, 1020, 970, 886, 862, 778, 734, 704, 692, 682.

HRMS (ESI) for **$C_{19}H_{17}BrO_5$** (405.0338 (M^+ + H)): 405.0326 (M^+ + H).

Synthesis of 2-benzoyl-3-cyanobenzoic acid ethyl ester (69n):



According to **TP 1**, the metalation of ethyl 3-cyanobenzoate (**67i**; 350 mg, 2.0 mmol) was finished within 25 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The reaction mixture was cooled to –20 °C, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 15 min. Then, benzoyl chloride (353 mg, 2.5 mmol) was added at –20 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 7 h. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 3:2) furnished **69n** (406 mg, 73%) as a colourless solid.

m.p.: 138.4-140.6 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.34 (d, *J*=7.9 Hz, 1 H), 7.93 (d, *J*=7.9 Hz, 1 H), 7.75 (d, *J*=7.5 Hz, 2 H), 7.69 (t, J=7.9 Hz, 1 H), 7.60 (d, *J*=7.3 Hz, 1 H), 7.47 (t, *J*=7.8 Hz, 2 H), 4.14 (q, *J*=7.2 Hz, 2 H), 1.06 (t, *J*=7.2 Hz, 3 H).

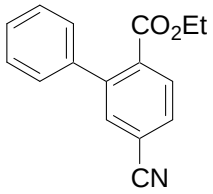
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 193.81, 164.22, 145.69, 136.82, 136.28, 134.61, 134.22, 130.46, 129.65, 129.51, 129.08, 116.07, 111.94, 62.52, 13.75.

MS (70 eV, EI) *m/z* (%): 280 (9), 279 (46) [M^+], 235 (88), 234 (18), 206 (8), 174 (28), 105 (100), 77 (24).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1716, 1670, 1474, 1444, 1366, 1272, 1160, 1018, 936, 923, 768, 707, 659.

HRMS (EI) for **$C_{17}H_{13}NO_3$** (279.0895): 279.0873.

Preparation of ethyl 5-cyanobiphenyl-2-carboxylate (69o)



According to **TP 1**, the metalation of ethyl 4-cyanobenzoate (**69j**; 350 mg, 2.0 mmol) was finished within 24 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). Then, $Pd(dba)_2$ (56 mg; 5 mol-%), P(*o*-furyl)$_3$ (46 mg; 10 mol-%) and iodobenzene (408 mg, 2.0 mmol) are added and the reaction mixture is stirred for 5 h at 25 °C. The reaction mixture is quenched with a sat. aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers are washed with brine (25 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 7:1) furnished **69o** as a yellowish oil (540 mg, 85%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.13-8.17 (m, 1 H), 7.89-7.91 (m, 1 H), 7.70-7.77 (m, 2 H), 7.40-7.47 (m, 2 H), 7.29-7.34 (m, 2 H), 4.10 (q, *J*=7.3 Hz, 2 H), 0.98 (t, *J*=7.2 Hz, 3 H).

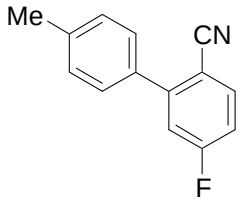
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.37, 143.20, 139.11, 135.53, 134.04, 132.17, 130.23, 130.06, 128.39, 128.19, 116.30, 114.77, 61.63, 13.62.

MS (70 eV, EI) *m/z*: 251 (35) [M^+], 223 (11), 207 (16), 206 (100), 178 (16), 177 (16), 151 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3098, 3052, 2990, 2980, 2938, 2904, 2232, 1712, 1674, 1602, 1578, 1568, 1558, 1504, 1480, 1472, 1444, 1398, 1366, 1350, 1318, 1280, 1250, 1186, 1158, 1138, 1124, 1106, 1076, 1048, 1020, 968, 920, 902, 872, 854, 842, 788, 764, 710, 696, 668, 642, 630, 614, 604, 580, 566.

HRMS (EI) for **$C_{16}H_{13}NO_2$** (251.0946): 251.0941.

Synthesis of 5-fluoro-4'-methylbiphenyl-2-carbonitrile (69p):



According to **TP 1**, the metalation of 4-fluorobenzonitrile (**67k**; 242 mg, 2.0 mmol) was completed within 48 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 4-iodotoluene (436 mg, 2.0 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 20:1) furnished the compound **69p** (371 mg, 88%) as a colourless solid.

m.p.: 105.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.79 (dd, *J*=7.2, 2.1 Hz, 1 H), 7.63-7.67 (m, 1 H), 7.40-7.49 (m, 2 H), 7.32 (d, *J*=7.8 Hz, 2 H,) 7.28 (d, *J*=1.5 Hz, 1 H), 2.45 (s, 3 H).

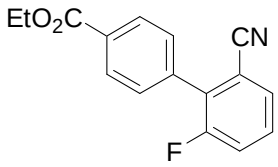
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 160.10 (d, $^1J_{CF}$=258 Hz), 138.84, 134.95 (d, $^3J_{CF}$=5.2 Hz), 132.72 (d, $^2J_{CF}$=19 Hz), 130.98, 130.78, 130.46 (d, $^4J_{CF}$=1.3 Hz), 129.52, 128.73 (d, $^4J_{CF}$=2.8 Hz), 118.11, 117.55 (d, $^2J_{CF}$=25 Hz), 108.85 (d, $^3J_{CF}$=4.1 Hz), 21.25.

MS (70 eV, EI) *m/z* (%): 211 (98) [M^+], 210 (39), 183 (17), 111 (18), 97 (38), 95 (18), 91 (39), 85 (25), 83 (41), 74 (19), 71 (35), 70 (19), 69 (50), 67 (18), 59 (29), 57 (71), 56 (22), 55 (42), 45 (15), 44 (100), 43 (41), 41 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3106, 3074, 3048, 2922, 2360, 2342 2228, 2176, 1910, 1890, 1762, 1652, 1618, 1608, 1584, 1520, 1486, 1420, 1392, 1378, 1308, 1286, 1272, 1252, 1226, 1212, 1194, 1172, 1122, 1040, 1022, 968, 942, 912, 880, 816, 796, 740, 732, 706, 678, 656, 642, 608, 576, 568.

HRMS (EI) for **$C_{14}H_{10}FN$** (211.0797): 211.0775.

Synthesis of 6'-cyano-2'-fluorobiphenyl-4-carboxylic acid ethyl ester (69q):



According to **TP 1**, the metalation of 3-fluorobenzonitrile (**67l**; 242 mg, 2.0 mmol) was completed within 30 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (607 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 6:1) furnished the compound **69q** (388 mg, 72%) as a colourless solid. **m.p.**: 104.5-106.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.16-8.19 (m, 2 H), 7.54-7.61 (m, 3 H), 7.38-7.50 (m, 2 H), 4.40 (q, *J*=7.2 Hz, 2 H), 1.40 (t, *J*=7.3 Hz, 3 H).

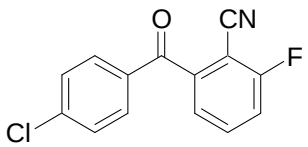
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.96, 159.35 (d, $^1J_{CF}$=250 Hz), 135.69, 132.15 (d, $^2J_{CF}$=19 Hz), 131.20, 130.10 (d, $^3J_{CF}$=8.8 Hz), 129.84 (d, $^4J_{CF}$=1.8 Hz), 129.75, 129.52 (d, $^3J_{CF}$=4.8 Hz), 120.83 (d, $^2J_{CF}$=23 Hz), 116.94 (d, $^4J_{CF}$=4.3 Hz), 114.06 (d, $^4J_{CF}$=4.3 Hz), 61.18, 14.30.

MS (70 eV, EI) *m/z* (%): 269 (22) [M^+], 240 (33), 224 (13), 223 (100), 197 (16), 196 (28), 195 (16), 169 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960, 2232, 1723, 1714, 1612, 1578, 1464, 1451, 1408, 1368, 1296, 1271, 1257, 1190, 1176, 1159, 1104, 1082, 1033, 1025, 1007, 979, 967, 957, 915, 888, 861, 798, 770, 730, 700, 633, 602.

HRMS (EI) for **$C_{16}H_{12}FNO_2$** (269.0852): 269.0840.

Synthesis of 2-(4-chlorobenzoyl)-6-fluorobenzonitrile (69r):



According to **TP 1**, the metalation of 2-fluorobenzonitrile (**67m**; 242 mg, 2.0 mmol) was completed within 144 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). The reaction mixture was cooled to –20 °C, CuCN·2LiCl (1.0 M

solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 15 min. Then, 4-chlorobenzoyl chloride (438 mg, 2.5 mmol) was added at –20 °C. The reaction mixture was slowly warmed to 25 °C stirred at 25 °C for 10 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 1:1) furnished the compound **69r** (330 mg, 63%) as a yellowish solid.

m.p.: 137.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.78-7.85 (m, 2 H), 7.73 (ddd, *J*=8.9, 3.5, 2.2 Hz, 2 H), 7.47 (ddd, *J*=8.9, 2.3, 2.2 Hz, 2 H), 7.42 (t, *J*=7.8 Hz, 1 H).

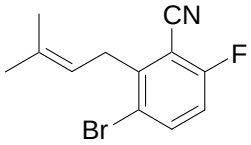
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 189.76, 160.27 (d, $^1J_{CF}$=265 Hz), 140.89, 136.36, 135.35 (d, $^3J_{CF}$=3.6 Hz), 134.71, 131.06 (d, $^4J_{CF}$=1.3 Hz), 129.37, 129.22, 127.78 (d, $^2J_{CF}$=14 Hz), 125.28 (d, $^3J_{CF}$=4.4 Hz), 113.05, 102.77 (d, $^2J_{CF}$=16 Hz).

MS (70 eV, EI) *m/z* (%): 261 (14), 259 (43) [M^+], 148 (24), 141 (31), 139 (100), 120 (11), 111 (23), 75 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3088, 3070, 2360, 2340, 2238, 1930, 1660, 1610, 1586, 1570, 1540, 1484, 1448, 1402, 1370, 1316, 1302, 1294, 1280, 1250, 1236, 1202, 1190, 1172, 1160, 1132, 1114, 1090, 1074, 1024, 1012, 1000, 990, 962, 936, 850, 836, 814, 792, 748, 736, 716, 680, 668, 642, 628, 608, 560.

HRMS (EI) for **$C_{14}H_7ClFNO$** (259.0200): 259.0189.

Synthesis of 3-bromo-6-fluoro-2-(3-methyl-but-2-enyl)-benzonitrile (69s)



According to **TP 1**, the metalation of 5-bromo-2-fluorobenzonitrile (**67n**; 400 mg, 2.0 mmol) was completed within 5.5 h at 25 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). Then CuCN·2LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and 1-bromo-3-methyl-but-2-ene (360 mg, 2.4 mmol) were added and stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 75:1) furnished **69s** (455 mg, 85%) as a colourless solid.

m.p.: 47.8-49.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.00-7.06 (m, 1 H), 6.72-6.77 (m, 1 H), 4.92-4.90 (m, 1 H), 2.84 (d, *J*=7.4 Hz, 2 H), 1.50 (d, *J*=1.1 Hz, 3 H), 1.37 (s, 3 H).

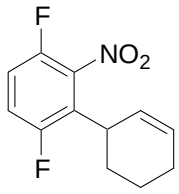
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.53 (d, $^1J_{CF}$=257 Hz), 137.56 (d, $^3J_{CF}$=5.6 Hz), 135.20, 133.05, 132.02 (d, $^2J_{CF}$=16 Hz), 119.41, 116.73 (d, $^3J_{CF}$=4.2 Hz), 112.77, 103.44 (d, $^2J_{CF}$=18Hz), 27.03 (d, $^4J_{CF}$=2.2 Hz), 25.51, 17.50.

MS (70 eV, EI) *m/z* (%): 269 (24), 267 (25), [M^+], 251 (14), 249 (15), 187 (20), 173 (13), 172 (100), 171 (18), 157 (14), 133 (11), 55 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3088, 3032, 2977, 2928, 2857, 2237, 1732, 1603, 1573, 1484, 1463, 1452, 1436, 1402, 1377, 1350, 1287, 1261, 1244, 1209, 1175, 1152, 1117, 1101, 1094, 1074, 1011, 985, 967, 898, 862, 838, 774, 734, 721.

HRMS (EI) for **$C_{12}H_{11}BrFN$** (267.0059): 267.0047.

Synthesis of 2-cyclohex-2-enyl-1,4-difluoro-3-nitrobenzene (69t):



According to **TP 1**, the metalation of 1,4-difluoro-2-nitrobenzene (**67o**; 318 mg, 2.0 mmol) was completed within 3.5 h at 0 °C using a solution of $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.40 M in THF, 2.8 mL, 1.1 mmol). 3-Bromo-cyclohexene (400 mg, 2.5 mmol) and CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) were added at 0 °C and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (4 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/CH_2Cl_2 = 5:1) furnished **69t** (392 mg, 82%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.07-7.21 (m, 2 H), 5.84-5.91 (m, 1 H), 5.51-5.59 (m, 1 H), 3.55-3.63 (m, 1 H), 1.99-2.17 (m, 3 H), 1.86-1.95 (m, 2 H), 1.58-1.70 (m, 1 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 156.80 (t, J_{CF}=246, 2.8 Hz), 149.78 (t, J_{CF}=246, 2.8 Hz), 129.36 (d, $^4J_{CF}$=2.0 Hz), 127.51 (t, J_{CF}=18, 1.3 Hz), 125.70 (d, $^5J_{CF}$=1.3 Hz), 118.51 (m), 115.32 (m).

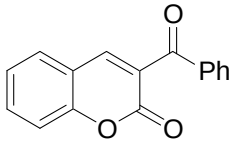
MS (70 eV, EI) *m/z* (%): 239 (21) [M^+], 223 (26), 222 (71), 221 (22), 220 (21), 205 (34), 204 (100), 203 (93), 202 (16), 194 815), 192 (31), 183 (23), 182 (77), 181 (16), 179 (34), 177 (16), 170 (16), 169 8199, 168 828), 166 (959, 165 (25), 164 (379, 156 827), 155 (21), 153 (35), 152 816), 151 847), 146 8169, 128 8229, 127 842), 69 (21), 67 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3028, 2938, 2865, 1598, 1539, 1479, 1457, 1449, 1434, 1363, 1288, 1265, 1236, 1196, 1137, 1052, 1034, 971, 944, 920, 895, 881, 864, 819, 805, 771, 743, 721, 705, 686, 637, 623, 603.

HRMS (EI) for **$C_{12}H_{11}F_2NO_2$** (239.0758): 239.0745.

Larger Scale Synthesis

Preparation of 3-benzoyl-2*H*-chromen-2-one (70a)



A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 125 mL, 110 mmol). Coumarin (**55**; 14.6 g, 100 mmol) is added neatly and the mixture is stirred for 2 h at 25 °C. The resulting mixture is cooled to –20 °C, then PhCOCl (14.2 g, 100 mmol, 1.0 equiv) and CuCN·2LiCl (1.0 M solution in THF, 10 mL, 10 mmol) were added. After slow warming to 25 °C within 5 h, the reaction mixture is quenched with a mixture of a sat. aqueous NH_4Cl solution (300 mL) and conc. aqueous NH_3-solution (50 mL) and extracted with Et_2O (3 x 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*heptane/ethyl acetate) to give **70a** as a yellowish solid (17.8 g, 71%).

m.p.: 136.0-137.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.11 (s, 1 H), 7.90 (d, J = 8.4 Hz, 2 H), 7.67-7.57 (m, 3 H), 7.51-7.44 (m, 2 H), 7.40 (d, J=8.5 Hz, 1 H), 7.34 (d, J=7.5 Hz, 1 H).

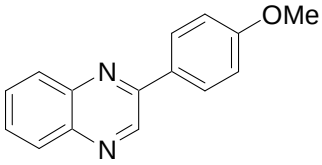
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 191.61, 158.42, 154.78, 145.32, 136.24, 133.85, 133.59, 129.51, 129.16, 128.58, 127.02, 124.98, 118.23, 116.91.

MS (70 eV, EI) *m/z*: 251 (13), (250) (100) [M^+], 222 (24), 221 (59), 173 (21), 105 (98), 77 (61), 51 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3061, 1712, 1656, 1607, 1595, 1580, 1563, 1487, 1453, 1449, 1445, 1363, 1318, 1305, 1297, 1264, 1237, 1214, 1182, 1164, 1144, 1120, 1073, 1041, 1026, 1000, 962, 952, 946, 937, 920, 865, 857, 816, 793, 769, 759, 754, 736, 696, 681.

HRMS (EI) for **$C_{16}H_{10}O_3$** (250.0630): 250.0605.

Preparation of 2-(4-methoxyphenyl)quinoxaline (70b)



A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 125 mL, 110 mmol). Quinoxaline (**61h**; 13.0 g, 100 mmol) is added and the mixture is stirred for 3 h at 25 °C. Then, $Pd(dba)_2$ (280 mg; 0.5 mol-%), P(*o*-furyl)$_3$ (230 mg; 1 mol-%) and 4-iodoanisole (23.4 g, 100 mmol, 1.00 equiv) are added and the reaction mixture is stirred for 2 h at 25 °C. The reaction mixture is quenched with a sat. aqueous NH_4Cl solution (250 mL) and extracted with Et_2O (3 x 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*heptane/ethyl acetate) to give **70b** as a colourless solid (19.4 g, 82%).

m.p.: 100.2-101.9 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 9.28 (s, 1 H), 8.16 (d, *J* =8.8Hz, 2 H), 8.12 (t, *J*=8.1.Hz, 2 H), 7.77-7.67 (m, 2 H), 7.11 (d, *J*=8.8 Hz, 2 H), 3.88 (s, 3 H).

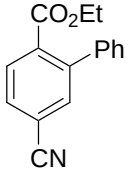
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 161.52, 151.41, 143.00, 142.26, 141.11, 130.27, 129.36, 129.20, 129.13, 129.02, 114.62, 55.47.

MS (70 eV, EI) *m/z*: 236 (100) [M+], 233 (14), 221 (17), 209 (12), 166 (8), 118 (8), 57 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3057, 3005, 2930, 2833, 1602, 1576, 1536, 1488, 1427, 1291, 1270, 1246, 1226, 1181, 1130, 1030, 957, 847, 810, 795, 758, 728, 670, 655, 630, 609.

HRMS (EI) for **$C_{15}H_{12}N_2O$** (236.0950): 236.0945.

Preparation of ethyl 5-cyanobiphenyl-2-carboxylate (69o)



A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 125 mL, 110 mmol). Ethyl 4-cyanobenzoate (**67j**; 17.5 g, 100 mmol) is added and the mixture is stirred for 48 h at 25 °C. Then, $Pd(dba)_2$ (280 mg; 0.5 mol-%), P(*o*-furyl)$_3$ (230 mg; 1 mol-%) and iodobenzene (20.4 g, 100 mmol, 1.00 equiv) are added and the reaction mixture is stirred for 5 h at 25 °C. The reaction mixture is quenched with a sat. aqueous NH_4Cl solution (250 mL) and extracted with Et_2O (3 x 250 mL). The combined organic layers are washed with brine

(250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by column chromatography (pentane/ether = 7:1) to give **69o** as a yellowish oil (21.1 g, 84%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.13-8-17 (m, 1 H), 7.89-7.91 (m, 1 H), 7.70-7.77 (m, 2 H), 7.40-7.47 (m, 2 H), 7.29-7.34 (m, 2 H), 4.10 (q, *J*=7.3 Hz, 2 H), 0.98 (t, *J*=7.2 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.37, 143.20, 139.11, 135.53, 134.04, 132.17, 130.23, 130.06, 128.39, 128.19, 116.30, 114.77, 61.63, 13.62.

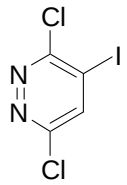
MS (70 eV, EI) *m/z*: 251 (35) [M^+], 223 (11), 207 (16), 206 (100), 178 (16), 177 (16), 151 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3098, 3052, 2990, 2980, 2938, 2904, 2232, 1712, 1674, 1602, 1578, 1568, 1558, 1504, 1480, 1472, 1444, 1398, 1366, 1350, 1318, 1280, 1250, 1186, 1158, 1138, 1124, 1106, 1076, 1048, 1020, 968, 920, 902, 872, 854, 842, 788, 764, 710, 696, 668, 642, 630, 614, 604, 580, 566.

HRMS (EI) for **$C_{16}H_{13}NO_2$** (251.0946): 251.0941.

13.5 Functionalization of 3,6-Dichloropyridazine (71)

Synthesis of 3,6-dichloro-4-iodopyridazine (73a)



To a solution of the zincated dichloropyridazine **72** (2 mmol), iodine (761 mg, 3.0 mmol) dissolved in THF (6 mL) was added dropwise and stirred for 1 h at –78 °C. The reaction mixture was quenched with a mixture of a sat. aq. NH_4Cl solution (10 mL) and a sat. aq. $Na_2S_2O_3$ solution (10 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 5:1) furnished the compound **73a** (451 mg, 82%) as a colourless solid.

m.p.: 145.1-146.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.06 (s, 1H).

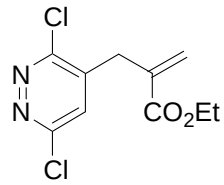
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 159.70, 153.85, 139.73, 105.37.

MS (70 eV, EI) *m/z* (%): 274 (95) [M^+], 127 (23), 123 (10), 121 (70), 119 (100), 86 (15), 84 (43), 49 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3092, 3020, 1796, 1516, 1488, 1464, 1332, 1296, 1276, 1236, 1152, 1136, 1060, 1044, 992, 956, 900, 812, 764, 728, 672, 660, 628, 608, 588, 564.

HRMS (EI) for **$C_4HCl_2IN_2$** (273.8561): 273.8538.

Synthesis of 2-(3,6-dichloropyridazin-4-ylmethyl)acrylic acid ethyl ester (73b)



To a solution of the zincated dichloropyridazine **72** (2.0 mmol), CuCN·2LiCl (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added and the reaction mixture was stirred for 5 min. Then, ethyl 2-(bromomethyl)acrylate (483 mg, 2.5 mmol) was added and stirred for 1 h at –78 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (15 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 4:1) furnished the compound **73b** (451 mg, 82%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 7.39 (s, 1H), 6.45 (s, 1 H), 5.75 (s, 1 H), 4.18 (q, *J*=7.2 Hz, 2 H), 3.72 (s, 2 H), 1.25 (q, *J*=7.2 Hz, 3 H).

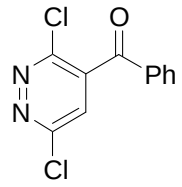
^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 165.50, 156.82, 155.91, 141.36, 134.67, 129.91, 129.87, 61.46, 34.75, 14.06.

MS (70 eV, EI) *m/z* (%): 260 (7) [M^+], 227 (22), 225 (77), 217 (10), 215 (16), 199 (34), 198 (9), 197 (100), 189 (8) 187 (11), 123 (9), 63 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 1709, 1632, 1566, 1476, 1464, 1444, 1406, 1359, 1319, 1294, 1276, 1255, 1206, 1172, 1132, 1100, 1048, 1023, 957, 938, 918, 872, 858, 817, 772, 747, 729, 684, 640, 633, 617, 610, 607, 597, 583, 580, 570, 566.

HRMS (EI) for **$C_{10}H_{10}Cl_2N_2O_2$** (260.0119): 260.0113.

Synthesis of (3,6-dichloropyridazin-4-yl)phenylmethanone (73c)



To a solution of the zincated dichloropyridazine **72** (2.0 mmol), CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 30 min. Then, benzoyl chloride (353 mg, 2.5 mmol) was added at –78 °C. The reaction mixture was slowly warmed to –20 °C and stirred at this temperature for 16 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (15 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether, 3:1) furnished the compound **73c** (368 mg, 73%) as a colourless solid.

m.p.: 100.2-101.5 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 7.78 (d, *J*=7.2 Hz, 2 H), 7.72 (t, *J*=7.6 Hz, 1 H), 7.56 (t, *J*=7.9 Hz, 2 H), 7.51 (s, 1 H).

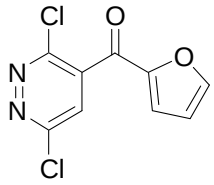
^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 189.05, 156.23, 151.71, 140.00, 135.48, 133.98, 130.02, 129.34, 127.71.

MS (70 eV, EI) *m/z* (%): 254 (23), 252 (38) [M^+], 106 (21), 105 (97), 77 (100), 51 (28).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3069, 1665, 1632, 1614, 1590, 1574, 1501, 1487, 1444, 1338, 1324, 1306, 1289, 1257, 1247, 1239, 1222, 1173, 1167, 1155, 1134, 1103, 1070, 1052, 1024, 999, 988, 981, 968, 932, 902, 852, 821, 799, 756, 714, 699, 681, 653, 624, 612, 599, 587, 584, 579, 575, 559.

HRMS (EI) for **$C_{11}H_6Cl_2N_2O$** (251.9857): 251.9844.

Synthesis of (3,6-dichloropyridazin-4-yl)furan-2-ylmethanone (73d)



To a solution of the zincated dichloropyridazine **72** (2.0 mmol), CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 30 min. Then, 2-furoyl chloride (326 mg, 2.5 mmol) was added at –78 °C. The reaction mixture was slowly warmed to –20 °C and stirred at this temperature for 16 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 3:1) furnished the compound **73d** (330 mg, 68%) as a colourless solid.

m.p.: 135.6-136.8 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.74 (d, *J*=0.7 Hz, 1 H), 7.56 (s, 1 H), 7.33 (d, *J*=3.2 Hz, 1 H), 6.72 (dd, *J*=3.6, 1.5 Hz, 1 H).

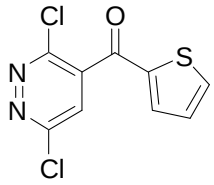
^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 175.78, 156.16, 151.83, 150.53, 149.44, 138.50, 127.89, 122.39, 113.71.

MS (70 eV, EI) *m/z* (%): 244 (62), 242 (94) [M^+], 96 (18), 95 (100), 84 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3113, 3041, 1657, 1623, 1558, 1505, 1462, 1391, 1353, 1319, 1282, 1243, 1203, 1190, 1183, 1165, 1149, 1119, 1081, 1040, 1034, 981, 931, 927, 911, 883, 872, 864, 802, 789, 778, 768, 740, 692, 683, 644, 641, 630, 620, 591, 570, 552.

HRMS (EI) for **$C_9H_4Cl_2N_2O_2$** (241.9650): 241.9658.

Synthesis of (3,6-dichloropyridazin-4-yl)thiophen-2-ylmethanone (73e)



To a solution of the zincated dichloropyridazine **72** (2.0 mmol), CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 30 min. Then, 2-thiophene acid chloride (346 mg, 2.5 mmol) was added at –78 °C. The reaction mixture was slowly warmed to –20 °C and stirred at this temperature for 16 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (15 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*.

Purification by column chromatography (pentane/diethyl ether = 3:1) furnished the compound **73e** (339 mg, 66%) as a colourless solid.

m.p.: 158.1-159.8 °C.

^{1}H-NMR (CDCl$_3$, 600 MHz) δ: 7.94 (d, *J*=6.2 Hz, 1 H), 7.55 (s, 1 H), 7.46 (d, *J*=3.8 Hz, 1 H), 7.21-7.24 (m, 1 H).

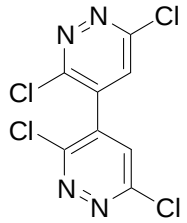
^{13}C-NMR (CDCl$_3$, 150 MHz) δ: 180.63, 156.14; 151.68, 141.13, 139.30, 138.15, 136.82, 129.11, 127.44.

MS (70 eV, EI) *m/z* (%): 260 (66), 258 (99) [M$^+$], 113 (23), 112 (28), 111 (100), 84 (12), 83 (25), 57 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3116, 3069, 1630, 1597, 1561, 1507, 1501, 1419, 1402, 1364, 1355, 1343, 1325, 1312, 1270, 1256, 1230, 1206, 1197, 1180, 1142, 1105, 1072, 1054, 1040, 958, 934, 911, 863, 860, 853, 826, 807, 793, 757, 735, 693, 678, 662, 655, 610, 593, 579, 574, 570, 563, 553.

HRMS (EI) for **C$_9$H$_4$Cl$_2$N$_2$OS** (257.9421): 257.9414.

Synthesis of (3,6,3',6')-tetrachloro-[4,4']bipyridazinyl (73f)



To a solution of the zincated dichloropyridazine **72** (2.0 mmol), chloranil (290 mg, 1.2 mmol) dissolved in THF (9 mL) was added dropwise at –78 °C and the resulting reaction mixture was stirred for 4 h at –78 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (15 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 1:1) furnished the compound **73f** (262 mg, 88%) as a colourless solid.

m.p.: 164.5-166.5 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.56 (s, 2H).

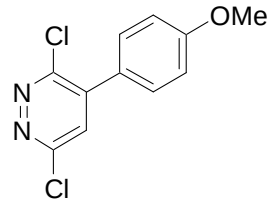
^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 156.10, 153.32, 134.78, 129.59.

MS (70 eV, EI) *m/z* (%): 296 (100) [M$^+$], 295 (9), 294 (72), 233 (19), 231 (21), 208 (11), 206 (15), 205 (10), 203 (9), 198 (19), 197 (12), 196 (29), 195 (15), 145 (10), 143 (12), 118 (11), 108 (8), 84 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3031, 1684, 1546, 1434, 1392, 1349, 1327, 1281, 1139, 903, 781, 753, 712, 632, 568.

HRMS (EI) for **$C_8H_2Cl_2N_4$** (293.9034): 293.9037.

Synthesis of 3,6-dichloro-4-(4-methoxyphenyl)pyridazine (73g)



To a solution of the zincated dichloropyridazine **72** (2.0 mmol), $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-4-methoxybenzene (500 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was allowed to warm up within 4 h to -20 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 6:1) furnished the compound **73g** (366 mg, 76%) as a colourless solid.

m.p.: 106.5-107.9 °C.

^{1}H-NMR (DMSO, 400 MHz) δ: 8.06 (s, 1 H), 7.61 (ddd, *J*=9.4, 2.9, 2.5 Hz, 2 H), 7.10 (ddd, *J*=9.4, 2.9, 2.5 Hz, 2 H), 3.83 (s, 3 H).

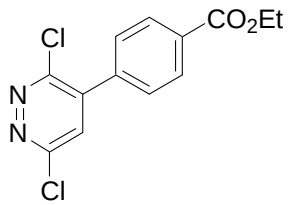
^{13}C-NMR (DMSO, 100 MHz) δ: 160.68, 155.64, 154.47, 142.19, 130.97, 130.18, 124.88, 114.09, 55.34.

MS (70 eV, EI) *m/z* (%): 256 (58), 255 (12), 254 (100) [M^+], 213 (11), 210 (17), 166 (11), 156 (11) 114 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3016, 2934, 2842, 1604, 1578, 1552, 1510, 1464, 1448, 1440, 1372, 1360, 1332, 1314, 1288, 1258, 1244, 1212, 1190, 1136, 1122, 1058, 1044, 1026, 960, 944, 920, 858, 830, 814, 792, 780, 756, 724, 700, 680, 642, 614, 590, 578.

HRMS (EI) for **$C_{11}H_8Cl_2N_2O$** (254.0014): 254.0007.

Synthesis of 4-(3,6-dichloropyridazin-4-yl)benzoic acid ethyl ester (73h)



To a solution of the zincated dichloropyridazine **72** (2.0 mmol), $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula

to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (607 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was allowed to warm up within 4 h to –20 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 4:1) furnished the compound **73h** (481 mg, 81%) as a colourless solid.

m.p.: 81.4-82.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.18 (ddd, *J*=8.6, 1.9, 1.7 Hz, 2 H), 7.56 (ddd, *J*=8.6, 1.9, 1.7 Hz, 2 H), 7.51 (s, 1 H), 4.42 (q, *J*=7.1 Hz, 2 H), 1.42 (t, *J*=7.0 Hz, 3 H).

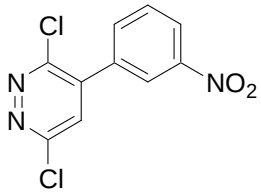
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.55, 156.08, 154.43, 141.80, 137.21, 132.21, 130.01, 129.48, 128.94, 61.49, 14.28.

MS (70 eV, EI) *m/z* (%): 298 (23), 296 (39) [M^+], 270 (34), 268 (53), 255 (11), 254 (12), 253 (62), 252 (17), 251 (100), 188 (10), 153 (17), 126 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3062, 3038, 2984, 2910, 1716, 1612, 1556, 1540, 1482, 1408, 1390, 1364, 1350, 1328, 1314, 1274, 1186, 1136, 1126, 1102, 1060, 1040, 1016, 980, 964, 924, 880, 858, 842, 772, 750, 720, 700, 668, 654, 638, 612, 590, 554.

HRMS (EI) for **$C_{13}H_{10}Cl_2N_2O_2$** (296.0119): 296.0118.

Synthesis of 3,6-dichloro-4-(3-nitrophenyl)pyridazine (73i)



To a solution of the zincated dichloropyridazine **72** (2.0 mmol), $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-3-nitrobenzene (510 mg, 2.1 mmol) dissolved in THF (2 mL). The reaction mixture was allowed to warm up within 4 h to –20 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 3:1) furnished the compound **73i** (415 mg, 77%) as a pale yellow solid.

m.p.: 174.0-175.2 °C.

^{1}H-NMR (DMSO, 400 MHz) δ: 8.52 (t, *J*=8.2 Hz, 1 H), 8.40 (ddd, *J*=8.4, 2.3, 1.1 Hz, 1 H), 8.27 (s, 1 H), 8.09 (dt, *J*=7.8, 1.4 Hz, 1 H), 7.85 (t, *J*=8.2 Hz, 1 H).

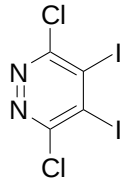
^{13}C-NMR (DMSO, 100 MHz) δ: 155.76, 154.17, 147.65, 140.51, 135.86, 134.54, 131.21, 130.22, 124.69, 124.35.

MS (70 eV, EI) *m/z* (%): 273 (10) 271 (60), 270 (11), 269 (100) [M^+], 241 (11), 195 (14), 160 (35), 153 (16), 126 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3094, 3056, 1614, 1580, 1558, 1522, 1494, 1478, 1348, 1328, 1304, 1280, 1244, 1226, 1190, 1176, 1136, 1112, 1100, 1090, 1066, 1046, 1002, 942, 920, 904, 838, 814, 790, 758, 730, 686, 668, 626, 598, 562.

HRMS (EI) for **$C_{10}H_5Cl_2N_3O_2$** (268.9759): 269.9763.

Synthesis of 3,6-dichloro-4,5-iodopyridazine (75a)



A dry and argon flushed 25-mL Schlenck-tube, equipped with a magnetic stirring bar was charged with a solution of 6-dichloro-4-iodo-pyridazine (**73a**, 550 mg, 2.0 mmol) in dry THF (5 mL). The solution was cooled to –78 °C and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol) was added dropwise and the resulting mixture was stirred for 3 h at -78 °C. Iodine (761 mg, 3.00 mmol) dissolved in THF (6 mL) was added dropwise and stirred for 1 h at –78 °C. The reaction mixture was quenched with mixture of a sat. aq. NH_4Cl solution (10 mL) and a sat. aq. $Na_2S_2O_3$ solution (10 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Recrystallization (CH_2Cl_2) furnished the compound **75a** (448 mg, 56%) as a colourless solid.

m.p.: 193.8 °C (decomposition).

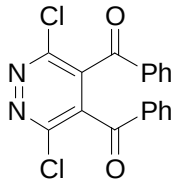
^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 157.78, 124.81.

MS (70 eV, EI) *m/z* (%):400 (100) [M^+], 254 (11), 247 (16), 245 (25), 237 (14), 236 (10), 126 (21), 120 (50), 118 (67), 83 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3092, 1516, 1488, 1464, 1332, 1296, 1276, 1236, 1152, 1136, 1060, 1044, 992, 956, 900, 812, 764, 728, 672, 660, 628, 608, 564.

HRMS (EI) for **$C_4Cl_2I_2N_2$** (399.7528): 399.7518.

Synthesis of (5-benzoyl-3,6-dichloropyridazin-4-yl)phenylmethanone (75b)



A dry and argon flushed 25-mL Schlenck-tube, equipped with a magnetic stirring bar was charged with a solution of (3,6-dichloropyridazin-4-yl)phenylmethanone (**73c**; 504 mg, 2.0 mmol) in dry THF (5 mL). The solution was cooled to –78 °C and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol) was added dropwise and the resulting mixture was stirred for 3 h at –78 °C. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 30 min. Then, benzoyl chloride (353 mg, 2.5 mmol) was added at –78 °C. The reaction mixture was slowly warmed to –20 °C and stirred at this temperature for 16 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 1:1) furnished the compound **75b** (548 mg, 77%) as a pale yellow solid.

m.p.: 166.8-168.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.63-7.73 (m, 6 H), 7.46-7.51 (m, 4 H).

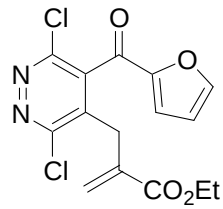
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 188.95, 152.02, 138.05, 135.47, 134.27, 129.93, 129.17.

MS (70 eV, EI) *m/z* (%): 356 (7) [M^+], 105 (100), 77 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1668, 1594, 1580, 1450, 1336, 1318, 1258, 1180, 1166, 1150, 1002, 990, 962, 852, 812, 798, 754, 714, 700, 680, 668, 628, 614, 566.

HRMS (EI) for **$C_{18}H_{10}Cl_2N_2O_2$** (356.0119): 356.0114.

Synthesis of 2-[3,6-dichloro-5-(furan-2-carbonyl)pyridazin-4-ylmethyl] acrylic acid ethyl ester (75c)



A dry and argon flushed 25-mL Schlenck-tube, equipped with a magnetic stirring bar was charged with a solution of (3,6-dichloro-pyridazin-4-yl)-furan-2-yl-methanone (**73d**; 486 mg, 2.0 mmol) in dry THF (5 mL). The solution was cooled to –78 °C and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol) was added dropwise and the resulting mixture was

stirred for 3 h at –78 °C. CuCN·2LiCl (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added and the reaction mixture was stirred for 5 min. Then, ethyl 2-(bromomethyl)acrylate (483 mg, 2.5 mmol) was added and stirred for 1 h at –78 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 2:1) furnished the compound 7**5c** (534 mg, 75%) as a pale yellow solid.

m.p.: 129.8-131.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.67 (d, *J*=2.4 Hz, 1 H), 7.28 (d, *J*=3.4 Hz, 1 H), 6.65-6.67 (m, 1 H), 6.22 (t, *J*=1.3 Hz, 1 H), 5.24 (t, *J*=1.7 Hz, 1 H), 4.16 (q, *J*=7.3 Hz, 2 H), 3.58-3.85 (m, 2 H), 1.25 (t, *J*=7.0 Hz, 3 H).

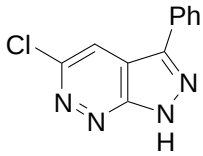
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 176.46, 165.25, 157.95, 151.59, 150.89, 149.44, 138.78, 134.58, 127.88, 127.75, 122.53, 121.56, 113.67, 61.35, 31.95, 14.06.

MS (70 eV, EI) *m/z* (%): 354 (1) [M^+], 285 (11), 284 (10), 283 (62), 282 (22), 281 (100), 256 (13), 255 (12), 254 (17), 95 (71), 81 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1668, 1594, 1580, 1450, 1336, 1318, 1258, 1180, 1166, 1150, 1002, 990, 962, 852, 812, 798, 754, 714, 700, 680, 668, 628, 614, 566.

HRMS (EI) for **$C_{15}H_{12}Cl_2N_2O_4$** (354.0174): 354.0170.

Synthesis of 5-chloro-3-phenyl-1H-pyrazolo[3,4-c]pyridazine (76a)



A 50-mL round bottom flask, equipped with a magnetic stirring bar was charged with a suspension of (3,6-dichloro-pyridazin-4-yl)-phenyl-methanone (**73c**; 504 mg, 2.0 mmol) in EtOH (25 mL). $N_2H_4·H_2O$ (0.6 mL, 6 mmol) was added in one portion and the resulting mixture was refluxed for 30 min. After cooling to 25 °C CH_2Cl_2 (100 mL) was added and the organic layer was washed with water (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The residue was recrystallized from MeOH giving **76a** as a yellow solid (305 mg, 66%).

m.p.: 255.6-256.6 °C.

^{1}H-NMR (DMSO, 400 MHz) δ: 14.55 (s, 1 H), 8.71 (s, 1 H), 8.04-8.09 (m, 2 H), 7.48, 7.54 (m, 2 H), 7.41-7.47 (m, 1 H).

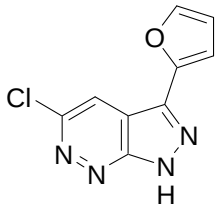
^{13}C-NMR (DMSO, 100 MHz) δ: 155.37, 147.36, 142.47, 131.22, 129.16, 129.05, 126.58, 120.48, 115.96.

MS (70 eV, EI) *m/z* (%): 232 (26), 231 (11), 230 (100) [M^+], 140 (18), 113 (15), 77 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3093, 2993, 2974, 2918, 2893, 2841, 1587, 1510, 1457, 1433, 1394, 1382, 1362, 1287, 1258, 1194, 1177, 1145, 1083, 1068, 1037, 1030, 1004, 992, 932, 910, 879, 865, 832, 801, 786, 776, 756, 688, 676, 620, 604, 593, 584, 579, 575, 571, 559.

HRMS (EI) for **$C_{11}H_7ClN_4$** (230.0359): 230.0339.

Synthesis of 5-chloro-3-furan-2-yl-1H-pyrazolo[3,4-*c*]pyridazine (76b)



A 50-mL round bottom flask, equipped with a magnetic stirring bar was charged with a suspension (3,6-dichloro-pyridazin-4-yl)-furan-2-yl-methanone (**73d**; 486 mg, 2.0 mmol) in EtOH (25 mL). $N_2H_4 \cdot H_2O$ (0.6 mL, 6 mmol) was added in one portion and the resulting mixture was refluxed for 30 min. After cooling to 25 °C CH_2Cl_2 (100 mL) was added and the organic layer was washed with water (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The residue was recrystallized from MeOH giving **76b** as a yellow solid (328 mg, 75%).

m.p.: 256.8-257.5 °C.

^{1}H-NMR (DMSO, 400 MHz) δ: 14.71 (s, 1 H), 8.63 (s, 1 H), 7.86-7.92 (m, 1 H), 7.31 (d, *J*=3.5 Hz, 1 H), 6.72 (dd, *J*=3.2, 1.6 Hz, 1 H).

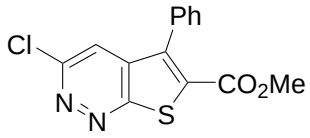
^{13}C-NMR (DMSO, 100 MHz) δ: 154.85, 147.35, 145.88, 143.94, 135.19, 120.05, 115.32, 111.95, 109.18.

MS (70 eV, EI) *m/z* (%): 220 (30) [M^+], 218 (100), 128 (32), 101 (18), 98 (27), 71 (30).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3132, 3108, 3092, 3000, 2958, 2906, 2852, 1584, 1524, 1512, 1496, 1460, 1416, 1378, 1370, 1330, 1284, 1264, 1224, 1200, 1180, 1164, 1144, 1126, 1102, 1074, 1034, 1010, 968, 936, 900, 882, 844, 820, 798, 774, 738, 688, 668, 648, 624, 592, 570, 558.

HRMS (EI) for **$C_9H_5ClN_4O$** (220.0152): 220.0139.

Synthesis of 3-chloro-5-phenylthieno[2,3-c]pyridazine-6-carboxylic acid methyl ester (77a)



A 50-mL round bottom flask, equipped with a magnetic stirring bar was charged with a suspension of (3,6-dichloro-pyridazin-4-yl)-phenyl-methanone (**73c**; 504 mg, 2.0 mmol) in MeOH (25 mL). $HSCH_2CO_2Me$ (265 mg, 2.5 mmol) and NEt_3 (500 mg, 5 mmol) were added in one portion and the resulting mixture was refluxed for 6 h. After cooling to 25 °C, CH_2Cl_2 (100 mL) was added and the organic layer was washed with water (3 x 30 mL) and NaOH (2 M, 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The residue was recrystallized from MeOH giving **77a** as a pale yellow solid (482 mg, 79%).

m.p: 160.0-161.1 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 7.62 (s, 1 H), 7.50-7.55 (m, 3 H), 7.36 (dd, *J*=7.4, 2.1 Hz, 2 H), 3.85 (s, 3 H).

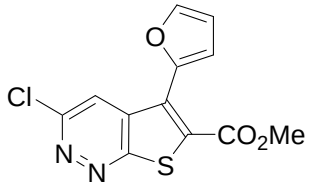
^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 163.31, 161.49, 152.61, 139.47, 137.41, 135.94, 131.24, 129.38, 129.354, 128.70, 122.07, 53.12.

MS (70 eV, EI) *m/z* (%): 306 (42), 305 (1), 304 (100) [M^+], 272 (22), 244 (27), 217 (21), 215 (46), 182 (25), 138 (12), 43 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950, 1698, 1658, 1554, 1498, 1486, 1448, 1432, 1378, 1330, 1304, 1284, 1244, 1198, 1178, 1140, 1114, 1078, 1054, 1030, 998, 978, 918, 902, 864, 814, 778, 766, 742, 704, 676, 658, 622, 614, 592, 566, 560.

HRMS (EI) for **$C_{14}H_9ClN_2O_2S$** (304.0073): 304.0060.

Synthesis of 3-chloro-5-furan-2-ylthieno[2,3-c]pyridazine-6-carboxylic acid methyl ester (77b)



A 50-mL round bottom flask, equipped with a magnetic stirring bar was charged with a suspension (3,6-dichloro-pyridazin-4-yl)-furan-2-yl-methanone (**73d**; 486 mg, 2.0 mmol) in MeOH (25 mL). $HSCH_2CO_2Me$ (265 mg, 2.5 mmol) and NEt_3 (500 mg, 5 mmol) were added in one portion and the resulting mixture was refluxed for 6 h. After cooling to 25 °C, CH_2Cl_2

(100 mL) was added and the organic layer was washed with water (3 x 30 mL) and NaOH (2 M, 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The residue was recrystallized from MeOH giving **77b** as a pale yellow solid (500 mg, 85%).

m.p.: 159.2-160.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.40 (s, 1 H), 7.67 (d, *J*=1.5 Hz, 1 H), 7.38 (d, *J*=3.4 Hz, 1 H), 6.64 (dd, *J*=3.5, 1.8 Hz, 1 H), 3.98 (s, 3 H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 162.81, 161.44, 152.70, 146.02, 143.69, 135.71, 133.17, 127.50, 123.91, 115.38, 112.11, 53.32.

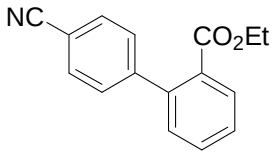
MS (70 eV, EI) *m/z* (%): 296 (39), 295 (15), 294 (100) [M^+], 268 (11), 266 (40).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3178, 3148, 3138, 3126, 3110, 2956, 1728, 1568, 1536, 1518, 1482, 1446, 1430, 1384, 1360, 1328, 1282, 1226, 1216, 1186, 1158, 1144, 1118, 1090, 1082, 1056, 1034, 998, 952, 920, 906, 900, 888, 832, 810, 796, 756, 684, 668, 640, 624, 594, 584, 560.

HRMS (EI) for **$C_{12}H_7ClN_2O_3S$** (293.9866): 293.9873.

13.6 Directed Zincations Using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (60) and Microwave Irradiation

Synthesis of 4'-cyanobiphenyl-2-carboxylic acid ethyl ester (80a):



According to **TP 3**, the metalation of ethyl benzoate (**78a**; 300 mg, 2.0 mmol) was completed within 5 h at 120 °C using a solution of $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.40 M in THF, 3.00 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 4-iodobenzonitrile (504 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 15 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 4:1) furnished the compound **80a** (411 mg, 82%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.94 (dd, *J*=7.7, 0.9 Hz, 1 H), 7.66-7.69 (m, 2 H), 7.56 (td, *J*=7.6, 1.5 Hz, 1 H), 7.48 (td, *J*=7.6, 1.4 Hz, 1 H), 7.40 (ddd, *J*=8.4, 1.8, 1.6 Hz, 2 H), 7.30 (dd, *J*=7.6, 0.8 Hz, 1 H), 4.11 (q, *J*=7.1 Hz, 2 H), 1.05 (t, *J*=7.1 Hz, 3 H).

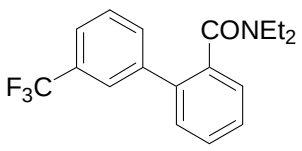
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.85, 146.82, 141.1, 131.97, 131.88, 130.73, 130.63, 129.49, 128.51, 119.14, 111.18, 61.38, 14.00.

MS (70 eV, EI) *m/z* (%): 251 (30) [M^+], 223 (17), 207 (17), 206 (100), 178 (21), 177 (17), 151 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2227, 1713, 1608, 1598, 1576, 1509, 1479, 1464, 1445, 1400, 1390, 1365, 1286, 1275, 1245, 1172, 1128, 1110, 1087, 1047, 1015, 1005, 886, 852, 839, 795, 761, 734, 711, 703, 668, 653, 644, 631, 608, 600, 592, 573, 554.

HRMS (EI) for **$C_{16}H_{13}NO_2$** (251.0946): 251.0938.

Synthesis of 3'-trifluoromethyl-biphenyl-2-carboxylic acid diethylamide (80b)



According to **TP 3**, the metalation of *N*,*N*-diethylbenzamide (**78b**; 344 mg, 2.0 mmol) was completed within 5 h at 120 °C using a solution of $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.40 M in

THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-3-trifluoromethylbenzene (598 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 9:1) furnished the compound **80b** (546 mg, 85%) as a brownish oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.67-7.72 (m, 2 H), 7.58-7.63 (m, 1 H), 7.36-7.52 (m, 5 H), 3.72 (br, 1 H), 2.96 (br, 2 H), 2.72 (br, 1 H), 0.88 (t, *J*=7.1 Hz, 3 H), 0.78 (t, *J*=7.1 Hz, 3 H).

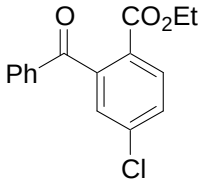
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.25, 140.85, 137.13, 136.70, 132.60 (q, $^4J_{CF}$=1.5 Hz), 130.91 (q, $^2J_{CF}$=32 Hz), 129.72, 129.38, 129.07, 128.50, 127.22, 125.64 (q, $^3J_{CF}$=4.1 Hz), 121.72 (q, $^3J_{CF}$=3.7 Hz), 122.13 (q, $^1J_{CF}$=272 Hz), 42.62, 38.67, 13.67, 12.16y.

MS (70 eV, EI) *m/z* (%): 321 (44) [M^+], 320 (100), 300 (18), 292 (12), 250 (29), 249 (24), 248 (16), 202 (11), 201 (95), 176 (10), 152 (31), 149 (20), 57 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2975, 2935, 1624, 1599, 1569, 1498, 1480, 1470, 1459, 1423, 1382, 1364, 1332, 1287, 1280, 1257, 1246, 1221, 1162, 1119, 1096, 1074, 1048, 1023, 1001, 944, 905, 883, 870, 822, 806, 776, 760, 732, 703, 657, 628, 620, 608, 600, 585, 573, 555.

HRMS (EI) for **$C_{18}H_{18}F_3NO$** (321.1340): 321.1347.

Synthesis of 2-benzoyl-4-chloro-benzoic acid ethyl ester (69f):



According to **TP 3**, the metalation of ethyl 4-chlorobenzoate (**67c**; 370 mg, 2.0 mmol) was completed within 2 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). The reaction mixture was cooled to –30 °C, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, benzoyl chloride (353 mg, 2.5 mmol) was added at –30 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 6:1) furnished the compound **69f** (502 mg, 86%) as a pale yellow solid.

m.p.: 78.9-80.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J*=8.4 Hz, 1 H), 7.73-7.77 (m, 2 H), 7.52-7.57 (m, 2H), 7.41–7.46 (m, 2 H), 7.36 (d, *J*=8.4 Hz, 1 H), 4.07 (q, *J*=7.1 Hz, 2 H), 1.04 (t, *J*=7.1 Hz, 3 H).

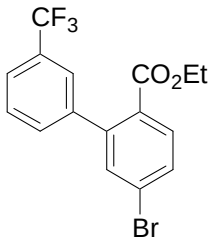
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 195.54, 165.22, 143.44, 139.24, 136.85, 133.69, 131.93, 129.89, 129.61, 128.89, 127.96, 127.82, 61.98, 13.82.

MS (70 eV, EI) *m/z* (%): 288 (24) [M^+], 245 (16), 244 (15), 243 (35), 213 (11), 211 (36), 183 (56), 152 (21), 105 (100), 77 (45), 57 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 2909, 1712, 1677, 1619, 1590, 1583, 1560, 1490, 1473, 1450, 1445, 1385, 1363, 1319, 1311, 1283, 1267, 1243, 1177, 1153, 1134, 1105, 1089, 1074, 1021, 1001, 979, 966, 954, 942, 899, 875, 860, 843, 815, 808, 780, 770, 712, 698, 690, 643, 619, 609, 591, 585.

HRMS (EI) for **$C_{16}H_{13}ClO_3$** (288.0553): 288.0550.

Synthesis of 5-bromo-3'-trifluoromethyl-biphenyl-2-carboxylic acid ethyl ester (69i):



According to **TP 3**, the metalation of ethyl 4-bromobenzoate (**67f**; 458 mg, 2.0 mmol) was completed within 2 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-3-trifluoromethylbenzene (598 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 60 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 15:1) furnished the compound **69i** (619 mg, 83%) as a yellowish oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.79 (d, *J*=8.3 Hz, 1 H), 7.63 (d, *J*=7.6 Hz, 1 H), 7.59 (dd, *J*=8.3, 1.9 Hz, 1 H) 7.46-7.54 (m, 4 H), 4.06 (q, *J*=7.2 Hz, 2 H), 0.98 (t, *J*=7.2 Hz, 3 H).

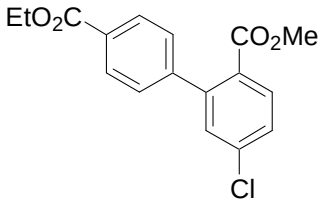
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 167.10, 142.94, 141.05, 133.56, 131.84, 131.63 (q, $^4J_{CF}$=1.3 Hz), 131.03, 130.39 (q, $^2J_{CF}$=32 Hz), 129.66, 128.51, 126.03, 125.23 (q, $^3J_{CF}$=3.9 Hz), 124.34 (q, $^3J_{CF}$=3.9 Hz), 123.81 (q, $^1J_{CF}$=272 Hz), 61.23, 13.51.

MS (70 eV, EI) *m/z* (%): 374 (42), 372 (38) [M^+], 346 (26), 345 (11), 344 (25), 330 (17), 329 (94), 328 (16), 327 (100), 248 (38), 221 (11), 220 (68), 219 (28), 201 (18), 170 (10), 43 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 1715, 1585, 1557, 1492, 1444, 1432, 1384, 1365, 1328, 1272, 1238, 1164, 1122, 1094, 1072, 1035, 1016, 905, 885, 860, 834, 803, 778, 753, 701, 688, 657, 626, 615, 608, 591, 568, 560, 554.

HRMS (EI) for **$C_{16}H_{12}BrF_3O_2$** (371.9973): 371.9955.

Synthesis of 5-chlorobiphenyl-2,4'-dicarboxylic acid 4'-ethyl ester 2-methyl ester (80c):



According to **TP 3**, the metalation of methyl 4-chlorobenzoate (**67e**; 340 mg, 2.0 mmol) was completed within 2 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (607 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 8:1) furnished the compound **80c** (485 mg, 73%) as a yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.08 (d, *J*=8.6 Hz, 2 H), 7.85 (d, *J*=8.6 Hz, 1 H), 7.43 (dd, *J*=8.3, 2.1 Hz, 1 H), 7.32-7.37 (m, 3 H), 4.40 (q, *J*=7.2 Hz, 2 H), 3.63 (s, 3 H), 1.41 (t, *J*=6.9 Hz, 3 H).

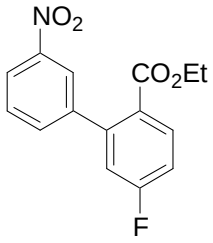
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 167.51, 166.32, 144.71, 143.58, 137.67, 131.66, 130.63, 129.75, 129.37, 128.73, 128.24, 127.92, 61.06, 52.15, 14.35.

MS (70 eV, EI) *m/z* (%): 320 (15), 318 (51) [M^+], 290 (17), 287 (13), 275 (34), 274 (17), 273 (100), 259 (14), 217 (11), 215 (32), 152 (15), 151 (12), 150 (12), 121 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 2952, 1712, 1610, 1592, 1574, 1558, 1472, 1434, 1408, 1388, 1368, 1268, 1244, 1180, 1100, 1032, 1016, 962, 888, 858, 834, 794, 770, 700, 668, 652, 636, 590, 574.

HRMS (EI) for **$C_{17}H_{15}ClO_4$** (318.0659): 318.0657.

Synthesis of 5-fluoro-3'-nitrobiphenyl-2-carboxylic acid ethyl ester (80d):



According to **TP 3**, the metalation of ethyl 4-fluorobenzoate (**67a**; 336 mg, 2.0 mmol) was completed within 1.25 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-3-nitrobenzene (510 mg, 2.1 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 6:1) furnished the compound **80d** (503 mg, 87%) as a yellowish solid.

m.p.: 66.4-68.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.24 (dt, *J*=7.6, 1.7 Hz, 1 H), 8.15-8.18 (m, 1 H), 8.02 (dd, *J*=8.7, 5.7 Hz, 1 H), 7.56-7.63 (m, 2 H), 7.14-7.21 (m, 1 H), 7.04 (dd, *J*=9.1, 2.4 Hz, 1 H), 4.11 (q, *J*=7.1 Hz, 2 H), 1.07 (t, *J*=7.1 Hz, 3 H).

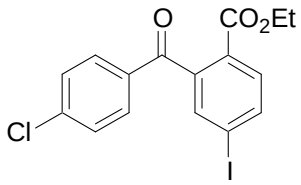
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.23, 164.09 (d, $^1J_{CF}$=255 Hz), 147.83, 143.28 (d, $^3J_{CF}$=8.5 Hz), 142.15 (d, J_{CF}=1.5 Hz), 134.40, 133.31 (d, $^3J_{CF}$=9.0 Hz), 128.88, 128.35, 123.32, 122.46, 118.88 (d, $^2J_{CF}$=23 Hz), 115.30 (d, $^2J_{CF}$=21 Hz), 61.21, 13.77.

MS (70 eV, EI) *m/z* (%): 289 (40) [M^+], 261 (30), 245 (25), 244 (100), 228 (28), 214 (31), 199 (12), 198 (42), 197 (28), 186 (15), 170 (40), 169 (43).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3079, 2994, 2985, 2923, 2908, 2876, 1710, 1651, 1605, 1584, 1571, 1528, 1500, 1490, 1478, 1469, 1451, 1411, 1390, 1366, 1359, 1346, 1309, 1290, 1278, 1266, 1239, 1190, 1168, 1125, 1115, 1107, 1082, 1040, 1020, 1002, 983, 972, 941, 932, 903, 880, 871, 858, 834, 816, 780, 762, 740, 716, 688, 675, 628, 621, 614, 601, 592, 582, 579, 576, 573, 563, 560, 557.

HRMS (EI) for **$C_{15}H_{12}FNO_4$** (289.0750): 289.0743.

Synthesis of 2-(4-chlorobenzoyl)-4-iodobenzoic acid ethyl ester (80e):



According to **TP 3**, the metalation of ethyl 4-iodobenzoate (**78c**; 552 mg, 2.0 mmol) was completed within 3 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). The reaction mixture was cooled to –30 °C, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (438 mg, 2.5 mmol) was added at –30 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 4 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 6:1) furnished the compound **80e** (597 mg, 72%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.88-7.95 (m, 1 H), 7.76 (d, *J*=8.3 Hz, 1 H), 7.67 (d, *J*=9.0 Hz, 3 H), 7.40 (d, *J*=8.7 Hz, 2 H), 4.09 (q, *J*=7.3 Hz, 2 H), 1.08 (t, *J*=7.2 Hz, 3 H).

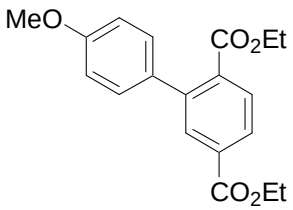
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 193.86, 165.16, 142.59, 139.89, 138.87, 136.21, 135.11, 131.55, 130.64, 128.95, 128.54, 99.85, 61.82, 13.68.

MS (70 eV, EI) *m/z* (%): 416 (16), 414 (44) [M^+], 370 (13), 369 (24), 335 (11), 303 (38), 275 (59), 149 (11), 141 (30), 139 (100), 113 (10), 111 (28), 75 (17), 71 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3089, 2987, 2939, 2900, 1712, 1677, 1589, 1578, 1555, 1488, 1469, 1444, 1401, 1377, 1367, 1273, 1264, 1180, 1145, 1109, 1086, 1014, 973, 959, 941, 884, 871, 846, 840, 786, 767, 746, 713, 697, 683, 655, 630, 618, 599.

HRMS (EI) for **$C_{16}H_{12}ClIO_3$** (413.9520): 413.9508.

Synthesis of 4'-methoxybiphenyl-2,5-dicarboxylic acid diethyl ester (80f):



According to **TP 3**, the metalation of terephthalic acid diethyl ester (**78d**; 444 mg, 2.0 mmol) was completed) within 4 h at 90 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed

by the addition of 1-iodo-4-methoxybenzene (500 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 14 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 5:1) furnished the compound **80f** (488 mg, 74%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.01-8.03 (m, 2 H), 7.79-7.81 (m, 1 H), 7.27 (d, *J*=7.3 Hz, 2 H), 6.94 (d, *J*=7.3 Hz, 2 H), 4.40 (q, *J*=7.1 Hz, 2 H), 4.14 (q, *J*=7.1 Hz, 2 H), 3.8 (s, 3 H), 1.40 (t, *J*=7.1 Hz, 3 H), 1.07 (t, *J*=7.1 Hz, 3 H).

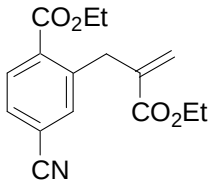
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 168.72, 166.05, 159.50, 142.10, 135.47, 133.03, 132.76, 131.82, 129.77, 127.94, 113.88, 61.62, 61.53, 55.56, 14.53, 14.04.

MS (70 eV, EI) *m/z* (%): 329 (16), 329 (100) [M^+], 283 (33), 211 (8), 139 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 1714, 1609, 1579, 1515, 1463, 1444, 1420, 1403, 1365, 1279, 1231, 1176, 1107, 1042, 1028, 1017, 917, 873, 846, 831, 805, 755, 738, 709, 674, 638, 624, 617, 580, 565, 561.

HRMS (EI) for **$C_{19}H_{20}O_5$** (328.1311): 328.1304.

Synthesis of 4-cyano-2-(2-ethoxycarbonylallyl)benzoic acid ethyl ester (80g):



According to **TP 3**, the metalation of ethyl 4-cyanobenzoate (**67j**; 350 mg, 2.0 mmol) was completed within 1 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). The reaction mixture was cooled to –15 °C, CuCN·2LiCl (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added and the reaction mixture was stirred for 5 min. Then, ethyl 2-(bromomethyl)acrylate (483 mg, 2.5 mmol) was added at –15 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 5:1) furnished the compound **80g** (435 mg, 76%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.95 (d, *J*=7.8 Hz, 1 H), 7.58 (m, 2 H), 6.26 (s, 1 H), 5.34 (s, 1 H), 4.36 (q, *J*=7.1 Hz, 2 H), 4.19 (q, *J*=7.1 Hz, 2 H), 4.03 (s, 2 H), 1.36 (t, *J*=7.2 Hz, 3 H), 1.26 (t, *J*=7.0 Hz, 3 H).

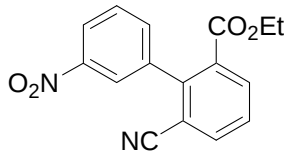
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.31, 166.08, 141.20, 139.06, 134.69, 134.67, 131.11, 129.99, 126.66, 117.92, 115.29, 61.69, 60.95, 35.47, 14.13, 14.11.

MS (70 eV, EI) *m/z* (%): 287 (4) [M^+], 242 (33), 241 (96), 214 (54), 213 (35), 196 (13), 195 (14), 186 (56), 185 (78), 170 (100), 169 (87), 168 (41), 167 (14), 158 (19), 157 (13), 156 (28), 142 (25), 141 (25), 140 (57), 139 (12), 129 (12), 115 (29), 114 (13), 113 (17), 70 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 2232, 1712, 1632, 1607, 1475, 1465, 1445, 1402, 1367, 1327, 1294, 1257, 1221, 1194, 1172, 1132, 1093, 1075, 1020, 949, 928, 903, 867, 844, 817, 790, 779, 747, 703, 681, 668, 646, 642, 628, 624, 618, 605, 601, 595, 589, 583, 579, 576, 570, 562, 558, 554.

HRMS (EI) for **$C_{16}H_{17}NO_4$** (287.1158): 287.1161.

Synthesis of 6-fluoro-3'-nitrobiphenyl-2-carboxylic acid ethyl ester (80h):



According to **TP 3**, the metalation of ethyl 3-cyanobenzoate (**67i**; 370 mg, 2.0 mmol) was completed within 1 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-3-nitrobenzene (510 mg, 2.1 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 15 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 2:1) furnished the compound **80h** (367 mg, 62%) as a yellowish solid.

m.p.: 116.1-117.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.29-8.37 (m, 1 H), 8.15-8.25 (m, 2 H), 7.92 (dd, *J*=7.8, 1.2 Hz, 1 H), 7.60-7.70 (m, 3 H), 4.10 (q, *J*=7.0 Hz, 2 H), 1.03 (t, *J*=7.2 Hz, 3 H).

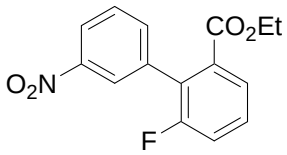
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.40, 143.46, 139.00, 135.91, 134.67, 134.46, 132.33, 129.36, 129.06, 123.86, 123.54, 116.74, 114.71, 61.79, 13.71.

MS (70 eV, EI) *m/z* (%): 297 (12), 296 (62) [M^+], 268 (37), 252 (23), 251 (100), 235 (28), 234 (12), 222 (13), 221 (31), 206 (19), 205 (48), 204 (41), 193 (12), 178 (13), 177 (37), 176 (31), 166 (12), 151 (10), 150 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3080, 2990, 2232, 1707, 1671, 1582, 1532, 1481, 1460, 1444, 1392, 1367, 1350, 1285, 1232, 1181, 1162, 1142, 1116, 1103, 1094, 1084, 1016, 990, 897, 876, 869, 826, 814, 797, 784, 770, 761, 745, 728, 689, 681, 645, 576, 571.

HRMS (EI) for **$C_{16}H_{12}N_2O_4$** (296.0797): 296.0790.

Synthesis of 6-fluoro-3'-nitrobiphenyl-2-carboxylic acid ethyl ester (80i):



According to **TP 3**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed within 1 h at 80 °C using a solution of $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-3-nitrobenzene (510 mg, 2.1 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 6:1) furnished the compound **80i** (532 mg, 92%) as a yellowish solid.

m.p.: 68.9-70.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.25 (dt, *J*=7.5, 2.1 Hz, 1 H), 8.14-19 (m, 1 H), 7.76-7.80 (m, 1 H), 7.57-7.63 (m, 2 H), 7.48 (td, *J*=8.1, 5.3 Hz, 1 H), 7.31-7.36 (td, *J*=8.8, 1.3 Hz, 1 H), 4.09 (q, *J*=7.2 Hz, 2 H), 1.03 (t, *J*=7.1 Hz, 3 H).

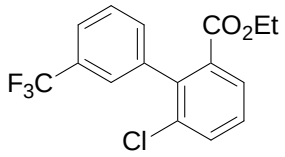
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.15 (d, $^4J_{CF}$=3.5 Hz), 159.62 (d, $^1J_{CF}$=245 Hz), 147.94, 136.02 (d, J_{CF}=0.5 Hz), 135.53 (d, J_{CF}=1.5 Hz), 132.78 (d, J_{CF}=2.2 Hz), 129.89 (d, $^3J_{CF}$=8.6 Hz), 128.80, 127.74 (d, $^2J_{CF}$=17 Hz), 126.15 (d, $^4J_{CF}$=3.5 Hz), 124.52, 122.66, 110.29 (d, $^2J_{CF}$=23 Hz).

MS (70 eV, EI) *m/z* (%): 290 (12), 289 (67) [M^+], 261 (42), 245 (23), 244 (100), 243 (11), 228 (28), 213 (45), 199 (18), 198 (55), 197 (36), 186 (15),171 (12), 170 (41), 169 (48), 168 (11), 159 (13), 157 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3087, 2987, 2960, 2946, 2903, 1723, 1683, 1606, 1571, 1527, 1488, 1478, 1449, 1426, 1392, 1364, 1348, 1282, 1264, 1256, 1234, 1200, 1177, 1143, 1113, 1102, 1090, 1080, 1027, 1002, 990, 985, 967, 952, 935, 923, 907, 879, 866, 820, 809, 756, 741, 725, 702, 686, 681, 642.

HRMS (EI) for **$C_{15}H_{12}FNO_4$** (289.0750): 289.0738.

Synthesis of 6-chloro-3'-trifluoromethyl-biphenyl-2-carboxylic acid ethyl ester (80j):



According to **TP 3**, the metalation of ethyl 3-chlorobenzoate (**67b**; 370 mg, 2.0 mmol) was completed within 2 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-3-trifluoromethylbenzene (598 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 60 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 15:1) furnished the compound **80j** (506 mg, 77%) as a yellowish oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.81 (dd, *J*=7.8, 1.2 Hz, 1 H), 7.61-7.66 (m, 2 H), 7.53 (t, *J*=7.8 Hz, 1 H), 7.51 (s, 1 H), 7.38-7.44 (m, 2 H), 3.99 (q, *J*=7.2 Hz, 2 H), 0.90 (t, *J*=7.2 Hz, 3 H).

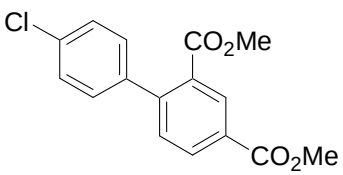
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 166.83, 139.11, 138.89, 134.43, 133.72, 132.63, 132.48, 130.33 (q, ^2J=32 Hz), 128.97, 128.36, 128.26, 126.03 (q, ^3J=3.5 Hz), 124.32 (q, ^3J=3.5 Hz), 124.05 (q, ^1J=272 Hz), 61.22, 13.39.

MS (70 eV, EI) *m/z* (%): 330 (13), 328 (36) [M^+], 300 (25), 285 (35), 284 (18), 283 (100), 263 (12), 247 (14), 235 (14), 215 (36), 214 (15), 198 (10), 42 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984, 1716, 1615, 1589, 1562, 1492, 1476, 1444, 1423, 1392, 1367, 1329, 1280, 1248, 1193, 1176, 1164, 1150, 1121, 1095, 1072, 1025, 1016, 922, 906, 887, 863, 826, 803, 761, 744, 722, 701, 663, 639, 624, 612, 607, 593, 590, 554.

HRMS (EI) for **$C_{16}H_{12}ClF_3O_2$** (328.0478): 328.0469.

Synthesis of 4'-chlorobiphenyl-2,4-dicarboxylic acid dimethyl ester (69e):



According to **TP 2**, the metalation of isophthalic acid dimethyl ester (**67g**; 388 mg, 2.0 mmol) was completed within 2 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-chloro-4-iodobenzene (524 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 5:1) furnished the compound **69e** (481 mg, 79%) as a yellowish solid.

m.p.: 54.8-56.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.53 (d, *J*=1.8 Hz, 1 H), 8.20 (dd, *J*=7.5, 1.8 Hz, 1 H), 7.38-7.45 (m, 2 H), 7.24-7.29 (m, 3 H), 3.98 (s, 3 H), 3.73 (s, 3 H).

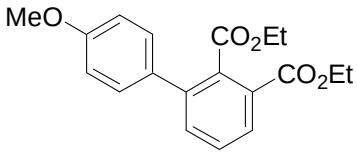
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.78, 165.97, 145.68, 138.76, 134.11, 132.22, 131.36, 130.98, 129.54, 129.54, 128.42, 52.42, 52.27.

MS (70 eV, EI) *m/z* (%): 306 (16), 304 (61) [M^+], 275 (27), 274 (12), 273 (100), 151 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950, 1711, 1608, 1595, 1576, 1557, 1504, 1476, 1458, 1444, 1437, 1409, 1391, 1306, 1297, 1283, 1273, 1240, 1196, 1182, 1140, 1116, 1106, 1096, 1087, 1018, 1005, 988, 963, 948, 929, 877, 863, 834, 820, 811, 789, 769, 738, 712, 702, 662, 642, 631, 612, 605, 601, 583, 576, 569, 564, 558.

HRMS (EI) for **$C_{16}H_{13}ClO_4$** (304.0502): 304.0499.

Synthesis of 4'-methoxybiphenyl-2,5-dicarboxylic acid diethyl ester (80k):



According to **TP 3**, the metalation of phthalic acid diethyl ester (**78e**; 444 mg, 2.0 mmol) was completed within 4 h at 90 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-4-methoxybenzene (500 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 14 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 15 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by

column chromatography (pentane/diethyl ether = 5:1) furnished the compound **80k** (464 mg, 71%) as a colourless solid.

m.p.: 77.9-79.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.96 (dd, *J*=6.8, 2.4 Hz, 1 H), 7.46-7.52 (m, 2 H), 7.27-7.32 (m, 2 H), 6.90-6.94 (m, 2 H), 4.36 (q, *J*=7.1 Hz, 2 H), 4.15 (q, *J*=7.1 Hz, 2 H), 3.83 (s, 3 H), 1.36 (t, *J*=7.1 Hz, 3 H), 1.08 (t, *J*=7.2 Hz, 3 H).

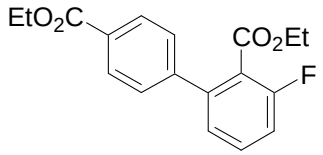
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.11, 166.09, 159.55, 140.46, 135.12, 134.36, 131.96, 130.14, 129.16, 128.82, 128.63, 113.84, 61.76, 61.50, 55.53, 14.39, 14.03.

MS (70 eV, EI) *m/z* (%): 329 (20), 328 (96) [M^+], 283 (23), 256 (18), 255 (100), 237 (36), 209 (12), 139 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977, 2933, 1725, 1710, 1672, 1607, 1588, 1581, 1515, 1495, 1482, 1461, 1450, 1440, 1409, 1386, 1362, 1301, 1278, 1254, 1243, 1195, 1178, 1150, 1107, 1064, 1033, 1019, 1011, 987, 931, 902, 884, 875, 863, 856, 837, 825, 815, 760, 747, 720, 700, 694, 652, 638, 623, 619, 612, 608, 582, 571, 559, 554.

HRMS (EI) for **$C_{19}H_{20}O_5$** (328.1311): 328.1308.

Synthesis of 3-fluorobiphenyl-2,4'-dicarboxylic acid diethyl ester (80l):



According to **TP 3**, the metalation of ethyl 2-fluorobenzoate (**78f**; 336 mg, 2.0 mmol) was completed within 3 h at 95 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (607 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 15 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 6:1) furnished the compound **80l** (469 mg, 74%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.06 (dt, *J*=8.5, 1.9 Hz, 2 H), 7.40-7.47 (m, 3 H), 7.11-7.18 (m, 2 H), 4.38 (q, *J*=7.0 Hz, 2 H), 4.13 (q, *J*=7.2 Hz, 2 H), 1.39 (t, *J*=7.1 Hz, 3 H), 1.05 (t, *J*=7.1 Hz, 3 H).

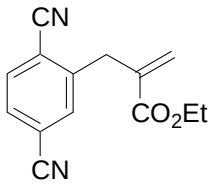
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.23, 165.18, 159.72 (d, $^1J_{CF}$=252 Hz), 143.86, 141.53, 131.32 (d, $^3J_{CF}$=9.0 Hz), 129930, 129.60, 128.93, 128.42, 128.30, 125.30 (d, $^3J_{CF}$=3.3 Hz), 121.71 (d, $^2J_{CF}$=17 Hz), 115.30 (d, $^2J_{CF}$=22 Hz), 61.67, 61.07, 14.29, 13.72.

MS (70 eV, EI) *m/z* (%): 316 (56) [M^+], 288 (18), 272 (18), 271 (100), 243 (38), 215 (11), 199 (52), 170 (19), 169 (12), 151 (12), 123 (11), 111 (11), 97 (15), 95 (10), 83 (16), 71 (11), 57 (25), 44 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 1713, 1608, 1578, 1565, 1464, 1454, 1404, 1390, 1366, 1339, 1262, 1239, 1174, 1101, 1086, 1060, 1019, 901, 860, 849, 802, 768, 736, 725, 703, 669, 639, 621, 612, 601, 588, 578, 573, 556.

HRMS (EI) for **$C_{18}H_{17}FO_4$** (316.1111): 316.1099.

Synthesis of 2-(2,5-dicyanobenzyl)acrylic acid ethyl ester (80m):



According to **TP 3**, the metalation of terephthalonitrile (**78g**; 256 mg, 2.0 mmol) was completed within 3 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). The reaction mixture was cooled to –15 °C, CuCN·2LiCl (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added and the reaction mixture was stirred for 5 min. Then, ethyl 2-(bromomethyl)acrylate (483 mg, 2.5 mmol) was added at –15 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 5:1) furnished the compound **80m** (322 mg, 67%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.74 (dd, *J*=8.0, 0.5 Hz, 1 H), 7.69 (dd, *J*=1.6, 0.5 Hz, 1 H), 7.61 (dd, *J*=8.0, 1.6 Hz, 1 H), 6.40 (d, *J*=0.6 Hz, 1 H), 5.75 (d, *J*=0.6 Hz, 1 H), 4.18 (q, *J*=7.1 Hz, 2 H), 3.89 (s, 2 H), 1.26 (t, *J*=7.1 Hz, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 165.64, 144.15, 136.72, 133.57, 133.39, 132.76, 130.37, 128.91, 117.19, 116.46, 116.28, 61.29, 36.53, 14.07.

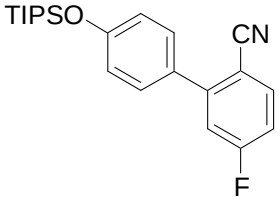
MS (70 eV, EI) *m/z* (%): 240 (2) [M^+], 212 (31), 195 (25), 194 (19), 168 (15), 167 (42), 166 (100), 165 (11), 141 (27), 140 (22), 139 (11), 114 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3082, 3047, 2985, 2962, 2944, 2916, 2907, 2232, 2227, 1704, 1669, 1638, 1631, 1605, 1552, 1500, 1486, 1476, 1442, 1424, 1412, 1403, 1369, 1340, 1313, 1287,

1271, 1214, 1210, 1195, 1158, 1150, 1116, 1097, 1089, 1029, 977, 965, 953, 942, 902, 887, 863, 850, 839, 823, 807, 779, 746, 721, 681, 652, 642, 624, 610, 600, 586, 576, 572, 565, 561, 557.

HRMS (EI) for **$C_{14}H_{12}N_2O_2$** (240.0899): 240.0888.

Synthesis of 5-fluoro-4'-triisopropylsilanyloxy-biphenyl-2-carbonitrile (80n):



According to **TP 3**, the metalation of 4-fluorobenzonitrile (**67k**; 242 mg, 2.0 mmol) was completed within 3 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of (4-iodophenoxy)-triisopropylsilane (827 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 50:1) furnished the compound **80n** (655 mg, 89%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.74 (dd, *J*=7.1, 2.2 Hz, 1 H), 7.57 (ddd, *J*=8.5, 4.5, 2.2 Hz, 1 H), 7.39 (dd, *J*=8.8, 1.6 Hz, 2 H), 7.22 (dd, *J*=10.2, 8.5 Hz, 1 H), 6.94-6.99 (m, 2 H), 1.24-1.33 (m, 3 H), 1.13 (s, 9 H) 1.11 (s, 9 H).

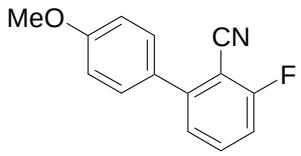
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 162.28 (d, $^1J_{CF}$=257 Hz), 157.00, 135.01 (d, $^3J_{CF}$=5.5 Hz), 132.61 (d, $^3J_{CF}$=9.6 Hz), 130.61 (d, $^2J_{CF}$=15 Hz), 130.29, 130.26, 126.12, 120.45, 118.43, 117.71 (d, $^2J_{CF}$=25 Hz), 109.01, 18.15, 12.91.

MS (70 eV, EI) *m/z* (%): 369 (19) [M^+], 327 (20), 326 (83), 299 (10), 298 (44), 271 (22), 270 (100), 257 (11), 256 (59), 240 (14), 196 (11), 135 (11), 135 (44), 128 (11), 77 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2944, 2891, 2866, 2231, 1606, 1515, 1487, 1463, 1391, 1268, 1253, 1234, 1174, 1123, 1106, 1039, 1012, 996, 909, 881, 839, 826, 761, 742, 727, 706, 683, 670, 640, 610, 590, 572, 568.

HRMS (EI) for **$C_{22}H_{28}FNOSi$** (369.1924): 369.1925.

Synthesis of 3-fluoro-4'-methoxy-biphenyl-2-carbonitrile (80o):



According to **TP 3**, the metalation of 2-fluorobenzonitrile (**67m**; 242 mg, 2.0 mmol) was completed within 3 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-4-methoxybenzene (500 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 9:1) furnished the compound **80o** (401 mg, 88%) as a yellowish solid.

m.p.: 106.7-109.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.66 (td, *J*=7.7, 1.8 Hz, 1 H), 7.56 (ddd, *J*=7.7, 5.8, 1.7 Hz, 1 H), 7.43-7.49 (m, 2 H), 7.29 (td, *J*=7.8, 0.5 Hz, 1 H), 6.97–7.03 (m, 2 H), 3.86 (s, 3 H).

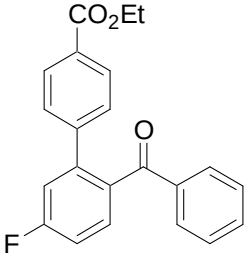
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 160.44 (d, $^1J_{CF}$=260 Hz), 160.21, 135.58 (d, $^3J_{CF}$=4.4 Hz), 131.94, 130.35 (d, $^2J_{CF}$=13 Hz), 130.34 (d, $^3J_{CF}$=3.3 Hz), 126.04 (d, $^4J_{CF}$=1.1 Hz), 114.49, 102.41 (d, $^2J_{CF}$=17 Hz), 55.61.

MS (70 eV, EI) *m/z* (%): 228 (15), 227 (100) [M^+], 212 (23), 184 (30), 158 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2236, 1608, 1515, 1464, 1454, 1441, 1413, 1298, 1285, 1254, 1248, 1217, 1191, 1175, 1159, 1113, 1096, 1088, 1069, 1061, 1025, 981, 947, 860, 828, 803, 792, 781, 738, 718, 699, 694, 642, 636, 625, 616, 608, 597, 593, 582, 579, 576, 567, 554.

HRMS (EI) for **$C_{14}H_{10}FNO$** (227.0746): 227.0734.

Synthesis of 2'-benzoyl-5'-fluoro-biphenyl-4-carboxylic acid ethyl ester (80p):



According to **TP 3**, the metalation of 4-fluoro-benzophenone (**78h**; 400 mg, 2.0 mmol) was completed within 5 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF,

3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (607 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 60 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 6:1) furnished the compound **80p** (485 mg, 70%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.87 (dt, *J*=8.5, 1.8 Hz, 2 H), 7.58-7.65 (m, 2 H), 7.48-7.55 (m, 1 H), 7.38-7.45 (m, 1 H), 7.24-7.32 (m, 4 H), 7.16 (ddd, *J*=8.9, 7.1, 2.1 Hz, 2 H), 4.30 (q, *J*=7.0 Hz, 2 H), 1.35 (t, *J*=7.0 Hz, 3 H).

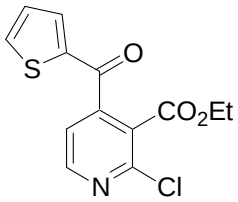
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 197.08, 166.07, 163.46 (d, $^1J_{CF}$=252 Hz), 143.52 (d, $^4J_{CF}$=2.0 Hz), 143.05 (d, $^3J_{CF}$=8.4 Hz), 137.14, 135.04 (d, $^4J_{CF}$=3.3 Hz), 133.17, 131.35 (d, $^3J_{CF}$=8.9 Hz), 129.85, 129.77, 129.61, 128.74, 128.27, 117.06 (d, $^2J_{CF}$=22 Hz), 114.61 (d, $^2J_{CF}$=22 Hz), 60.98, 14.24.

MS (70 eV, EI) *m/z* (%): 348 (100) [M^+], 347 (53), 320 (15), 319 (49), 304 (13), 303 (61), 276 (15), 275 (58), 271 (35), 247 (13), 246 (13), 244 (10), 243 (10), 199 (45), 171 (11), 170 (23), 169 (10), 105 (51), 77 (29).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 1711, 1662, 1597, 1580, 1565, 1479, 1464, 1447, 1414, 1398, 1367, 1313, 1269, 1179, 1146, 1099, 1073, 1034, 1017, 1000, 929, 857, 828, 799, 775, 745, 726, 713, 702, 695, 653, 639, 612, 591, 579, 576, 569, 562, 558, 552.

HRMS (EI) for **$C_{22}H_{17}FO_3$** (348.1162): 348.1154.

Synthesis of 2-chloro-4-(thiophene-2-carbonyl)nicotinic acid ethyl ester (80q):



According to **TP 3**, the metalation of ethyl 2-chloronicotinate (**64g**; 370 mg, 2.0 mmol) was completed within 1 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). The reaction mixture was cooled to –30 °C, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, thiophene-2-carbonyl chloride (365 mg, 2.5 mmol) was added at –30 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 2 h. The reaction mixture was

quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (CH_2Cl_2) furnished the compound **80q** (476 mg, 80%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.56 (d, *J*=4.9 Hz, 1 H), 7.79 (dd, *J*=4.9, 1.2 Hz, 1 H), 7.44 (ddd, *J*=3.9, 1.2, 0.4 Hz, 1 H), 7.39-7.43 (m, 1 H), 7.13 (ddd, *J*=5.0, 3.8, 0.4 Hz, 1 H), 4.19 (q, *J*=7.2 Hz, 2 H), 1.16 (t, *J*=7.1 Hz, 3 H).

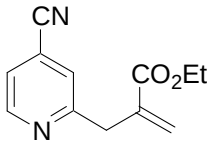
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 184.66, 164.05, 150.67, 149.46, 147.91, 141.92, 136.50, 136.01, 128.54, 127.33, 120.66, 62.54, 13.48.

MS (70 eV, EI) *m/z* (%): 295 (21) [M^+], 252 (26), 250 (19), 249 (33), 214 (20), 111 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 1728, 1643, 1575, 1543, 1512, 1464, 1449, 1407, 1380, 1354, 1285, 1257, 1208, 1166, 1117, 1057, 1009, 925, 856, 788, 765, 725, 702, 660, 618, 599, 595, 589, 579, 564.

HRMS (EI) for **$C_{13}H_{10}ClNO_3S$** (295.0070): 295.0064.

Synthesis of 2-(4-cyanopyridin-2-ylmethyl)acrylic acid ethyl ester (80r):



According to **TP 3**, the metalation of 4-cyanopyridine (**78i**; 208 mg, 2.0 mmol) was completed within 1 h at 80 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). The reaction mixture was cooled to –15 °C, CuCN·2LiCl (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added and the reaction mixture was stirred for 5 min. Then, ethyl 2-(bromomethyl)acrylate (483 mg, 2.5 mmol) was added at –15 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 1:1) furnished the compound **80r** (294 mg, 68%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.69 (d, *J*=5.0 Hz, 1 H), 7.46 (s, 1 H), 7.38 (d, *J*=4.7 Hz, 1 H), 6.35 (s, 1 H), 5.70 (s, 1 H), 4.16 (q, *J*=7.0 Hz, 2 H), 3.87 (s, 2 H), 1.23 (t, *J*=7.2 Hz, 3 H).

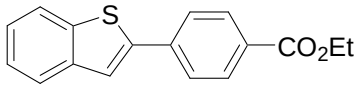
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.24, 160.94, 150.27, 137.35, 128.07, 124.82, 122.83, 120.72, 116.55, 60.97, 40.75, 14.08.

MS (70 eV, EI) *m/z* (%): 216 (3) [M^+], 187 (50), 171 (36), 144 (37), 143 (100), 142 (48), 118 (10), 116 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 2937, 2238, 1710, 1632, 1594, 1549, 1474, 1446, 1428, 1399, 1368, 1332, 1301, 1288, 1249, 1212, 1190, 1138, 1112, 1097, 1025, 995, 952, 941, 920, 903, 873, 857, 840, 817, 778, 749, 734, 703, 629, 606, 598, 594, 588, 579, 573, 570, 565, 558, 553.

HRMS (EI) for **$C_{12}H_{12}N_2O_2$** (216.0899): 216.0896.

Synthesis of 4-benzothiophen-2-ylbenzoic acid ethyl ester (80s):



According to **TP 3**, the metalation of benzothiophene (**61k**; 268 mg, 2.0 mmol) was completed within 1 h at 120 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**160**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (607 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 9:1) furnished the compound **80s** (532 mg, 95%) as a colourless solid. **m.p.**: 175.6-177.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.09 (dt, *J*=8.7, 1.9 Hz, 2 H), 7.76-7.86 (m, 4 H), 7.65 (d, *J*=0.5 Hz, 1 H), 7.31-7.40 (m, 2 H), 4.40 (q, *J*=7.2 Hz, 2 H), 1.42 (t, *J*=7.1 Hz, 3 H).

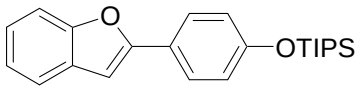
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.42, 143.06, 140.70, 140.07, 138.67, 130.46, 130.12, 126.38, 125.15, 124.98, 142.17, 122.58, 121.24, 61.33, 14.60.

MS (70 eV, EI) *m/z* (%): 283 (22), 282 (100) [M^+], 254 (42), 238 (13), 237 (72), 209 (18), 208 (32), 165 (32), 118 (10), 104 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 1702, 1665, 1602, 1562, 1527, 1457, 1446, 1431, 1407, 1363, 1336, 1316, 1275, 1248, 1232, 1190, 1184, 1123, 1107, 1071, 1017, 975, 961, 940, 873, 867, 852, 824, 769, 741, 725, 693, 675.

HRMS (EI) for **$C_{17}H_{14}O_2S$** (282.0715): 282.0722.

Synthesis of (4-benzofuran-2-yl-phenoxy)-triisopropyl-silane (80t):



According to **TP 3**, the metalation of benzofuran (**61l**; 236 mg, 2.0 mmol) was completed within 1 h at 120 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of (4-iodophenoxy)-triisopropylsilane (827 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 1000:1) furnished the compound **80t** (699 mg, 95%) as a colourless solid.

m.p.: 50.4-52.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.74-7.80 (m, 2 H), 7.50-7.60 (m, 2 H), 7.21-7.30 (m, 2 H), 6.99 (ddd, *J*=9.2, 2.7, 2.5 Hz, 2 H), 6.90 (d, *J*=0.9 Hz, 1 H), 1.26-1.37 (m, 3 H), 1.18 (s, 9 H), 1.16 (s, 9 H).

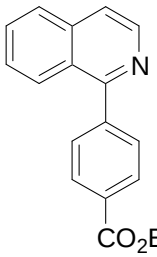
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 156.96, 156.44, 155.00, 129.78, 126.62, 124.00, 123.86, 123.06, 120.83, 120.53, 111.24, 99.95, 18.19, 12.96.

MS (70 eV, EI) *m/z* (%): 367 (31), 366 (100) [M^+], 324 (16), 323 (62), 296 (12), 295 (50), 281 (16), 268 (13), 267 (65), 253 (44), 221 (10), 165 (22), 134 (14), 133 (86), 126 (22), 75 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960, 2944, 2886, 2864, 1607, 1585, 1564, 1498, 1469, 1462, 1450, 1413, 1383, 1366, 1288, 1254, 1234, 1208, 1166, 1142, 1102, 1076, 1062, 1033, 1017, 1009, 991, 927, 903, 883, 843, 818, 802, 748, 735, 724, 687, 662, 644, 616, 607, 600.

HRMS (EI) for **$C_{23}H_{30}O_2Si$** (366.2015): 366.2013.

Synthesis of 4-isoquinolin-1-yl-benzoic acid ethyl ester (80u):



According to **TP 3**, the metalation of isoquinoline (**78j**; 258 mg, 2.0 mmol) was completed within 1 h at 120 °C using a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**60**; 0.40 M in THF, 3.0 mL, 1.2 mmol). $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (607 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was

stirred at 25 °C for 1 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 3:1) furnished the compound **80u** (452 mg, 82%) as a yellowish solid.

m.p.: 78.6-80.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.61 (d, *J*=5.7 Hz, 1 H), 8.21 (dt, *J*=8.3, 1.7 Hz, 2 H), 8.02 (dd, *J*=8.5, 0.8 Hz, 1 H), 7.88 (d, *J*=8.2 Hz, 1 H), 7.76 (ddd, *J*=8.4, 1.8, 1.6 Hz, 2 H), 7.65-7.71 (m, 2 H), 7.51-7.56 (m, 1 H), 4.42 (q, *J*=7.1 Hz, 2 H), 1.42 (t, *J*=7.1 Hz, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.34, 159.51, 143.79, 142.16, 136.75, 130.43, 130.13, 129.90, 129.52, 127.43, 127.07, 127.01, 126.50, 120.39, 61.08, 14.31.

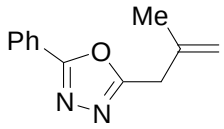
MS (70 eV, EI) *m/z* (%): 277 (46) [M^+], 276 (39), 248 (39), 232 (12), 205 (13), 204 (100), 203 (24), 101 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3052, 2997, 2978, 2957, 2906, 1713, 1668, 1651, 1618, 1609, 1585, 1570, 1551, 1509, 1499, 1479, 1467, 1457, 1448, 1407, 1395, 1386, 1366, 1355, 1318, 1310, 1269, 1210, 1181, 1163, 1124, 1102, 1062, 1027, 1021, 980, 973, 965, 955, 899, 875, 869, 865, 857, 841, 838, 822, 800, 796, 770, 751, 744, 721, 702, 676, 652, 600, 589, 581, 572, 559.

HRMS (EI) for **$C_{18}H_{15}NO_2$** (277.1103): 277.1097.

13.7 Directed Zincation of Functionalized Aromatics and Heteroaromatics using [(tBu)N(iPr)]$_2$Zn·2MgCl$_2$·2LiCl (87)

Synthesis of 2-(2-methylallyl)-5-phenyl-1,3,4-oxadiazole (89a)



According to **TP 1**, the metalation of 2-phenyl-1,3,4-oxadiazole (**61a**; 290 mg, 2.0 mmol) was completed within 45 min at 25 °C using [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl (**87**; 0.50 M in THF, 2.4 mL, 1.2 mmol). The reaction mixture was cooled to 0 °C, then CuCN·2LiCl (1 M solution in THF, 0.2 mL, 0.2 mmol) and 3-bromo-2-methylpropene (324 mg, 2.2 mmol) were added and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 4:1) to give **89a** (352 mg, 88%) as a colourless solid.

m.p.: 56.3-57.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.05 (dt, *J*=5.5, 2.1 Hz, 3 H), 7.47-7.56 (m, 2 H), 4.98 (d, *J*=15.5 Hz, 2 H), 3.67 (s, 2 H), 1.86 (s, 3 H).

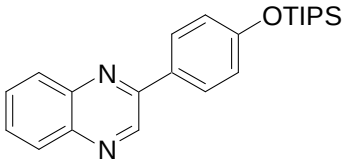
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.06, 164.76, 138.38, 131.62, 129.01, 126.81, 123.94, 114.97, 34.08, 22.21.

MS (70 eV, EI) *m/z* (%): 201 (11), 200 (100) [M^+], 199 (26), 185 (17), 160 (72), 77 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2979, 2935, 2919, 1739, 1653, 1607, 1568, 1550, 1484, 1450, 1428, 1394, 1374, 1335, 1292, 1266, 1227, 1217, 1184, 1178, 1092, 1071, 1048, 1019, 1007, 990, 981, 976, 964, 960, 923, 917, 898, 858, 799, 773, 710, 694, 686, 665, 642, 633, 628, 622, 615, 610, 606, 601.

HRMS (EI) for **$C_{12}H_{12}N_2O$** (200.0950): 200.0948.

Synthesis of 2-(4-(triisopropylsilyloxy)phenyl)quinoxaline (89b)



According to **TP 1**, the metalation of quinoxaline (**61h**, 272 mg, 2.0 mmol) was completed within 9 h at 25 °C using [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl (**87**; 0.50 M in THF, 2.4 mL,

1.2 mmol). A solution of Pd(dba)$_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) in THF (2 mL) was added, followed by (4-iodophenoxy)-triisopropylsilane (827 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 9:1) to give **89b** (613 mg, 81%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.28 (s, 1 H), 8.09 (t, *J*=7.2 Hz, 4 H), 7.67 (td, *J*=14.3, 6.8 Hz, 2 H), 7.05 (d, *J*=8.4 Hz, 2 H), 1.24-1.35 (m, 3 H), 1.12 (d, *J*=7.2 Hz, 18 H).

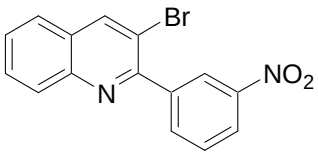
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 158.39, 151.57, 143.12, 142.26, 141.11, 130.18, 129.51, 129.36, 129.05, 129.02, 128.94, 120.62, 17.91, 12.69.

MS (70 eV, EI) *m/z* (%): 379 (13), 378, (45) [M^+], 336 (30), 335 (30), 308 (12), 307 (55), 293 (14), 280 (18), 279 (100), 265 (52), 205 (11), 139 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2943, 2891, 2866, 1602, 1576, 1544, 1514, 1488, 1462, 1422, 1389, 1336, 1313, 1269, 1229, 1169, 1134, 1125, 1107, 1071, 1047, 1011, 996, 957, 906, 882, 840, 760, 738, 729, 683, 661, 654, 643, 630, 626, 621, 606.

HRMS (EI) for **$C_{23}H_{30}N_2OSi$** (378.2127): 378.2133.

Synthesis of 3-bromo-2-(3-nitrophenyl)quinoline (89c)



According to **TP 1**, the metalation of 3-bromoquinoline (**61j**, 416 mg, 2.0 mmol) was completed within 4 h at 25 °C using [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl (**87**; 0.50 M in THF, 2.4 mL, 1.2 mmol). A solution of Pd(dba)$_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) in THF (2 mL) was added, followed by 3-iodonitrobenzene (500 mg, 2.0 mmol). The reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with CH_2Cl_2 (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by recrystallization (CH_2Cl_2, Et_2O) to give **89c** (564 mg, 86%) as a colourless solid.

m.p.: 209.8-211.3.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.70 (t, *J*=1.7 Hz, 1 H), 8.57 (s, 1 H), 8.36 (ddd, *J*=8.3, 2.4, 1.0 Hz, 1 H), 8.11-8.20 (m, 2 H), 7.78-7.88 (m, 2 H), 7.67-7.74 (m, 2 H).

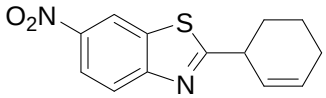
^{13}C-NMR (75 MHz, CDCl$_3$) δ: 155.37, 151.70, 147.98, 146.60, 140.47, 135.68, 130.61, 129.58, 129.06, 128.53, 128.20, 126.61, 124.90, 123.73, 116.00.

MS (70 eV, EI) *m/z* (%):331 (10), 330 (60), 329 (13), 328 (60) [M$^+$], 285 (18), 284 (100), 283 (18), 282 (95), 249 (49), 219 (11), 204 (12), 203 (71), 202 (33), 201 (13), 176 (12), 142 (13), 141 (11), 127 (10), 101 (22), 88 (17), 75 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2989, 2970, 1739, 1530, 1488, 1482, 1435, 1400, 1394, 1372, 1366, 1348, 1300, 1276, 1270, 1262, 1241, 1229, 1217, 1195, 1147, 1130, 1103, 1087, 1072, 1058, 968, 955, 907, 902, 892, 857, 818, 790, 781, 749, 743, 740, 709, 682, 669, 661, 622, 606, 603.

HRMS (EI) for **$C_{15}H_9BrN_2O_2$** (327.9847): 327.9841.

Synthesis of 2-(cyclohex-2-enyl)-6-nitrobenzothiazole (89d)



According to **TP 1**, the metalation of 6-nitrobenzothiazole (**64a**, 360 mg, 2.0 mmol) was completed within 1 h at –50 °C using [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl (**87**; 0.50 M in THF, 2.4 mL, 1.2 mmol). Then CuCN·2LiCl (1 M solution in THF, 0.2 mL, 0.2 mmol) and 3-bromocyclohexene (355 mg, 2.2 mmol) were added and stirred at –50 °C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 9:1) to give **89d** (410 mg, 79%) as a yellow solid.

m.p.: 97.0-98.3 °C.

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 8.80, (s, 1H), 8.35 (d, *J*=8.9 Hz, 1 H), 8.08 (d, *J*=8.9 Hz, 1 H), 6.06-6.13 (m, 1 H), 5.94-6.01 (m, 1 H), 3.98-4.06 (m, 1 H), 2.15-2.29 (m, 3 H), 1.94-2.06 (m, 1 H), 1.72-1.88 (m, 2 H).

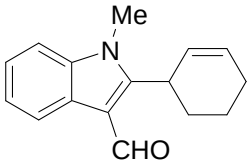
^{13}C-NMR (75 MHz, CDCl$_3$) δ: 183.20, 157.19, 144.63, 135.44, 131.55, 125.82, 122.91, 121.47, 118.18, 41.06, 30.19, 24.79, 20.42.

MS (70 eV, EI) *m/z* (%): 261 (16), 260 (100) [M$^+$], 259 (32), 245 (22), 232 (13), 231 (49), 214 (18), 213 (19), 194 (46), 79 (16), 67 (13), 63 (21), 44 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3109, 2952, 2927, 2905, 1569, 1559, 1512, 1444, 1429, 1340, 1333, 1291, 1281, 1245, 1223, 1172, 1129, 1120, 1072, 1041, 972, 908, 891, 867, 838, 814, 750, 728, 723, 675, 653, 638, 622.

HRMS (EI) for **$C_{13}H_{12}N_2O_2S$** (260.0619): 260.0608.

Synthesis of 2-(cyclohex-2-enyl)-1-methyl-1*H*-indole-3-carbaldehyde (89e)



According to **TP 1**, the metalation of 1-methyl-1*H*-indole-3-carbaldehyde (**64f**, 318 mg, 2.0 mmol) was completed within 1.25 h at 25 °C using [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl (**87**; 0.50 M in THF, 2.4 mL, 1.2 mmol). The reaction mixture was cooled to 0 °C, then CuCN·2LiCl (1 M solution in THF, 0.2 mL, 0.2 mmol) and 3-bromocyclohexene (355 mg, 2.2 mmol) were added and stirred at 0 °C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 3:1) to give **89e** (240 mg, 50%) as a yellow oil.

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 10.34 (s, 1 H), 8.25-8.41 (m, 1 H), 7.27-7.38 (m, 3 H), 5.98-6.04 (m, 1 H), 5.80-5.87 (m, 1 H), 3.80 (s, 3 H), 3.78-3.85 (m, 1 H), 2.12-2.23 (m, 3 H), 1.94-2.06 (m, 1 H), 1.79-1.86 (m, 2 H).

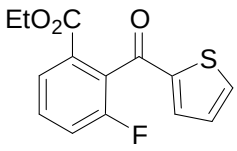
^{13}C-NMR (75 MHz, CDCl$_3$) δ: 185.31, 153.85, 137.24, 129.43, 127.49, 125.69, 123.32, 122.98, 121.65, 114.28, 109.30, 34.06, 30.76, 30.47, 24.60, 22.18.

MS (70 eV, EI) *m/z* (%): 240 (14), 239 (100) [M^+], 238 (13), 222 (19), 210 (11), 210 (14), 184 (38), 182 (14), 167 (17), 157 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930, 2859, 1739, 1683, 1641, 1611, 1580, 1517, 1468, 1447, 1413, 1386, 1323, 1294, 1246, 1223, 1218, 1186, 1156, 1126, 1104, 1073, 1048, 1038, 1015, 982, 932, 917, 890, 860, 818, 801, 747, 729, 702, 674, 656, 642, 635, 631, 626, 622, 616, 611, 605.

HRMS (EI) for **C$_{16}$H$_{17}$NO** (239.1310): 239.1302.

Synthesis of ethyl-3-fluoro-2-(2-thienylcarbonyl)benzoate (89f)



According to **TP 1**, the metalation of ethyl 3-fluorobenzoate (**57**, 336 mg, 2.0 mmol) was completed within 20 h at 25 °C using [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl (**87**; 0.50 M in THF, 2.4 mL, 1.2 mmol). After cooling to –40 °C, CuCN·2LiCl (2.2 mL, 1 M solution in THF, 2.2 mmol) was added, followed by 2-thiophene carbonyl chloride (322 mg, 2.2 mmol). The mixture was briefly warmed with to 25 °C and stirred for 12 h. The reaction mixture was

quenched with sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 5:1) to give **89f** (417 mg, 75%) as a colourless solid.

m.p.: 89.8-91.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.91-7.95 (m, 1 H), 7.74 (dd, *J*=5.0, 1.2 Hz, 1 H), 7.56 (td, *J*=8.1, 5.4 Hz, 1 H), 7.34-7.42 (m, 2 H), 7.11 (dd, *J*=5.0, 3.7 Hz, 1 H), 4.21 (q, *J*=7.2 Hz, 2 H), 1.16 (t, *J*=7.2 Hz, 3 H).

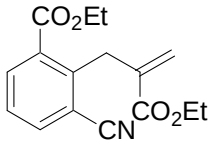
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 184.46, 164.56 (d, $^4J_{CF}$=3.0 Hz), 159.09 (d, $^1J_{CF}$=248 Hz), 144.60, 134.65, 134.11, 130.85 (d, $^3J_{CF}$=8 Hz), 130.79, 128.89 (d, $^2J_{CF}$=20 Hz), 128.13, 126.26 (d, J_{CF}=3.5 Hz), 120.23 (d, $^2J_{CF}$=21 Hz), 61.88, 13.60.

MS (70 eV, EI) *m/z* (%): 278 (46) [M^+], 234 (27), 233 (36), 167 (31), 111 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3094, 2986, 1716, 1650, 1606, 1577, 1560, 1522, 1517, 1476, 1448, 1419, 1413, 1391, 1363, 1353, 1278, 1237, 1194, 1158, 1148, 1112, 1085, 1067, 1051, 1024, 994, 957, 928, 914, 884, 863, 849, 824, 813, 803, 763, 752, 725, 684, 667, 648, 633, 621, 615, 607.

HRMS (EI) for **$C_{14}H_{11}FO_3S$** (278.0413): 278.0405.

Synthesis of ethyl 3-cyano-2-(2-(ethoxycarbonyl)allyl)benzoate (89g)



According to **TP 1**, the metalation of ethyl 3-cyanobenzoate (**67i**, 350 mg, 2.0 mmol) was completed within 36 h at 25 °C using [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl (**87**; 0.50 M in THF, 2.4 mL, 1.2 mmol). The reaction mixture was cooled to 0 °C, then CuCN·2LiCl (1 M solution in THF, 0.2 mL, 0.2 mmol) and ethyl 2-(bromomethyl)acrylate (420 mg, 2.2 mmol) were added and 0 °C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 2:1) to give **89g** (413 mg, 72%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.12 (dd, *J*=7.9, 1.5 Hz, 1 H), 7.83 (dd, *J*=7.7, 1.5 Hz, 1 H), 6.20-6.28 (m, 1 H), 5.02-5.07 (m, 1 H), 7.47 (t, *J*=7.9 Hz, 1 H), 4.35 (q, *J*=7.2 Hz, 2 H), 4.27 (s, 2 H), 4.25 (q, *J*=7.2 Hz, 2 H), 1.36 (t, *J*=7.1, 3 H), 1.32 (t, *J*=7.1, 3 H).

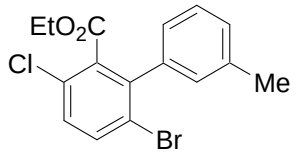
^{13}C-NMR (75 MHz, CDCl$_3$) δ: 166.20, 165.95, 143.13, 138.48, 136.09, 134.77, 132.72, 127.38, 125.51, 117.30, 115.98, 61.77, 61.04, 34.03, 14.19, 14.08.

MS (70 eV, EI) *m/z* (%): 287 (4) [M$^+$], 242 (24), 241 (60), 214 (14), 213 (74), 186 (30), 185 (100), 170 (73), 169 (57), 168 (35), 167 (17), 158 (10), 156 (12), 141 (16), 140 (36).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984, 2940, 2901, 2230, 1714, 1635, 1583, 1448, 1393, 1367, 1268, 1207, 1190, 1173, 1130, 1095, 1084, 1066, 1057, 1022, 947, 863, 818, 766, 754, 682, 669, 646, 641, 635, 623, 601.

HRMS (EI) for **C$_{16}$H$_{17}$NO$_4$** (287.1158): 287.1156.

Synthesis of ethyl 6-bromo-3-‘methylbiphenyl-2-carboxylate (89h)



According to **TP 1**, the metalation of ethyl 5-bromo-2-chlorobenzoate (**88**, 525 mg, 2.0 mmol) was completed within 60 h at 25 °C using [(*t*Bu)N(*i*Pr)]$_2$Zn·2MgCl$_2$·2LiCl (**87**; 0.50 M in THF, 2.4 mL, 1.2 mmol). A solution of Pd(dba)$_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) in THF (2 mL) was added, followed by 3-iodo-toluene (436 mg, 2.0 mmol). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous MgSO$_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 30:1) to give **89h** (470 mg, 67%) as a red oil.

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.62 (d, *J*=8.4 Hz, 1 H), 7.24-7.33 (m, 2 H), 7.19 (d, *J*=7.7 Hz, 1 H), 7.05 (d, *J*=7.7 Hz, 2 H), 4.03 (q, *J*=7.1 Hz, 2 H), 2.37 (s, 3 H), 0.96 (t, *J*=7.1 Hz, 3 H).

^{13}C-NMR (75 MHz, CDCl$_3$) δ: 165.62, 141.66, 137.73, 137.59, 135.75, 134.16, 134.04, 129.86, 129.52, 129.12, 127.88, 126.37, 122.17, 61.67, 21.39, 13.59.

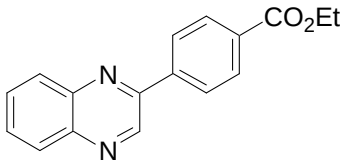
MS (70 eV, EI) *m/z* (%): 356 (22), 355 (14), 354 (82), 353 (10), 352 (62) [M$^+$], 326 (17), 324 (12), 311 (27), 310 (29), 309 (100), 308 (32), 307 (77), 295 (35), 294 (27), 230 (22), 229 (19), 228 (60), 200 (12), 199 (19), 166 (18), 165 (55), 164 (25), 163 (22), 44 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 1732, 1606, 1586, 1574, 1461, 1436, 1403, 1386, 1364, 1281, 1257, 1241, 1162, 1135, 1098, 1057, 1010, 912, 876, 859, 811, 793, 777, 762, 752, 702, 654, 645, 620, 612, 606.

HRMS (EI) for **C$_{16}$H$_{14}$BrClO$_2$** (351.9866): 351.9859.

13.8 Directed Metalation of Aromatics and Heteroaromatics Using *in situ* Protocols

Synthesis of 3 ethyl 4-quinoxalin-2-ylbenzoate (63o):



According to **TP 4**, the metalation of quinoxaline (**61h**; 260 mg, 2.0 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg) and P(*o*-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (607 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 3:1) to give **63o** (440 mg, 79%) as a colourless solid.
m.p.: 88.8-90.9 °C.

^{1}H-NMR (300 Hz, $CDCl_3$) δ: 9.34 (s, 1 H), 8.30-8.11 (m, 6 H), 7.84-7.75 (m, 2 H), 4.43 (q, *J*=7.1 Hz, 2 H), 1.43 (t, *J*=7.1 Hz, 3 H).

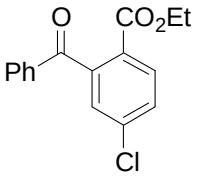
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.14, 150.69, 143.11, 142.29, 141.80, 140.68, 131.83, 130.55, 130.29, 130.10, 129.76, 129.15, 127.42, 61.26, 14.34.

MS (70 eV, EI) *m/z* (%): 279 (17), 278 (100) [M^+], 250 (36), 234 (23), 233 (87), 206 (14), 205 (35), 102 (13), 76 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922, 1713, 1607, 1541, 1467, 1445, 1432, 1405, 1363, 1337, 1310, 1293, 1271, 1233, 1213, 1183, 1126, 1099, 1048, 1017, 988, 978, 958, 914, 895, 875, 861, 852, 840, 796, 772, 758, 752, 740, 720, 711, 698, 668, 637, 615.

HRMS (EI) for **$C_{17}H_{14}N_2O_2$** (278.1055): 278.1030.

Synthesis of 2-benzoyl-4-chlorobenzoic acid ethyl ester (69f):



According to **TP 4**, the metalation of ethyl 4-chlorobenzoate (**67c**; 370 mg, 2.0 mmol) was completed within 20 h at 25 °C. The reaction mixture was cooled to –40 °C, then CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (350 mg,

2.5 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 10 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 7:1) to give **69f** (479 mg, 83%) as a colourless solid.

m.p.: 78.9-80.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J*=8.4 Hz, 1 H), 7.77-7.73 (m, 2 H), 7.57-7.52 (m, 2 H), 7.46–7.41 (m, 2 H), 7.36 (d, *J*=8.4 Hz, 1 H), 4.07 (q, *J*=7.1 Hz, 2 H), 1.04 (t, *J*=7.1 Hz, 3 H).

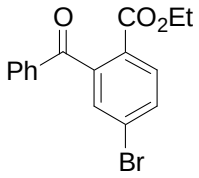
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 195.54, 165.22, 143.44, 139.24, 136.85, 133.69, 131.93, 129.89, 129.61, 128.89, 127.96, 127.82, 61.98, 13.82.

MS (70 eV, EI) *m/z* (%): 288 (24) [M^+], 245 (16), 244 (15), 243 (35), 213 (11), 211 (36), 183 (56), 152 (21), 105 (100), 77 (45), 57 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 2909, 1712, 1677, 1619, 1590, 1583, 1560, 1490, 1473, 1450, 1445, 1385, 1363, 1319, 1311, 1283, 1267, 1243, 1177, 1153, 1134, 1105, 1089, 1074, 1021, 1001, 979, 966, 954, 942, 899, 875, 860, 843, 815, 808, 780, 770, 712, 698, 690, 643, 619, 609, 591, 585.

HRMS (EI) for **$C_{16}H_{13}ClO_3$** (288.0553): 288.0550.

Synthesis of 2-benzoyl-4-bromobenzoic acid ethyl ester (101a):



According to **TP 4**, the metalation of ethyl 4-bromobenzoate (**67f**; 458 mg, 2.0 mmol) was completed within 20 h at 25 °C. The reaction mixture was cooled to –40 °C, then CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (350 mg, 2.5 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 7:1) to give **101a** (526 mg, 79%) as a colourless solid.

m.p.: 90.8-92.6 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.94 (d, *J*=8.4 Hz, 1 H), 7.76-7.74 (m, 2 H), 7.70 (dd, *J*=8.4, 1.8 Hz, 1 H),7.58-7.55 (m, 1 H), 7.53 (d, *J* = 1.8 Hz, 1 H), 7.46-7.43 (m, 2 H), 4.07 (q, *J*=7.2 Hz, 2 H), 1.04 (t, *J*=7.2 Hz, 3 H).

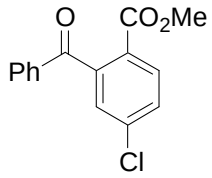
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 195.13, 165.10, 143.22, 136.62, 133.42, 132.66, 131.71, 130.58, 129.37, 128.60, 128.08, 127.40, 61.75, 13.56.

MS (70 eV, EI) *m/z* (%): 334 (10), 332 (10) [M^+], 289 (14), 287 (14), 257 (18), 255 (18), 229 (27), 227 (27), 180 (10), 152 (23), 151 (12), 105 (100), 77 (63), 76 (10), 75 (17), 51 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 1711, 1677, 1582, 1554, 1471, 1450, 1362, 1266, 1243, 1135, 1097, 1020, 948, 898, 858, 842, 778, 759, 681, 689, 697, 711.

HRMS (EI) for **$C_{16}H_{13}O_3Br$** (332.0048): 332.0048.

Synthesis of 2-benzoyl-4-chlorobenzoic acid methyl ester (101b):



According to **TP 4**, the metalation of methyl 4-chlorobenzoate (**67e**; 340 mg, 2.0 mmol) was completed within 20 h at 25 °C. The reaction mixture was cooled to –40 °C, then CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (350 mg, 2.5 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 20 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 6:1) to give **101b** (473 mg, 86%) as a colourless solid.

m.p.: 98.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J*=8.4 Hz, 1 H), 7.72-7.75 (m, 2 H), 7.52-7.59 (m, 2 H), 7.42-7.46 (m, 2 H), 7.37 (d, *J*=2.1 Hz, 1 H), 3.61 (s, 3 H).

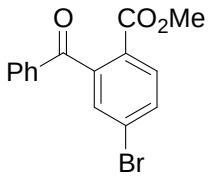
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 195.35, 165.44, 143.31, 139.10, 136.55, 133.41, 131.61, 129.72, 129.23, 128.63, 127.83, 127.38, 52.34.

MS (70 eV, EI) *m/z* (%): 274 (26) [M^+], 243 (21), 197 (80), 152 (10), 105 (100), 77 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1717, 1668, 1595, 1585, 1564, 1452, 1434, 1388, 1317, 1280, 1272, 1257, 1181, 1157, 1142, 1104, 1074, 1026, 1001, 979, 952, 934, 929, 902, 860, 849, 834, 807, 786, 768, 711, 700, 693, 671, 660, 645, 634, 629, 624, 620, 612, 608.

HRMS (EI) for **$C_{15}H_{11}ClO_3$** (274.0397): 274.0393.

Synthesis of 2-benzoyl-4-bromobenzoic acid methyl ester (101c):



According to **TP 4**, the metalation of methyl 4-bromobenzoate (**100a**; 428 mg, 2.0 mmol) was completed within 20 h at 25 °C. The reaction mixture was cooled to –40 °C, then CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (339 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred overnight. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 6:1) to give **101c** (542 mg, 85%) as a yellow solid.

m.p.: 125.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.94 (d, *J*=8.75 Hz, 1 H), 7.70-7.78 (m, 3 H), 7.56-7.65 (m, 2 H), 7.44 7.49 (m, 2 H), 3.63 (s, 3 H).

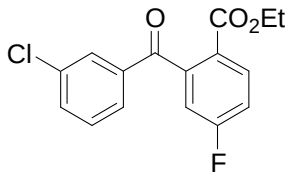
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 195.26, 165.62, 143.36, 136.59, 133.45, 132.77, 131.68, 130.72, 129.27, 128.67, 127.89, 127.57, 52.39.

MS (70 eV, EI) *m/z* (%): 319 (21), 317 (21) [M^+], 288 (14), 286 (14), 242 (60), 240 (61), 105 (100), 77 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3072, 1666, 1582, 1555, 1455, 1433, 1381, 1270, 1192, 1177, 1140, 1092, 948, 907, 859, 831, 788, 759, 701, 687.

HRMS (EI) for **$C_{15}H_{11}BrO_3$** (317.9892): 317.9884.

Synthesis of 2-(3-chlorobenzoyl)-4-fluorobenzoic acid ethyl ester (101d):



According to **TP 4**, the metalation of ethyl 4-fluorobenzoate (**67a**; 336 mg, 2.0 mmol) was completed within 10 h at 25 °C. The reaction mixture was cooled to –40 °C, then CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) and 3-chlorobenzoyl chloride (438 mg, 2.5 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 10 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was

evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 5:1) to give **101d** (520 mg, 85%) as a colourless solid.

m.p.: 90.1-93.4 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.11 (dd, *J*=8.6, 5.2 Hz, 1 H), 7.74 (t, *J*=1.9 Hz, 1 H), 7.59 (ddd, *J*=7.7, 1.4, 1.3 Hz, 1 H), 7.53 (ddd, *J*=8.0, 2.3, 1.2 Hz, 1 H), 7.37 (t, *J*=7.9 Hz, 1 H), 7.23-7.27 (m, 1 H), 7.05 (dd, *J*=8.3, 2.6 Hz, 1 H), 4.11 (q, *J*=7.2 Hz, 2 H), 1.10 (t, *J*=7.2 Hz, 3 H).

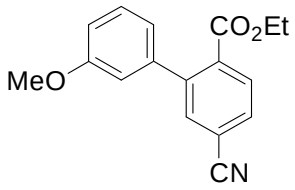
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 193.96 (d, $^{4}J_{CF}$=1.3 Hz), 164.88 (d, $^{1}J_{CF}$=256 Hz), 164.61, 143.80 (d, $^{3}J_{CF}$=7.4 Hz), 138.20, 134.98, 133.29, 133.1 (d, $^{3}J_{CF}$=9.3 Hz), 129.93, 129.07, 127.42, 125.21 (d, $^{4}J_{CF}$=3.4 Hz), 116.79 (d, $^{2}J_{CF}$=22 Hz), 114.93 (d, $^{2}J_{CF}$=24 Hz), 61.75, 13.70.

MS (70 eV, EI) *m/z* (%): 306 (25) [M^+], 263 (18), 262 (19), 261 (51), 195 (54), 170 (20), 168 (10), 167 (100), 141 (20) 139 (61).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3106, 3072, 2994, 2942, 2884, 2872, 1711, 1685, 1664, 1608, 1588, 1576, 1482, 1468, 1452, 1432, 1396, 1368, 1292, 1266, 1240, 1192, 1164, 1152, 1126, 1112, 1070, 1056, 1044, 1022, 986, 960, 928, 864, 826, 810, 776, 758, 742, 682, 674, 650, 590, 572.

HRMS (EI) for **$C_{16}H_{12}ClFO_3$** (306.0459): 306.0451.

Synthesis of 5-cyano-3'-methoxybiphenyl-2-carboxylic acid ethyl ester (101e):



According to **TP 4**, the metalation of ethyl 4-cyanobenzoate (**67j**; 370 mg, 2.0 mmol) was completed within 4 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) in THF (2 mL) was added, followed by 3-iodoanisole (598 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 6:1) to give **101e** (490 mg, 87%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, *J*=8.6 Hz, 1 H), 7.67-7.71 (m, 2 H), 7.28-7.34 (m, 1 H), 6.86 (ddd, *J*=8.4, 2.5, 1.0 Hz, 1 H), 6.81-6.87 (m, 2 H), 4.12 (q, *J*=7.1 Hz, 2 H), 3.82 (s, 3 H), 1.01 (t, *J*=7.1 Hz, 3 H).

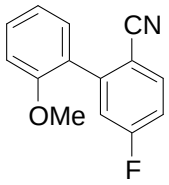
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.37, 159.50, 142.89, 140.33, 135.57, 133.89, 130.61, 130.08, 129.44, 120.64, 117.87, 114.64, 113.76, 113.71, 61.65, 55.31, 13.60.

MS (70 eV, EI) *m/z* (%): 282 (21), 281 (100) [M^+], 253 (12), 237 (21), 236 (65), 210 (14), 209 (77), 206 (12), 193 (21), 179 (11), 177 (12), 165 (13), 164 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2229, 1713, 1598, 1586, 1485, 1464, 1442, 1419, 1402, 1392, 1321, 1305, 1281, 1270, 1249, 1225, 1172, 1166, 1143, 1102, 1082, 1052, 1030, 994, 985, 923, 906, 892, 875, 855, 794, 781, 770, 755, 728, 697, 645, 627, 622, 617, 613.

HRMS (EI) for **$C_{17}H_{15}NO_3$** (281.1052): 281.1048.

Synthesis of 5-fluoro-2'-methoxybiphenyl-2-carbonitrile (101f):



According to **TP 4**, the metalation of 4-fluorobenzonitrile (**67k**; 242 mg, 2.0 mmol) was completed within 8 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) in THF (2 mL) was added, followed by 2-iodoanisole (598 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 5 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 9:1) to give **101f** (520 mg, 85%) as a colourless solid.

m.p.: 100.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.69 (dd, *J*=6.4, 2.1 Hz, 1 H), 7.67-7.72 (m, 1 H), 7.45-7.51 (m, 1 H), 7.27-7.32 (m, 2 H), 7.05-7.14 (m, 2 H), 3.87 (s, 3 H).

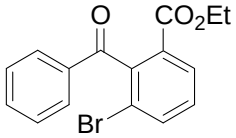
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 162.43 (d, $^1J_{CF}$=256 Hz), 156.62, 136.38 (d, $^3J_{CF}$=5.5 Hz), 130.07 (d, $^3J_{CF}$=9.3 Hz), 131.00, 130.37, 128.04 (d, $^2J_{CF}$=18 Hz), 122.38, 120.66, 118.25, 116.91 (d, $^2J_{CF}$=24 Hz), 111.10, 108.14 (d, $^4J_{CF}$=3.9 Hz), 55.57.

MS (70 eV, EI) *m/z* (%): 228 (14), 227 (100) [M^+], 212 (30), 184 (19), 158 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2227, 1597, 1580, 1501, 1488, 1465, 1434, 1402, 1308, 1297, 1281, 1263, 1240, 1225, 1170, 1160, 1112, 1056, 1031, 1025, 934, 898, 851, 831, 795, 748, 740, 723, 678, 634, 620.

HRMS (EI) for **$C_{14}H_{10}FNO$** (227.0746): 227.0739.

Synthesis of 2-benzoyl-3-bromobenzoic acid ethyl ester (101g):



According to **TP 4**, the metalation of ethyl 3-bromobenzoate (**100b**; 460 mg, 2.0 mmol) was completed within 4 h at 25 °C. The reaction mixture was cooled to –40 °C, then CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (350 mg, 2.5 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 8:1) to give **101g** (606 mg, 91%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.93 (d, *J*=8.4 Hz, 1 H), 7.74 (dt, *J*=8.3, 1.6 Hz, 2 H), 7.69 (dd, *J*=8.4, 2.0 Hz, 1 H), 7.54-7.58 (m, 1 H), 7.52 (d, *J*=2.0 Hz, 1 H), 7.41-7.46 (m, 2 H), 4.06 (q, *J*=7.1 Hz, 2 H), 1.03 (t, *J*=7.1 Hz, 3 H).

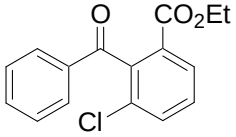
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 195.13, 165.07, 143.18, 136.57, 133.41, 132.63, 131.68, 130.54, 129.34, 128.58, 128.02, 127.39, 61.73, 13.54.

MS (70 eV, EI) *m/z* (%): 334 (32), 332 (32) [M^+], 290 (20), 289 (565), 288 (22), 287 (55), 257 (68), 255 (70), 229 (88), 227 (88), 181 (11), 180 (15), 152 (33), 151 (12), 106 (13), 105 (100), 77 (56).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 1712, 1676, 1598, 1583, 1555, 1474, 1471, 1450, 1444, 1383, 1362, 1318, 1310, 1281, 1267, 1243, 1178, 1156, 1135, 1116, 1097, 1074, 1024, 1020, 1000, 965, 948, 898, 859, 842, 826, 815, 805, 778, 759, 712, 697, 689, 681, 662, 654, 641, 633, 626, 622, 619, 612, 603.

HRMS (EI) for **$C_{16}H_{13}BrO_3$** (332.0048): 332.0034.

Synthesis of 2-benzoyl-3-chlorobenzoic acid methyl ester (69e):



According to **TP 4**, the metalation of ethyl 3-chlorobenzoate (**67b**; 370 mg, 2.0 mmol) was completed within 3 h at 25 °C. The reaction mixture was cooled to –40 °C, then CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (350 mg, 2.5 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL)

and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 6:1) to give **69e** (606 mg, 91%) as a colourless solid.

m.p.: 108.6-109.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.08 (m, 1 H), 7.81 (m, 2 H), 7.44-7.68 (m, 5 H), 4.17 (q, *J*=7.1 Hz, 2 H), 1.10 (t, *J*=7.1 Hz, 3 H).

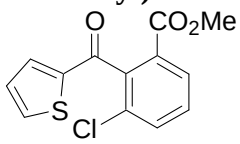
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 194.52, 164.82, 140.65, 136.91, 134.15, 133.63, 131.97, 130.89, 130.11, 129.24, 128.93, 62.09, 13.84.

MS (70 eV, EI) *m/z* (%): 290 (19), 288 (43) [M^+], 242 (32), 211 (73), 211 (26), 185 (32), 183 (100), 152 (10), 151 (13), 105 (87), 77 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1706, 1672, 1584, 1564, 1430, 1366, 1284, 1202, 1152, 1074, 1028, 928, 866, 764, 744, 734, 702, 652, 618.

HRMS (EI) for **$C_{16}H_{13}ClO_3$** (288.0553): 288.0569.

Synthesis of 3-chloro-2-(thiophene-2-carbonyl)benzoic acid methyl ester (101h):



According to **TP 4**, the metalation of methyl 3-chlorobenzoate (**100c**; 340 mg, 2.0 mmol) was completed within 5 h at 25 °C. The reaction mixture was cooled to –40 °C, then CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) and 2-thiophene acid chloride (365 mg, 2.5 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 20 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 4:1) to give **101h** (443 mg, 82%) as a colourless solid.

m.p.: 134.7 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.01 (d, *J*=9.1 Hz, 1 H), 7.69 (d, *J*=4.8 Hz, 1 H), 7.64 (d, *J*=8.1 Hz, 1 H), 7.48 (t, *J*=7.9 Hz, 1 H), 7.27 (dd, *J*=3.6, 1.2 Hz, 1 H), 7.07 (dd, *J*=4.8, 3.8 Hz, 1 H), 3.73 (s, 3 H).

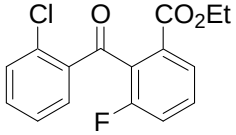
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 186.41, 164.89, 144.08, 139.94, 134.44, 134.04, 133.67, 131.97, 130.16, 128.91, 128.14, 52.59.

MS (70 eV, EI) *m/z* (%): 208 (35) [M^+], 251 (15), 249 (36), 221 (11), 197 (25), 111 (100), 59 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1722, 1653, 1586, 1567, 1517, 1455, 1434, 1412, 1349, 1274, 1235, 1207, 1159, 1112, 1083, 1049, 1034, 971, 882, 867, 861, 848, 817, 765, 746, 736, 722, 680, 674, 662, 645, 639, 634, 631, 621, 608, 605.

HRMS (EI) for **$C_{13}H_9ClO_3S$** (279.9961): 279.9963.

Synthesis of (2'-chloro)-2-benzoyl-3-fluorobenzoic acid ethyl ester (101i):



According to **TP 4**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed within 2 h at 25 °C. The reaction mixture was cooled to –40 °C, then CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) and 2-chlorobenzoyl chloride (0.31 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 8:1) to give **101i** (574 mg, 94%) as a yellowish solid.

m.p.: 104.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.84 (dd, *J*=7.8, 1.0 Hz, 1 H), 7.72-7.77 (m, 1 H), 7.43-7.54 (m, 3 H), 7.27-7.35 (m, 2 H), 4.20 (q, *J*=7.0 Hz, 2 H), 1.15 (t, *J*=7.2 Hz, 3 H).

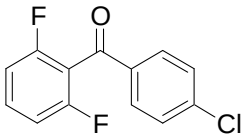
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 190.59, (d, $^3J_{CF}$=1.3 Hz), 164.94, 159.09 (d, $^1J_{CF}$=248 Hz), 135.16, 133.99, 133.37, 132.35, 131.60, 131.06 (d, $^3J_{CF}$=3.3 Hz), 130.81 (d, $^3J_{CF}$=8.3 Hz), 130.50, 126.72, 126.15 (d, $^3J_{CF}$=3.3 Hz), 120.04 (d, $^2J_{CF}$=22 Hz), 61.90, 13.77.

MS (70 eV, EI) *m/z* (%): 306 (5) [M^+], 272 (17), 271 (88), 261 (34), 243 (10), 195 (23), 170 (10), 168 (11), 167 (100), 141 (25), 139 (75), 111 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1712, 1686, 1608, 1587, 1575, 1566, 1482, 1468, 1452, 1444, 1431, 1367, 1292, 1265, 1239, 1191, 1165, 1152, 1125, 1112, 1070, 1056, 1043, 1023, 960, 953, 928, 863, 826, 809, 776, 758, 742, 683, 675, 651, 637, 618, 612.

HRMS (EI) for **$C_{16}H_{12}ClFO_3$** (306.0459): 306.0452.

Synthesis of (4-chlorophenyl)-(2,6-difluorophenyl)methanone (101j):



According to **TP 4**, the metalation of 1,3-difluorobenzene (**100d**; 228 mg, 2.0 mmol) was completed within 6 h at 25 °C. The reaction mixture was cooled to –40 °C, then CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) and 4-chlorobenzoyl chloride (438 mg, 2.5 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 29:1) to give **101j** (402 mg, 80%) as a colourless solid.

m.p.: 75.5 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.80 (d, J=8.6 Hz, 2 H), 7.43-7.48 (m, 3 H), 6.98-7.03 (m, 2 H).

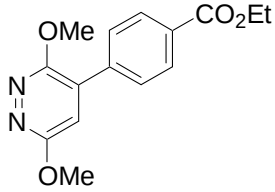
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 187.64, 159.74 (dd, $^1J_{CF}$=252 Hz, $^3J_{CF}$=7.7 Hz), 140.80, 135.19, 132.21 (t, J_{CF}=9.8 Hz), 130.94, 129.14, 116.52, 112.01 (dd, $^2J_{CF}$=22 Hz, $^3J_{CF}$=4.2 Hz).

MS (70 eV, EI) *m/z* (%): 254 (18), 252 (52) [M^+], 141 (53), 141 (38), 139 (100), 113 (13), 111 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1670, 1623, 1586, 1574, 1556, 1488, 1461, 1401, 1311, 1286, 1272, 1233, 1182, 1172, 1151, 1144, 1113, 1091, 1057, 1022, 1015, 999, 977, 957, 926, 880, 846, 830, 814, 789, 769, 751, 731, 715, 695, 680, 667, 662, 656, 636, 628, 607.

HRMS (EI) for **$C_{13}H_7ClF_2O$** (252.0153): 252.0147.

Synthesis of 4-(3,6-dimethoxypyridazin-4-yl) benzoic acid ethyl ester (101k):



According to **TP 4**, the metalation of 3,6-dimethoxypyridazine (**100e**; 278 mg, 2.0 mmol) was completed within 5 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (607 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 7 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 4:1) to give **101k** (374 mg, 65%) as a colourless solid.

m.p.: 96.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.12 (d, *J*=8.3 Hz, 2 H), 7.66 (d, *J*=8.0 Hz, 2 H), 6.96 (s, 1 H), 4.40 (q, *J*=7.3 Hz, 2 H), 4.08 (s, 6 H), 1.40 (t, *J*=7.2 Hz, 3 H).

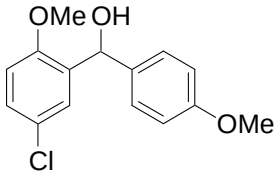
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 166.00, 162.57, 159.32, 137.75, 133.07, 131.11, 129.62, 128.98, 119.46, 61.21, 54.93, 54.68, 14.30.

MS (70 eV, EI) *m/z* (%): 289 (10), 288 (54), 287 (100), 259 (29), 243 (17), 215 (10), 129 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 1705, 1604, 1571, 1469, 1412, 1368, 1274, 1251, 1215, 1186, 1131, 1106, 1001, 895, 862, 773, 709.

HRMS (EI) for **$C_{15}H_{16}N_2O_4$** (288.1110): 288.1083.

Synthesis of (5-chloro-2-methoxyphenyl)-(4-methoxyphenyl)methanol (105a):



According to **TP 5**, the metalation of 4-chloroanisole (**102a**; 284 mg, 2.0 mmol) was completed within 24 h at 25 °C. The reaction mixture was cooled to 0 °C and then 4-methoxy benzaldehyde (680 mg, 5 mmol) was added. The mixture was allowed to warm to 25 °C and stirred for 7 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (30 mL) and aq. HCl (2 M, 8 mL) and extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 5:1) to give **105a** (418 mg, 75%) as a yellowish solid.

m.p.: 88.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.25-7.31 (m, 3 H), 7.19 (dd, *J*=8.7, 2.7 Hz, 1 H), 6.83-6.87 (m, 2 H), 6.78 (d, *J*=8.5 Hz, 1 H), 5.98 (s, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H).

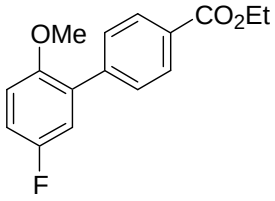
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 158.98, 155.09, 134.81, 134.04, 128.09, 127.84, 127.33, 125.88, 113.72, 111.90, 71.02, 55.73, 55.25.

MS (70 eV, EI) *m/z* (%): 280 (23), 279 (13), 278 (71) [M^+], 262 (21), 261 (15), 260 (54), 247 (20), 245 (19), 171 (33), 170 (10), 169 (100), 166 (14), 155 (16), 137 (39), 135 (58), 121 (31), 117 (11), 109 (51), 108 (36), 77 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3324, 3004, 2932, 2836, 1713, 1608, 1586, 1511, 1482, 1464, 1441, 1422, 1408, 1338, 1302, 1290, 1246, 1196, 1172, 1126, 1110, 1093, 1060, 1029, 1019, 1008, 939, 906, 896, 844, 828, 809, 794, 776, 735, 710, 702, 674, 654, 642, 625, 611, 606, 602.

HRMS (EI) for **$C_{15}H_{15}ClO_3$** (278.0710): 278.0694.

Synthesis of 5'-fluoro-2'-methoxybiphenyl-4-carboxylic acid ethyl ester (105b):



According to **TP 5**, the metalation of 4-fluoroanisole (**102b**; 252 mg, 2.0 mmol) was completed within 15 h at 25 °C. The reaction mixture was cooled to 0 °C, then $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (607 mg, 2.2 mmol) and the reaction mixture was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (30 mL) and aq. HCl (2 M, 8 mL) and extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 29:1) to give **105b** (420 mg, 77%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.09 (ddd, *J*=8.6, 1.9, 1.7 Hz, 2 H), 7.58 (dt, *J*=8.5, 1.8 Hz, 2 H), 6.99-7.08 (m, 2 H), 6.9 (dd, *J*=8.9, 4.5 Hz, 1 H), 4.40 (q, *J*=7.1 Hz, 2 H), 3.77 (s, 3 H), 1.40 (t, *J*=7.0 Hz, 3 H).

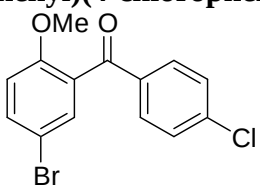
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.38, 156.97 (d, $^1J_{CF}$=239 Hz), 152.57 (d, J_{CF}=2.3 Hz), 141.95 (d, J_{CF}=1.5 Hz), 130.75 (d, J_{CF}=7.5 Hz), 129.58, 129.29, 129.24, 129.22, 117.20, (d, $^2J_{CF}$=24 Hz), 115.00 (d, $^2J_{CF}$=22 Hz), 112.36 (d, J_{CF}=8.2 Hz), 60.88, 56.08, 14.29.

MS (70 eV, EI) *m/z* (%): 275 (15), 274 (100), 246 (21), 203 (17), 229 (87), 187 (25), 186 (50), 157 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 2941, 2906, 2837, 1710, 1608, 1596, 1567, 1516, 1492, 1465, 1444, 1424, 1398, 1367, 1312, 1269, 1254, 1233, 1178, 1100, 1038, 1019, 896, 881, 856, 806, 777, 746, 728, 718, 702, 656, 636, 620, 611.

HRMS (EI) for **$C_{16}H_{15}FO_3$** (274.1005): 274.1001.

Synthesis of (5-bromo-2-methoxyphenyl)(4-chlorophenyl)methanone (105c):



According to **TP 5**, the metalation of 4-bromoanisole (**102c**; 372 mg, 2.0 mmol) was completed within 28 h at 25 °C. The reaction mixture was cooled to 0 °C, then $ZnCl_2$ (1.0 M

solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. The reaction mixture was then cooled to –40 °C, then CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) and 4-chlorobenzoyl chloride (437 mg, 2.5 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (30 mL) and aq. HCl (2 M, 8 mL) and extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 14:1) to give **105c** (515 mg, 79%) as a colourless solid.

m.p.: 85.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.71 (ddd, *J*=8.7, 2.4, 2.2 Hz, 2 H), 7.56 (dd, *J*=8.7, 2.4 Hz, 1 H), 7.45 (d, *J*=2.7 Hz, 1 H), 7.40 (ddd, *J*=8.9, 2.3, 2.1 Hz, 2 H), 6.87 (d, *J*=8.7 Hz, 1 H), 3.69 (s, 3 H).

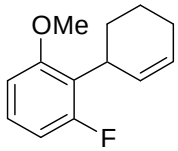
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 193.45, 156.29, 139.70, 135.60, 134.67, 132.02, 131.07, 130.10, 128.69, 113.28, 112.96, 55.86.

MS (70 eV, EI) *m/z* (%): 328 (33), 327 (40), 326 (87), 325 (26), 324 (85) [M^+], 309 (29), 308 (12), 307 (18), 291 (32), 289 (27), 119 (19), 228 (10), 227 (47), 214 (78), 212 (87), 209 (28), 202 (13), 201 (77), 199 (72), 172 (23), 170 (22), 157 (18), 155 (16), 139 (100), 134 (10), 113 (25), 111 (90), 77 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1721, 1668, 1662, 1587, 1570, 1483, 1460, 1452, 1438, 1402, 1390, 1370, 1310, 1294, 1262, 1240, 1180, 1157, 1147, 1122, 1109, 1091, 1022, 1015, 975, 952, 947, 935, 918, 894, 881, 862, 851, 830, 812, 768, 762, 744, 730, 714, 702, 690, 684, 665, 627, 620, 612.

HRMS (EI) for **$C_{14}H_{10}BrClO_2$** (323.9553): 323.9545.

Synthesis of 2-cyclohex-2-enyl-1-fluoro-3-methoxybenzene (105d):



According to **TP 5**, the metalation of 3-fluoroanisole (**102d**; 252 mg, 2.0 mmol) was completed within 20 min at –5 °C. The reaction mixture was cooled to –20 °C, then $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. Then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) 3-bromocyclohexene (810 mg, 5 mmol) were added. The mixture was stirred at –20 °C for 1 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (30 mL) and aq. HCl (2 M, 8 mL) and extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration,

the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 1000:1) to give **105d** (360 mg, 87%) as a colourless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.08-7.14 (m, 1 H), 6.60-6.68 (m, 2 H), 5.72-5.77 (m, 1 H), 5.60-5.65 (m, 1 H), 3.92-3.97 (m, 1 H), 3.81 (s, 3 H), 2.12-2.18 (m, 1 H), 2.04-2.09 (m, 1 H), 1.82-1.90 (m, 3 H), 1.66-1.73 (m, 1 H).

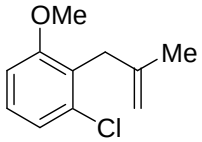
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 162.71 (d, $^1J_{CF}$=245 Hz), 158.61 (d, J_{CF}=9.3 Hz), 130.46 (d, J_{CF}=1.4 Hz) 127.14 (d, J_{CF}=11 Hz), 125.61 (d, J_{CF}=2.09 Hz), 121.69 (d, $^2J_{CF}$=15 Hz), 108.51 (d, $^2J_{CF}$=24 Hz), 106.41 (d, J_{CF}=2.8 Hz), 55.95 (d, J_{CF}=0.6 Hz), 32.16 (d, J_{CF}=1.4 Hz), 28.38 (d, $^1J_{CF}$=1.7 Hz), 24.67, 23.09.

MS (70 eV, EI) *m/z* (%): 207 (15), 206 (100) [M^+], 205 (14), 191 (41), 178 (35), 177 (20), 165 (33), 163 (26), 152 (33), 150 (13), 149 (35), 174 (25), 146 (16), 139 (28), 137 (22), 135 (11), 133 (18), 125 (24), 115 (12), 109 (46), 81 (16), 79 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3021, 2932, 2859, 2837, 1611, 1584, 1469, 1439, 1349, 1334, 1327, 1303, 1292, 1266, 1234, 1222, 1187, 1164, 1136, 1083, 1045, 987, 941, 928, 899, 876, 846, 779, 727, 643, 615.

HRMS (EI) for **$C_{13}H_{15}FO$** (206.1107): 206.1100.

Synthesis of 1-chloro-3-methoxy-2-(2-methylallyl)benzene (105e):



According to **TP 5**, the metalation of 3-chloroanisole (**102e**; 284 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to 0 °C, then $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. Then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and metallyl bromide (670 mg, 5 mmol) were added. The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (30 mL) and aq. HCl (2 M, 8 mL) and extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **105e** (335 mg, 85%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.12 (t, J=8.1 Hz, 1 H), 7.00 (dd, J=8.1, 1.1 Hz, 1 H), 6.78 (dd, J=8.3, 1.0 Hz, 1 H), 4.72-4.75 (m, 1 H), 4.40-4.44 (m, 1 H), 3.81 (s, 3 H), 3.49 (s, 2 H), 1.81 (d, J=0.7 Hz, 3 H).

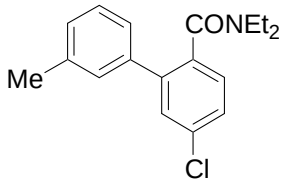
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 158.68, 143.13, 135.57, 127.50, 126.77, 121.63, 109.99, 108.89, 55.90, 34.52, 23.03.

MS (70 eV, EI) *m/z* (%): 198 (14), 196 (30) [M^+], 167 815), 166 (100), 157 (13), 156 (13), 155 (43), 136 (15), 127 (13), 125 (37), 111 (10), 97 (15), 91 (15), 85 (16), 83 (17), 77 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3079, 2937, 2837, 1652, 1591, 1577, 1462, 1435, 1374, 1312, 1263, 1230, 1216, 1181, 1080, 1043, 1004, 929, 922, 886, 840, 823, 767, 722, 659, 649, 626, 620.

HRMS (EI) for **$C_{11}H_{13}ClO$** (196.0655): 196.0635.

Synthesis of 5-chloro-N,N-diethyl-3'-methylbiphenyl-2-carboxamid (105f):



According to **TP 5**, the metalation of 4-chloro-*N*,*N*-diethylbenzamide (**102f**; 372 mg, 2.0 mmol) was completed within 3 h at 0 °C. Then, $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) and 3-iodotoluene (654 mg, 3.0 mmol) and the reaction mixture was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (30 mL) and aq. HCl (2 M, 8 mL) and extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 3:1) to give **105f** (417 mg, 73%) as a yellowish solid.

m.p.: 54.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.28 (d, 2.1 Hz, 1 H) 7.25 (dd, J=8.1, 1.8 Hz, 1 H), 7.19 (d, *J*=8.1 Hz, 1 H), 7.15 (t, *J*=2.7 Hz, 3 H), 7.03-7.08 (m, 1 H), 2.72 (br, 4 H), 2.26 (s, 3 H), 0.71 (2 t, *J*=6.9 Hz, 6 H).

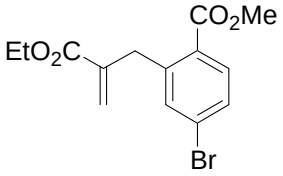
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 169.62, 140.38, 138.46, 138.05, 134.77, 134.61, 129.38, 128.83, 128.50, 128.40, 127.52, 125.80, 42.40, 38.55, 21.42, 13.41.

MS (70 eV, EI) *m/z* (%): 303 (6), 302 (14), 301 (18) [M^+], 300 (34), 272 (4), 232 (6), 231 (31), 230 (17), 229 (100), 217 (3), 215 (9), 210 (6), 201 (4), 199 (2), 195 (5), 194 (6), 193 (3), 186 (7), 167 (8), 166 (49), 165 (52), 164 (6), 163 (6), 151 (4), 139 (3).

IR (ATR) (cm^{-1}): 3243, 3042, 2968, 2929, 2868, 1894, 1625, 1590, 1516, 1458, 1439, 1424, 1377, 1363, 1348, 1316, 1294, 1251, 1219, 1184, 1129, 1100, 1083, 1069, 1052, 998, 947, 890, 867, 820, 787, 763, 701, 656.

HRMS (EI) for **$C_{18}H_{20}ClNO$** (301.1233): 301.1219.

Synthesis of 4-bromo-2-(2-ethoxycarbonylallyl)benzoic acid methyl ester (105g):



According to **TP 5**, the metalation of methyl 4-bromobenzoate (**100a**; 428 mg, 2.0 mmol) was completed within 2 h at 0 °C. Then, $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. Then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and ethyl 2-(bromomethyl)acrylate (772 mg, 4 mmol) were added. The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (30 mL) and aq. HCl (2 M, 8 mL) and extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 20:1) to give **105g** (327 mg, 51%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.67 (dd, *J*=5.7, 3.3 Hz, 1 H), 7.32 (dd, *J*=5.7, 0.9 Hz, 1 H), 7.30 (d, *J*=2.1 Hz, 1 H), 6.11 (q, *J*=1.2 Hz, 1 H), 5.17 (q, *J*=1.2 Hz, 1 H), 4.09 (q, *J*=8.4 Hz, 2 H), 3.89 (s, 2 H), 3.73 (s, 3 H), 1.16 (t, *J*=7.2 Hz, 3 H).

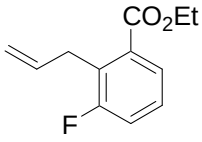
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.85, 166.51, 142.43, 139.53, 134.25, 132.24, 129.66, 128.71, 126.65, 125.96, 60.75, 52.01, 35.51, 15.05.

MS (70 eV, EI) *m/z* (%): 326 (5) [M^+], 297 (21), 296 (100), 268 (19), 294 (96), 283 (30), 282 (70), 280 (64), 268 (97), 266 (94), 254 (32), 253 (52), 252 (27), 240 (32), 239 (22), 238 (44), 237 (18), 236 (17), 224 (23), 223 (48), 222 (38), 221 (36), 211 (24), 209 (26), 195 (10).

IR (ATR) (cm^{-1}): 3425, 2982, 2952, 1713, 1632, 1587, 1561, 1478, 1433, 1391, 1368, 1255, 1191, 1128, 1092, 1075, 1025, 948, 857, 813, 775, 726.

HRMS (EI) for **$C_{14}H_{15}BrO_4$** (326.0154): 326.0146.

Synthesis of 2-allyl-3-fluoro-benzoic acid ethyl ester (105h):



According to **TP 5**, the metalation of ethyl 3-fluorobenzoate (**57**, 336 mg, 2.0 mmol) was completed within 1 h at 0 °C. Then, $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. Then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and allyl bromide (600 mg, 5 mmol) were added and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (30 mL) and aq.

HCl (2 M, 8 mL) and extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 200:1) to give **105h** (337 mg, 81%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ**:** 7.55 (ddd, *J*=7.8, 1.5, 0.9 Hz, 1 H), 7.04-7.17 (m, 1 H), 7.06 (dd, *J*=8.4 Hz, 1 H), 5.86-5.90 (m, 1 H), 4.87-4.93 (m, 2 H), 4.24 (q, J=7.2, Hz, 2 H), 3.62-3.70 (m, 2 H), 1.27 (t, *J*=7.2 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.77, 161.37 (d, $^1J_{CF}$=245 Hz), 135.90, 134.32 (d, $^3J_{CF}$=4.3 Hz), 128.46 (d, $^2J_{CF}$=17 Hz), 127.24 (d, $^3J_{CF}$=8.9 Hz), 126.08 (d, $^4J_{CF}$=3.5 Hz), 118.72 (d, $^2J_{CF}$=24 Hz), 115.44, 61.19, 29.79, 14.22.

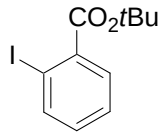
MS (70 eV, EI) *m/z* (%): 209 (10), 208 (61) [M^+], 194 (8), 193 (64), 180 (15), 179 (13), 166 (9), 165 (85), 164 (22), 163 (73), 162 (56), 161 (21), 152 (16), 151 (10), 151 (8), 149 (15), 135 (56), 134 (50), 133 (100), 123 (9), 115 (32), 109 (24), 108 (10), 107 (16), 83 (11).

IR (ATR) (cm^{-1}): 3081, 2982, 2939, 1719, 1637, 1610, 1456, 1366, 1260, 1195, 1139, 1095, 1024, 995, 957, 914, 754.

HRMS (EI) für **$C_{12}H_{13}FO_2$** (208.0900): 208.0887.

13.9 Directed Metalation of Functionalized Aromatics and Heteroaromatics Using Aluminum-Bases

Synthesis of 2-iodobenzoic acid *tert*-butyl ester (114):



According to **TP 6**, the metalation of *tert*-butyl benzoate (**46a**; 356 mg, 2.0 mmol) was completed using [(*t*Bu)N(*i*Pr)]$_3$Al·3LiCl (**107**; 0.23 M solution in THF, 8.7 mL, 2.0 mmol) within 3 h at –5 °C. The reaction mixture was cooled to –15 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. I_2 (635 mg, 2.5 mmol) dissolved in THF (5 mL) was added dropwise and the mixture was stirred for 30 min at -15 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. Sat. $Na_2S_2O_3$ (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 25:1) furnished the compound **114** (369 mg, 65%) as a yellowish oil.

According to **TP 6**, the metalation of *tert*-butyl benzoate (**46a**; 356 mg, 2.0 mmol) was completed using TMP_3Al·3LiCl (**108**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 3 h at -5 °C. The reaction mixture was cooled to –15 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. I_2 (635 mg, 2.5 mmol) dissolved in THF (5 mL) was added dropwise and the mixture was stirred for 30 min at –15 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. Sat. $Na_2S_2O_3$ (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 25:1) furnished the compound **114** (395 mg, 65%) as a yellowish oil.

According to **TP 6**, the metalation of *tert*-butyl benzoate (**46a**; 356 mg, 2.0 mmol) was completed using ($C_{12}H_{26}N)_3Al$·3LiCl (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 3 h at –5 °C. The reaction mixture was cooled to –15 °C, $ZnCl_2$ (1.0 M solution in THF,

2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. I_2 (635 mg, 2.5 mmol) dissolved in THF (5 mL) was added dropwise and the mixture was stirred for 30 min at -15 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. Sat. $Na_2S_2O_3$ (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 25:1) furnished the compound **114** (432 mg, 71%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.72 (dd, J = 7.8, 1.7 Hz, 1 H), 7.70 (dd, J = 7.8 Hz, J=1.7 Hz, 1 H), 7.40 (dd, J=7.8; 1.3 Hz, 1 H), 7.12 (td, J=7.8, 1.8 Hz, 1 H) 1.64 (s, 9 H).

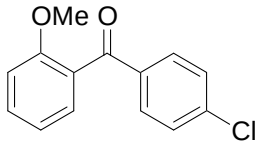
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.04, 141.21, 137.73, 132.23, 130.69, 128.08, 93.64, 82.91, 28.42.

MS (70 eV, EI) *m/z* (%): 304 (5) [M^+], 290 (55) 248 (84), 230 (100), 203 (28), 121 (13), 104 (14), 76 (86), 69 (27), 59 (22).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977, 2931, 1712, 1569, 1457, 1366, 1291, 1247, 1168, 1114, 1022, 847, 769.

HRMS (EI) for **$C_{11}H_{13}O_2I$** (303.9960): 303.9887.

Synthesis of (4-chloro-phenyl)-(2-methoxyphenyl)methanone (115):



According to **TP 6**, the metalation of anisole (**113**; 216 mg, 2.0 mmol) was completed using [(*t*Bu)N(*i*Pr)]$_3$Al·3LiCl (**107**; 0.23 M solution in THF, 8.7 mL, 2.0 mmol) within 15 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (460 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 8 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 5:1) furnished the compound **115** (314 mg, 64%) as a colourless solid.

According to **TP 6**, the metalation of anisole (**113**; 216 mg, 2.0 mmol) was completed using $TMP_3Al·3LiCl$ (**108**; 0.3 M solution in THF, 6.7 mL, 2.0 mmol) within 11 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (460 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 2 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 5:1) furnished the compound **115** (365 mg, 74%) as a colourless solid.

According to **TP 6**, the metalation of anisole (**113**; 216 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al·3LiCl$ (**111**; 0.3 M solution in THF, 6.7 mL, 2.0 mmol) within 9 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (460 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 2 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 5:1) furnished the compound **115** (390 mg, 79%) as a colourless solid.

m.p.: 80.9-83.2 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.73 (ddd, *J*=8.9, 2.3, 2.1 Hz, 2 H), 7.47 (dt, *J*=8.6, 1.9 Hz 1 H), 7.39 (ddd, *J*=8.8, 2.4, 2.1 Hz, 2 H), 7.35 (dd, *J*=7.4, 1.4 Hz, 1 H), 7.05 (t, *J*=7.5 Hz, 1 H), 6.98 (d, *J*=8.3 Hz, 1 H), 3.71 (s, 3 H).

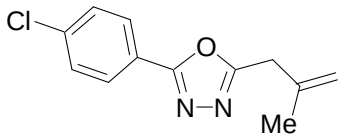
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 195.21, 157.28, 139.24, 136.24, 132.20, 131.12, 129.64, 128.51, 128.31, 120.63, 111.42, 55.54.

MS (70 eV, EI) *m/z* (%): 248 (14), 246 (35) [M^+], 231 (10), 229 (19), 211 (28), 141 (22), 139 (80), 135 (100), 121 (33), 113 (11), 111 (36), 92 813), 77 (22), 75 (15), 69 (13), 57 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2974, 2935, 2837, 1659, 1627, 1599, 1584, 1509, 1486, 1464, 1451, 1431, 1398, 1365, 1303, 1294, 1263, 1241, 1185, 1177, 1159, 1151, 1109, 1085, 1071, 1046, 1022, 1013, 972, 959, 940, 923, 859, 846, 830, 798, 766, 751, 740, 703, 683, 654, 628, 607, 600, 593, 581, 560, 554.

HRMS (EI) for **$C_{14}H_{11}ClO_2$** (246.0448): 246.0450.

Synthesis of 2-(4-chlorophenyl)-5-(2-methylallyl)-1,3,4-oxadiazole (125)



According to **TP 6**, the metalation of 2-(4-chlorophenyl)-1,3,4-oxadiazole (**124**; 362 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 4.7 mL, 1.4 mmol) within 30 min at –45 °C. $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 0.5 mL, 0.5 mmol), followed by the addition of 2-methyl allylbromide (340 mg, 2.5 mmol) and the resulting solution was stirred for 1 h at –45 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 3:1) furnished the compound **125** (347 mg, 74%) as a colourless solid.

m.p.: 82.5-84.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.95 (d, *J*=8.7 Hz, 2 H), 7.45 (d, *J*=8.7 Hz, 2 H), 4.97 (d, *J*=1.2 Hz, 1 H), 4.92 (d, *J*=1.1 Hz, 1 H), 3.63 (s, 2 H), 1.83 (s, 3 H).

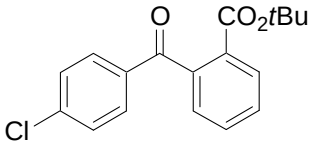
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 164.88, 164.19, 138.18, 137.82, 129.34, 128.03, 122.39, 115.01, 34.00, 22.12.

MS (70 eV, EI) *m/z* (%): 239 (30), 235 (16), 234 (100) [M^+], 233 (28), 219 (20), 196 (18), 194 (70), 140 (11), 139 (33), 137 (13), 111 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2918, 1654, 1603, 1586, 1566, 1547, 1482, 1466, 1460, 1449, 1424, 1408, 1380, 1335, 1303, 1277, 1266, 1255, 1229, 1180, 1169, 1114, 1092, 1043, 1025, 1005, 965, 913, 899, 846, 828, 806, 791, 768, 760, 740, 732, 712, 707, 694, 662, 646, 636, 630, 624, 612.

HRMS (EI) for **$C_{12}H_{11}ClN_2O$** (234.0560): 234.0553.

Synthesis of 2-(4-chlorobenzoyl)-benzoic acid *tert*-butyl ester (127a):



According to **TP 6**, the metalation of *tert*-butyl benzoate (**46a**; 356 mg, 2.0 mmol) was completed using $TMP_3Al{\cdot}3LiCl$ (**108**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 3 h at -5 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (460 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 2 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 7:1) furnished the compound **127a** (475 mg, 75%) as a colourless oil.

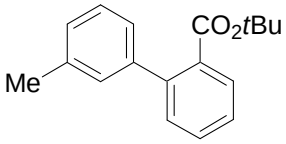
According to **TP 6**, the metalation of *tert*-butyl benzoate (**46a**; 356 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 3 h at -5 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (460 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 2 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 7:1) furnished the compound **127a** (513 mg, 81%) as a colourless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.99 (dd, *J*=7.6, 1.4 Hz, 1 H), 7.67-7.72 (m, 2 H), 7.52-7.59 (m, 2 H), 7.37-7.40 (m, 2 H), 7.31 (dd, *J*=7.5, 1.3 Hz, 1 H), 1.25 (s, 9 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ: 195.51, 164.94, 140.50, 139.47, 135.65, 131.97, 130.98, 130.86, 130.04, 129.64, 128.72, 127.38, 82.66, 27.51.

MS (70 eV, EI) *m/z* (%): 316 (3) [M^+], 262 (10), 261 (28), 260 (20), 245 (22), 244 (10), 243 (79), 182 (12), 181 (100), 152 (28), 149 (17), 138 (28), 111 (13), 57 (43).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3002, 2977, 2932, 1710, 1673, 1585, 1573, 1479, 1457, 1445, 1399, 1393, 1367, 1298, 1288, 1257, 1171, 1151, 1125, 1089, 1035, 1013, 960, 930, 885, 864, 843, 801, 776, 746, 737, 708, 685, 674, 653, 646, 636, 629, 617, 600, 582.
HRMS (EI) for **$C_{18}H_{17}ClO_3$** (316.0866): 316.0865.

Synthesis of 3'-methylbiphenyl-2-carboxylic acid *tert*-butyl ester (127b):



According to **TP 6**, the metalation of *tert*-butyl benzoate (**46a**; 356 mg, 2.0 mmol) was completed using $TMP_3Al{\cdot}3LiCl$ (**108**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 3 h at -5 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 3-iodotoluene (438 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting solution was warmed to 25 °C and stirred at 25 °C for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 50:1) furnished the compound **127b** (425 mg, 79%) as a colourless oil.

According to **TP 6**, the metalation of *tert*-butyl benzoate (**46a**; 356 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2 mmol) within 3 h at -5 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 3-iodotoluene (438 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting solution was warmed to 25 °C and stirred at 25 °C for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$.

After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 50:1) furnished the compound **127b** (413 mg, 77%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.75 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.46 (td, *J*=7.5, 1.5 Hz, 1 H), 7.37 (td, *J*=7.6, 1.4 Hz, 1 H), 7.26-7.34 (m, 2 H), 7.11-7.17 (m, 3 H), 2.37 (s, 3 H), 1.25 (s, 9 H).

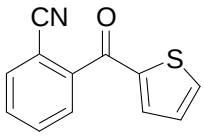
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 168.21, 142.10, 141.75, 137.33, 133.09, 130.52, 130.39, 129.46, 129.44, 127.93, 127.68, 126.96, 125.59, 81.14, 27.55, 21.35.

MS (70 eV, EI) *m/z* (%): 268 (7) [M^+], 213 (17), 212 (100), 211 (25), 195 (53), 194 (13), 165 (26), 152 (17), 58 (11), 57 (189.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976, 1704, 1598, 1476, 1446, 1392, 1366, 1296, 1246, 1172, 1126, 1102, 1092, 1050, 1036, 882, 872, 846, 790, 754, 732, 712, 700, 662, 624, 586, 574, 568.

HRMS (EI) for **$C_{18}H_{20}O_2$** (268.1463): 268.1451.

Synthesis of 2-(thiophene-2-carbonyl)benzonitrile (127c)



According to **TP 6**, the metalation of benzonitrile (**126a**; 206 mg, 2.0 mmol) was completed using $TMP_3Al{\cdot}3LiCl$ (**108**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 4 h at –10 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. Then, $CuCN{\cdot}2LiCl$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Subsequently, 2-thiophene acid chloride (365 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 5 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 2:1) furnished the compound **127c** (296 mg, 70%) as a yellowish solid.

According to **TP 6**, the metalation of benzonitrile (**126a**; 206 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 4 h at -10 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL,

2.2 mmol) was added and the mixture was stirred for 15 min. Then, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Subsequently, 2-thiophene acid chloride (365 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 5 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 2:1) furnished the compound **127c** (302 mg, 71%) as a yellowish solid.

m.p.: 88.5-90.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.75-7.85 (m, 3 H), 7.62-7.73 (m, 2 H), 7.52 (dd, *J*=3.9, 1.2 Hz, 1 H), 7.17 (dd, *J*=5.0, 3.8 Hz, 1 H).

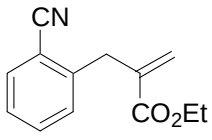
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 185.37, 142.67, 141.66, 136.16, 135.99, 134.22, 132.16, 131.28, 129.27, 128.35, 111.63.

MS (70 eV, EI) *m/z* (%): 214 (14), 213 (100) [M^+], 212 (26), 186 (10), 185 (80), 171 (60), 130 (22).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2232, 1640, 1588, 1570, 1514, 1484, 1412, 1358, 1350, 1288, 1276, 1266, 1230, 1190, 1166, 1152, 1120, 1094, 1076, 1048, 1036, 1006, 964, 918, 894, 882, 860, 844, 790, 758, 742, 720, 710, 684, 668, 644, 626, 560.

HRMS (EI) for **$C_{12}H_7NOS$** (213.0248): 213.0227.

Synthesis of 2-(2-cyanobenzyl)acrylic acid ethyl ester (127d)



According to **TP 6**, the metalation of benzonitrile (**126a**; 206 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al·3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 4 h at -10 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added, followed by the addition of ethyl 2-(bromomethyl)acrylate (483 mg, 2.5 mmol) and the resulting solution was stirred for 1 h at -30 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine

(40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 9:1) furnished the compound **127d** (297 mg, 69%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.56-7.64 (m, 1 H), 7.52-7.57 (m, 1 H), 7.28-7.37 (m, 2 H), 6.29-6.33 (m, 1 H), 5.52-5.58 (m, 1 H), 4.17 (q, *J*=7.1 Hz, 2 H), 3.85 (s, 2 H), 1.24 (t, *J*=7.2 Hz, 3 H).

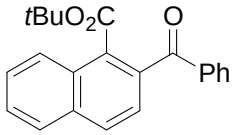
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.14, 142.56, 138.10, 132.84, 132.67, 130.13, 127.43, 126.98, 117.85, 112.93, 60.92, 36.47, 14.04.

MS (70 eV, EI) *m/z* (%): 215 (5) [M^+], 187 (16), 170 (16), 169 (15), 142 (31), 141 (100), 116 (13), 115 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984, 2950, 2908, 2226, 1712, 1634, 1600, 1486, 1466, 1448, 1434, 1406, 1368, 1328, 1302, 1276, 1254, 1198, 1178, 1138, 1094, 1024, 952, 930, 874, 858, 840, 816, 760, 718, 680, 668, 648, 624, 604, 560.

HRMS (EI) for **$C_{13}H_{13}NO_2$** (215.0946): 215.0926.

Synthesis of (1-*tert*-butylnaphthalen-2-yl)phenylmethanone (127e):



According to **TP 6**, the metalation of *tert*-butyl 1-naphthanoate (**126b**; 456 mg, 2.0 mmol) was completed using $TMP_3Al{\cdot}3LiCl$ (**108**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 6 h at –5 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $CuCN{\cdot}2LiCl$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, benzoyl chloride (354 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 8:1) furnished the compound **127e** (518 mg, 78%) as a colourless solid.

According to **TP 6**, the metalation of *tert*-butyl 1-naphthanoate (**126b**; 456 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 5 h at –5 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF,

2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, benzoyl chloride (354 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 8:1) furnished the compound **127e** (505 mg, 76%) as a colourless solid.

m.p.: 141.2-142.5 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.40 (d, *J*=8.6 Hz, 1 H), 7.98 (d, *J*=8.1 Hz, 1 H), 7.91 (d, *J*=7.2 Hz, 1 H), 7.85 (d, *J*=7.2 Hz, 2 H), 7.56-7.64 (m, 3 H), 7.42-7.49 (m, 3 H), 1.32 (s, 9 H).

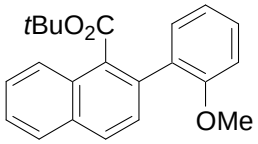
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 196.76, 166.34, 137.15, 137.09, 134.15, 133.26, 131.04, 130.35, 130.17, 129.99, 128.50, 128.29, 127.95, 127.43, 126.06, 124.39, 83.06, 27.49.

MS (70 eV, EI) *m/z* (%): 332 (34), [M^+], 277 (18), 276 (93), 260 (12), 259 (57), 233 (17), 232 (100), 231 (60), 230 (10), 203 (15), 202 (59), 201 (12), 200 (16), 199 (61), 155 (28), 127 (11), 126 (11), 105 (65), 77 (34), 57 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2974, 1722, 1670, 1594, 1578, 1568, 1504, 1466, 1448, 1428, 1392, 1378, 1366, 1314, 1304, 1284, 1244, 1170, 1154, 1132, 1076, 1064, 1048, 1036, 1024, 1000, 982, 964, 952, 938, 924, 878, 868, 852, 840, 816, 804, 794, 752, 720, 698, 686, 670, 652, 616, 598, 574, 554.

HRMS (EI) for **$C_{22}H_{20}O_3$** (332.1412): 332.1409.

Synthesis of 1-*tert*-butyl-2-(2-methoxyphenyl)naphthalene (127f):



According to **TP 6**, the metalation of *tert*-butyl 1-naphthanoate (**126b**; 456 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al·3LiCl$ (**111**; 0.30 M solution in THF, 7 mL, 2.0 mmol) within 5 h at –5 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 2-iodoanisole (515 mg, 2.2 mmol). The resulting solution was warmed to 25 °C and stirred at 25 °C for 12 h. The

reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 20:1) furnished the compound **127f** (529 mg, 79%) as a colourless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.08 (d, *J*=9.1 Hz, 1 H), 7.87 (t, *J*=8.1 Hz, 2 H), 7.48-7.55 (m, 2 H), 7.42 (d, *J*=8.6 Hz, 1 H), 7.34-7.38 (m, 1 H), 7.26 (d, *J*=1.4 Hz, 1 H), 6.96-7.02 (m, 2 H), 3.75 (s, 3 H), 1.25 (s, 9 H).

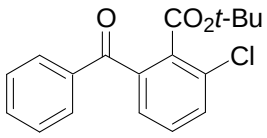
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 167.89, 156.77, 134.88, 132.53, 131.91, 131.16, 130.15, 130.00, 129.01, 128.75, 128.33, 128.05, 126.95, 126.01, 125.16, 120.31, 110.75, 81.48, 55.56, 27.64.

MS (70 eV, EI) *m/z* (%): 334 (24), 279 (12), 278 (59), 261 (17), 248 (18), 247 (100), 246 (40), 219 (11), 218 (36), 203 (16), 202 (16), 189 (19), 185 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2976, 2932, 2836, 1712, 1602, 1582, 1496, 1464, 1434, 1392, 1380, 1366, 1346, 1280, 1244, 1234, 1162, 1134, 1080, 1048, 1026, 1008, 966, 952, 934, 914, 892, 868, 846, 822, 804, 788, 750, 694, 668, 650, 624, 598, 582, 566.

HRMS (EI) for **$C_{22}H_{22}O_3$** (334.1569): 334.1567.

Synthesis of 2-benzoyl-6-chlorobenzoic acid *tert*-butyl ester (127g):



According to **TP 6**, the metalation of *tert*-butyl 2-chlorobenzoate (**126c**; 425 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 7 h at –45 °C. The reaction mixture was cooled to –60 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, benzoyl chloride (350 mg, 2.5 mmol) was added at –60 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 10 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 8:1) furnished the compound **127g** (474 mg, 75%) as a colourless solid.

m.p.: 67.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.77-7.80 (m, 2 H), 7.53-7.60 (m, 2 H), 7.43-7.47 (m, 2 H), 7.32-7.40 (m, 2 H), 1.35 (s, 9 H).

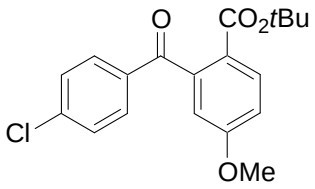
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 194.96, 164.37, 139.77, 136.60, 133.37, 132.54, 132.21, 130.12, 129.98, 129.88, 128.46, 127.16, 83.42, 27.56.

MS (70 eV, EI) *m/z* (%): 316 (1) [M^+], 263 (10), 261 (30), 245 (31), 244 (15), 243 (100), 181 (47), 152 (15), 105 (43), 77 (22), 57 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3076, 2984, 2936, 1710, 1662, 1594, 1560, 1474, 1450, 1432, 1392, 1368, 1318, 1298, 1286, 1258, 1200, 1176, 1144, 1110, 1078, 1060, 1036, 1000, 982, 956, 934, 920, 862, 842, 818, 786, 772, 746, 736, 708, 694, 668, 652, 616, 602, 578, 570, 556.

HRMS (EI) for **$C_{18}H_{17}ClO_3$** (316.0866): 316.0864.

Synthesis of 2-(4-chlorobenzoyl)-4-methoxybenzoic acid *tert*-butyl ester (127h):



According to **TP 6**, the metalation of *tert*-butyl 4-methoxybenzoate (**126d**; 416 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 10 h at –5 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (438 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 10 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 10:1) furnished the compound **127h** (395 mg, 57%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.98 (d, *J*=8.7 Hz, 1 H), 7.71 (ddd, *J*=8.7, 2.5, 2.3 Hz, 2 H), 7.39 (ddd, *J*=9.0, 2.3, 2.2 Hz, 2 H), 7.02 (dd, *J*=8.7, 2.6 Hz, 1 H), 6.78 (d, *J*=2.6 Hz, 1 H), 3.85 (s, 3 H), 1.24 (s, 9 H).

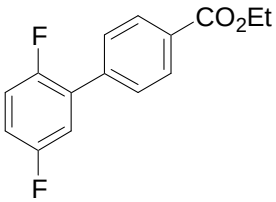
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 195.25, 164.59, 162.55, 142.71, 139.55, 135.56, 132.36, 130.89, 128.76, 122.91, 114.99, 112.44, 82.27, 55.66, 27.65.

MS (70 eV, EI) *m/z* (%): 346 (23) [M^+], 292 (30), 291 (20), 290 (100), 275 (26), 274 (12), 276 (69), 246 (18), 212 (16), 211 (73), 179 (76), 140 832), 139 (12), 139 (87), 135 (27), 134 (54), 111 (21), 58 (10), 57 (32), 44 (41).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3076, 2986, 2974, 2936, 2862, 2846, 1700, 1668, 1596, 1586, 1570, 1498, 1484, 1468, 1454, 1406, 1394, 1368, 1326, 1298, 1278, 1264, 1236, 1168, 1134, 1078, 1020, 1010, 966, 876, 864, 854, 840, 824, 784, 764, 740, 714, 684, 668, 640, 626, 604, 574, 566.

HRMS (EI) for **$C_{19}H_{19}ClO_4$** (346.0972): 346.0964.

Synthesis of 2',5'-difluorobiphenyl-4-carboxylic acid ethyl ester (127i):



According to **TP 6**, the metalation of 1,4-difluorobenzene (**126e**; 228 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 2 h at –40 °C. Then, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (607 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting solution was warmed to 25 °C and was stirred at 25 °C for 3 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 80:1) furnished the compound **127i** (413 mg, 79%) as a colourless solid.

m.p.: 48.7-49.6 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.11 (d, *J*=8.1 Hz, 2 H), 7.59 (dd, *J*=8.1, 1.4 Hz, 2 H), 7.10-7.17 (m, 2 H), 7.03 (td, *J*=8.2, 3.6 Hz, 1 H), 4.40 (q, *J*=7.2 Hz, 2 H), 1.41 (t, *J*=7.2 Hz, 3 H).

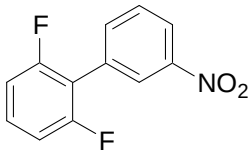
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 166.21, 158.03 (dd, J_{CF}=242, 2.7 Hz), 158.68 (dd, J_{CF}=219, 2.4 Hz), 139.10 (d, J_{CF}=1.6 Hz), 130.11, 129.75, 129.35 (d, J_{CF}=7.9 Hz), 129.25 (d, J_{CF}=7.9 Hz), 128.83 (d, J_{CF}=3.5 Hz), 117.48-115.89 (m), 61.10, 14.33.

MS (70 eV, EI) *m/z* (%): 262 (40) [M^+], 234 (27), 218 (15), 217 (100), 189 (32), 188 (35), 169 (11), 58 (27), 44 (15), 43 (67).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2998, 2990, 1712, 1668, 1610, 1592, 1570, 1518, 1494, 1482, 1466, 1442, 1400, 1382, 1370, 1318, 1304, 1276, 1246, 1222, 1182, 1126, 1118, 1100, 1036, 1020, 934, 900, 888, 872, 860, 850, 814, 780, 758, 726, 716, 698, 668, 656, 634, 614, 596, 574, 568, 556.

HRMS (EI) for **$C_{15}H_{12}F_2O_2$** (262.0805): 262.0803.

Synthesis of 2,6-difluoro-3'-nitrobiphenyl (127j):



According to **TP 6**, the metalation of 1,3-difluorobenzene (**100d**; 228 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 1.5 h at –40 °C. The reaction mixture was cooled to –50 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 3-iodo-nitrobenzene (548 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting solution was warmed to 25 °C and was stirred at 25 °C for 0.5 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 40:1) furnished the compound **127j** (398 mg, 88%) as a colourless solid.

m.p.: 119.5-120.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.36 (d, *J*=1.2 Hz, 1 H), 8.26 (ddd, *J*=8.3, 2.3, 1.2 Hz, 1 H), 7.80 (dt, *J*=7.8, 1.3 Hz, 1 H), 7.63 (t, *J*=8.0 Hz, 1 H), 7.37 (tt, *J*=8.5, 6.3 Hz, 1 H), 7.03 (m, 2 H).

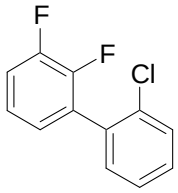
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 159.42 (d, J_{CF}=252 Hz), 159.39 (d, J_{CF}=1.6 Hz), 148.24, 136.39 (t, J_{CF}=252 Hz), 130.87, 130.23 (t, J_{CF}=10.5 Hz), 129.24, 125.43 (t, J_{CF}=2.3 Hz), 123.14, 116.13 (d, J_{CF}=18 Hz), 112.08-111.82 (m).

MS (70 eV, EI) *m/z* (%): 235 (100) [M^+], 190 (14), 189 (97), 188 (95), 177 (18), 94 (10) 57 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1626, 1590, 1572, 1528, 1492, 1468, 1426, 1350, 1308, 1280, 1268, 1224, 1102, 1090, 1072, 1034, 996, 988, 940, 902, 878, 806, 782, 742, 718, 708, 682, 658, 588, 578, 564.

HRMS (EI) for **$C_{12}H_7F_2NO_2$** (235.0445): 235.0444.

Synthesis of 2'-chloro-2,3-difluorobiphenyl (127k):



According to **TP 6**, the metalation of 1,2-difluorobenzene (**126f**; 228 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 3 h at –40 °C. The reaction mixture was cooled to –50 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 2-iodo-chlorobenzene (548 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting solution was warmed to 25 °C and was stirred at 25 °C for 1 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 1000:1) furnished the compound **127k** (399 mg, 89%) as a colourless solid.

m.p.: 50.1-50.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.48-7.51 (m, 1 H), 7.31-7.37 (m, 3 H), 7.11-7.22 (m, 2 H), 7.04-7.08 (m, 1 H).

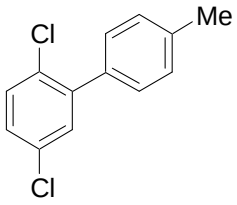
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 150.35 (dd, J_{CF}=248, 12.8 Hz), 147.45 (dd, J_{CF}=248, 12.8 Hz), 140.25, 133.73 (d, J_{CF}=2.4 Hz), 131.51 (d, J_{CF}=1.1 Hz), 129.73, 129.67, 129.22 (t, J_{CF}=7.0 Hz), 126.70, 126.30-126.24 (m), 123.78-123.66 (m), 116.90 (dd, J_{CF}=17, 1.0 Hz).

MS (70 eV, EI) *m/z* (%): 226 (35), 225 (14), 224 (100) [M^+], 189 (24), 188 (46), 169 (10), 97 (12), 91 (11), 85 (10), 71 (14), 69 (12), 57 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1934, 1626, 1588, 1566, 1494, 1476, 1458, 1434, 1420, 1388, 1336, 1314, 1264, 1218, 1194, 1166, 1128, 1110, 1058, 1046, 1030, 1006, 996, 984, 950, 898, 870, 820, 790, 758, 736, 726, 710, 658, 614, 592, 580, 554.

HRMS (EI) for **$C_{12}H_7ClF_2$** (224.0204): 224.0190.

Synthesis of 2,5-dichloro-4'-methylbiphenyl (127l):



According to **TP 6**, the metalation of 1,4-dichlorobenzene (**126g**; 294 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 3 h at –60 °C. $ZnCl_2$ (1.0 M solution in THF, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 4-iodotoluene (480 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting solution was warmed to 25 °C and was stirred at 25 °C for 2 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane) furnished the compound **127l** (403 mg, 85%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, *J*=8.6 Hz, 1 H), 7.29-7.34 (m, 3 H), 7.21-7.26 (m, 3 H), 2.41 (s, 3 H).

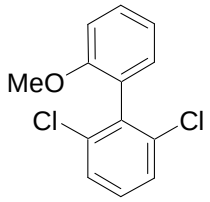
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 141.95, 137.96, 135.31, 132.50, 131.14, 130.96, 130.88, 129.11, 128.90, 128.22, 21.25.

MS (70 eV, EI) *m/z* (%): 238 (60), 237 (20), 236 (100) [M^+], 201 (23), 166 (73), 165 (85), 164 (13), 163 (13), 111 (15), 97 (25), 91 (16), 85 (25), 83 (22), 82 (18), 81 (14), 71 (32), 57 (49).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3026, 2924, 1906, 1882, 1614, 1586, 1554, 1512, 1474, 1456, 1406, 1378, 1308, 1286, 1242, 1184, 1134, 1110, 1096, 1070, 1048, 1028, 1012, 962, 948, 886, 832, 810, 778, 726, 708, 678, 668, 642, 582, 568.

HRMS (EI) for **$C_{13}H_{10}Cl_2$** (236.0160): 236.0157.

Synthesis of 2,6-dichloro-2'-methoxybiphenyl (127m):



According to **TP 6**, the metalation of 1,3-dichlorobenzene (**126h**; 294 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 4.5 h at –60 °C. $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 2-iodoanisole (514 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting solution was warmed to 25 °C and was stirred at 25 °C for 2 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 200:1) furnished the compound **127m** (396 mg, 78%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.40-7.44 (m, 1 H), 7.38 (d, *J*=8.2 Hz, 2 H), 7.21 (dd, *J*=8.4, 7.6 Hz, 1 H), 7.11-7.14 (m, 1 H), 7.00-7.07 (m, 2 H), 3.78 (s, 3 H).

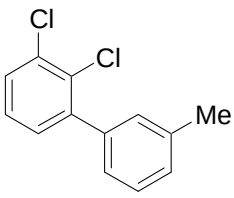
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 156.66, 136.70, 135.54, 130.74, 129.86, 128.91, 127.73, 126.09, 120.48, 111.20, 55.79.

MS (70 eV, EI) *m/z* (%): 254 (40), 252 (67) [M^+], 217 (26), 204 (28), 203 (11), 202 (100), 182 (32), 139 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2938, 2836, 1602, 1584, 1556, 1500, 1458, 1426, 1378, 1292, 1260, 1234, 1190, 1162, 1152, 1134, 1122, 1100, 1078, 1048, 1026, 1002, 968, 886, 850, 802, 784, 778, 750, 726, 678, 668, 658, 636, 586, 570, 562.

HRMS (EI) for **$C_{13}H_{10}Cl_2O$** (252.0109): 252.0099.

Synthesis of 2,3-dichloro-3'-methylbiphenyl (127n)



According to **TP 6**, the metalation of 1,2-dichlorobenzene (**126i**; 294 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 4.5 h at –60 °C. $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 3-iodotoluene (480 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting solution was warmed to 25 °C and was stirred at 25 °C for 2 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane) furnished the compound **127n** (385 mg, 81%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.44 (dd, *J*=6.0, 3.6 Hz, 1 H), 7.31 (d, *J*=7.8 Hz, 1 H), 7.18-7.24 (m, 5 H), 2.40 (s, 3 H).

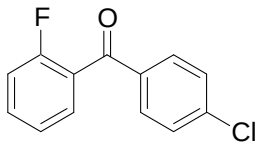
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 143.00, 139.24, 137.77, 133.50, 131.10, 129.89, 129.44, 129.28, 128.65, 127.98, 127.03, 126.31, 21.44.

MS (70 eV, EI) *m/z* (%): 240 (11), 239 (11), 238 (64), 237 (21), 236 (100) [M^+], 135 (10), 201 (22), 167 (10), 166 (68), 165 (82), 164 (12), 163 (12), 82 (17), 57 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3056, 3024, 2920, 1608, 1582, 1556, 1450, 1426, 1396, 1204, 1184, 1154, 1116, 1096, 1062, 1042, 1000, 880, 794, 776, 756, 734, 718, 702, 668, 642, 624, 614, 594, 568.

HRMS (EI) for **$C_{13}H_{10}Cl_2$** (236.0160): 236.0151.

Synthesis of (4-chlorophenyl)-(2-fluorophenyl)methanone (127o):



According to **TP 6**, the metalation of fluorobenzene (**126j**; 192 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 3 h at -10 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (460 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 12 h. The reaction mixture was

quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 30:1) furnished the compound **127o** (313 mg, 67%) as a colourless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.77 (dd, *J*=8.6, 1.2 Hz, 2 H), 7.52-7.56 (m, 2 H), 7.44 (ddd, *J*=8.8, 2.3, 2.1 Hz, 2 H), 7.27 (td, *J*=7.5, 1.0 Hz, 1 H), 7.16 (t, *J*=8.9 Hz, 1 H).

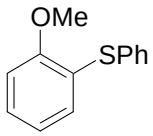
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 192.19, 160.00 (d, $^1J_{CF}$=252 Hz), 139.91, 135.75, 133.37 (d, $^3J_{CF}$=8.4 Hz), 131.13 (d, J_{CF}=1.3 Hz), 130.73 (d, $^4J_{CF}$=2.7 Hz), 128.82, 126.55 (d, $^2J_{CF}$=15 Hz), 125.44 (d, $^4J_{CF}$=3.7 Hz), 116.33 (d, $^2J_{CF}$=22 Hz).

MS (70 eV, EI) *m/z* (%): 236 (12), 234 (36) [M^+], 228 (18), 199 (32), 170 (14), 141 (37), 139 (100), 123 (44), 111 (32), 97 (12), 95 (14), 83 (13), 81 (11), 74 (23), 59 (37).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2927, 1662, 1610, 1587, 1572, 1481, 1450, 1400, 1302, 1293, 1283, 1267, 1250, 1217, 1176, 1159, 1146, 1100, 1089, 1033, 1014, 981, 952, 928, 844, 823, 813, 772, 752, 742, 722, 701, 676, 649, 629, 612, 607, 585, 576, 569.

HRMS (EI) for **$C_{13}H_8ClFO$** (234.0248): 234.0235.

Synthesis of 1-methoxy-2-(phenylthio)benzene (129a):



According to **TP 6**, the metalation of anisole (**115**; 216 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 9 h at 25 °C. $PhSSO_2Ph$ (1.12 mg, 4.4 mmol) was added and the reaction mixture was stirred for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 35:1) furnished the compound **129a** (390 mg, 65%) as a colourless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.34 (dt, *J*=8.3, 1.7 Hz, 2 H), 7.30 (td, *J*=6.6, 1.8 Hz, 2 H), 7.22-7.26 (m, 2 H), 7.08 (dd, *J*=7.9, 1.7 Hz, 1 H), 6.85-6.91 (m, 2 H), 3.86 (s, 3 H).

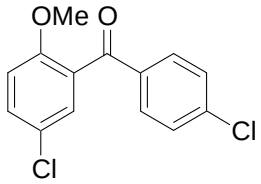
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 157.28, 134.46, 131.58, 131.45, 129.11, 128.30, 127.03, 124.06, 121.21, 110.83, 55.86.

MS (70 eV, EI) *m/z* (%): 217 (16), 216 (100), 171 (10), 168 (13), 129 (11), 97 (12), 91 (13), 83 (14), 81 (11), 74 (11), 71 (14), 69 (18), 59 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3057, 3002, 2934, 2834, 1713, 1577, 1474, 1461, 1447, 1438, 1431, 1293, 1273, 1239, 1180, 1161, 1130, 1084, 1064, 1041, 1022, 999, 919, 899, 896, 846, 798, 791, 739, 705, 689, 680, 637, 626, 616, 608, 576, 553.

HRMS (EI) for **$C_{13}H_{12}OS$** (216.0609): 216.0596.

Synthesis of (5-chloro-2-methoxyphenyl)-(4-chlorophenyl)methanone (129b):



According to **TP 6**, the metalation of 4-chloroanisole (**102a**; 285 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 4 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (460 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 15:1) furnished the compound **129b** (480 mg, 85%) as a colourless solid.

m.p.: 88.0-89.7 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.68-7.72 (m, 2 H), 7.36-7.40 (m, 3 H), 7.28-7.30 (m, 1 H), 6.90 (d, *J*=8.8 Hz, 1 H), 3.67 (s, 3 H).

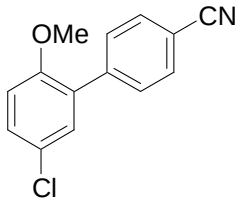
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 193.46, 155.68, 139.57, 135.50, 131.65, 130.98, 129.51, 129.09, 128.59, 125.73, 112.76, 55.81.

MS (70 eV, EI) *m/z* (%): 284 (10), 282 (45), 281 (13), 280 (64), 265 (17), 263 (25), 247 (10), 227 (10), 209 (11), 171 (27), 169 (98), 157 (28), 155 (80), 141 (32), 139 (100), 126 823), 113 (23), 111 (76), 76 (11), 75 (30).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3086, 3070, 3056, 3008, 2935, 2892, 2833, 1721, 1656, 1633, 1598, 1584, 1566, 1483, 1466, 1451, 1443, 1404, 1397, 1336, 1304, 1294, 1273, 1262, 1242, 1177, 1160, 1137, 1125, 1111, 1091, 1016, 977, 954, 935, 908, 899, 887, 852, 819, 772, 745, 733, 698, 687, 667, 641, 632, 604, 573.

HRMS (EI) for **$C_{14}H_{10}Cl_2O_2$** (280.0058): 280.0047.

Synthesis of 5'-chloro-2'-methoxybiphenyl-4-carbonitrile (129c):



According to **TP 6**, the metalation of 4-chloroanisole (**102a**; 285 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 4 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 4-iodobenzonitrile (504 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting mixture was warmed to 25 °C and was stirred at 25 °C for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 4:1) furnished the compound **129c** (380 mg, 82%) as a colourless solid.

m.p.: 110.0-111.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.66-7.71 (m, 2 H), 7.57-7.61 (m, 2 H), 7.32 (dd, *J*=8.8, 2.6 Hz, 1 H), 7.26 (d, *J*=2.6 Hz, 1 H), 6.92 (d, *J*=8.8 Hz, 1 H), 3.80 (s, 3 H).

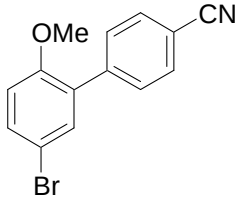
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 154.98, 141.95, 131.85, 130.27, 130.12, 129.38, 129.36, 125.99, 118.89, 112.66, 111.06, 55.90.

MS (70 eV, EI) *m/z* (%): 245 (38), 243 (100) [M^+], 228 (20), 194 (12), 193 (91), 164 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3006, 2984, 2956, 2846, 2360, 2228, 1714, 1608, 1598, 1512, 1484, 1456, 1442, 1416, 1390, 1368, 1312, 1268, 1238, 1180, 1142, 1102, 1034, 1022, 968, 948, 936, 926, 878, 858, 838, 824, 802, 776, 740, 724, 694, 662, 644, 586, 574.

HRMS (EI) for **$C_{14}H_{10}ClNO$** (243.0451): 243.0438.

Synthesis of 5'-bromo-2'-methoxybiphenyl-4-carbonitrile (129d):



According to **TP 6**, the metalation of 4-bromoanisole (**102c**; 374 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 5 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 4-iodobenzonitrile (504 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting mixture was warmed to 25 °C and was stirred at 25 °C for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 4:1) furnished the compound **129d** (444 mg, 77%) as a colourless solid.

m.p.: 114.0-116.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, *J*=8.6 Hz, 2 H), 7.59 (d, *J*=8.6 Hz, 2 H), 7.46 (dd, *J*=8.8, 2.6 Hz, 1 H), 7.40 (d, *J*=2.4 Hz, 1 H), 6.87 (d, *J*=8.6 Hz, 1 H), 3.79 (s, 3 H).

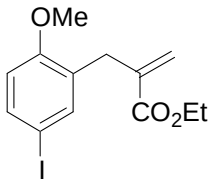
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.44, 141.80, 133.04, 132.34, 131.81, 130.51, 130.10, 118.87, 113.15, 113.08, 111.01, 55.81.

MS (70 eV, EI) *m/z* (%): 289 (49), 287 (50) [M^+], 194 (17), 193 (100), 164 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2224, 1606, 1486, 1474, 1461, 1436, 1385, 1291, 1268, 1239, 1229, 1177, 1140, 1112, 1092, 1078, 1027, 1017, 974, 959, 940, 905, 847, 840, 827, 814, 776, 746, 734, 726, 710, 702, 688, 659, 646, 638, 624, 612, 602.

HRMS (EI) for **$C_{14}H_{10}BrNO$** (286.9946): 286.9940.

Synthesis of 2-(5-iodo-2-methoxybenzyl)acrylic acid ethyl ester (129e)



According to **TP 6**, the metalation of 4-iodoanisole (**128a**; 468 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 8 h at 25 °C. The reaction mixture was cooled to 0 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 0.5 mL, 0.5 mmol), followed by the addition of ethyl 2-(bromomethyl)acrylate (483 mg, 2.5 mmol) and the resulting solution was stirred for 1 h at 0 °C. The reaction mixture was

quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and aq. HCl (2 M, 5 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 40:1) furnished the compound **129e** (512 mg, 73%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.52 (dd, *J*=8.6, 2.3 Hz, 1 H), 7.37 (d, *J*=2.3 Hz, 1 H), 6.82 (d, *J*=8.6 Hz, 1 H), 6.10 (d, *J*=1.4 Hz, 1 H), 5.41 (q, *J*=1.5 Hz, 1 H), 4.12 (q, *J*=7.2 Hz, 2 H), 3.73 (s, 3 H), 3.48 (s, 2 H), 1.19 (t, *J*=7.1 Hz, 3 H).

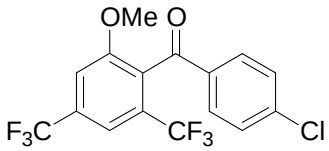
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.01, 157.04, 138.35, 137.98, 136.23, 129.54, 126.02, 113.59, 82.85, 60.37, 55.48, 31.02, 13.98.

MS (70 eV, EI) *m/z* (%): 347 (16), 346 (100), [M^+], 324 (19), 315 (39), 309 (14), 300 (15), 287 (23), 272 (49), 257 (48), 233 (11), 174 (22), 146 (14), 145 (15), 131 (24), 115 (13), 103 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976, 2936, 2904, 2836, 1712, 1631, 1587, 1486, 1462, 1440, 1397, 1367, 1301, 1275, 1245, 1198, 1173, 1132, 1119, 1026, 946, 880, 852, 804, 754, 733, 725, 688, 670, 659, 653, 647, 636, 625, 616, 608.

HRMS (EI) for **$C_{13}H_{15}IO_3$** (346.0066): 346.0058.

Synthesis of (4-chlorophenyl)-[2-methoxy-4,6-*bis*-(trifluoromethyl)phenyl]methanone (129f):



According to **TP 6**, the metalation of 3,5-*bis*-trifluoromethylanisole (**128b**; 520 mg, 2 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 1 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (460 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 2 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified

by column chromatography (pentane/diethyl ether = 19:1) to give **129f** (633 mg, 83%) as a colourless solid.

m.p.: 107.2 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 7.86 (s, 1 H), 7.79 (s, 1 H), 7.74 (ddd, *J*=9.0, 2.4, 2.2 Hz, 2 H), 7.60 (ddd, *J*=9.0, 2.3, 2.2 Hz, 2 H), 3.83 (s, 3 H).

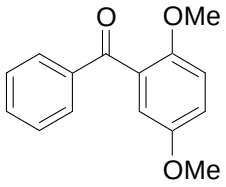
^{13}C-NMR (100 MHz, DMSO) δ: 191.39, 157.44, 139.49, 134.30 (q, J_{CF}=2.0 Hz), 132.12 (q, $^2J_{CF}$=32 Hz), 130.69, 129.96, 129.34, 128.20 (q, $^2J_{CF}$=33 Hz), 122.94 (q, $^1J_{CF}$=273 Hz), 122.58 (q, $^1J_{CF}$=273 Hz), 114.97, (m), 113.44, 57.19.

MS (70 eV, EI) *m/z* (%): 384 (10), 382 (30) [M^+], 270 (63), 256 (23), 250 (12), 141 (35), 139 (100), 111 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1684, 1623, 1483, 1462, 1429, 1401, 1368, 1306, 1275, 1249, 1202, 188, 1157, 1122, 1101, 1041, 1033, 1014, 929, 889, 881, 870, 858, 841, 770, 760, 727, 688, 676, 650, 610, 605.

HRMS (EI) for **$C_{16}H_9ClF_6O_2$** (382.0195): 382.0191.

Synthesis of (2,5-dimethoxyphenyl)phenylmethanone (129g)



According to **TP 6**, the metalation of 1,4-dimethoxybenzene (**128c**; 276 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 15 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, benzoyl chloride (350 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 9:1) furnished the compound **129g** (325 mg, 75%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.81 (dd, *J*=8.5, 1.2 Hz, 2 H), 7.51-7.58 (m, 1 H), 7.42 (t, *J*=7.5 Hz, 2 H), 6.97-7.03 (m, 1 H), 6.90-6.94 (m, 2 H), 3.78 (s, 3 H), 3.65 (s, 3 H).

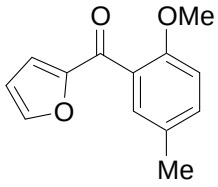
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 196.10, 153.47, 151.47, 137.62, 132.95, 129.80, 129.51, 128.20, 117.32, 114.43, 113.09, 56.33, 55.84.

MS (70 eV, EI) *m/z* (%): 243 (19), 242 (100) [M^+], 227 (18), 225 (24), 184 (14), 165 (64), 151 (63), 105 (41), 77 (51), 51 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3092, 3056, 2918, 2850, 2836, 1660, 1630, 1614, 1596, 1580, 1558, 1522, 1494, 1464, 1448, 1410, 1348, 1326, 1304, 1280, 1242, 1220, 1176, 1144, 1136, 1114, 1100, 1090, 1074, 1066, 1044, 1020, 1002, 966, 942, 920, 902, 884, 838, 814, 758, 732, 702, 686, 668, 642, 626, 598, 572.

HRMS (EI) for **$C_{15}H_{14}O_3$** (242.0943): 242.0936.

Synthesis of (2,5-dimethoxyphenyl)furan-2-ylmethanone (129h)



According to **TP 6**, the metalation of 4-methylanisole (**128d**; 244 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 6 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 2-furoyl chloride (327 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 5:1) furnished the compound **129h** (325 mg, 75%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.62 (d, *J*=1.7 Hz, 1 H), 7.21 (t, *J*=2.4 Hz, 2 H), 7.02 (d, *J*=3.4 Hz, 1 H), 6.88 (d, *J*=8.3 Hz, 1 H), 6.51 (dd, *J*=3.4, 1.7 Hz, 1 H), 3.76 (s, 3 H), 2.30 (s, 3 H).

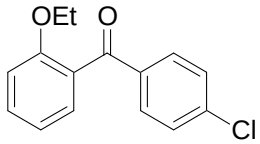
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 183.20, 155.38, 153.05, 146.98, 132.59, 129.85, 129.65, 127.80, 120.21, 112.12, 111.64, 55.88, 20.30.

MS (70 eV, EI) *m/z* (%): 217 (15), 216 (100) [M^+], 200 (10), 199 (72), 188 (18), 187 (69), 185 (10), 171 (30), 149 (73), 145 (16), 135 (44), 134 (11), 128 (12), 119 (20), 115 (15), 106 (17), 105 (11), 95 (42), 91 (43), 89 (10), 78 (15), 77 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984, 2910, 1716, 1652, 1610, 1556, 1496, 1484, 1464, 1444, 1408, 1388, 1364, 1350, 1328, 1314, 1272, 1186, 1166, 1136, 1126, 1102, 1060, 1040, 1016, 970, 924, 918, 882, 858, 840, 826, 810, 772, 750, 720, 700, 672, 654, 638, 612, 590, 574.

HRMS (EI) for **$C_{13}H_{12}O_3$** (216.0786): 216.0773.

Synthesis of (4-chlorophenyl)-(2-ethoxyphenyl)methanone (129i):



According to **TP 6**, the metalation of phenetole (**128e**; 244 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 20 mmol) within 10 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (438 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 2 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 19:1) furnished the compound **129i** (445 mg, 85%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.71 (ddd, *J*=8.9, 2.3, 2.2 Hz, 2 H), 7.36-7.48 (m, 4 H), 6.99-7.06 (m, 1 H), 6.94 (d, *J*=8.5 Hz, 1 H), 3.94 (q, *J*=6.9 Hz, 2 H), 1.08 (t, *J*=6.9 Hz, 3 H).

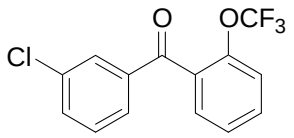
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 195.49, 156.76, 138.90, 136.72, 132.28, 130.92, 129.76, 128.55, 128.34, 120.62, 112.36, 63.97, 14.28.

MS (70 eV, EI) *m/z* (%): 262 (10), 261 (22), 260 (25) [M^+], 242 (10), 233 (12), 231 (29), 225 (15), 197 (20), 181 (20), 149 (14), 139 (35), 121 (100), 120 (13), 111 (20), 73 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 1658, 1598, 1586, 1486, 1474, 1448, 1398, 1368, 1304, 1294, 1236, 1174, 1162, 1152, 1118, 1088, 1040, 1014, 970, 930, 916, 844, 802, 752, 744, 730, 682, 660, 628, 606, 578, 556.

HRMS (EI) for **$C_{15}H_{13}ClO_2$** (260.0604): 260.0585.

Synthesis of (3-chlorophenyl)-(2-trifluoromethoxyphenyl)methanone (129j)



According to **TP 6**, the metalation of trifluoromethoxybenzene (**128f**; 324 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 3 h at 0 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 3-chlorobenzoyl chloride (438 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 2 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 19:1) furnished the compound **129j** (486 mg, 81%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.76 (t, J=1.9 Hz, 1 H), 7.54-7.65 (m, 3 H), 7.48-7.52 (m, 1 H), 7.42-7.45 (m, 1 H), 7.34-7.40 (m, 2 H).

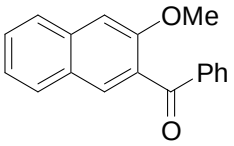
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 192.51, 146.34 (q, J_{CF}=2.1 Hz), 138.56, 134.84, 133.43, 132.39, 130.17, 129.81, 129.53, 127.92, 126.91, 121.28 (q, J_{CF}=1.3 Hz), 121.16 (q, $^1J_{CF}$=259 Hz).

MS (70 eV, EI) *m/z* (%): 302 (21), 301 (14), 300 (59) [M^+], 190 (11), 189 (88), 141 (30), 139 (100), 123 (24), 111 (37), 95 (31), 75 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1674, 1606, 1592, 1572, 1488, 1470, 1450, 1424, 1294, 1248, 1204, 1160, 1104, 1076, 1042, 1000, 962, 954, 944, 922, 898, 806, 768, 754, 726, 702, 686, 674, 640, 624, 598, 586, 568, 560.

HRMS (EI) for **$C_{14}H_8ClF_3O_2$** (300.0165): 300.0167.

Synthesis of (3-methoxynaphthalen-2-yl)phenylmethanone (129k)



According to **TP 6**, the metalation of 2-methoxynaphthalene (**128g**; 316 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 9 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF,

2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, benzoyl chloride (350 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and aq. HCl (2 M, 5 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 10:1) furnished the compound **129k** (410 mg, 78%) as a yellowish solid.

m.p.: 68.6 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.89 (d, *J*=7.2 Hz, 2 H), 7.88 (s, 1 H), 7.80 (d, *J*=8.6 Hz, 2 H), 7.57 (t, *J*=7.4 Hz, 1 H), 7.53 (t, *J*=7.6 Hz, 1 H), 7.45 (t, *J*=7.9 Hz, 2 H), 7.40 (t, *J*=7.4 Hz, 1 H), 7.27 (s, 1 H), 3.84 (s, 3 H).

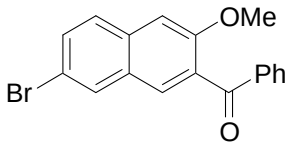
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 195.93, 154.94, 137.62, 135.26, 133.01, 130.46, 129.81, 129.50, 128.25, 128.18, 127.85, 127.61, 126.54, 124.34, 106.07, 55.49.

MS (70 eV, EI) *m/z* (%): 263 (21), 262 (95) [M^+], 245 (17), 244 (10), 186 (13), 185 (81), 172 (11), 171 (100), 142 (11), 127 (39), 114 (12), 105 (32), 77 (42), 44 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3078, 3032, 3008, 2960, 2944, 2834, 1658, 1628, 1596, 1578, 1540, 1500, 1466, 1450, 1430, 1384, 1370, 1358, 1332, 1272, 1250, 1230, 1216, 1192, 1174, 1142, 1098, 1074, 1020, 980, 950, 940, 906, 890, 860, 830, 816, 786, 760, 746, 734, 718, 702, 686, 672, 632, 622, 588, 564, 554.

HRMS (EI) for **$C_{18}H_{14}O_2$** (262.0994): 262.0986.

Synthesis of (7-bromo-3-methoxynaphthalen-2-yl)phenylmethanone (129l)



According to **TP 6**, the metalation of 6-bromo-2-methoxynaphthalene (**128h**; 468 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al·3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 8 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, benzoyl chloride (350 mg, 2.5 mmol) was added at –30 °C. The

resulting solution was slowly warmed to 25 °C and stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and aq. HCl (2 M, 5 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 10:1) furnished the compound **129l** (525 mg, 77%) as a yellowish solid.

m.p.: 108.8-109.5 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.94 (d, *J*=1.9 Hz, 1 H), 7.82 (d, *J*=7.2 Hz, 2 H), 7.71 (s, 1 H), 7.66 (d, *J*=9.1 Hz, 1 H), 7.55-7.59 (m, 2 H), 7.43 (t, *J*=7.9 Hz, 2 H), 7.19 (s, 1 H), 3.83 (s, 3 H)

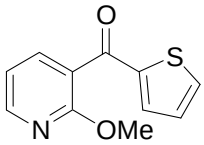
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 195.56, 155.33, 137.40, 133.75, 133.31, 131.58, 130.94, 130.24, 129.91, 129.03, 128.43, 128.36, 128.25, 117.93, 106.15, 55.68.

MS (70 eV, EI) *m/z* (%): 342 (81), 340 (85) [M^+], 265 (38), 263 (38), 251 (81), 249 (83), 126 (31), 111 (23), 105 (53), 99 (20), 97 (40), 95 (23), 85 (41), 83 (36), 82 (21), 81 (27), 77 (42), 71 (66), 70 (23), 69 (54), 57 (100), 55 (42).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2974, 2938, 1662, 1622, 1588, 1580, 1490, 1458, 1448, 1410, 1384, 1360, 1314, 1302, 1252, 1208, 1174, 1160, 1144, 1106, 1090, 1062, 1026, 1018, 944, 918, 898, 866, 848, 820, 804, 796, 754, 734, 692, 638, 606, 570.

HRMS (EI) for **$C_{18}H_{13}BrO_2$** (340.0099): 340.0092.

Synthesis of (2-methoxypyridin-3-yl)thiophen-2-ylmethanone (129m)



According to **TP 6**, the metalation of 2-methoxypyridine (**128i**; 324 mg, 2.0 mmol) was completed using $TMP_3Al{\cdot}3LiCl$ (**108**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 3.5 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 2-thiophene acid chloride (365 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 2 h. The reaction mixture was quenched with a sat. aq. $NaHCO_3$ solution (50 mL) and extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and

with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 4:1) furnished the compound **129m** (355 mg, 81%) as a yellowish solid.

According to **TP 6**, the metalation of 2-methoxypyridine (**128i**; 324 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 3 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 2-thiophene acid chloride (365 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 2 h. The reaction mixture was quenched with a sat. aq. $NaHCO_3$ solution (50 mL) and extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 4:1) furnished the compound **129m** (373 mg, 85%) as a yellowish solid.

m.p.: 64.1-65.0 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.30 (dd, *J*=5.2, 1.9 Hz, 1 H), 7.70-7.75 (m, 2 H), 7.47 (d, *J*=3.8 Hz, 1 H), 7.09-7.13 (m, 1 H), 6.98 (dd, *J*=7.2, 5.2 Hz, 1 H), 3.94 (s, 3 H).

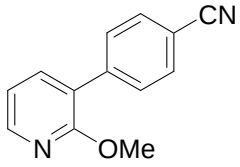
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 186.33, 160.80, 149.10, 144.17, 138.30, 135.06, 135.02, 128.10, 122.61, 116.24, 53.82.

MS (70 eV, EI) *m/z* (%): 219 (51) [M^+], 218 (10), 188 (13), 186 (14), 136 (21), 122 (400), 111 (100), 97 (12), 78 (18), 45 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3096, 1632, 1600, 1584, 1576, 1540, 1516, 1462, 1408, 1398, 1352, 1306, 1294, 1256, 1234, 1178, 1148, 1104, 1074, 1064, 1046, 1012, 982, 960, 888, 852, 826, 800, 776, 760, 738, 726, 696, 668, 652, 608, 570, 560.

HRMS (EI) for **$C_{11}H_9NO_2S$** (219.0354): 219.0339.

Synthesis of 4-(2-methoxypyridin-3-yl)benzonitrile (129n)



According to **TP 6**, the metalation of 2-methoxypyridine (**128ip**; 324 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within

3 h at 25 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 4-iodobenzonitrile (504 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting mixture was warmed to 25 °C and was stirred at 25 °C for 12 h. The reaction mixture was quenched with a sat. aq. $NaHCO_3$ solution (50 mL) and extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 4:1) furnished the compound **129n** (344 mg, 82%) as a yellowish solid.

m.p.: 124.7 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.21 (dd, *J*=5.2, 1.9 Hz, 1 H), 7.65-7.71 (m, 4 H), 7.61 (dd, *J*=7.6, 1.9 Hz, 1 H), 7.01 (dd, *J*=7.4, 5.0 Hz, 1 H), 3.98 (s, 3 H).

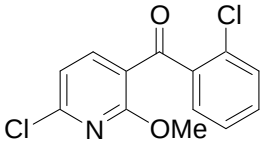
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 160.58, 147.01, 141.51, 138.63, 131.98, 129.83, 122.70, 118.86, 117.24, 111.13, 53.72.

MS (70 eV, EI) *m/z* (%): 210 (60) [M^+], 209 (100), 193 (20), 191 (15), 181 (14), 179 (30), 146 (31), 140 (12), 132 (11), 131 (77), 103 (35), 91 (129, 77 (26), 58 (28), 43 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3062, 3024, 2998, 2956, 2902, 2224, 1734, 1636, 1606, 1582, 1462, 1450, 1444, 1412, 1396, 1340, 1312, 1290, 1250, 1224, 1204, 1184, 1174, 1156, 1112, 1078, 1016, 1000, 984, 972, 946, 914, 892, 854, 828, 788, 770, 742, 730, 704, 684, 668, 650, 610, 592, 574, 564.

HRMS (EI) for **$C_{13}H_{10}N_2O$** (210.0793): 210.0786.

Synthesis of (6-chloro-2-methoxypyridin-3-yl)-(2-chlorophenyl)methanone (129o)



According to **TP 6**, the metalation of 6-chloro-2-methoxypyridine (**128j**; 283 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 3.5 h at 0 °C. The reaction mixture was cooled to –30 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 2-chlorobenzoyl chloride (460 mg, 2.5 mmol) was added at –30 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 4 h. The

reaction mixture was quenched with a sat. aq. $NaHCO_3$ solution (50 mL) and extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 14:1) furnished the compound **129o** (507 mg, 90%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.95 (d, *J*=8.0 Hz, 1 H), 7.31-7.44 (m, 4 H), 7.01 (d, *J*=8.0 Hz, 1 H), 3.80 (s, 3 H).

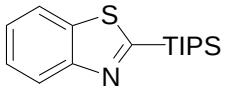
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 192.27, 161.68, 152.71, 142.72, 139.35, 131.59, 131.31, 129.76, 129.48, 126.83, 120.03, 116.94, 54.57.

MS (70 eV, EI) *m/z* (%): 283 (28), 282 (14), 281 (47) [M^+], 248 (14), 246 (34), 172 (37), 170 (100), 156 (25), 141 (16), 139 (48), 111 (19), 102 (11), 73 (21), 57 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 1656, 1574, 1558, 1462, 1432, 1422, 1374, 1290, 1272, 1264, 1160, 1134, 1094, 1054, 1010, 930, 888, 828, 786, 766, 742, 706, 686, 642, 618.

HRMS (EI) for **$C_{13}H_9Cl_2NO_2$** (281.0010): 280.9999.

Synthesis of 2-triisopropylsilanylbenzothiazole (130a):



A dry and argon flushed 100-mL Schlenk-Tube, equipped with a magnetic stirring bar was charged with a solution of the benzothiazole (20 mmol, 2.68 g) in dry THF (20 mL) and then cooled to –70 °C. A freshly prepared LDA solution (1 M in THF/*n*-hexane, 20 mL, 20.0 mmol) was added dropwise and the reaction mixture was stirred for 0.5 h at this temperature. Then, TIPSCl (30 mmol, 5.8 g) was added and the reaction mixture was stirred for 2 h at –78 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (50 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 200:1) furnished the compound **130a** (5.00 g, 86%) slightly yellow oil.

^{1}H-NMR (400 MHz, DMSO) δ: 8.16 (d, *J*=8.0 Hz, 2 H), 7.45-7.55 (m, 2 H), 1.47 (dt, *J*=15.0, 7.5 Hz, 3 H), 1.13 (d, *J*=7.4 Hz, 18 H).

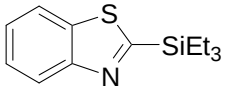
^{13}C-NMR (100 MHz, DMSO) δ: 171.74, 155.26, 135.13, 125.92, 125.38, 123.03, 121.95, 18.26, 11.05.

MS (70 eV, EI) *m/z* (%): 291 (26), [M^+], 250 (22), 249 (77), 248 (100), 220 (20), 207 (16), 206 (33), 192 (18), 178 (23), 164 (11), 162 (9), 151 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2942, 2892, 2864, 1464, 1456, 1426, 1316, 1292, 1276, 1256, 1248, 1072, 1014, 994, 918, 880, 824, 804, 756, 728, 674, 658, 646, 602, 580, 574, 556.

HRMS (EI) for **$C_{16}H_{25}NSSi$** (291.1477): 291.1475.

Synthesis of 2-triethylsilanylbenzothiazole (130b):



A dry and argon flushed 100-mL Schlenk-Tube, equipped with a magnetic stirring bar was charged with a solution of the benzothiazole (20 mmol, 2.68 g) in dry THF (20 mL) and then cooled to 0 °C. Freshly titrated TMPMgCl·LiCl (1 M in THF, 22 mL, 22.0 mmol) was added dropwise and the reaction mixture was stirred for 1 h. Then, Et_3SiCl (30 mmol, 4.5 g) was added and the reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (50 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (Al_2O_3; pentane/diethyl ether = 100:1) furnished the compound **130b** (4.18 g, 84 %) slightly yellow oil.

^{1}H-NMR (400 MHz, DMSO) δ: 8.12 (d, *J*=7.8 Hz, 2 H), 7.46 (dd, *J*=16.6, 7.9 Hz, 2 H), 0.76-1.08 (m, 15 H).

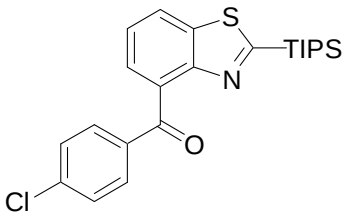
^{13}C-NMR (100 MHz, DMSO) δ: 171.72, 155.51, 135.31, 125.92, 125.31, 122.98, 122.01, 7.03, 3.13.

MS (70 eV, EI) *m/z* (%): 249 (4) [M^+], 222 (20), 221 (100), 220 (34), 192.900 (38), 165 (28), 137 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2940, 2884, 2861, 1462, 1457, 1423, 1314, 1290, 1273, 1258, 1247, 1072, 1013, 991, 919, 878, 827, 803, 759, 730, 675, 660, 648, 600, 582, 575, 557.

HRMS (EI) for **$C_{13}H_{19}NSSi$** (249.1007): 249.0999.

Synthesis of (4-chlorophenyl)-(2-triisopropylsilanylbenzothiazol-4-yl)methanone (132a):



According to **TP 6**, the metalation of 2-triisopropylsilanyl-benzothiazole (**130a**; 216 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al·3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL,

2.0 mmol) within 12 h at 25 °C. The reaction mixture was cooled to –10 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (438 mg, 2.5 mmol) was added at -10 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 7 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 35:1) furnished the compound **132a** (715 mg, 83%) as a yellow oil.

^{1}H-NMR (400 MHz, DMSO) δ: 8.44 (dd, *J*=8.0, 1.2 Hz, 1 H), 7.74-7.78 (m, 1 H), 7.60-7.69 (m, 3 H), 7.47-7.51 (m, 2 H), 1.18-1.28 (m, 3 H), 0.96 (d, *J*=7.4 Hz, 18 H).

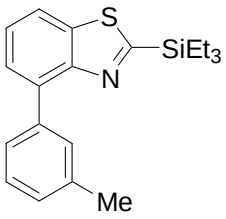
^{13}C-NMR (100 MHz, DMSO) δ: 194.95, 173.54, 152.12, 137.80, 136.85, 135.80, 132.84, 131.15, 128.44, 126.11, 125.48, 125.30, 18.05, 10.89.

MS (70 eV, EI) *m/z* (%): 429 (8) [M^+], 389 (23), 388 (47), 387 (55), 386 (100), 344 (9), 302 (9), 258 (11), 150 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2942, 2890, 2866, 1660, 1588, 1574, 1486, 1462, 1436, 1398, 1390, 1368, 1306, 1286, 1238, 1204, 1174, 1160, 1146, 1106, 1090, 1070, 1016, 1002, 986, 970, 936, 882, 852, 816, 792, 758, 744, 724, 680, 650.

HRMS (EI) for **$C_{23}H_{28}ClNOSSi$** (429.1349): 429.1346.

Synthesis of 4-*m*-tolyl-2-triethylsilanyl-benzothiazole (132b)



According to **TP 6**, the metalation of 2-triethylsilanyl-benzothiazole (**130b**; 499 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al·3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 12 h at 25 °C. The reaction mixture was cooled to –10 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 3-iodotoluene (480 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting solution was warmed to 25 °C

and was stirred at 25 °C for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (Al_2O_3; pentane/diethyl ether = 100:1) furnished the compound **132b** (564 mg, 81%) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.13 (dd, *J*=6.7, 1.1 Hz, 1 H), 7.82 (s, 1 H), 7.69 (d, *J*=7.5 Hz, 1 H), 7.64 (dd, *J*=6.5, 1.1 Hz, 1 H), 7.54 (t, *J*=7.7 Hz, 1 H), 7.36 (t, *J*=7.7 Hz, 1 H), 7.21 (d, *J*=7.5 Hz, 1 H), 2.37 (s, 3 H), 1.03 (m, 9 H), 0.89 (m, 6 H).

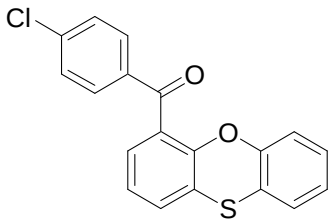
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 172.86, 152.70, 138.27, 136.95, 136.54, 135.17, 130.46, 128.13, 127.95, 126.41, 125.66, 125.57, 121.15, 21.04, 7.05, 3.25.

MS (70 eV, EI) *m/z* (%): 339 (8) [M^+], 213 (25), 311 (100), 310 (38), 283 (22), 255 (11), 252 (27), 127 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3056, 2952, 2934, 2910, 2874, 1606, 1588, 1572, 1490, 1456, 1412, 1378, 1314, 1302, 1284, 1236, 1210, 1180, 1158, 1096, 1062, 1008, 984, 968, 948, 908, 898, 880, 868, 846, 800, 768, 754, 736, 720, 698, 654.

HRMS (EI) for **$C_{20}H_{25}NSSi$** (339.1477): 339.1470.

Synthesis of (4-chlorophenyl)phenoxathiin-4-ylmethanone (134):



According to **TP 6**, the metalation of phenoxathiine (**133**; 400 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 12 h at 25 °C. The reaction mixture was cooled to –10 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (438 mg, 2.5 mmol) was added at –10 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 7 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography

(pentane/diethyl ether = 30:1) furnished the compound **134** (523 mg, 77%) as a yellowish solid.

m.p.: 83.2-84.7 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 7.73 (ddd, J=8.9, 2.4, 2.2 Hz, 2 H), 7.57-7.61 (m, 2 H), 7.50-7.54 (m, 1 H), 7.34-7.37 (m, 1 H), 7.25-7.30 (m, 2 H), 7.07-7.12 (m, 2 H), 6.11-6.16 (m, 1 H).

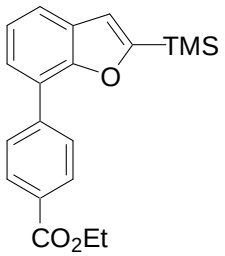
^{13}C-NMR (100 MHz, DMSO) δ: 193.12, 150.62, 148.72, 138.51, 135.88, 130.85, 129.54, 129.01, 128.38, 128.30, 127.67, 127.11, 125.52, 125.18, 121.22, 119.46, 117.21.

MS (70 eV, EI) *m/z* (%): 340 (39), 339 (21), 338 (100) [M^+], 227 (29), 199 (11), 171 (14), 141 (13), 139 (38), 111 (17), 44 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3066, 1722, 1652, 1586, 1568, 1486, 1470, 1442, 1422, 1402, 1306, 1276, 1262, 1216, 1176, 1160, 1142, 1120, 1110, 1090, 1072, 1032, 1016, 976, 962, 952, 930, 906, 870, 848, 834, 820, 798, 782, 746, 730, 718, 708, 678, 654, 628, 604.

HRMS (EI) for **$C_{19}H_{11}ClO_2S$** (338.0168): 338.0157.

Synthesis of 4-(2-trimethylsilanylbenzofuran-7-yl)benzoic acid ethyl ester (136)



According to **TP 6**, the metalation of 2-trimethylsilanyl-benzofuran (**135**; 380 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 8 h at 25 °C. The reaction mixture was cooled to –10 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (607 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting solution was warmed to 25 °C and was stirred at 25 °C for 6 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography on alumina (pentane/diethyl ether = 100:1) furnished the compound **136** (564 mg, 81%) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.05-8.11 (m, 4 H), 7.69 (d, *J*=7.6 Hz, 1 H), 7.60 (d, *J*=7.4 Hz, 1 H), 7.35 (t, *J*=7.6 Hz, 1 H), 7.27 (s, 1 H), 4.34 (q, *J*=7.0 Hz, 2 H), 1.35 (t, *J*=7.1 Hz, 3 H), 0.34 (s, 9 H).

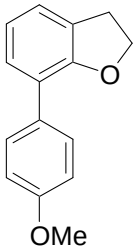
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 165.44, 163.34, 154.40, 140.58, 129.50, 128.81, 128.75, 128.24, 123.87, 123.33, 122.97, 121.63, 116.61, 60.71, 14.14, -1.93.

MS (70 eV, EI) *m/z* (%): 339 (24), 338 (100) [M^+], 323 (27), 293 (12), 263 (14), 251 (23), 235 (33), 139 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2974, 2959, 2904, 1705, 1610, 1540, 1479, 1479, 1473, 1394, 1366, 1284, 1267, 1244, 1217, 1178, 1157, 1129, 1099, 1065, 1056, 1026, 969, 937, 905, 840, 795, 762, 744, 696, 644, 635, 625, 621.

HRMS (EI) for **$C_{20}H_{22}O_3Si$** (338.1338): 338.1333.

Synthesis of 7-(4-methoxyphenyl)-2,3-dihydrobenzofuran (138)



According to **TP 6**, the metalation of 2,3-dihydro-benzofuran (**137**; 240 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 12 h at 25 °C. The reaction mixture was cooled to –10 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 4-iodoanisole (514 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting solution was warmed to 25 °C and was stirred at 25 °C for 2 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 50:1) furnished the compound **138** (385 mg, 85%) as a colourless solid.

m.p.: 125.6-126.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.63 (ddd, *J*=9.3, 2.9, 2.6 Hz, 2 H), 7.20-7.26 (m, 1 H), 7.14 (dq, *J*=7.2, 1.2 Hz, 1 H), 6.89-6.98 (m, 3 H), 4.60 (t, *J*=8.8 Hz, 2 H), 3.83 (s, 3 H), 3.26 (t, *J*=8.8 Hz, 2 H).

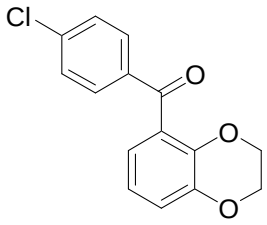
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 158.74, 156.97, 129.81, 129.42, 127.59, 127.42, 123.39, 123.26, 120.82, 113.81, 70.91, 55.29, 29.90.

MS (70 eV, EI) *m/z* (%): 227 (15), 226 (100) [M^+], 212 (9), 211 (54), 183 (9), 153 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3026, 3016, 2970, 2928, 2916, 2900, 2838, 1608, 1594, 1572, 1514, 1506, 1470, 1452, 1436, 1404, 1326, 1304, 1272, 1242, 1200, 1176, 1146, 1110, 1092, 1062, 1030, 984, 968, 942, 894, 840, 826, 790, 770, 742, 720, 668, 640, 612, 566.

HRMS (EI) for **$C_{15}H_{14}O_2$** (226.0994): 226.0980.

Synthesis of (4-chlorophenyl)-(2,3-dihydrobenzo[1,4]dioxin-5-yl)methanone (140a):



According to **TP 6**, the metalation of benzo[1,4]dioxane (**139a**; 272 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 12 h at 25 °C. The reaction mixture was cooled to –10 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 20 min. Then, 4-chlorobenzoyl chloride (460 mg, 2.5 mmol) was added at –10 °C. The resulting solution was slowly warmed to 25 °C and stirred at this temperature for 10 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 10:1) furnished the compound **140a** (427 mg, 78%) as a yellowish solid.

m.p.: 146.9-148.9 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 7.74 (ddd, *J*=8.9, 2.5, 2.2 Hz, 2 H), 7.58 (ddd, *J*=8.9, 2.5, 2.2 Hz, 2 H), 7.06 (dd, *J*=8.0, 1.8 Hz, 1 H), 6.95 (t, *J*=7.7 Hz, 1 H), 6.89 (dd, *J*=7.5, 1.7 Hz, 1 H), 4.22-4.29 (m, 2 H), 4.12-4.17 (m, 2 H).

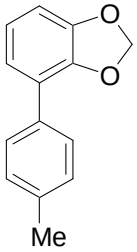
^{13}C-NMR (100 MHz, DMSO) δ: 193.59, 143.56, 141.31, 138.29, 135.58, 131.14, 128.80, 127.85, 121.07, 120.78, 119.50, 64.04, 63.87.

MS (70 eV, EI) *m/z* (%): 276 (17), 274 (53) [M^+], 163 (100), 139 (26), 111 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950, 1656, 1598, 1586, 1572, 1488, 1468, 1450, 1396, 1382, 1366, 1312, 1304, 1280, 1260, 1240, 1220, 1192, 1172, 1156, 1110, 1088, 1042, 1014, 990, 954, 924, 894, 860, 834, 800, 790, 752, 732, 722, 684, 668, 658, 628, 604, 580, 554.

HRMS (EI) for **$C_{15}H_{11}ClO_3$** (274.0397): 274.0394.

Synthesis of 4-*p*-tolylbenzo[1,3]dioxole (140b):



According to **TP 6**, the metalation of benzo[1,3]dioxole (**139b**; 244 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 12 h at 25 °C. The reaction mixture was cooled to –10 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. $Pd(dba)_2$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%) dissolved in THF (4 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 4-iodotoluene (480 mg, 2.2 mmol) dissolved in THF (2 mL). The resulting solution was warmed to 25 °C and was stirred at 25 °C for 2 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 5 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 50:1) furnished the compound **140b** (318 mg, 75%) as a colourless solid.

m.p.: 95.9 -97.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.24-7.29 (m, 4 H), 6.81-6.91 (m, 2 H), 6.77 (dd, *J*=7.6, 1.6 Hz, 1 H), 5.94 (s, 2 H), 2.27 (s, 3 H).

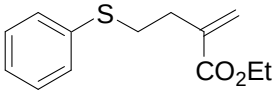
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 147.17, 136.40, 135.85, 130.16, 129.89, 127.90, 125.69, 123.39, 121.47, 107.52, 100.57, 20.01.

MS (70 eV, EI) *m/z* (%): 213 (14), 212 (100) [M^+], 211 (18), 181 (13), 169 (13), 165 (13), 153 (17), 152 (20), 141 (11), 135 (11), 105 (11), 76 (12), 57 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2914, 1590, 1498, 1472, 1436, 1380, 1360, 1280, 1270, 1252, 1202, 1186, 1158, 1130, 1120, 1086, 1056, 1024, 936, 910, 886, 832, 798, 784, 760, 736, 724, 664, 628, 604.

HRMS (EI) for **$C_{14}H_{12}O_2$** (212.0837): 212.0834.

Synthesis of 2-(2-phenylsulfanylethyl)acrylic acid ethyl ester (142)



According to **TP 6**, the metalation of thioanisole (**141**; 248 mg, 2.0 mmol) was completed using $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**111**; 0.30 M solution in THF, 6.7 mL, 2.0 mmol) within 15 h at 25 °C. The reaction mixture was cooled to 0 °C, $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 15 min. CuCN·2LiCl (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added, followed by the addition of ethyl 2-(bromomethyl)acrylate (483 mg, 2.5 mmol) and the resulting solution was stirred for 1 h at 0 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (50 mL) and aq. HCl (2 M, 10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aq. NH_3 solution (2 M, 30 mL) and with brine (40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. Purification by column chromatography (pentane/diethyl ether = 30:1) furnished the compound **6a** (276 mg, 59%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32-7.37 (m, 2 H), 7.25-7.31 (m, 2 H), 7.13-7.16 (m, 1 H), 6.22 (d, *J*=1.2 Hz, 1 H), 5.59 (q, *J*=1.2 Hz, 1 H), 4.20 (q, *J*=7.1 Hz, 2 H), 3.04-3.10 (m, 2 H), 2.63 (ddd, *J*=8.1, 6.9, 1.2 Hz, 2 H), 1.29 (t, *J*=7.0 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.59, 138.64, 136.16, 129.06, 128.87, 126.56, 125.88, 60.76, 32.32, 32.24, 14.17.

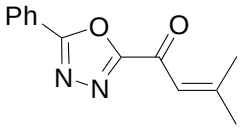
MS (70 eV, EI) *m/z* (%): 236 (15) [M^+], 127 (52), 123 (100), 110 (11), 99 (41), 81 (11), 51 (11), 45 (52).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2980, 2930, 1710, 1630, 1584, 1480, 1438, 1408, 1368, 1302, 1270, 1228, 1180, 1120, 1094, 1026, 980, 948, 898, 860, 810, 738, 720, 690, 668, 658, 642, 606, 576, 568, 554.

HRMS (EI) for **$C_{13}H_{16}O2S$** (236.0871): 236.0860.

13.10 Directed Metalation of Aromatics and Heteroaromatics Using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (143)

Synthesis of 3-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)but-2-en-1-one (149a):



According to **TP 7**, the metalation of 2-phenyl-1,3,4-oxadiazole (**61a**; 458 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 0.5 h at –45 °C. Then, 3,3-dimethyl acryloyl chloride (260 mg, 2.2 mmol) was added, and the resulting mixture was stirred for 2 h at –45 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 4:1) to give **149a** (342 mg, 75%) as a yellowish solid. (Please note: unstable in solution!)

m.p.: 64.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.01-8.03 (m, 2 H), 7.44-7.54 (m, 3 H), 6.11 (dt, *J*=2.5, 1.3 Hz, 1 H), 1.90 (d, *J*=1.3 Hz, 3 H), 1.80 (d, *J*=1.3 Hz, 3 H).

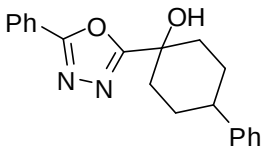
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.11, 165.57, 144.57, 132.12, 129.03, 127.20, 123.30, 120.02, 69.37, 27.07, 19.29.

MS (70 eV, EI) *m/z* (%): 228 (87) [M^+], 227 (80), 211 (72), 200 (34), 160 (100), 147 (13), 129 (11), 118 (12), 105 (29), 104 (23), 103 (37), 96 (21), 83 (84), 82 (74), 77 (56), 55 (55).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3183, 3064, 2971, 2885, 1721, 1666, 1609, 1590, 1552, 1484, 1449, 1375, 1291, 1204, 1178, 1138, 1089, 1068, 1038, 1022, 970, 958, 926, 906, 779, 766, 734, 707, 688.

HRMS (ESI) for **$C_{13}H_{12}N_2O_2$** (228.0899): 229.0973.

Synthesis of 4-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)cyclohexanol (149b):



According to **TP 7**, the metalation of 2-phenyl-1,3,4-oxadiazole (**61a**; 458 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within

0.5 h at –45 °C. Then, 4-phenyl cyclohexanone (350 mg, 2.0 mmol) was added, and the resulting mixture was stirred for 1 h at –45 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 1:2) to give **149b** (512 mg, 80%) as a yellowish solid.

m.p.: 122.0-124.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.99-8.10 (m, 2 H), 7.43-7.55 (m, 3 H), 7.24-7.32 (m, 2 H), 7.14-7.21 (m, 3 H), 4.31 (br, 1 H), 2.71-2.80 (m, 2 H), 2.63-2.69 (m, 1 H), 1.94-2.10 (m, 4 H), 1.62-1.78 (m, 2 H).

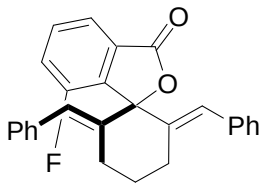
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.64, 164.86, 145.56, 131.76, 128.92, 128.26, 126.94, 126.69, 126.09, 123.48, 70.03, 42.86, 36.88, 30.75.

MS (70 eV, EI) *m/z* (%): 320 (56) [M^+], 303 (15), 302 (53), 287 (15), 249 (33), 174 (100), 160 (27), 156 (16), 147 (37), 146 (42), 145 (19), 130 (16), 119 (55), 118 (20), 117 (55), 115 (30), 108 (20), 105 (40), 104 (86), 103 (87), 91 (79), 90 (16), 77 (43), 76 (24).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3326, 2949, 2936, 1558, 1549, 1493, 1484, 1449, 1437, 1366, 1351, 1222, 1192, 1181, 1137, 1126, 1091, 1072, 1063, 1024, 1006, 965, 927, 920, 904, 888, 872, 858, 836, 808, 802, 792, 776, 759, 746, 722, 702, 682, 648, 631.

HRMS (EI) for **$C_{20}H_{20}N_2O_2$** (320.1525): 320.1522.

Synthesis of 2,6-dibenzylidene-7'-fluorospiro[cyclohexane-1,1'-isobenzofuran]-3'-one (153a):



According to **TP 7**, the metalation of methyl 3-fluorobenzoate (**151a**; 308 mg, 2.0 mmol) was completed using $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 45 min at –5 °C. Then, 2,6-dibenzylidenecyclohexanone (550 mg, 2.0 mmol) was added, and the resulting mixture was stirred for 1 h at –5 °C. The reaction mixture was quenched with brine (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (Al_2O_3, pentane/diethyl ether = 8:1) to give **153a** (690 mg, 87%) as a colourless solid.

m.p.: 133.5 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.86 (d, J=7.4 Hz, 1 H), 7.66 (td, J=7.9, 4.3 Hz, 1 H), 7.49 (t, J=8.4 Hz, 1 H), 7.29-7.33 (m, 4 H), 7.21-7.25 (m, 2 H), 7.13-7.18 (m, 4 H), 6.09 (s, 2 H), 3.03 (dt, J=14.5, 4.2 Hz, 2 H), 2.67-2.74 (m, 2 H), 1.94-1.99 (m, 1 H), 1.61 (m, 1 H).

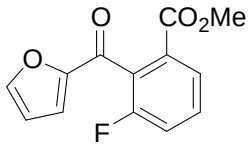
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 167.73 (d, $^4J_{CF}$=1.7 Hz), 157.20 (d, $^1J_{CF}$=253 Hz), 137.95 (d, J_{CF}=1.1 Hz), 136.35, 134.35 (d, $^2J_{CF}$=17 Hz), 132.24 (d, $^3J_{CF}$=6.5 Hz), 130.41 (d, $^3J_{CF}$=3.3 Hz), 128.95, 128.11, 127.11, 126.75 (d, J_{CF}=1.1 Hz), 122.67 (d, J_{CF}=4.0 Hz), 121.09 (d, $^2J_{CF}$=21 Hz), 94.18 (d, $^3J_{CF}$=4 Hz), 26.63, 25.73.

MS (70 eV, EI) *m/z* (%): 397 (21), 396 (63) [M^+], 353 (29), 352 (100), 324 (16), 323 (19), 309 (30), 307 (17), 292 (23), 275 (22), 274 (18), 273 (15), 261 (52), 259 (23), 247 (19), 246 (30), 245 (66), 233 (43), 221 (16), 220 (21), 183 (39), 115 (22), 105 (21), 91 (39).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3133, 3082, 1715, 1656, 1609, 1568, 1463, 1455, 1438, 1386, 1284, 1242, 1232, 1206, 1188, 1172, 1152, 1080, 1019, 1000, 973, 966, 931, 898, 882, 871, 846, 824, 796, 770, 758, 741, 684, 618.

HRMS (EI) for **$C_{27}H_{21}FO_2$** (396.1526): 396.1519.

Synthesis of 3-fluoro-2-(furan-2-carbonyl)benzoic acid methyl ester (153b):



According to **TP 7**, the metalation of methyl 3-fluorobenzoate (**151a**; 308 mg, 2.0 mmol) was completed using $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 45 min at –5 °C. Then, 2-furoyl chloride (287 mg, 2.2 mmol) was added, and the resulting mixture was stirred for 1 h at –5 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with aq. NH_3 (2 M, 30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 4:1) to give **153b** (425 mg, 85%) as a colourless solid.

m.p.: 133.5 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.75 (dd, J=7.8, 1.1 Hz, 1 H), 7.58 (dd, J=1.7, 0.8 Hz, 1 H), 7.51 (td, J=8.1, 5.5 Hz, 1 H), 7.33 (td, J=8.5, 1.1 Hz, 1 H), 7.03 (d, J=3.6 Hz, 1 H), 6.53 (dd, J=3.6, 1.7 Hz, 1 H), 3.73 (s, 3 H).

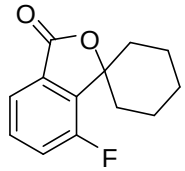
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 179.68 (d, $^3J_{CF}$=1.7 Hz), 165.09 (d, $^4J_{CF}$=3.3 Hz), 159.27 (d, $^1J_{CF}$=249 Hz), 152.77, 147.17, 131.03 (d, $^3J_{CF}$=8.4 Hz), 130.75 (d, J_{CF}=3.6 Hz), 128.27 (d, $^2J_{CF}$=20 Hz), 126.03 (d, J_{CF}=3.3 Hz), 120.25 (d, $^2J_{CF}$=22 Hz), 118.77, 112.48, 52.54.

MS (70 eV, EI) *m/z* (%): 248 (83) [M^+], 220 (47), 219 (62), 217 (77), 205 (46), 181 (88), 160 (25), 150 (23), 148 (28), 133 (33), 127 (32), 123 (40), 97 (29), 95 (100), 83 (33), 81 (25), 71 (27), 69 (55), 57 (63), 55 (59), 44 (49).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3133, 3082, 1715, 1656, 1609, 1568, 1463, 1455, 1438, 1386, 1284, 1242, 1232, 1206, 1188, 1172, 1152, 1080, 1019, 1000, 973, 966, 931, 898, 882, 871, 846, 824, 796, 770, 758, 741, 684, 618.

HRMS (EI) for **$C_{13}H_9FO_4$** (248.0485):248.0476.

Synthesis of 7-fluoro-3*H*-spiro[2-benzofuran-1,1'-cyclohexan]-3-one (153c):



According to **TP 7**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 0.5 h at 0 °C. Then, cyclohexanone (216 mg, 2.2 mmol), premixed with $LaCl_3 \cdot 2LiCl$ (0.50 M in THF, 1.0 mL, 0.5 mmol) was added, and the resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 9:1) to give **153c** (360 mg, 82%) as a colourless solid.

m.p.: 160.0 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 7.59-7.64 (m, 1 H), 7.52-7.58 (m, 1 H), 7.41-7.48 (m, 1 H), 2.06-2.11 (m, 2 H), 1.64-1.81 (m, 6 H), 1.29-1.57 (m, 2 H).

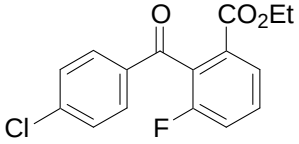
^{13}C-NMR (100 MHz, DMSO) δ: 167.32 (d, $^4J_{CF}$=1.5 Hz), 155.96 (d, $^1J_{CF}$=250 Hz), 139.36 (d, $^2J_{CF}$=17 Hz), 131.37 (d, $^3J_{CF}$=5.3 Hz), 128.08 (d, $^3J_{CF}$=4.3 Hz), 123.23 (d, $^4J_{CF}$=2.2 Hz), 120.88 (d, $^2J_{CF}$=20 Hz), 85.02 (d, $^3J_{CF}$=4.0 Hz), 34.16, 34.15, 23.90, 21.61.

MS (70 eV, EI) *m/z* (%): 220 (26) [M^+], 177 (59), 165 (14), 164 (78), 127 (18), 123 (15), 114 (12), 111 (13), 97 (33), 84 (17), 83 (36), 82 (13), 81 (19), 77 (13), 71 (35), 70 (27), 69 (53), 57 (60), 56 (31), 55 (57), 44 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2939, 2867, 2850, 1761, 1714, 1598, 1482, 1467, 1452, 1354, 1291, 1278, 1250, 1239, 1230, 1219, 1174, 1146, 1104, 1076, 1056, 1036, 983, 916, 862, 834, 814, 780, 754, 704, 674, 649, 632, 611.

HRMS (EI) for **$C_{13}H_{13}FO_2$** (220.0900): 220.0882.

Synthesis of ethyl 2-(4-chlorobenzoyl)-3-fluorobenzoate (153d):



According to **TP 7**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 0.5 h at 0 °C. Then, 4-chlorobenzoyl chloride (385 mg, 2.2 mmol) was added, and the resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with aq. NH_3 (2 M, 30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 7:1) to give **153d** (538 mg, 88%) as a colourless solid.

m.p.: 133.1 °C °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J*=7.8 Hz, 1 H), 7.77 (dt, 2 H), 7.52-7.61 (m, 1 H), 7.45 (dt, *J*=8.9, 2.3, 2.1 Hz, 2 H), 7.38 (td, *J*=8.5, 1.2 Hz, 1 H), 4.19 (q, *J*=7.1 Hz, 2 H), 1.14 (t, *J*=7.2 Hz, 3 H).

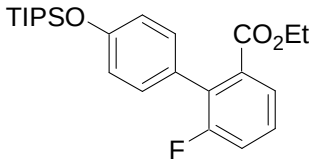
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 194.44 (d, $^3J_{CF}$=1.0 Hz), 164.54 (d, $^4J_{CF}$=3.6 Hz), 159.04 (d, $^1J_{CF}$=248 Hz), 140.00, 135.44, 130.84 (d, J_{CF}=3.4 Hz), 130.79 (d, $^3J_{CF}$=8.0 Hz), 130.30, 129.06 (d, $^2J_{CF}$=20 Hz), 126.29 (d, J_{CF}=3.4 Hz), 120.29 (d, $^2J_{CF}$=22 Hz), 61.92, 13.70.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2996, 1713, 1674, 1585, 1477, 1451, 1401, 1368, 1289, 1268, 1199, 1180, 1154, 1091, 1027, 965, 929, 847, 761, 748, 706, 685.

MS (70 eV, EI) *m/z* (%): 306 (41) [M^+], 261 (32), 195 (38), 167 (100), 141 (29), 139 (95), 111 (28).

HRMS (EI) for **$C_{16}H_{12}ClFO_3$** (306.0459): 306.0461.

Synthesis of 6-fluoro-4'-triisopropylsilanyloxybiphenyl-2-carboxylic acid ethyl ester (153e):



According to **TP 7**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 0.5 h at 0 °C. (4-iodophenoxy)(triisopropyl)silane (825 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 0 °C and the mixture was stirred for 2 h at 0 °C and 1 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 30:1) to give **153e** (657 mg, 79%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.48-7.52 (m, 1 H), 7.27-7.32 (m, 1 H), 7.17-7.21 (m, 1 H), 7.08-7.13 (m, 2 H), 6.86 (ddd, *J*=9.1, 2.8, 2.5 Hz, 2 H), 4.00 (t, *J*=7.1 Hz, 2 H), 1.13-1.35 (m, 21 H), 0.94 (t, *J*=7.1 Hz, 3 H).

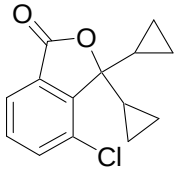
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.02 (d, $^4J_{CF}$=3.6 Hz), 159.77 (d, $^1J_{CF}$=246 Hz), 155.83, 134.33 (d, J_{CF}=2.8 Hz), 130.46 (d, $^4J_{CF}$=1.6 Hz), 129.25 (d, $^2J_{CF}$=18 Hz), 128.31 (d, $^3J_{CF}$=8.5 Hz), 126.51, 124.99 (d, $^3J_{CF}$=3.6 Hz), 119.36, 118.35 (d, $^2J_{CF}$=24 Hz), 61.11, 17.91, 13.70, 12.70.

MS (70 eV, EI) *m/z* (%): 417 (11), 416 (35) [M^+], 374 (25), 373 (91), 345 (30), 327 (16), 317 (14), 299 (26), 285 (14), 272 (17), 271 (100), 258 (13), 257 (64), 144 (21), 136 (41), 129 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2945, 2893, 2867, 1718, 1606, 1578, 1568, 1515, 1454, 1390, 1367, 1261, 1244, 1176, 1138, 1102, 1077, 1021, 997, 953, 910, 882, 838, 808, 766, 753, 720, 681, 662, 646.

HRMS (EI) for **$C_{24}H_{33}FO_3Si$** (416.2183): 416.2179.

Synthesis of 4-chloro-3,3-dicyclopropyl-3*H*-isobenzofuran-1-one (153f):



According to **TP 7**, the metalation of ethyl 3-chlorobenzoate (**67b**; 370 mg, 2.0 mmol) was completed using $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 3.5 h at 0 °C. Then, dicyclopropyl ketone (242 mg, 2.2 mmol), premixed with $LaCl_3{\cdot}2LiCl$ (0.5 M in THF, 1.0 mL, 0.5 mmol) was added, and the resulting mixture was stirred for 1 h at

0 °C. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (Al_2O_3, pentane/diethyl ether = 9:1) to give **153f** (342 mg, 69%) as a colourless solid.

m.p.: 105.5 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 7.88 (dd, *J*=7.8, 1.0 Hz, 1 H), 7.80 (dd, *J*=7.6, 1.0 Hz, 1 H), 7.63 (t, *J*=7.6 Hz, 1 H), 1.66-1.73 (m, 2 H), 0.63-0.73 (m, 4 H), 0.27-0.35 (m, 2 H), -0.02-0.05 (m, 2 H).

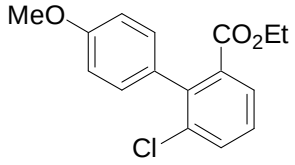
^{13}C-NMR (100 MHz, DMSO) δ: 167.77, 149.80, 135.83, 131.47, 127.38, 127.12, 124.22, 86.25, 15.46, 2.48, -0.48.

MS (70 eV, EI) *m/z* (%): 248 (1), [M^+], 222 (33), 221 (14), 220 (100), 209 (22), 207 (64), 194 (12), 192 (38), 191 (14), 189 (18), 179 (10), 157 (13), 151 (15), 139 (12), 138 (11), 129 (21), 128 (17), 127 (12), 116 (18), 115 (36), 110 (12), 75 (18), 69 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3394, 3089, 3009, 2926, 2855, 1798, 1760, 1734, 1672, 1606, 1584, 1458, 1423, 1376, 1325, 1265, 1213, 1197, 1176, 1164, 1130, 1106, 1052, 1043, 1024, 1016, 1002, 991, 972, 930, 912, 880, 854, 828, 816, 805, 782, 762, 702, 668, 616.

HRMS (EI) for **$C_{14}H_{13}ClO_2$** (248.0604): 248.0602.

Synthesis of ethyl 6-chloro-4'-methoxybiphenyl-2-carboxylate (153g):



According to **TP 7**, the metalation of ethyl 3-chlorobenzoate (**67b**; 370 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 3.5 h at 0 °C. Then, 4-iodoanisole (491 mg, 2.1 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 0 °C and the mixture was stirred for 2 h at 0 °C and 1 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 20:1) to give **153g** (435 mg, 75%) as a colourless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.67 (dd, *J*=7.9, 1.3 Hz, 1 H), 7.58 (dd, *J*=8.0, 1.3 Hz, 1 H), 7.32 (t, *J*=7.9 Hz, 1 H), 7.14-7.18 (m, 2 H), 6.92-6.96 (m, 2 H), 4.01 (q, *J*=7.2 Hz, 2 H), 3.84 (s, 3 H), 0.97 (t, *J*=7.1 Hz, 3 H).

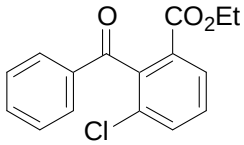
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 167.75, 159.09, 139.83, 134.81, 134.57, 132.15, 130.34, 130.26, 128.10, 127.62, 113.25, 61.11, 55.20, 13.69.

MS (70 eV, EI) *m/z* (%): 292 (30), 291 (15), 290 (100) [M^+], 262 (14), 247 (16), 245 (45), 211 (15), 210 (33), 139 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 2960, 2936, 2906, 2837, 1717, 1612, 1589, 1578, 1560, 1515, 1464, 1453, 1435, 1412, 1390, 1366, 1284, 1243, 1192, 1176, 1148, 1106, 1084, 1035, 1018, 1001, 892, 862, 830, 804, 763, 749, 736, 711, 636.

HRMS (EI) for **$C_{16}H_{15}ClO_3$** (290.0710): 290.0709.

Synthesis of ethyl 2-benzoyl-3-chlorobenzoate (69e):



According to **TP 7**, the metalation of ethyl 3-chlorobenzoate (**67b**; 370 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 3.5 h at 0 °C. Then, benzoyl chloride (310 mg, 2.2 mmol) was added, and the resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with aq. NH_3 (2 M, 30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 7:1) to give **69e** (538 mg, 81%) as a colourless solid.

m.p.: 108.6-109.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.08 (m, 1 H), 7.81 (m, 2 H), 7.44-7.68 (m, 5 H), 4.17 (q, *J*=7.1 Hz, 2 H), 1.10 (t, *J*=7.1 Hz, 3 H).

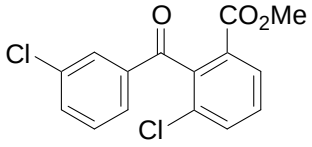
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 194.52, 164.82, 140.65, 136.91, 134.15, 133.63, 131.97, 130.89, 130.11, 129.24, 128.93, 62.09, 13.84.

MS (70 eV, EI) *m/z* (%): 290 (19), 288 (43) [M^+], 242 (32), 211 (73), 211 (26), 185 (32), 183 (100), 152 (10), 151 (13), 105 (87), 77 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1706, 1672, 1584, 1564, 1430, 1366, 1284, 1202, 1152, 1074, 1028, 928, 866, 764, 744, 734, 702, 652, 618.

HRMS (EI) for **$C_{16}H_{13}ClO_3$** (288.0553): 288.0569.

Synthesis of methyl 3-chloro-2-(4-chlorobenzoyl)benzoate (153h):



According to **TP 7**, the metalation of methyl 3-chlorobenzoate (**100c**; 342 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 3.5 h at 0 °C. Then, 3-chlorobenzoyl chloride (385 mg, 2.2 mmol) was added, and the resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with aq. NH_3 (2 M, 30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 5:1) to give **153h** (517 mg, 84%) as a colourless solid.

m.p.: 115.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.03 (dd, *J*=7.9, 1.2 Hz, 1 H), 7.77 (t, *J*=1.9 Hz, 1 H), 7.60-7.67 (m, 2 H), 7.47-7.55 (m, 2 H), 7.38 (t, *J*=7.9 Hz, 1 H), 3.73 (s, 3 H).

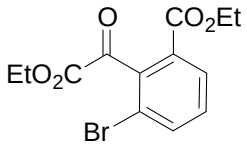
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 193.07, 164.91, 139.97, 138.12, 135.03, 134.12, 133.31, 131.70, 130.28, 130.21, 130.05, 128.94, 128.64, 126.99, 52.62.

MS (70 eV, EI) *m/z* (%): 310 (11), 308 (17) [M^+], 277 (12), 199 (34), 197 (100), 139 (31), 111 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3092, 3065, 3008, 2951, 1716, 1675, 1641, 1585, 1571, 1429, 1291, 1278, 1255, 1207, 1188, 1149, 1114, 1076, 976, 960, 802, 770, 734, 720, 681, 671, 650.

HRMS (EI) for **$C_{15}H_{10}Cl_2O_3$** (308.0007): 308.0008.

Synthesis of 3-bromo-2-ethoxyoxalylbenzoic acid ethyl ester (153i):



According to **TP 7**, the metalation of ethyl 3-bromobenzoate (**100b**; 458 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 2.5 h at 25 °C. Then, the reaction mixture was cooled to 0 °C, ethyl oxalyl chloride (300 mg, 2.2 mmol) was added, and the resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with aq. NH_3 (2 M, 30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in*

vacuo. The crude product was purified by column chromatography (pentane/diethyl ether = 8:1) to give **153i** (425 mg, 65%) as a colourless solid.

m.p.: 74.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.97 (dd, *J*=7.9, 1.1 Hz, 1 H), 7.76 (dd, *J*=8.0, 0.7 Hz, 1 H), 7.37 (t, *J*=7.9 Hz, 1 H), 4.35 (q, *J*=7.2 Hz, 2 H) 4.31 (q, *J*=7.2 Hz, 2 H), 1.33 (t, *J*=6.9 Hz, 3 H), 1.31 (t, *J*=6.9 Hz, 3 H).

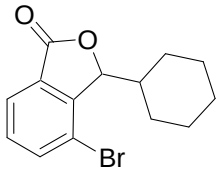
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 185.95, 165.04, 158.83, 140.87, 136.97, 130.85, 130.74, 128.68, 119.43, 62.68, 62.38, 13.90, 13.85.

MS (70 eV, ESI) *m/z* (%): 329 (46) [M^++H], 270 (100), 186 (48).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3072, 3014, 2988, 2972, 2938, 2871, 1758, 1729, 1692, 1654, 1639, 1585, 1559, 1480, 1458, 1446, 1438, 1391, 1369, 1296, 1258, 1202, 1161, 1109, 1093, 1074, 1011, 971, 894, 865, 835, 824, 764, 728, 714, 679.

HRMS (ESI) for **$C_{13}H_{13}BrO_5$** (327.9946): 329.0019.

Synthesis of 4-bromo-3-cyclohexyl-2-benzo[c]furan-1(3*H*)-one (153j):



According to **TP 7**, the metalation of ethyl 3-bromobenzoate (**100b**; 458 mg, 2.0 mmol) was completed using $TMP_3La·3MgCl_2·5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 2.5 h at 25 °C. Then, the reaction mixture was cooled to 0 °C, cyclohexane carbaldehyde (246 mg, 2.2 mmol) was added, and the resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with a sat. aq. $NaHCO_3$ solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (Al_2O_3, pentane/diethyl ether = 6:1) to give **153ja** (465 mg, 79%) as a colourless solid.

m.p.: 102.9-105.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, *J*=7.0 Hz, 1 H), 7.76 (dd, *J*=7.9, 0.9 Hz, 1 H), 7.38 (t, *J*=7.7 Hz, 1 H), 5.35 (d, *J*=2.3 Hz, 1 H), 2.47-2.55 (m, 1 H), 1.80-1.94 (m, 2 H), 1.60-1.66 (m, 2 H), 1.07-1.38 (m, 4 H), 0.76-0.89 (m, 2 H).

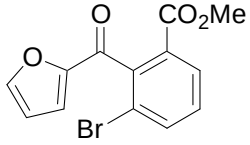
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.46, 147.64, 137.48, 130.66, 129.06, 124.47, 116.53, 85.76, 38.68, 30.41, 26.53, 23.88.

MS (70 eV, EI) *m/z* (%): 294 (2) [M^+], 213 (100), 212 (19), 211 (93), 83 (17), 75 (11), 55 (28), 41 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2924, 2855, 1759, 1679, 1456, 1450, 1343, 1279, 1254, 1176, 1124, 1070, 1050, 976, 957, 816, 790, 784, 766, 738, 656.

HRMS (EI) for **$C_{14}H_{15}BrO_2$** (294.0255): 294.0245.

Synthesis of methyl 3-bromo-2-(2-furoyl)benzoate (153k):



According to **TP 7**, the metalation of methyl 3-bromobenzoate (**151b**; 458 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 2 h at 25 °C. Then, the reaction mixture was cooled to 0 °C, 2-furoyl chloride (287 mg, 2.2 mmol) was added, and the resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with aq. NH_3 (2 M, 30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 3:1) to give **153k** (358 mg, 58%) as a colourless solid.

m.p.: 104.4 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 8.02 (dd, *J*=7.9, 1.1 Hz, 1 H), 7.79 (dd, *J*=8.1, 1.1 Hz, 1 H), 7.57 (d, *J*=1.0 Hz, 1 H), 7.38 (t, *J*=7.9 Hz, 1 H), 7.01 (d, *J*=3.4 Hz, 1 H), 6.52 (dd, *J*=3.6, 1.7 Hz, 1 H), 3.73 (s, 3 H).

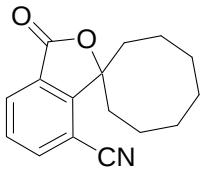
^{13}C-NMR (100 MHz, DMSO) δ: 182.56, 164.86, 152.24, 146.99, 140.98, 137.03, 130.40, 130.37, 129.29, 120.45, 118.51, 112.47, 52.56.

MS (70 eV, EI) *m/z* (%): 310 (47), 308 (46) [M^+], 282 (12), 281 (30), 280 (16), 279 (48), 277 (20), 267 (17), 265 (14), 243 (49), 241 (50), 114 (16), 95 (100), 75 (30), 74 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3133, 3122, 3062, 2949, 2853, 1720, 1658, 1586, 1568, 1463, 1432, 1392, 1383, 1284, 1278, 1229, 1210, 1184, 1156, 1148, 1085, 1077, 1014, 971, 954, 871, 848, 774, 763, 744, 727, 707, 681.

HRMS (EI) for **$C_{13}H_9BrO_4$** (307.9684): 307.9682.

Synthesis of 3-oxo-3*H*-spiro[2-benzofuran-1,1'-cyclooctane]-7-carbonitrile (153l):



According to **TP 7**, the metalation of ethyl 3-cyanobenzoate (**67i**; 350 mg, 2.0 mmol) was completed using $TMP_3La·3MgCl_2·5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 1.25 h at 0 °C. Then, cyclooctanone (277 mg, 2.2 mmol), premixed with $LaCl_3·2LiCl$ (0.5 M in THF, 1.0 mL, 0.5 mmol) was added, and the resulting mixture was stirred for 5 h at 0 °C. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (Al_2O_3, pentane/diethyl ether: CH_2Cl_2 = 300:100:1) to give **153l** (332 mg, 74%) as a colourless solid. (Please note: unstable in solution!)

m.p.:75.7 °C.

^{1}H-NMR (400 MHz, THF) δ: 8.21-8.31 (m, 1 H), 7.59-7.93 (m, 2 H), 4.66 (dd, *J*=9.4, 2.7 Hz, 1H), 2.31-2.75 (m, 5 H), 1.73-2.01 (m, 3 H), 1.29-1.62 (m, 5 H).

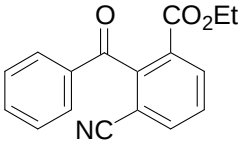
^{13}C-NMR (100 MHz, THF) δ: 195.07, 136.82, 133.93, 133.25, 132.14, 130.55, 118.37, 114.22, 62.27, 40.85, 36.75, 32.39, 29.56, 28.76, 27.51, 26.54.

MS (70 eV, EI) *m/z* (%): 255 (15) [M^+], 227 (16), 184 (18), 171 (13), 170 (12), 158 (19), 146 (15), 145 (24), 130 (100), 102 (39), 82 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2933, 2919, 2852, 2232, 1706, 1678, 1600, 1461, 1445, 1429, 1412, 1365, 1352, 1343, 1332, 1323, 1317, 1291, 1279, 1251, 1245, 1230, 1201, 1185, 1175, 1159, 1146, 1116, 1103, 1085, 1064, 1037, 1000, 992, 978, 926, 821, 792, 776, 749, 738, 687, 676, 656.

HRMS (EI) for **$C_{16}H_{17}NO_2$** (255.1259): 255.1250.

Synthesis of ethyl 2-benzoyl-3-cyanobenzoate (69h):



According to **TP 7**, the metalation of ethyl 3-cyanobenzoate (**67i**; 350 mg, 2.0 mmol) was completed using $TMP_3La·3MgCl_2·5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 1.25 h at 0 °C. Then, benzoyl chloride (310 mg, 2.2 mmol) was added, and the resulting

mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with aq. NH_3 (2 M, 30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 4:1) to give **69h** (474 mg, 85%) as a colourless solid.

m.p.: 138.4-140.6 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.34 (d, *J*=7.9 Hz, 1 H), 7.93 (d, *J*=7.9 Hz, 1 H), 7.75 (d, *J*=7.5 Hz, 2 H), 7.69 (t, *J*=7.9 Hz, 1 H), 7.60 (d, *J*=7.3 Hz, 1 H), 7.47 (t, *J*=7.8 Hz, 2 H), 4.14 (q, *J*=7.2 Hz, 2 H), 1.06 (t, *J*=7.2 Hz, 3 H).

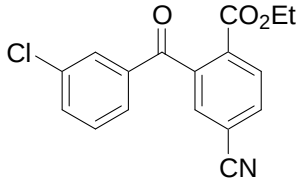
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 193.81, 164.22, 145.69, 136.82, 136.28, 134.61, 134.22, 130.46, 129.65, 129.51, 129.08, 116.07, 111.94, 62.52, 13.75.

MS (70 eV, EI) *m/z* (%): 280 (9), 279 (46) [M^+], 235 (88), 234 (18), 206 (8), 174 (28), 105 (100), 77 (24).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1716, 1670, 1474, 1444, 1366, 1272, 1160, 1018, 936, 923, 768, 707, 659.

HRMS (EI) for **$C_{17}H_{13}NO_3$** (279.0895): 279.0873.

Synthesis of 2-(3-chlorobenzoyl)-4-cyano-benzoic acid ethyl ester (153m):



According to **TP 7**, the metalation of ethyl 4-cyanobenzoate (**67i**; 350 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 3 h at –25 °C. Then, the reaction mixture was cooled to –40 °C, 3-chlorobenzoyl chloride (385 mg, 2.2 mmol) was added and the resulting mixture was stirred for 2 h at –40 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with aq. NH_3 (2 M, 30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 4:1) to give **153m** (425 mg, 68%) as a colourless solid.

m.p.: 96.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.17 (d, *J*=8.3 Hz, 1 H), 7.86 (dd, *J*=8.1, 1.6 Hz, 1 H), 7.71 (t, *J*=1.8 Hz, 1 H), 7.65 (d, *J*=1.5 Hz, 1 H), 7.52-7.59 (m, 2 H), 7.39 (t, *J*=7.8 Hz, 1 H), 4.15 (q, *J*=7.0 Hz, 2 H), 1.11 (t, *J*=7.2 Hz, 3 H).

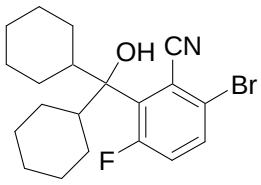
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 193.55, 164.60, 142.18, 138.23, 135.57, 134.06, 133.66, 133.46, 131.45, 131.39, 130.49, 129.49, 127.87, 117.39, 116.74, 62.86, 14.01.

MS (70 eV, EI) *m/z* (%): 315 (12), 313 (33) [M^+], 270 (17), 269 (17), 268 (39), 202 (36), 177 (28), 174 (100), 141 (34), 138 (94), 11 (37), 75 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3072, 2929, 2873, 2235, 1721, 1679, 1591, 1573, 1471, 1446, 1427, 1389, 1367, 1278, 1257, 1194, 1174, 1164, 1132, 1084, 1074, 1013, 992, 920, 911, 883, 861, 794, 749, 737, 703, 674, 649, 631.

HRMS (EI) for **$C_{17}H_{12}ClNO_3$** (313.0506): 313.0509.

Synthesis of 6-bromo-2-(dicyclohexylhydroxymethyl)-3-fluorobenzonitrile (153n):



According to **TP 7**, the metalation of 2-bromo-5-fluorobenzonitrile (**67o**; 400 mg, 2.0 mmol) was completed using $TMP_3La·3MgCl_2·5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 0.5 h at –35 °C. Then, dicyclohexyl ketone (427 mg, 2.2 mmol) was added, and the resulting mixture was stirred for 2 h at –35 °C and 2 h at –10 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 9:1) to give **153n** (519 mg, 66%) as a colourless solid.

m.p.: 140.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.55 (dd, *J*=8.6, 4.1 Hz, 1 H), 7.07 (t, *J*=8.7 Hz, 1 H), 2.14-2.22 (m, 2 H), 1.61-1.65 (m, 8 H), 0.97-1.38 (m, 11 H), 0.77-0.89 (m, 2 H).

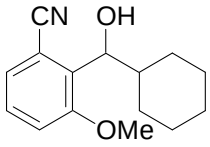
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 155.90 (d, $^1J_{CF}$=250 Hz), 136.76 (d, $^2J_{CF}$=19 Hz), 134.87 (d, $^3J_{CF}$=6.6 Hz), 120.27 (d, $^2J_{CF}$=23 Hz), 113.44 (d, $^3J_{CF}$=3.3 Hz), 95.24, 41.76, 27.35, 27.30, 26.81, 26.47, 26.28, 26.13.

MS (70 eV, EI) *m/z* (%): 395 (25), 393 (22) [M^+], 313 (55), 312 (100), 311 (55), 310 (96), 269 (21), 267 (22), 229 (51), 227 (56), 83 (16), 55 (21), 44 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2938, 2926, 2894, 2862, 2848, 1663, 1466, 1448, 1336, 1286, 1272, 1240, 1226, 1179, 1122, 1056, 1044, 996, 976, 933, 875, 838, 815, 686, 667, 657, 630.

HRMS (EI) for **$C_{20}H_{25}BrFNO$** (393.1104): 393.1091.

Synthesis of 2-(cyclohexylhydroxymethyl)-3-methoxybenzonitrile (153o):



According to **TP 7**, the metalation of 3-methoxybenzonitrile (**151c**; 266 mg, 2.0 mmol) was completed using $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 1.5 h at 25 °C. Then, cyclohexane carbaldehyde (246 mg, 2.2 mmol) was added, and the resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 7:1) to give **153o** (363 mg, 74%) as a colourless solid.

m.p.: 108.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35-7.48 (m, 2 H), 6.97 (d, *J*=7.5 Hz, 1 H), 6.54 (br, 1 H), 5.40 (s, 1 H), 3.87 (s, 3 H), 2.11-2.18 (m, 1 H), 1.75-1.83 (m, 2 H), 1.50-1.63 (m, 3 H), 0.88-1.38 (m, 6 H).

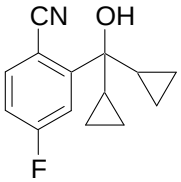
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 154.23, 134.10, 130.29, 117.11, 115.65, 114.78, 113.16, 55.48, 40.22, 30.42, 26.58, 26.12, 25.89, 24.55.

MS (70 eV, ESI) *m/z* (%): 246 (100) [M^++H], 164 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3295, 2968, 2938, 2920, 2853, 2363, 1760, 1750, 1679, 1656, 1604, 1492, 1464, 1448, 1439, 1379, 1363, 1354, 1329, 1316, 1273, 1234, 1223, 1210, 1189, 1182, 1169, 1105, 1092, 1074, 1058, 1022, 975, 955, 945, 904, 879, 851, 841, 827, 812, 801, 788, 771, 747, 724, 668, 641.

HRMS (ESI) for **$C_{15}H_{19}NO_2$** (245.1416): 246.1488.

Synthesis of 2-(dicyclopropylhydroxymethyl)-4-fluorobenzonitrile (153p):



According to **TP 7**, the metalation of 4-fluorobenzonitrile (**67k**; 242 mg, 2.0 mmol) was completed using $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**143**; 0.33 M in THF, 2.2 mL0.72 mmol) within 1 h at 0 °C. Then, dicyclopropyl ketone (242 mg, 2.2 mmol) was added, and the resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed

brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 8:1) to give **153p** (354 mg, 77%) as a colourless solid.

m.p.: 110.7 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.96 (dd, *J*=7.1, 2.2 Hz, 1 H), 7.54 (ddd, *J*=8.5, 4.3, 2.2 Hz, 1 H), 7.11 (dd, *J*=11.2, 8.4 Hz, 1 H), 1.68 (d, *J*=4.9 Hz, 1 H), 1.29-1.38 (m, 2 H), 0.61-0.69 (m, 2 H), 0.54 (ddd, *J*=14.2, 8.8, 5.4 Hz, 2 H), 0.27-0.37 (m, 4 H).

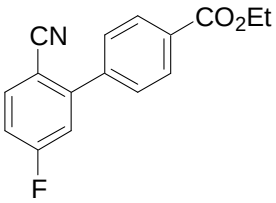
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 162.37 (d, $^1J_{CF}$=257 Hz), 136.56 (d, $^2J_{CF}$=14 Hz), 132.73 (d, J_{CF}=10 Hz), 132.51 (d, $^3J_{CF}$=6.5 Hz), 118.52, 117.45 (d, $^2J_{CF}$=26 Hz), 107.99 (d, J_{CF}=3.6 Hz), 72.77 19.31, 2.35, 0.08.

MS (70 eV, EI) *m/z* (%): 231 (1) [M^+], 204 (11), 203 (100), 202 (10), 190 (80), 188 (17), 161 (22), 149 (13), 148 (28), 147 (34), 134 (11), 120 (16), 69 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3461, 3005, 2241, 1585, 1485, 1464, 1422, 1405, 1343, 1300, 1260, 1240, 1212, 1180, 1142, 1134, 1117, 1099, 1054, 1035, 1025, 1005, 984, 955, 948, 920, 905, 872, 843, 828, 816, 790, 729, 716, 675, 650, 623, 613.

HRMS (EI) for **$C_{14}H_{14}FNO$** (231.1059): 231.1064.

Synthesis of 2'-cyano-5'-fluorobiphenyl-4-carboxylic acid ethyl ester (153q):



According to **TP 7**, the metalation of 4-fluorobenzonitrile (**67k**; 242 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL0.72 mmol) within 1 h at 0 °C. Ethyl 4-iodobenzoate (552 mg, 2.0 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 0 °C and the mixture was stirred for 1.5 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 10:1) to give **153q** (393 mg, 73%) as a colourless solid.

m.p.: 121.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.14 (ddd, *J*=8.4, 1.7, 1.6 Hz, 2 H), 7.78 (dd, *J*=7.0, 2.2 Hz, 1 H), 7.67 (ddd, *J*=8.6, 4.5, 2.2 Hz, 1 H), 7.55-7.61 (m, 2 H), 7.25-7.33 (m, 1 H), 4.40 (q, *J*=7.2 Hz, 2 H), 1.41 (t, *J*=7.2 Hz, 3 H).

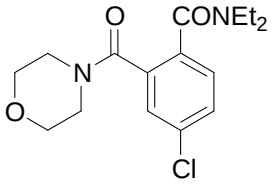
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.97, 161.92 (d, $^1J_{CF}$=259 Hz), 137.60 (d, $^4J_{CF}$=1.7 Hz), 134.93 (d, $^4J_{CF}$=4.4 Hz), 133.73 (d, $^3J_{CF}$=9.8 Hz), 130.73, 129.93, 129.87 (d, $^2J_{CF}$=15 Hz), 128.85 (d, J_{CF}=3.3 Hz), 117.76 (d, J_{CF}=24 Hz), 117.74, 10.15 (d, J_{CF}=3.9 Hz), 61.20, 14.30.

MS (70 eV, EI) *m/z* (%): 269 (6), [M^+], 241 (44), 225 (18), 224 (100), 196 (28), 195 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3110, 3066, 2983, 2939, 2230, 1705, 1668, 1608, 1584, 1568, 1485, 1464, 1443, 1420, 1389, 1375, 1366, 1319, 1273, 1252, 1222, 1190, 1174, 1101, 1037, 1015, 971, 953, 930, 880, 858, 824, 776, 751, 728, 705, 695, 610.

HRMS (EI) for **$C_{16}H_{12}FNO_2$** (269.0852): 269.0865.

Synthesis of 4-chloro-*N*,*N*-diethyl-2-(morpholin-4-ylcarbonyl)benzamide (153r):



According to **TP 7**, the metalation of 4-chloro-*N*,*N*-diethylbenzamide (**102f**; 424 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 2 h at 0 °C. Then, the reaction mixture was cooled to 0 °C and morphinoyl chloride (300 mg, 2.0 mmol) was added, and the resulting mixture was stirred for 5 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with EtOAc (5 × 50 mL). The combined organic layers were washed with aq. NH_3 (2 M, 30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/EtOAc/CH_2Cl_2 = 100:100:1) to give **153r** (408 mg, 63%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.38 (dd, *J*=7.3, 2.2 Hz, 1 H), 7.26-7.28 (m, 1 H), 7.25 (d, *J*=8.3 Hz, 1 H), 3.47-3.70 (m, 8 H), 3.18-3.33 (m, 4 H), 1.19 (t, *J*=7.1 Hz, 3 H), 1.08 (t, *J*=7.1 Hz, 3 H).

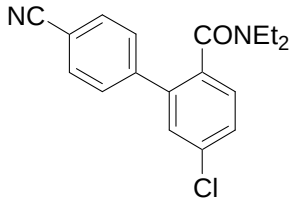
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.44, 167.35, 135.60, 134.69, 133.77, 129.07, 127.52, 126.46, 66.64, 66.42, 47.88, 43.48, 42.18, 39.20, 13.81, 12.64.

MS (70 eV, EI) *m/z* (%): 324 (13) [M^+], 323 (16), 254 (11), 252 (31), 240 (35), 239 (20), 238 (100), 237 (12), 224 (17), 212 (10), 208 (14), 194 (12), 182 (16), 166 (19), 165 (18), 163 (47), 138 (27), 137 (13), 11 (13), 86 (16), 75 (11), 72 (76).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3549, 3503, 2971, 2934, 2859, 1632, 1590, 1562, 1494, 1456, 1430, 1382, 1363, 1348, 1280, 1250, 1220, 1194, 1161, 1112, 1100, 1070, 1021, 941, 908, 876, 844, 832, 791, 733, 617.

HRMS (EI) for **$C_{16}H_{21}ClN_2O_3$** (324.1241): 324.1233.

Synthesis of 5-chloro-4'-cyanobiphenyl-2-carboxylic acid diethylamide (153s):



According to **TP 7**, the metalation of 4-chloro-*N*,*N*-diethylbenzamide (**102f**; 424 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 2 h at 0 °C. 4-Iodobenzonitrile (480 mg, 2.1 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 0 °C and the mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with EtOAc (5 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/Et_2O/CH_2Cl_2 = 40:10:1) to give **153s** (408 mg, 63%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.59-7.62 (m, 2 H), 7.50-55 (m, 2 H), 7.26-7.37 (m, 3 H), 3.53 (br, 2 H), 2.75 (br, 2 H), 0.85 (t, *J*=7.0 Hz, 3 H), 0.73 (t, *J*=7.2 Hz, 3 H).

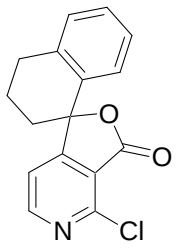
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.71, 142.95, 138.05, 134.91, 134.70, 132.11, 129.42, 129.20, 128.68, 128.42, 118.34, 111.92, 42.38, 38.57, 13.45, 11.91.

MS (70 eV, EI) *m/z* (%): 313 (21), 312 (26) [M^+], 311 (53), 242 (30), 241 (15), 240 (100), 178 (11), 177 (80), 176 (13), 150 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3474, 3057, 2976, 2936, 2875, 2228, 1713, 1623, 1592, 1567, 1549, 1509, 1486, 1457, 1428, 1382, 1364, 1348, 1313, 1288, 1250, 1220, 1190, 1180, 1102, 1084, 1071, 1032, 1016, 944, 877, 842, 819, 771, 752, 733, 696, 655.

HRMS (EI) for **$C_{18}H_{17}ClN_2O$** (312.1029): 312.1024.

Synthesis of 4-chloro-3',4'-dihydro-2'*H*,3*H*-spiro[furo[3,4-*c*]pyridine-1,1'-naphthalen]-3-one (153r):



According to **TP 7**, the metalation of ethyl 2-chloronicotinate (**64g**; 370 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 0.75 h at –20 °C. Then, α-tetralone (292 mg, 2.0 mmol) was added, and the resulting mixture was stirred for 2 h at –20 °C. The reaction mixture was quenched with a sat. aq. $NaHCO_3$ solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (Al_2O_3, pentane/diethyl ether = 1:1) to give **153r** (407 mg, 74%) as a yellowish solid.

m.p.: 202.5 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 8.68 (d, *J*=5.1 Hz, 1 H), 7.62 (d, *J*=5.3 Hz, 1 H), 7.25-7.32 (m, 2 H), 7.05-7.10 (m, 1 H), 6.65 (d, *J*=8.0 Hz, 1 H), 2.92-2.98 (m, 2 H), 2.28-2.37 (m, 1 H), 2.14-2.23 (m, 1 H), 1.88-2.09 (m, 2 H).

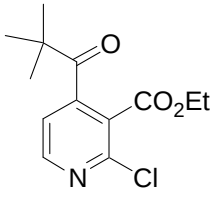
^{13}C-NMR (100 MHz, DMSO) δ: 165.65, 164.97, 154.35, 147.69, 138.36, 132.14, 129.49, 129.28, 127.94, 126.65, 119.66, 117.78, 85.10, 34.83, 28.43, 19.11.

MS (70 eV, EI) *m/z* (%): 287 (22), 285 (60) [M^+], 269 (36), 268 (53), 267 (99), 266 (100), 257 (15), 250 (26), 242 (12), 240 (27), 232 (12), 2231 (23), 230 (22), 229 (27), 222 (11), 213 (28), 207 (13), 206 (73), 205 (12), 204 (43), 203 (15), 202 (11), 194 (22), 193 (23), 178 (18), 177 (14), 166 820), 165 (14), 152 (11), 151 (13), 115 (13), 88 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950, 2919, 2850, 1755, 1683, 1589, 1573, 1450, 1442, 1436, 1426, 1401, 1274, 1252, 1225, 1202, 1190, 1162, 1133, 1113, 1095, 1061, 1048, 1035, 998, 952, 925, 894, 882, 868, 857, 841, 826, 803, 768, 752, 723, 711, 648, 617.

HRMS (EI) for **$C_{16}H_{12}ClNO_2$** (285.0557): 285.0551.

Synthesis of 2-chloro-4-(2,2-dimethyl-propionyl)-nicotinic acid ethyl ester (153u):



According to **TP 7**, the metalation of ethyl 2-chloronicotinate (**64g**; 370 mg, 2.0 mmol) was completed using $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 0.75 h at –20 °C. Then, 2,2-dimethylpropanoic anhydride (372 mg, 2.0 mmol) was added, and the resulting mixture was stirred for 2 h at –20 °C. The reaction mixture was quenched with a sat. aq. $NaHCO_3$ solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 6:1) to give **153u** (458 mg, 85%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.43 (d, *J*=4.9 Hz, 1 H), 7.20 (d, *J*=5.0 Hz, 1 H), 4.33 (q, *J*=7.2 Hz, 2 H), 1.33 (t, *J*=7.1 Hz, 3 H), 1.24 (s, 9 H).

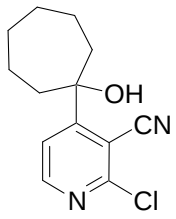
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 209.04, 164.60, 150.73, 150.01, 140.08, 126.40, 118.14, 62.54, 44.49, 27.21, 13.81.

MS (70 eV, EI) *m/z* (%): 269 (1) [M^+], 214 (11), 213 (22), 212 (25), 199 (13), 186 (32), 184 (100), 127 (23), 113 (17), 97 (15), 83 (19), 71 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977, 2938, 2908, 2874, 1727, 1696, 1574, 1538, 1479, 1463, 1449, 1394, 1380, 1364, 1271, 1222, 1185, 1127, 1097, 1065, 1042, 999, 939, 854, 831, 796, 778, 744, 705, 644, 626.

HRMS (ESI) for **$C_{13}H_{16}ClNO_3$** (269.0819): 270.0890.

Synthesis of 2-chloro-4-(1-hydroxycycloheptyl)-nicotinonitrile (154v):



According to **TP 7**, the metalation of 2-chloro, 3-cyanopyridine (**151d**; 276 mg, 2.0 mmol) was completed using $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 0.75 h at –30 °C. Then, cycloheptanone (224 mg, 2.0 mmol) was added, and the resulting mixture was stirred for 2 h at –30 °C. The reaction mixture was quenched with a sat. aq. $NaHCO_3$ solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 3:1) to give **154v** (455 mg, 71%) as a yellowish solid.

m.p.: 105.9 °C.

^{1}H-NMR (400 MHz, DSMO) δ: 8.68 (d, *J*=5.1 Hz, 1 H), 7.88 (d, *J*=5.1 Hz, 1 H), 2.02-2.09 (m, 2 H), 1.88-1.92 (m, 2 H), 1.62-1.74 (m, 9 H).

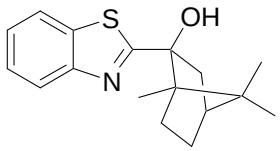
^{13}C-NMR (100 MHz, DMSO) δ: 167.26, 165.00, 154.10, 147.44, 118.21, 116.75, 89.06, 38.03, 28.14, 22.12.

MS (70 eV, EI) *m/z* (%): 250 (3) [M^+], 233 (18), 222 (12), 206 (12), 196 (14), 195 (16), 194 (41), 184 (19), 183 (32), 182 (44), 181 (100), 139 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3520, 3069, 2936, 2863, 2234, 1768, 1728, 1595, 1583, 1570, 1536, 1521, 1460, 1445, 1402, 1372, 1352, 1305, 1285, 1266, 1249, 1222, 1182, 1157, 1104, 1088, 1070, 1056, 1036, 1015, 994, 960, 920, 905, 861, 853, 841, 820, 800, 736, 711, 702.

HRMS (EI) for **$C_{13}H_{15}ClN_2O$** (250.0873): 250.0861.

Synthesis of 2-benzothiazol-2-yl-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol (154w):



According to **TP 7**, the metalation of benzothiazole (**61f**; 270 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 0.5 h at 0 °C. Then, camphor (304 mg, 2.0 mmol) was added, and the resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 4:1) to give **154w** (477 mg, 83%) as a yellowish solid.

m.p.: 88.8 °C.

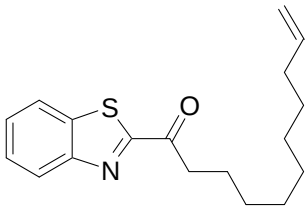
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.99 (dd, *J*=7.7, 0.9 Hz, 1 H), 7.84 (m, 1 H), 7.32-7.47 (m, 2 H), 3.21 (s, 1 H), 2.46-2.53 (m, 1 H), 2.34-2.43 (m, 1 H), 1.93 (t, *J*=4.4 Hz, 1 H), 1.75 (ddd, *J*=15.7, 12.1, 7.7 Hz, 1 H), 1.36-1.46 (m, 1 H), 1.29-1.34 (m, 1 H), 1.23 (s, 3 H), 1.08 (s, 3 H), 1.02 (td, *J*=9.0, 4.6 Hz, 1 H), 0.92 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 178.17, 152.77, 135.20, 125.78, 124.82, 122.97, 121.36, 83.90, 54.38, 50.19, 46.53, 45.34, 30.88, 26.68, 21.15, 21.00, 9.93.

MS (70 eV, EI) *m/z* (%): 287 (48), [M^+], 179 (11), 178 (100), 177 (86), 149 (67), 136 (30), 135 (17), 95 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3489, 3351, 2952, 2930, 2872, 1733, 1503, 1480, 1454, 1437, 1388, 1370, 1312, 1298, 1277, 1256, 1241, 1216, 1197, 1182, 1159, 1146, 1131, 1116, 1100, 1069, 1014, 1003, 973, 962, 950, 913, 884, 863, 835, 789, 758, 729, 706, 676, 658, 621, 611, 605.
HRMS (EI) for **$C_{17}H_{21}NOS$** (287.1344): 287.1340.

Synthesis of 1-benzothiazol-2-yl-undec-10-en-1-one (154x):



According to **TP 7**, the metalation of benzothiazole (**61f**; 270 mg, 2.0 mmol) was completed using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**143**; 0.33 M in THF, 2.2 mL, 0.72 mmol) within 0.5 h at 0 °C. Then, 10-undecene acid chloride (376 mg, 2.0 mmol) was added, and the resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with aq. NH_3 (2 M, 30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 6:1) to give **154x** (463 mg, 77%) as a yellowish solid.

m.p.: 49.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.10-8.20 (m, 1 H), 7.90-8.00 (m, 1 H), 7.45-7.60 (m, 2 H), 5.72-5.85 (m, 1 H), 4.88-5.02 (m, 2 H), 3.17-3.32 (m, 2 H), 1.95-2.09 (m, 2 H), 1.74-1.88 (m, 2 H), 1.27-1.42 (m, 9 H).

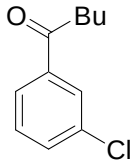
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 195.57, 166.61, 153.57, 139.13, 137.23, 127.52, 126.86, 125.35, 122.38, 114.10, 38.56, 33.75, 29.30, 29.26, 29.16, 29.04, 28.87, 23.95.

MS (70 eV, EI) *m/z* (%): 302 (13), 301 (52), [M^+], 273 (21), 232 (18), 230 (13), 104 (12), 202 (12), 190 (20), 189 (18), 188 (12), 178 (33), 177 (52), 176 (34), 163 (26), 162 (87), 149 (100), 136 (61), 135 (71), 134 (38), 108 (14), 69 (14), 55 (60), 43 (17), 41 (59).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2918, 2850, 1688, 1640, 1551, 1486, 1468, 1426, 1400, 1379, 1360, 1315, 1290, 1249, 1215, 1189, 1161, 1083, 1070, 1004, 975, 946, 926, 902, 868, 846, 758, 730, 721, 704, 650.

HRMS (EI) for **$C_{18}H_{23}NOS$** (301.1500): 301.1486.

Synthesis of 1-(3-chlorophenyl)pentan-1-one (159):



Freshly titrated *n*BuLi (2.56 M; 1.2 mL, 3.0 mmol) was dissolved in dry THF (3 mL) at -30 °C. Then, $ZnCl_2$ (1.0 M solution in THF, 1.5 mL, 1.5 mmol) was added and the mixture was stirred for 30 min at –30°C. Subsequently, $LaCl_3 \cdot 2LiCl$ (0.50 M solution in THF, 1.0 mL, 1.0 mmol) was added, followed by 3-chlorobenzoyl chloride (553 mg, 3.0 mmol) and the resulting mixture was stirred for 1 h at –30 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 9:1) to give **159** (512 mg, 87%) as a colourless solid.

Freshly titrated *n*BuLi (2.56 M; 1.2 mL, 3.0 mmol) was dissolved in dry THF (3 mL) at -30 °C. Then, $ZnCl_2$ (1.0 M solution in THF, 3.0 mL, 3.0 mmol) was added and the mixture was stirred for 30 min at –30°C. Subsequently, $LaCl_3 \cdot 2LiCl$ (0.50 M solution in THF, 1.0 mL, 1.0 mmol) was added, followed by 3-chlorobenzoyl chloride (553 mg, 3.0 mmol) and the resulting mixture was stirred for 3 h at –30 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 9:1) to give **159** (482 mg, 82%) as a colourless solid.

m.p.: 38.2-38.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.89 (t, *J*=1.9 Hz, 1 H), 7.79 (dt, *J*=7.8, 1.3 Hz, 1 H), 7.48 (ddd, *J*=8.0, 2.1, 1.1 Hz, 1 H), 7.36 (t, *J*=7.8 Hz, 1 H), 2.87-2.93 (m, 2 H), 1.64-1.72 (m, 2 H), 1.33-1.43 (m, 2 H), 0.90-0.95 (m, 3 H).

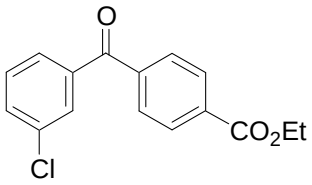
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 199.00, 138.57, 134.80, 132.67, 129.81, 128.07, 126.04, 38.33, 26.20, 22.33, 13.83.

MS (70 eV, EI) *m/z* (%): 196 (9) [M^+], 156 (25), 154 (64), 141 (31), 139 (100), 111 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3078, 2968, 2952, 2930, 2890, 2870, 2863, 1723, 1676, 1573, 1465, 1424, 1404, 1376, 1336, 1276, 1261, 1193, 1172, 1114, 1105, 1080, 1066, 1036, 996, 902, 812, 781, 734, 705, 680.

HRMS (EI) for **$C_{11}H_{13}ClO$** (196.0655): 196.0655.

Synthesis of 4-(3-chlorobenzoyl)benzoic acid ethyl ester (162):



Ethyl 4-iodobenzoate (828 mg, 3.0 mmol) was dissolvd in dry THF (5 mL) and cooled to -30 °C. Freshly titrated *i*PrMgCl·LiCl (1.35 M; 2.2 mL, 3.0 mmol) was added –30 °C and the mixture was stirred for 20 min. Then, $ZnCl_2$ (1.0 M solution in THF, 1.5 mL, 1.5 mmol) was added and the mixture was further stirred for 30 min at –30°C. Subsequently, $LaCl_3 \cdot 2LiCl$ (0.50 M solution in THF, 1.0 mL, 1.0 mmol) was added, followed by 3-chlorobenzoyl chloride (553 mg, 3.0 mmol) and the resulting mixture was warmed to 25 °C and stirred for 12 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (40 mL), extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 7:1) to give **162** (734 mg, 85%) as a colourless solid.

m.p.: 78.1-80.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.10-8.15 (m, 2 H), 7.79 (ddd, *J*=8.4, 1.8, 1.6 Hz, 2 H), 7.74 (t, *J*=1.9 Hz, 1 H), 7.63 (dt, *J*=7.8, 1.3 Hz, 1 H), 7.54 (ddd, *J*=8.0, 2.2, 1.2 Hz, 1 H), 7.40 (t, *J*=7.8 Hz, 1 H), 4.39 (q, *J*=7.0 Hz, 2 H), 1.39 (t, *J*=7.1 Hz, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 194.43, 165.56, 140.37, 138.52, 134.68, 133.87, 132.73, 129.82, 129.69, 129.61, 129.49, 128.05, 61.41, 14.21.

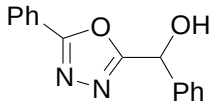
MS (70 eV, EI) *m/z* (%): 209 (20), 289 (13), 288 (50) [M^+], 260 (20), 245 (26), 244 (13), 243 (62), 180 (17), 178 (12), 177 (100), 152 (27), 151 (14), 149 (50), 141 (31), 139 (85), 121 (11), 113 (16), 111 (47), 104 (22), 77 (10), 76 (34), 75 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 2974, 2963, 2934, 2925, 1711, 1678, 1648, 1566, 1419, 1406, 1367, 1301, 1271, 1252, 1184, 1173, 1150, 1120, 1101, 1077, 1058, 1019, 961, 875, 760, 739, 722, 695.

HRMS (EI) for **$C_{16}H_{13}ClO_3$** (288.0553): 288.0546.

13.11 Directed Metalation of Aromatics and Heteroaromatics Using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (165)

Synthesis of phenyl(5-phenyl-1,3,4-oxadiazol-2-yl)methanol (166a):



According to **TP 8**, the metalation of 2-phenyl-1,3,4-oxadiazole (**61a**; 290 mg, 2.0 mmol) was completed using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol) within 30 min at 0 °C. Then, PhCHO (254 mg. 2.4 mmol) was added at 0 °C and the mixture was stirred for another 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 1:1) to give **166a** (390 mg, 77%) as a colourless solid.

m.p.: 154.7 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 7.90-7.99 (m, 2 H), 7.51-7.63 (m, 5 H), 7.31-7.42 (m, 3 H), 6.78 (d, *J*=5.3 Hz, 1 H), 6.09 (d, *J*=5.3 Hz, 1 H).

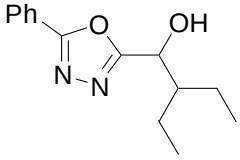
^{13}C-NMR (100 MHz, DMSO) δ: 167.38, 164.18, 139.34, 132.04, 129.43, 128.41, 128.14, 126.52, 126.46, 123.12, 66.43.

MS (70 eV, EI) *m/z* (%): 253 (17), 252 (100) [M^+], 223 (10), 147 (24), 145 (33), 132 (11), 107 (40), 106 (13), 105 (89), 104 (17), 103 (14), 79 (21), 77 (56).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3437, 3086, 3061, 1610, 1568, 1552, 1490, 1451, 1418, 1340, 1311, 1261, 1213, 1195, 1086, 1064, 1027, 1017, 1003, 957, 920, 835, 821, 775, 741, 707, 701, 692, 683, 657, 646, 637, 626, 616, 610, 602.

HRMS (EI) for **$C_{15}H_{12}N_2O_2$** (252.0899): 252.0893.

Synthesis of 2-ethyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)butan-1-ol (166b):



According to **TP 8**, the metalation of 2-phenyl-1,3,4-oxadiazole (**61a**; 292 mg, 2.0 mmol) was completed using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol) within 30 min at 0 °C. Then, 2-ethyl butanal (240 mg, 2.4 mmol) was added at 0 °C and the mixture was stirred for another 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl

solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 2:3) to give **166b** (364 mg, 74%) as a colourless solid.

m.p.: 79.3-80.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.00-8.03 (m, 2 H), 7.43-7.54 (m, 3 H), 5.01 (d, *J*=6.0 Hz, 1 H), 3.47 (br, 1 H), 1.80-1.88 (m, 1 H), 1.30-1.58 (m, 4 H), 0.91 (t, *J*=7.4 Hz, 3 H), 0.90 (t, *J*=7.4 Hz, 3 H).

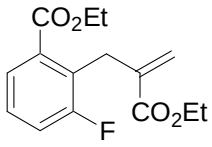
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.83, 164.95, 131.79, 129.00, 126.93, 123.62, 67.92, 45.68, 21.83, 21.10, 11.30, 10.94.

MS (70 eV, EI) *m/z* (%): 246 (3) [M^+], 177 (12), 176 (100), 174 (23), 105 (20), 104 (38), 103 (18), 77 (20), 43 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3304, 2962, 2937, 2924, 2876, 1609, 1590, 1563, 1553, 1490, 1465, 1453, 1374, 1353, 1331, 1317, 1293, 1270, 1232, 1166, 1160, 1089, 1070, 1042, 1025, 1012, 991, 968, 959, 919, 862, 788, 777, 769, 754, 736, 702, 689, 618.

HRMS (EI) for **$C_{14}H_{18}N_2O_2$** (246.1368): 246.1367.

Synthesis of 2-(2-ethoxycarbonylallyl)-3-fluorobenzoic acid ethyl ester (171a)



According to **TP 8**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed within 1 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). The reaction mixture was cooled to 0 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and ethyl 2-(bromomethyl)acrylate (483 mg, 2.5 mmol) were added and stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 12:1) to give **171a** (476 mg, 85%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, *J*=7.8 Hz, 1 H), 7.29 (td, *J*=7.9, 5.5 Hz, 1 H), 7.20 (ddd, *J*=9.5, 8.3, 1.4 Hz, 1 H), 6.15 (q, *J*=1.4 Hz, 1 H), 5.04 (dt, *J*=1.8, 1.0 Hz, 1 H), 4.30 (q, *J*=7.0 Hz, 2 H), 4.23 (q, *J*=7.2 Hz, 2 H), 4.01 (s, 2 H), 1.32 (t, *J*=7.2 Hz, 3 H), 1.29 (t, *J*=7.2 Hz, 3 H).

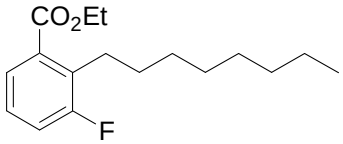
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.72, 166.49 (d, $^4J_{CF}$=3.5 Hz), 161.46 (d, $^1J_{CF}$=246 Hz), 138.87 (d, $^4J_{CF}$=1.0 Hz), 132.89 (d, $^3J_{CF}$=3.8 Hz), 127.82 (d, $^3J_{CF}$=8.8 Hz), 126.92 (d, $^2J_{CF}$=17 Hz), 126.83, 124.34, 118.81 (d, $^2J_{CF}$=23 Hz), 61.26, 60.79, 27.65 (d, $^3J_{CF}$=5.4 Hz), 14.16, 14.08.

MS (70 eV, EI) *m/z* (%): 280 (5) [M^+], 235 (19), 234 (53), 207 (33), 206 (100), 179 (24), 178 (67), 163 (40), 162 (43), 161 (37), 160 (11), 151 (15), 149 (18), 135 (12), 134 (12), 133 (37).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1713, 1635, 1611, 1580, 1458, 1406, 1367, 1345, 1261, 1217, 1172, 1129, 1095, 1074, 1025, 977, 942, 868, 845, 816, 756, 730, 645, 637, 624, 615.

HRMS (EI) for **$C_{15}H_{17}FO_4$** (280.1111): 280.1112.

Synthesis of 3-fluoro-2-octylbenzoic acid ethyl ester (171b):



According to **TP 8**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed within 1 h at 25 °C using $TMP_2Mn·2MgCl_2·4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). The reaction mixture was cooled to 0°C, then $CuCl_2·2LiCl$ (1.0 M solution in THF, 0.1 mL, 0.1 mmol), followed by 1-iodooctane (576 mg, 2.4 mmol) and the resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and 2 M HCl (10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **171b** (420 mg, 75%) as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.59-7.61 (m, 1 H), 7.12-7.21 (m, 2 H), 4.36 (q, *J*=7.1 Hz, 2 H), 2.90-2.95 (m, 2 H), 1.52-1.60 (m, 3 H), 1.38 (t, *J*=7.0 Hz, 3 H), 1.22-1.35 (m, 9 H), 0.88 (t, *J*=7.0 Hz, 3 H).

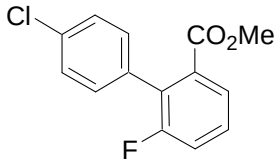
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.11 (d, $^4J_{CF}$=3.7 Hz), 161.37 (d, $^1J_{CF}$=244 Hz), 132.30 (d, $^3J_{CF}$=4.6 Hz), 131.60 (d, $^2J_{CF}$=17 Hz), 126.56 (d, $^3J_{CF}$=9.0 Hz), 125.93 (d, $^4J_{CF}$=3.5 Hz), 118.44 (d, $^2J_{CF}$=23 Hz), 61.11, 31.88, 30.70 (d, J_{CF}=1.0 Hz), 29.83, 29.42, 29.26, 26.01 (d, J_{CF}=4.0 Hz), 22.66, 14.25, 14.09.

MS (70 eV, EI) *m/z* (%): 280 (25) [M^+], 236 (13), 235 (82), 182 (100), 167 (28), 164 (18), 163 (30), 154 (32), 153 (55), 150 (18), 149 (65), 137 (16), 136 (69), 135 (11), 109 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956, 2926, 2871, 2856, 1722, 1579, 1456, 1391, 1378, 1366, 1258, 1205, 1174, 1142, 1099, 1072, 1045, 1025, 955, 919, 867, 839, 816, 756, 723.

HRMS (EI) for **$C_{17}H_{25}FO_2$** (280.1839): 280.1837.

Synthesis of ethyl 3-cyano-2-cyclohex-2-en-1-ylbenzoate (171c)



According to **TP 8**, the metalation of methyl 3-fluorobenzoate (**151a**; 308 mg, 2.0 mmol) was completed within 1.25 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, 1-iodo-4-chlorobenzene (523 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 25 °C and the mixture was stirred for 4 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 10:1) to give **171c** (422 mg, 80%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.67-7.72 (m, 1 H), 7.39-7.47 (m, 3 H), 7.23-7.35 (m, 3 H), 3.66 (s, 3 H).

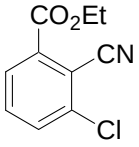
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.27 (d, $^4J_{CF}$=3.5 Hz), 159.65 (d, $^1J_{CF}$=246 Hz), 133.87, 132.96 (d, $^5J_{CF}$=2.5 Hz), 132.40, 130.58, 129.07 (d, $^3J_{CF}$=8.5 Hz), 128.88 (d, $^2J_{CF}$=17 Hz), 128.81, 126.61 (d, $^3J_{CF}$=3.5 Hz), 118.97 (d, $^2J_{CF}$=23 Hz), 52.15.

MS (70 eV, EI) *m/z* (%): 266 (18), 264 (54) [M^+], 235 (28), 234 (13), 233 (100), 170 (51), 85 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3002, 2952, 2848, 1726, 1610, 1596, 1577, 1498, 1454, 1433, 1398, 1291, 1273, 1268, 1243, 1194, 1172, 1139, 1102, 1090, 1021, 1006, 988, 918, 894, 829, 799, 764, 751, 720, 684, 632.

HRMS (EI) for **$C_{14}H_{10}ClFO_2$** (264.0353): 264.0345.

Synthesis of 3-chloro-2-cyanobenzoic acid ethyl ester (171d)



According to **TP 8**, the metalation of ethyl 3-chlorobenzoate (**67b**; 370 mg, 2.0 mmol) was completed within 2 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, TosCN (400 mg, 2.0 mmol) was added at 25 °C and the mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL),

extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 10:1) to give **171d** (357 mg, 85%) as a colourless solid.

m.p.: 96.5-97.3 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.02 (dd, *J*=7.8, 1.2 Hz, 1 H), 7.68-7.73 (m, 1 H), 7.59 (t, *J*=7.9 Hz, 1 H), 4.45 (q, *J*=7.0 Hz, 2 H), 1.43 (t, *J*=7.2 Hz, 3 H).

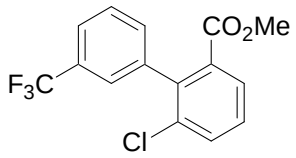
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 163.31, 139.34, 135.04, 133.49, 132.93, 129.21, 114.22, 113.32, 62.70, 14.05.

MS (70 eV, EI) *m/z* (%): 211 (10), 209 (33) [M^+], 183, (12), 164 (100), 137 (30), 100 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3086, 3066, 2986, 2229, 1724, 1688, 1581, 1567, 1480, 1455, 1437, 1392, 1370, 1274, 1206, 1167, 1120, 1108, 1071, 1024, 938, 901, 868, 830, 802, 776, 762, 728, 710, 691, 684, 676, 668, 658, 644, 636, 620, 608.

HRMS (EI) for **$C_{10}H_8ClNO_2$** (209.0244): 209.0245.

Synthesis of methyl 6-chloro-3'-(trifluoromethyl)biphenyl-2-carboxylate (171e)



According to **TP 8**, the metalation of methyl 3-chlorobenzoate (**100c**; 340 mg, 2.0 mmol) was completed within 2 h at 25 °C using $TMP_2Mn·2MgCl_2·4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, 1-iodo-3-trifluoromethylbenzene (598 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 25 °C and the mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 20:1) to give **171e** (484 mg, 77%) as a yellowish oil.

^{1}H-NMR (400 MHz, DMSO) δ: 7.83 (ddd, *J*=7.9, 5.8, 1.2 Hz, 2 H), 7.76 (d, *J*=8.0 Hz, 1 H), 7.66 (t, *J*=7.7 Hz, 1 H), 7.58 (t, *J*=8.0 Hz, 1 H), 7.50-7.54 (m, 2 H), 3.50 (s, 3 H).

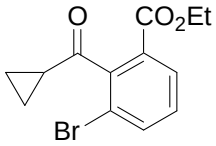
^{13}C-NMR (100 MHz, DMSO) δ: 166.27, 138.47, 138.17, 133.36, 133.05 (q, $^4J_{CF}$=1.3 Hz) 133.03, 132.76, 129.84, 129.05, 128.73 (q, $^2J_{CF}$=31 Hz) 128.28, 126.86 (q, $^1J_{CF}$=272 Hz), 125.43 (q, $^3J_{CF}$=3.91 Hz), 124.41 (q, $^3J_{CF}$=3.9 Hz), 52.10.

MS (70 eV, EI) *m/z* (%): 316 (17), 314 (50) [M^+], 285 (36), 284 (17), 283 (100), 262 (12), 247 (17), 220 (34), 219 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 1730, 1615, 1593, 1562, 1493, 1456, 1432, 1424, 1329, 1282, 1249, 1201, 1177, 1164, 1121, 1096, 1072, 1025, 1002, 971, 903, 847, 825, 802, 761, 744, 724, 701, 663, 647, 639, 628, 622, 618, 609.

HRMS (EI) for **$C_{15}H_{10}ClF_3O_2$** (314.0321): 314.0321.

Synthesis of (2-bromo-6-methylphenyl)cyclopropyl-methanone (171f)



According to **TP 8**, the metalation of ethyl 3-bromobenzoate (**100b**; 458 mg, 2.0 mmol) was completed within 2 h at 25 °C using $TMP_2Mn·2MgCl_2·4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). The reaction mixture was cooled to –30 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.4 mL, 0.4 mmol) and cyclopropanecarbonyl chloride (260 mg, 2.5 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 6:1) to give **171f** (518 mg, 79%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.97 (dd, *J*=7.9, 1.1 Hz, 1 H), 7.76 (dd, *J*=8.0, 1.2 Hz, 1 H), 7.30 (t, *J*=8.0 Hz, 1 H), 4.33 (q, *J*=7.3 Hz, 2 H), 2.15-2.24 (m, 1 H), 1.39-1.45 (m, 2 H), 1.35 (t, *J*=7.2 Hz, 3 H), 1.11-1.17 (m, 2 H).

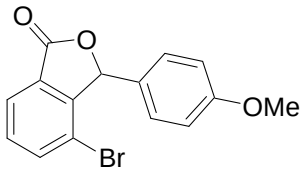
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 205.13, 164.80, 144.97, 136.95, 129.65, 129.56, 129.32, 118.66, 61.90, 22.87, 14.12, 13.55.

MS (70 eV, EI) *m/z* (%): 296 (9) [M^+], 257 (13), 255 (12), 253 (18), 252 (27), 251 (22), 250 (27), 242 (17), 240 (16), 289 (89), 227 (100), 224 (19), 115 (34), 92 (12), 75 (36), 74 (11), 69 (36), 61 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 2933, 2904, 1712, 1685, 1584, 1560, 1512, 1484, 1444, 1430, 1418, 1367, 1326, 1268, 1202, 1176, 1157, 1126, 1107, 1077, 1062, 1033, 1026, 986, 977, 930, 898, 870, 818, 811, 789, 760, 740, 706, 660, 643, 636, 629, 612, 602.

HRMS (EI) for **$C_{13}H_{13}BrO_3$** (296.0048): 296.0045.

Synthesis of 4-bromo-3-(4-methoxyphenyl)-2-benzo[c]furan-1(3*H*)-one (171g)



According to **TP 8**, the metalation of methyl 3-bromobenzoate (**151b**; 428 mg, 2.0 mmol) was completed within 2 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, 4-methoxybenzaldehyde (326 mg, 2.4 mmol) was added and the mixture was stirred for additional 2 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (Al_2O_3; pentane/diethyl ether = 3:1) to give **171g** (517 mg, 81%) as a yellowish solid.

m.p.: 158.9 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 7.93-8.01 (m, 2 H), 7.61 (t, *J*=7.7 Hz, 1 H), 7.16 (ddd, *J*=9.3, 2.9, 2.6 Hz, 2 H), 6.94 (ddd, *J*=9.2, 2.9, 2.5 Hz, 2 H), 6.59 (s, 1 H), 3.75 (s, 3 H).

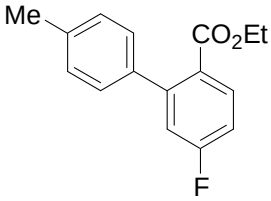
^{13}C-NMR (100 MHz, DMSO) δ: 168.59, 159.97, 148.02, 138.06, 131.87, 129.89, 128.04, 126.34, 124.40, 117.14, 114.17, 82.51, 55.15.

MS (70 eV, EI) *m/z* (%): 320 (31), 318 (41) [M^+], 196 (15), 195 (100), 180 (20), 152 (35), 151 (13), 135 (15), 75 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3009, 2935, 2840, 1762, 1607, 1583, 1514, 1472, 1456, 1442, 1437, 1428, 1332, 1307, 1297, 1289, 1280, 1258, 1250, 1206, 1195, 1180, 1174, 1166, 1138, 1124, 1110, 1066, 1043, 1027, 989, 966, 933, 891, 854, 838, 822, 811, 785, 751, 720, 688, 678, 668, 660, 653, 648, 642, 634, 627, 618.

HRMS (EI) for **$C_{15}H_{11}BrO_3$** (317.9892): 317.9882.

Synthesis of 5-fluoro-4'-methylbiphenyl-2-carboxylic acid ethyl ester (171i):



According to **TP 8**, the metalation of ethyl 4-fluorobenzoate (**67a**; 334 mg, 2.0 mmol) was completed within 1.5 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, 4-iodotoluene (480 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 25 °C and the mixture was stirred for 3 h at 25 °C. The reaction mixture was

quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 7:1) to give **171i** (406 mg, 79%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.80-7.85 (m, 1 H), 7.15-7.20 (m, 4 H), 7.02-7.10 (m, 2 H), 4.10 (q, *J*=7.0 Hz, 2 H), 2.40 (s, 3 H), 1.04 (t, *J*=7.0 Hz, 3 H).

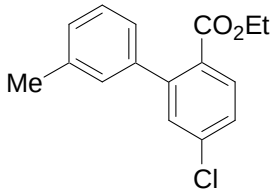
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.74, 163.88 (d, $^1J_{CF}$=252 Hz), 145.44 (d, $^3J_{CF}$=8.6 Hz), 137.50 (d, $^4J_{CF}$=1.5 Hz), 137.36, 132.28, 132.18, 128.74, 128.11, 128.05, 127.23 (d, $^3J_{CF}$=2.9 Hz), 117.59 (d, $^2J_{CF}$=22 Hz), 113.86 (d, $^2J_{CF}$=22 Hz), 60.94, 21.16, 13.68.

MS (70 eV, EI) *m/z* (%): 258 (48) [M^+], 230 (19), 229 (12), 214 (17), 213 (100), 199 (10), 192 (14). 185 (11), 184 (10), 183 (30), 170 (28), 165 (31), 74 (17), 59 (27), 45 (20), 44 (14), 43 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2928, 2904, 2872, 1710, 1654, 1608, 1592, 1580, 1568, 1518, 1506, 1480, 1466, 1450, 1412, 1390, 1366, 1274, 1238, 1182, 1154, 1094, 1034, 1016, 938, 932, 920, 900, 876, 854, 832, 816, 778, 770, 746, 708, 692, 668, 648, 634, 618, 608, 586, 574, 560.

HRMS (EI) for **$C_{16}H_{15}FO_2$** (258.1056): 258.1041.

Synthesis of ethyl 5-chloro-3'-methylbiphenyl-2-carboxylate (171j)



According to **TP 8**, the metalation of ethyl 4-chlorobenzoate (**67c**; 370 mg, 2.0 mmol) was completed within 3 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, 1-iodotoluene (480 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 25 °C and the mixture was stirred for 6 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 30:1) to give **171j** (411 mg, 75%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.72-7.78 (m, 1 H), 7.33-7.38 (m, 2 H), 7.24-7.29 (m, 1 H), 7.16-7.18 (m, 1 H), 7.06-7.10 (m, 2 H), 4.08 (q, *J*=7.0 Hz, 2 H), 2.37 (s, 3 H), 0.99 (t, *J*=7.0 Hz, 3 H).

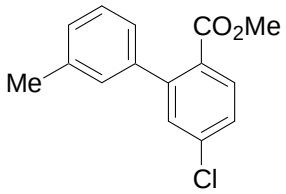
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.92, 144.34, 140.11, 137.69, 137.04, 131.16, 130.60, 129.60, 128.90, 128.34, 127.98, 127.15, 125.33, 61.06, 21.38, 13.62.

MS (70 eV, EI) *m/z* (%): 276 (29), 275 (17), 274 (96) [M^+], 246 (13), 245 (14), 231 (529, 230 (27), 229 (100), 217 (30), 215 (30), 166 (54), 165 (71).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 2925, 1713, 1607, 1590, 1560, 1465, 1445, 1384, 1364, 1276, 1241, 1190, 1172, 1131, 1100, 1047, 1017, 880, 831, 788, 777, 760, 699, 687, 628, 605.

HRMS (EI) for **$C_{16}H_{15}ClO_2$** (274.0761): 274.0754.

Synthesis of methyl 5-chloro-3'-methylbiphenyl-2-carboxylate (171k)



According to **TP 8**, the metalation of methyl 4-chlorobenzoate (**67e**; 341 mg, 2.0 mmol) was completed within 3 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, 3-iodotoluene (480 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 25 °C and the mixture was stirred for 6 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 20:1) to give **171k** (417 mg, 80%) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, *J*=9.0 Hz, 1 H), 7.36 (dq, *J*=4.4, 2.2 Hz, 2 H), 7.27 (t, *J*=7.5 Hz, 1 H), 7.16-7.19 (m, 1 H), 7.10-7.12 (m, 1 H), 7.05-7.08 (m, 1 H), 3.63 (s, 3 H), 2.39 (s, 3 H).

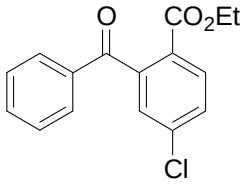
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 168.22, 144.43, 139.91, 137.80, 137.22, 131.21, 130.73, 129.08, 128.76, 128.46, 127.97, 127.15, 125.28, 52.05, 21.42.

MS (70 eV, EI) *m/z* (%): 262 (19), 261 (16), 260 (62) [M^+], 259 (15), 231 (32), 230 (16), 229 (100), 166 (35), 165 (38).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3027, 1719, 1606, 1590, 1559, 1469, 1432, 1385, 1283, 1276, 1242, 1189, 1130, 1102, 1048, 1015, 1000, 964, 881, 836, 820, 790, 777, 759, 739, 714, 699, 687, 674, 668, 663, 661, 655, 648, 643, 638, 629, 620, 614, 611, 608, 603.

HRMS (EI) for **$C_{15}H_{13}ClO_2$** (260.0604): 260.0598.

Synthesis of 2-benzoyl-4-chlorobenzoic acid ethyl ester (69f):



According to **TP 8**, the metalation of ethyl 4-chlorobenzoate (**67c**; 370 mg, 2.0 mmol) was completed within 3 h at 25 °C using $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). The reaction mixture was cooled to –30 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.4 mL, 0.4 mmol) and benzoyl chloride (336 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 3 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 6:1) to give **69f** (479 mg, 83%) as a colourless solid.

m.p.: 78.9-80.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J*=8.4 Hz, 1 H), 7.77-7.73 (m, 2 H), 7.57-7.52 (m, 2H), 7.46–7.41 (m, 2 H), 7.36 (d, *J*=8.4 Hz, 1 H), 4.07 (q, *J*=7.1 Hz, 2 H), 1.04 (t, *J*=7.1 Hz, 3 H).

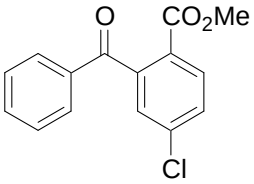
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 195.54, 165.22, 143.44, 139.24, 136.85, 133.69, 131.93, 129.89, 129.61, 128.89, 127.96, 127.82, 61.98, 13.82.

MS (70 eV, EI) *m/z* (%): 288 (24) [M^+], 245 (16), 244 (15), 243 (35), 213 (11), 211 (36), 183 (56), 152 (21), 105 (100), 77 (45), 57 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 2909, 1712, 1677, 1619, 1590, 1583, 1560, 1490, 1473, 1450, 1445, 1385, 1363, 1319, 1311, 1283, 1267, 1243, 1177, 1153, 1134, 1105, 1089, 1074, 1021, 1001, 979, 966, 954, 942, 899, 875, 860, 843, 815, 808, 780, 770, 712, 698, 690, 643, 619, 609, 591, 585.

HRMS (EI) for **$C_{16}H_{13}ClO_3$** (288.0553): 288.0550.

Synthesis of 2-benzoyl-4-chlorobenzoic acid methyl ester (101b):



According to **TP 8**, the metalation of methyl 4-chlorobenzoate (**67e**; 341 mg, 2.0 mmol) was completed within 3 h at 25 °C using $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**165**; 0.50 M in THF, 2.4 mL,

2.4 mmol). The reaction mixture was cooled to –30 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.4 mL, 0.4 mmol) and benzoyl chloride (336 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 3 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 6:1) to give **101b** (434 mg, 79%) as a colourless solid.

m.p.: 98.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J*=8.4 Hz, 1 H), 7.72-7.75 (m, 2 H), 7.52-7.59 (m, 2 H), 7.42-7.46 (m, 2 H), 7.37 (d, *J*=2.1 Hz, 1 H), 3.61 (s, 3 H).

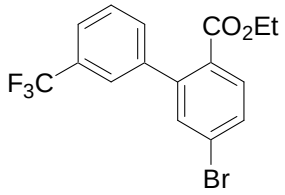
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 195.35, 165.44, 143.31, 139.10, 136.55, 133.41, 131.61, 129.72, 129.23, 128.63, 127.83, 127.38, 52.34.

MS (70 eV, EI) *m/z* (%): 274 (26) [M^+], 243 (21), 197 (80), 152 (10), 105 (100), 77 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1717, 1668, 1595, 1585, 1564, 1452, 1434, 1388, 1317, 1280, 1272, 1257, 1181, 1157, 1142, 1104, 1074, 1026, 1001, 979, 952, 934, 929, 902, 860, 849, 834, 807, 786, 768, 711, 700, 693, 671, 660, 645, 634, 629, 624, 620, 612, 608.

HRMS (EI) for **$C_{15}H_{11}ClO_3$** (274.0397): 274.0393.

Synthesis of 5-bromobiphenyl-2,4'-dicarboxylic acid diethyl ester (69i)



According to **TP 8**, the metalation of ethyl 4-bromobenzoate (**67f**; 458 mg, 2.0 mmol) was completed within 3.5 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, 1-iodo-3-trifluoromethylbenzene (598 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 25 °C and the mixture was stirred for 5 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 15:1) to give **69i** (582 mg, 78%) as a yellowish oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.79 (d, *J*=8.3 Hz, 1 H), 7.63 (d, *J*=7.6 Hz, 1 H), 7.59 (dd, *J*=8.3, 1.9 Hz, 1 H) 7.54-7.46 (m, 4 H), 4.06 (q, *J*=7.2 Hz, 2 H), 0.98 (t, *J*=7.2 Hz, 3 H).

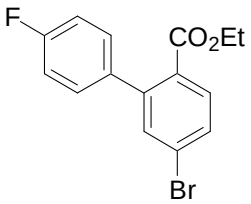
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 167.1, 142.9, 141.0, 133.5, 131.8, 131.6 (q, $^4J_{CF}$=1.3 Hz), 131.0, 130.4 (q, $^2J_{CF}$=32 Hz), 129.7, 128.5, 126.0, 125.2 (q, $^3J_{CF}$=3.9 Hz), 124.3 (q, $^3J_{CF}$=3.9 Hz), 123.8 (q, $^1J_{-F}$=272 Hz), 61.2, 13.5.

MS (70 eV, EI) *m/z* (%): 374 (42), 372 (38) [M^+], 346 (26), 345 (11), 344 (25), 330 (17), 329 (94), 328 (16), 327 (100), 248 (38), 221 (11), 220 (68), 219 (28), 201 (18), 170 (10), 43 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 1715, 1585, 1557, 1492, 1444, 1432, 1384, 1365, 1328, 1272, 1238, 1164, 1122, 1094, 1072, 1035, 1016, 905, 885, 860, 834, 803, 778, 753, 701, 688, 657, 626, 615, 608, 591, 568, 560, 554.

HRMS (EI) for **$C_{16}H_{12}BrF_3O_2$** (371.9973): 371.9955.

Synthesis of 5-bromo-4'-fluorobiphenyl-2-carboxylic acid ethyl ester (171l)



According to **TP 8**, the metalation of ethyl 4-bromobenzoate (**67f**; 458 mg, 2.0 mmol) was completed within 3.5 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, 1-fluoro-4-iodobenzene (488 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 25 °C and the mixture was stirred for 5 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 15:1) to give **171l** (582 mg, 72%) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, *J*=8.4 Hz, 1 H), 7.52-7.56 (m, 1 H), 7.49 (d, *J*=1.9 Hz, 1 H), 7.22-7.27 (m, 2 H), 7.05-7.11 (m, 2 H), 4.09 (q, *J*=7.1 Hz, 2 H), 1.04 (t, *J*=7.1 Hz, 3 H).

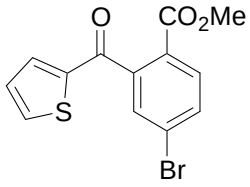
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.59, 162.47 (d, $^1J_{CF}$=246 Hz), 143.35, 136.11, 133.63, 131.50, 130.45, 129.94 (d, $^3J_{CF}$=8.0 Hz), 129.85, 125.73, 115.03 (d, ^2J_C=22 Hz), 61.18, 13.71.

MS (70 eV, EI) *m/z* (%): 324 (56), 323 (15), 322 (67) [M^+], 296 (15), 295 (10), 294 (15), 280 (15), 279 (81), 278 (17), 277 (99), 199 (22), 198 (73), 171 (15), 170 (100), 169 (21), 168 (11), 85 (16), 57 (14), 44 (40), 43 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3038, 2984, 2937, 1700, 1660, 1606, 1585, 1554, 1508, 1466, 1400, 1386, 1363, 1285, 1247, 1228, 1212, 1157, 1137, 1103, 1093, 1080, 1025, 1015, 970, 960, 897, 863, 839, 830, 815, 780, 761, 723, 706, 668, 635, 612.

HRMS (EI) for **$C_{15}H_{12}BrFO_2$** (322.0005): 321.9991.

Synthesis of methyl 4-bromo-2-(2-thienylcarbonyl)benzoate (171m)



According to **TP 8**, the metalation of methyl 4-bromobenzoate (**100a**; 428 mg, 2.0 mmol) was completed within 3.5 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). The reaction mixture was cooled to –30 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.4 mL, 0.4 mmol) and 2-thiophene acid chloride (365 mg, 2.5 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 6:1) to give **171m** (518 mg, 79%) as a colourless solid.

m.p.: 98.9 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.89 (d, *J*=8.1 Hz, 1 H), 7.67-7.72 (m, 2 H), 7.60 (d, *J*=1.9 Hz, 1 H), 7.26 (d, *J*=3.8 Hz, 1 H), 7.07 (dd, *J*=4.8, 3.8 Hz, 1 H), 3.67 (s, 3 H).

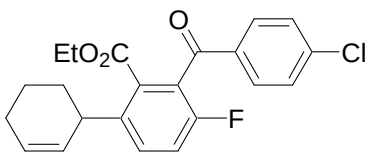
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 187.24, 165.55, 143.86, 142.61, 134.84, 134.45, 132.97, 131.75, 130.65, 128.16, 127.81, 127.21, 52.44.

MS (70 eV, EI) *m/z* (%): 327 (18), 326 (94), 325 (13), 324 (100) [M^+], 298 (22), 296 (23), 295 (61), 294 (18), 293 (78), 243 (50), 241 (60), 158 (50), 154 (13), 113 (14), 111 (96), 75 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3094, 2954, 1771, 1722, 1647, 1584, 1559, 1520, 1512, 1479, 1438, 1418, 1407, 1380, 1352, 1274, 1255, 1235, 1194, 1155, 1136, 1094, 1084, 1075, 1051, 956, 928, 905, 882, 852, 826, 790, 751, 727, 694, 677, 649, 637, 630, 621, 617, 612, 608, 602.

HRMS (EI) for **$C_{13}H_9BrO_3S$** (323.9456): 323.9455.

Synthesis of ethyl 2-(4-chlorobenzoyl)-6-cyclohex-2-en-1-yl-3-fluorobenzoate (174)



According to **TP 8**, the metalation of ethyl 2-(4-chlorobenzoyl)-3-fluorobenzoate (**153b**; 306 mg, 1.0 mmol) was completed within 2 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**;

0.50 M in THF, 2.4 mL, 2.4 mmol). The reaction mixture was cooled to 0 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and 3-bromocyclohexene (391 mg, 2.4 mmol) were added and stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 9:1) to give **174** (286 mg, 74%) as a yellowish oil.

^{1}H-NMR (400 MHz, DMSO) δ: 7.87 (d, *J*=8.0 Hz, 1 H), 7.72 (ddd, *J*=9.0, 2.3, 2.2 Hz, 2 H), 7.61 (ddd, *J*=9.0, 2.3, 2.2 Hz, 2 H), 7.52 (t, *J*=7.8 Hz, 1 H), 5.98 (ddd, *J*=9.9, 6.1, 3.6 Hz, 1 H), 5.64 (dd, *J*=10.2, 2.3 Hz, 1 H), 4.08 (q, *J*=7.1 Hz, 2 H), 3.74 (td, *J*=4.9, 2.6 Hz, 1 H), 2.02-2.10 (m, 2 H), 1.93-2.01 (m, 1 H), 1.58-1.65 (m, 3 H), 1.02 (t, *J*=7.0 Hz, 3 H).

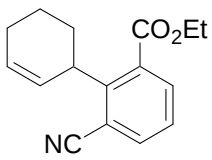
^{13}C-NMR (100 MHz, DMSO) δ: 190.98 (d, $^3J_{CF}$=1.6 Hz), 163.91 (d, $^4J_{CF}$=3.1 Hz), 156.18 (d, $^1J_{CF}$=245 Hz), 138.76, 138.43 (d, $^2J_{CF}$=15 Hz) 135.22, 130.44 (d, $^3J_{CF}$=5.6 Hz), 130.31, 129.76, 129.19, 128.21 (d, $^2J_{CF}$=21 Hz), 127.73 (d, $^3J_{CF}$=3.9 Hz), 127.32, 126.10 (d, $^4J_{CF}$=3.1 Hz), 61.46, 34.06 (d, $^5J_{CF}$=1.9 Hz), 29.53, 24.21, 20.16, 13.48.

MS (70 eV, EI) *m/z* (%): 388 (30), 387 (19), 386 (100) [M^+], 341 (15), 247 (37), 140 (15), 138 (48), 111 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 2930, 2859 1779, 1718, 1681, 1587, 1572, 1481, 1446, 1423, 1399, 1367, 1283, 1184, 1164, 1132, 1090, 1025, 1012, 944, 899, 891, 883, 842, 781, 741, 725, 684, 668, 662, 647, 642, 634, 630, 623, 618, 611, 601.

HRMS (EI) for **$C_{22}H_{20}ClFO_3$** (386.1085): 386.1085.

Synthesis of ethyl 3-cyano-2-cyclohex-2-en-1-ylbenzoate (177a)



According to **TP 8**, the metalation of ethyl 3-cyanobenzoate (**67i**; 350 mg, 2.0 mmol) was completed within 45 min at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and 3-bromocyclohexene (391 mg, 2.4 mmol) were added and stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 15:1) to give **177a** (449 mg, 88%) as a yellowish oil.

^{1}H-NMR (400 MHz, DMSO) δ: 7.93 (dd, *J*=7.7, 1.5 Hz, 1 H), 7.79 (dd, *J*=7.8, 1.4 Hz, 1 H), 7.50 (t, *J*=7.8 Hz, 1 H), 5.87 (dq, *J*=10.1, 3.3 Hz, 1 H), 5.49 (dd, *J*=10.1, 1.7 Hz, 1 H), 4.20-4.33 (m, 2 H), 3.97-4.02 (m, 1 H), 1.84-2.07 (m, 5 H), 1.55-1.63 (m, 1 H), 1.28 (t, *J*=7.1 Hz, 3 H).

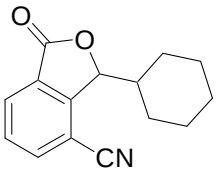
^{13}C-NMR (100 MHz, DMSO) δ: 167.11, 146.93, 136.64, 133.86, 133.05, 129.34, 127.34, 127.02, 117.10, 112.38, 61.38, 40.38, 29.27, 23.96, 22.25, 13.78.

MS (70 eV, EI) *m/z* (%): 255 (10) [M^+], 210 (20), 209 (100), 208 (32), 191 (22), 190 (14), 181 (12), 180 (37), 153 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2934, 2865, 2226, 1719, 1684, 1580, 1472, 1456, 1443, 1391, 1367, 1280, 1254, 1176, 1139, 1130, 1112, 1050, 1019, 984, 919, 899, 877, 863, 848, 810, 789, 754, 741, 722, 694, 686, 632, 612, 607.

HRMS (EI) for **$C_{16}H_{17}NO_2$** (255.1259): 255.1256.

Synthesis of 3-cyclohexyl-1-oxo-1,3-dihydro-2-benzo[c]furan-4-carbonitrile (177b)



According to **TP 8**, the metalation of ethyl 3-cyanobenzoate (**67i**; 350 mg, 2.0 mmol) was completed within 45 min at 0 °C using $TMP_2Mn·2MgCl_2·4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, cyclohexane carbaldehyde (235 mg, 2.1 mmol) was added and the resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (Al_2O_3; pentane/diethyl ether = 3:1) to give **177b** (366 mg, 76%) as a colourless solid.

m.p.: 115.8 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 8.29 (d, *J*=7.6 Hz, 1 H), 8.17 (d, *J*=7.6 Hz, 1 H), 7.80 (t, *J*=7.7 Hz, 1 H), 5.87 (d, *J*=2.3 Hz, 1 H), 2.21-2.30 (m, 1 H), 1.97 (dd, *J*=12.6, 2.4 Hz, 1 H), 1.75-1.83 (m, 1 H), 1.59 (dd, *J*=8.1, 4.4 Hz, 2 H), 1.37-1.47 (m, 1 H), 1.25-1.35 (m, 1 H), 1.04-1.13 (m, 2 H), 0.71-0.82 (m, 2 H).

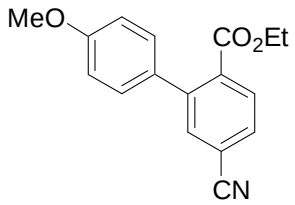
^{13}C-NMR (100 MHz, DMSO) δ: 168.11, 150.80, 138.63, 130.50, 129.94, 127.22, 115.65, 106.12, 84.10, 29.80, 25.89, 25.42, 25.14, 23.87.

MS (70 eV, EI) *m/z* (%): 241 (4) [M^+], 160 (10), 159 (100), 83 (24), 55 (29).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2923; 2854; 2233; 1759; 1685; 1608; 1596; 1480; 1453; 1376; 1347; 1313; 1286; 1262; 1235; 1179; 1168; 1145; 1098; 1087; 1078; 1070; 1058; 999; 985; 966; 957; 929; 908; 898; 884; 856; 843; 822; 792; 775; 743; 713; 696; 684; 676; 662; 645; 630; 617; 605.

HRMS (EI) for **$C_{15}H_{15}NO_2$** (241.1103): 241.1098.

Synthesis of 5-cyano-4'-methoxy-biphenyl-2-carboxylic acid ethyl ester (177c)



According to **TP 8**, the metalation of ethyl 4-cyanobenzoate (**67j**; 370 mg, 2.0 mmol) was completed within 1.25 h at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, 4-iodoanisole (480 mg, 2.1 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 0 °C and the mixture was stirred for 4 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 6:1) to give **177c** (407 mg, 77%) as a colourless solid.

m.p.: 76.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.79-7.85 (m, 1 H), 7.65 (s, 1 H), 7.64 (dd, *J*=7.0, 1.6 Hz, 1 H), 7.22 (dd, *J*=9.3, 2.6 Hz, 2 H), 6.94 (ddd, *J*=9.2, 2.9, 2.5 Hz, 2 H), 4.14 (q, *J*=7.1 Hz, 2 H), 3.84 (s, 3 H), 1.06 (t, *J*=7.1 Hz, 3 H).

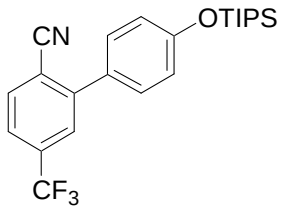
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.61, 159.66, 142.67, 135.45, 134.01, 131.25, 130.08, 129.39, 117.97, 114.59, 113.85, 61.61, 55.32, 13.73.

MS (70 eV, EI) *m/z* (%): 282 (21), 281 (100) [M^+], 253 (18), 237 (13) 236 (61), 193 (15), 165 (11), 164 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2938, 2838, 2231, 1714, 1607, 1577, 1515, 1482, 1461, 1440, 1397, 1364, 1289, 1242, 1175, 1137, 1107, 1047, 1030, 1017, 902, 888, 856, 847, 839, 786, 738, 712, 688, 645, 628, 618, 606, 602.

HRMS (EI) for **$C_{17}H_{15}NO_3$** (281.1052): 281.1039.

Synthesis of 5-trifluoromethyl-4'-triisopropylsilanyloxy-biphenyl-2-carbonitrile (177d)



According to **TP 8**, the metalation of 4-trifluoromethyl-benzonitrile (**175a**; 342 mg, 2.0 mmol) was completed within 5 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, (4-iodophenoxy)(triisopropyl)silane (825 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 25 °C and the mixture was stirred for 5 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 50:1) to give **177d** (494 mg, 59%) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.85-7.87 (m, 1 H), 7.74-7.77 (m, 1 H), 7.62-7.66 (m, 1 H), 7.45 (ddd, *J*=9.2, 2.9, 2.5 Hz, 2 H), 7.00 (ddd, *J*=9.2, 2.9, 2.5 Hz, 2 H), 1.24-1.33 (m, 3 H), 1.09-1.14 (m, 18 H).

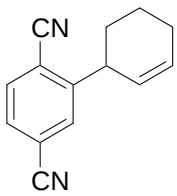
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.44, 146.16, 134.51 (q, $^2J_{CF}$=32 Hz), 134.33, 129.97, 129.28, 126.74 (q, $^3J_{CF}$=3.8 Hz), 123.59 (q, $^3J_{CF}$=3.8 Hz), 120.37, 116.18 (q, $^1J_{CF}$=272 Hz), 109.99, 17.89, 12.67.

MS (70 eV, EI) *m/z* (%): 419 (7) [M^+], 377 (17), 376 (72), 348 (30), 321 (18), 320 (100), 306 (48), 290 (10), 160 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2948, 2893, 2868, 2231, 1606, 1516, 1489, 1444, 1423, 1402, 1391, 1333, 1273, 1256, 1173, 1134, 1107, 1074, 1034, 997, 905, 882, 838, 817, 746, 725, 677, 661, 646, 638, 634, 624.

HRMS (EI) for **$C_{23}H_{28}F_3NOSi$** (419.1892): 419.1893.

Synthesis of 2-cyclohex-2-en-1-ylterephthalonitrile (177e)



According to **TP 8**, the metalation of phthalonitrile (**78g**; 256 mg, 2.0 mmol) was completed within 3.5 h at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and 3-bromocyclohexene

(391 mg, 2.4 mmol) were added and stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 9:1) to give **177e** (325 mg, 78%) as a colourless solid.

m.p.: 110.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.72 (d, *J*=7.9 Hz, 1 H), 7.66 (d, *J*=1.5 Hz, 1 H), 7.58 (dd, *J*=7.9, 1.5 Hz, 1 H), 6.03-6.12 (m, 1 H), 5.54-6.63 (m, 1 H), 3.84-3.93 (m, 1 H), 2.09-2.20 (m, 3 H), 1.60-1.72 (m, 2 H), 1.44-1.57 (m, 1 H).

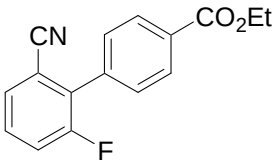
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 151.59, 133.40, 132.07, 131.57, 129.88, 126.26, 117.39, 116.41, 116.29, 116.28, 39.74, 31.24, 24.61, 20.33.

MS (70 eV, EI) *m/z* (%): 209 (10), 208 (67) [M^+], 207 (100), 193 (35), 192 (20), 191 (26), 190 (20), 180 (24), 179 (31), 167 (13), 165 (11), 153 (15), 152 (12), 141 (10), 140 (16), 54 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3033, 2929, 2858, 2837, 2228, 1605, 1554, 1488, 1448, 1436, 1406, 1339, 1294, 1261, 1191, 1159, 1138, 1074, 1042, 1000, 970, 936, 917, 898, 868, 835, 824, 775, 749, 741, 724, 700, 675, 656, 641, 637, 630, 623, 615, 609, 603.

HRMS (EI) for **$C_{14}H_{12}N_2$** (208.1000): 208.0990.

Synthesis of 6'-cyano-2'-fluorobiphenyl-4-carboxylic acid ethyl ester (69q)



According to **TP 8**, the metalation of 3-fluorobenzonitrile (**67l**; 242 mg, 2.0 mmol) was completed within 1.5 h at 0 °C using $TMP_2Mn·2MgCl_2·4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, ethyl 4-iodobenzoate (607 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 0 °C and the mixture was slowly warmed to 25 °C and stirred for 8 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 8:1) to give **69q** (420 mg, 78%) as a colourless solid.

m.p.: 104.5-106.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.16-8.19 (m, 2 H), 7.54-7.61 (m, 3 H), 7.38-7.50 (m, 2 H), 4.40 (q, *J*=7.2 Hz, 2 H), 1.40 (t, *J*=7.3 Hz, 3 H).

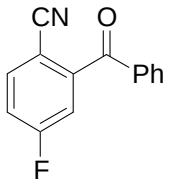
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.96, 159.35 (d, $^1J_{CF}$=250 Hz), 135.69, 132.15 (d, $^2J_{CF}$=19 Hz), 131.20, 130.10 (d, $^3J_{CF}$=8.8 Hz), 129.84 (d, $^4J_{CF}$=1.8 Hz), 129.75, 129.52 (d, $^3J_{CF}$=4.8 Hz), 120.83 (d, $^2J_{CF}$=23 Hz), 116.94 (d, $^4J_{CF}$=4.3 Hz), 114.06 (d, $^4J_{CF}$=4.3 Hz), 61.18, 14.30.

MS (70 eV, EI) *m/z* (%): 269 (22) [M^+], 240 (33), 224 (13), 223 (100), 197 (16), 196 (28), 195 (16), 169 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960, 2232, 1723, 1714, 1612, 1578, 1464, 1451, 1408, 1368, 1296, 1271, 1257, 1190, 1176, 1159, 1104, 1082, 1033, 1025, 1007, 979, 967, 957, 915, 888, 861, 798, 770, 730, 700, 633, 602.

HRMS (EI) for **$C_{16}H_{12}FNO_2$** (269.0852): 269.0840.

Synthesis of 6'-cyano-2'-fluoro-biphenyl-4-carboxylic acid ethyl ester (177f)



According to **TP 8**, the metalation of 4-fluorobenzonitrile (**67k**; 242 mg, 2.0 mmol) was completed within 1.5 h at 0 °C using $TMP_2Mn·2MgCl_2·4LiCl$ (**165**; 0.5 M in THF, 2.4 mL, 2.4 mmol). The reaction mixture was cooled to –30 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.4 mL, 0.4 mmol) and benzoyl chloride (336 mg, 2.4 mmol) were added. The mixture was allowed to warm to 0 °C and stirred for 6 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 4:1) to give **177f** (369 mg, 82%) as a colourless solid.

m.p.: 77.8-88.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.87-7.77 (m, 4 H), 7.67-7.62 (m, 1 H), 7.52-7.17 (m, 2 H), 7.30 (t, J = 8.8 Hz, 1 H).

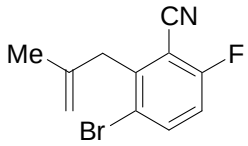
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 190.8, 161.4 (d, $^1J_{CF}$=245 Hz), 136.6 (d, $^3J_{CF}$=9.8 Hz), 136.3, 135.5 (d, $^3J_{CF}$=4.6 Hz), 134.2, 129.8 (d, J_{CF}=0.8 Hz), 128.8, 117.9 (d, $^2J_{CF}$=23.5 Hz), 117.2, 109.2 (d, J_{CF}=3.9 Hz).

MS (70 eV, EI) *m/z* (%): 225 (29) [M^+], 148 (14), 105 (100), 77 (30), 74 (16), 59 (22), 45 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3348, 3103, 1066, 1049, 2921, 2229, 1963, 1908, 1733, 1652, 1637, 1597, 1578, 1533, 1484, 1449, 1404, 1363, 1316, 1302, 1280, 1230, 1198, 1178, 1134, 1106, 1072, 1024, 1000, 974, 922, 881, 853, 830, 807, 740, 728, 714, 696, 672, 645, 623.

HRMS (EI) for $C_{14}H_8FNO$: (225.0590): 225.0589

Synthesis of 3-bromo-6-fluoro-2-(2-methylprop-2-en-1-yl)benzonitrile (177g)



According to **TP 8**, the metalation of 5-bromo-2-fluorobenzonitrile (**175b**; 400 mg, 2.0 mmol) was completed within 0.5 h at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then CuCN·2LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and 2-methyl allyl bromide (300 mg, 2.4 mmol) were added and stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 60:1) to give **177g** (421 mg, 83%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.58 (ddd, J=11.8, 5.6, 2.5 Hz, 2 H), 4.90 (s, 1 H), 4.70 (s, 1 H), 3.34 (s, 2 H), 1.71 (s, 3 H).

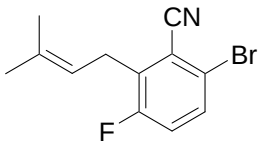
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.59 (d, $^1J_{CF}$=259 Hz), 141.49, 138.79(d, $^3J_{CF}$=5.4 Hz), 133.60, 130.52 (d, $^2J_{CF}$=17 Hz), 116.75 (d, $^3J_{CF}$=4.1 Hz), 113.88 (d, $^5J_{CF}$=0.8 Hz), 112.77, 103.14 (d, $^2J_{CF}$=18 Hz), 36.46, 22.09.

MS (70 eV, EI) *m/z* (%): 253 (12) [M^+], 175 (15), 174 (100), 160 (11), 159 (63), 158 (7), 154 (16), 147 (17), 134 (20), 133 (17), 59 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3082, 2239, 1653, 1573, 1466, 1447, 1405, 1376, 1271, 1243, 1228, 1211, 1022, 897, 873, 862, 822, 755, 746, 722, 706, 687, 676, 664, 654, 637, 633, 627, 624, 620, 616, 611, 602.

HRMS (EI) for **$C_{11}H_9BrFN$** (252.9902): 252.9894.

Synthesis of 6-bromo-3-fluoro-2-(3-methyl-but-2-enyl)benzonitrile (69t)



According to **TP 8**, the metalation of 5-bromo-2-fluorobenzonitrile (**67o**; 400 mg, 2.0 mmol) was completed within 0.5 h at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and 1-bromo-3-methyl-but-2-ene (360 mg, 2.4 mmol) were added and stirred for 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 75:1) to give **69t** (493 mg, 92%) as a colourless solid.

m.p.: 47.8-49.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.00-7.6 (m, 1 H), 6.72-6.77 (m, 1 H), 4.92-4.90 (m, 1 H), 2.84 (d, *J*=7.4 Hz, 2 H), 1.50 (d, *J*=1.1 Hz, 3 H), 1.37 (s, 3 H).

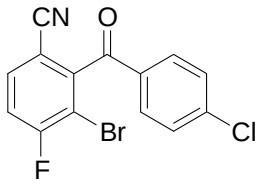
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.53 (d, $^1J_{CF}$=257 Hz), 137.56 (d, $^3J_{CF}$=5.6 Hz), 135.20, 133.05, 132.02 (d, $^2J_{CF}$=16 Hz), 119.41, 116.73 (d, $^3J_{CF}$=4.2 Hz), 112.77, 103.44 (d, $^2J_{CF}$=18Hz), 27.03 (d, $^4J_{CF}$=2.2 Hz), 25.51, 17.50.

MS (70 eV, EI) *m/z* (%): 269 (24), 267 (25), [M^+], 251 (14), 249 (15), 187 (20), 173 (13), 172 (100), 171 (18), 157 (14), 133 (11), 55 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3088, 3032, 2977, 2928, 2857, 2237, 1732, 1603, 1573, 1484, 1463, 1452, 1436, 1402, 1377, 1350, 1287, 1261, 1244, 1209, 1175, 1152, 1117, 1101, 1094, 1074, 1011, 985, 967, 898, 862, 838, 774, 734, 721.

HRMS (EI) for **$C_{12}H_{11}BrFN$** (267.0059): 267.0047.

Synthesis of 3-bromo-2-(4-chlorobenzoyl)-4-fluorobenzonitrile (177h)



According to **TP 8**, the metalation of 3-bromo-4-fluorobenzonitrile (**175c**; 400 mg, 2.0 mmol) was completed within 0.5 h at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). The reaction mixture was cooled to –30 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.4 mL, 0.4 mmol) and 4-chlorobenzoyl chloride (420 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 12 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 9:1) to give **177h** (550 mg, 81%) as a colourless solid.

m.p.: 158.8-160.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.04 (dd, *J*=5.8, 1.9 Hz, 1 H), 7.76 (dd, *J*=5.8, 1.9 Hz, 1 H), 7.72 (ddd, *J*=8.8, 2.3, 2.1 Hz, 2 H), 7.49 (ddd, *J*=8.8, 2.3, 2.1 Hz, 2 H).

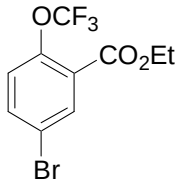
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 188.54 (d, $^4J_{CF}$=1.2 Hz), 158.70 (d, $^1J_{CF}$=261 Hz), 141.26, 139.51 (d, J_{CF}=1.9 Hz), 134.08, 133.49 (d, $^3J_{CF}$=3.4 Hz), 131.07, 129.34, 128.89 (d, $^2J_{CF}$=18 Hz), 115.77, 111.67 (d, $^2J_{CF}$=23 Hz), 110.41.

MS (70 eV, EI) *m/z* (%): 339 (25), 337 (20) [M^+], 141 (29), 139 (100), 111 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2232, 1742, 1680, 1632, 1598, 1572, 1468, 1444, 1409, 1390, 1368, 1318, 1302, 1285, 1276, 1243, 1215, 1196, 1160, 1111, 1029, 967, 953, 935, 916, 904, 880, 859, 840, 818, 810, 749, 729, 699.

HRMS (EI) for **$C_{14}H_6BrClFNO$** (336.9305): 336.9318.

Synthesis of ethyl 5-bromo-2-(trifluoromethoxy)benzoate (177i)



According to **TP 8**, the metalation of 1-bromo-4-trifluoromethoxybenzene (**175d**; 480 mg, 2.0 mmol) was completed within 10 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, the mixture was cooled to 0 °C and ethyl cyanoformate (240 mg, 2.4 mmol) was added. After warming to 25 °C, the mixture was stirred for additional 4 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 40:1) to give **177i** (480 mg, 77%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, *J*=2.7 Hz, 1 H), 7.66 (dd, *J*=8.8, 2.5 Hz, 1 H), 7.20 (dd, *J*=9.4, 1.9 Hz, 1 H), 4.39 (q, *J*=7.1 Hz, 2 H), 1.38 (t, *J*=7.1 Hz, 3 H).

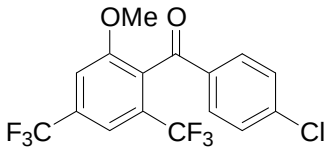
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 163.32, 146.62 (q, $^4J_{CF}$=1.3 Hz), 136.24, 134.85, 127.01, 124.34 (d, J_{CF}=1.2 Hz), 121.42 (q, $^1J_{CF}$=272 Hz), 120.32, 62.05, 14.01.

MS (70 eV, EI) *m/z* (%): 314 (27), 312 (24) [M^+], 286 (54), 284 (52), 270 (13), 269 (100), 268 (18), 267 (94), 233 (19), 203 (22), 201 (31), 175 (25), 173 (35), 111 (10), 97 (10), 94 (25), 85 (10), 83 (11), 63 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1737, 1721, 1597, 1482, 1405, 1389, 1366, 1287, 1248, 1209, 1160, 1092, 1033, 1016, 924, 902, 881, 841, 810, 782, 728, 694, 652, 620, 616, 611, 601.

HRMS (EI) for **$C_{10}H_8BrF_3O_3$** (311.9609): 311.9599.

Synthesis of (4-chlorophenyl)-(2-methoxy-4,6-*bis*-trifluoromethylphenyl)methanone (129f):



According to **TP 8**, the metalation of 3,5-*bis*-trifluoromethyl-anisole (**128b**; 520 mg, 2.0 mmol) was completed using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol) within 2 h at 25 °C. The reaction mixture was cooled to –30 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.4 mL, 0.4 mmol) and 4-chlorobenzoyl chloride (420 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 3 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 19:1) to give **129f** (643 mg, 84%) as a colourless solid.

m.p.: 107.2 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 7.86 (s, 1 H), 7.79 (s, 1 H), 7.74 (ddd, *J*=9.0, 2.4, 2.2 Hz, 2 H), 7.60 (ddd, *J*=9.0, 2.3, 2.2 Hz, 2 H), 3.83 (s, 3 H).

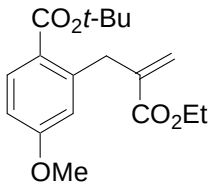
^{13}C-NMR (100 MHz, DMSO) δ: 191.39, 157.44, 139.49, 134.30 (q, J_{CF}=2.0 Hz), 132.12 (q, $^2J_{CF}$=32 Hz), 130.69, 129.96, 129.34, 128.20 (q, $^2J_{CF}$=33 Hz), 122.94 (q, $^1J_{CF}$=273 Hz), 122.58 (q, $^1J_{CF}$=273 Hz), 114.97, (m), 113.44, 57.19.

MS (70 eV, EI) *m/z* (%): 384 (10), 382 (30) [M^+], 270 (63), 256 (23), 250 (12), 141 (35), 139 (100), 111 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1684, 1623, 1483, 1462, 1429, 1401, 1368, 1306, 1275, 1249, 1202, 188, 1157, 1122, 1101, 1041, 1033, 1014, 929, 889,, 881, 870, 858, 841, 770, 760, 727, 688, 676, 650, 610, 605.

HRMS (EI) for **$C_{16}H_9ClF_6O_2$** (382.0195): 382.0191.

Synthesis of *tert*-butyl 2-[2-(ethoxycarbonyl)prop-2-en-1-yl]-4-methoxybenzoate (177k)



According to **TP 8**, the metalation of *tert*-butyl 4-methoxybenzoate (**126d**; 416 mg, 2.0 mmol) was completed within 30 h at 25 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). The mixture was cooled to 0 °C, CuCN·2LiCl (1.0 M solution in THF,

0.1 mL, 0.1 mmol) and ethyl 2-(bromomethyl)acrylate (463 mg, 2.4 mmol) were added and then stirred for 2 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 20:1) to give **177k** (468 mg, 73%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.85 (d, *J*=8.7 Hz, 1 H), 6.77 (dd, *J*=8.7, 2.6 Hz, 1 H), 6.70 (d, *J*=2.8 Hz, 1 H), 6.19 (d, *J*=1.2 Hz, 1 H), 5.18 (d, *J*=1.6 Hz, 1 H), 4.21 (q, *J*=7.1 Hz, 2 H), 3.98 (s, 2 H), 3.80 (s, 3 H), 1.51 (s, 9 H), 1.27 (t, *J*=7.1 Hz, 3 H).

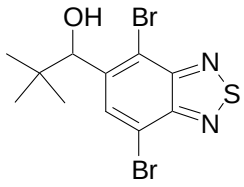
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.06, 166.48, 161.90, 141.83, 140.32, 133.05, 125.47, 124.44, 116.78, 111.49, 80.80, 60.70, 55.28, 36.38, 28.16, 14.20.

MS (70 eV, EI) *m/z* (%): 320 (2) [M^+], 264 (27), 247 (31), 246 (100), 219 (25), 218 (58), 191 (45), 190 (43), 175 (30), 174 (97), 173 (24), 146 (13), 145 (11), 131 (12), 57 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2979, 2971, 2932, 2906, 1708, 1631, 1604, 1571, 1498, 1457, 1392, 1367, 1322, 1248, 1165, 1124, 1085, 1032, 953, 854, 819, 782, 749, 708, 683, 654, 647, 640, 632, 629, 618, 615, 611, 607, 604.

HRMS (EI) for **$C_{18}H_{24}O_5$** (320.1624): 320.1624.

Synthesis of 1-(3,6-dibromo-2,1,3-benzothiadiazol-5-yl)-2,2-dimethylpropan-1-ol (180a)



According to **TP 8**, the metalation of 3,6-dibromo-2,1,3-benzothiadiazole (**178a**; 290 mg, 2.0 mmol) was completed within 2.5 h at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, *t*BuCHO (206 mg. 2.4 mmol) was added at 0 °C and the mixture was stirred for another 3 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 10:1) to give **180a** (596 mg, 78%) as a yellowish solid.

m.p.: 149.7 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 7.99 (s, 1 H), 5.94 (d, *J*=4.5 Hz, 1 H), 4.91 (d, *J*=4.5 Hz, 1 H), 0.95 (s, 9 H).

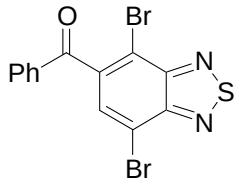
^{13}C-NMR (100 MHz, DMSO δ: 152.65, 151.22, 145.11, 133.19, 113.19, 111.40, 76.83, 37.18, 26.04.

MS (70 eV, EI) *m/z* (%): 377 (2) [M^+], 326 (97), 325 (22), 324 (96), 323 (22), 322 (97), 321 (10), 244 (32), 242 (40), 216 (18), 214 (18), 57 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3527, 2949, 2861, 1592, 1494, 1477, 1463, 1395, 1368, 1360, 1327, 1300, 1282, 1254, 1233, 1211, 1173, 1161, 1074, 1014, 998, 943, 938, 906, 891, 876, 840, 833, 806, 801, 787, 778, 765, 750, 744, 735, 730, 725, 709, 695, 690, 681, 675, 671, 667, 661, 657, 647, 641, 636, 632, 622, 616, 611, 606, 601.

HRMS (EI) for **$C_{11}H_{12}Br_2N_2OS$** (377.9037): 377.9037.

Synthesis of (3,6-dibromo-2,1,3-benzothiadiazol-5-yl)(phenyl)methanone (180b)



According to **TP 8**, the metalation of 3,6-dibromo-2,1,3-benzothiadiazole (**178a**; 290 mg, 2.0 mmol) was completed within 2.5 h at 0 °C using $TMP_2Mn·2MgCl_2·4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, $ZnCl_2$ (1.0 M solution in THF, 2.4 mL, 1.2 mmol) was added at 0 °C and stirred for 20 min. Benzoyl chloride (336 mg, 2.4 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added and the mixture was stirred for 3 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 9:1) to give **180b** (610 mg, 77%) as a yellowish solid.

m.p.: 155.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.83-7.89 (m, 2 H), 7.79 (s, 1 H), 7.63-7.69 (m, 1 H), 7.48-7.55 (m, 2 H).

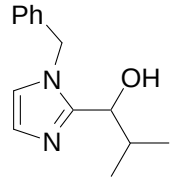
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 193.49, 152.88, 152.80, 141.58, 134.94, 134.59, 132.34, 131.23, 129.04, 114.45, 111.61.

MS (70 eV, EI) *m/z* (%): 400 (12), 398 (23), 396 (12) [M^+], 321 (13), 319 (55), 318 (10), 317 (54), 238 (13), 105 (100), 77 (50), 51 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3055, 2970, 1738, 1677, 1669, 1595, 1580, 1492, 1448, 1383, 1365, 1316, 1310, 1294, 1279, 1230, 1217, 1182, 1154, 1120, 1074, 1033, 1019, 1000, 982, 941, 919, 901, 892, 885, 876, 853, 839, 825, 803, 774, 761, 741, 737, 719, 708, 696, 686, 667, 652, 647, 639, 630, 623, 615, 611, 606.

HRMS (EI) for **$C_{13}H_6Br_2N_2OS$** (395.8568): 395.8563.

Synthesis of 1-(1-benzyl-1*H*-imidazol-2-yl)-2-methyl-propan-1-ol (180c):



According to **TP 8**, the metalation of 1-benzyl-1*H*-imidazol (**61c**; 316 mg, 2.0 mmol) was completed using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol) within 30 min at 0 °C. Then, isobutyraldehyde (173 mg, 2.4 mmol) was added at 0 °C and the mixture was stirred for another 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (6 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (diethyl ether/CH_2Cl_2= 9:1) to give **180c** (377 mg, 82%) as a colourless solid.

m.p.: 140.0 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 7.24-7.35 (m, 3 H), 7.12-7.17 (m, 2 H), 7.03 (d, *J*=1.2 Hz, 1 H), 6.82 (d, *J*=1.2 Hz, 1 H), 5.29 (s, 1 H), 5.27 (s, 2 H), 4.17 (dd, *J*=8.4, 6.3 Hz, 1 H), 2.02-2.10 (m, 1 H), 0.95 (d, *J*=6.7 Hz, 3 H), 0.61 (d, *J*=6.7 Hz, 3 H).

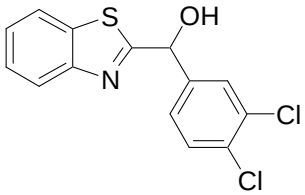
^{13}C-NMR (100 MHz, DMSO) δ: 148.94, 137.95, 128.44, 127.32, 126.93, 126.45, 120.56, 71.14, 48.36, 32.54, 19.25, 18.99.

MS (70 eV, EI) *m/z* (%): 230 (4) [M^+], 188 (13), 187 (100), 92 (14), 91 (16), 65 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3300, 3139, 3118, 1497, 1480, 1468, 1455, 1432, 1362, 1276, 1256, 1166, 1103, 1076, 1039, 944, 924, 854, 823, 765, 751, 736, 711, 691, 677, 673, 669.

HRMS (EI) for **$C_{14}H_{18}N_2O$** (230.1419): 230.1414.

Synthesis of benzothiazol-2-yl-(3,4-dichlorophenyl)methanol (180d):



According to **TP 8**, the metalation of benzothiazole (**61f**; 270 mg, 2.0 mmol) was completed using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol) within 30 min at 0 °C. Then, 3,4-dichlorobenzaldehyde (420 mg, 2.4 mmol) was added at 0 °C and the mixture was stirred for another 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (6 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by

column chromatography (pentane/diethyl ether = 2:1) to give **180d** (544 mg, 88%) as a pale yellow solid.

m.p.: 117.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J*=8.2 Hz, 1 H), 7.83 (dd, *J*=8.0, 1.2 Hz, 1 H), 7.63 (d, *J*=2.0 Hz, 1 H), 7.40-7.48 (m, 2 H), 7.33-7.39 (m, 2 H), 6.09 (s, 1 H), 4.08 (br, 1 H).

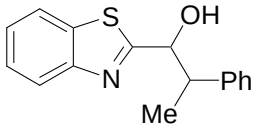
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 173.77, 152.34, 140.86, 135.07, 132.96, 132.70, 130.71, 128.61, 126.38, 125.95, 125.49, 123.09, 121.86, 73.02.

MS (70 eV, EI) *m/z* (%): 311 (31), 310 (12), 309 (47) [M^+], 175 (12), 173 (15), 164 (13), 136 (66), 135 (100), 108 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3302, 3060, 3025, 1579, 1766, 1509, 1494, 1453, 1438, 1398, 1314, 1178, 1157, 1119, 1110, 1069, 1048, 1039, 1027, 1013, 1001, 903, 888, 855, 839, 785, 778, 760, 731, 699, 670, 610, 602.

HRMS (EI) for **$C_{14}H_9Cl_2NOS$** (308.9782): 308.9764.

Synthesis of 1-benzothiazol-2-yl-2-phenyl-propan-1-ol (180e):



According to **TP 8**, the metalation of benzothiazole (**61f**; 270 mg, 2.0 mmol) was completed using $TMP_2Mn·2MgCl_2·4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol) within 30 min at 0 °C. Then, 2-phenylpropanal (280 mg, 2.0 mmol) was added at 0 °C and the mixture was stirred for another 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (6 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 4:1) to give **180e** (441 mg, 82%) as a pale yellow solid.

m.p.: 129.1-130.7 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.93 (d, *J*=8.2 Hz, 1 H), 7.83 (d, *J*=8.0 Hz, 1 H), 7.44-7.47 (m, 1 H), 7.30-7.38 (m, 5 H), 7.23-7.26 (m, 1 H), 3.58 (br 1 H), 5.19 (s, 1 H), 3.50-3.56 (m, 1 H), 1.34 (d, *J*=7.0 Hz, 3 H).

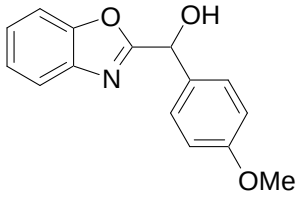
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 175.02, 152.59, 142.75, 134.79, 128.53, 128.05, 126.89, 125.98, 124.86, 122.71, 121.68, 76.25, 46.08, 13.98.

MS (70 eV, EI) *m/z* (%): 269 (9) [M^+], 165 (28), 164 (100), 163 (14), 136 (23), 109 (17), 106 (15), 105 (63), 91 (11), 90 (10), 77 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3292, 3061, 3029, 2965, 1509, 1494, 1453, 1438, 1314, 1178, 1157, 1119, 1110, 1069, 1048, 1039, 1027, 1013, 1001, 906, 785, 760, 731, 699, 670, 610, 602.

HRMS (EI) for **$C_{16}H_{15}NOS$** (269.0874): 269.0874.

Synthesis of benzoxazol-2-yl-(4-methoxyphenyl)methanol (180f):



According to **TP 8**, the metalation of benzoxazole (**61g**; 236 mg, 2.0 mmol) was completed using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol) within 1 h at 0 °C. Then, 4-methoxy benzaldehyde (330 mg, 2.4 mmol) was added at 0 °C and the mixture was stirred for another 1 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (6 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 4:1) to give **180f** (377 mg, 74%) as a pale yellow solid.

m.p.: 95.7 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 7.65-7.73 (m, 2 H), 7.41-7.46 (m, 2 H), 7.31-7.38 (m, 2 H), 6.90-6.95 (m, 2 H), 6.50-6.56 (d, *J*=4.9 Hz, 1 H), 5.94 (d, *J*=4.9 Hz, 1 H), 3.73 (s, 3 H).

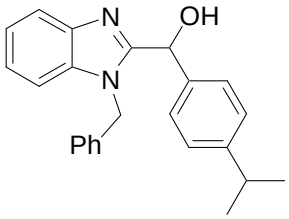
^{13}C-NMR (100 MHz, DMSO) δ: 167.13, 158.96, 150.07, 140.40, 132.18, 127.86, 125.19, 124.44, 119.77, 113.71, 110.84, 68.47, 55.06.

MS (70 eV, EI) *m/z* (%): 256 (10), 255 (72) [M^+], 226 (17), 137 (100), 136 (26), 135 (27), 120 (11), 119 (11), 109 (15), 77 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3244, 2980, 2959, 1610, 1574, 1509, 1476, 1455, 1441, 1402, 1304, 1288, 1251, 1244, 1234, 1192, 1176, 1164, 1149, 1107, 1047, 1028, 1002, 971, 936, 896, 863, 838, 834, 788, 760, 748, 727, 627.

HRMS (EI) for **$C_{15}H_{13}NO_3$** (255.0895): 255.0889.

Synthesis of (1-benzyl-1*H*-benzimidazol-2-yl)(4-isopropylphenyl)methanol (180g)



According to **TP 8**, the metalation of 1-benzyl-1*H*-benzimidazole (**178b**; 416 mg, 2.0 mmol) was completed within 0.5 h at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, 4-isopropylbenzaldehyde (355 mg, 2.4 mmol) was added and the mixture was stirred for 5 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 1:1) to give **180g** (598 mg, 84%) as a colourless solid.

m.p.: 173.5 °C.

^{1}H-NMR (400 MHz, DMSO) δ: 7.61-7.63 (m, 1 H), 7.31 (d, *J*=7.8 Hz, 2 H), 7.09-7.20 (m, 8 H), 6.92-6.97 (m, 2 H), 6.53 (d, *J*=5.1 Hz, 1 H), 6.11 (d, *J*=5.1 Hz, 1 H), 5.45-5.55 (m, 2 H), 2.83 (sept, *J*=7.1 Hz, 1 H), 1.16 (s, 3 H), 1.15 (s, 3 H).

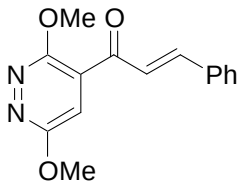
^{13}C-NMR (100 MHz, DMSO) δ: 155.56, 147.32, 141.96, 138.73, 136.73, 135.46, 128.23, 127.13, 126.67, 126.03, 125.98, 122.22, 121.54, 119.11, 110.67, 68.86, 46.80, 33.07, 23.84.

MS (70 eV, EI) *m/z* (%): 357 (16), 356 (63) [M^+], 355 (11), 340 (23), 339 (14), 325 (10), 295 (13), 266 (17), 265 (92), 249 (18), 223 (52), 221 (10), 210 (19), 209 (98), 208 (23), 207 (35), 206 (17), 205 (13), 147 (23), 145 (14), 91 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3152, 3134, 3091, 3063, 1606, 1511, 1497, 1468, 1455, 1414, 1352, 1331, 1314, 1297, 1288, 1259, 1245, 1227, 1197, 1183, 1154, 1060, 1050, 1031, 1020, 1016, 1002, 916, 889, 861, 854, 810, 782, 768, 761, 750, 728, 714, 695, 683, 679, 668, 661, 657, 650, 643, 636, 626, 622, 614, 609, 604.

HRMS (EI) for **$C_{24}H_{24}N_2O$** (356.1889): 356.1883.

Synthesis of (2*E*)-1-(3,6-dimethoxypyridazin-4-yl)-3-phenylprop-2-en-1-one (180h)



According to **TP 8**, the metalation of 3,6-dimethoxypyridazine (**100e**; 280 mg, 2.0 mmol) was completed within 0.5 h at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). The reaction mixture was cooled to -30 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.4 mL, 0.4 mmol) and 3-phenyl-acryloyl chloride (400 mg, 2.4 mmol) were added. The mixture was allowed to warm to 0 °C and stirred for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude

product was purified by column chromatography (pentane/diethyl ether = 2:1) to give **180h** (475 mg, 88%) as a yellow solid.

m.p.: 109.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.55-7.61 (m, 3 H), 7.38-7.44 (m, 3 H), 7.23 (d, *J*=16.1 Hz, 1 H), 7.11 (s, 1 H), 4.12 (s, 3 H), 4.08 (s, 3 H).

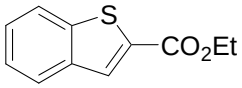
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 189.35, 162.58, 158.31, 146.69, 134.07, 131.42, 131.27, 129.05, 128.75, 124.73, 119.83, 55.13, 54.91.

MS (70 eV, EI) *m/z* (%): 271 (11), 270 (72) [M^+], 269 (37), 242 (13), 131 (100), 117 (58), 103 (52), 77 (22).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3028, 2951, 1644, 1617, 1595, 1575, 1540, 1495, 1461, 1452, 1446, 1373, 1364, 1342, 1330, 1296, 1272, 1233, 1206, 1196, 1153, 1132, 1080, 1072, 1017, 999, 972, 925, 895, 874, 848, 815, 781, 774, 765, 727, 712, 687, 668, 654, 645, 640, 635, 628, 620, 616, 610, 608, 601.

HRMS (EI) for **$C_{15}H_{14}N_2O_3$** (270.1004): 270.0997.

Synthesis of benzothiophene-2-carboxylic acid ethyl ester (180i):



According to **TP 8**, the metalation of benzothiophene (**61k**; 268 mg, 2.0 mmol) was completed using $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol) within 2 h at 25 °C. Then, ethyl cyanoformate (220 mg, 2.2 mmol) was added at 25 °C and the mixture was stirred for another 5 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 30:1) to give **180i** (392 mg, 95%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, *J*=0.7 Hz, 1 H), 7.81-7.89 (m, 2 H), 7.36-7.47 (m, 2 H), 4.40 (q, *J*=7.1 Hz, 2 H), 1.41 (t, *J*=7.1 Hz, 3 H).

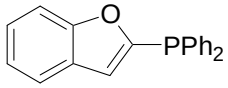
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 162.82, 142.15, 138.69, 133.83, 130.35, 126.83, 125.47, 124.84, 122.72, 61.57, 14.31.

MS (70 eV, EI) *m/z* (%): 206 (58) [M^+], 178 (36), 162 (15), 161 (100), 134 (13), 133 (18), 89 (29).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3055, 2975, 2902, 1702, 1594, 1560, 1522, 1476, 1459, 1432, 1389, 1366, 1335, 1313, 1284, 1243, 1173, 1156, 1131, 1077, 1054, 1014, 986, 942, 866, 845, 805, 754, 720, 685, 627, 615, 604.

HRMS (EI) for **$C_{11}H_{10}O_2S$** (206.0402): 206.0386.

Synthesis of benzofuran-2-yl-diphenyl-phosphane (180j):



According to **TP 8**, the metalation of benzofuran (**61l**; 236 mg, 2.0 mmol) was completed using $TMP_2Mn·2MgCl_2·4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol) within 2 h at 25 °C. Then, chloro-diphenylphosphane (530 mg, 2.4 mmol) was added at 25 °C and the mixture was stirred for another 5 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **180j** (498 mg, 82%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.46-7.58 (m, 6 H), 7.35-7.40 (m, 6 H), 7.20-7.30 (m, 2 H), 6.88-6.90 (m, 1 H).

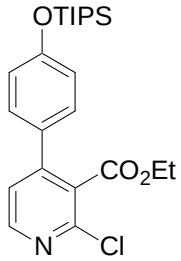
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 158.13, 158.10, 156.67 (d, $^2J_{CP}$=17 Hz), 135.02 (d, $^3J_{CP}$=7.0 Hz), 133.69, 133.43, 132.52, 131.66 (d, $^1J_{CP}$=12 Hz), 129.16, 128.64 (d, $^1J_{CP}$=13 Hz), 128.61, 128.52, 127.94 (d, $^3J_{CP}$=5.2 Hz), 124.97, 122. 73, 121.07, 117.51(d, $^2J_{CP}$=19 Hz), 111.52.

MS (70 eV, EI) *m/z* (%): 303 (19), 302 (100), 301 (23), 290 (11), 225 (23), 224 (19), 194 (58), 185 (18), 183 (19), 178 (14), 165 (15), 108 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1476, 1443, 1435, 1299, 1251, 1221, 1182, 1159, 1111, 1088, 1060, 1026, 999, 987, 921, 916, 887, 853, 849, 822, 790, 754, 741, 725, 691, 668, 639, 613, 606.

HRMS (EI) for **$C_{20}H_{15}PO$** (302.0861): 302.0855.

Synthesis of ethyl 2-chloro-4-{4-[(triisopropylsilyl)oxy]phenyl}nicotinate (180k)



According to **TP 8**, the metalation of ethyl 2-chloronicotinate (**64g**; 370 mg, 2.0 mmol) was completed within 0.5 h at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). Then, (4-iodophenoxy)(triisopropyl)silane (825 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 2.5 mol-%) were added at 0 °C and the mixture was stirred for 5 h at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 15:1) to give **180k** (666 mg, 77%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.41 (d, *J*=5.1 Hz, 1 H), 7.29 (ddd, *J*=9.1, 2.4, 2.3 Hz, 3 H), 6.93 (ddd, *J*=9.1, 2.9, 2.6 Hz, 2 H), 4.21 (q, *J*=7.0 Hz, 2 H), 1.23-1.33 (m, 3 H), 1.06-1.16 (m, 21 H).

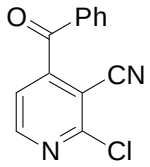
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.02, 157.32, 150.09, 149.56, 147.86, 129.28, 129.01, 122.97, 120.20, 62.03, 17.83, 13.72, 12.61.

MS (70 eV, EI) *m/z* (%): 433 (23) [M^+], 393 (12), 392 (41), 391 (32), 390 (100), 364 (13), 362 (30), 344 (12), 334 (25), 316 (16), 209 (17), 289 (10), 288 (41), 276 (11), 274 (27), 252 (19), 238 (19), 145 (15), 144 (24), 137 (10), 103 (13), 75 (17), 59 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2944, 2892, 2867, 1735, 1605, 1578, 1533, 1512, 1452, 1389, 1379, 1362, 1264, 1214, 1196, 1174, 1131, 1106, 1064, 1055, 1014, 997, 906, 882, 854, 834, 822, 780, 736, 687, 681, 661, 644, 623, 605.

HRMS (EI) for **$C_{23}H_{32}ClNO_3Si$** (433.1840): 433.1840.

Synthesis of 4-benzoyl-2-chloronicotinonitrile (180l)



According to **TP 8**, the metalation of 2-chloronicotinonitrile (**151d**; 278 mg, 2.0 mmol) was completed within 0.75 h at 0 °C using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ (**165**; 0.50 M in THF, 2.4 mL, 2.4 mmol). The reaction mixture was cooled to –30 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.4 mL, 0.4 mmol) and benzoyl chloride (336 mg, 2.4 mmol) were added. The mixture was allowed to warm to 0 °C and stirred for 6 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 4:1) to give **180l** (345 mg, 71%) as a yellowish solid.

m.p.: 109.7 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.71 (d, *J*=4.8 Hz, 1 H), 7.79 (d, *J*=8.1 Hz, 2 H), 7.70 (t, *J*=7.6 Hz, 1 H), 7.54 (t, *J*=7.9 Hz, 2 H), 7.43 (d, *J*=4.8 Hz, 1 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ: 190.72, 154.31, 152.39, 152.37, 135.21, 134.03, 130.27, 129.16, 120.87, 112.72, 108.61.

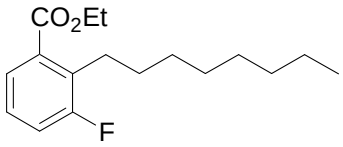
MS (70 eV, EI) *m/z* (%): 242 (9) [M^+], 214 (13), 207 (18), 105 (100), 77 (53), 51 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2944, 2892, 2867, 1735, 1605, 1578, 1533, 1512, 1452, 1389, 1379, 1362, 1264, 1214, 1196, 1174, 1131, 1106, 1064, 1055, 1014, 997, 906, 882, 854, 834, 822, 780, 736, 687, 681, 661, 644, 623, 605.

HRMS (EI) for **$C_{13}H_7ClN_2O$** (242.0247): 242.0249.

13.12 Directed Metalation of Aromatics Using Iron-Bases

Synthesis of 3-fluoro-2-octylbenzoic acid ethyl ester (171b) using 1-iodooctane:



According to **TP 9**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using {TMP_2Fe} (**190**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 3 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodooctane (576 mg, 2.4 mmol) and the resulting mixture was stirred for 8 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **171b** (459 mg, 82%) as a colourless liquid.

According to **TP 9**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 3 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodooctane (576 mg, 2.4 mmol) and the resulting mixture was stirred for 7 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **171b** (493 mg, 88%) as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.59-7.61 (m, 1 H), 7.12-7.21 (m, 2 H), 4.36 (q, J=7.1 Hz, 2 H), 2.90-2.95 (m, 2 H), 1.52-1.60 (m, 3 H), 1.38 (t, J=7.0 Hz, 3 H), 1.22-1.35 (m, 9 H), 0.88 (t, J=7.0 Hz, 3 H).

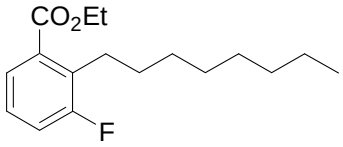
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.11 (d, $^4J_{CF}$=3.7 Hz), 161.37 (d, $^1J_{CF}$=244 Hz), 132.30 (d, $^3J_{CF}$=4.6 Hz), 131.60 (d, $^2J_{CF}$=17 Hz), 126.56 (d, $^3J_{CF}$=9.0 Hz), 125.93 (d, $^4J_{CF}$=3.5 Hz), 118.44 (d, $^2J_{CF}$=23 Hz), 61.11, 31.88, 30.70 (d, J_{CF}=1.0 Hz), 29.83, 29.42, 29.26, 26.01 (d, J_{CF}=4.0 Hz), 22.66, 14.25, 14.09.

MS (70 eV, EI) *m/z* (%): 280 (25) [M^+], 236 (13), 235 (82), 182 (100), 167 (28), 164 (18), 163 (30), 154 (32), 153 (55), 150 (18), 149 (65), 137 (16), 136 (69), 135 (11), 109 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956, 2926, 2871, 2856, 1722, 1579, 1456, 1391, 1378, 1366, 1258, 1205, 1174, 1142, 1099, 1072, 1045, 1025, 955, 919, 867, 839, 816, 756, 723.

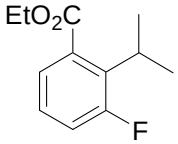
HRMS (EI) for **$C_{17}H_{25}FO_2$** (280.1839): 280.1837.

Synthesis of 3-fluoro-2-octylbenzoic acid ethyl ester (171b) using 1-bromooctane:



According to **TP 9**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 3 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-bromooctane (461 mg, 2.4 mmol) and the resulting mixture was stirred for 20 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **171b** (414 mg, 74%) as a colourless liquid.

Synthesis of 3-fluoro-2-isopropylbenzoic acid ethyl ester (187a):



According to **TP 9**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 3 h. Then, 4-fluorostyrene (**186**; 24 mg. 0:2 mmol) was added, followed by 2-bromopropane (295 mg, 2.4 mmol) and the resulting mixture was stirred for 36 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **187a** (294 mg, 70%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.36 (ddd, *J*=7.6, 1.5, 0.6 Hz, 1 H), 7.12-7.21 (m, 2 H), 4.35 (q, *J*=7.2 Hz, 2 H), 3.44-3.54 (m, 1 H), 1.38 (t, *J*=7.0 Hz, 3 H), 1.35 (d, *J*=7.0 Hz, 3 H), 1.34 (d, *J*=7.0 Hz, 3 H).

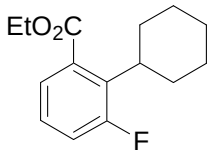
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.27 (d, $^4J_{CF}$=4.0 Hz), 162.39 (d, $^1J_{CF}$=247 Hz), 134.98 (d, $^2J_{CF}$=15 Hz), 133.57 (d, $^3J_{CF}$=6.6 Hz), 126.89 (d, $^3J_{CF}$=9.0 Hz), 124.70 (d, $^4J_{CF}$=3.5 Hz), 118.85 (d, $^2J_{CF}$=24 Hz), 61.33, 29.05, 21.38, 21.32, 14.21.

MS (70 eV, EI) *m/z* (%): 210 (25) [M^+], 167 (24), 165 (46), 164 (64), 163 (76), 150 (12), 149 (100), 147 (18), 135 (52), 133 (15), 121 (22), 115 (15), 109 (25), 101 (29), 75 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2967, 2938, 2878, 1720, 1609, 1578, 1466, 1450, 1390, 1366, 1286, 1256, 1210, 1180, 1149, 1134, 1110, 1094, 1077, 1057, 1021, 936, 929, 865, 810, 760, 744, 728.

HRMS (EI) for **$C_{12}H_{15}FO_2$** (210.1056): 210.1059.

Synthesis of 3-fluoro-2-cyclohexylbenzoic acid ethyl ester (187b) using 2-iodocyclohexane:



According to **TP 9**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 3 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 2-iodocyclohexane (504 mg, 2.4 mmol) and the resulting mixture was stirred for 10 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **187b** (415 mg, 83%) as a colourless liquid.

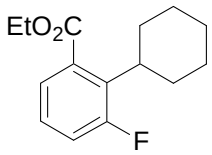
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35 (ddd, *J*=7.6, 1.5, 0.4 Hz, 1 H), 7.04-7.20 (m, 2 H), 4.36 (q, *J*=7.1 Hz, 2 H), 3.01-3.13 (m, 1 H), 1.68-1.93 (m, 7 H), 1.39 (t, *J*=7.1 Hz, 3 H), 1.26-1.37 (m, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.45 (d, $^4J_{CF}$=3.9 Hz), 162.21 (d, $^1J_{CF}$=248 Hz), 134.02 (d, $^3J_{CF}$=6.8 Hz), 133.57 (d, $^2J_{CF}$=15 Hz), 126.90 (d, $^3J_{CF}$=9.0 Hz), 124.76 (d, $^4J_{CF}$=3.1 Hz), 118.88 (d, $^2J_{CF}$=24 Hz), 61.30, 40.07 (d, J_{CF}=2.0 Hz), 30.90 (d, J_{CF}=4.0 Hz), 27.04, 25.97, 14.24.

MS (70 eV, EI) *m/z* (%): 250 (40) [M^+], 205 (94), 204 (100), 203 (29), 187 (38), 186 (99), 185 (61), 176 (20), 175 (37), 165 (22), 163 (34), 162 (20), 159 (16), 153 (27), 149 (41), 147 (31), 133 (32), 109 (27), 83 (18), 71 (20), 69 (24).

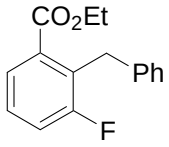
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 2854, 1720, 1576, 1448, 1390, 1366, 1284, 1258, 1243, 1228, 1194, 1175, 1145, 1122, 1096, 1071, 1023, 1002, 944, 894, 860, 834, 803, 754, 733.
HRMS (EI) for **$C_{15}H_{19}FO_2$** (250.1369): 250.1363.

Synthesis of 3-fluoro-2-cyclohexylbenzoic acid ethyl ester (187b) using 2-bromo-cyclohexane:



According to **TP 9**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 3 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 2-bromocyclohexane (391 mg, 2.4 mmol) and the resulting mixture was stirred for 40 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **187b** (300 mg, 60%) as a colourless liquid.

Synthesis of 3-fluoro-2-benzylbenzoic acid ethyl ester (187c):



According to **TP 9**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 3 h. The reaction mixture was cooled to –5 °C, benzyl chloride (302 mg, 2.4 mmol) was added and the resulting mixture was stirred for 2 h at –5 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **187c** (455 mg, 88%) as a colourless liquid.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.67 (m, 1 H), 7.12-7.29 (m, 7 H), 4.41 (d, *J*=1.9 Hz, 2 H), 4.28 (q, *J*=7.1 Hz, 2 H), 1.28 (t, *J*=7.1 Hz, 3 H).

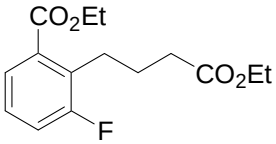
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.84 (d, $^4J_{CF}$=3.9 Hz), 161.50 (d, $^1J_{CF}$=245 Hz), 140.01, 132.56 (d, $^3J_{CF}$=4.2 Hz), 129.16 (d, $^2J_{CF}$=17 Hz), 128.35 (d, $^4J_{CF}$=1.1 Hz), 128.20, 127.55, 127.46, 126.19 (d, $^3J_{CF}$=3.5 Hz), 125.88, 118.85 (d, $^2J_{CF}$=24 Hz), 61.23, 30.97, 14.12.

MS (70 eV, EI) *m/z* (%): 258 (3) [M^+], 213 (31), 212 (100), 184 (12), 183 (41), 151 (16), 83 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3064, 3030, 2983, 2938, 1718, 1604, 1496, 1452, 1391, 1367, 1259, 1216, 1182, 1172, 1159, 1132, 1112, 1096, 1075, 1025, 969, 912, 865, 843, 829, 798, 785, 755, 730, 720, 695.

HRMS (EI) for **$C_{16}H_{15}FO_2$** (258.1056): 258.1052.

Synthesis of 2-(3-ethoxycarbonyl-propyl)-3-fluorobenzoic acid ethyl ester (187d):



According to **TP 9**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 3 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 4-iodo-butyric acid ethyl ester (581 mg, 2.4 mmol) and the resulting mixture was stirred for 13 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 10:1) to give **187d** (451 mg, 80%) as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.65 (ddd, *J*=7.6, 1.5, 0.7 Hz, 1 H), 7.14-7.25 (m, 2 H), 4.35 (q, *J*=7.2 Hz, 2 H), 4.11 (q, *J*=7.2 Hz, 2 H), 3.00 (ddd, *J*=9.6, 5.9, 2.2 Hz, 2 H), 2.33-2.39 (m, 2 H), 1.89-1.97 (m, 2 H), 1.38 (t, *J*=7.2 Hz, 3 H), 1.24 (t, *J*=7.2 Hz, 3 H).

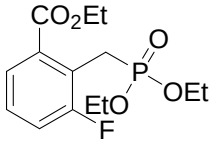
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 173.34, 162.66 (d, $^4J_{CF}$=3.9 Hz), 161.39 (d, $^1J_{CF}$=245 Hz), 132.11 (d, $^3J_{CF}$=4.2 Hz), 130.38 (d, $^2J_{CF}$=17 Hz), 127.04 (d, $^3J_{CF}$=8.8 Hz), 126.19 (d, $^3J_{CF}$=3.5 Hz), 118.67 (d, $^2J_{CF}$=24 Hz), 61.18, 60.23, 34.08, 25.58 (d, J_{CF}=1.2 Hz), 25.16 (d, J_{CF}=4.2 Hz), 14.23, 14.21.

MS (70 eV, EI) *m/z* (%): 282 (5) [M^+], 238 (10), 237 (75), 236 (100), 208 (33), 195 (20), 194 (45), 191 (36), 190 (38), 180 (13), 167 (53), 166 (44), 165 (19), 164 (18), 163 (59), 162 (22), 161 (12), 153 (29), 150 (12), 179 (79), 136 (16), 135 (39),109 (20), 107 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 2940, 2908, 2887, 1719, 1611, 1579, 1457, 1391, 1368, 1320, 1259, 1174, 1154, 1129, 1096, 1059, 1023, 935, 865, 838, 817, 757.

HRMS (EI) for **$C_{15}H_{19}FO_4$** (282.1267): 282.1259.

Synthesis of 2-(diethoxyphosphorylmethyl)-3-fluorobenzoic acid ethyl ester (187e):



According to **TP 9**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 3 h. The reaction mixture was cooled to –10 °C, diethyl iodomethyl phosphonate (333 mg, 2.4 mmol) was added and the resulting mixture was stirred for 2 h at –10 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 5 mL), extracted with EtOAc (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/EtOAc = 2:1) to give **187e** (430 mg, 68%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, *J*=7.8 Hz, 1 H), 7.18-7.30 (m, 2 H), 4.36 (q, *J*=7.1 Hz, 2 H), 4.14-4.21 (m, 2 H), 3.98-4.05 (m, 2 H), 3.89 (d, *J*=1.8 Hz, 1 H), 3.83 (d, *J*=1.9 Hz, 1 H), 1.39 (t, *J*=7.0 Hz, 3 H) 1.35 (t, *J*=7.0 Hz, 3 H) 1.21 (t, *J*=7.0 Hz, 3 H).

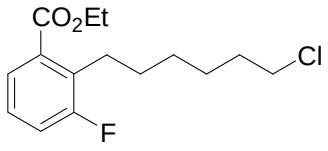
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.74 (d, ^4J=3.9 Hz), 161.08 (dd, *J*=245, 6.5 Hz), 132.59 (t, *J*=3.0 Hz), 127.82 (dd, *J*=8.8, 3.8 Hz), 126.45 (t, *J*=3.5 Hz), 126.19 (dd, *J*=17, 6.6 Hz), 118.67 (dd, *J*=24, 3.6 Hz), 63.45 (d, *J*=6.5 Hz), 62.05 (d, *J*=6.5 Hz), 61.35, 23.08 (dd *J*=138, 4.6 Hz), 16.36 (d, *J*=5.7 Hz), 16.22 (d, *J*=6.5 Hz), 14.16.

MS (70 eV, EI) *m/z* (%): 318 (20) [M^+], 272 (29), 244 (27), 216 (100), 195 (10), 153 (19), 136 (39) 108 (28).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3453, 2984, 2939, 1718, 1642, 1582, 1459, 1392, 1368, 1265, 1164, 1120, 1098, 1048, 1017, 951, 850, 839, 789, 754, 701.

HRMS (ESI) for **$C_{14}H_{20}FO_5P$** (318.1032): 319.1107.

Synthesis of 2-(6-chlorohexyl)-3-fluorobenzoic acid ethyl ester (187f):



According to **TP 9**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 3 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-chloro-6-iodo-hexane (590 mg, 2.4 mmol) and the resulting mixture was stirred for 13 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **187f** (486 mg, 85%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.56-7.65 (m, 1 H), 7.11-7.24 (m, 2 H), 4.35 (q, J=7.0 Hz, 2 H), 3.51 (t, J=6.8 Hz, 2 H), 2.94 (td, J=7.8, 2.3 Hz, 2 H), 1.71-1.84 (m, 2 H), 1.55-1.64 (m, 2 H), 1.35-1.51 (m, 4 H), 1.38 (t, J=7.0 Hz, 3 H).

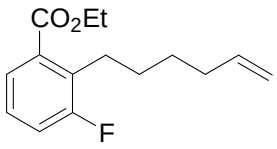
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.91 (d, $^4J_{CF}$=3.6 Hz), 161.34 (d, $^1J_{CF}$=244 Hz), 132.14 (d, $^3J_{CF}$=4.6 Hz), 131. 35 (d, $^2J_{CF}$=17 Hz), 126.67 (d, $^3J_{CF}$=8.8 Hz), 126.01 (d, $^4J_{CF}$=3.3 Hz), 118.48 (d, $^2J_{CF}$=24 Hz), 61.09, 45.05, 32.54, 30.35 (d, $^4J_{CF}$=1.0 Hz), 28.94, 26.64, 25.81 (d, $^3J_{CF}$=4.1 Hz), 14.23.

MS (70 eV, EI) *m/z* (%): 286 (34) [M^+], 243 (29), 242 (17), 241 (85), 240 (11), 205 (17), 203 (17), 195 (12), 185 (11), 183 (12), 182 (100), 167 (37), 164 (13). 163 (27), 154 (33), 153 (99), 150 (23), 149 (89), 137 (19), 136 (57), 135 (16), 109 (32), 108 (13), 69 (14), 41 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2935, 2860, 1720, 1579, 1456, 1391, 1366, 1258, 1204, 1173, 1144, 1087, 1070, 1023, 974, 929, 866, 840, 816, 756, 727, 675, 651.

HRMS (EI) for **$C_{15}H_{20}ClFO_2$** (286.1136): 286.1137.

Synthesis of 3-fluoro-2-hex-5-enylbenzoic acid ethyl ester (187g):



According to **TP 9**, the metalation of ethyl 3-fluorobenzoate (**57**; 336 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 3 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 6-iodo-hex-1-ene (504 mg, 2.4 mmol) and the resulting mixture was stirred for 10 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column

chromatography (pentane:/diethyl ether = 100:1) to give **187g** (384 mg, 77%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.57-7.64 (m, 1 H), 7.11-7.23 (m, 2 H), 5.74-5.87 (m, 1 H), 4.90-5.02 (m, 2 H), 4.36 (q, *J*=7.2 Hz, 2 H), 2.95 (td, *J*=7.7, 2.3 Hz, 2 H), 2.04-2.12 (m, 2 H), 1.42-1.65 (m, 4 H), 1.38 (t, *J*=7.0 Hz, 3 H).

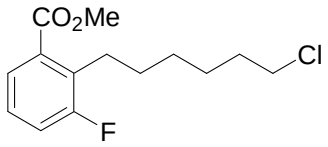
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.98 (d, $^4J_{CF}$=3.6 Hz), 161.36 (d, $^1J_{CF}$=244 Hz), 138.83, 132.22 (d, $^3J_{CF}$=4.6 Hz), 131.40 (d, $^2J_{CF}$=17 Hz), 126.63 (d, $^3J_{CF}$=8.8 Hz), 125.98 (d, $^3J_{CF}$=3.3 Hz), 118.46 (d, $^2J_{CF}$=24 Hz), 114.30, 61.08, 33.58, 30.11, 29.00, 25.81 (d, J_{CF}=4 Hz), 14.23.

MS (70 eV, EI) *m/z* (%): 250 (19) [M^+], 205 (37), 204 (45), 194 (22), 167 (22), 166 (39), 165 (26), 163 (38), 162 (66), 153 (76), 149 (54), 136 (47), 135 (33), 109 (31), 108 (21), 99 (24), 97 (25), 85 (62), 83 (29), 71 (77), 69 (44), 57 (100), 56 (24), 55 (52), 43 (66).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3078, 2980, 2931, 2860, 1721, 1641, 1611, 1579, 1456, 1416, 1391, 1366, 1262, 1206, 1173, 1140, 1099, 1072, 1025, 993, 937, 910, 867, 839, 816, 755, 642, 632, 626.

HRMS (EI) for **$C_{15}H_{19}FO_2$** (250.1369): 250.1365.

Synthesis of 2-(6-chlorohexyl)-3-fluorobenzoic acid methyl ester (187h):

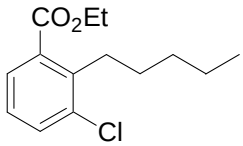


According to **TP 9**, the metalation of methyl 3-fluorobenzoate (**151a**; 308 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 3.5 h. Then, 4-fluorostyrene (**4**; 24 mg, 0.2 mmol) was added, followed by 1-chloro-6-iodohexane (590 mg, 2.4 mmol) and the resulting mixture was stirred for 10 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 80:1) to give **187h** (431 mg, 79%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.60-7.64 (m, 1 H), 7.11-7.23 (m, 2 H), 3.88 (s, 3 H), 3.51 (t, *J*=6.7 Hz, 2 H), 2.94 (dt, *J*=7.8, 2.2 Hz, 2 H), 1.71-1.82 (m, 2 H), 1.38-1.61 (m, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.18 (d, $^4J_{CF}$=3.4 Hz), 160.88 (d, $^1J_{CF}$=246 Hz), 131.71 (d, $^2J_{CF}$=17 Hz), 131.60 (d, $^3J_{CF}$=4.6 Hz), 126.66 (d, $^3J_{CF}$=9.0 Hz), 126.10 (d, $^4J_{CF}$=3.3 Hz), 118.63 (d, $^2J_{CF}$=24 Hz), 52.07, 45.03, 32.51, 30.27, 28.90, 26.58, 25.74 (d, $^4J_{CF}$=4.1 Hz).
MS (70 eV, EI) *m/z* (%): 272 (18) [M^+], 243 (21), 241 (59), 227 (11), 205 (11), 199 (13), 181 (21), 168 (74), 167 (41), 163 (23), 155 (14), 150 (24), 149 (100), 137 (53), 136 (77), 135 (15), 127 (18), 123 (13), 121 (11), 114 (14), 109 (50), 108 (16), 101 (13), 97 (16), 95 (11), 85 (15), 83 (20), 81 (19), 71 (24), 70 (14), 69 (51), 67 (11), 57 (43).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2936, 2860, 1723, 1610, 1579, 1457, 1434, 1260, 1206, 1169, 1144, 1086, 1075, 1001, 888, 834, 813, 779, 755, 727, 650.
HRMS (EI) for **$C_{14}H_{18}ClFO_2$** (272.0979): 272.0973.

Synthesis of 3-chloro-2-pentylbenzoic acid ethyl ester (187i):



According to **TP 9**, the metalation of ethyl 3-chlorobenzoate (**67b**; 370 mg, 2.0 mmol) was completed using {TMP_2Fe} (**190**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 36 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodopentane (475 mg, 2.4 mmol) and the resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 60:1) to give **187i** (372 mg, 73%) as a colourless liquid.

According to **TP 9**, the metalation of ethyl 3-chlorobenzoate (**67b**; 370 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 36 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodopentane (475 mg, 2.4 mmol) and the resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 60:1) to give **187i** (413 mg, 81%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.65 (dd, *J*=7.8, 1.3 Hz, 1 H), 7.47 (dd, *J*=7.8, 1.2 Hz, 1 H), 7.15 (t, *J*=7.8 Hz, 1 H), 4.36 (q, *J*=7.1 Hz, 2 H), 2.96-3.04 (m, 2 H), 1.53-1.64 (m, 2 H), 1.38 (t, *J*=7.2 Hz, 3 H), 1.32-1.40 (m, 4 H), 0.86-0.95 (m, 3 H).

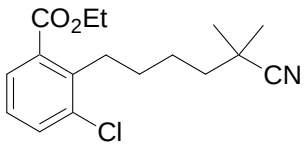
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.54, 141.30, 135.58, 132.88, 132.62, 128.56, 126.44, 61.24, 32.11, 30.89, 29.53, 22.45, 14.25, 14.04.

MS (70 eV, EI) *m/z* (%): 254 (28) [M^+], 211 (37), 210 (18), 209 (100), 208 (12), 200 (13), 198 (44), 183 (22), 179 (15), 171 (18), 170 (21), 169 (23), 167 (27), 166 (17), 165 (73), 154 (21), 153 (17), 152 (69), 125 (21), 115 (10), 89 (15), 77 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957, 2930, 2872, 2860, 1721, 1458, 1435, 1390, 1378, 1366, 1271, 1244, 1220, 1188, 1179, 1153, 1100, 1086, 1020, 978, 964, 886, 862, 841, 822, 806, 787, 755, 729, 716.

HRMS (EI) for **$C_{14}H_{19}ClO_2$** (254.1074): 254.1063.

Synthesis of 3-chloro-2-(5-cyano-5,5-dimethylpentyl)benzoic acid ethyl ester (187j):



According to **TP 9**, the metalation of ethyl 3-chlorobenzoate (**67b**; 370 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 36 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 6-iodo-2,2-dimethyl-hexanenitrile (602 mg, 2.4 mmol) and the resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 10:1) to give **187j** (436 mg, 71%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.70 (dd, *J*=7.0, 1.3 Hz, 1 H), 7.48 (dd, *J*=7.0, 1.3 Hz, 1 H), 7.17 (t, *J*=7.9 Hz, 1 H), 4.37 (q, *J*=7.0 Hz, 2 H), 3.02-3.07 (m, 2 H), 1.52-1.69 (m, 6 H), 1.39 (t, *J*=7.0 Hz, 3 H), 1.34 (s, 6 H).

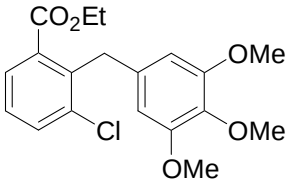
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.26, 140.77, 135.59, 132.77, 132.67, 128.77, 126.68, 125.17, 61.30, 40.72, 32.39, 30.71, 29.60, 26.70, 26.61, 25.53, 14.26.

MS (70 eV, EI) *m/z* (%): 307 (5) [M^+], 272 (43), 262 (32), 261 (17), 246 (49), 236 (16), 234 (63), 226 (21), 220 (18), 207 (21), 195 (18), 193 (67), 169 (41), 167 (33), 166 (20), 165 (100), 125 (18), 115 (24), 89 (25), 83 (17), 77 (23), 69 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 2939, 2864, 2234, 1719, 1590, 1568, 1458, 1435, 1391, 1366, 1274, 1248, 1224, 1200, 1173, 1156, 1101, 1082, 1065, 1054, 1018, 944, 910, 888, 861, 828, 810, 788, 758, 735, 717, 700.

HRMS (EI) for **$C_{17}H_{22}ClNO_2$** (307.1339): 307.1333.

Synthesis of 3-chloro-2-(5-cyano-5,5-dimethylpentyl)benzoic acid ethyl ester (187k):



According to **TP 9**, the metalation of ethyl 3-chlorobenzoate (**67b**; 370 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 36 h. The reaction mixture was cooled to –10 °C, 5-chloromethyl-1,2,3-trimethoxybenzene (520 mg, 2.4 mmol) was added and the resulting mixture was stirred for 2 h at –10 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/EtOAc = 25:1) to give **187k** (455 mg, 68%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.74 (dd, *J*=7.8, 1.3 Hz, 1 H), 7.57 (dd, *J*=8.1, 1.3 Hz, 1 H), 7.28 (t, *J*=7.8 Hz, 1 H), 6.37 (s, 2 H), 4.50 (s, 2 H), 4.30 (q, *J*=7.1 Hz, 2 H), 3.81 (s, 3 H), 3.78 (s, 6 H), 1.30 (t, *J*=7.1 Hz, 3 H).

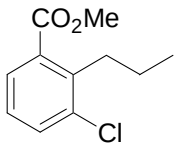
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.35, 152.91, 138.34, 136.36, 136.20, 135.12, 133.72, 132.85, 128.66, 127.40, 105.63, 61.36, 60.75, 55.96, 35.60, 14.10.

MS (70 eV, EI) *m/z* (%): 366 (35), 365 (24), 364 (100) [M^+], 319 (15), 305 (13), 303 (34), 289 (22), 287 (61), 260 (32), 169 (19), 167 (62).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956, 2933, 2830, 1708, 1588, 1507, 1458, 1430, 1420, 1390, 1363, 1331, 1323, 1282, 1242, 1185, 1174, 1144, 1128, 1101, 1079, 1048, 1016, 965, 943, 918, 880, 861, 840, 811, 783, 763, 750, 732, 720, 704, 690, 673, 665.

HRMS (ESI) for **$C_{19}H_{21}ClO_5$** (364.1078): 365.1152.

Synthesis of 3-chloro-2-propylbenzoic acid methyl ester (187l):



According to **TP 9**, the metalation of methyl 3-chlorobenzoate (**100c**; 374 mg, 2.0 mmol) was completed using {TMP_2Fe} (**190**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 36 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodo-propane (408 mg, 2.4 mmol) and the resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 50:1) to give **187l** (246 mg, 58%) as a colourless liquid.

According to **TP 9**, the metalation of methyl 3-chlorobenzoate (**100c**; 374 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 36 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodopropane (408 mg, 2.4 mmol) and the resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 50:1) to give **187l** (276 mg, 65%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.67 (dd, *J*=7.8, 1.4 Hz, 1 H), 7.48 (dd, *J*=8.0, 1.4 Hz, 1 H), 7.16 (t, *J*=7.9 Hz, 1 H), 3.89 (s, 3 H), 2.97-3.04 (m, 2 H), 1.56-1.68 (m, 2 H), 1.00 (t, *J*=7.3 Hz, 3 H).

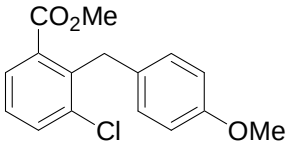
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.82, 141.41, 135.71, 132.81, 132.37, 128.68, 126.49, 52.22, 32.75, 23.15, 14.29.

MS (70 eV, EI) *m/z* (%): 212 (22) [M^+], 185 (10), 183 (50), 182 (13), 181 (100), 180 (12), 167 (16), 165 (49), 153 (18), 125 (23), 115 (11), 89 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2959, 2873, 1725, 1590, 1568, 1464, 1455, 1433, 1376, 1350, 1285, 1251, 1200, 1156, 1103, 1081, 1072, 975, 925, 878, 837, 825, 806, 754, 718, 675.

HRMS (EI) for **$C_{11}H_{13}ClO_2$** (212.0604): 212.0592.

Synthesis of 3-chloro-2-(4-methoxybenzyl)benzoic acid methyl ester (187m):



According to **TP 9**, the metalation of methyl 3-chlorobenzoate (**100c**; 340 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 36 h. The reaction mixture was cooled to –10 °C, 4-methoxy benzyl chloride (377 mg, 2.4 mmol) was added and the resulting mixture was stirred for 2 h at –10 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/EtOAc = 20:1) to give **187m** (383 mg, 68%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.76 (dd, *J*=7.8, 1.3 Hz, 1 H), 7.58 (dd, *J*=8.0, 1.4 Hz, 1 H), 7.27-7.31 (m, 1 H), 7.03-7.08 (m, 2 H), 6.79-6.83 (m, 2 H), 4.50 (s, 2 H), 3.84 (s, 3 H), 3.79 (s, 3 H).

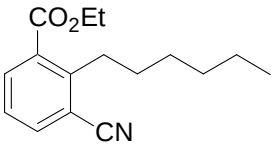
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.68, 157.73, 139.27, 136.43, 133.05, 131.52, 129.29, 128.84, 127.23, 113.68, 113.61, 55.15, 52.29, 34.81.

MS (70 eV, EI) *m/z* (%): 292 (14), 290 (39) [M^+], 260 (36), 259 (24), 258 (100), 243 (13), 241 (11), 224 (19), 223 (65), 217 (15), 215 (43), 195 (25), 181 (10), 180 (10), 167 (15), 153 (12), 152 (39), 151 (12), 121 (36), 69 (12), 57 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950, 2930, 2836, 1719, 1609, 1583, 1511, 1457, 1436, 1420, 1301, 1280, 1246, 1200, 1179, 1145, 1105, 1080, 1033, 977, 942, 923, 909, 846, 826, 816, 803, 771, 748, 724, 700.

HRMS (EI) for **$C_{16}H_{15}ClO_3$** (290.0710): 290.0698.

Synthesis of 3-cyano-2-hexylbenzoic acid ethyl ester (187n):



According to **TP 9**, the metalation of ethyl 3-cyanobenzoate (**67i**; 370 mg, 2.0 mmol) was completed using {TMP_2Fe} (**190**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 18 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodohexane (542 mg, 2.4 mmol) and the resulting mixture was stirred for 10 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 20:1) to give **187n** (402 mg, 78%) as a colourless liquid.

According to **TP 9**, the metalation of ethyl 3-cyanobenzoate (**67i**; 370 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 36 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodohexane (542 mg, 2.4 mmol) and the resulting mixture was stirred for 7 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 20:1) to give **187n** (419 mg, 81%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.01 (dd, *J*=7.9, 1.2 Hz, 1 H), 7.73 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.33 (t, *J*=7.8 Hz, 1 H), 4.38 (q, *J*=7.2 Hz, 2 H), 3.11-3.19 (m, 2 H), 1.58-1.68 (m, 2 H), 1.39 (t, *J*=7.2 Hz, 3 H), 1.28-1.49 (m, 6 H), 0.83-0.93 (m, 3 H).

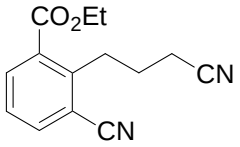
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.41, 148.04, 135.96, 134.55, 131.71, 126.26, 117.67, 114.67, 61.56, 32.73, 31.49, 31.46, 29.49, 22.56, 14.21, 14.02.

MS (70 eV, EI) *m/z* (%): 259 (10) [M^+], 230 (26), 216 (24), 214 (40), 203 (49), 189 (64), 188 (29), 174 (45), 170 (23), 165 (23), 161 (43), 156 (43), 143 (31), 127 (31), 111 (26), 97 (51), 85 (36), 83 (58), 77 (23), 69 (50), 57 (100), 55 (82), 43 (71), 41 (52).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956, 2929, 2872, 2858, 2228, 1722, 1582, 1461, 1444, 1391, 1378, 1367, 1265, 1251, 1203, 1175, 1143, 1098, 1023, 864, 820, 761, 725.

HRMS (EI) for **$C_{16}H_{21}NO_2$** (259.1572): 259.1565.

Synthesis of 3-cyano-2-(3-cyanopropyl)benzoic acid ethyl ester (187o):



According to **TP 9**, the metalation of ethyl 3-cyanobenzoate (**67i**; 370 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 18 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 4-iodobutyronitrile (468 mg, 2.4 mmol) and the resulting mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 1:1) to give **187o** (363 mg, 75%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.12 (dd, *J*=8.0, 1.4 Hz, 1 H), 7.78 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.42 (t, *J*=7.8 Hz, 1 H), 4.41 (q, *J*=7.1 Hz, 2 H), 3.25-3.34 (m, 2 H), 2.50 (t, *J*=7.3 Hz, 2 H), 2.00-2.13 (m, 2 H), 1.41 (t, *J*=7.1 Hz, 3 H).

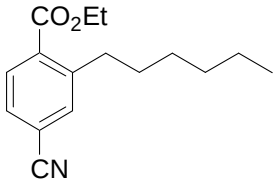
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.75, 145.40, 136.25, 135.06, 131.62, 127.27, 118.97, 117.21, 114.90, 61.90, 31.68, 26.58, 17.20, 14.22.

MS (70 eV, EI) *m/z* (%): 242 (5) [M^+], 197 (34), 196 (63), 174 (23), 157 (10), 156 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 2940, 2246, 2228, 1716, 1583, 1461, 1447, 1426, 1392, 1367, 1280, 1260, 1205, 1177, 1133, 1096, 1085, 1057, 1017, 915, 864, 830, 817, 762.

HRMS (EI) for **$C_{14}H_{14}N_2O_2$** (242.1055): 242.1055.

Synthesis of 4-cyano-2-hexylbenzoic acid ethyl ester (187p):



According to **TP 9**, the metalation of ethyl 3-cyanobenzoate (**67j**; 370 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 36 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodohexane (542 mg, 2.4 mmol) and the resulting mixture was stirred for 7 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 20:1) to give **187p** (370 mg, 70%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.92 (d, *J*=7.9 Hz, 1 H), 7.48-7.55 (m, 2 H), 4.38 (q, *J*=7.1 Hz, 2 H), 2.87-2.97 (m, 2 H), 1.52-1.62 (m, 2 H), 1.39 (t, *J*=7.1 Hz, 3 H), 1.26-1.38 (m, 6 H), 0.83-0.93 (m, 3 H).

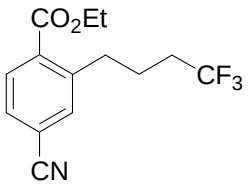
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.54, 145.29, 134.28, 134.25, 130.86, 129.13, 118.18, 115.03, 61.56, 34.01, 31.60, 31.44, 29.23, 22.54, 14.20, 14.02.

MS (70 eV, EI) *m/z* (%): 259 (42) [M^+], 214 (100), 189 (75), 173 (64), 170 (41), 161 (65), 158 (25), 157 (30), 156 (85), 149 (31), 143 (45), 142 (33), 116 (26), 115 (28), 83 (29), 81 (39), 71 (35), 69 (68), 57 (62), 55 (61), 44 (26), 43 (71), 41 (61).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957, 2928, 2871, 2858, 2233, 1723, 1607, 1562, 1490, 1464, 1402, 1391, 1378, 1366, 1260, 1173, 1143, 1100, 1070, 1017, 899, 869, 842, 786, 725, 701.

HRMS (EI) for **$C_{16}H_{21}NO_2$** (259.1572): 259.1562.

Synthesis of 4-cyano-2-(4,4,4-trifluorobutyl)benzoic acid ethyl ester (187q):



According to **TP 9**, the metalation of ethyl 3-cyanobenzoate (**67j**; 370 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 36 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1,1,1-trifluoro-4-iodobutane (571 mg, 2.4 mmol) and the resulting mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 8:1) to give **187q** (370 mg, 65%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.96 (d, *J*=8.1 Hz, 1 H), 7.53-7.59 (m, 2 H), 4.39 (q, *J*=7.1 Hz, 2 H), 3.00-3.06 (m, 2 H), 2.08-2.24 (m, 2 H), 1.82-1.93 (m, 2 H), 1.40 (t, *J*=7.1 Hz, 3 H).

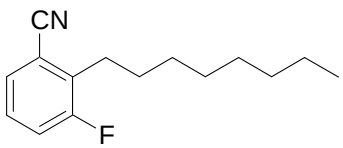
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.98, 143.66, 134.23, 133.98, 131.39, 129.88, 126.90 (q, $^1J_{CF}$=272 Hz), 117.84, 115.56, 61.76, 33.47 (q, $^2J_{CF}$=29 Hz), 32.92, 23.70 (q, $^3J_{CF}$=2.8 Hz), 14.16.

MS (70 eV, EI) *m/z* (%): 285 (48), [M^+], 257 (24), 240 (71), 239 (23), 238 (17), 174 (29), 173 (100), 172 (25), 160 (31), 156 (71), 152 (38), 128 (18), 127 (17), 116 (18), 97 (26), 85 (24), 83 (29), 71 (30), 69 (33), 57 (57), 55 (43), 43 (39).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984, 2945, 2880, 2234, 1721, 1608, 1564, 1492, 1464, 1448, 1390, 1368, 1354, 1336, 1275, 1251, 1223, 1208, 1174, 1128, 1101, 1077, 1011, 987, 943, 901, 868, 844, 788, 770, 702, 657.

HRMS (EI) for **$C_{14}H_{14}F_3NO_2$** (285.0977): 285.0976.

Synthesis of 3-fluoro-2-octylbenzonitrile (187r):



According to **TP 9**, the metalation of 3-fluorobenzonitrile (**67l**; 242 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 9 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodooctane (576 mg,

2.4 mmol) and the resulting mixture was stirred for 10 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **187r** (373 mg, 80%) as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.43 (m, 1 H), 7.23-7.25 (m, 2 H), 2.82-2.88 (m, 2 H), 1.59-1.67 (m, 2 H), 1.23-1.41 (m, 10 H), 0.85-0.88 (m, 3 H).

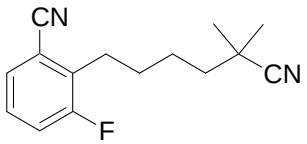
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 160.80 (d, $^1J_{CF}$=248 Hz), 134.22 (d, $^2J_{CF}$=19 Hz), 128.42 (d, $^4J_{CF}$=3.8 Hz), 127.94 (d, $^3J_{CF}$=8.8 Hz), 120.04 (d, $^2J_{CF}$=23 Hz), 115.05 (d, $^4J_{CF}$=4.2 Hz), 114.34 (d, $^3J_{CF}$=6.5 Hz), 31.81, 29.99 (d, J_{CF}=1.1 Hz), 29.31, 29.24, 29.15, 28.99 (d, J_{CF}=1.5 Hz), 22.63, 14.08.

MS (70 eV, EI) *m/z* (%): 233 (3) [M^+], 199 (12), 190 (11), 165 (33), 163 (14), 162 (46), 148 (18), 135 (43), 134 (27), 127 (17), 125 (11), 123 (10), 120 (11), 113 (10), 111 (21), 107 (10), 105 (11), 99 (16), 97 (35), 95 (10), 91 (11), 85 (30), 84 (13), 83 (35), 82 (16), 81 (17), 77 (14), 71 (57), 70 (25), 69 (39), 68 (11), 67 (14), 57 (100), 56 (23), 55 (50), 44 (23), 43 (63).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956, 2926, 2856, 2232, 1576, 1462, 1378, 1252, 1192, 1162, 1114, 1067, 962, 919, 792, 732, 723, 673.

HRMS (EI) for **$C_{15}H_{20}FN$** (233.1580): 233.1569.

Synthesis of 2-(5-cyano-5,5-dimethylpentyl)-3-fluorobenzonitrile (187s):



According to **TP 9**, the metalation of 3-fluorobenzonitrile (**67l**; 242 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 9 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 6-iodo-2,2-dimethyl-hexanenitrile (602 mg, 2.4 mmol) and the resulting mixture was stirred for 8 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 10:1) to give **187s** (341 mg, 70%) as a colourless solid.

m.p.: 73.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35-7.40 (m, 1 H), 7.20-7.30 (m, 2 H), 2.86 (td, J=7.6, 1.5 Hz, 2 H), 1.53-1.70 (m, 6 H), 1.31 (s, 6 H).

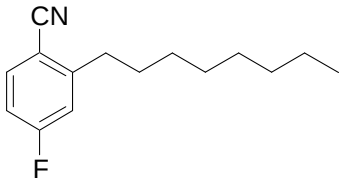
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.74 (d, $^1J_{CF}$=248 Hz), 133.29 (d, $^2J_{CF}$=19 Hz), 128.66 (d, J_{CF}=3.7 Hz), 128.28 (d, $^3J_{CF}$=8.8 Hz), 124.92, 120.16 (d, $^2J_{CF}$=23 Hz), 116.87 (d, J_{CF}=4.3 Hz), 114.25 (d, $^3J_{CF}$=6.3 Hz), 40.50, 32.25, 29.67 (d, J_{CF}=1.1 Hz), 27.54 (d, J_{CF}=2.3 Hz), 26.60, 24.83.

MS (70 eV, EI) *m/z* (%): 244 (36) [M^+], 243 (10), 229 (34), 225 (29), 216 (18), 202 (47), 201 (10), 176 (18), 174 (15), 162 (20), 161 (14), 155 (11), 149 (40), 148 (47), 147 (21), 135 (27), 134 (100), 83 (11), 71 (23), 69 (11), 55 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977, 2939, 2867, 2232, 1574, 1464, 1253, 1234, 1218, 1205, 1194, 1164, 1122, 1073, 1062, 958, 934, 901, 832, 795, 737, 701, 692, 672.

HRMS (EI) for **$C_{15}H_{17}FN_2$** (244.1376): 244.1374.

Synthesis of 4-fluoro-2-octylbenzonitrile (187t):



According to **TP 9**, the metalation of 4-fluorobenzonitrile (**67k**; 242 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 18 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodooctane (576 mg, 2.4 mmol) and the resulting mixture was stirred for 7 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 100:1) to give **187t** (387 mg, 80%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.39-7.53 (m, 2 H), 7.03-7.14 (m, 1 H), 2.62-2.64 (m, 2 H), 1.26-1.62 (m, 12 H), 0.85-0.89 (m, 3 H).

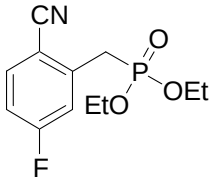
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 163.53 (d, $^1J_{CF}$=255 Hz), 134.85 (d, $^3J_{CF}$=6.8 Hz), 131.85 (d, $^3J_{CF}$=9.4 Hz), 131.70 (d, $^2J_{CF}$=17 Hz), 118.38, 116.49 (d, $^2J_{CF}$=24 Hz), 108.22 (d, $^4J_{CF}$=4.0 Hz), 31.81, 29.66 (d, J_{CF}=1.1 Hz), 29.27, 29.17, 29.15, 28.65 (d, J_{CF}=1.5 Hz), 22.63, 14.07.

MS (70 eV, EI) *m/z* (%): 233(14), [M^+], 165 (42), 162 (13), 149 (19), 148 (21), 136 (11), 135 (100), 134 (42), 120 (11), 107 (11), 97 (14), 85 (12), 83 (16), 77 (15), 71 (18), 70 (12), 69 (20), 57 (73), 55 (29), 44 (16), 43 (38), 41 (30).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2926, 2856, 2232, 1609, 1590, 1494, 1466, 1410, 1378, 1248, 1215, 1140, 1128, 1095, 895, 824, 787, 772, 734, 723, 687.

HRMS (EI) for **$C_{15}H_{20}FN$** (233.1580): 233.1571.

Synthesis of (2-cyano-5-fluorobenzyl)phosphonic acid diethyl ester (187u):



According to **TP 9**, the metalation of 4-fluorobenzonitrile (**67k**; 242 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 18 h. The reaction mixture was cooled to –10 °C, diethyl iodomethyl phosphonate (333 mg, 2.4 mmol) was added and the resulting mixture was stirred for 2 h at –10 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 5 mL), extracted with EtOAc (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/EtOAc = 1:1) to give **187u** (390 mg, 72%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.71 (td, *J*=4.6, 2.4 Hz, 1 H), 7.54-7.62 (m, 1 H), 7.15-7.23 (m, 1 H), 4.05-4.21 (m, 4 H), 3.21 (d, *J*=22 Hz, 2 H), 1.32 (m, 6 H).

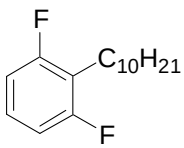
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 163.09 (dd, *J*=256, 7.1 Hz), 135.99 (t, *J*= 5.1 Hz), 133.04 (dd, *J*=9.4, 3.4 Hz), 121.72 (dd, *J*=17, 9.0 Hz), 117.79, 116.81 (dd, *J*=24, 3.1 Hz), 108.68 (dd, *J*=4.0, 3.4 Hz), 62.45 (d, *J*=6.7 Hz), 26. 18 (dd, *J*=141, 2.9 Hz), 16.29 (d, *J*=6.0 Hz), 14.16.

MS (70 eV, EI) *m/z* (%): 271 (26) [M^+], 223 (25), 215 (10), 212 (12), 198 (10), 195 (14), 137 (21), 135 (38), 134 (54), 124 (12), 109 (100), 107 (29), 91 (15), 80 (34), 69 (11), 57 (12), 55 (12), 43 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3465, 2985, 2929, 2232, 1610, 1591, 1498, 1444, 1392, 1370, 1249, 1228, 1211, 1162, 1095, 1047, 1018, 963, 855, 820, 792, 733, 709, 685.

HRMS (EI) for **$C_{12}H_{15}FNO_3P$** (271.0774): 271.0767.

Synthesis of 2-decyl-1,3-difluorobenzene (187v):



According to **TP 9**, the metalation of 1,3-difluorobenzene (**100d**; 228 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 10 h.

Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iododecane (536 mg, 2.0 mmol) and the resulting mixture was stirred for 10 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane) to give **187v** (391 mg, 77%) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.09 (tt, J=8.3, 6.5 Hz, 1 H), 6.74-6.87 (m, 2 H), 2.59-2.69 (m, 2 H), 1.48-1.62 (m, 2 H), 1.22-1.36 (m, 14 H), 0.82-0.93 (m, 3 H).

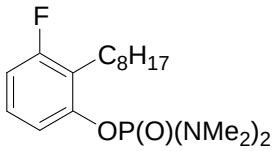
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.60 (dd, J_{CF}=246, 9.1 Hz), 126.93 (t, J_{CF}=10 Hz), 118.27 (t, J_{CF}=21 Hz), 110.86 (d, J_{CF}=9 Hz), 110.85 (d, J_{CF}=24 Hz), 31.89, 29.59, 29.55, 29.53, 29.36, 29.34, 29.31, 22.68, 22.27 (t, J_{CF}=2.3 Hz), 14.10.

MS (70 eV, EI) *m/z* (%): 254 (53) [M^+], 141 (10), 128 (20), 127 (100), 123 (22), 122 (11), 99 (11), 97 (15), 85 (57), 83 (16), 71 (84), 70 (12), 69 (18), 57 (93), 56 (14), 55 (27),43 (83).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956, 2924, 2855, 1625, 1590, 1564, 1468, 1378, 1265, 1235, 1194, 1180, 1116, 1062, 993, 957, 779, 724, 689, 667.

HRMS (EI) for **$C_{16}H_{24}F_2$** (254.1846): 254.1832.

Synthesis of 3-fluoro,2-octylphenyl-*N,N,N',N'*-tetramethyldiamido-phosphate (189a):



According to **TP 9**, the metalation of 3-fluoro-phenyl-*N,N,N',N'*-tetramethyldiamido-phosphate (**188a**; 492 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 30 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodooctane (576 mg, 2.4 mmol) and the resulting mixture was stirred for 30 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with EtOAc (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc) to give **189a** (608 mg, 85%) as a colourless liquid.

^{1}H-NMR (400 MHz, DMSO) δ: 7.18-7.24 (m, 1 H), 7.03 (dd, J=8.4, 1.0 Hz, 1 H), 6.94 (t, J=8.8 Hz, 1 H), 2.64 (s, 6 H), 2.62 (s, 6 H), 1.46-1.53 (m, 2 H), 1.20-1.31 (m, 12 H), 0.81-0.86 (m, 3 H).

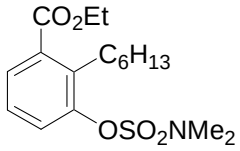
^{13}C-NMR (100 MHz, DMSO) δ: 160.88 (d, $^{1}J_{CF}$=243 Hz), 150.29 (dd *J* =8.6, 5.8 Hz), 127.36 (dd *J* =10, 1.1 Hz), 120.67 (dd *J* =19, 7.1 Hz), 115.08 (t *J* =3.1 Hz), 110.58 (dd *J* =23, 1.0 Hz), 36.15, 36.12, 31.16, 28.97, 28.89, 28.68, 28.51, 22.70 (d, $^{3}J_{CF}$=2.7 Hz), 22.00, 13.87.

MS (70 eV, EI) *m/z* (%): 358 (48), [M^+], 326 (9), 288 (14), 273 (95), 228 (11), 135 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3459, 2925, 2855, 2812, 1615, 1587, 1464, 1378, 1308, 1261, 1223, 1180, 1113, 1065, 977, 854, 814, 783, 757, 727, 689, 672.

HRMS (ESI) for **$C_{18}H_{32}FN_2O_2P$** (358.2185): 359.2261.

Synthesis of 3-dimethylsulfamoyloxy-2-hexylbenzoic acid ethyl ester (189b):



According to **TP 9**, the metalation of 3-dimethylsulfamoyloxy-benzoic acid ethyl ester (**188b**; 546 mg, 2.0 mmol) was completed using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 60 h. Then, 4-fluorostyrene (**186**; 24 mg, 0.2 mmol) was added, followed by 1-iodohexane (509 mg, 2.4 mmol) and the resulting mixture was stirred for 30 h at 25 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with EtOAc (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/EtOAc 4:1) to give **189b** (471 mg, 66%) as a colourless liquid.

^{1}H-NMR (400 MHz, DMSO) δ: 7.64 (dd, *J*=7.6, 1.4 Hz, 1 H), 7.52 (dd, *J*=8.2, 1.4 Hz, 1 H), 7.39 (d, *J*=7.8 Hz, 1 H), 4.31 (q, *J*=7.1 Hz, 2 H), 2.99 (s, 6 H), 2.87-2.92 (m, 2 H), 1.44-1.49 (m, 2 H), 1.30 (t, *J*=7.1 Hz, 3 H), 1.23-1.31 (m, 6 H), 0.82-0.86 (m, 3 H).

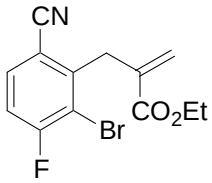
^{13}C-NMR (100 MHz, DMSO) δ: 166.57, 148.42, 135.57, 132.69, 127.88, 127.12, 124.65, 61.03, 38.20, 30.92, 30.02, 28.87, 26.34, 21.92, 13.91, 13.77.

MS (70 eV, EI) *m/z* (%): 357 (45) [M^+], 312 (69), 264 (18), 258 (21), 254 (26), 249 (24), 248 (26), 222 (67), 219 (18), 203 (51), 191 (19), 161 (19), 160 (33), 151 (100), 147 (21), 133 (21), 133 (18), 108 (98), 107 (28), 91 (17), 77 (18), 55 (24), 45 (31) 44 (65).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957, 2929, 2857, 1720, 1602, 1576, 1451, 1414, 1369, 1261, 1249, 1202, 1182, 1161, 1140, 1096, 1055, 1025, 971, 932, 869, 846, 823, 765, 745.

HRMS (EI) for **$C_{17}H_{27}NO_5S$** (357.1610): 357.1598.

Synthesis of 2-(2-bromo-6-cyano-3-fluorobenzyl)acrylic acid ethyl ester (189c)



According to **TP 9**, the metalation of 3-bromo-4-fluorobenzonitrile (**175c**; 400 mg, 2.0 mmol) was completed within 2 h at 25 °C using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**181**; 0.50 M in THF, 3.0 mL, 3.0 mmol) within 2 h. Then, the reaction mixture was cooled to 0 °C, CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and ethyl 2-(bromomethyl)acrylate (463 mg, 2.4 mmol) were added and stirred for 1 h at 0 °C. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl solution (40 mL) and HCl (2 M; 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane/diethyl ether = 25:1) to give **189c** (468 mg, 75%) as a colourless solid.

m.p.: 59.8-61.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.73 (dd, *J*=5.9, 2.1 Hz, 1 H), 7.50 (dd, *J*=6.2, 2.1 Hz, 1 H), 6.34 (s, 1 H), 5.59-5.65 (m, 1 H), 4.19 (q, *J*=7.1 Hz, 2 H), 3.69 (s, 2 H), 1.27 (t, *J*=7.1 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.82, 160.21 (d, $^1J_{CF}$=257 Hz), 136.84, 135.51 (d, J_{CF}=1.7 Hz), 134.21 (d, $^3J_{CF}$=5.1 Hz), 129.47 (d, $^2J_{CF}$=18 Hz), 127.95 (d, J_{CF}=1.1 Hz), 116.75 (d, J_{CF}=1.1 Hz), 110.45 (d, $^2J_{CF}$=24 Hz), 109.45 (d, $^3J_{CF}$=4.9 Hz), 61.18, 31.38 (d, $^4J_{CF}$=2.2 Hz), 14.07.

MS (70 eV, EI) *m/z* (%): 313 (14), 311 (14) [M^+], 269 (12), 267 (13), 266 (12), 239 (17), 159 (37), 158 (29), 155 (12), 141 (14), 127 (16), 113 (19), 111 (16), 99 (29), 97 (28), 85 (62), 84 (12), 83 (28), 71 (94), 70 (16), 69 (31), 57 (100), 56 (19), 55 (35), 43 (61), 41 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3079, 2988, 2934, 2232, 1718, 1681, 1632, 1598, 1572, 1468, 1444, 1409, 1390, 1368, 1318, 1302, 1285, 1276, 1243, 1215, 1196, 1160, 1111, 1029, 967, 953, 935, 916, 904, 880, 859, 840, 818, 810, 749, 729, 699.

HRMS (EI) for **$C_{13}H_{11}BrFNO_2$** (310.9957): 310.9957.

14 Curriculum Vitae

Stefan Hans Wunderlich

Contact:	Fürstenrieder Straße 172 D-81377 Munich, Germany Fon: 0049 89 72484663 E-Mail: swuch@cup.uni-muenchen.de
Citizenship:	German
Date of birth:	05.12.1980
Place of birth:	Rosenheim, Germany
Languages:	German (mother tongue) English (fluently) French (basics)
Personal Interests:	Sports (Squash, Skiing, Soccer) Hiking Cooking Movies

Education, Studies and Scientific Background:

10/2006-11/2009	PhD thesis in the group of Prof. Knochel on the "Preparation of Highly Functionalized Aryl and Heteroaryl Organometallics by C-H Activation of Aromatics and Heterocycles using Hindered TMP-Amide Bases of Zn, Al, Mn, Fe and La"

03/2006-08/2006	Master's thesis on the "Development of a Non-Nucleophilic Zinc Base for the Preparation of Functionalized Aromatics and Heteroaromatics" in the group of Prof. Dr. P. Knochel (Master average grade: 1.3)
10/2001-01/2006	Studies in Chemistry at LMU Munich, Master of Science examinations 01/2006
07/2000-08/2001	Military service
06/2000	Graduation (Abitur; main subjects: mathematics/chemistry; average grade: 1.7)
1991-2000	High school "Gymnasium Bad Aibling"
1987-1991	Primary school in Großkarolinenfeld

Publications

1 F. Kopp, S. H. Wunderlich, P. Knochel. **Halogen-magnesium exchange on unprotected aromatic and heteroaromatic carboxylic acids.** *Chem. Commun.* **2007,** *46*, 2075-2077.

2 R. Bobka, J. N. Roedel, B. Neumann, C. Krinninger, P. Mayer, S. H. Wunderlich, A. Penger, I.-P Lorenz. **Neutral mono- and cationic bis-aziridine d_6-metal complexes of the type [(π -arene)M(Az)Cl_2] and [(π -arene)M(Az)$_2$Cl]Cl (π -arene/M = η_6-C_6Me_6/Ru; η_5-C_5Me_5/Rh, Ir).** *Z. Anor. Allg. Chem.* **2007**, 633 (11-12).

3 S. H. Wunderlich, P. Knochel. **(TMP)$_2$Zn·2MgCl$_2$·2LiCl: A Chemoselective Base for the Directed Zincation of Sensitive Arenes and Heteroarenes.** *Angew. Chem. Int. Ed.* **2007**, *46*, 7685-7688.

4 S. H. Wunderlich, P. Knochel. **High Temperature Metalation of Functionalized Aromatics and Heteroaromatics Using (TMP)$_2$Zn·2MgCl$_2$·2LiCl and Microwave Irradiation**. *Org. Lett.* **2008**, *10*, 4705-4707.

5 S. H. Wunderlich, P. Knochel. **Efficient Mono- and bis-Functionalization of 3,6-Ddichloropyridazine using $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.** *Chem. Commun.* **2008,** *47*, 6387-6389.

6 Z. Dong, G. C. Clososki, S. H. Wunderlich, A. Unsinn, J. Li, P. Knochel. **Direct Zincation of Functionalized Aromatics and Heterocycles by Using a Magnesium Base in the Presence of $ZnCl_2$.** *Chem. Eur. J.* **2009**, *15*, 457-468.

7 S. H. Wunderlich, P. Knochel. **Aluminum Bases for the Highly Chemoselective Preparation of Aryl and Heteroaryl Aluminum Compounds.** *Angew. Chem. Int. Ed.* **2009**, *48*, 1501-1504.

8 C. J. Rohbogner, S. H. Wunderlich, G. C. Clososki, P. Knochel. **New Mixed Li/Mg- and Li/Mg/Zn-Amides for the chemoselective Metalation of Arenes and Heteroarenes**. *Eur. J. Org. Chem.* **2009**, 1781-1795.

9 S. H. Wunderlich, M. Kienle, P. Knochel.. **Directed Manganation of Functionalized Arenes and Heterocycles Using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$.** *Angew. Chem. Int. Ed.* **2009**, *48*, 7256-7260.

10 S. H. Wunderlich, P. Knochel. **Preparation of Functionalized Aryl-Fe(II)-Compounds and a Ni-Catalyzed Cross-Coupling with Alkyl Halides.** *Angew. Chem. Int. Ed.* **2009**, *48*, 9717-9720.

11 S. H. Wunderlich, P. Knochel. **Atom-Economical Preparation of Aryl and Heteroaryl- Lanthanum Reagents by Directed ortho-Metalation using TMP_3[La]**. *Chem. Eur. J.*. **2009**, *manuscript accepted.*

12 S. H. Wunderlich, C. J. Rohbogner A. Unsinn, P. Knochel.. **Large Scale Preparation of Functionalized Organometallics *via* Directed *ortho*-Metalation Using Mg- and Zn-Amide Bases.** *Organic Process Research & Development, manuscript accepted.*

13 S. H. Wunderlich, T. Bresser, C. Dunst, G. Monzon, P. Knochel. **Efficient Preparation of Functionalized Organometallics *via* Directed *ortho*-Metalation**. *Synthesis, manuscript submitted*.

14 A. Unsinn, S. H. Wunderlich, P. Knochel. **Unusual Regioselectivities in the Metalation using Aluminium Bases**. *Org. Lett, manuscript in preparation.*

15 A. Unsinn, S. H. Wunderlich, B. Haag, P. Knochel. **Accelerated Zincations Mediated by TMPMgCl·LiCl for an Efficient and Mild Functionalization of Aromatics and Heterocycles.** *Chem. Eur. J., manuscript in preparation.*

16 S. H. Wunderlich, M. Kienle, S. Matthe, P. Knochel. **Convenient Preparation of Transition Metal Organometallics *via* Directed Metalation.** *Chem. Eur. J., manuscript in preparation.*

17 S. H. Wunderlich, A. Unsinn. P. Knochel. **Aluminum Bases for the Highly Chemoselective Preparation of Aryl and Heteroaryl Aluminum Compounds.** *Eur. J. Org. Chem., manuscript in preparation.*

Books and Reviews

1 P. Knochel, P. Appukkuttan, A. Gavryshin, G. Manolikakes, A. Metzger, M. Mosrin, F. M.; Piller, C. J. Rohbogner, M. A. Schade, S. H. Wunderlich. **"Functionalization of Heterocyclic Compounds using Polyfunctional Magnesium and Zinc Reagents"**, *Pfizer In-House Journal Synthon*, **2008**.

2 T. Thaler, H. Ren, N. Gommermann, G. C. Clososki, C. J. Rohbogner, S. H. Wunderlich, P. Knochel. **New catalytic Cu-, Pd- and stoichiometric Mg-, Zn-mediated bond activations.** Activating Unreactive Substrates (2009), 359-377.

3 P. Knochel, S. H. Wunderlich, B. Haag. **Chemo- and Regioselective Metalations of Arenes and Heteroarenes Using Hindered Metal Amides.** *Angew. Chem., Int. Ed.* **2009**, *manuscript in preparation.*

Patent Application

P. Knochel, S. H. Wunderlich. **Process for preparation of diamidozinc bases as metalation reagents for aromatic and heterocyclic compounds.** PCT/EP2008/055895.

Poster Presentations

"S. H. Wunderlich P. Knochel. **"$(TMP)_2Zn \cdot 2MgCl_2 \cdot 2LiCl$: A New Highly Chemoselective Base for the Directed Zincation of Sensitive Aromatics and Heteroaromatics"** at 5th Asian-European Symposium on Metal-Mediated Efficient Organic Synthesis, May 25th to 28th 2008, Obernai, France.

Talks

"**$(TMP)_2Zn \cdot 2MgCl_2 \cdot 2LiCl$: A New Highly Chemoselective Base for the Directed Zincation of Sensitive Aromatics and Heteroaromatics**"; Presentation at Sanovi-Aventis, June 11th 2008 in Frankfurt/Main, Germany.

"**$(TMP)_2Zn \cdot 2MgCl_2 \cdot 2LiCl$: A New Highly Chemoselective Base for the Directed Zincation of Sensitive Aromatics and Heteroaromatics**"; Presentation at the "Organisch-Chemisches Kolloquium" at LMU, June 23rd 2008 in Munich, Germany.

"New Amide Bases for the Efficient Preparation of Highly Functionalized Organometallics"; Presentation at BASF, May 27th 2009 in Ludwigshafen, Germany.

Acknowledgements and Awards

Dr. Klaus Römer Prize, LMU, Munich, 2007.