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

Metalation and Functionalization of Pyridones, Naphthyridones and Pyrones Using TMP-Bases
and
Generation of Aryl and Heteroaryl Magnesium Reagents in Toluene by Br/Mg- and Cl/Mg-Exchange

von

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aus

Schweinfurt

2018

ERKLÄRUNG

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Paul Knochel betreut.

EIDESSTATTLICHE VERSICHERUNG

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, 03.09.2018

……..……

(Dorothée Ziegler)

Dissertation eingereicht am:	03.09.2018
1. Gutachter:	Prof. Dr. Paul Knochel
2. Gutachter:	Prof. Dr. Oliver Trapp
Mündliche Prüfung am:	16.10.2018

This work was carried out from August 2015 to August 2018 under the guidance of Prof. Dr. Paul Knochel at the Department of Chemistry of the Ludwig-Maximilians-Universität, Munich.

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

I would also like to express my gratitute to Prof. Dr. Oliver Trapp for agreeing to be second reviewer of my thesis, as well as Prof. Dr. Franz Bracher, Prof. Dr. Manfred Heuschmann, Prof. Dr. Konstantin Karaghiosoff and Dr. Henry Dube for their interest shown in this manuscript by accepting to be members of my defense committee. In addition, special thanks go to Prof. Dr. Konstantin Karaghiosoff for his great support during my whole Ph.D. and his interest in this manuscript.

Furthermore, I would like to express my gratitude to Moritz Balkenhohl, Lucie Grokenberger, Marthe Ketels, Marcel Leroux, Ferdinand Lutter, Juri Skotnitzki and Fabian Schnitter for careful correction of this manuscript

I would like to thank all past and present members I have met in the Knochel group for their kindness, their help and for creating a wonderfull ambience inside and outside of the lab. Especially I want to mention all my former and current lab mates of F2.017, Prof. Dr. Zhibing Dong, Alexander Kremsmaier, Dr. Jeffrey Hammann, Dr. Ilya Makarov, Dr. Kohei Moriya, Dr. Varvara Morozova, Dr. Lydia Klier, Dr. Meike Simon, Juri Skotnitzki, Shu-Mei Yang, who gave me the best working and living atmosphere one can imagine.

Moreover, I thank my former students Laura Kikqu and Nicolas Müller for their excellent contributions during their internships.

I would also like to thank Peter Dowling, Sophie Hansen, Dr. Vladimir Malakhov and Yulia Tsvik for their help organizing everyday life in the lab and the office, as well as the analytical team of the LMU for their invaluable help.

Very special thanks go to Marthe Ketels for her invaluable help in every situation and for any kind of discussions on chemical problems during my whole Ph.D. and for simply being my friend for the past nine years. I want to thank Moritz Balkenhohl for his friendship and support and all the nice moments we shared together in the lab.

I would like to thank my whole family, especially my parents, and my friends for their great support, for their love, patience and belief in me, throughout my studies and my Ph.D..

Finally, I thank Fabian for his never-ending love and always being there for me.

Parts of this Ph.D. Thesis have been published

A) Communications

1) "Directed Zincation or Magnesiation of the 2-Pyridone and 2,7-Naphthyridone Scaffold Using TMP-Bases"
D. S. Ziegler, Robert Greiner, Henning Lumpe, Laura Kqiku, Konstantin Karaghiosoff, Paul Knochel, *Org. Lett.* **2017**, *19*, 5760.

2) "Generation of Aryl and Heteroaryl Magnesium Reagents in Toluene by Br/Mg- or Cl/Mg-Exchange"
D. S. Ziegler, Konstantin Karaghiosoff, Paul Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 6701; *Angew. Chem.* **2018**, *57*, 6811.

3) "Directed Zincation or Magnesiation of 2- and 4-Pyrones and their Derivatives"
D. S. Ziegler, L. Klier, N. Müller, K. Karaghiosoff, P. Knochel, *Synthesis* **2018**, *50*, 4383.

4) "Improving the Halogen-Magnesium Exchange by Using new Turbo-Grignard Reagents"
D. S. Ziegler, B. Wie, P. Knochel, *Chem. - Eur. J.* **2018**, DOI: 10.1002/chem.201803904.

B) Patent

"Kohlenwasserstoff-lösliche Halogen- und Thiolat-/Magnesium-Austauschreagenzien"
D. S. Ziegler, M. Simon, Paul Knochel, DE 2018200805.1, *a national patent application has been filed.*

C) Poster

"Regio- and Chemoselective Metalation of Pyrone, Pyridone, Naphthyridone and Dioxinone Using TMP-Bases"
D. S. Ziegler, R. Greiner, H. Lumpe, P.Knochel, *BOSS XV conference* **2018**, Antwerp, Belgium.

“Ἄνδρα μοι ἔννεπε, Μοῦσα, πολύτροπον, ὃς μάλα πολλὰ

πλάγχθη, ἐπεὶ Τροίης ἱερὸν πτολίεθρον ἔπερσε·

πολλῶν δ' ἀνθρώπων ἴδεν ἄστεα καὶ νόον ἔγνω,

πολλὰ δ' ὅ γ' ἐν πόντῳ πάθεν ἄλγεα ὃν κατὰ θυμόν,

ἀρνύμενος ἥν τε ψυχὴν καὶ νόστον ἑταίρων.”

Odyssee, Homer

Abbreviations

Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	undefined aryl substituent
ATR	attenuated total reflection
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bpy	2,2'-bipyridine
Bu	butyl
calc.	calculated
CCDC	Cambridge Crystallographic Data Center
Cy	cylohexyl
d	doublet (NMR)
dba	*trans,trans*-dibenzylideneacetone
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppp	propane-1,3-diylbis(diphenylphosphane)
d.r.	diastereomeric ratio
EX	electrophile
EI	electron ionization (MS)
e.g.	for example
equiv	equivalents
ESI	electrospray ionization (MS)
Et	ethyl
etc.	*et cetera*
FG	functional group
GC	gas chromatography
Het	undefined heteroaryl substituent
Hex	hexyl
HRMS	high resolution mass spectroscopy
i	*iso*
IR	infrared
J	coupling constant (NMR)
M	mol L^{-1}
M	metal
M_n	number average molar mass

Me	methyl
Mes	mesityl
MOM	methoxymethyl
MEM	2-methoxyethoxymethyl
M.p.	melting point
MS	mass spectrometry
Nf	nonaflate
NIS	*N*-iodosuccinimide
NMP	1-methylpyrrolidin-2-one
NMR	nuclear magnetic resonance
o	*ortho*
PDI	polydispersity index
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
PG	protecting group
Ph	phenyl
Piv	pivaloyl
PMDTA	*N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
q	quartet (NMR)
R	undefined organic substituent
s	*sec*
s	singulet (NMR)
sat.	saturated
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	*tert*
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
TP	typical procedure
Ts	tosyl
Vol	volume

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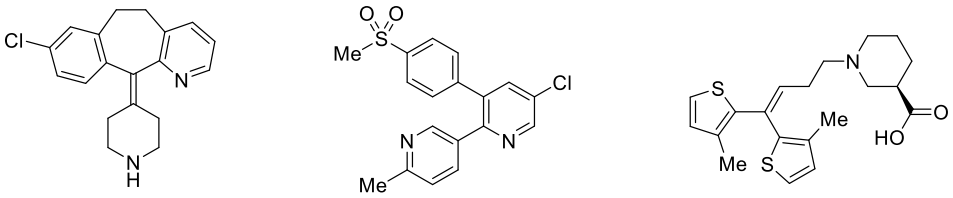
A. INTRODUCTION

1 Overview

Over recent decades, organometallic chemistry has changed the practice in science and industry. Since the early 1950s, organometallic chemistry has grown to become an important industrial tool, especially in the formation of complex molecules in medicinal, agrochemical or synthetic fragrance chemistry as well as in many other fields.[1] In case of the agrochemical industry, new technologies such as synthetic herbicides, insecticides and fungicides contributed significantly to developments in the area of chemical crop protection.[2] Population growth as well as greater economic prosperity in emerging markets raised the demand for food production while natural resources are limited.[3] Therefore, there is a need for new innovations and progress in agrochemical industry. Similar to the advance in food production due to population growth, the research-based pharmaceutical industry entered a new era in medicines development. Scientists have been attempting to find new synthetic methods for the preparation of drugs to cure malignant disease like cancer or HIV. The interest in the design and synthesis of small molecule drugs for the pharmaceutical industry has increased and is nowadays a significant discipline in modern drug discovery and organic chemistry.[4] Under the top-selling agents are a lot of small molecules, which can be prepared over several steps and with the help of organometallic compounds. Desloratadine (**1**), Etoricoxib (**2**) as well as Tiagabine (**3**) represent such small molecules, which are synthesized by organometallics.[5] Due to this fact, the development of new synthetic routes, using organometallic reagents as well as the development of new organometallic reagents is of great importance for the chemical industry.



Desloratadine (**1**) Etoricoxib (**2**) Tiagabine (**3**)

Figure 1: Selected important top-selling drugs (Desloratadine (**1**), Etoricoxib (**2**), Tiagabine (**3**)).

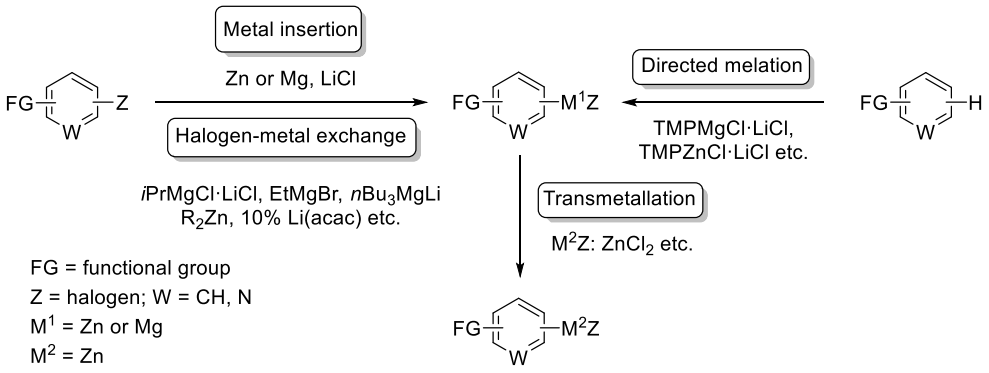
The nature of the metal and the carbon hybridization is significant for the behavior and the reactivity of the organometallic reagent. In general, the ionic character of the carbon-metal bond, depending on the difference in electronegativity of the metal and the carbon atom, is responsible for the reactivity of the organometallic compound. For instance, a high ionic character accompanied with a lower stability are

[1] a) G. W. Parshall, *Organometallics* **1987**, *6*, 687; b) *Applications of Organometallic compounds* (Ed.: I. Omae), Wiley-VCH Verlag GmbH & Co KGaA, Weinheim, **1998**.
[2] P. A. Urech, *Plant Pathol.* **1999**, *48*, 689.
[3] Food and Agriculture Organization of the United Nations (FAO), World Agriculture Towards 2030/2050. The 2012 Revision.
[4] a) D. P. Rotella, *ACS Chem. Neurosci.* **2016**, *7*, 1315; b) H.-J. Federsel, *Acc. Chem. Res.* **2009**, *42*, 671.
[5] M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2013**, *9*, 2265.

represented by lithium or sodium organometallics. Such compounds display an exceptional reactivity towards a variety of electrophiles but require low temperature for their reactions and possess a low functional group tolerance. A more covalent carbon-metal bond and consequently a higher stability and functional group compatibility is offered by organomagnesium reagents. In comparison to lithium and magnesium reagents, organozinc or boron reagents are less reactive, due to their covalent metal carbon bond. Thus, they are compatible with most functional groups applied in organic synthesis.[6] With this diverse reactivities, various synthetic problems can be solved and therefore organometallic compounds play an important role in modern synthetic chemistry.

2 Preparation of Polyfunctional Zinc and Magnesium Organometallic Reagents

The beginning of organometallic chemistry can be traced back to the year 1760, when de Gassicourt reported the first organometallic reagent, the so-called "Cadet's fuming liquid" containing cacodyl oxide $[(CH_3)_2As]_2O$.[7] Since this time, including the pioneering work of Frankland[8] and Grignard,[9] various approaches to prepare polyfunctional organometallics especially for magnesium and zinc have been developed. The three most commonly used strategies include oxidative insertion, halogen-metal exchange and directed metalation. Another approach to organometallic reagents offers transmetalation (Scheme 1).

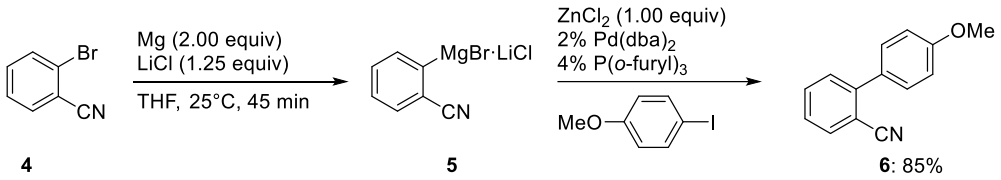


Scheme 1: Preparation of organomagnesium and organozinc reagents *via* different pathways.

[6] *Handbook of Functionalized Organometallics Vol. 1 and 2* (Ed.: P. Knochel), Wiley-VCH Verlag GmbH & Co KGaA, Weinheim, **2005**.
[7] D. Seyferth, *Organometallics* **2001**, *20*, 1488.
[8] E. Frankland, *Liebigs Ann. Chem.* **1849**, *71*, 171.
[9] V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322.

2.1 Oxidative Insertion

One of the most common methods for the preparation of zinc and magnesium organometallic reagents is the oxidative insertion. The method was first described in 1849 by Frankland, who prepared diethylzinc by the reaction of granulated zinc with ethyliodide.[8] Another milestone in this field was the work on organomagnesium reagents from Grignard. He discovered that methyliodide reacted with magnesium turnings in diethylether, affording the first organomagnesium compound.[9] Since that time a remarkable rise of organometallic chemistry began and a wide range of investigations were made. The direct insertion of magnesium into the halogen carbon bond takes place in short reaction times but sensitive functional groups complicate the preparation of these Grignard reagents. Usually, an activation of the metal surface by using 1,2-dibromoethane, iodine or DIBAL-H is required for reducing the induction time. However, by adding LiCl, Knochel and co-workers developed an oxidative insertion method under mild conditions to prepare organomagnesium reagents with high functional group tolerance.[6] For example the use of magnesium turnings in the presence of LiCl led to a magnesium insertion into 2-chlorobenzonitrile (**4**) in THF at 25 °C within 45 min. Compared to the previous method, the reaction required 5 h and decomposition was observed without the addition of LiCl. After transmetallation of magnesium species **5** to zinc, the zinc intermediate underwent a Pd-catalyzed Negishi cross-coupling with 4-iodoanisole to furnish the arylated benzonitrile **6** (Scheme 2).[10]



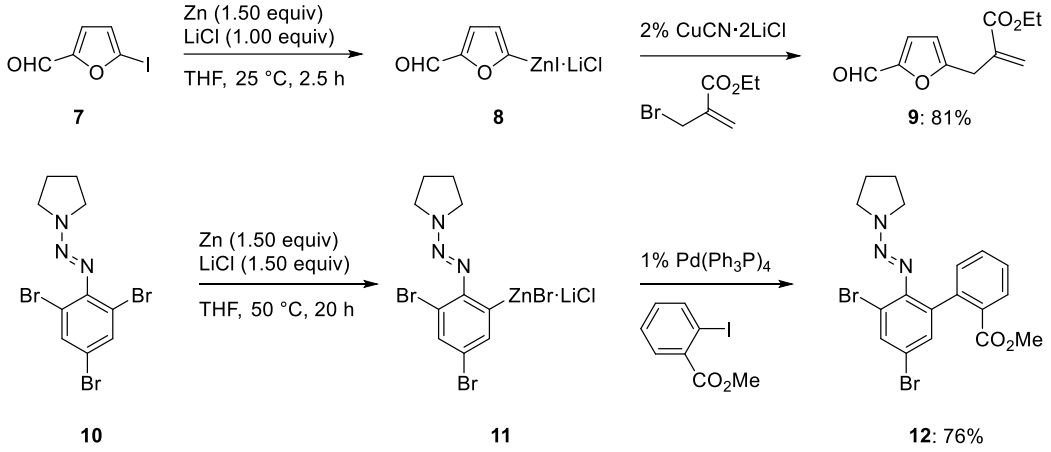
4 **5** **6**: 85%

Scheme 2: Preparation of biaryl **6** using magnesium insertion in the presence of LiCl.

Furthermore, this method could be extended to a variety of metals such as zinc,[11] manganese,[12] aluminum[13] or indium.[14] The use of commercially available zinc powder for the insertion into highly functionalized aromatic and heteroaromatic halides was also shown by Knochel. Thereby, a broad range of functional groups like esters, aldehydes and nitriles could be tolerated.[11] The role of LiCl during the

[10] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.
[11] 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.
[12] Z. Peng, P. Knochel, *Org. Lett.* **2011**, *13*, 3198.
[13] a) T. D. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313; b) T. D. Blümke, T. Klatt, K. Koszinowski, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9926.
[14] 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.

insertion of zinc into organic halides was investigated by several groups.[15] Examples of this oxidative insertion are shown in Scheme 3. Furan iodide derivative **7** could be converted into the corresponding organozinc compound **8** under mild conditions and subsequently underwent a copper-catalyzed allylation with ethyl 2-bromomethyl acrylate to yield **9** in 81% yield.[11a] Furthermore, the preparation and cross-coupling reaction of the zinc reagent **11** with methyl 2-iodobenzoate furnished compound **12** in 76% yield (Scheme 3).[11b]



Scheme 3: Preparation of functionalized (hetero)arenes using a zinc insertion in the presence of LiCl.

2.2 Halogen-Metal Exchange

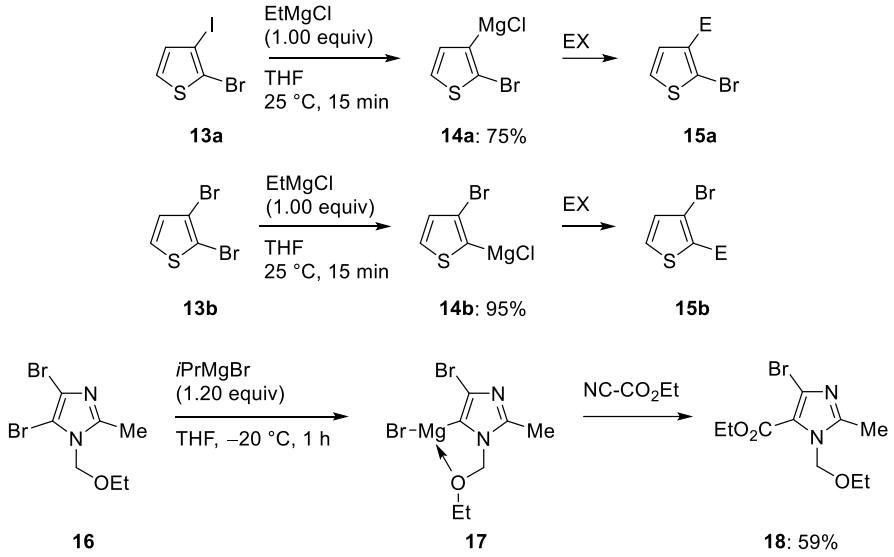
Besides the selective insertion of metals into organic halides, a commonly used method for the preparation of organometallic reagents is the halogen-metal exchange. In general, the driving force for this reaction type is the formation of a more stable organometallic species compared to the exchange reagent itself ($sp > sp^2_{vinyl} > sp^2_{aryl} > sp^3_{prim} > sp^3_{sec}$).[6,16] Discovered by Gilman[17] and Wittig,[18] the halogen-lithium exchange has proven its synthetic utility over the years for preparing a wide range of lithium organometallics.[19] Nevertheless, the high reactivity of the carbon-lithium bond has precluded the use of this method for preparing polyfunctional lithium reagents at convenient reaction temperatures.[20] On the other hand, the iodine-magnesium exchange proved to be advantageous for the

[15] K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771; b) J. E. Fleckenstein, K. Koszinowski, *Organometallics* **2011**, *30*, 5018; c) C. Feng, D. W. Cunningham, Q. T. Easter, S. A. Blum, *J. Am. Chem. Soc.* **2016**, *138*, 11156.
[16] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.
[17] a) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106; b) R. G. Jones, H. Gilman, *Org. React.* **1951**, *6*, 339.
[18] G. Wittig, U. Pockels, H. Dröge, *Chem. Ber.* **1938**, *71*, 1903.
[19] a) J. Clayden, *Organolithiums: Selectivity for Synthesis* (Ed.: J. Clayden), Pergamon, Oxford, **2002**; b) C. Nájera, J. M. Sansano, M. Yus, *Tetrahedron* **2003**, *59*, 9255.
[20] Notable exceptions: a) A. Nagaki, H. Kim, H. Usutani, C. Matsuo, J.-i. Yoshida, *Org. Biomol. Chem.* **2010**, *8*, 1212; b) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Comm.* **2011**, *2*, 264; c) A. Nagaki, K. Imai, S. Ishiuchi, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914; d) H. Kim, H.-J. Lee, D.-P. Kim, *Angew. Chem. Int. Ed.* **2015**, *54*, 1877.

preparation of polyfunctional organomagnesium reagents because of the less ionic character of the carbon-magnesium bond.[21] Whereas the halogen-lithium exchange is one of the fastest reactions in organic synthesis,[22] iodine-magnesium and especially bromine-magnesium exchanges are considerably slow.[23]

2.2.1 Halogen-Magnesium Exchange

The halogen-magnesium exchange reaction was used for generating magnesium carbenoids as shown by Köbrich[24] and Villieras.[25] This exchange reaction has also found to be a convenient method for converting iodo- or bromo-heterocycles into the corresponding magnesiated heterocycles.[21a] General, the iodine-magnesium exchange takes place faster than the corresponding bromine-magnesium exchange and the more stabilized the resulting magnesium species is, the faster the exchange reaction takes place.



Scheme 4: Regioselectivity of the bromine-magnesium exchange.

An elegant application was shown by Christophersen: whereas 2-bromo-3-iodothiophene (**13a**) produced 3-magnesiated bromothiophene **14a** *via* an iodine-magnesium exchange,

[21] a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; b) 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; c) N. M. Barl, V. Werner, C. Sämann, P. Knochel, *Heterocycles* **2014**, *88*, 827; d) G. Dagousset, C. Francois, T. Leon, R. Blanc, E. Sansiaume-Dagousset, P. Knochel, *Synthesis* **2014**, *46*, 3133; e) D. Tilly, F. Chevallier, F. Mongin, P. C. Gros, *Chem. Rev.* **2014**, *114*, 1207; f) R. Li-Yuan Bao, R. Zhao, L. Shi, *Chem. Commun.* **2015**, *51*, 6884.

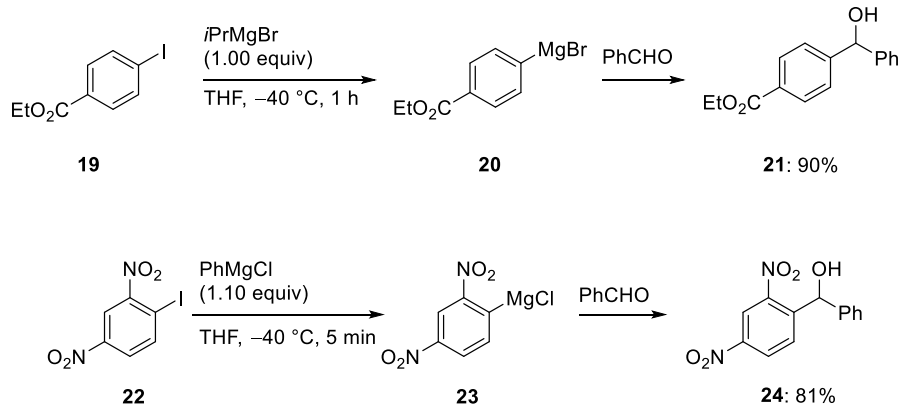
[22] W. F. Bailey, J. J. Patricia, T. T. Nurmi, W. Wang, *Tetrahedron Lett.* **1986**, *27*, 1861.

[23] a) L. Shi, Y. Chu. P. Knochel, H. Mayr, *Angew. Chem. Int. Ed.* **2008**, *47*, 202; b) L. Shi, Y. Chu, P. Knochel, H. Mayr, *Org. Lett.* **2009**, *11*, 3502; c) L. Shi, Y. Chu, P. Knochel, H. Mayr, *J. Org. Chem.* **2009**, *74*, 2760; d) L. Shi, Y. Chu, P. Knochel, H. Mayr, *Org. Lett.* **2012**, *14*, 2602.

[24] G. Köbrich, P. Buck, *Chem. Ber.* **1970**, *103*, 1412.

[25] J. Villieras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Soc. Chim. Fr.* **1986**, 470.

2,3-dibromothiophene (**13b**) reacted with EtMgCl at 25 °C in THF providing the more stabilized Grignard reagent **14b**. Quenching reactions with various electrophiles (EX) produced the corresponding 3- and 2-substituted thiophenes **15a–b** in satisfactory yields (Scheme 4).[26] The regioselectivity of the bromine-magnesium exchange can also be triggered by the presence of a directing group which coordinates the exchange reagent and directs the exchange reaction. For example, the dibromoimidazole derivative **16** complexed *i*PrMgBr at the ethoxy group and directed the exchange reaction, producing a very stable Grignard reagent **17** which, after trapping with NC-CO_2Et provided the bromoimidazole **18** in 59% yield.[27] The presence of electron-withdrawing substituents always accelerated the bromine-magnesium exchange and gave for the first time access to arylmagnesium reagents bearing a carbethoxy group or a nitro group. Thus, ethyl 4-iodobenzoate (**19**) reacted with *i*PrMgBr at −40 °C within 1 h, providing the functionalized arylmagnesium bromide **20**. After addition to PhCHO, the expected alcohol **21** was obtained in 90% yield.[28a] Similarly, various iodonitroarenes underwent a fast iodine-magnesium exchange reaction with PhMgCl or mesitylmagnesium bromide at −40 °C within a few minutes, furnishing novel nitro-substituted arylmagnesium reagents.[28] Attempts for preparing such nitro-substituted Grignard reagents using magnesium turnings resulted in a complete reaction inhibition and only led to reduced products.[29] However, the reaction of 2-iodo-1,5-dinitrobenzene (**22**) with PhMgCl at −40 °C for 5 min provided the corresponding Grignard reagent **23**. After reaction with PhCHO, the alcohol **24** was obtained in 81% yield (Scheme 5).[30]



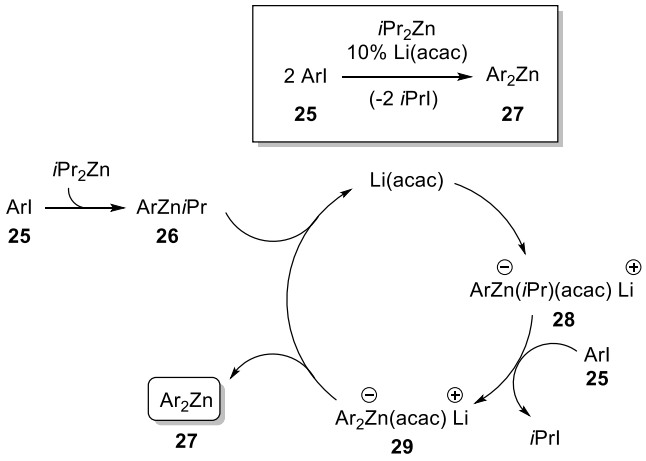
Scheme 5: Chemoselective iodine-magnesium exchange reaction.

[26] C. Christophersen, M. Begtrup, S. Ebdrup, H. Petersen, P. Vedso, *J. Org. Chem.* **2003**, *68*, 9513.
[27] a) M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 7449; b) M. Abarbri, J. Thibonnet, L. Berillon, F. Dehmel, M. Rottlaender, P. Knochel, *J. Org. Chem.* **2000**, *65*, 4618.
[28] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; b) G. Varchi, A. Ricci, G. Cahiez, P. Knochel, *Tetrahedron* **2000**, *56*, 2727; c) W. Dohle, D. M. Lindsay, P. Knochel, *Org. Lett.* **2001**, *3*, 2871; d) Y. Nakamura, S. Yoshida, T. Hosoya, *Chem. Lett.* **2017**, *46*, 858.
[29] a) T. Severin, D. Bätz, H. Krämer, *Chem. Ber.* **1971**, *104*, 950; b) G. Bartoli, G. Palmieri, M. Bosco, R. Dalpozzo, *Tetrahedron Lett.* **1989**, *30*, 2129; c) M. Bosco, R. Dalpozzo, G. Bartoli, G. Palmieri, M. Petrini, *J. Chem. Soc.* **1991**, 657.
[30] a) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 1610; b) I. Sapountzis, H. Dube, R. Lewis, N. Gommermann, P. Knochel, *J. Org. Chem.* **2005**, *70*, 2445.

As a rule, iodo-arenes and iodo-heterocycles were often sufficiently reactive to undergo an iodine-magnesium exchange with standard exchange reagents (ethyl-, isopropyl- or phenyl-magnesium halides). Useful applications have been reported such as the synthesis of alkaloids such as kealiinines A–C.[31] However, an extension to aryl and heteroaryl bromides was not always possible[32] and the use of lithium trialkylmagnesiates[33] was often required, which reduces the chemoselectivity of the Grignard reagent preparation.

2.2.2 The Study of a Related Exchange Reaction: the I/Zn-Exchange

The iodine-zinc exchange gave new hints for increasing the rate of the bromine-magnesium exchange: the treatment of an aryl iodide (ArI) of type **25** with *i*Pr_2Zn in NMP at 25 °C readily leads to the mixed zinc reagent ArZn*i*Pr **26**. However, this zinc reagent does not react with a second equivalent of **25** to produce *bis*-arylzinc **27** despite numerous experiments. It was found that the addition of catalytic amounts (10 %) of Li(acac) is tentatively producing the ate-intermediate **28** which is more nucleophilic and able to perform an iodine-zinc exchange on ArI **25** to produce the new ate-species **29** and *i*PrI. This ate-species **29** breaks down to Ar_2Zn **27** and regenerates Li(acac) which can reenter this catalytic cycle (Scheme 6).[34]

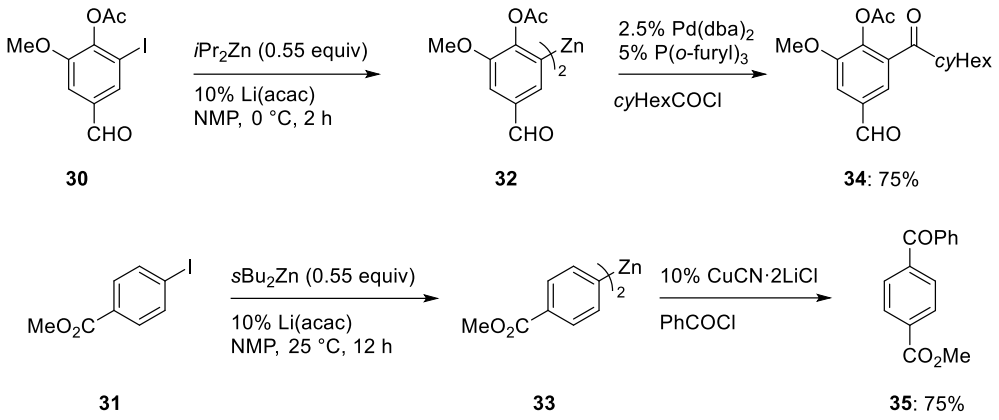


Scheme 6: Proposed mechanism of the iodine-zinc exchange reaction.

Since a carbon-zinc bond is quite covalent and does not react in the absence of catalysts with most electrophilic functional groups, it was possible to prepare a wide range of highly functionalized zinc

[31] J. Das, P. B. Koswatta, J. D. Jones, M. Yousufuddin, C. J. Lovely, *Org. Lett.* **2012**, *14*, 6210.
[32] a) J. Thibonnet, P. Knochel, *Tetrahedron Lett.* **2000**, *41*, 3319; b) O. Ryabtsova, T. Verhelst, M. Baeten, C. M. L. Vande Velde, B. U. W. Maes, *J. Org. Chem.* **2009**, *74*, 9440.
[33] a) K. Kitagawa, A. Inoue, H. Shinokubo, K. Oshima, *Angew. Chem. Int. Ed.* **2000**, *39*, 2481; b) A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2001**, *66*, 4333; c) A. Inoue, J. Kondo, H. Shinokubo, K. Oshima, *Chem. - Eur. J.* **2002**, *8*, 1730; d) L. Struk, J. G. Sosnicki, *Synthesis* **2012**, *44*, 735.
[34] a) F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017; b) L.-Z. Gong, P. Knochel, *Synlett* **2005**, *2005*, 267.

organometallics bearing for example an aldehyde **30** and a methyl ester function **31** *via* this exchange reaction[34]. In this last synthesis, a very convenient preparation of *s*Bu_2Zn was employed, starting from commercially available *s*BuLi.[34a] Further quenching with appropriate electrophilic reagents produced polyfunctional products **34**–**35** (Scheme 7).[34a]

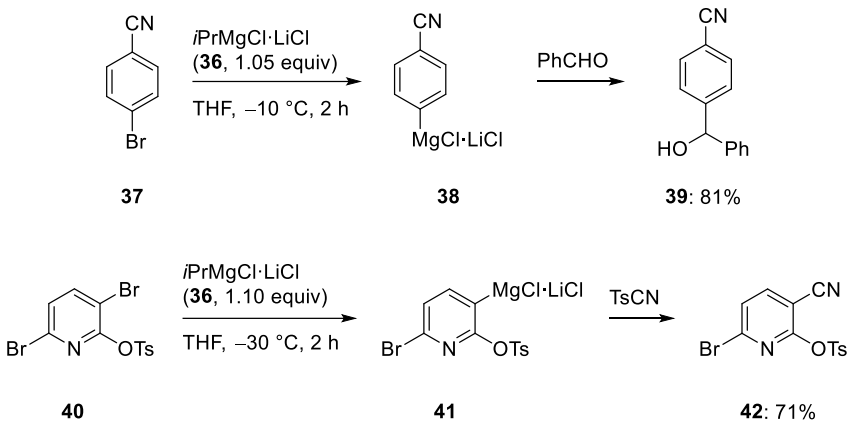


Scheme 7: Iodine-zinc exchange reaction catalyzed by Li(acac) in NMP.

2.2.3 Preparation and Reactions of the *turbo*-Grignard *i*PrMgCl·LiCl (36)

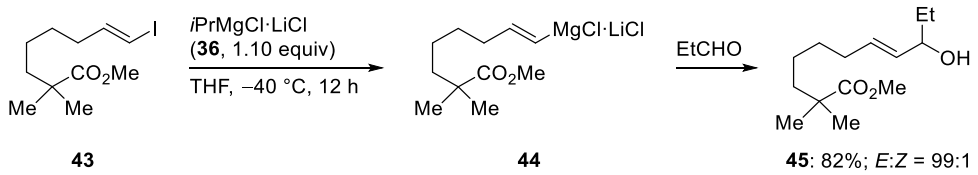
The use of Li(acac) in the iodine-magnesium exchange reaction led to an extension of the iodine- and of the bromine-magnesium exchange reaction. Unfortunately Li(acac) could not be used for catalyzing a halogen-magnesium exchange, since this lithium salt was decomposed by Grignard reagents. It was found that LiCl was perfectly suited as promotor. Thus, the bimetallic reagent *i*PrMgCl·LiCl (**36**) gave excellent results and considerably accelerated the bromine- and iodine-magnesium exchange.[16,35] More importantly, this reagent allowed the use of aryl and heteroaryl bromides as cheap and readily available substrates. In addition, highly functionalized aryl and heteroaryl iodides could be used as well. For example, 4-bromobenzonitrile (**37**) was converted with *i*PrMgCl·LiCl (**36**) to the corresponding Grignard reagent **38** at −7 °C within 2 h. Quenching with benzaldehyde led to alcohol **39** in 81% yield (Scheme 8).[35a]

[35] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159; c) T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 1958; d) J. Nickel, M. Fernandez, L. Klier, P. Knochel, *Chem. - Eur. J.* **2016**, *22*, 14397.



Scheme 8: Selective bromine-magnesium exchange reaction triggered by *i*PrMgCl·LiCl (**36**).

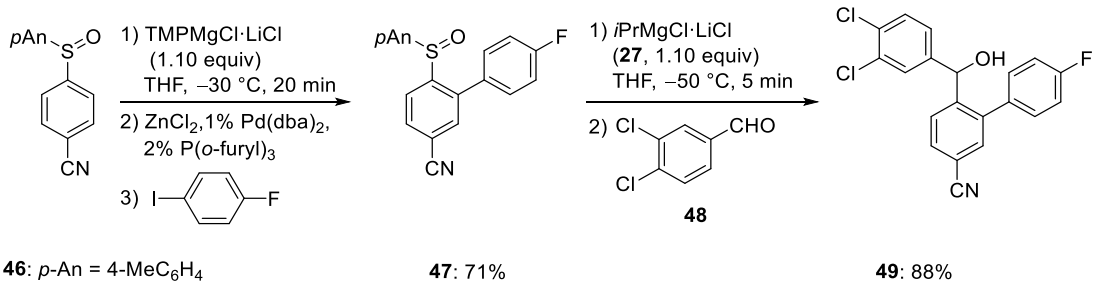
Polybromides such as **40** exclusively underwent a mono-exchange reaction with *i*PrMgCl·LiCl (**36**).The dibromo-pyridine **40** underwent an exchange at position C(3), since this position leads to the most stabilized Grignard reagent **41**. After cyanation by using tosyl cyanide, the nitrile **42** was obtained in 71% yield.[36] This mild exchange reaction was compatible with various sensitive functionalities.[37] Functionalized alkenylmagnesium derivatives were also obtained *via* an iodine- or bromine-magnesium exchange. For example, the polyfunctional alkenyl iodide **43** reacted with **36** at −40 °C furnishing *E*-alkenylmagnesium derivative **44**. After reaction with propionaldehyde, the alcohol **45** was obtained in 82% yield (Scheme 9).[38]



Scheme 9: Preparation of alkenylmagnesium reagents using *i*PrMgCl·LiCl (**36**).

[36] H. Ren, P. Knochel, *Chem. Commun.* **2006**, 726.
[37] C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543.
[38] H. Ren, A. Krasovskiy, P. Knochel, *Org. Lett.* **2004**, *6*, 4215.

*i*PrMgCl·LiCl (**36**) was also an efficient reagent for performing a sulfoxide-magnesium exchange (Scheme 10).[39] The sulfoxide-magnesium exchange was well studied by Satoh[40] and Hoffmann.[41] Remarkably, this exchange reaction could be efficiently done with *i*PrMgCl·LiCl (**36**) and allows *meta*- and *para*-difunctionalization of arenes[39a] and heterocycles.[39b,c] The metalation of aryl sulfoxide **46** with TMPMgCl·LiCl[42] followed by a Negishi cross-coupling produced the polyfunctional sulfoxide **47**. This compound **47** underwent a fast sulfoxide-magnesium exchange at −50 °C within 5 min, producing an intermediate Grignard reagent. By addition of aldehyde **48**, benzonitrile **49** was furnished in 88% yield (Scheme 10).[39c]



Scheme 10: Preparation of polyfunctional arenes and pyridines using a sulfoxide-magnesium exchange.

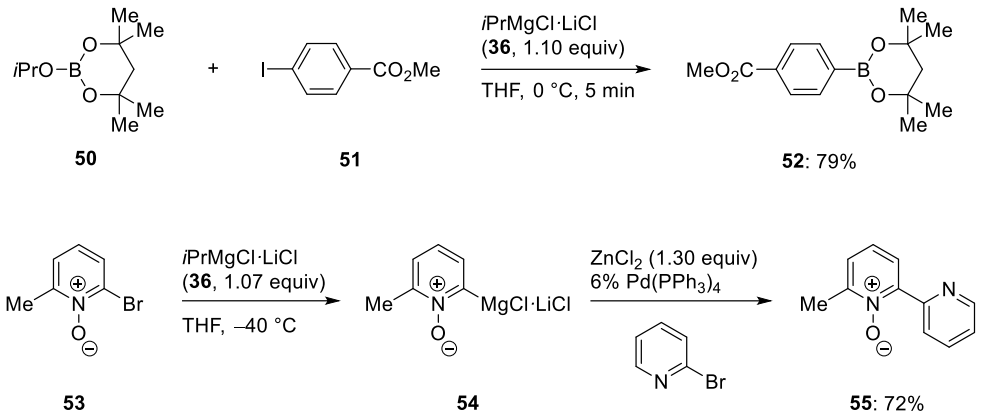
Since the initial report[35a] the *turbo*-Grignard (**36**) has become a very popular exchange reagent and numerous applications have been reported in industry as well as in academia.

[39] a) F. F. Fleming, S. Gudipati, V. A. Vu, R. J. Mycka, P. Knochel, *Org. Lett.* **2007**, *9*, 4507; b) C. B. Rauhut, L. Melzig, P. Knochel, *Org. Lett.* **2008**, *10*, 3891; c) L. Melzig, C. B. Rauhut, P. Knochel, *Synthesis* **2009**, 1041; d) L. Melzig, C. B. Rauhut, N. Naredi-Rainer, P. Knochel, *Chem. - Eur. J.* **2011**, *17*, 5362; e) N. M. Barl, E. S. Sansiaume-Dagousset, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 10093; f) D. Nath, F. F. Fleming, *Chem. - Eur. J.* **2013**, *19*, 2023; g) M. Hughes, T. Boultwood, G. Zeppetelli, J. A. Bull, *J. Org. Chem.* **2013**, *78*, 844; h) C. Sämann, E. Coya, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 1430.

[40] a) T. Satoh, T. Oohara, Y. Ueda, K. Yamakawa, *J. Org. Chem.* **1989**, *54*, 3130; b) T. Satoh, K. Horiguchi, *Tetrahedron Lett.* **1995**, *36*, 8235; c) T. Satoh, K. Takano, H. Ota, H. Someya, K. Matsuda, M. Koyama, *Tetrahedron* **1998**, *54*, 5557.

[41] a) R. W. Hoffmann, P. G. Nell, *Angew. Chem. Int. Ed.* **1999**, *38*, 338; b) R. W. Hoffmann, B. Hölzer, O. Knopff, K. Harms, *Angew. Chem. Int. Ed.* **2000**, *39*, 3072; c) R. W. Hoffmann, B. Hölzer, O. Knopff, *Org. Lett.* **2001**, *3*, 1945; d) B. Holzer, R. W. Hoffmann, *Chem. Commun.* **2003**, 732; e) R. W. Hoffmann, *Chem. Soc. Rev.* **2003**, *32*, 225.

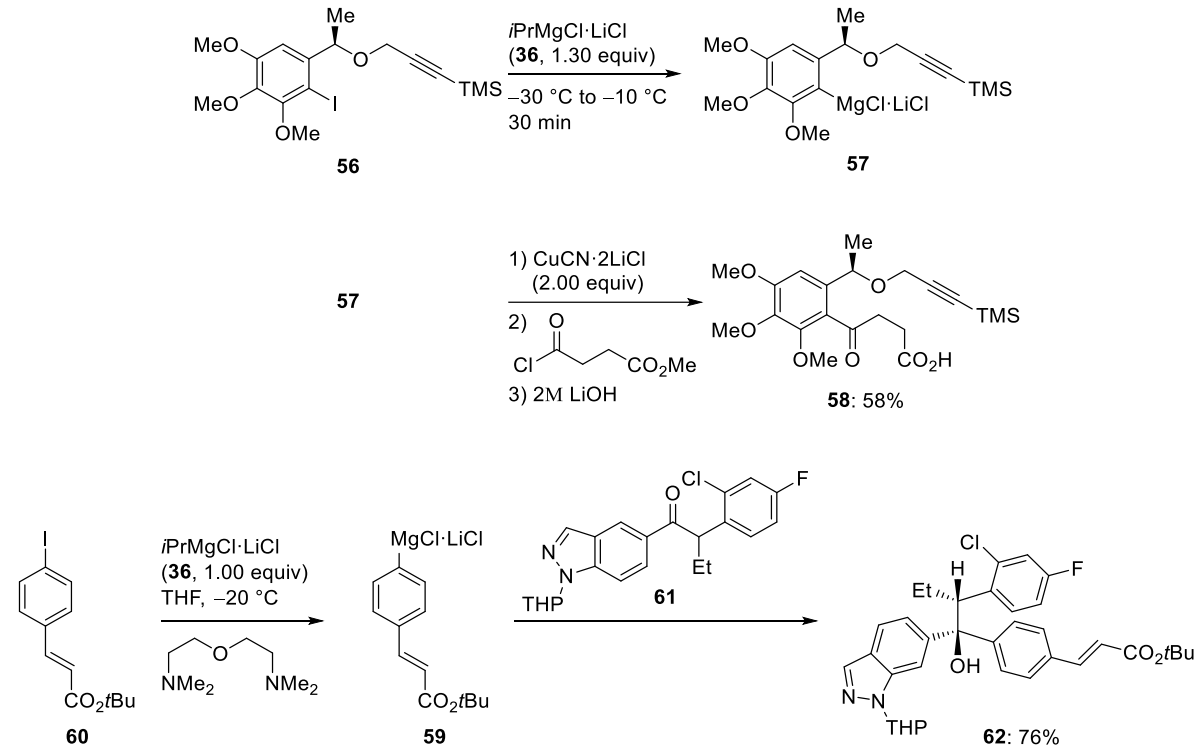
[42] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.



Scheme 11: Preparation of polyfunctional Grignard reagents using **36**.

The bromine-magnesium exchange was used to generate arylboronic acids after transmetalation of the intermediate Grignard reagent with $B(OMe)_3$.[43] Remarkably, an *in situ* borylation could be readily achieved since *i*PrMgCl·LiCl (**36**) reacts only slowly with the borate **50**. Thus, the treatment of iodobenzoate **51** with **36** in the presence of dioxaborinane **50** provided the arylboronic ester **52** in 79% yield.[44] Bromopyridine *N*-oxides such as **53** underwent a bromine-magnesium exchange at −40 °C forming the Grignard reagent **54**. After transmetalation to zinc and palladium-catalyzed cross-coupling, the desired functionalized pyridine *N*-oxide **55** was obtained in 72% yield (Scheme 11).[45] The *turbo*-Grignard *i*PrMgCl·LiCl (**36**) was used to generate complex Grignard intermediates for natural product synthesis. For instance, Schmalz showed that the aryl iodide **56** was converted to the corresponding Grignard reagent **57** and acylated after transmetalation to a copper species, leading to polyfunctional arene **58** in 58% yield (Scheme 12).[46] *i*PrMgCl·LiCl (**36**) was also used in a synthetic pathway for a selective estrogen receptor degrader. The polyfunctional Grignard reagent **59** was prepared from **60** using **36** in the presence of bis(2-dimethylaminoethyl)ether at −20 °C. After the addition of ketone **61**, alcohol **62** was obtained as one diastereoisomer (Scheme 12).[47]

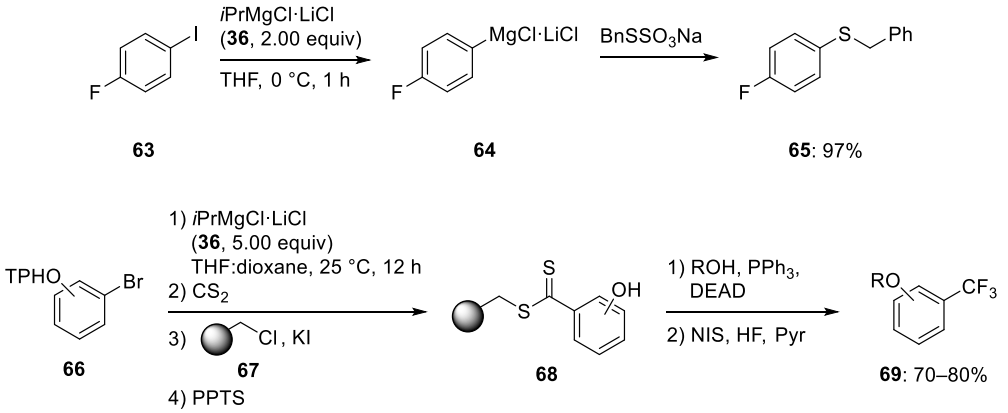
[43] T. Leermann, F. R. Leroux, F. Colobert, *Org. Lett.* **2011**, *13*, 4479.
[44] E. Demory, V. Blandin, J. Einhorn, P. Y. Chavant, *Org. Process Res. Dev.* **2011**, *15*, 710.
[45] X.-F. Duan, Z.-Q. Ma, F. Zhang, Z.-B. Zhang, *J. Org. Chem.* **2009**, *74*, 939.
[46] A. O. Termath, S. Ritter, M. König, D. P. Kranz, J. M. Neudörfl, A. Prokop, H. G. Schmalz, *Eur. J. Org. Chem.* **2012**, 4501.
[47] N.-K. Lim, T. Cravillion, S. Savage, A. McClory, C. Han, H. Zhang, A. Di Pasquale, F. Gosselin, *Org. Lett.* **2018**, *20*, 1114.



Scheme 12: Preparation of natural product **58** and drug intermediates **62** using **36**.

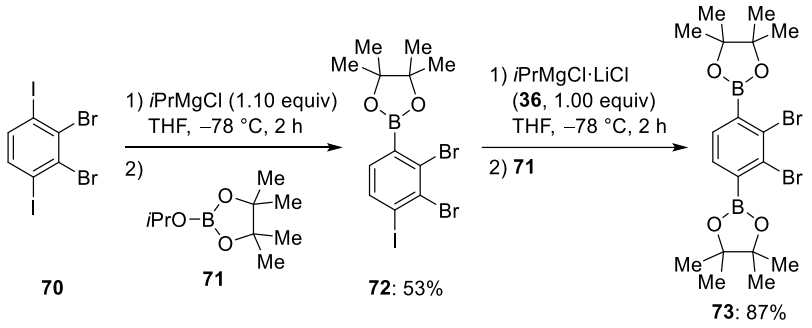
Further applications towards the synthesis of tryptamines were reported.[48] Reeves showed that Grignard reagents, obtained *via* an iodine-magnesium exchange, reacted with various Bunte salts such as $BnSSO_3Na$ to produce the corresponding thioethers in excellent yields.[49] Therefore, aryl iodide **63** was converted with **36** to Grignard reagent **64** which after reaction with $BnSSO_3Na$ provided thioether **65** in 97% yield.[49] Bräse showed that the *turbo*-Grignard reagent **36** allowed an efficient linkage of THP-protected ethers to the solid phase. Thus, treatment of bromide **66** with *i*PrMgCl·LiCl (**36**) produced the corresponding Grignard reagent which, after treatment with CS_2 followed by the Merrifield resin **67**, gave immobilized dithioester **68** with a high loading efficiency. The use of **36** proved to be compatible with carbonyls, nitriles, acetals and other halides present in the bromides of type **66**. Etherification on the solid phase of **68** with Mitsunobu conditions followed by a fluorinating cleavage using a mixture of *N*-iodosuccinimide (NIS) and Olah's reagent (HF, Pyr) provided the trifluoromethyl derivatives of type **69** in 70–80% yield (Scheme 13).[50]

[48] a) K. C. Nicolaou, A. Krasovskiy, V. É. Trépanier, D. Y. K. Chen, *Angew. Chem.* **2008**, *120*, 4285; b) K. C. Nicolaou, A. Krasovskiy, U. Majumder, V. É. Trépanier, D. Y. K. Chen, *J. Am. Chem. Soc.* **2009**, *131*, 3690.
[49] J. T. Reeves, K. Camara, Z. S. Han, Y. Xu, H. Lee, C. A. Busacca, C. H. Senanayake, *Org. Lett.* **2014**, *16*, 1196.
[50] M. Döbele, M. S. Wiehn, S. Bräse, *Angew. Chem. Int. Ed.* **2011**, *50*, 11533.



Scheme 13: Preparation of fluorinated arenes using the *turbo*-Grignard reagent **36**.

The multi-functionalization of polyhalogenoarenes such as **70** was performed by using both *i*PrMgCl and *i*PrMgCl·LiCl (**36**) as shown by Leroux. In particular, the treatment of **70** with *i*PrMgCl at −78 °C followed by the addition of the dioxaborolane **71** provided the boronic ester **72** in 53% yield. Subsequent addition of **36** at −78 °C led to a selective iodine-magnesium exchange furnishing, after the addition of **71**, the dibromo-derivative **73** in ca. 87% yield (Scheme 14).[51]

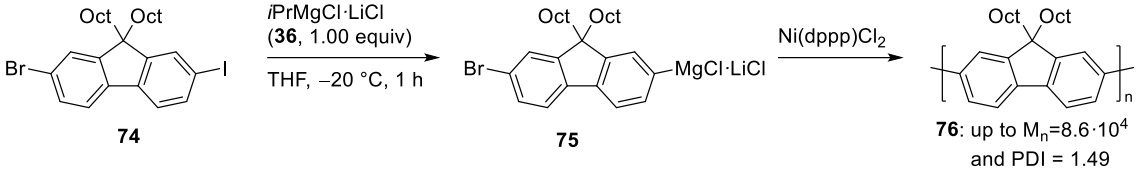


Scheme 14: Selective halogen-magnesium exchanges using *i*PrMgCl·LiCl (**36**).

Bromine-magnesium exchanges were performed in continuous flow with microreactors using *i*PrMgCl·LiCl (**36**).[52] Furthermore, conjugated polymers were also prepared using **36**.[53] For instance, the treatment of the dihalogenofluorene derivative **74** with *i*PrMgCl·LiCl (**36**) at −20 °C in THF selectively provided the Grignard reagent **75,** which underwent a polymerization at 0 °C. In the presence

[51] V. Diemer, F. R. Leroux, F. Colobert, *Eur. J. Org. Chem.* **2011**, 327.
[52] a) H. Wakami, J.-i. Yoshida, *Org. Process Res. Dev.* **2005**, *9*, 787; b) T. Tricotet, D. F. O'Shea, *Chem. - Eur. J.* **2010**, *16*, 6678; c) T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Process Res. Dev.* **2012**, *16*, 1102; d) Q. Deng, R. Shen, Z. Zhao, M. Yan, L. Zhang, *Chem. Eng. J.* **2015**, *262*, 1168; e) S. Korwar, S. Amir, P. N. Tosso, B. K. Desai, C. J. Kong, S. Fadnis, N. S. Telang, S. Ahmad, T. D. Roper, B. F. Gupton, *Eur. J. Org. Chem.* **2017**, 6495.
[53] a) S. Wu, L. Huang, H. Tian, Y. Geng, F. Wang, *Macromolecules* **2011**, *44*, 7558; b) Y. Nanashima, A. Yokoyama, T. Yokozawa, *Macromolecules* **2012**, *45*, 2609; c) Y. Takeoka, K. Umezawa, T. Oshima, M. Yoshida, M. Yoshizawa-Fujita, M. Rikukawa, *Polym. Chem.* **2014**, *5*, 4132; d) F. Pammer, U. Passlack, *ACS Macro Lett.* **2014**, *3*, 170; e) Z.-K. Yang, N.-X. Xu, R. Takita, A. Muranaka, C. Wang, M. Uchiyama, *Nature Comm.* **2018**, *9*, 1587.

of catalytic amounts of Ni(dppp)Cl_2, leading to poly(9,9-dioctylfluorene) (**76**) with a M_n as high as $8.6 \cdot 10^4$ and a polydispersity index of 1.49. Without LiCl, the polymerization afforded a lower molecular weight product (Scheme 15).[54]



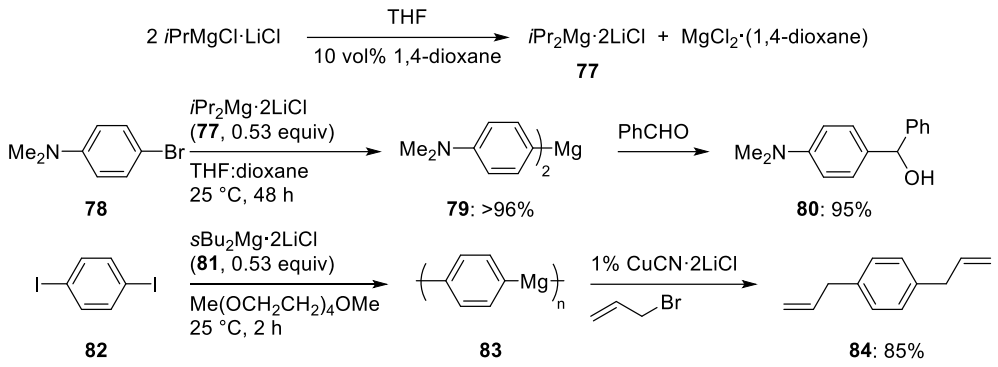
Scheme 15: LiCl-promoted polymerization using *turbo*-Grignard reagent **36**.

2.2.4 Preparation of Improved *Turbo*-Grignard Reagents

Although in the original patent[55] the use of other anion donor ligands for improving the rate of the halogen-magnesium exchange such as alkoxides and amides was mentioned, efforts to improve the exchange power of *i*PrMgCl·LiCl (**36**) were first made by preparing dialkylmagnesium complexed with two equivalents of LiCl.[35b] The presence of lithium chloride was essential for achieving high exchange rates. Accordingly, the treatment of two equivalents of *i*PrMgCl·LiCl (**36**) with 10 vol% of 1,4-dioxane displaced the Schlenk-equilibrium towards formation of **77**. The reaction of the electron-rich aryl bromide 4-bromoanisole with **36** at 25 °C for 24 h produced the corresponding Grignard reagent with only 31% conversion, whereas the reagent **77** led to the di(4-methoxyphenyl)magnesium complexed with LiCl with 100% conversion after 10 h at 25 °C. This behavior was quite general and could also be applied to the bromoaniline derivative **78**, which was converted to the diarylmagnesium reagent **79** in ca. 96% conversion (compared to 16% conversion using **36**). Addition of benzaldehyde provided the alcohol **80** in 95% yield (Scheme 16).[35b]

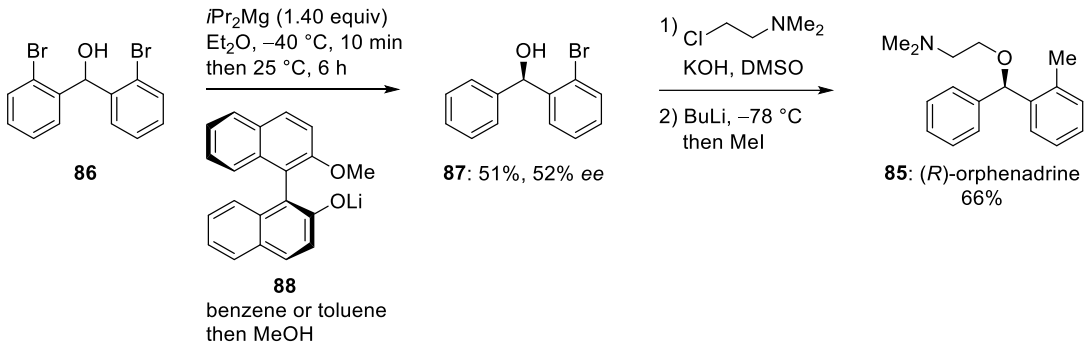
[54] a) L. Huang, S. Wu, Y. Qu, Y. Geng, F. Wang, *Macromolecules* **2008**, *41*, 8944; b) E. L. Lanni, A. J. McNeil, *J. Am. Chem. Soc.* **2009**, *131*, 16573; c) M. C. Stefan, A. E. Javier, I. Osaka, R. D. McCullough, *Macromolecules* **2009**, *42*, 30.

[55] a) J. Farkas, S. J. Stoudt, E. M. Hanawalt, A. D. Pajerski, H. G. Richey, *Organometallics* **2004**, *23*, 423; b) P. Knochel, A. Krasovskiy, *EP1582523A1* **2005**.



Scheme 16: Preparation of magnesium reagents using *i*Pr_2Mg·2LiCl (**77**).

Similarly, *s*Bu_2Mg·2LiCl (**81**) prepared from *s*BuLi and *s*BuMgCl in THF reacted with 1,4-diiodobenzene (**82**) in the presence of $Me(OCH_2CH_2)OMe$, leading to the *bis*-magnesium reagent **83**. Copper-catalyzed allylation with allyl bromide gave 1,4-diallylbenzene (**84**) in 85% yield. Brückner showed that in presence of various additives, especially $LiOCH_2CH_2NMe_2$, *i*Pr_2Mg underwent a complete bromine-magnesium exchange on (*o*-bromophenyl)ethanol within 6 h at 25 °C in ether.[56] This fast bromine-magnesium exchange was used for the enantioselective synthesis of (*R*)-orphenadrine (**85)**. The reaction of *i*Pr_2Mg in ether with the chiral lithium alcoholate of binol-derivative **86**, the subsequent solvent removal and switch to toluene furnished the chiral alcohol **87** in 51% yield and 52% *ee* after the addition of the dibromide **88**. After an *O*-alkylation and methylation (*R*)-orphenadrine (**85**) was obtained (Scheme 17).[56]

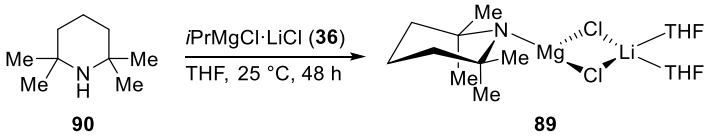


Scheme 17: Desymmetrization of benzhydryl alcohol **85** *via* an enantioselective bromine-magnesium exchange.

[56] D. Sälinger, R. Brückner, *Chem. - Eur. J.* **2009**, *15*, 6688.

2.3 Directed Metalation

Another approach towards organometallic species is the directed metalation using metal bases. Since the pioneering work of Snieckus,[57] Quéguiner,[58] and Schlosser,[59] lithium bases like lithium dialkylamides (R_2NLi) have been used extensively for the metalation of diverse unsaturated substrates at low temperatures. Despite the frequent use of lithium reagents for metalations in chemical literature, the high reactivity of lithium bases has hampered their use for functionalized substrates. Hauser (R_2NMgX or $(R_2N)_2Mg$) and Eaton (TMP_2Mg), which developed magnesium amides as metalating agents, provided bases with higher tolerance towards sensitive functional groups.[6,60] Mulzer demonstrated the use of these sterically hindered TMP-bases in organic synthesis and applied them in natural product synthesis. However, due to their low solubility as well as their low kinetic basicity, a large excess of magnesium bases and electrophiles was required to achieve high conversion.[61]
These limitations have lowered their general use until *Knochel* and co-workers developed a highly reactive LiCl-solubilized 2,2,6,6-tetramethylpiperidine (TMP) metal amide base, TMPMgCl·LiCl (**89**), and improved the synthesis of metalated aromatics and heteroaromatics. The first LiCl-solubilized metal amide base was prepared in 2006 by reacting *i*PrMgCl·LiCl (**36**) with TMP-H (**90**) in THF (Scheme 18). The resulting base exhibited an excellent solubility in common organic solvents as well as improved kinetic basicity.[42]



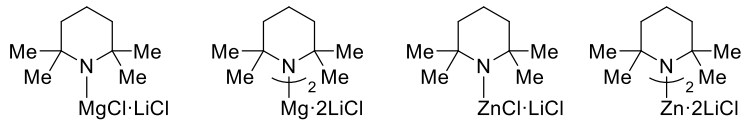
90 **89**

Scheme 18: Preparation of TMPMgCl·LiCl (**89**) by using *i*PrMgCl·LiCl (**36**) and TMP-H (**90**).

In the following years a number of new TMP-bases were established.[42b] The most important of these sterical hindered TMP-bases are TMPMgCl·LiCl (**89**),[42a] $TMP_2Mg{\cdot}2MgCl_2{\cdot}2LiCl$ (**91**),[62] TMPZnCl·LiCl (**92**)[63] and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**)[64] (Figure 2). Since the development of the described LiCl solubilized TMP-bases, the scope of the metalation of unsaturated substrates was

[57] a) P. Beak, V. Snieckus, *Acc. Chem. Res.* **1982**, *15*, 306; b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; c) L. Green, B. Chauder, V. Snieckus, *J. Heterocyclic Chem.* **1999**, *36*, 1453; d) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; e) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069.
[58] a) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489; b) F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4059.
[59] a) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376; b) M. Schlosser, F. Mongin, *Chem. Soc. Rev.* **2007**, *36*, 1161.
[60] a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295; b) P. E. Eaton, C. H. Lee, Y. Xiong, *J. Am. Chem. Soc* **1989**, *111*, 8016; c) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc.* **1993**, *115*, 11370.
[61] W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.
[62] G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681.
[63] M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837.
[64] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.

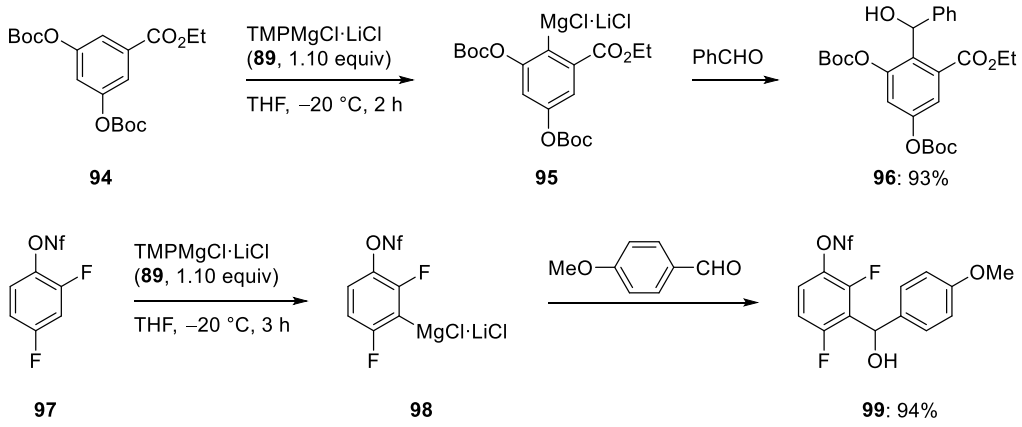
considerably expanded. TMP-bases offered the possibility to the chemo- and regioselectively functionalization of a wide range of aromatic systems, as well as highly functionalized heterocycles and non-aromatic, unsaturated systems. The high kinetic basicity of the TMP-bases, their high functional-group tolerance, and the practical metalation conditions were especially remarkable.[42b]



89 **91** **92** **93**

Figure 2: TMP-derived, mixed metal/lithium amide bases.

Due to the high functional group tolerance of TMPMgCl·LiCl (**89**), a huge variety of polyfunctional aromatics and heteroaromatics could be converted into the corresponding magnesium species, which could be further reacted with electrophiles.[42] For example, the magnesiation with TMPMgCl·LiCl (**89**) allowed the metalation of the highly functionalized benzene derivative **94** by using an OBoc as a directing group. Using this method, the magnesium derivative **95** was smoothly converted into **96** in 93% yield.[65] Also, substrates bearing electrophilic groups such as nonaflates were magnesiated with **89** providing the Grignard reagent **98**. Addition of an aromatic aldehyde led to the expected product **99** in 94% yield (Scheme 19).[66]

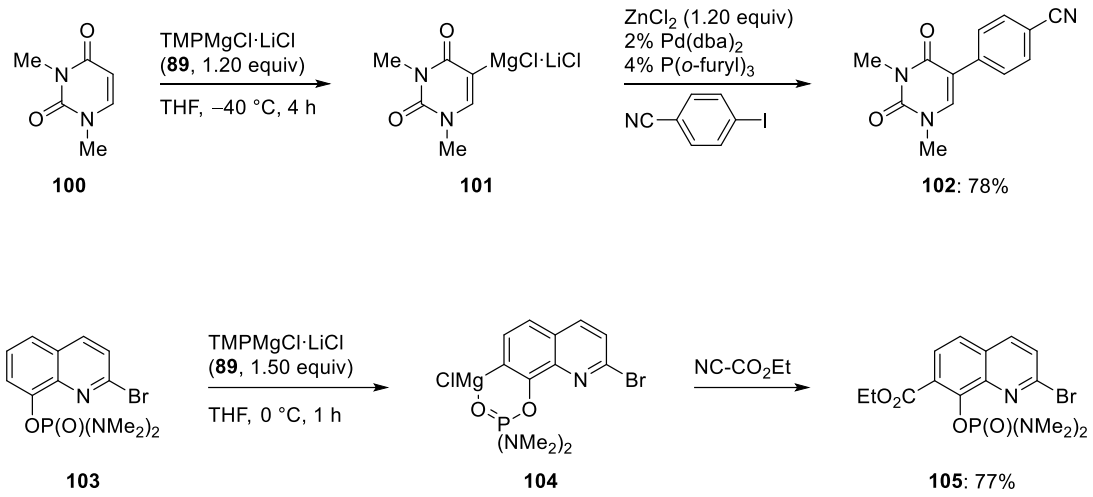


Scheme 19: Metalation of polyfunctional aromatics using TMPMgCl·LiCl (**89**).

Furthermore, electronpoor and -rich heteroaromatics could be metalated using TMPMgCl·LiCl (**89**). Thus, protected uracils **100** reacted with TMPMgCl·LiCl (**89**) at −40 °C in 4 h and provided the C(5) metalated heterocycle **101** in a regioselective manner. Transmetalation with $ZnCl_2$, followed by a Pd-catalyzed Negishi cross-coupling with 4-iodobenzonitrile led to the arylated methyl protected uracil

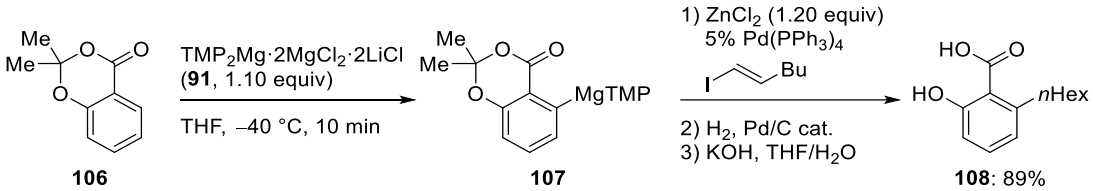
[65] W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *24*, 5673.
[66] G. Monon, P. Knochel, *Synthesis* **2010**, 304.

102 in 78% yield (Scheme 20).[67] Interestingly, *N*-heterocycles such as **103** bearing an *N*,*N*,*N*',*N*'-tetramethyldiaminophosphorodiamidate group as directing group were metalated at 0 °C within 1 h. By using **89**, the desired product **105** was afforded in 77% yield after the reaction with NC-CO_2Et (Scheme 20).[68]



Scheme 20: Metalation of heteroaromatics using TMPMgCl·LiCl (**89**).

Aromatic substrates bearing electron-donating or weakly-accepting substituents were difficult to magnesiate at low temperature. The higher reactivity of $TMP_2Mg{\cdot}2MgCl_2{\cdot}2LiCl$ (**91**) enabled the magnesiation of moderately activated aromatics and heteroraromatics and solved this problem. For instance, $TMP_2Mg{\cdot}2MgCl_2{\cdot}2LiCl$ (**91**) allowed the magnesiation of dimethyl-1,3-benzodioxan-4-one (**106**) at −40 °C in 10 min. After transmetalation with $ZnCl_2$ and Pd-catalyzed cross-coupling with (*E*)-1-hexenyl iodide, the 6-substituted benzodioxane was obtained in 77% yield. Subsequent hydrogenation and deprotection produced the natural product **108** in 89% yield, which was found in the essential oil of *Pelargonium sidoides DC* (Scheme 21).[62]

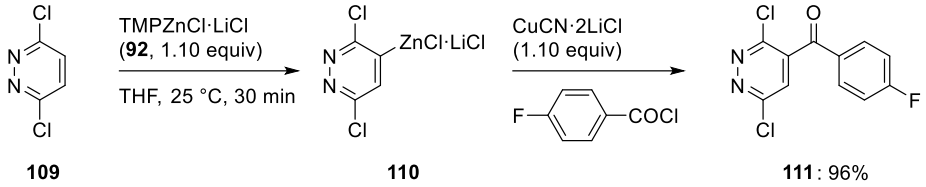


Scheme 21: Magnesiation of dimethyl-1,3-benzodioxan-4-one (**108**) by using $TMP_2Mg{\cdot}2MgCl_2{\cdot}2LiCl$ (**91**).

Several sensitive aromatics and heterocyclic substrates such as electron-poor *N*-heterocycles could be metalated with TMPZnCl·LiCl (**92**). Consequently, **92** displays a higher tolerance towards functional

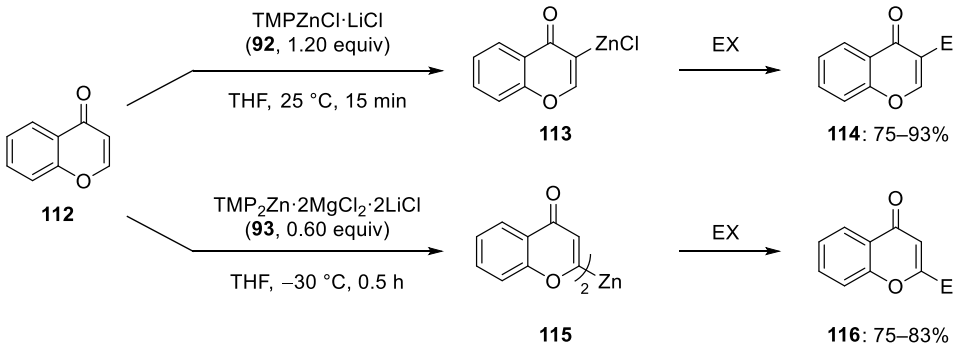
[67] L. Klier, E. Aranzamendi, D. Ziegler, J. Nickel, K. Karaghiosoff, T. Carell, P. Knochel, *Org. Lett.* **2016**, *18*, 1068.
[68] C. J. Rohbogner, S. Wirth, P. Knochel, *Org. Lett.* **2010**, *12*, 1984.

groups such as nitro, aldehyde or methyl ketone groups and the high thermal stability of these zinc organometallics (up to 120 °C) enabled the direct metalation under a wide range of conditions. [42b,63] For example, the sensitive pyridazine heterocycle **109**, which previously could only be metalated at low temperatures in moderate yields,[58a] was zincated at 25 °C within 30 min. A copper-mediated acylation led to the ketone **111** in 96% yield (Scheme 22).[63]



Scheme 22: Zincation of sensitive pyrazine **109** by using TMPZnCl·LiCl (**92**).

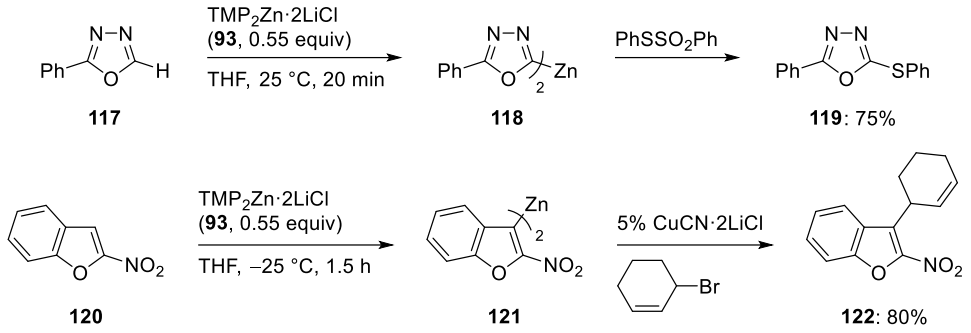
Furthermore, TMPZnCl·LiCl (**92**) allowed the regioselective zincation of chromones of type **112** at 25 °C in 15 min. Quenching with various electrophiles led to C(3) functionalized products of type **114** in 75–93% yield. The C(2)-selective zincation was achieved by using the more powerful zinc base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**), providing the bis-heterocyclic zinc reagent **115**. Subsequent reaction of the organometallic species with electrophiles afforded the desired products of type **116** in 75–83% yield (Scheme 23).[69]



Scheme 23: Regioselective zincation of chromone **112** by using TMPZnCl·LiCl (**92**) and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**).

The zinc base **93** was also used for the metalation of sensitive heterocycles such as oxadiazole **117**, which was prone to undergo fragmentation during metalation process.[64,70] Also, sensitive functional groups could be tolerated by using **93**. Thus, 2-nitrobenzofuran was zincated at −25 °C within 1.5 h, leading to benzofuran **122** in 80% yield after copper catalyzed allylation (Scheme 24).[64]

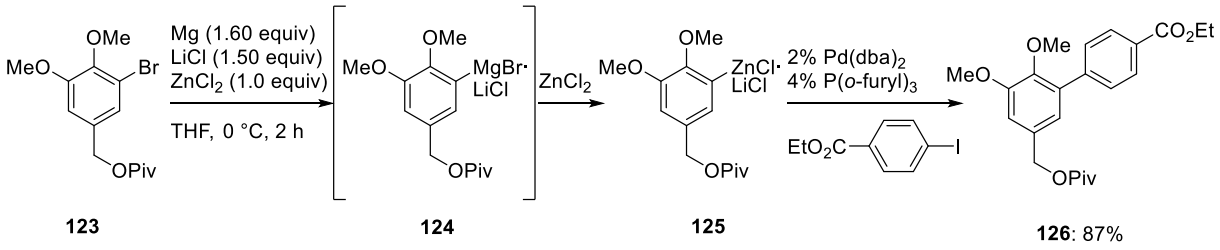
[69] L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584.
[70] a) A. Turck, N. Plé, L. Mojovic, G. Quéguiner, *J. Heterocycl. Chem.* **1990**, *27*, 1377; b) L. Mojovic, A. Turck, N. Plé, M. Dorsy, B. Ndzi, G. Quéguiner, *Tetrahedron* **1996**, *52*, 10417.



Scheme 24: Zincation of sensitive heterocycles by using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**).

2.4 Transmetalation

The transmetalation of organometallic compounds offers another approach for the preparation of organozinc or organomagnesium compounds by addition of a metal salt. Driving force for the transmetalation reaction is the formation of a more covalent carbon-metal bond and along with it the formation of a more stable reagent. For example, the sensitive functionalized arene **126** was prepared by a magnesium insertion in the presence of $ZnCl_2$. Thereby, the unstable magnesium reagent **124** was directly transmetalated using $ZnCl_2$ to form the comparatively stable zinc reagent **125**. After a Negishi cross-coupling, the arylated product **126** was obtained in 87% yield.[71]



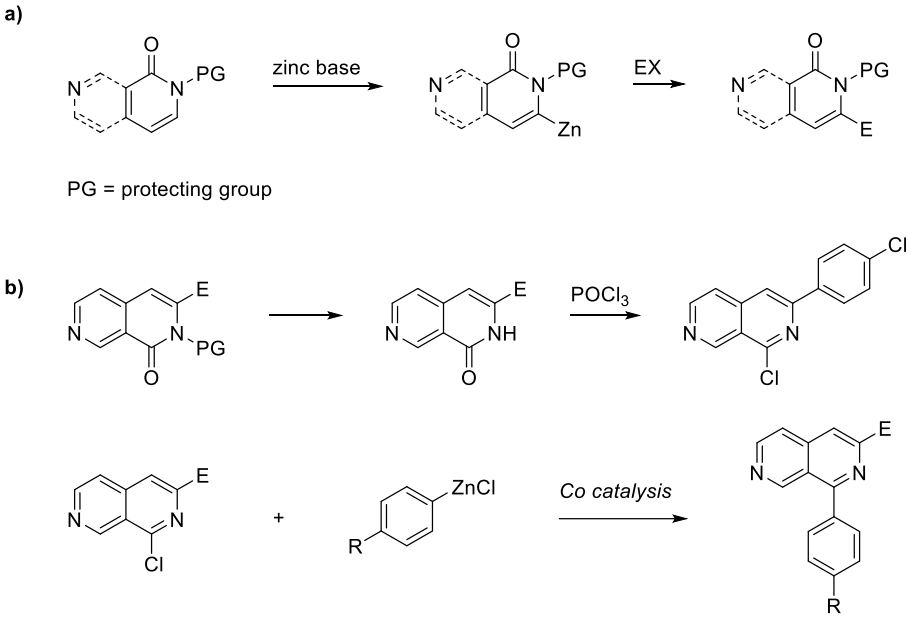
Scheme 25: Preparation of the functionalized arene **126** reagent *via* in situ generated zinc reagents.

All these different methods allow the synthesis of functionalized organomagnesium or organozinc reagents, which have found widespread uses in organic synthesis.

[71] F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. - Eur. J.* **2009**, *15*, 7192.

3 Objectives

Based on previous results on directed metalation, the aim of the first project was the development of a method for the regioselective metalation and functionalization of 2-pyridones by using TMP-bases. These scaffolds are of great interest due to the number of biologically active molecules bearing such a moiety and their appeareance in pharmaceutical agents. Starting from protected 2-pyridones, the metalation should lead to the corresponding zincated 2-pyridone by using a zinc amide. These heterocyclic zinc species can react with various electrophiles furnishing highly functionalized 2-pyridones. It should be envisioned that these synthetic sequences are general and therefore can be applied in metalation and functionalization of protected 2,7-naphthyridones. After deprotection, the functionalized 2,7-naphthyridones should be converted into the corresponding naphthyridines and subsequent Negishi cross-couplings should lead to highly functionalized naphthyridines.[72]

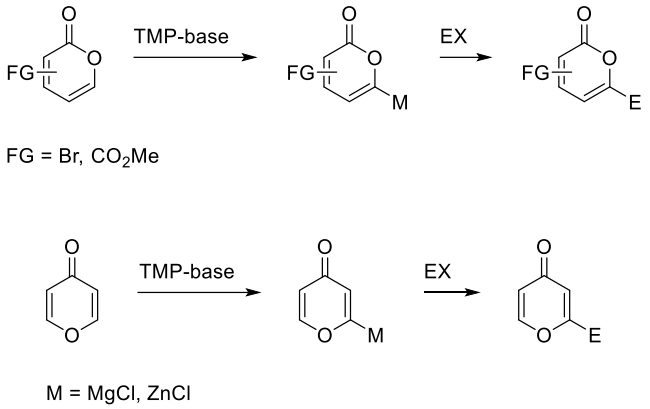


Scheme 26: a) Functionalization of the 2-pyridone and 2,7-naphthyridone scaffold using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$. b) Co-catalyzed Negishi cross-couplings of chlorinated 2,7-naphthyridines.

Additionally, pyrones can be used in a broad range of synthetic applications, in particular as dienes in Diels-Alder reactions as well as precursors for the preparation of more complex heterocyclic systems in natural products. For that reason, a regio- and chemoselective metalation and functionalization of 2- and 4-pyrone derivatives should be investigated. Starting from commercially available 2- and 4-pyrones, successive metalations using TMP-bases should lead to the corresponding magnesiated or zincated 2-pyrones. These resulting organometallic reagents can react with various electrophiles,

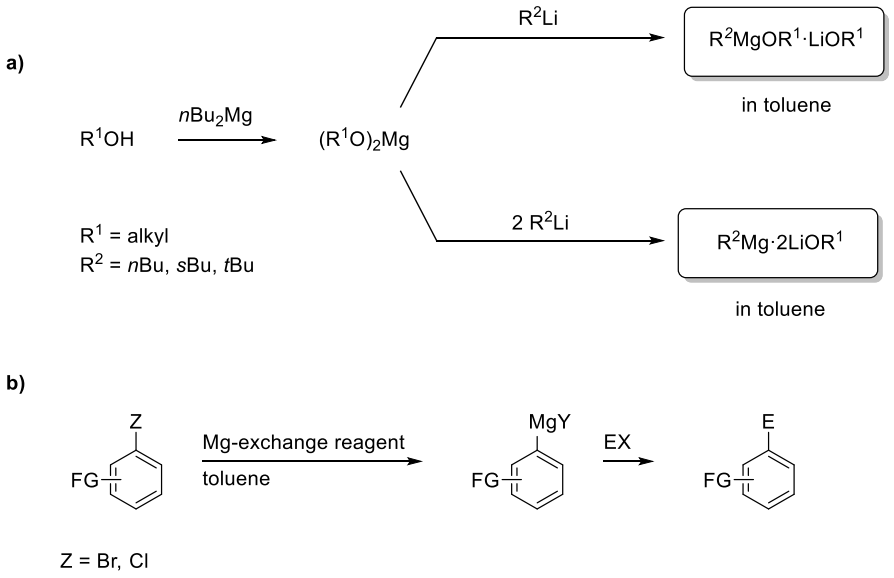
[72] This project was developed in cooperation with Robert Greiner see: R. Greiner, Dissertation **2018**, LMU München.

providing highly functionalized 2-pyrones. Furthermore, the metalation should be extended to functionalized pyrones such as methyl coumalate.



Scheme 27: Functionalization of the 2- and 4-pyrone scaffold using TMP-bases.

Finally, new magnesium reagents in non-polar solvents should be developed using magnesiumalkoxides and alkyllithium reagents for the preparation. Grignard reagents are commonly prepared in ethereal solvents and their preparation in toluene or hydrocarbons is almost unknown. Therefore, it was anticipated that these weakly-coordinated magnesium reagents should display an unusual reactivity. Furthermore, it was proposed that these organomagnesium reagents allow very fast bromine-magnesium exchanges and, for the first time, a chlorine-magnesium exchange on various aryl chlorides, leading to functionalized (hetero)aryl- and di(hetero)arylmagnesium derivatives in toluene.



Scheme 28: a) Preparation of new magnesium exchange reagents in toluene. b) Halogen-magnesium exchange in toluene.

B. RESULTS AND DISCUSSION

1 Directed Zincation or Magnesiation of the 2-Pyridone and 2,7-Naphthyridone Scaffold using TMP-Bases

1.1 Introduction

The selective functionalization of 2-pyridone (**127**) and 2,7-naphthyridone (**128**) is an important synthetic goal due to the pharmaceutical relevance of many substituted 2-pyridones and 2,7-naphthyridones.[73] These heterocycles are known to display antibiotic, antifungal, anticancer, and antiviral activity.[74] Typical pharmaceutically and biologically active derivatives are milrinone (**129**),[75] ciclopirox (**130**),[76] pirfenidone (**131**),[77] and lophocladine A (**132**) (Figure 3).[78]

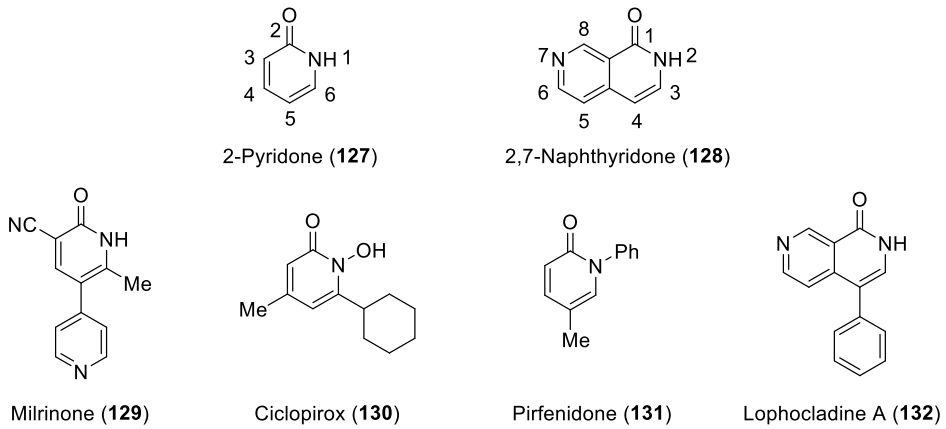


Figure 3: Structures of 2-pyridone (**127**) and 2,7-naphthyridone (**128**) and their pharmaceutically and biologically active derivatives.

[73] a) T. Ukita, Y. Nakamura, A. Kubo, Y. Yamamoto, Y. Moritani, K. Saruta, T. Higashijima, J. Kotera, K. Fujishige, M. Takagi, K. Kikkawa, K. Omori, *Bioorg. Med. Chem*. **2003**, *13*, 2341; b) H. J. Jessen, K. Gademann, *Nat. Prod. Rep.* **2010**, *27*, 1168; c) G. Yu, P. N. Praveen Ra, M. A. Chowdhury, K. R. A. Abdellatif, Y. Dong, D. Das, C. A. Velázquez, M. R. Suresh, E. E. Knaus, *Bioorg. Med. Chem*. **2010**, *20*, 2168; d) W. S. Hamama, M. Waly, I. El-Hawary, H. H. Zoorob, *Synth. Commun.* **2014**, *44*, 1730.

[74] a) N. C. Desai, K. M. Rajpara, V. V. Joshi, *Bioorg. Med. Chem*. **2013**, *23*, 2714; b) Z. Lv, Y. Zhabg, M. Zhang, H. Chen, Z. Sun, D. Geng, C. Niu, K. Li, *Eur. J. Med. Chem.* **2013**, *67*, 447; c) H. Jia, Y. Song, J. Yu, P. Zhan, D. Rai, X. Liang, C. Ma, X. Liu, *Eur. J. Med. Chem.* **2017**, *136*, 144; d) S. Singh, J.-I. Goo, H. Noh, S. J. Lee, M. W. Kim, H. Park, H. B. Jalani, K. Lee, C. Kim, W.-K. Kim, C. Ju, Y. Choi, *Bioorg. Med. Chem*. **2017**, *25*, 1394.

[75] a) K. T. Santhosh, O. Elkhateeb, N. Nolette, O. Outbih, A. J. Halayko, S. Dakshinamurti, *Br. J. Pharmacol.* **2010**, *163*, 1223; b) M. Ravinder, B. Mahendar, S. Mattapally, K. V. Hamsini, T. N. Reddy, C. Rohit, K. Srinivas, S. K. Banerjee, *Bioorg. Med. Chem*. **2012**, *22*, 6010.

[76] D. Monti, L. Saccomani, P. Chetoni, S. Burgalassi, S. Tampucii, F. Mailland, *Br. J. Dermatol*. **2011**, *165*, 99.

[77] a) K. Takakura, K. Mizukami, H. Mitori, T. Noto, Y. Tomura, *Eur. J. Pharma*. **2014**, *737*, 106; b) E. S. Kim, G. M. Keating, *Drugs* **2015**, *75*, 219.

[78] a) K. Kumpan, A. Nathubhai, C. Zhang, P. J. Wood, M. D. Lloyd, A. S. Thompson, T. Haikarainen, L. Lehtiö, M. D. Threadgill, *Bioorg. Med. Chem*. **2015**, *23*, 3013; b) S. Theeramunkong, O. Vajragupta, M. Chawannuch, *Med. Chem. Res.* **2016**, *25*, 2959.

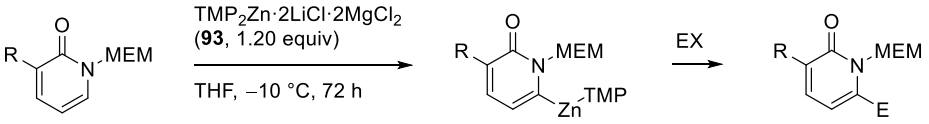
Functionalizations of these 2-pyridones *via* lithiation have been reported.[58b,79] Alternatively, a regioselective direct C-H activation allows the functionalization of 2-pyridone (**127**) either at position C(3) or C(6).[80] Recently, it was found that a broad array of functionalized aromatic and heteroaromatic compounds could be metalated with various TMP-derived Mg- and Zn-bases.[42b,81] Preliminary metalation studies have shown that TMPLi[82] and TMPMgCl·LiCl (**89**)[42a,83] led to the decomposition of protected 2-pyridones or 2,7-naphthyridones even at low temperatures or produced a complex mixture of products. Therefore, the use of more selective metalating agents was investigated. TMPZnCl·LiCl (**92**)[63,84] and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**)[64,69,85] have been proven to be especially efficient for performing zincations of sensitive (hetero)arenes, as these metalations produce organozinc derivatives which tolerate a range of functional groups. Herein, the functionalization of MEM-protected 2-pyridones like **133** and **134** as well as the MEM-protected 2,7-naphthyridone (**135**) using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**)[64] followed by reactions with various electrophiles (EX) is reported.

[79] a) P. Meghani, J. A. Joule, *J. Chem. Soc., Perkin Trans. 1* **1988**, 1; b) F. Effenberger, W. Daub, *Chem. Ber.* **1991**, *124*, 2119.
[80] a) Y. Nakao, H. Idei, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc*. **2009**, *131*, 15996; b) A. Nakatani, K. Hirano, T. Satoh, M. Miura, *Chem. - Eur. J.* **2013**, *19*, 7691; c) A. Modak, S. Rana, D. Maiti, *J. Org. Chem.* **2015**, *80*, 296.
[81] a) D. Haas, D. Sustac-Roman, S. Schwarz, P. Knochel, *Org. Lett.* **2016**, *18*, 6380; b) J. Nafe, P. Knochel, *Synthesis* **2016**, *48*, 103; c) L. Klier, D. S. Ziegler, R. Rahimoff, M. Mosrin, P. Knochel, *Org. Process Res. Dev.* **2017**, *21*, 660; d) A. Castello-Mico, J. Nafe, K. Higashida, K. Karaghiosoff, M. Gingras, P. Knochel, *Org. Lett.* **2017**, *19*, 360.
[82] a) C. L. Kissel, B. Rickborn, *J. Org. Chem.* **1972**, *37*, 2060; b) R. A. Olofson, C. M. Dougherty, *J. Am. Chem. Soc*. **1973**, *95*, 581; c) M. Uzelac, A. R. Kennedy, E. Hevia, R. E. Mulvey, *Angew. Chem. Int. Ed*. **2016**, *55*, 13147.
[83] a) R. E. Mulvey, *Organometallics* **2006**, *25*, 1060; b) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802; c) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497; d) P. Garcia-Alvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.
[84] a) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406; b) T. Bresser, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1914; c) S. Duez, A. K. Steib, S. M. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 7686; d) A. Unsinn, M. J. Ford, P. Knochel, *Org. Lett.* **2013**, *15*, 1128; e) D. Haas, M. Mosrin, P. Knochel, *Org. Lett.* **2013**, *15*, 6162; f) J. Shen, B. Wong, C. Gu, H. Zhang, *Org. Lett.* **2015**, *17*, 4678.
[85] a) M. Mosrin, P. Knochel, *Chem. - Eur. J.* **2009**, *15*, 1468; b) J. M. Hammann, D. Haas, P. Knochel, *Angew. Chem. Int. Ed*. **2015**, *54*, 4478; c) M. Tichý, S. Smoleň, E. Tloušťová, R. Pohl, T. Oždian, K. Hejtmánková, B. Lišková, S. Gurská, P. Džubák, M. Hajdúch, M. Hocek, *J. Med. Chem.* **2017**, *60*, 2411.

1.2 Functionalization of MEM-Protected 2-Pyridones

Treatment of the MEM-protected 2-pyridone derivative **133** with the zinc amide **93** (1.20 equiv, −10 °C, 72 h) led to the quantitative formation of the corresponding zincated 2-pyridone **136**. The zinc reagent **136** was quenched by various electrophiles furnishing 2-pyridones of type **137** (Table 1). Thus, quenching of **136** with iodine provided the 6-iodo-2-pyridone **137a** in 93% yield (entry 1). Additionally, Negishi cross-coupling[86] of **136** proceeded with various aryl iodides containing electron-withdrawing or -donating substituents in the presence of 4% $Pd(dba)_2$ and 8% of tris(*o*-furyl)phosphine[87] affording a variety of arylated pyridone derivatives (**137b**–**f**) in 66–88% yield (entries 2–6). This zincation was extended to the MEM-protected 3-cyano-2-pyridone **134**, which was metalated with **93** (1.20 equiv, −10 °C, 72 h) to give the C(6)-zincated heterocycle **138**. After iodolysis, the desired product **139a** was isolated in 80% yield (entry 7). Pd-catalyzed cross-coupling of **138** with 4-iodoanisole provided the arylated 3-cyano-2-pyridone **139b** in 68% yield (entry 8). Moreover, 2-iodothiophene underwent a Negishi cross-coupling[86] with the zinc species **138**, to afford the 3-cyano-2-pyridone **139c** in 80% yield (entry 9).

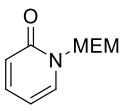
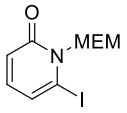
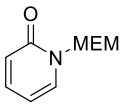
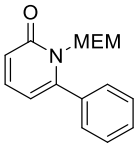
Table 1: Zincation of MEM-protected 2-pyridone **133** or **134** and reaction with electrophiles.



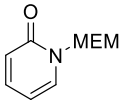
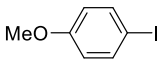
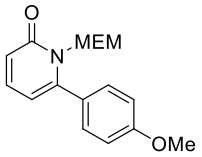
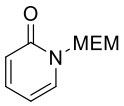
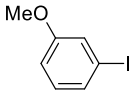
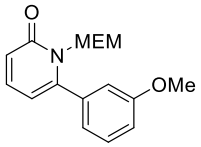
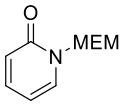
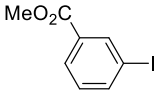
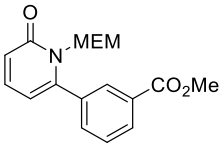
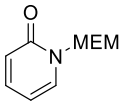
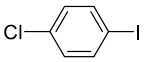
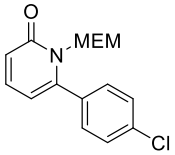
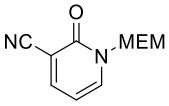
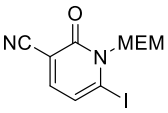
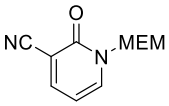
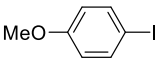
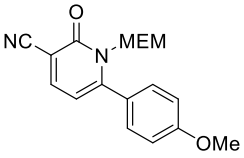
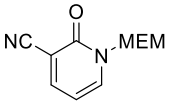
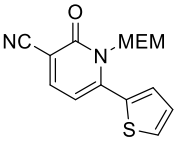
133: R = H
134: R = CN

136: R = H
138: R = CN

137a–f: R = H
139a–c: R = CN

Entry	Substrate	Electrophile (EX)	Product/Yield[a]
1	 **133**	I_2	 **137a**, 93%
2	 **133**		 **137b**, 92%[b]

[86] a) E.-i. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) E.-i. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[87] a) V. Farina, S. R. Baker, D. A. Benigni, C. Jr. Sapino, *Tetrahedron Lett.* **1988**, *29*, 5739; b) V. Farina, S. R. Baker, D. A. Benigni, S. I. Hauck, C. Jr. Sapino, *J. Org. Chem.* **1990**, *55*, 5833.

			
3	**133**		**137c**, 66%[b]
			
4	**133**		**137d**, 70%[b]
			
5	**133**		**137e**, 80%[b]
			
6	**133**		**137f**, 88%[b]
		I_2	
7	**134**		**139a**, 80%
			
8	**134**		**139b**, 68%[b]
			
9	**134**		**139c**, 80%[b]

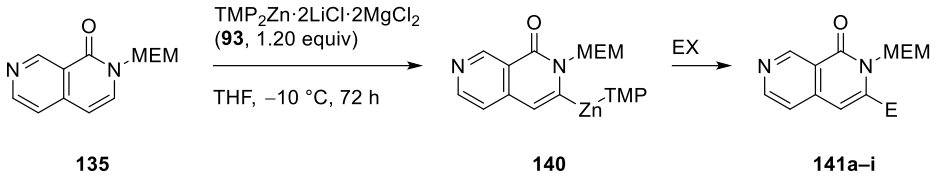
[a] Yield of isolated, analytically pure product. [b] Obtained by Negishi cross-coupling[86] using 4% $Pd(dba)_2$ and 8% P(*o*-furyl)$_3$.[87]

1.3 Functionalization of MEM-Protected 2,7-Naphthyridone Derivative

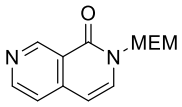
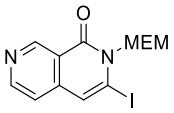
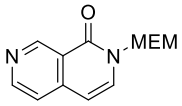
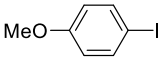
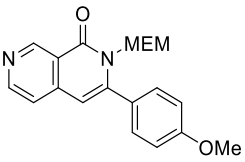
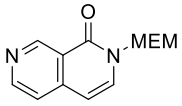
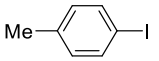
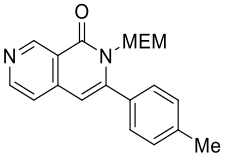
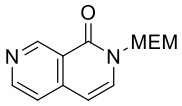
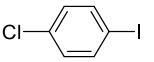
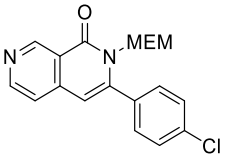
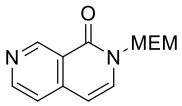
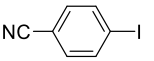
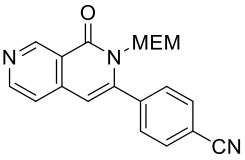
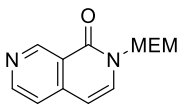
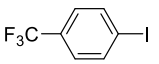
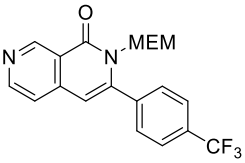
The scope of this zincation using the zinc-base **93** on a MEM-protected 2,7-naphthyridone derivative **135** was explored. The MEM-protecting group was essential to achieve a regioselective zincation of 2,7-naphthyridone **135** in position 3 with the zinc base (**93**, 1.20 equiv, −10 °C, 72 h). The resulting zinc reagent **140** was readily functionalized by reaction with various electrophiles to furnish 3-substituted 2,7-naphthyridones of type **141** (Table 2). After iodolysis, compound **141a** was isolated in 92% yield (entry 1). The X-ray structure of compound **141a** confirmed exclusive iodination at position 3.[88] Furthermore, the zinc reagent **140** underwent smooth Pd-catalyzed Negishi cross-coupling reactions[86] with aryl iodides to afford the 3-arylated 2,7-naphthyridones **141b–f** in 46–86% yield (entries 2–6). The cross-coupling with 4-iodoaniline proceeded smoothly using an inverse addition with 4% $Pd(OAc)_2$ and 8% of Buchwald's SPhos[89] *via* syringe pump, to afford the desired product **141g** in 76% yield (entry 7).[90] Furthermore, the zinc intermediate **140** reacted with 5-bromo-benzo[*d*][1,3]dioxole in the presence of 4% PEPPSI-*i*Pr[91] to afford the corresponding product **141h** in 80% yield (entry 8). Transmetalation of **140** with $CuCN{\cdot}2LiCl$[92] (1.10 equiv, −10 °C, 10 min) and subsequent reaction with 2-thiophenecarbonyl chloride provided the 2,7-naphthyridone **141i** in 52% yield (entry 9).

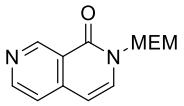
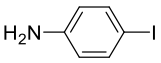
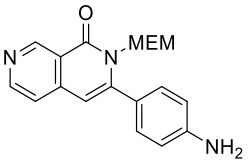
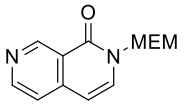
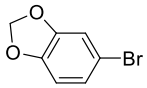
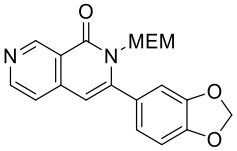
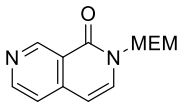
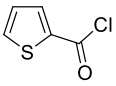
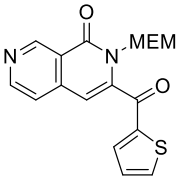
[88] CCDC-1565047 (**141a**) contains the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
[89] R. Martin, R.; S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.
[90] a) G. Manolikakes, M. A. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765; b) G. Manolikakes, M. A. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *73*, 8422.
[91] a) N. Hadei, E. A. B. Kantchev, C.J. O'Brie, J. Christopher, M. G. Organ, *Org. Lett.* **2005**, *7*, 3805; b) C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Chem. - Eur. J.* **2010**, *23*, 4343.
[92] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

Table 2: Zincation of MEM-protected 2,7-naphthyridone **135** and subsequent reaction with electrophiles.



135 **140** **141a–i**

Entry	Substrate	Electrophile (EX)	Product/Yield[a]
		I_2	
1	**135**		**141a**, 92%
			
2	**135**		**141b**, 81%[b]
			
3	**135**		**141c**, 84%[b]
			
4	**135**		**141d**, 86%[b]
			
5	**135**		**141e**, 74%[b]
			
6	**135**		**141f**, 46%[b]

7	 **135**		 **141g**, 76%[c]
8	 **135**		 **141h**, 80%[d]
9	 **135**		 **141i**, 52%[e]

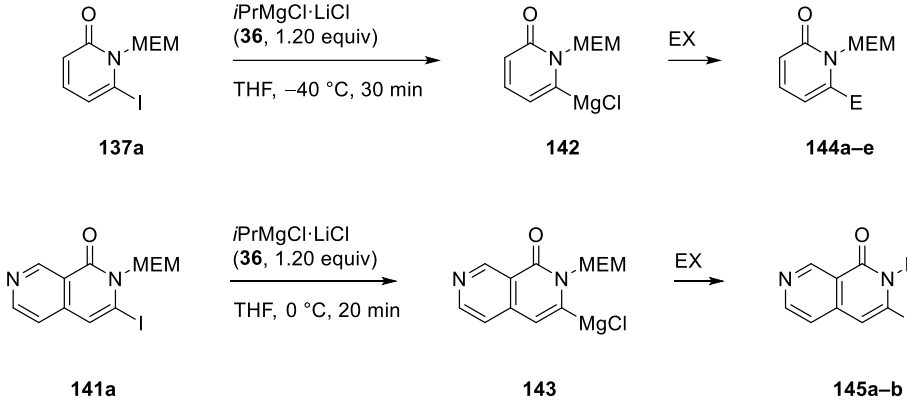
[a] Yield of isolated, analytically pure product. [b] Obtained by Negishi cross-coupling[86] using 4% $Pd(dba)_2$ and 8% P(*o*-furyl)$_3$.[87] [c] Obtained by Negishi cross-coupling[86] using 4% $Pd(OAc)_2$ and 8% SPhos. [d] Obtained by Negishi cross-coupling[86] using 4% PEPPSI-*i*Pr.[91] [e] Obtained after transmetalation with CuCN·2LiCl (1.10 equiv).[92]

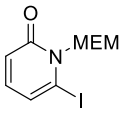
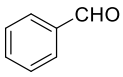
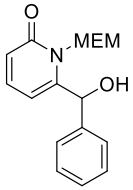
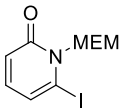
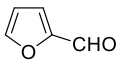
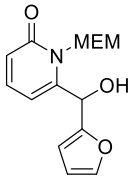
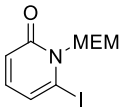
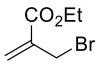
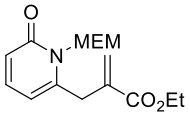
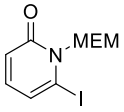
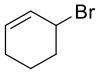
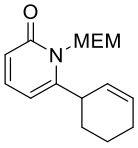
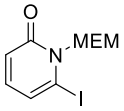
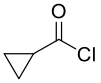
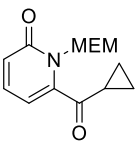
1.4 I/Mg-Exchange of Iodinated 2-Pyridone and Iodinated 2,7-Naphthyridone

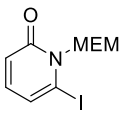
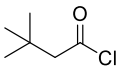
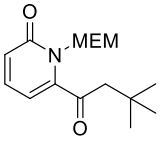
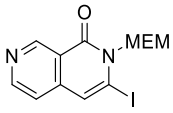
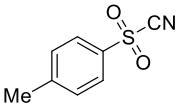
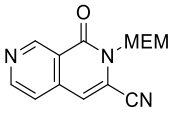
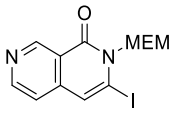
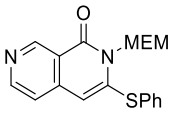
In order to extend the electrophile range, 6-magnesiated pyridone **142** and magnesiated naphthyridone **143** were prepared by treating the corresponding iodo-heterocycles **137a** and **141a** with *i*PrMgCl·LiCl (**36**)[35a,b] at −40 °C or 0 °C (Table 3). The magnesium intermediate **142** reacted readily with aldehydes, such as benzaldehyde or furfural, providing the corresponding alcohols **144a–b** in 80–84% yield (entries 1–2). After magnesiation of **137a** and transmetalation with CuCN·2LiCl[92] (1.20 equiv, −40 °C, 30 min), a copper-mediated allylation with ethyl 2-(bromomethyl)acrylate[93] or 3-bromocyclohex-1-ene led to 6-allylated 2-pyridones **144c–d** in 65–76% yield (entries 3–4). Copper-mediated acylation with cyclopropanecarbonyl chloride or *tert*-butyl acetyl chloride gave 2-pyridone ketones **144e–f** in 72–76% yield (entries 5–6). Quenching the magnesiated 2,7-naphthyridone **143** with *p*-toluenesulfonyl cyanide or *S*-phenyl benzenethiosulfonate afforded the desired products **145a–b** in 60–72% yield (entries 7–8).

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

Table 3: Iodine-magnesium exchange of iodinated 2-pyridone **137a** and 2,7-naphthyridone **141a** and reaction with various electrophiles.



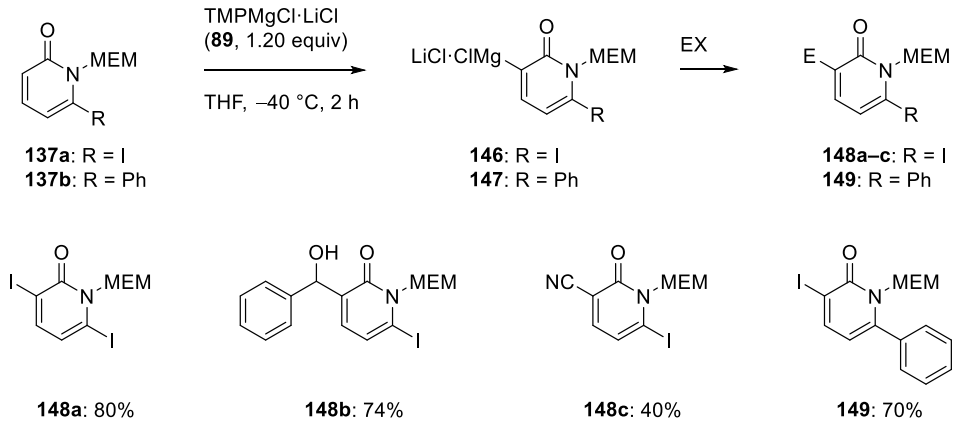
Entry	Substrate	Electrophile (EX)	Product/Yield[a]
1	 **137a**		 **144a**, 80%
2	 **137a**		 **144b**, 84%
3	 **137a**		 **144c**, 65%[b]
4	 **137a**		 **144d**, 76%[b]
5	 **137a**		 **144e**, 76%[b]

			
6	**137a**		**144f**, 72%[b]
			
7	**141a**		**145a**, 60%
		PhSSO$_2$Ph	
8	**141a**		**145b**, 72%

[a] Yield of isolated, analytically pure product. [b] Obtained after transmetalation with CuCN·2LiCl[92] (1.20 equiv).

1.5 Second Metalation of 6-Substituted 2-Pyridones

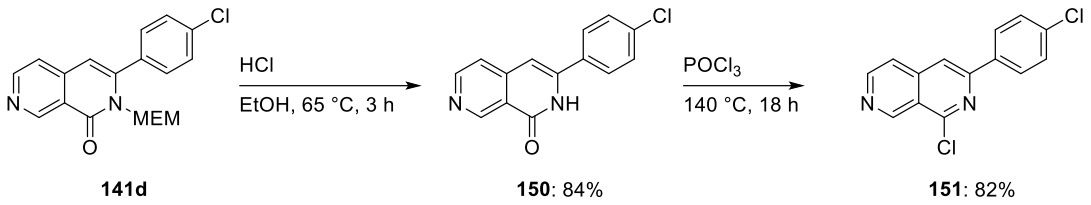
A second metalation of the 6-substituted 2-pyridones **137a** and **137b** occured at position C(3) using TMPMgCl·LiCl (**89**).[42a] Thus, treatment of the 6-iodinated 2-pyridone **137a** with the magnesium amide **89** (1.20 equiv, −40 °C, 2 h) led to the quantitative formation of 3-magnesiated pyridone **146** (Scheme 29). The magnesium reagent **146** reacted with iodine, benzaldehyde or *p*-toluenesulfonyl cyanide, to provide the 3,6-disubstituted 2-pyridones **148a–c** in 40–80% yield. Furthermore, the 6-arylated 2-pyridone **137b** was metalated in position C(3) with **89** (1.20 equiv, −40 °C, 2 h) and this magnesiated species **147** was then iodinated to provide iodo-derivative **149** in 70% yield.



Scheme 29: 3,6-Disubstituted pyridones of type **148** and **149** obtained by regioselective magnesiation of 2-pyridone derivatives of type **137** using TMPMgCl·LiCl (**89**)[42a] and quenching with electrophiles.

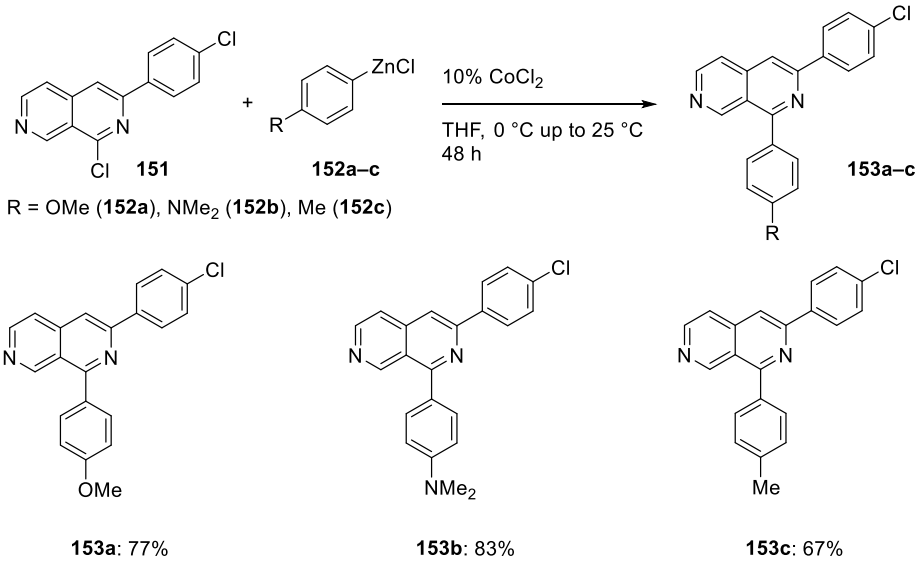
1.6 Further Functionalization of the 2,7-Naphthyridone Scaffold

As an application of this method, the functionalized MEM-protected 2,7-naphthyridone **141d** was converted into a bioactive deprotected 2,7-naphthyridone, which acts as an inhibitor of tankyrase (**150**).[78a] The MEM-group was selectively removed by treatment with HCl at 65 °C, which furnished the unprotected 2,7-naphthyridone **150** in 84% yield (Scheme 30). Further functionalization at C(1) of the 2,7-naphthyridone scaffold **150** was achieved by chlorination with $POCl_3$ leading to the naphthyridine **151** in 82% yield (Scheme 30).



Scheme 30: Preparation of a functionalized halonaphthyridine from naphthyridone **141d**.

Finally, treatment of the 1-chloro-3-(4-chlorophenyl)-2,7-naphthyridine (**151**) with arylzinc chlorides **152a–c**[94] in the presence of 10% $CoCl_2$[94,95] in THF (0 °C up to 25 °C, 48 h) gave the cross-coupling products **153a–c** in 67–83% yield (Scheme 31).



Scheme 31: Cobalt-catalyzed Negishi cross-couplings[86] of chlorinated 2,7-naphthyridine **151**.

[94] D. Haas, J. M. Hammann, F. H. Lutter, P. Knochel, *Angew. Chem. Int. Ed.* **2016**, *55*, 3809.
[95] G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435.

2 Directed Zincation or Magnesiation of 2- and 4-Pyrones and their Derivatives

2.1 Introduction

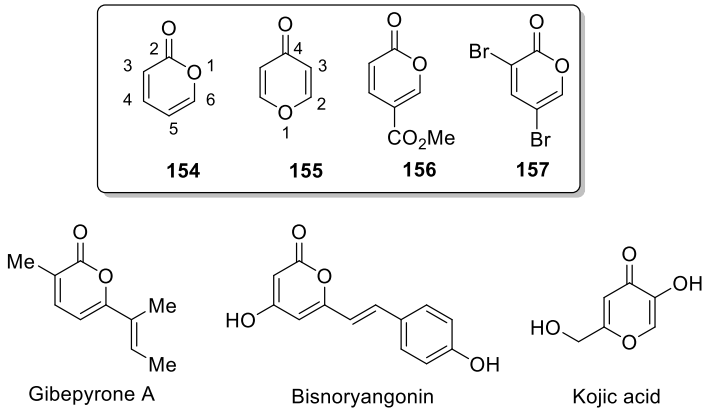


Figure 4: Structures of 2- and 4-pyrone (**154** and **155**) and their derivatives.

Pyrones are important scaffolds that are highly biologically active, widely distributed in biological processes of bacteria, microbial, plants and animals and are therefore interesting heterocycles in modern drug discovery (Figure 4).[96] Furthermore, the resulting functionalized pyrones can be used in a broad range of synthetic applications, in particular as dienes in Diels-Alder reactions[97] as well as precursors for the preparation of more complex heterocyclic systems in natural products.[98] Therefore, a number of methods have been developed to derivatize this core structure by transition-metal-catalyzed cross-couplings.[99] Despite the synthetic utility of pyrones, the preparation of substituted derivatives of this class of heterocycles can be accomplished only with difficulties, often requiring multi-step syntheses.[100]

[96] a) F. A. Macias, A. M. Simonet, P.C. Pacheco, A. F. Barrero, E. Cabrera, D. J. Jiménez-González, *Agric. Food Chem.* **2000**, *48*, 3003; b) G. P. McGlacken, I. J. S. Fairlamb, *Nat. Prod. Rep.* **2005**, *22*, 369; c) H. Gao, R. Popescu, B. Kopp, Z. Wang, Z. *Nat. Prod. Rep.* **2011**, *28*, 953; d) A. Ligresti, R. Villano, M. Allará, I. Ujváry, V. Di Marzo, *Pharmacol. Res.* **2012**, *66*, 163; e) Z. S. Bhat, M. A. Rather, M. Maqbool, H.UL Lah, S. K. Yousuf, Z. Ahmad, *Biomed. Pharmacother.* **2017**, *91*, 265.

[97] a) C.-G. Cho, Y.-W. Kim, Y.-K. Lim, J.-S. Park, H. Lee, S. Koo, *J. Org. Chem.* **2002**, *67*, 290; b) P. Zhao, C. M. Beaudry, *Angew. Chem. Int. Ed.* **2014**, *126*, 10668; c) P. Gan, M. W. Smith, N. R. Braffman, S. A. Snyder, *Angew. Chem. Int. Ed.* **2016**, *55*, 3625.

[98] a) M. Luparia, M. T. Oliveira, D. Audisio, F. Frébault, R. Goddard, N. Maulide, *Angew. Chem. Int. Ed.*, **2011**, *50*, 12631; b) C.-X. Zhuo, A. Fürstner, *Angew. Chem. Int. Ed.* **2016**, *55*, 6051; c) J. Preindl, S. Schulthoff, C. Wirtz, J. Lingnau, A. Fürstner, *Angew. Chem. Int. Ed.* **2017**, *56*, 7525.

[99] a) F. Frébault, M. T. Oliveira, E. Wöstefeld, N. Maulide, *J. Org. Chem.* **2010**, *75*, 7962; b) M.-T. Nolan, L. M. Pardo, A. M. Prendergast, G. P. McGlacken, *J. Org. Chem.* **2015**, *80*, 10904.

[100] a) M. Grigalunas, O. Wiest, P. Helquist, *Org. Lett.* **2016**, *18*, 5724; b) D. Dobler, O. Reiser, *J. Org. Chem.* **2016**, *81*, 10357.

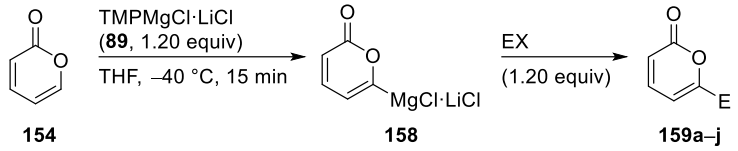
Herein, the functionalization of 2- and 4-pyrones (**154** and **155**) and methyl coumalate (**156**) as well as the 3,5-dibrominated 2-pyrone **157** using TMPMgCl·LiCl[42a,81b,101] (**89**), TMPZnCl·LiCl[63,81d,84,102] (**92**) and $TMP_2Zn·2LiCl·2MgCl_2$[64,67,85] (**93**) followed by reactions with various electrophiles (EX) is reported.

2.2 Functionalization of 2-Pyrone

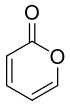
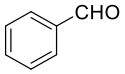
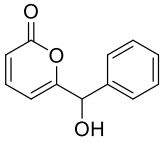
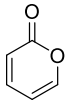
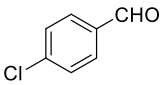
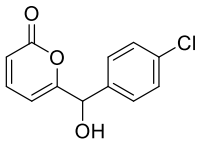
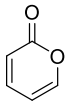
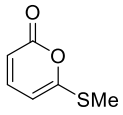
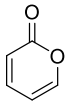
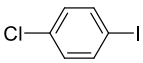
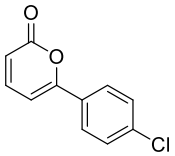
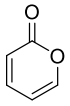
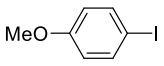
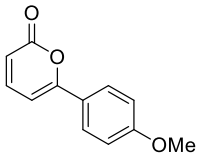
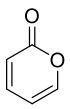
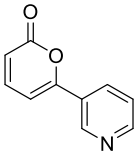
2-Pyrone (**154**) was treated with TMPMgCl·LiCl[42a] (**89**, 1.20 equiv) for 15 min at –40 °C in THF, which resulted in the coordination of the TMP-base to the oxygen atom O(1), inducing a magnesiation in position C(6). This method led to a magnesium species of type **158**, which, after quenching with aldehydes, gave the alcohols **159a**[103] and **159b** in 60–72% yield (Table 4, entries 1–2). Reaction of the magnesium intermediate **158** with *S*-methyl methanethiosulfonate led to the thiolated 2-pyrone **159c** in 95% yield (entry 3). After transmetalation of the magnesium species to zinc using $ZnCl_2$, a Negishi cross-coupling[86] was performed with aryl iodides containing electron-withdrawing or -donating substituents in the presence of 4% $Pd(dba)_2$ and 8% tris (*o*-furyl)phosphine[87] affording arylated 2-pyrones **159d–f** in 75–95% yield (entries 4–6). Reaction of this zinc species in a Pd-catalyzed cross-coupling with (*E*)-2-bromobut-2-ene provided **159g** in 95% yield (entry 7). After transmetalation to the corresponding copper-species using CuCN·2LiCl[92] (1.20 equiv, −40 °C, 30 min) and subsequent reaction with 3-bromocyclohex-1-ene led to the allylated product **159h** in 50% yield (entry 8). Moreover, acylation reactions of the copper intermediates using various acid chlorides afforded 6-acyl-2-pyrones **159i–j** in 44–60% yield (entries 9–10).

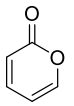
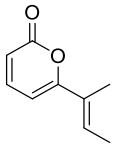
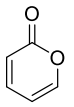
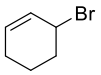
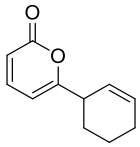
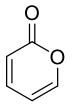
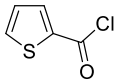
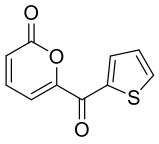
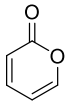
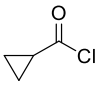
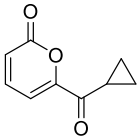
[101] a) M. Balkenhohl, C. Francois, D. Sustac-Roman, P. Quinio, P. Knochel, *Org. Lett.* **2017**, *19*, 536; b) M. Balkenhohl, R. Greiner, I. S. Makarov, B. Heinz, K. Karaghiosoff, H. Zipse, P. Knochel, *Chem. - Eur. J.* **2017**, *23*, 13046.
[102] M. Balkenhohl, B. Salgues, T. Hirai, K. Karaghiosoff, P. Knochel, *Org Lett.* **2018**, *20*, 3114.
[103] CCDC-1847973 (**159a**) contains the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 4: Magnesiation of 2-pyrone (**154**) leading to the metalated species **158** followed by reactions with several electrophiles.



154 **158** **159a–j**

Entry	Substrate	Electrophile (EX)	Product/Yield[a]
			
1	**154**		**159a**, 72%
			
2	**154**		**159b**, 60%
		$MeSSO_2Me$	
3	**154**		**159c**, 95%
			
4	**154**		**159d**, 75%[b]
			
5	**154**		**159e**, 90%[b]
			
6	**154**		**159f**, 95%[b]

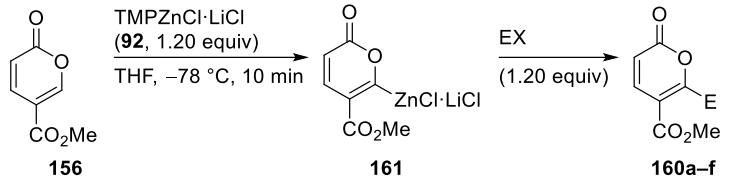
			
7	**154**		**159g**, 95%[c]
			
8	**154**		**159h**, 50%[d]
			
9	**154**		**159i**, 44%[d]
			
10	**154**		**159j**, 60%[d]

[a] Yield of isolated, analytically pure product. [b] Obtained by Negishi cross-coupling[86] using 4% $Pd(dba)_2$ and 8% P(*o*-furyl)$_3$.[87] [c] Obtained by Negishi cross-coupling[86] using 4% PEPPSI-*i*Pr.[91] [d] Obtained after transmetalation with CuCN·2LiCl[92] (1.20 equiv).

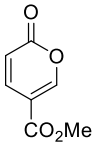
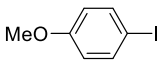
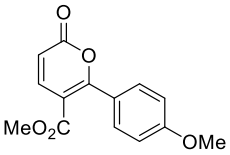
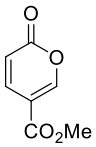
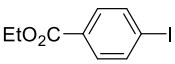
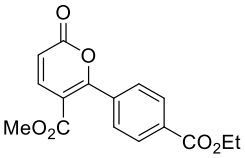
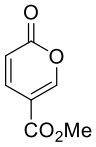
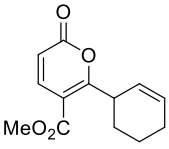
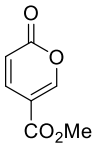
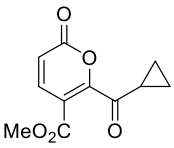
2.3 Functionalization of 2-Pyrone Derivatives

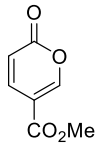
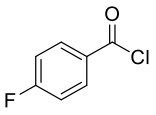
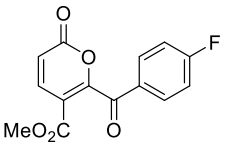
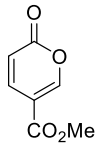
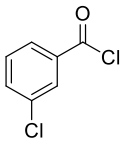
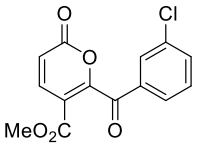
2-Pyrones bearing an ester functionality in the C(5) position also underwent metalation using TMPZnCl·LiCl[63] (**92**, 1.20 equiv, −78 °C, 10 min), allowing a facile functionalization of the C(6) position. Pd-catalyzed Negishi cross-couplings[86] with aryl iodides led to cross-coupling products **160a–b** in 45–58% yield (Table 5, entries 1–2). Transmetalation of **161** with CuCN·2LiCl[92] (1.20 equiv, −40 °C, 30 min) and subsequent reaction with allyl bromide provided methyl coumalate **160c** in 70% yield (entry 3). The corresponding reaction with acyl chlorides afforded the expected ketones **160d–f** in 40–64% yield (entries 4–6).

Table 5: Zincation of methyl coumalate (**156**) leading to the metalated species **161** followed by reactions with several electrophiles.



156 **161** **160a–f**

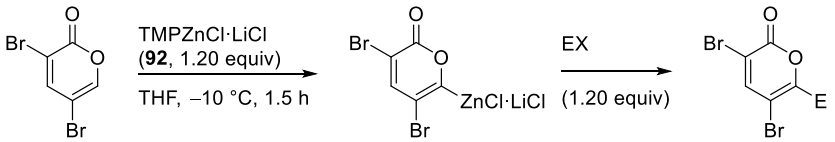
Entry	Substrate	Electrophile (EX)	Product/Yield[a]
			
1	**156**		**160a**, 45%[b]
			
2	**156**		**160b**, 58%[b]
			
3	**156**		**160c**, 70%[c]
			
4	**156**		**160d**, 40%[c]

5		**156**		 **160e**, 55%[c]
6		**156**		 **160f**, 64%[c]

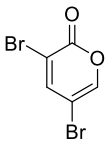
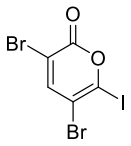
[a] Yield of isolated, analytically pure product. [b] Obtained by Negishi cross-coupling[86] using 4% $Pd(dba)_2$ and 8% P(*o*-furyl)$_3$.[87] [c] Obtained after transmetalation with CuCN·2LiCl[92] (1.20 equiv).

The scope of this zincation using the zinc-base **92** on 3,5-dibrominated 2-pyrone **157**[97] achieving a regioselective zincation of 3,5-dibromo-2*H*-pyran-2-one (**157**) at position C(6) with the zinc base (**92**, 1.20 equiv, −10 °C, 1.5 h) was explored. The resulting zinc reagent **162** was readily functionalized by reaction with various electrophiles to furnish 6-substituted 3,5-dibromo-2*H*-pyran-2-one of type **163** (Table 6). Similarly, iodolysis, Pd-catalyzed Negishi cross-coupling[86] and Cu-mediated allylation or acylation, provided the C(6)-substituted pyrones **163a–e** in 53–64% yield (entries 1–5).[104]

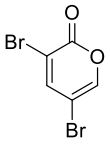
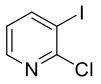
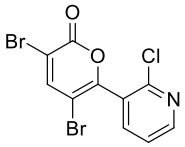
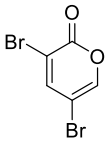
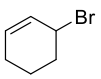
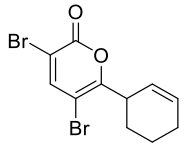
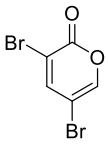
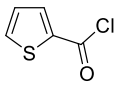
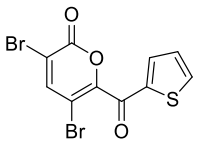
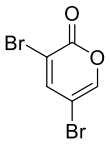
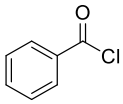
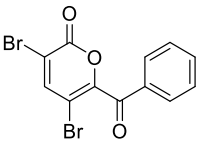
Table 6: Zincation of 3,5-dibromo-2*H*-pyran-2-one (**157**) leading to the metalated species **162** followed by reactions with several electrophiles.



157 **162** **163a–e**

Entry	Substrate	Electrophile (EX)	Product/Yield[a]
1	 **157**	I_2	 **163a**, 64%

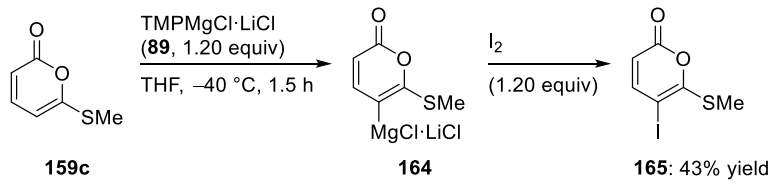
[104] CCDC-1851127 (**163a**) contains the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

			
2	**157**		**163b**, 60%[b]
			
3	**157**		**163c**, 60%[c]
			
4	**157**		**163d**, 55%[c]
			
5	**157**		**163e**, 53%[c]

[a] Yield of isolated, analytically pure product. [b] Obtained by Negishi cross-coupling[86] using 4% $Pd(dba)_2$ and 8% P(*o*-furyl)$_3$.[87] [c] Obtained after transmetalation with CuCN·2LiCl[92] (1.20 equiv).

2.4 Further Functionalization of Substituted 2-Pyrone

A second metalation of the 6-substituted 2-pyrone **159c** and **159e** occured at position C(3) or C(5) using TMPMgCl·LiCl[42a] (**89**). Thus, the 6-thiolated 2-pyrone **159c** was metalated in position C(5) with **89** (1.20 equiv, −40 °C, 1.5 h) and this magnesiated species **164** was then iodinated to provide iodo-derivative **165** in 43% yield (Scheme 32).

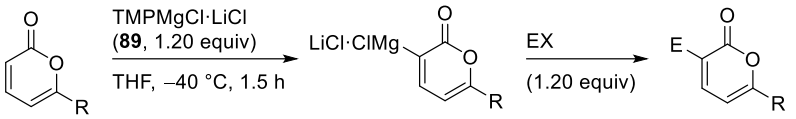


Scheme 32: Further functionalization of the 6-substituted 2-pyrone **159c**.

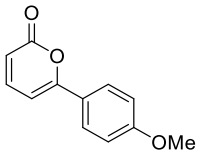
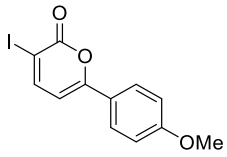
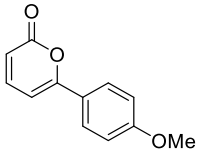
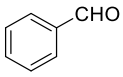
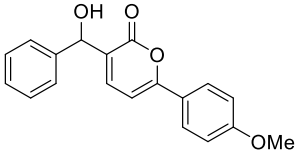
Furthermore, treatment of the 6-arylated 2-pyrone **159e** with **89** (1.20 equiv, –40 °C, 1.5 h) led to the quantitative formation of 3-magnesiated pyrone **166** (Table 7). The magnesium reagent **166** reacted

with iodine and benzaldehyde, to provide the 3,6-disubstituted 2-pyrones **167a–b** in 45–95% yield (entries 1–2).

Table 7: A second metalation of the 6-substituted 2-pyrone **159e**.



R = 4-anisyl: **159e** **166** **167a–b**

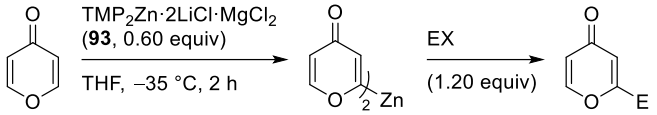
Entry	Substrate	Electrophile (EX)	Product/Yield[a]
1	 **159c**	I_2	 **167a**, 95%[b]
2	 **159e**		 **167b**, 45%

[a] Yield of isolated, analytically pure product. [b] Obtained by Negishi cross-coupling[86] using 4% $Pd(dba)_2$ and 8% P(*o*-furyl)$_3$.[87]

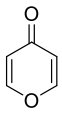
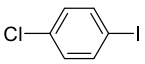
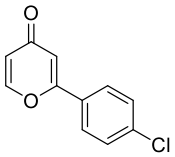
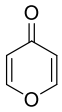
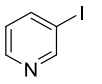
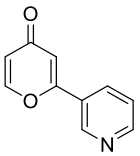
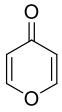
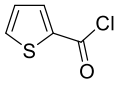
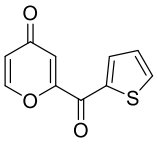
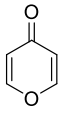
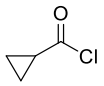
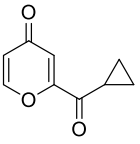
2.5 Functionalization of 4-Pyrone Scaffold

In order to extend the substrate scope, a 2-zincated 4-pyrone (**168**) was prepared by treating 4-pyrone (**155**) with $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$[64] (**93**) at –35 °C for 2 h (Table 8). The zinc intermediate **168** reacted readily with aryl iodides in the presence of 4% $Pd(dba)_2$ and 8% P(*o*-furyl)$_3$,[87] providing the corresponding arylated products **169a**–**b** in 50–86% yield (Table 8, entries 1–3). Copper-mediated acylation with thiophene-2-carbonyl chloride or cyclopropanecarbonyl chloride gave 4-pyrone ketones **169c**–**169d** in 50–71% yield (entries 3–4).

Table 8: Zincation of 4-pyrone (**155**) leading to the metalated species **168** followed by reactions with several electrophiles.



155 **168** **169a–e**

Entry	Substrate	Electrophile (EX)	Product/Yield[a]
			
1	**155**		**169a**, 50%[b]
			
2	**155**		**169b**, 86%[b]
			
3	**155**		**169c**, 71%[c]
			
4	**155**		**169d**, 50%[c]

[a] Yield of isolated, analytically pure product. [b] Obtained by Negishi cross-coupling[86] using 4% $Pd(dba)_2$ and 8% P(*o*-furyl)$_3$.[87] [c] Obtained after transmetalation with $CuCN{\cdot}2LiCl$[92] (1.20 equiv).

3 Generation of Aryl and Heteroaryl Magnesium Reagents in Toluene by Br/Mg- or Cl/Mg-Exchange

3.1 Introduction

Organomagnesium halides are key intermediates in organic synthesis.[6] They are usually prepared by a direct insertion of magnesium turnings,[105] Rieke magnesium,[106] or magnesium powder, and lithium chloride[10] to organic halides. The heterogenous nature of this reaction complicates scale-up and industrial use.[83] A deprotomagnesiation of arenes or heteroarenes can also be accomplished using soluble hindered magnesium amides.[42b,83b,107] Alternatively, various organomagnesium halides can be prepared *via* a halogen-magnesium exchange by treating aryl or heteroaryl iodides or bromides with an alkylmagnesium halide[108] or better with *i*PrMgCl·LiCl (**36**).[23,35] Furthermore, synthetically useful reagents for halogen-metal exchange are lithium organomagnesiates (R_3MgLi). However, in this case, lithium triorgano magnesiates are produced.[21e] All these preparation methods provide Grignard reagents in ethereal solvents such as diethyl ether or THF and only a few methods have been reported describing the preparation of magnesium organometallics in non-polar solvents.[109] The synthesis of Grignard reagents in hydrocarbons or toluene is of great interest, since these weakly-coordinated Grignard reagents may display an original and unusual reactivity. Also, Grignard reagents in hydrocarbons or toluene are industrial friendly reagents, as such solvents improve aqueous extraction during work-ups.[110] Herein, new halogen-magnesium exchange reagents *s*BuMgOR·LiOR (**170a**) and *s*Bu_2Mg·2LiOR (**170b**) (R = 2-ethylhexyl), that allow very fast bromine-magnesium exchanges and, for the first time, a chlorine-magnesium exchange on various electron-rich aryl chlorides are reported.

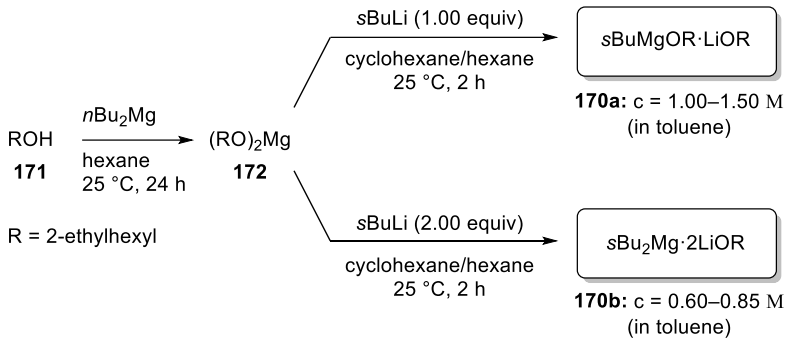
3.2 Optimization of Reaction Conditions

First, a convenient synthesis of **170a** and **170b** was developed. Thus, the magnesium alkoxide was prepared by treating *n*Bu_2Mg (0.70 M in hexane, 1.00 equiv) with 2-ethylhexanol (**171**, 2.00 equiv) at

---

[105] *Grignard Reagents, New Developments* (Ed.: H. G. Jr. Richey.), Wiley-VCH Verlag GmbH & Co KGaA, Weinheim, **2000**.
[106] a) R. D. Rieke, T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4324; b) R. D. Rieke, *Science* **1989**, *246*, 1260; c) *Active Metals* (Ed.: A. Fuerstner), Wiley-VCH Verlag GmbH & Co KGaA, Weinheim, **1995**; d) J. Lee, R. Velarde-Ortitz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428.
[107] M. Balkenhohl, P. Knochel, *SynOpen* **2018**, *2*, 78.
[108] D. R. Rieke, M. S. Sell, In *Handbook of Grignard reagents* (Eds.: G. S. Silvermann, P. E. Rakita) **1996**.
[109] a) C. G. Screttas, M. Micha-Screttas, *J. Organomet. Chem.* **1985**, *290*, 1; b) C. G. Screttas, B. R. Steele, *J. Org. Chem.* **1989**, *54*, 1013; c) T. Iida, T. Wada, K. Tomimoto, T. Mase, *Tetrahedron Lett.* **2001**, *42*, 4841; d) L. Chtcheglova, S. Carlotii, A. Deffieux, N. Poirier, M. Barbier, FR-2840901, **2003**; e) E. S. Baillie, T. D. Bluemke, A. R. Clegg, Kennedy, J. Klett, L. Russo, M. de Tullio, E. Hevia, *Chem. Commun.* **2014**, *50*, 12859.
[110] a) *Solvent Recovery Handbook* (Ed.: I. M. Smallwood), Blackwell Science Ltd., Oxford, **2002**; b) L. Delhaye, A. Ceccato, P. Jacobs, C. Köttgen, A. Merschaert, *Org. Process Res. Dev.* **2007**, *11*, 160.

25 °C for 24 h.[111,112] The addition of one or two equivalents of *s*BuLi (1.21 M in cyclohexane) to the colorless gel (**172**) at 25 °C for 2 h provided slightly yellow solutions of **170a** and **170b**. Removal of the solvent *in vacuo* produced a foam which readily dissolves in toluene, affording a 1.00–1.50 M solution of **170a** and a 0.60–0.85 M slightly yellow solution of **170b** (Scheme 33).[113]



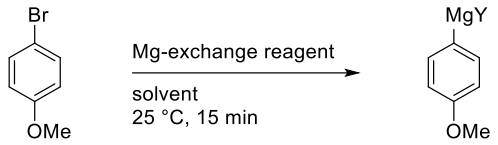
Scheme 33: Preparation of the new exchange reagents **170a** and **170b**.

Both **170a–b** are very powerful exchange reagents, which for the first time, allow the synthesis of arylmagnesium reagents in toluene.[114] In preliminary experiments, the bromine-magnesium exchange on 4-bromoanisole (**173a**) was examined (Table 9).

In THF, *i*PrMgCl·LiCl (**36**)[35a,b] required 27 h at 25 °C to complete the exchange reaction and produced the desired arylmagnesium halide **174a** (Y = Cl). However, less than 1% of **174a** was formed with this exchange reagent after 15 min reaction time (entry 1).[115] The currently most powerful available exchange reagent *s*Bu$_2$Mg·2LiCl (**81**)[35b] led to 13% of **174a** (Y = 4-anisyl) after 15 min (entry 2). A full conversion with this reagent required 8 h reaction time. Switching to toluene showed, that both of these reagents were unreactive.

[111] H. Thoms, M. Epple, H. Viebrock, A. Reller, *J. Mater. Chem.* **1995**, *5*, 589.
[112] Alternatively, a magnesium alkoxide solution (0.94 M in heptane) is commercially available from Albemarle, Frankfurt: U. Wietelmann, U. Emmel, J. Roeder, M. Steinbild, K. Papstein, K. (Albemarle), WO-2010146122, **2010**.
[113] Further detailed screening tables can be found in the EXPERIMENTAL PART.
[114] The reactions were also performed in other apolar solvents such as hexane and cyclohexane or in cyclopentyl methyl ether (CPME).
[115] Yield of **174a** determined by GC-analysis of water quenched reaction aliquots with undecane as internal standard.

Table 9: Bromine-magnesium exchange for 4-bromoanisole (**173a**) using various magnesium-exchange reagents at 25 °C.



173a **174a**

Entry	Mg-exchange reagent	Equiv	Solvent	Yield(%)[a]
1	*i*PrMgCl·LiCl (**36**)	1.20	THF	1 [0][b]
2	*s*Bu_2Mg·2LiCl (**81**)	0.60	THF	13 [0][b]
3	*s*BuMgOR·LiOR (**170a**)	1.20	toluene	85
4	*s*BuMgOR·LiOR (**170a**)	1.20	toluene	99[c]
5	*s*BuMgOR·LiOR (**170a**)	1.20	THF	14[c]

[a] Yield of **174a** determined by GC-analysis of water quenched reaction aliquots with undecane as internal standard. [b] Yield obtained in toluene. [c] Yield obtained in the presence of TMEDA (1.20 equiv).

However, the addition of the new reagent *s*BuMgOR·LiOR (**170a**) to **173a** in toluene provided **174a** (Y = OR·LiOR) in 85% yield within 15 min reaction time (entry 3). The addition of TMEDA (1.20 equiv) further improved the reaction conversion to 99% (entry 4).[116] The addition of TMEDA to *i*PrMgCl·LiCl (**36**)[35a,b] or *s*Bu_2Mg·2LiCl (**81**) [35b] had no effect. Interestingly, the rate of the bromine-magnesium exchange using **174a** in THF instead of toluene was considerably decreased and only a conversion of 14% was observed (entry 5). This showed, that there is a real advantage for carrying out the bromine-magnesium exchange in non-polar solvents such as toluene.

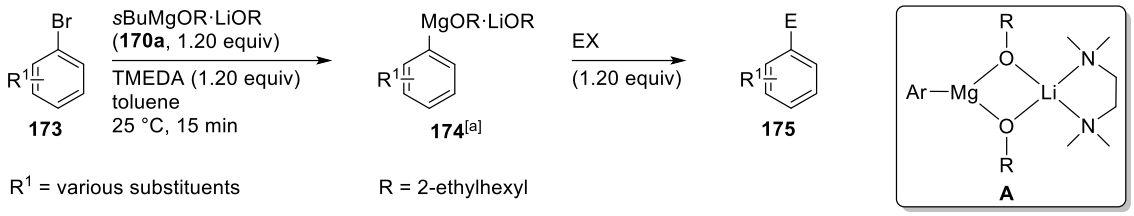
3.3 Aryl Magnesium Reagents in Toluene by Br/Mg-Exchange

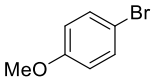
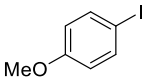
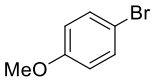
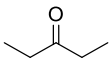
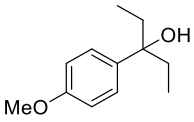
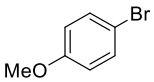
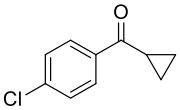
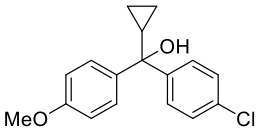
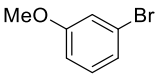
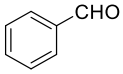
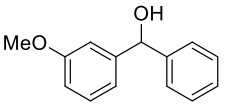
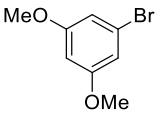
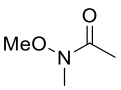
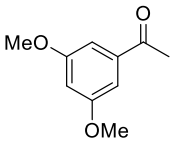
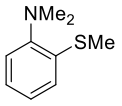
Quenching of **174a** (Y = OR·LiOR·TMEDA) with iodine furnished the aryl iodide **175a** in 70% yield (25 °C, 30 min; Table 10, entry 1). Usually, arylmagnesium reagents do not add well to ketones.[21b,117,118] However, trapping **174a** in toluene with ketones furnished the tertiary alcohols **175b–c** in 80–86% yield (25 °C, 2 h; entries 2–3). Related aryl bromides such as 3-bromoanisole (**173b**) or 1-bromo-3,5-dimethoxybenzene (**173c**) underwent a complete bromine-magnesium exchange by treatment with **170a**

[116] F. M. Perna, A. Salomone, M. Dammacco, S. Florio, V. Capriati, *Chem. - Eur. J.* **2011**, *17*, 8216.
[117] a) M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998; b) M. Hatano, O. Ito, S. Suzuki, K. Ishihara, *J. Org. Chem.* **2010**, *75*, 5008.
[118] Notable exceptions: a) C. Vidal, J. García-Álvarez, A. Hernán-Gómez, A. R. Kennedy, E. Hevia, *Angew. Chem. Int. Ed.* **2014**, *53*, 5969; b) L. Cicco, S. Sblendorio, R. Mansueto, F. M. Perna, A. Salmone, S. Florio, V. Capriati, *Chem. Sci*. **2016**, *7*, 1192.

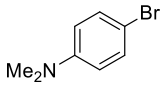
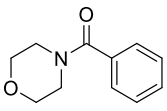
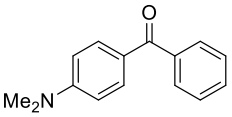
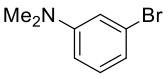
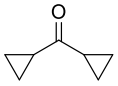
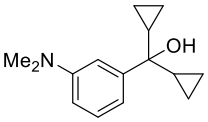
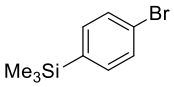
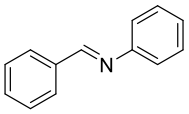
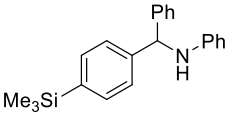
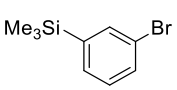
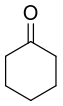
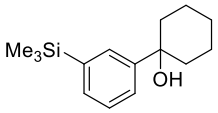
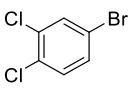
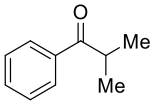
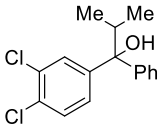
(25 °C, 15 min). These Grignard reagents were added to PhCHO or were acylated with a Weinreb amide,[119] furnishing the desired products **175d** and **175e** in 89–95% yield (25 °C, 1 h; entries 4–5).

Table 10: Bromine-magnesium exchange for aryl bromides of type **173** leading, *via* intermediate organomagnesiums of type **174**, to functionalized arenes of type **175**.



Entry	Arylbromide	Electrophile (EX)	Product/Yield[b]
		I_2	
1	**173a**		**175a**, 70%
			
2	**173a**		**175b**, 80%
			
3	**173a**		**175c**, 86%
			
4	**173b**		**175d**, 95%
			
5	**173c**		**175e**, 89%
		$MeSO_2SMe$	
6	**173d**		**175f**, 84%[c]

[119] S. M. Weinreb, S. Nahm, *Tetrahedron Lett.* **1981**, *22*, 3815.

			
7	**173e**		**175g**, 65%[d]
			
8	**173f**		**175h**, 80%[e]
			
9	**173g**		**175i**, 86%
			
10	**173h**		**175j**, 75%
			
11	**173i**		**175k**, 72%

[a] TMEDA has been omitted for the sake of clarity. [b] Yield of analytically pure isolated product. [c] The reaction time was 1 h. [d] The reaction time was 4 h. [e] The reaction time was 2 h.

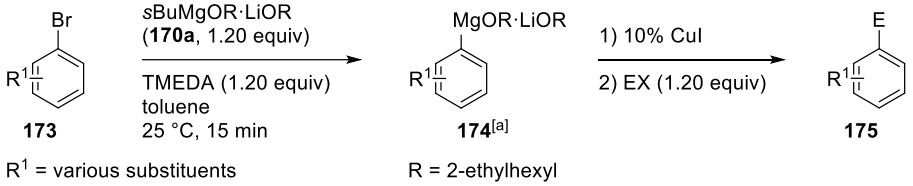
Also, bromoanilines **173d–f** which are very reluctant to undergo a bromine-magnesium exchange with previously known exchange reagents,[23,35b] were converted into the corresponding arylmagnesium alkoxides within 1–4 h at 25 °C in toluene. Their trapping with $MeSO_2SMe$, morpholino(phenyl) methanone[120] or dicyclopropyl ketone produced the polyfunctional aniline derivatives **175f**–**h** in 65–84% yield (25 °C, 1–2 h; entries 6–8). Similar electron-rich aryl bromides such as **173g** and **173h** were converted to the Grignard reagents and were quenched with cyclohexanone or *N*-benzylideneamine, leading to **175i** and **175j** in 75–86% yield (25 °C, 2 h; entries 9–10). Finally, electron-poor aryl bromide **173i** underwent the bromine-magnesium exchange at 25 °C within 15 min and gave after quenching with a ketone the product **175k** in 72% yield (25 °C, 2 h; entry 11). These results demonstrated, that arylmagnesium alkoxides of type **174** complexed with LiOR and TMEDA are superior nucleophiles, since they react smoothly with various ketones. The structure of the magnesium reagents **174** were tentatively proposed to be **A** (Table 10).

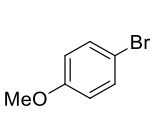
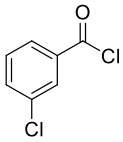
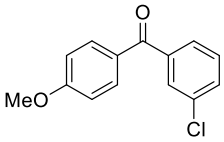
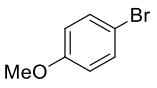
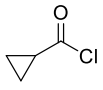
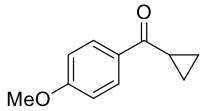
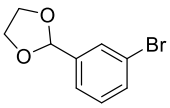
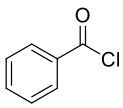
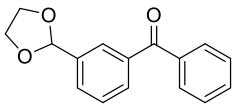
[120] a) R. Peters, P. Waldmeier, A. Joncour, *Org. Process Res. Dev.* **2005**, *9*, 508; b) Y. Chen, M. Ellwart, G. Toupalas, Y. Ebe, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 4612.

3.4 Aryl Magnesium Reagents in Toluene by Br/Mg-Exchange and Subsequent Copper-Catalyzed Reactions

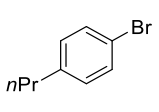
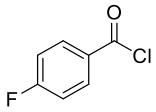
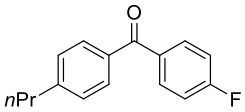
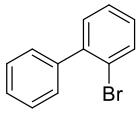
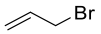
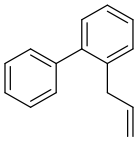
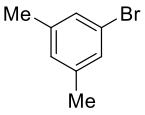
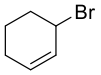
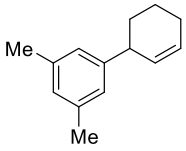
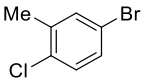
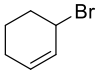
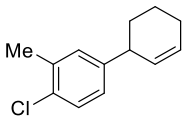
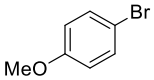
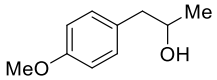
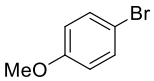
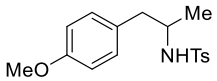
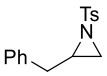
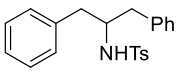
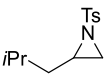
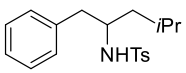
Furthermore, the Grignard reagents **174** (Y = OR·LiOR·TMEDA) underwent a range of copper-catalyzed reactions such as acylations with various acyl chlorides in toluene leading to ketones **175l**–**o** in 60–95% yield (10% CuI, 0 °C, 1 h; Table 11, entries 1–4). Also, allylations of arylmagnesium alkoxides were realized at 25 °C with allylic bromides, providing products **175p**–**r** in 89–92% yield (entries 5–7). The opening of epoxides and aziridines with arylmagnesium reagents is also a challenging reaction that often required Lewis acids or harsh reaction conditions.[121] It was found that epoxides like propylene oxide, or aziridines such as 2-methyl-1-tosylaziridine, 2-benzyl-1-tosylaziridine or 2-isobutyl-1-tosylaziridine were opened under mild conditions (25 °C, 4–10 h), leading to the expected products **175s**–**175v** in 73–95% yield (entries 8–11).

Table 11: Bromine-magnesium exchange for aryl bromides of type **173** leading, *via* intermediate organomagnesiums of type **174**, to functionalized arenes of type **175** in the presence of 10% CuI.



Entry	Arylbromide	Electrophile (EX)	Product/Yield[b]
1	 **173a**		 **175l**, 95%
2	 **173a**		 **175m**, 60%
3	 **173j**		 **175n**, 70%

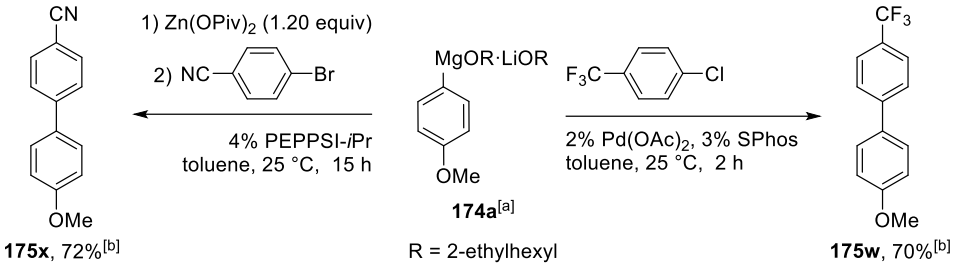
[121] a) M. J. Eis, J. E. Wrobel, B. Ganem *J. Am. Chem. Soc.* **1984**, *106*, 3693; b) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *Tetrahedron Lett.* **1989**, 2387; c) D. Tanner, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599; d) *Aziridines and Epoxides in Organic Synthesis* (Ed: A. Yudin), Wiley-VCH Verlag GmbH & Co KGaA, Weinheim, **2006**; e) S. Stankovic, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. Van Speybroeck, N. De Kimpe, H.-J. Ha, *J. Chem. Soc. Rev.* **2012**, *41*, 643; f) K. L. Jensen, E. A. Standley, T. F. Jamison, *J. Am. Chem. Soc* **2014**, *136*, 11145.

			
4	**173k**		**175o**, 64%
			
5	**173l**		**175p**, 92%
			
6	**173m**		**175q**, 90%
			
7	**173n**		**175r**, 89%
			
8	**173a**		**175s**, 92%
			
9	**173a**		**175t**, 73%
			
10	**173o**		**175u**, 95%
			
11	**173o**		**175v**, 92%

[a] TMEDA has been omitted for the sake of clarity. [b] Yield of analytically pure isolated product.

3.5 Aryl Magnesium Reagents in Toluene by Br/Mg-Exchange and Subsequent Palladium-Catalyzed Cross-Couplings

The arylmagnesium alkoxides of type **174** (Y = OR·LiOR·TMEDA) also participate in Pd-catalyzed cross-couplings (Scheme 34).



Scheme 34: Cross-couplings of organomagnesium intermediate **174a**: [a] TMEDA has been omitted for the sake of clarity. [b] Yield of analytically pure isolated product.

Thus, *p*-anisylmagnesium derivative (**174a**; Y = OR·LiOR·TMEDA) underwent a Kumada cross-coupling[122] with 1-chloro-4-(trifluoromethyl)benzene in the presence of 2% $Pd(OAc)_2$ and 3% SPhos[89] (25 °C, 2 h), producing the biphenyl **175w** in 70% yield. Transmetalation with $Zn(OPiv)_2$[123] in toluene led to a milky suspension which reacted with 4-bromobenzonitrile (25 °C, 15 h) *via* a Negishi cross-coupling using 4% of PEPPSI-*i*Pr,[91,86,124] furnishing the desired product **175x** in 72% yield (Scheme 34).

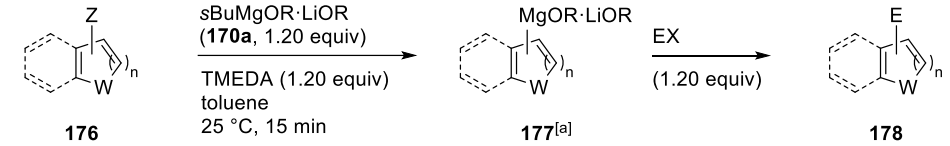
3.6 Heteroaryl Magnesium Reagents in Toluene by Br/Mg-Exchange

This method was extended to the preparation of some heterocyclic magnesium alkoxides. Thus, the treatment of 5-bromobenzofuran (**176a**) with *s*BuMgOR·LiOR (**170a**, 1.20 equiv) for 15 min at 25 °C led to the corresponding heteroarylmagnesium alkoxide **177a** in ca. 90% yield. Quenching with benzoyl chloride in the presence of 10% CuI provided the benzofuran derivative **178a** in 70% yield (Table 12, entry 1). Similarly, 3-bromobenzothiophene **176b** was converted to the corresponding organomagnesium alkoxide **177b**. Quenching with morpholino(phenyl) methanone[120] gave benzothiophene **178b** in 65% yield (−10 °C, 15 min; entry 2). Also, *N*-methyl-5-bromoindole (**176c**) and the 3-bromoazaindole **176d** were converted into the corresponding organomagnesium alkoxides **177c** and **177d**. After quenching with benzofuran-2-carbaldehyde, the desired products **178c–d** were obtained in 62–70% yield (entries 3–4). The pyridine derivatives **176e** and **176f** were converted into

[122] a) R. Martin, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3844; b) G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 205; c) X. Hua, J. Masson-Makdissi, R. J. Sullivan, S. G. Newman, *Org. Lett.* **2016**, *18*, 5312.
[123] Y.-H. Chen, M. Ellwart, V. Malakhov, P. Knochel, *Synthesis* **2017**, *49*, 3215.
[124] a) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540; b) D.-Y. Wang, K. Morimoto, Z.-K. Yang, C. Wang, M. Uchiyama, *Chem. Asian J.* **2017**, *12*, 2554.

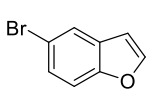
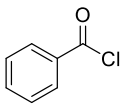
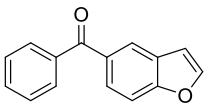
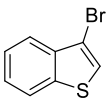
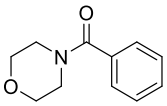
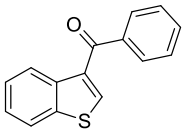
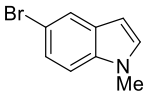
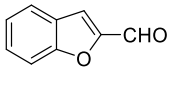
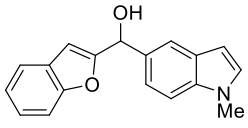
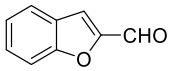
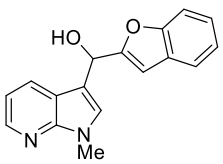
the Grignard reagents **177e** and **177f** and were quenched with aldehydes, leading to the alcohols **178e** and **178f** in 68–72% yield (−30 °C, 1 h; entries 5–6). Interestingly, the treatment of 2,3,4,5-tetrachlorothiophene[125] (**176g**) with **170a** (2.40 equiv) led to a double chlorine-magnesium exchange, providing a bis-magnesium species, which after a copper-catalyzed allylation with allyl bromide, gave 2,5-bis-allylthiophene **178g** in 60% yield (entry 7).

Table 12: Bromine-magnesium exchange for heteroaryl bromides and chlorides of type **176** leading, *via* intermediate organomagnesiums of type **177**, to functionalized heteroarenes of type **178**.

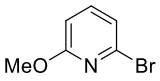
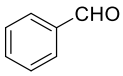
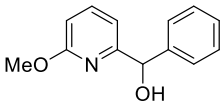
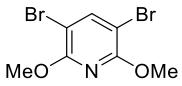
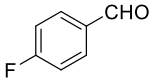
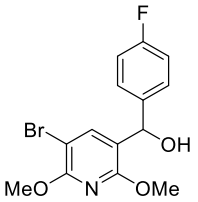
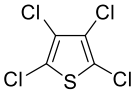
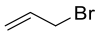
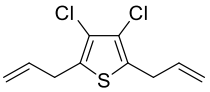


176 **177**[a] **178**

W = N, O, S; Z = Br, Cl; n = 1, 2 R = 2-ethylhexyl

Entry	Heteroarylhalides	Electrophile (EX)	Product/Yield[b]
			
1	**176a**		**178a**, 70%[c]
			
2	**176b**		**178b**, 65%[d]
			
3	**176c**		**178c**, 62%
			
4	**176d**		**178d**, 70%[e]

[125] Previously, it was found that **176** is the only substrate, which undergoes a fast mono-chlorine-magnesium exchange using *i*PrMgCl·LiCl (**36**): M. Abarbri, J. Thibonnet, L. Bérillon, F. Dehmel, M. Rottländer, P. Knochel, *J. Org. Chem.* **2000**, *65*, 4618.

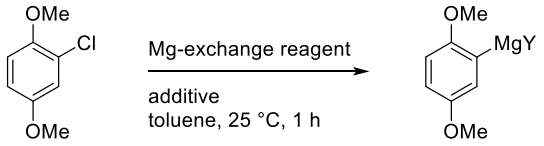
			
5	**176e**		**178e**, 72%[f]
			
6	**176f**		**178f**, 68%[f]
			
7	**176g**		**178g**, 60%[g]

[a] TMEDA has been omitted for the sake of clarity. [b] Yield of analytically pure isolated product. [c] 10% CuI was added. [d] The reaction temperature was −10 °C. [e] The reaction time was 3 h. [f] The reaction time was 1 h at −30 °C [g] The reaction time was 4 h.

3.7 Aryl Magnesium Reagents in Toluene by Cl/Mg-Exchange

This excellent propensity of magnesium exchange reagent **170a** for undergoing chlorine-magnesium exchanges was used to explore the scope of such an almost unknown chlorine-magnesium exchange.[125] 2-Chloro-1,4-dimethoxybenzene (**179a**) was used as substrate and was submitted to various Grignard exchange reagents (Table 13). It was found that *i*PrMgCl·LiCl (**36**)[35a,b] or *s*Bu$_2$Mg·2LiCl (**81**)[35b] did not react with **179a**, even in the presence of TMEDA or PMDTA. Also, *s*BuMgOR·LiOR (**170a**, R = 2-ethylhexyl) gave no exchange under various conditions (entries 1–3). After extensive experimentations, it was found, that *s*Bu$_2$Mg·2LiOR (**170b**, 0.60 equiv) led to 48% of a chlorine-magnesium exchange affording a bis-magnesium reagent of type **180** after 1 h reaction time at 25 °C (entry 4). The addition of TMEDA (0.60 equiv) improved the conversion to 59% and the addition of PMDTA (0.60 equiv) instead of TMEDA further increased the conversion to 75% yield (entries 5 and 6).

Table 13: Chlorine-magnesium exchange on aryl chloride **179a** using various magnesium-exchange reagents.



179a **180a**

Entry	Mg-exchange reagent	Equiv	Additive	Yield (%)[a]
1	*i*PrMgCl·LiCl (**36**)	1.20	PMDTA	0 [0][b]
2	*s*Bu$_2$Mg·2LiCl (**81**)	0.60	PMDTA	0 [0][b]
3	*s*BuMgOR·LiOR (**170a**)	1.20	PMDTA	0 [0][b]
4	*s*Bu$_2$Mg·2LiOR (**170b**)	0.60	-	48
5	*s*Bu$_2$Mg·2LiOR (**170b**)	0.60	TMEDA	59
6	*s*Bu$_2$Mg·2LiOR(**170b**)	0.60	PMDTA	73 [20][c]

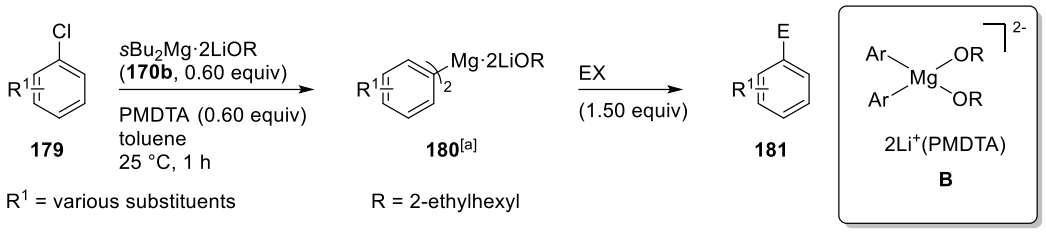
[a] Yield of **180a** determined by GC-analysis of water quenched reaction aliquots. [b] Yield obtained in toluene. [c] Yield obtained in THF.

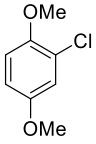
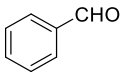
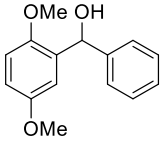
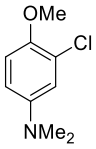
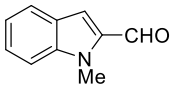
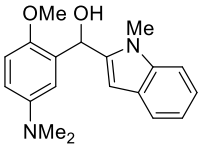
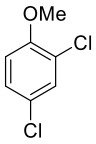
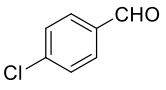
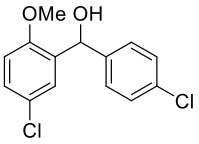
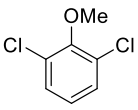
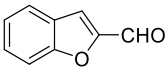
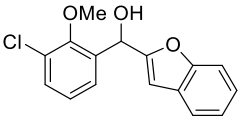
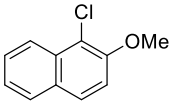
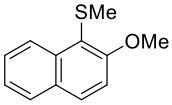
The addition of benzaldehyde (1.50 equiv) led to the alcohol **181a** in 61% yield (25 °C, 1 h; Table 14, entry 1). This chlorine-magnesium exchange was extended to a range of aryl chlorides bearing a methoxy group[126] in *ortho*-position. For all these substrates the chlorine-magnesium exchange was completed within 1 h at 25 °C and produced a diarylmagnesium species **180** of tentative structure **B**. Quenching with various electrophiles (1.50 equiv) furnished the expected products **181b**–**f** in 50–75%

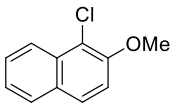
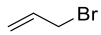
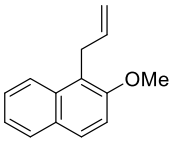
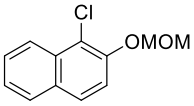
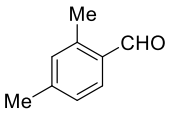
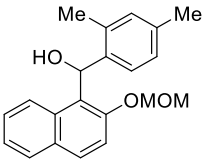
[126] This *o*-methoxy group facilitates the coordination of the magnesium exchange reagent (**170b**) and therefore accelerates the chlorine-magnesium exchange. Compare with: D. W. Slocum, E. A. Maulden, P. E. Whitley, T. K. Reinscheld, C. S. Jackson, J. B. Maddox, *Eur. J. Org. Chem.* **2017**, 6882.

yield (entries 2–6). In case of a stronger directing group such as MOM, the exchange reaction proceeded within 15 min at 25 °C and furnished after reaction with an aldehyde **181g** in 79% yield (entry 7).

Table 14: Chlorine-magnesium exchange for aryl chlorides of type **179** leading *via* intermediate organomagnesiums of type **180** to functionalized arenes of type **181.**



Entry	Arylchlorides	Electrophile (EX)	Product/Yield[b]
			
1	**179a**		**181a**, 61%
			
2	**179b**		**181b**, 70%
			
3	**179c**		**181c**, 50%
			
4	**179d**		**181d**, 70%
		$MeSO_2SMe$	
5	**179e**		**181e**, 62%

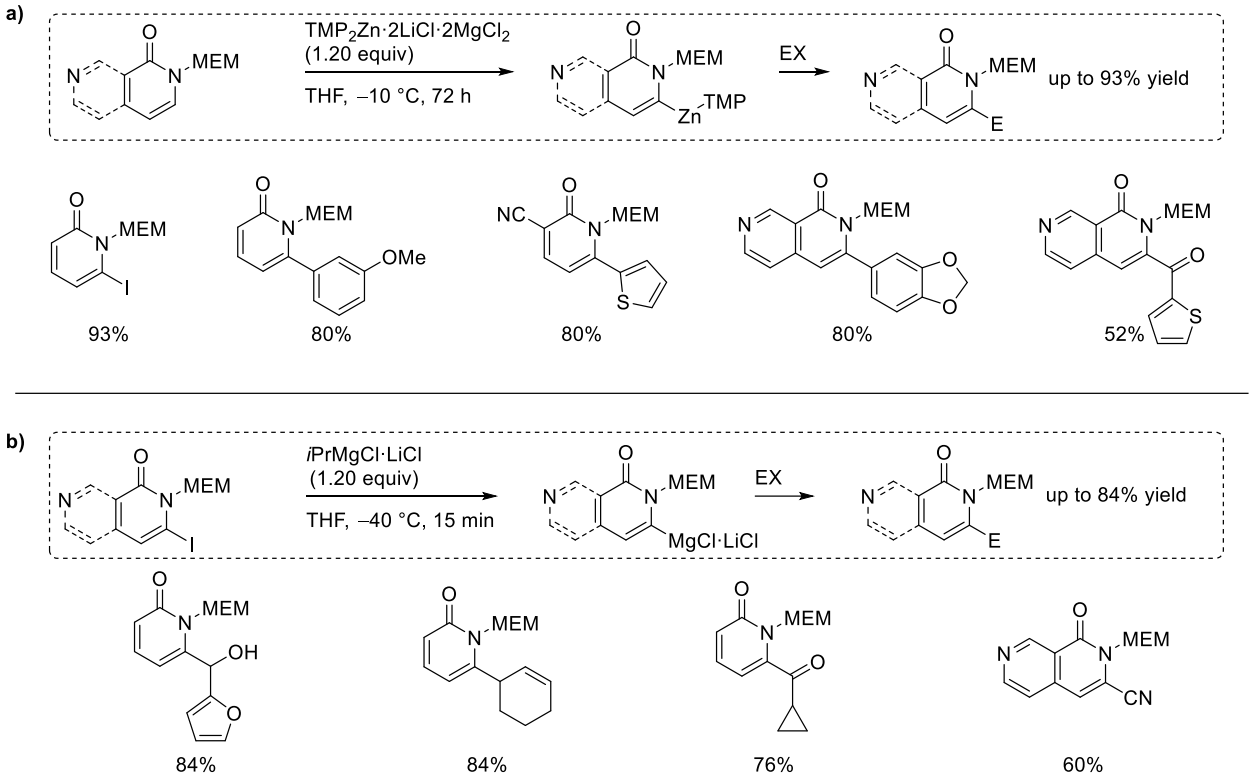
				
6	**179e**			**181f**, 75%[c]
				
7	**179f**			**181g**, 79%

[a] PMDTA has been omitted for the sake of clarity. [b] Yield of analytically pure isolated product. [c] 10% CuI was added.

4 Summary

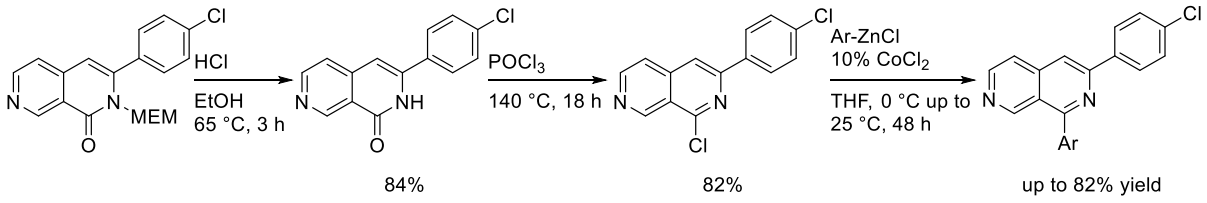
This work dealt with two different subjects: the first two topics were focused on the chemo- and regioselective functionalization of *N*- and *O*-containing heterocycles *via* directed metalation. The third topic dealt with the generation of new Grignard-reagents in non-polar solvents. First, 2-pyridones and 2,7-naphthyridones were metalated with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ under mild conditions (−10 °C, 72 h). The zincated intermediate could subsequently be quenched with various electrophiles affording functionalized 2-pyridones and 2,7-naphthyridones that are interesting synthetic scaffolds for the pharmaceutical industry. In addition, 2- and 4-pyrone and their derivatives such as methyl coumalate and 3,5-dibromo-2*H*-pyran-2-one were metalated and functionalized by using TMP-bases. Furthermore, the new exchange reagent *s*BuMgOR·LiOR (R = 2-ethylhexyl) was developed, which underwent extremely fast bromine-magnesium exchanges in toluene (30-110 times faster than previous exchange reagents), leading to new aryl and heteroaryl magnesium reagents with exceptional high reactivity. The new reagents ArMgOR·LiOR (R = 2-ethylhexyl) reacted with a wide range of electrophiles. Finally, the preparation of $sBu_2Mg \cdot 2LiOR$ (R = 2-ethylhexyl), which was the first reagent triggering a chlorine-magnesium exchange on electron-rich aryl chlorides, was reported. This method allowed the preparation of diarylmagnesium reagents ($Ar_2Mg \cdot 2LiOR$) in toluene.

4.1 Directed Zincation or Magnesiation of the 2-Pyridone and 2,7-Naphthyridone Scaffold using TMP-Bases



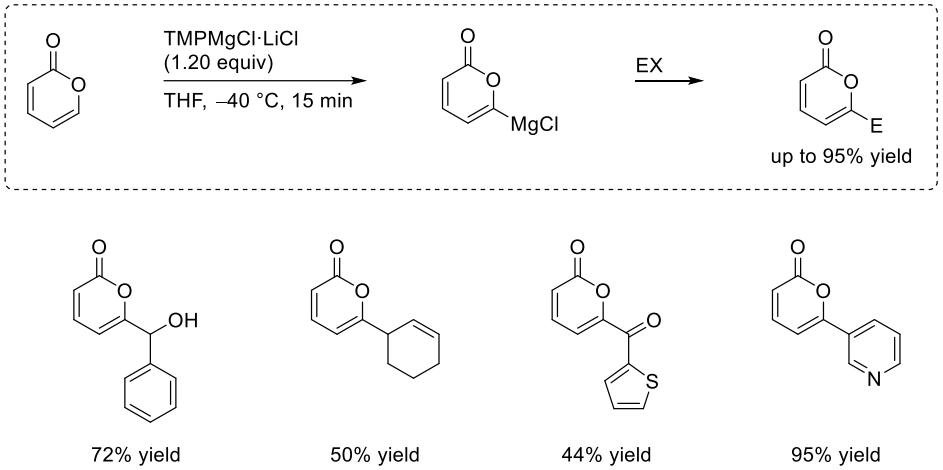
Scheme 35: a) Metalation of MEM-protected 2-pyridones and 2,7-naphthyridone using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$. b) Iodine-magnesium exchange of iodinated 2-pyridones and 2,7-naphthyridones.

A new and general method for the regioselective metalation of MEM-protected 2-pyridones as well as MEM-protected 2,7-naphthyridone using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ leading to a variety of new functionalized 2-pyridones and 2,7-naphthyridones was developed. Furthermore, an iodine-magnesium exchange of iodinated 2-pyridones and 2,7-naphthyridones using *i*PrMgCl·LiCl afforded magnesiated intermediates which reacted with a broad range of electrophiles. A second metalation of the 2-pyridone scaffold was achieved by using TMPMgCl·LiCl. Additionally, cobalt(II) chloride catalyzed cross-couplings of 1-chloro-2,7-naphthyridine with arylzinc halides led to the desired naphthyridines in satisfying yields.



Scheme 36: Preparation of a functionalized halonaphthyridine from naphthyridone and cobalt-catalyzed Negishi cross-couplings of chlorinated 2,7-naphthyridine.

4.2 Directed Zincation or Magnesiation of 2- and 4-Pyrones and their Derivatives

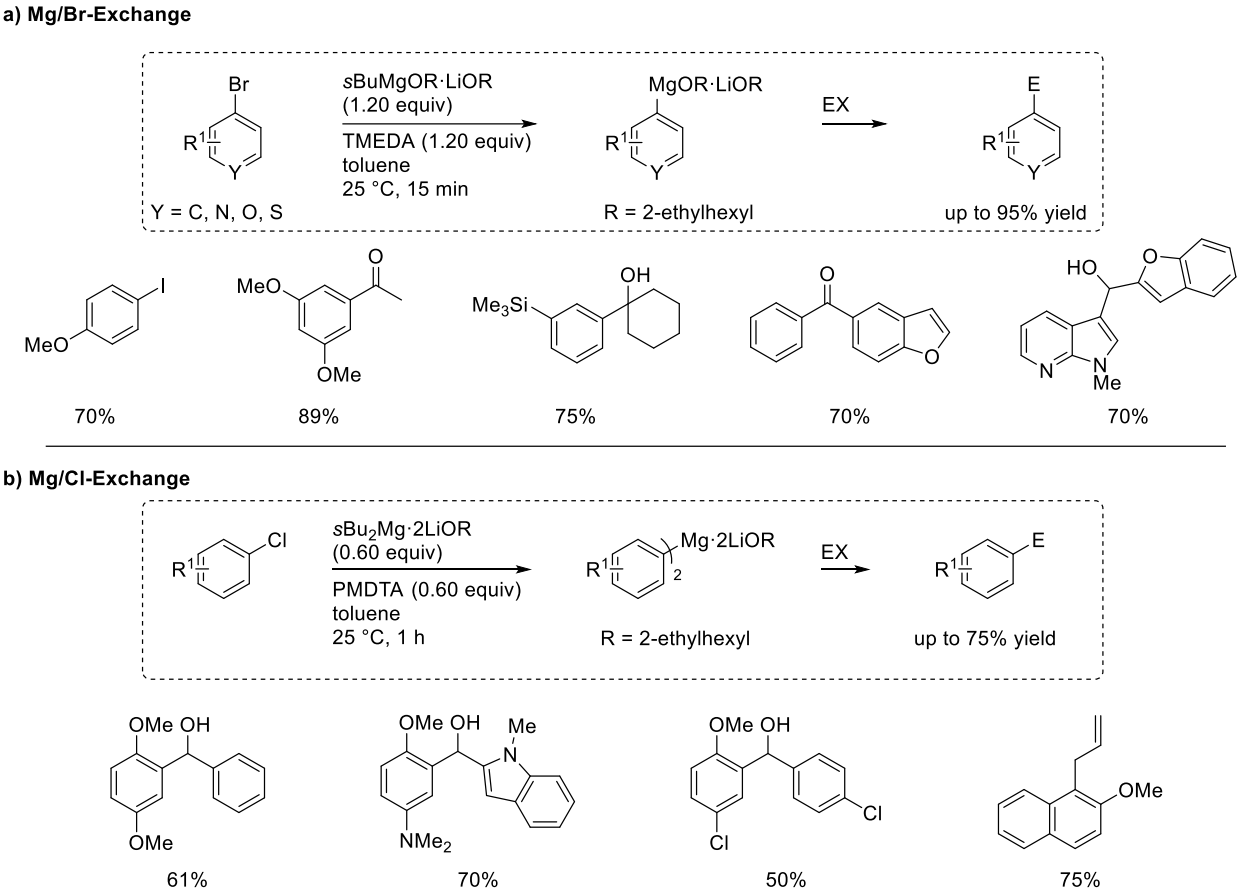


Scheme 37: Magnesiation of 2-pyrone leading to the metalated species followed by reactions with several electrophiles.

The regioselective metalation of 2-pyrone, methyl coumalate as well as the 3,5-dibrominated 2-pyrone using the reactive metal amides TMPMgCl·LiCl or TMPZnCl·LiCl was described. Electrophilic trapping led to a broad range of highly functionalized pyrones. After functionalization at the C(6)-position with various electrophiles, a selective magnesiation at the 3- or 5-position of the 2-pyrone heterocycle was achieved. As an extension of this project, the functionalization of the 4-pyrone scaffold in position 2 using TMP_2Zn 2LiCl $2MgCl_2$ was reported.

4.3 Generation of Aryl and Heteroaryl Magnesium Reagents in Toluene by Br/Mg- or Cl/Mg-Exchange

A method for preparing well soluble aryl and heteroaryl magnesium alkoxides complexed with one or two equivalents of lithium alkoxide (LiOR; R = 2-ethylhexyl) in toluene using the new exchange reagents *s*BuMgOR·LiOR and *s*Bu_2Mg·2LiOR was developed. These exchange reactions are ca. 30 times faster than the previous exchange reagent sBu_2Mg·2LiCl and ca. 110 times faster than *i*PrMgCl·LiCl (*turbo*-Grignard). Furthermore, the resulting Grignard reagent of type ArMgOR·LiOR or HetArMgOR·LiOR displayed an excellent reactivity in toluene adding well to ketones and opening epoxides and aziridines under mild conditions. Furthermore, *s*Bu_2Mg·2LiOR was able to trigger a chlorine-magnesium exchange leading to diarylmagnesium species (Ar_2Mg·2LiOR).



Scheme 38: a) Bromine-magnesium exchange of (hetero)aryl bromides leading *via* intermediate organomagnesiums to functionalized (hetero)arenes. b) Chlorine-magnesium exchange of aryl chlorides leading, *via* intermediate organomagnesiums, to functionalized arenes.

C. EXPERIMENTAL PART

1 General Considerations

1.1 Solvents

Solvents were dried according to standard procedures by distillation over drying agents as stated below and stored under argon. Otherwise they were obtained from commercial sources and used without further purification.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and then stored over molecular sieves.
PhMe was continuously refluxed and freshly distilled from sodium under nitrogen and stored over molecular sieves.
TMEDA and **PMDTA** were freshly distilled from calcium hydride under nitrogen.

Solvents for column chromatography were distilled prior to use.

1.2 Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid aldehydes and acyl chlorides were distilled prior to use.

TMPH was distilled prior to use and stored under argon.

***n*BuLi**, ***s*BuLi**, ***t*BuLi** solutions in hexane were purchased from Albemarle and the concentration was determined by titration against 1,10-phenanthroline in THF with *i*PrOH.[127]

***n*Bu$_2$Mg** solution in hexane was purchased from Albemarle and the concentration was determind by iodometric titration.[128]

Magnesium-2-ethylhexanolate was purchased from Albemarle and the concentration was determined by acidimetric titration.

***i*PrMgCl·LiCl (36)** solution in THF was obtained from Albemarle and the concentration was determind by iodometric titration.[128]

[127] H.-S. Lin, A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[128] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890.

CuCN·2LiCl[92] solution (1.00 M in THF) was prepared by drying CuCN (8.96 g, 100 mmol, 1.00 equiv) and LiCl (8.48 g, 200 mmol, 2.00 equiv) in a *Schlenk*-flask under vacuum for 5 h at 150 °C. After cooling to 25 °C, dry THF (100 mL) was added and stirred until the salts were dissolved.

$ZnCl_2$ solution (1.00 M in THF) was prepared by drying $ZnCl_2$ (27.3 g, 200 mmol) in a *Schlenk*-flask under vacuum for 5 h at 150 °C. After cooling to 25 °C, dry THF (200 mL) was added and stirred until the salts were dissolved.

Preparation of the reagent TMPMgCl·LiCl[42a] **(89)**

A dry and argon-flushed 500 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum, was charged with *i*PrMgCl·LiCl (**36**, 1.31 M in THF, 229 mL, 300 mmol, 1.00 equiv). Then, TMP-H (52.0 mL, 306 mmol, 1.02 equiv) was added and the mixture was stirred until gas evolution ceased (48 h). The freshly prepared TMPMgCl·LiCl (**89**) solution was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

Preparation of the reagent TMPZnCl·LiCl[84a] **(92)**

A dry and argon-flushed 500 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum, was charged with freshly distilled TMP-H (10.2 mL, 60 mmol, 1.00 equiv) dissolved in THF (60.0 mL). This solution was cooled to –40 °C and *n*BuLi (2.40 M in hexane, 25.0 mL, 60 mmol, 1.00 equiv) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm slowly to –10 °C for 1 h. $ZnCl_2$ (1.00 M in THF, 66.0 mL, 66 mmol, 1.10 equiv) was added dropwise and the resulting solution was stirred for 30 min at –10 °C and then for 30 min at 25 °C. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved. The freshly prepared TMPZnCl·LiCl (**92**) solution was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

Preparation of the reagent $TMP_2Zn·2MgCl_2·2LiCl$[64] **(93)**

A flame-dried and argon-flushed 500 mL *Schlenk*-flask, equipped with a magnetic stirring bar and rubber septum, was charged with a solution of TMPMgCl·LiCl (**89**, 1.20 M, 50.0 mL, 60 mmol, 1.00 equiv) and cooled to 0 °C. Then, $ZnCl_2$ (1.00 M in THF, 30.0 mL, 30 mmol, 0.50 equiv) was added over a period of 15 min. After stirring this mixture for 12 h at 25 °C, $TMP_2Zn·2MgCl_2·2LiCl$ (**93**) was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

1.3 Chromatography

Flash column chromatography was performed using silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck.

Thin layer chromatography was performed using aluminum plates covered with SiO_2 (Merck 60, F-254). The chromatograms were examined under UV light at 254 nm and/or by staining of the TLC plate with one of the solutions given below followed by heating with a heat gun:

- $KMnO_4$ stain: $KMnO_4$ (3.0 g), K_2CO_3 (20 g), 5% NaOH solution (5.00 mL), water (300 mL).
- Neat iodine absorbed on silica gel.

1.4 Analytical Data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments in $CDCl_3$. Chemical shifts are reported as δ-values in parts per million (ppm) relative to the residual solvent peak $CDCl_3$ (δH: 7.26; δC: 77.16), $(CD_3)_2CO$ (δH: 2.05; δC: 29.80), $(CD_3)_2SO$ (δH: 2.50; δC: 39.52) or C_6D_6 (δH: 7.16; δC: 128.06). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. If not otherwise noted, the coupling constants given are H-H-coupling constants for proton signals and C-F-coupling constants for carbon signals.

High resolution **Mass spectroscopy** (HR-MS) electron impact ionization (EI) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. EI was conducted with an electron energy of 70 eV. Electrospray ionization (ESI) spectra were recorded on a FINNIGAN LTQ FTICR instrument.

Gas chromatography (GC) was performed on machines of the types Hewlett-Packard 6890 or 5890 Series II (Hewlett Packard, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm; film thickness: 0.25 μm). The detection was accomplished using a flame ionization detector.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSamplIR II Diamond ATR sensor was used. Samples were measured neat. The absorption bands are reported in wavenumbers (cm^{-1}).

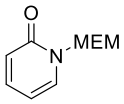
Melting points (M.p.) were determined on a BÜCHI B-540 apparatus and are uncorrected.

2 Directed Zincation or Magnesiation of the 2-Pyridone and 2,7-Naphthyridone Scaffold using TMP-Bases

2.1 Synthesis of Starting Material

Pyridine-2(1*H*)-one (**127**) was purchased from TCI. 3-Cyano-2(1*H*)-pyridinone was purchased from Sigma-Aldrich. 2,7-Naphthyridin-1(2*H*)-one (**128**) was prepared using known procedures.[129]

1-((2-Methoxyethoxy)methyl)pyridin-2(1*H*)-one (133)



According to a literature procedure,[130] in a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, pyridine-2(1*H*)-one (**127**, 4.00 g, 42 mmol, 1.00 equiv) was dissolved in THF (80 mL). NaH (1.21 g, 50 mmol, 1.20 equiv) was slowly added at 0 °C. The resulting mixture was stirred for 1 h, treated with MEMCl (7.20 mL, 63 mmol, 1.50 equiv) and stirred for 2 h at 0 °C. The solution was warmed to 25 °C, treated with water (50 mL) and the aq. layer was extracted with EtOAc (3 × 50 mL) and CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with sat. aq. NaCl solution and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **133** as a violet liquid (5.40 g, 30 mmol, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.40 (ddd, *J* = 6.9, 2.1, 0.6 Hz, 1H), 7.31 (ddd, *J* = 8.7, 6.5, 2.1 Hz, 1H), 6.53 (dt, *J* = 9.2, 0.9 Hz, 1H), 6.18 (td, *J* = 6.7, 1.3 Hz, 1H), 5.39 (s, 2H), 3.76–3.69 (m, 2H), 3.54–3.49 (m, 2H), 3.34 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.1, 140.2, 136.4, 121.4, 106.4, 77.2, 71.6, 69.0, 59.1.

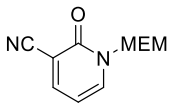
MS (EI, 70 eV): *m/z* (%) = 125 (52), 124 (11), 108 (30), 95 (100), 80 (47), 78 (33), 67 (15), 59 (10).

HRMS (EI): *m/z* calc. for [$C_9H_{14}NO_3$]: 184.0968; found: 184.0964 (M^+ + H).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3474, 2926, 2884, 2822, 1656, 1586, 1538, 1466, 1080, 868, 846, 766, 732.

[129] A. Zhang, C. Ding, C. Cheng, Q. Yao, *J. Comb. Chem*. **2007**, *9*, 916.
[130] N. H. Nguyen, C. Len, A.-S. Castanet, J. Mortier, *Beilstein J. Org. Chem.* **2011**,*7*, 1228.

1-((2-Methoxyethoxy)methyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (134)



According to a literature procedure,[130] in a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 3-cyano-2(1*H*)-pyridinone (4.00 g, 33 mmol, 1.00 equiv) was dissolved in THF (80 mL). NaH (0.96 g, 40 mmol, 1.20 equiv) was slowly added at 0 °C. The resulting mixture was stirred for 1 h, treated with MEMCl (5.69 mL, 50.0 mmol, 1.50 equiv) and stirred for 2 h at 0 °C. The solution was warmed to 25 °C, treated with water (50 mL) and the aq. layer was extracted with EtOAc (3 × 50 mL) and CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with sat. aq. NaCl solution and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **134** as a light-brown powder (5.15 g, 25 mmol, 74%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 (dd, *J* = 7.1, 2.1 Hz, 1H), 7.73 (dd, *J* = 6.9, 2.1 Hz, 1H), 6.32 (t, *J* = 7.0 Hz, 1H), 5.44 (s, 2H), 3.80–3.75 (m, 2H), 3.55–3.51 (m, 2H), 3.35 (s, 3H).

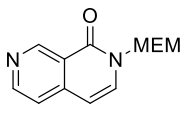
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.0, 147.8, 141.5, 115.4, 106.3, 105.7, 78.2, 71.5, 70.0, 59.2.

MS (EI, 70 eV): *m/z* (%) = 208 (13), 151 (10), 150 (33), 133 (35), 121 (35), 120 (23), 105 (45), 103 (26), 92 (13), 89 (41), 78 (19), 59 (100), 58 (33), 45 (39).

HRMS (EI): *m/z* calc. for [$C_{10}H_{12}N_2O_3$]: 208.0848; found: 208.0843 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3524, 2930, 2886, 2822, 2228, 1654, 1598, 1546, 1468, 1258, 1098, 1084, 860, 766.

2-((2-Methoxyethoxy)methyl)-2,7-naphthyridin-1(2*H*)-one (135)



According to a literature procedure,[131] in a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 2,7-naphthyridone (**128**, 260 mg, 1.8 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (50 mL). Diisopropylethylamin (0.51 mL, 3.7 mmol, 2.05 equiv) and MEMCl

[131] Smith, A. B.; Freeze, B. S., LaMarche, M. J.; Hirose, T.; Brouard, I.; Xian, M.; Sundermann, K.F.; Shaw, S. J.; Burlingame, M. A.; Horwitz, S. B.; Myles, D. C. *Org. Lett.* **2005**, *7*, 315.

(0.40 mL, 3.5 mmol, 1.95 equiv) were added at room temperature and the mixture was stirred for 12 h. The reaction mixture was poured into sat. aq. $NaHCO_3$ solution (100 mL) and the aq. phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with sat. aq. NaCl solution and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **135** as a light-brown powder (142 mg, 0.61 mmol, 34%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.55 (s, 1H), 8.69 (d, *J* = 5.4 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.32 (dd, *J* = 5.5, 0.8 Hz, 1H), 6.45 (dd, *J* = 7.4, 0.6 Hz, 1H), 5.45 (s, 2H), 3.76–3.71 (m, 2H), 3.52–3.48 (m, 2H), 3.32 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.0, 151.4, 151.1, 142.8, 135.5, 121.1, 119.2, 104.6, 76.9, 71.6, 69.0, 59.1.

MS (EI, 70 eV): *m/z* (%) = 234 (7), 176 (61), 175 (28), 160 (22), 159 (84), 147 (36), 146 (100), 129 (11), 128 (53), 84 (20), 77 (12), 59 (77), 57 (12), 46 (12), 45 (19).

HRMS (EI): *m/z* calc. for [$C_{12}H_{14}N_2O_3$]: 234.1004; found: 234.1011 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 3045, 2926, 2885, 1667, 1625, 1082, 1050, 844, 757.

M.p. (°C): 85 °C.

2.2 Typical Procedures (TP)

Typical procedure for the zincation of 2-pyridone 133 and 3-cyano-2-pyridone 134 using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (93) (TP1):

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 2-pyridone **133** or 3-cyano-2-pyridone **134** (1.00 equiv) were dissolved in dry THF (0.50 M solution). After the solution was cooled to −10 °C, $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 1.20 equiv) was added and the mixture was stirred at the same temperature. The completion of the metalation was achieved after 72 h, stated by TLC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF. Subsequent reactions with electrophiles were carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 20 mL) if not noted differently. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash-column chromatography.

Typical procedure for the zincation of 2,7-naphthyridone 135 using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (93) (TP2):

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 2,7-naphthyridone **135** (1.00 equiv) was dissolved in dry THF (0.50 M solution). After the solution was cooled to −10 °C, $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 1.20 equiv) was added and the mixture was stirred at the same temperature. The completion of the metalation was achieved after 72 h, stated by TLC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF. Subsequent reactions with electrophiles were carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 20 mL) if not noted differently. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash-column chromatography.

Typical procedure for the I/Mg-exchange of 6-iodo-2-pyridone (137a) using *i*PrMgCl·LiCl (36) (TP3):

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 2-pyridone **137a** (1.00 equiv) was dissolved in dry THF (0.50 M solution) and was cooled to −40 °C. *i*PrMgCl·LiCl (**36**, 1.20 equiv) was added dropwise and the mixture was stirred at the same temperature for 30 min. The completion of the exchange reaction was checked by TLC-analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution. Subsequent reactions with electrophiles were carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 20 mL) if not noted differently. The combined organic extracts

were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash-column chromatography.

Typical procedure for the I/Mg-exchange of 3-iodo-2,7-naphthyridone (141a) using *i*PrMgCl·LiCl (36) (TP4):

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 2,7-naphthyridon **141a** (1.00 equiv) was dissolved in dry THF (0.50 M solution) and was cooled to 0 °C. A solution of *i*PrMgCl·LiCl (**36**, 1.20 equiv) was added dropwise and the mixture was stirred at the same temperature. The completion of the exchange reaction was checked by TLC-analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution. Subsequent reactions with electrophiles were carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 20 mL) if not noted differently. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash-column chromatography.

Preparation of Zinc reagents (152a–c):[94]

LiCl (1.10 equiv) was dried under high vacuum and allowed to cool to room temperature, then Mg turnings (1.20 equiv), $ZnCl_2$ solution (1.00 M THF, 1.10 equiv) and THF (1.00 M, solution relating to the aryl bromide) were added. The reaction mixture was cooled to 0 °C and the corresponding aryl bromide (1.00 equiv) was added dropwise. The reaction was stirred until iodolysis of a reaction aliquot indicated full consumption of the starting material.

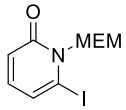
Typical Procedure (TP5) for the Cobalt-Catalyzed Cross-Couplings of Organozionc Reagents:[94]

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with dry $CoCl_2$ (10 mol %) and dry THF (1 mL). 1-Chloro-3-(4-chlorophenyl)-2,7-naphthyridine (**151**, 0.30 mmol, 1.00 equiv) was added at room temperature. Then, a solution of the appropriate zinc reagent (**152a**–**c**, 0.45 mmol, 1.50 equiv) was added dropwise over 15 min *via* syringe at 0 °C. The reaction was stirred and monitored by GC-MS-analysis (Undecane was used as an internal standard). Upon consumption of the starting material, sat. aq. NH_4Cl solution (2 mL) and EtOAc (2 mL) were added, the phases were separated and the aq. phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography on silica yielding the respective title compounds.

2.3 Directed Zincation of the 2-Pyridone and 2,7-Naphthyridone Scaffold with $TMP_2Zn·2MgCl_2·2LiCl$ (93)

2.3.1 Reaction of Zincated 2-Pyridone with Electrophiles

6-Iodo-1-((2-methoxyethoxy)methyl)pyridin-2(1*H*)-one (137a)



According to **TP1**, 2-pyridone **133** (92 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn·2MgCl_2·2LiCl$ (**93**, 0.36 M in THF, 1.67 mL, 0.60 mmol, 1.20 equiv). Iodine (152 mg, 0.60 mmol, 1.20 equiv) dissolved in dry THF (1 mL) was then added dropwise at −10 °C. The reaction was stirred for 30 min. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with EtOAc (3 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **137a** as a lightly brown solid (145 mg, 0.47 mmol, 93%).

Scale-up:

According to **TP1**, 2-pyridone **133** (549 mg, 3.00 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn·2MgCl_2·2LiCl$ (**93**, 0.36 M in THF, 10.0 mL, 3.60 mmol, 1.20 equiv). Iodine (914 mg, 3.60 mmol, 1.20 equiv) dissolved in dry THF (3 mL) was then added dropwise at −10 °C. The reaction was stirred for 30 min. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (20 mL), extracted with EtOAc (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **137a** as a lightly brown solid (832 mg, 2.60 mmol, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.93 (dd, *J* = 9.1, 7.0 Hz, 1H), 6.80 (dd, *J* = 7.0, 1.2 Hz, 1H), 6.48 (dd, *J* = 9.2, 1.2 Hz, 1H), 5.71 (s, 2H), 3.79–3.76 (m, 2H), 3.56–3.53 (m, 2H), 3.37 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.9, 140.0, 136.3, 121.3, 106.2, 76.7, 71.5, 68.9, 59.0.

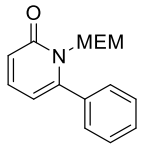
MS (EI, 70 eV): *m/z* (%) = 309 (1), 251 (24), 250 (13), 234 (22), 222 (59), 221 (100), 94 (12), 79 (17), 59 (22).

HRMS (EI): *m/z* calc. for [$C_9H_{13}INO_3$]: 309.9935 found: 309.9933 (M^+ + H).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2906, 2886, 1644, 1574, 1500, 1450, 1350, 1130, 1084, 904, 850, 786.

M.p. (°C): 96–98.

1-((2-Methoxyethoxy)methyl)-6-phenylpyridin-2(1*H*)-one (137b)



According to **TP1**, 2-pyridone **133** (92 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.36 M in THF, 1.67 mL, 0.60 mmol, 1.20 equiv) at −10 °C. $Pd(dba)_2$ (12 mg, 4 mol%), $P(2\text{-furyl})_3$ (9.0 mg, 8 mol%) and iodobenzene (122 mg, 0.60 mmol, 1.20 equiv) were added at −10 °C and the resulting mixture was stirred for 12 h at 25 °C. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **137b** as a brown liquid (118 mg, 0.47 mmol, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.53–7.47 (m, 2H), 7.46–7.40 (m, 3H), 7.33 (dd, *J* = 9.2, 6.8 Hz, 1H), 6.57 (dd, *J* = 9.2, 1.3 Hz, 1H), 6.06 (dd, *J* = 6.8, 1.3 Hz, 1H), 5.28 (s, 2H), 3.81–3.75 (m, 2H), 3.55–3.48 (m, 2H), 3.34 (s, 3H).

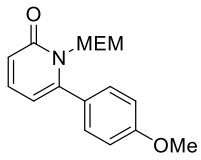
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.0, 150.6, 139.7, 135.0, 129.4, 129.3, 128.4, 119.9, 108.3, 74.3, 71.9, 69.0, 59.0.

MS (EI, 70 eV): *m/z* (%) = 259 (1), 201 (29), 200 (12), 184 (62), 183 (13), 172 (63), 171 (100), 156 (13), 154 (27), 143 (28), 131 (11), 128 (11), 127 (12), 115 (12), 77 (13), 59 (61).

HRMS (EI): *m/z* calc. for [$C_{15}H_{17}NO_3$]: 259.1208; found: 259.1195 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3448, 2928, 2888, 1654, 1582, 1538, 1468, 1080, 868, 846, 768.

1-((2-Methoxyethoxy)methyl)-6-(4-methoxyphenyl)pyridin-2(1*H*)-one (137c)



According to **TP1**, 2-pyridone **133** (92 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.36 M in THF, 1.67 mL, 0.60 mmol, 1.20 equiv) at −10 °C. $Pd(dba)_2$ (12 mg, 4 mol%), P(2-furyl)$_3$ (9.0 mg, 8 mol%) and 1-iodo-4-methoxybenzene (140 mg, 0.60 mmol, 1.20 equiv) were added at −10 °C and the resulting mixture was stirred for 12 h at 25 °C. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **137c** as a brown liquid (95 mg, 0.33 mmol, 66%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32–7.26 (m, 2H), 7.06 (dd, *J* = 2.4, 1.7 Hz, 1H), 7.01 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.94 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.53 (dd, *J* = 9.2, 1.3 Hz, 1H), 6.04 (dd, *J* = 6.8, 1.3 Hz, 1H), 5.25 (s, 2H), 3.80 (s, 3H), 3.79–3.76 (m, 2H), 3.50–3.46 (m, 2H), 3.28 (s, 3H).

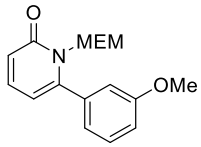
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.1, 160.4, 150.6, 139.6, 130.7, 127.3, 119.4, 113.7, 108.3, 74.3, 71.8, 68.9, 58.9, 55.4.

MS (EI, 70 eV): *m/z* (%) = 214 (39), 202 (25), 201 (100), 173 (11), 158 (19).

HRMS (EI): *m/z* calc. for [$C_{16}H_{19}NO_4$]: 289.1314; found: 289.1296 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2960, 2930, 1654, 1578, 1548, 1486, 1450, 1294, 1230, 1088, 1080, 1036, 840, 802, 792, 710.

1-((2-Methoxyethoxy)methyl)-6-(3-methoxyphenyl)pyridin-2(1*H*)-one (137d)



According to **TP1**, 2-pyridone **133** (92 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.36 M in THF, 1.67 mL, 0.60 mmol, 1.20 equiv) at −10 °C. $Pd(dba)_2$ (12 mg, 4 mol%), P(2-furyl)$_3$ (9.0 mg, 8 mol%) and 1-iodo-3-methoxybenzene (140 mg, 0.60 mmol, 1.20 equiv) were added at −10 °C and the resulting mixture was stirred for 12 h at 25 °C. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **137d** as a brown liquid (101 mg, 0.35 mmol, 70%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.30–7.22 (m, 2H), 7.03 (dd, *J* = 2.4, 1.7 Hz, 1H), 6.98 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.91 (ddd, *J* = 8.3, 2.6, 0.9 , 1H), 6.50 (dd, *J* = 9.2, 1.4 Hz, 1H), 6.02 (dd, *J* = 6.8, 1.4 Hz, 1H), 5.22 (s, 2H), 3.79–3.72 (m, 5H), 3.48–3.42 (m, 2H), 3.26 (s, 3H).

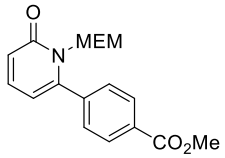
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 163.9, 159.2, 150.4, 139.6, 136.0, 129.4, 121.4, 119.7, 115.5, 114.6, 108.0, 74.3, 71.8, 69.0, 58.8, 55.3.

MS (EI, 70 eV): *m/z* (%) = 289 (1), 231 (36), 215 (10), 214 (69), 202 (57), 201 (100), 200 (33), 171 (11), 59 (38).

HRMS (EI): *m/z* calc. for [$C_{16}H_{19}NO_4$]: 289.1314; found: 289.1296 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932, 2838, 1654, 1608, 1506, 1456, 1292, 1248, 1080, 1028, 836, 800.

Methyl 4-(1-((2-methoxyethoxy)methyl)-6-oxo-1,6-dihydropyridin-2-yl)benzoate (137e)



According to **TP1**, 2-pyridone **133** (92 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.36 M in THF, 1.67 mL, 0.60 mmol, 1.20 equiv) at −10 °C. $Pd(dba)_2$ (12 mg, 4 mol%), P(2-furyl)$_3$ (9.0 mg, 8 mol%) and methyl 4-iodobenzoate (157 mg, 0.60 mmol, 1.20 equiv) were added at −10 °C and the resulting mixture was stirred for 12 h at 25 °C. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **137e** as a brown liquid (127 mg, 0.40 mmol, 80%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.12–8.04 (m, 2H), 7.58 (dd, *J* = 8.7, 0.8 Hz, 2H), 7.33 (ddd, *J* = 9.2, 6.8, 0.8 Hz, 1H), 6.58 (dd, *J* = 9.2, 1.3 Hz, 1H), 6.05 (dd, *J* = 6.8, 1.3 Hz, 1H), 5.23 (s, 2H), 3.93 (s, 3H), 3.79–3.73 (m, 2H), 3.51–3.46 (m, 2H), 3.32 (s, 3H).

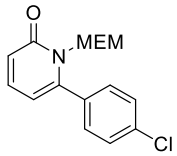
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 166.5, 163.8, 149.4, 139.5, 139.1, 131.0, 129.6, 129.4, 120.5, 108.4, 74.3, 71.8, 69.0, 59.0, 52.4.

MS (EI, 70 eV): *m/z* (%) = 286 (10), 259 (23), 242 (40), 241 (13), 230 (69), 229 (100), 198 (23), 154 (11), 89 (12), 59 (45).

HRMS (EI): *m/z* calc. for [$C_{17}H_{19}NO_5$]: 317.1263; found: 317.1277 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2886, 1722, 1660, 1586, 1548, 1436, 1276, 1102, 1084, 1022, 802, 772, 704.

6-(4-Chlorophenyl)-1-((2-methoxyethoxy)methyl)pyridin-2(1*H*)-one (137f)



According to **TP1**, 2-pyridone **133** (92 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.36 M in THF, 1.67 mL, 0.60 mmol, 1.20 equiv) at −10 °C. $Pd(dba)_2$ (12 mg, 4 mol%), $P(2\text{-furyl})_3$ (9.0 mg, 8 mol%) and 1-iodo-4-chlorobenzene (143 mg, 0.60 mmol, 1.20 equiv) were added at −10 °C and the resulting mixture was stirred for 12 h at 25 °C. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **137f** as a brown liquid (129 mg, 0.44 mmol, 88%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.50–7.44 (m, 2H), 7.44–7.39 (m, 2H), 7.32 (dd, *J* = 9.2, 6.8 Hz, 1H), 6.58 (dd, *J* = 9.2, 1.3 Hz, 1H), 6.04 (dd, *J* = 6.8, 1.3 Hz, 1H), 5.25 (s, 2H), 3.83–3.76 (m, 2H), 3.54–3.48 (m, 2H), 3.34 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 163.9, 149.4, 139.6, 135.8, 133.3, 130.8, 128.7, 120.3, 108.4, 74.3, 71.9, 69.0, 59.0.

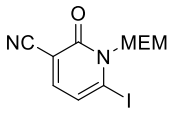
MS (EI, 70 eV): *m/z* (%) = 293 (1), 237 (15), 236 (11), 235 (51), 234 (16), 220 (18), 219 (64), 217 (13), 208 (27), 207 (57), 206 (97), 205 (77), 205 (100), 190 (17), 188 (20), 183 (33), 177 (21), 154 (12), 89 (26), 59 (99).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}ClNO_3$]: 293.0819; found: 293.0809 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 2880, 1658, 1596, 1548, 1488, 1088, 1016, 836, 798.

2.3.2 Reaction of Zincated 3-Cyano-2-pyridone with Electrophiles

6-Iodo-1-((2-methoxyethoxy)methyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (139a)



According to **TP1**, 3-cyano-2-pyridone **134** (104 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.36 M in THF, 1.67 mL, 0.60 mmol, 1.20 equiv) at −10 °C. Iodine (152 mg, 0.60 mmol, 1.20 equiv) dissolved in dry THF (1 mL) was then added dropwise at −10 °C. The reaction was stirred for 30 min. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with EtOAc (3 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **139a** as a lightly brown solid (116 mg, 0.40 mmol, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 (d, *J* = 7.2 Hz, 1H), 6.48 (d, *J* = 7.3 Hz, 1H), 5.66 (s, 2H), 3.83–3.80 (m, 2H), 3.55–3.52 (m, 2H), 3.34 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.1, 147.3, 121.2, 116.5, 112.3, 102.5, 77.7, 71.7, 70.2, 59.2.

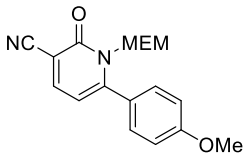
MS (EI, 70 eV): *m/z* (%) = 334 (5), 276 (34), 259 (37), 247 (60), 246 (45), 132 (10), 104 (17), 89 (77), 64 (16), 59 (100), 58 (12), 45 (25).

HRMS (EI): *m/z* calc. for [$C_{10}H_{11}IN_2O_3$]: 333.9814; found: 333.9810 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3090, 2926, 2882, 2228, 1652, 1594, 1548, 1450, 1270, 1240, 1154, 1098, 870, 778, 758.

M.p. (°C): 108–110.

1-((2-Methoxyethoxy)methyl)-6-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (139b)



According to **TP1**, 3-cyano-2-pyridone **134** (104 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.36 M in THF, 1.67 mL, 0.60 mmol, 1.20 equiv) at −10 °C. $Pd(dba)_2$ (12 mg, 4 mol%), P(2-furyl)$_3$ (9.0 mg, 8 mol%) and 1-iodo-4-methoxybenzene (140 mg, 0.60 mmol, 1.20 equiv) were added at −10 °C and the resulting mixture was stirred for 12 h at 25 °C. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **139b** as a lightly brown liquid (106 mg, 0.34 mmol, 68%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.79 (d, *J* = 7.4, 1H), 7.53–7.46 (m, 2H), 7.02–6.96 (m, 2H), 6.18 (d, *J* = 7.4, 1H), 5.31 (s, 2H), 3.94–3.89 (m, 2H), 3.87 (s, 3H), 3.59–3.51 (m, 2H), 3.36 (s, 3H).

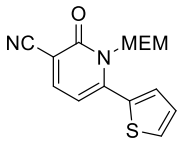
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 161.5, 161.4, 156.8, 146.8, 130.6, 125.9, 115.9, 114.3, 107.9, 103.7, 75.7, 71.9, 70.0, 59.1, 55.6.

MS (EI, 70 eV): *m/z* (%) = 314 (3), 256 (15), 239 (20), 227 (27), 226 (100), 89 (28), 61 (13), 59 (47), 45 (11), 43 (60).

HRMS (EI): *m/z* calc. for [$C_{17}H_{18}N_2O_4$]: 314.1267; found: 314.1255 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3524, 2930, 2886, 2822, 2228, 1654, 1598, 1546, 1468, 1258, 1098, 1084, 860, 766.

1-((2-Methoxyethoxy)methyl)-2-oxo-6-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile (139c)



According to **TP1**, 3-cyano-2-pyridone **134** (104 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.36 M in THF, 1.67 mL, 0.60 mmol, 1.20 equiv) at −10 °C. $Pd(dba)_2$ (12 mg, 4 mol%), P(2-furyl)$_3$ (9.0 mg, 8 mol%) and 2-iodothiophene (126 mg, 0.60 mmol, 1.20 equiv) were added at −10 °C and the resulting mixture was stirred for 12 h at 25 °C.

The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **139c** as a yellow liquid (116 mg, 0.40 mmol, 80%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.84–7.71 (m, 2H), 7.54 (dt, *J* = 5.1, 1.0 Hz, 1H), 7.16 (ddd, *J* = 5.1, 3.7, 0.8 Hz, 1H), 6.45–6.35 (m, 1H), 5.48 (s, 2H), 4.02–3.91 (m, 2H), 3.64–3.54 (m, 2H), 3.37 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 161.4, 149.4, 146.4, 133.6, 131.9, 129.9, 128.6, 115.7, 108.7, 104.0, 75.4, 71.8, 70.0, 59.1.

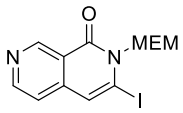
MS (EI, 70 eV): *m/z* (%) = 290 (3), 232 (19), 215 (15), 203 (21), 202 (100), 89 (20), 59 (30).

HRMS (EI): *m/z* calc. for [$C_{14}H_{14}N_2O_3S$]: 290.0725; found: 290.0720 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3096, 2926, 2880, 2226, 1656, 1544, 1450, 1328, 1078, 846, 778, 714.

2.3.3 Reaction of Zincated 2,7-Naphthyridone with Electrophiles

3-Iodo-2-((2-methoxyethoxy)methyl)-2,7-naphthyridin-1(2*H*)-one (141a)



According to **TP2**, 2,7-naphthyridone **135** (60 mg, 0.26 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.27 M in THF, 1.15 mL, 0.31 mmol, 1.20 equiv). Iodine (132 mg, 0.52 mmol, 1.20 equiv) dissolved in dry THF (2 mL) was then added dropwise at −10 °C. The resulting mixture was allowed to warm up to room temperature and was further stirred for 30 min. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with EtOAc (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **141a** as a brown crystalline solid (86 mg, 0.24 mmol, 92%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.52 (s, 1H), 8.73 (d, *J* = 5.4 Hz, 1H), 7.18 (d, *J* = 6.4 Hz, 1H), 7.15 (s, 1H), 5.79 (s, 2H), 3.82–3.77 (m, 2H), 3.57–3.53 (m, 2H), 3.35 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 161.7, 152.1, 152.0, 142.8, 120.2, 118.5, 117.5, 99.7, 80.7, 71.7, 69.1, 59.2.

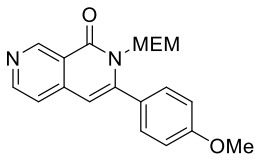
MS (EI, 70 eV): *m/z* (%) = 360 (3), 302 (14), 285 (16), 272 (39), 232 (13), 159 (11), 158 (17), 24 (145), 89 (88), 59 (100).

HRMS (EI): *m/z* calc. for [$C_{12}H_{13}IN_2O_3$]: 359.9971; found: 359.9983 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3080, 2953, 2921, 1662, 1597, 1197, 1088, 1036, 871, 789.

M.p. (°C): 120.

2-((2-Methoxyethoxy)methyl)-3-(4-methoxyphenyl)-2,7-naphthyridin-1(2*H*)-one (141b)



According to **TP2**, 2,7-naphthyridone **135** (60 mg, 0.26 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.27 M in THF, 1.15 mL, 0.31 mmol, 1.20 equiv). A solution of $Pd(dba)_2$ (6.00 mg, 4 mol%), P(2-furyl)$_3$ (5.00 mg, 8 mol%) and 1-iodo-4-methoxybenzene

(72 mg, 0.31 mmol, 1.20 equiv) in dry THF (1 mL) was added at −10 °C. The resulting mixture was allowed to warm up to room temperature and was further stirred for 12 h. The crude product was purified by column chromatography (*i*hex/EtOAc = 2:8) to give the title compound **141b** as a yellowish solid (72 mg, 0.21 mmol, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.56 (s, 1H), 8.68 (d, *J* = 5.1 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 5.1 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.33 (s, 1H), 5.32 (s, 2H), 3.85 (s, 3H), 3.81–3.74 (m, 2H), 3.55–3.47 (m, 2H), 3.32 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.2, 160.7, 151.2, 150.6, 149.9, 142.5, 130.7, 127.0, 120.0, 119.1, 113.9, 106.1, 74.3, 71.9, 69.1, 59.0, 55.5.

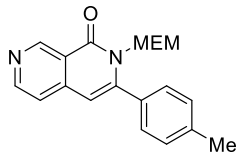
MS (EI, 70 eV): *m/z* (%) = 340 (10), 265 (55), 253 (38), 252 (100), 89 (12), 59 (43).

HRMS (EI): *m/z* calc. for [$C_{19}H_{20}N_2O_4$]: 340.1423; found: 340.1416 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3077, 2913, 2854, 1660, 1606, 1510, 1299, 1091, 947, 786.

M.p. (°C): 84–86.

2-((2-Methoxyethoxy)methyl)-3-(p-tolyl)-2,7-naphthyridin-1(2*H*)-one (141c)



According to **TP2**, 2,7-naphthyridone **135** (117 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.20 M in THF, 3.00 mL, 0.60 mmol, 1.20 equiv). A solution of $Pd(dba)_2$ (12 mg, 4 mol%), P(2-furyl)$_3$ (9.0 mg, 8 mol%) and 1-iodo-4-methylbenzene (131 mg, 0.60 mmol, 1.20 equiv) in dry THF (1 mL) was added at −10 °C. The resulting mixture was allowed to warm up to room temperature and was further stirred for 12 h. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **141c** as a yellow solid (135 mg, 0.42 mmol, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.55 (s, 1H), 8.66 (d, *J* = 5.4 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.27–7.21 (m, 3H), 6.30 (s, 1H), 5.29 (s, 2H), 3.75–3.71 (m, 2H), 3.50–3.45 (m, 2H), 3.29 (s, 3H), 2.38 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.1, 151.5, 151.1, 149.7, 142.1, 139.7, 131.8, 129.1, 129.1, 120.0, 118.9, 106.0, 74.1, 71.8, 68.9, 58.9, 21.4.

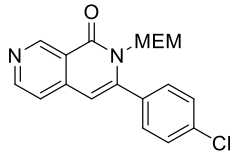
MS (EI, 70 eV): *m/z* (%) = 324 (4), 266 (13), 249 (59), 236 (100), 89 (10), 59 (39).

HRMS (EI): *m/z* calc. for [$C_{19}H_{20}N_2O_3$]: 324.1474; found: 324.1473 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3077, 2912, 2867, 1662, 1618, 1544, 1093, 1008, 882, 813.

M.p. (°C): 56–58.

3-(4-Chlorophenyl)-2-((2-methoxyethoxy)methyl)-2,7-naphthyridin-1(2*H*)-one (141d)



According to **TP2**, 2,7-naphthyridone **135** (117 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.20 M in THF, 3.00 mL, 0.60 mmol, 1.20 equiv). A solution of $Pd(dba)_2$ (12 mg, 4 mol%), P(2-furyl)$_3$ (9.0 mg, 8 mol%) and 1-chloro-4-iodobenzene (143 mg, 0.60 mmol, 1.20 equiv) in dry THF (1 mL) was added at −10 °C. The resulting mixture was allowed to warm up to room temperature and was further stirred for 12 h. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **141d** as a yellow crystalline solid (148 mg, 0.43 mmol, 86%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.58 (s, 1H), 8.71 (d, *J* = 5.5 Hz, 1H), 7.54–7.48 (m, 2H), 7.46–7.42 (m, 2H), 7.31 (dd, *J* = 5.5, 0.8 Hz, 1H), 6.33 (s, 1H), 5.29 (s, 2H), 3.80–3.74 (m, 2H), 3.53–3.47 (m, 2H), 3.32 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 163.0, 151.4, 151.1, 148.6, 142.2, 136.1, 133.1, 130.7, 128.8, 120.2, 119.1, 106.4, 74.2, 71.9, 69.1, 59.0.

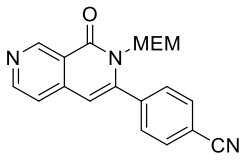
MS (EI, 70 eV): *m/z* (%) = 344 (4), 286 (22), 269 (35), 256 (87), 234 (35), 89 (39), 59 (100).

HRMS (EI): *m/z* calc. for [$C_{18}H_{17}ClN_2O_3$]: 344.0928; found: 344.0924 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 2917, 2871, 1657, 1618, 1092, 1008, 946, 881, 820.

M.p. (°C): 102.

4-(2-((2-Methoxyethoxy)methyl)-1-oxo-1,2-dihydro-2,7-naphthyridin-3-yl)benzonitrile (141e)



According to **TP2**, 2,7-naphthyridone **135** (117 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.20 M in THF, 3.00 mL, 0.60 mmol, 1.20 equiv). A solution of $Pd(dba)_2$ (12 mg, 4 mol%), P(2-furyl)$_3$ (9.0 mg, 8 mol%) and 4-iodobenzonitrile (137 mg, 0.60 mmol, 1.20 equiv) in dry THF (1 mL) was added at −10 °C. The resulting mixture was allowed to warm up to room temperature and was further stirred for 12 h. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **141e** as a yellow crystalline solid (124 mg, 0.37 mmol, 74%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.61 (s, 1H), 8.76 (s, 1H), 7.77 (d, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 5.2 Hz, 1H), 6.35 (s, 1H), 5.28 (s, 2H), 3.79–3.76 (m, 2H), 3.51–3.48 (m, 2H), 3.32 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.7, 151.3, 151.2, 147.8, 142.0, 138.9, 132.3, 130.2, 120.3, 119.3, 118.1, 113.8, 106.7, 74.2, 71.8, 69.1, 59.1.

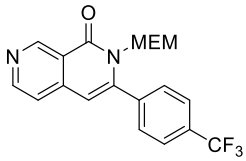
MS (EI, 70 eV): *m/z* (%) = 335 (2), 277 (20), 260 (39), 247 (61), 230 (13), 89 (55), 59 (100).

HRMS (EI): *m/z* calc. for [$C_{19}H_{17}N_3O_3$]: 335.1270; found: 335.1261 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3080, 3046, 2926, 2361, 2231, 1650, 1622, 1103, 1082, 850, 792.

M.p. (°C): 106–108.

2-((2-Methoxyethoxy)methyl)-3-(4-(trifluoromethyl)phenyl)-2,7-naphthyridin-1(2*H*)-one (141f)



According to **TP2**, 2,7-naphthyridone **135** (117 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.20 M in THF, 3.00 mL, 0.60 mmol, 1.20 equiv). A solution of $Pd(dba)_2$ (12 mg, 4 mol%), P(2-furyl)$_3$ (9.0 mg, 8 mol%) and 4-iodobenzotrifluoride (163 mg, 0.60 mmol, 1.20 equiv) in dry THF (1 mL) was added at −10 °C. The resulting mixture was

allowed to warm up to room temperature and was further stirred for 12 h. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **141f** as a yellow solid (88 mg, 0.23 mmol, 46%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.60 (s, 1H), 8.74 (d, *J* = 5.5 Hz, 1H), 7.77–7.69 (m, 4H), 7.34 (d, *J* = 5.9 Hz, 1H), 6.36 (s, 1H), 5.30 (s, 2H), 3.82–3.75 (m, 2H), 3.54–3.47 (m, 2H), 3.31 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.8, 151.3, 151.0, 148.4, 142.2, 138.1(d, *J* = 1.1 Hz), 132.1(q, *J* = 32.9 Hz), 129.9, 125.6 (q, *J* = 3.7 Hz), 122.5 (q, *J* = 272.8 Hz), 120.3, 119.3, 106.6, 74.2, 71.9, 69.1, 59.0.

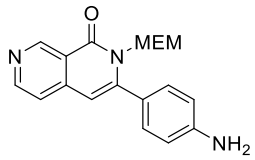
MS (EI, 70 eV): *m/z* (%) = 378 (2), 320 (21), 303 (50), 290 (81), 89 (43), 59 (100).

HRMS (EI): *m/z* calc. for [$C_{19}H_{17}F_3N_2O_3$]: 378.1191; found: 378.1187 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3080, 2926, 2891, 2824, 2361, 2340, 1660, 1611, 1126, 1107, 1065, 1007, 848.

M.p. (°C): 97–99.

3-(4-Aminophenyl)-2-((2-methoxyethoxy)methyl)-2,7-naphthyridin-1 (2*H*)-one (141g)



According to **TP2**, 2,7-naphthyridone **135** (117 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.20 M in THF, 3.00 mL, 0.60 mmol, 1.20 equiv). Using a syringe-pump, the zinc-species was then added dropwise to a solution of $Pd(OAc)_2$ (5.0 mg, 4 mol%), S-Phos (16 mg, 8 mol%) and 4-iodoaniline (131 mg, 0.60 mmol, 1.20 equiv) in dry THF (1 mL) over 1 h at room temperature.[90] The resulting mixture was further stirred for 12 h. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **141g** as a yellow solid (124 mg, 0.38 mmol, 76%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.51 (s, 1H), 8.62 (s, 1H), 7.32–7.27 (m, 2H), 7.24–7.21 (m, 1H), 6.71–6.65 (m, 2H), 6.27 (s, 1H), 5.31 (s, 2H), 4.10–3.98 (m, 2H), 3.74 (dt, *J* = 4.6, 2.4 Hz, 2H), 3.48 (dt, *J* = 4.6, 2.7 Hz, 2H), 3.29 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 163.3, 151.4, 150.9, 150.2, 148.0, 142.2, 130.4, 124.2, 119.7, 118.8, 114.3, 105.7, 74.4, 71.8, 68.8, 58.9.

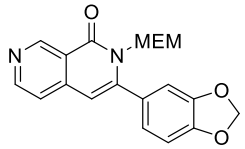
MS (EI, 70 eV): *m/z* (%) = 325 (31), 250 (52), 237 (100), 59 (39).

HRMS (EI): *m/z* calc. for [$C_{18}H_{19}N_3O_3$]: 325.1426; found: 325.1422 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3326, 3193, 2926, 1665, 1602, 1511, 1294, 1088, 1044, 832.

M.p. (°C): 109.

3-(Benzo[*d*][1,3]dioxol-5-yl)-2-((2-methoxyethoxy)methyl)-2,7-naphthyridin-1(2*H*)-one (141h)



According to **TP2**, 2,7-naphthyridone **135** (117 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.35 M in THF, 1.71 mL, 0.60 mmol, 1.20 equiv). A solution of PEPPSI-*i*Pr (14 mg, 4 mol%) and 5-bromobenzo[*d*][1,3]dioxole (121 mg, 0.60 mmol, 1.20 equiv) in dry THF (1 mL) was added at −10 °C. The resulting mixture was allowed to warm up to room temperature and was further stirred for 12 h at 60 °C. The crude product was purified by column chromatography (EtOAc / MeOH = 9.5:0.5) to give the title compound **141h** as a colorless solid (141 mg, 0.40 mmol, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.07 (s, 1H), 8.26 (d, *J* = 5.5 Hz, 1H), 6.99 (d, *J* = 5.5, 1H), 6.68 (s, 1H), 6.63 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.46 (d, *J* = 8.2 Hz, 1H), 5.98 (s, 1H), 5.65–5.61 (m, 2H), 4.91 (s, 2H), 3.36–3.30 (m, 2H), 3.10–3.04 (m, 2H), 2.86 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.8, 151.0, 150.0, 149.2, 148.7, 147.8, 143.5, 128.1, 123.5, 120.4, 119.7, 109.9, 108.5, 106.0, 101.8, 74.5, 71.9, 69.3, 59.1.

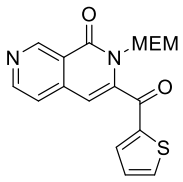
MS (EI, 70 eV): *m/z* (%) = 354 (14), 279 (20), 278 (12), 267 (34), 266 (100), 249 (23), 89 (10), 59 (41).

HRMS (EI): *m/z* calc. for [$C_{19}H_{18}N_2O_5$]: 354.1216; found: 354.1215 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3071, 2932, 2820, 1657, 1615, 1482, 1234, 1086, 1036, 821.

M.p. (°C): 107.

2-((2-Methoxyethoxy)methyl)-3-(thiophene-2-carbonyl)-2,7-naphthyridin-1(2*H*)-one (141i)



According to **TP2**, 2,7-naphthyridone **135** (117 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.20 M in THF, 3.00 mL, 0.60 mmol, 1.20 equiv). A solution of CuCN·2LiCl (1.00 M in THF, 0.55 mL, 0.55 mmol, 0.55 equiv) was added and the reaction mixture was stirred for 10 min at −10 °C before thiophene-2-carbonyl chloride (95 mg, 0.07 mL 0.65 mmol, 1.20 equiv) was added. The resulting mixture was allowed to warm up to room temperature and was further stirred for 12 h. The reaction mixture was quenched with a 10:1 mixture of sat. aq. NH_4Cl solution and NH_3 (10 mL), extracted with EtOAc (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc / *i*hex = gradient 2:8–10:0, then EtOAc/MeOH = 9.5:0.5) to give the title compound **141i** as an orange crystalline solid (88 mg, 0.26 mmol, 52%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.60 (s, 1H), 8.78 (d, *J* = 5.4 Hz, 1H), 7.82 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.75 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.36 (dd, *J* = 5.4, 0.7 Hz, 1H), 7.19 (dd, *J* = 4.9, 3.9 Hz, 1H), 6.71 (s, 1H), 5.76 (s, 2H), 3.53–3.49 (m, 2H), 3.22–3.17 (m, 2H), 3.10 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 181.5, 161.7, 152.1, 151.8, 142.4, 142.1, 140.5, 136.6, 136.2, 128.5, 121.0, 119.7, 108.1, 72.3, 71.1, 68.4, 58.9.

MS (EI, 70 eV): *m/z* (%) = 344 (2), 268 (100), 256 (36), 228 (17), 111 (35), 97 (18), 89 (25), 59 (84), 43 (16).

HRMS (EI): *m/z* calc. for [$C_{17}H_{16}N_2O_4S$]: 344.0831; found: 344.0830 (M^+).

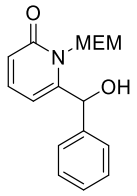
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3077, 2922, 2855, 1643, 1616, 1407, 1100, 855, 755, 724.

M.p. (°C): 79–81.

2.4 Further Functionalization of the 2-Pyridone and 2,7-Naphthyridone Scaffold

2.4.1 Reactions of Magnesiated 2-Pyridone with Electrophiles

6-(Hydroxy(phenyl)methyl)-1-((2-methoxyethoxy)methyl)pyridin-2(1*H*)-one (144a)



According to **TP3**, the iodine-magnesium exchange of 2-pyridone **137a** (155 mg, 0.50 mmol, 1.00 equiv) was completed within 30 min using a solution of *i*PrMgCl·LiCl (**36**, 1.00 M in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) at −40 °C. Benzaldehyde (0.06 mL, 0.60 mmol, 1.20 equiv) was added. The resulting mixture was further stirred for 1.5 h at 0 °C. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **144a** as a yellow liquid (92 mg, 0.32 mmol, 80%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.42–7.33 (m, 5H), 7.32–7.28 (m, 1H), 6.48 (dd, *J* = 9.2, 1.3 Hz, 1H), 6.20 (d, *J* = 6.9 Hz, 1H), 6.10 (s, 1H), 5.88 (d, *J* = 10.8 Hz, 1H), 5.42 (d, *J* = 10.8 Hz, 1H), 3.77 (t, *J* = 4.5 Hz, 2H), 3.59–3.45 (m, 2H), 3.35 (s, 3H).

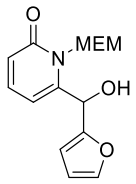
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.1, 151.4, 140.4, 139.9, 128.7, 128.3, 126.8, 119.7, 107.5, 71.7, 71.3, 71.2, 68.2, 58.9.

MS (EI, 70 eV): *m/z* (%) = 231 (28), 214 (22), 213 (19), 212 (23), 202 (14), 201 (100), 200 (52), 196 (13), 185 (32), 184 (99), 183 (31), 182 (17), 165 (32), 154 (10), 124 (17), 105 (10), 91 (11), 77 (12).

HRMS (EI): *m/z* calc. for [$C_{16}H_{19}NO_4$]: 289.1314; found: 289.1320 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3316, 2926, 2882, 1652, 1550, 1452, 1084, 1046, 800, 700.

6-(Furan-2-yl(hydroxy)methyl)-1-((2-methoxyethoxy)methyl)pyridin-2(1*H*)-one (144b)



According to **TP3**, the iodine-magnesium exchange of 2-pyridone **137a** (155 mg, 0.50 mmol) was completed within 30 min using a solution of *i*PrMgCl·LiCl (**36**, 1.00 M in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) at −40 °C. Furfural (0.05 mL, 0.60 mmol, 1.20 equiv) was added. The resulting mixture was further stirred for 1.5 h at 0 °C. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **144b** as a yellow liquid (118 mg, 0.42 mmol, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.38 (dd, *J* = 1.2 Hz, 1H), 7.29 (dd, *J* = 9.2, 6.9 Hz, 1H), 6.49 (dd, *J* = 9.2, 1.3 Hz, 1H), 6.37–6.34 (m, 2H), 6.30 (dd, *J* = 6.9, 1.3 Hz, 1H), 6.08 (d, *J* = 4.7 Hz, 1H), 5.95 (d, *J* = 10.9 Hz, 1H), 5.33 (d, *J* = 10.9 Hz, 1H), 4.48 (d, *J* = 4.9 Hz, 1H), 3.73 (dd, *J* = 4.9, 4.1 Hz, 2H), 3.56–3.50 (m, 1H), 3.47–3.42 (m, 1H), 3.31 (s, 3H).

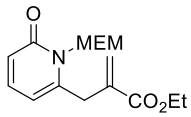
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.9, 153.0, 149.2, 142.8, 140.1, 120.2, 110.7, 108.3, 106.9, 71.7, 71.3, 68.1, 65.9, 58.9.

MS (EI, 70 eV): *m/z* (%) = 279 (1), 203 (16), 202 (12), 192 (11), 191 (100), 190 (32), 182 (19), 175 (32), 163 (25), 162 (34), 146 (69), 145 (31), 144 (22), 134 (11), 124 (20), 122 (23), 118 (13), 117 (38), 97 (12), 95 (15), 94 (15), 91 (10). 81 (66), 59 (48).

HRMS (EI): *m/z* calc. for [$C_{14}H_{17}NO_5$]: 279.1107; found: 279.1098 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3254, 2926, 2882, 1654, 1576, 1552, 1232, 1138, 1094, 1080, 1044, 812, 742.

Ethyl 2-((1-((2-methoxyethoxy)methyl)-6-oxo-1,6-dihydropyridin-2-yl)methyl)acrylate (144c)



According to **TP3**, the iodine-magnesium exchange of 2-pyridone **137a** (155 mg, 0.50 mmol, 1.00 equiv) was completed within 30 min using a solution of *i*PrMgCl·LiCl (**36**, 1.00 M in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) at −40 °C. A solution of CuCN·2LiCl (1.00 M in THF, 0.60 mmol,

0.60 mL, 1.20 equiv) was added and the reaction mixture was stirred for 30 min at −40 °C. Ethyl 2-(bromomethyl)acrylate (0.09 mL, 0.60 mmol, 1.20 equiv) was added. The resulting mixture was allowed to warm up to room temperature and was further stirred for 12 h. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **144c** as a yellow liquid (96 mg, 0.33 mmol, 65%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.22 (dd, *J* = 9.2, 6.9 Hz, 1H), 6.44 (d, *J* = 9.2 Hz, 1H), 6.32 (s, 1H), 5.96 (d, *J* = 6.8 Hz, 1H), 5.57 (d, *J* = 1.0 Hz, 2H), 5.46 (td, *J* = 1.6, 0.8 Hz, 1H), 4.24–4.17 (m, 2H), 3.78 (s, 2H), 3.76–3.72 (m, 2H), 3.53–3.48 (m, 2H), 3.34 (s, 3H), 1.27 (td, *J* = 7.1, 0.8 Hz, 3H).

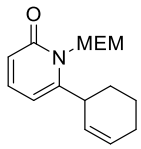
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 166.1, 164.4, 147.3, 139.8, 137.3, 127.3, 119.0, 107.3, 72.3, 71.6, 68.7, 61.3, 59.0, 34.5, 14.3.

MS (EI, 70 eV): *m/z* (%) = 220 (18), 218 (12), 207 (70), 190 (28), 174 (11), 162 (100), 161 (83), 148 (88), 147 (16), 146 (90), 135 (10), 134 (40), 133 (56), 132 (12), 118 (15), 117 (12), 106 (12), 104 (14), 59 (26).

HRMS (EI): *m/z* calc. for [$C_{15}H_{21}NO_5$]: 295.1420; found: 295.1409 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2928, 1714, 1662, 1586, 1550, 1240, 1136, 1096, 1050, 1024, 802.

6-(Cyclohex-2-en-1-yl)-1-((2-methoxyethoxy)methyl)pyridin-2(1*H*)-one (144d)



According to **TP3**, the iodine-magnesium exchange of 2-pyridone **137a** (155 mg, 0.50 mmol, 1.00 equiv) was completed within 30 min using a solution of *i*PrMgCl·LiCl (**36**, 1.00 M in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) at −40 °C. A solution of CuCN·2LiCl (1.00 M in THF, 0.60 mmol, 0.60 mL, 1.20 equiv) was added and the reaction mixture was stirred for 30 min at −40 °C. 3-Bromocyclohexene (0.04 mL, 0.60 mmol, 1.20 equiv) was added. The resulting mixture was allowed to warm up to room temperature and was further stirred for 12 h. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **144d** as a brown liquid (100 mg, 0.38 mmol, 76%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.23–7.16 (m, 1H), 6.39–6.32 (m, 1H), 6.02 (dd, *J* = 7.0, 1.3 Hz, 1H), 5.92–5.83 (m, 2H), 5.51 (dq, *J* = 10.1, 2.1 Hz, 1H), 5.35 (d, *J* = 10.6 Hz, 1H), 3.73 (qdd,

J = 11.3, 5.2, 3.7 Hz, 3H), 3.46 (ddd, *J* = 6.3, 3.5, 2.3 Hz, 2H), 3.30 (s, 3H), 1.99 (m, *J* = 13.4, 8.6, 5.9, 3.1 Hz, 3H), 1.70–1.43 (m, 3H).

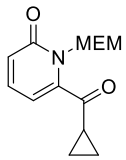
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 164.4, 154.0, 139.8, 129.6, 127.0, 118.0, 106.2, 71.6, 71.5, 68.6, 58.9, 36.5, 29.9, 24.6, 19.8.

MS (EI, 70 eV): *m/z* (%) = 263 (1), 205 (23), 188 (48), 187 (35), 186 (39), 176 (31), 175 (87), 174 (37), 172 (18), 160 (33), 159 (31), 158 (26), 147 (12), 146 (100), 134 (26), 133 (21), 130 (15), 122 (10), 117 (11), 109 (24), 59 (32).

HRMS (EI): *m/z* calc. for [$C_{15}H_{21}NO_3$]: 263.1521; found: 263.1516 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2876, 1658, 1586, 1548, 1450, 1134, 1096, 1084, 1050, 800, 774.

6-(Cyclopropanecarbonyl)-1-((2-methoxyethoxy)methyl)pyridin-2(1*H*)-one (144e)



According to **TP3**, the iodine-magnesium exchange of 2-pyridone **137a** (155 mg, 0.50 mmol, 1.00 equiv) was completed within 30 min using a solution of *i*PrMgCl·LiCl (**36**, 1.00 M in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) at −40 °C. A solution of CuCN·2LiCl (1.00 M in THF, 0.60 mmol, 0.60 mL, 1.20 equiv) was added and the reaction mixture was stirred for 30 min at −40 °C. Cyclopropanecarbonyl chloride (0.06 mL, 0.60 mmol, 1.20 equiv) was added. The resulting mixture was allowed to warm up to room temperature and was further stirred for 12 h. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **144e** as a yellow liquid (95 mg, 0.38 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 (dd, *J* = 9.3, 6.7 Hz, 1H), 6.65–6.56 (m, 2H), 5.71 (s, 2H), 3.60–3.56 (m, 2H), 3.47–3.43 (m, 2H), 3.30 (s, 3H), 2.33 (tt, *J* = 7.8, 4.5 Hz, 1H), 1.32–1.26 (m, 2H), 1.10 (dq, *J* = 7.5, 3.5 Hz, 2H).

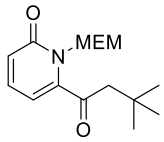
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 198.2, 162.6, 145.6, 138.2, 123.7, 108.4, 72.3, 71.4, 68.5, 59.0, 20.7, 13.2.

MS (EI, 70 eV): *m/z* (%) = 251 (2), 182 (20), 176 (51), 175 (63), 164 (25), 163 (55), 147 (24), 134 (17), 122 (11), 94 (15), 89 (33), 59 (100), 41 (10).

HRMS (EI): *m/z* calc. for [$C_{13}H_{17}NO_4$]: 251.1158; found: 251.1158 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3486, 2924, 2880, 1652, 1586, 1380, 1234, 1130, 1094, 1078, 1042, 1000, 850, 804.

6-(3,3-Dimethylbutanoyl)-1-((2-methoxyethoxy)methyl)pyridin-2(1*H*)-one (144f)



According to **TP3**, the iodine-magnesium exchange of 2-pyridone **137a** (155 mg, 0.50 mmol, 1.00 equiv) was completed within 30 min using a solution of *i*PrMgCl·LiCl (**36**, 1.00 M in THF, 0.60 mL, 0.60 mmol) at −40 °C. A solution of CuCN·2LiCl (1.00 M in THF, 0.60 mmol, 0.60 mL, 1.20 equiv) was added and the reaction mixture was stirred for 30 min at −40 °C. *tert*-Butylacetyl chloride (0.08 mL, 0.60 mmol, 1.20 equiv) was added. The resulting mixture was allowed to warm to room temperature and was further stirred for 12 h. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **144f** as a brown liquid (101 mg, 0.36 mmol, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.31–7.27 (m, 1H), 6.60–6.56 (m, 1H), 6.33 (dd, *J* = 6.7, 1.0 Hz, 1H), 5.70 (s, 2H), 3.55 (dd, *J* = 5.4, 3.7 Hz, 2H), 3.42 (dd, *J* = 5.7, 3.1 Hz, 2H), 3.27 (s, 3H), 2.74 (s, 2H), 1.06 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 197.8, 162.6, 146.0, 138.3, 123.4, 107.6, 72.1, 71.3, 68.5, 58.8, 53.4, 31.1, 29.6.

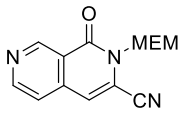
MS (EI, 70 eV): *m/z* (%) = 205 (59), 194 (12), 193 (62), 190 (14), 182 (21), 178 (14), 150 (92), 149 (25), 148 (100), 138 (44), 137 (44), 127 (13), 122 (13), 121 (14), 120 (43), 112 (11), 109 (21), 95 (11), 194 (13), 89 (42), 83 (12), 59 (59).

HRMS (EI): *m/z* calc. for [$C_{15}H_{23}NO_4$]: 281.1627; found: 281.0508 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2874, 1656, 1590, 1466, 1360, 1238, 1082, 1044, 802.

2.4.2 Reactions of Magnesiated 2,7-Naphthyridone with Electrophiles

2-((2-Methoxyethoxy)methyl)-1-oxo-1,2-dihydro-2,7-naphthyridine-3-carbonitrile (145a)



According to **TP4**, the iodine-magnesium exchange of 2,7-naphthyridone **141a** (72 mg, 0.20 mmol, 1.00 equiv) was completed within 20 min using a solution of *i*PrMgCl·LiCl (**36**, 1.30 M in THF, 0.15 mL, 0.20 mmol, 1.00 equiv). The Grignard reagent was then added dropwise to a solution of *p*-toluenesulfonyl cyanide (54 mg, 0.30 mmol) in dry THF (3 mL) at 0 °C *via* syringe. The resulting mixture was allowed to warm to room temperature and was further stirred for 12 h. The crude product was purified by column chromatography (EtOAc/MeOH = 9:1) to give the title compound **145a** as a light brown solid (32 mg, 0.12 mmol, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.64 (s, 1H), 8.89 (s, 1H), 7.44 (d, *J* = 5.2 Hz, 1H), 7.08 (s, 1H), 5.69 (s, 2H), 3.86–3.78 (m, 2H), 3.58–3.50 (m, 2H), 3.30 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.7, 152.5, 151.8, 140.1, 122.0, 120.4, 119.7, 115.6, 112.6, 75.5, 71.7, 69.8, 59.2.

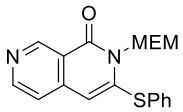
MS (EI, 70 eV): *m/z* (%) = 259 (1), 200 (14), 184 (33), 172 (14), 171 (159), 154 (25), 89 (55), 59 (100), 58 (21), 45 (21).

HRMS (EI): *m/z* calc. for [$C_{13}H_{13}N_3O_3$]: 259.0957; found: 259.0961 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 2925, 2854, 2236, 1665, 1616, 1126, 1071, 978, 791.

M.p. (°C): 74.

2-((2-Methoxyethoxy)methyl)-3-(phenylthio)-2,7-naphthyridin-1(2*H*)-one (145b)



According to **TP4**, the iodine-magnesium exchange of 2,7-naphthyridone **141a** (144 mg, 0.40 mmol, 1.00 equiv) was finished within 20 min, using a solution of *i*PrMgCl·LiCl (**36**, 1.30 M in THF, 0.31 mL, 0.40 mmol, 1.00 equiv). The Grignard reagent **143** was then added dropwise to a solution of S-phenyl benzenethiosulfonate (300 mg, 1.2 mmol) in dry THF (5 mL) at 0 °C *via* syringe. The resulting mixture was allowed to warm up to room temperature and was further stirred for 12 h. The reaction mixture was

quenched with sat. aq. $NaHCO_3$ solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **145b** as a brown-yellow solid (98 mg, 0.29 mmol, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.44 (s, 1H), 8.55 (d, *J* = 5.4 Hz, 1H), 7.54–7.49 (m, 2H), 7.45–7.41 (m, 3H), 6.99 (d, *J* = 5.5 Hz, 1H), 5.96 (s, 1H), 5.82 (s, 2H), 3.81–3.77 (m, 2H), 3.51 (dd, *J* = 5.3, 3.8 Hz, 2H), 3.33 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.8, 151.5, 151.1, 148.4, 141.6, 134.2, 130.1, 130.1, 129.9, 118.5, 118.1, 105.5, 74.0, 71.6, 69.0, 59.1.

MS (EI, 70 eV): *m/z* (%) = 342 (31), 267 (29), 254 (81), 195 (11), 165 (11), 145 (10), 89 (31), 59 (100).

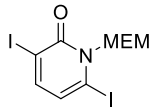
HRMS (EI): *m/z* calc. for [$C_{18}H_{18}N_2O_3S$]: 342.1038; found: 342.1034 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 2924, 2883, 2815, 1660, 1596, 1523, 1102, 1080, 740.

M.p. (°C): 68–70.

2.5 Direct Magnesiation of 6-Substituted 2-Pyridones

3,6-Diiodo-1-((2-methoxyethoxy)methyl)pyridin-2(1*H*)-one (148a)



In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 2-pyridone **137a** (155 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL) was cooled to −40 °C. TMPMgCl·LiCl (**89**, 1.06 M in THF, 0.57 mL, 0.60 mmol, 1.20 equiv) was added dropwise and the mixture was stirred at the same temperature for 2 h. Iodine (153 mg, 0.60 mmol, 1.20 equiv) dissolved in dry THF (1 mL) was then added dropwise at −40 °C. The resulting mixture was allowed to warm up to room temperature and was further stirred for 30 min. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with EtOAc (3 × 20 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/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **148a** as a brown liquid (173 mg, 0.40 mmol, 80%).

^{1}H-NMR (600 MHz, $CDCl_3$): 7.52 (d, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 7.5 Hz, 1H), 5.71 (s, 2H), 3.76–3.70 (m, 2H), 3.51–3.46 (m, 2H), 3.31 (s, 3H).

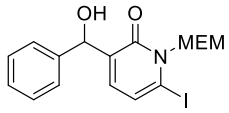
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 160.4, 149.1, 121.2, 100.4, 92.5, 82.9, 71.4, 69.3, 59.0.

MS (EI, 70 eV): *m/z* (%) = 326 (15), 310 (20), 298 (22), 297 (100), 155 (13), 154 (14), 115 (14), 89 (16), 59 (63).

HRMS (EI): *m/z* calc. for [$C_9H_{11}I_2NO_3$]: 385.0175; found: 385.0169 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2810, 1630, 1574, 1490, 1442, 1312, 1192, 1062, 1000, 802, 752.

3-(Hydroxy(phenyl)methyl)-6-iodo-1-((2-methoxyethoxy)methyl)pyridin-2(1*H*)-one (148b)



In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 2-pyridone **137a** (155 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL) was cooled down to −40 °C. TMPMgCl·LiCl (**89**, 1.06 M in THF, 0.57 mL, 0.60 mmol, 1.20 equiv) was added dropwise and the mixture was stirred at the same temperature for 2 h. Benzaldehyde (0.06 mL, 0.60 mmol, 1.20 equiv)

was then added dropwise at −40 °C. The resulting mixture was allowed to warm up to room temperature and was further stirred for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 × 20 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/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **148b** as a yellow liquid (154 mg, 0.37 mmol, 74%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.93 (d, *J* = 7.5 Hz, 1H), 7.41–7.30 (m, 5H), 6.05 (d, *J* = 3.8 Hz, 1H), 6.01–5.92 (m, 2H), 5.46 (d, *J* = 11.0 Hz, 1H), 4.05 (s, 1H), 3.78 (t, *J* = 4.4 Hz, 2H), 3.59–3.44 (m, 2H), 3.34 (s, 3H).

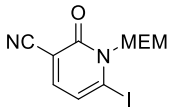
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.1, 152.3, 149.1, 139.9, 128.9, 128.6, 126.7, 108.9, 91.6, 73.9, 71.3, 71.3, 68.7, 59.0.

MS (EI, 70 eV): *m/z* (%) = 338 (18), 328 (10), 327 (78), 326 (28), 311 (12), 310 (30), 309 (15), 250 (18), 222 (18), 221 (13), 182 (22), 154 (32), 153 (17), 128 (17), 127 (100), 105 (40), 91 (30), 89 (11), 77 (22), 59 (32).

HRMS (EI): *m/z* calc. for [$C_{16}H_{18}INO_4$]: 415.0281; found: 415.0267 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3348, 2924, 2880, 1638, 1582, 1452, 1196, 1082, 1060, 1024, 844, 762, 734, 700.

6-Iodo-1-((2-methoxyethoxy)methyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (148c)



In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 2-pyridone **137a** (155 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL) was cooled to −40 °C. TMPMgCl·LiCl (**89**, 1.06 M in THF, 0.57 mL, 0.60 mmol, 1.20 equiv) was added dropwise and the mixture was stirred at the same temperature for 2 h. *p*-Toluenesulfonyl cyanide (108 mg, 0.60 mmol, 1.20 equiv) was then added dropwise at −40 °C. The resulting mixture was allowed to warm up to room temperature and was further stirred for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 × 20 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/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **148c** as a lightly brown solid (67 mg, 0.20 mmol, 40%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 (d, *J* = 7.2 Hz, 1H), 6.48 (d, *J* = 7.3 Hz, 1H), 5.66 (s, 2H), 3.83–3.80 (m, 2H), 3.55–3.52 (m, 2H), 3.34 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.1, 147.3, 121.2, 116.5, 112.3, 102.5, 77.7, 71.7, 70.2, 59.2.

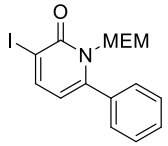
MS (EI, 70 eV): *m/z* (%) = 334 (5), 276 (34), 259 (37), 247 (60), 246 (45), 132 (10), 104 (17), 89 (77), 64 (16), 59 (100), 58 (12), 45 (25).

HRMS (EI): *m/z* calc. for [$C_{10}H_{11}IN_2O_3$]: 333.9814; found: 333.9810 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3090, 2926, 2882, 2228, 1652, 1548, 1450, 1200, 1078, 846, 716.

M.p. (°C): 108–110.

3-Iodo-1-((2-methoxyethoxy)methyl)-6-phenylpyridin-2(1*H*)-one (149)



In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 2-pyridone **137b** (130 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL) was cooled down to −40 °C. TMPMgCl·LiCl (**89**, 1.06 M in THF, 0.57 mL, 0.60 mmol, 1.20 equiv) was added dropwise and the mixture was stirred at the same temperature for 2 h. Iodine (154 mg, 0.60 mmol, 1.20 equiv) in dry THF (1 mL) was then added dropwise at −40 °C. The resulting mixture was allowed to warm to room temperature and was further stirred for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 × 20 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/MeOH/Et_3N = 9.7:0.3:0.05) to give the title compound **149** as a lightly brown liquid (90 mg, 0.35 mmol, 70%).

^{1}H-NMR (600 MHz, $CDCl_3$): 7.98 (d, *J* = 7.7 Hz, 1H), 7.54–7.38 (m, 5H), 5.88 (d, *J* = 7.3 Hz, 1H), 5.31 (s, 2H), 3.86–3.82 (m, 2H), 3.55–3.48 (m, 2H), 3.33 (d, *J* = 0.6 , 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 161.0, 151.4, 148.7, 134.2, 129.7, 129.2, 128.5, 109.5, 91.4, 76.4, 71.9, 69.7, 59.0.

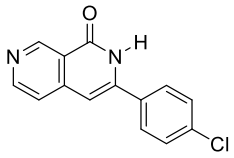
MS (EI, 70 eV): *m/z* (%) = 326 (15), 310 (20), 298 (22), 297 (100), 155 (13), 154 (14), 115 (14), 89 (16), 59 (63).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}INO_3$]: 385.0175; found: 385.0169 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2924, 2878, 1644, 1586, 1530, 1490, 1446, 1072, 844, 812, 762, 698.

2.6 Cleavage of the MEM-Protecting Group and Chlorination

3-(4-Chlorophenyl)-2,7-naphthyridin-1(2*H*)-one (150)



In order to remove the MEM-protecting group, 2,7-naphthyridone **141d** (680 mg, 2.0 mmol) was dissolved in EtOH (2 mL). Concentrated hydrochloric acid (1 mL) was added and the mixture was heated to 65 °C for 3 h. At the same temperature, the mixture was then evaporated to dryness under high vacuum. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **150** as a colorless solid (430 mg, 1.7 mmol, 84%).

^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ / ppm = 9.32 (s, 1H), 8.71 (d, *J* = 5.5 Hz, 1H), 7.85–7.80 (m, 2H), 7.63–7.58 (m, 3H), 6.94 (s, 1H).

^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ / ppm = 162.3, 151.0, 149.8, 144.1, 143.0, 134.9, 132.1, 129.0, 128.9, 119.7, 119.7, 101.8.

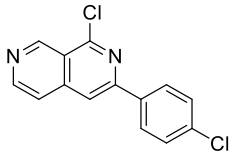
MS (ESI, 70 eV): *m/z* (%) = 257 (100), 235 (10).

HRMS (ESI): *m/z* calc. for [$C_{14}H_{10}ClN_2O$]: 257.0476; found: 257.0481 (M^+ + H).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 2876, 1710, 1666, 1612, 1450, 1360, 1220, 1088, 826.

M.p. (°C): 200.

1-Chloro-3-(4-chlorophenyl)-2,7-naphthyridine (151)



A pressure flask, equipped with a magnetic stirring bar, was charged with **150** (1.28 g, 5.0 mmol), followed by $POCl_3$ (10 mL). The reaction mixture was heated at 180 °C for 24 h. Then, the reaction was poured on ice (150 g) and was made alkaline with potassium carbonate. The mixture was extracted several times with EtOAc extensively. The combined organic layers were dried over $MgSO_4$, filtered

and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (*i*hex/EtOAc = 9:1) to afford the desired product **151** as a yellow solid (1.12 g, 4.1 mmol, 82%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.73 (s, 1H), 8.79 (d, *J* = 5.6 Hz, 1H), 8.12–8.06 (m, 2H), 7.95 (s, 1H), 7.70 (d, *J* = 5.7 Hz, 1H), 7.51–7.48 (m, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 153.4, 152.2, 151.5, 147.9, 141.9, 136.5, 135.6, 129.4, 128.7, 121.2, 119.5, 114.4.

MS (EI, 70 eV): *m/z* (%) = 274 (100), 241 (15), 239 (48), 204 (17), 177 (11), 176 (13).

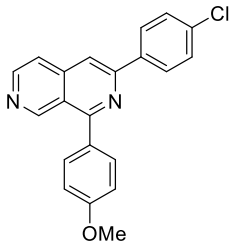
HRMS (EI): *m/z* calc. for [$C_{14}H_8Cl_2N_2$]: 274.0065; found: 274.00581 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2854, 1700, 1592, 1408, 1170, 1090, 1042, 1012, 836.

M.p. (°C): 189.

2.7 Cobalt-Catalyzed Negishi Cross-Couplings

3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-2,7-naphthyridine (153a)



According to **TP5**, the naphthyridine **151** (82 mg, 0.30 mmol, 1.00 equiv) was added to a solution of $CoCl_2$ (10 mol %) and dry THF (1 mL) at room temperature. Appropriate zinc reagent **152a** (0.45 mmol, 1.50 equiv) was added dropwise over 15 min via syringe at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 48 h. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **153a** as a lightly yellow solid (79 mg, 0.23 mmol, 77%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.53 (s, 1H), 8.67 (d, *J* = 5.5 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 2H), 7.89 (s, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 5.5 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 3.91 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 161.1, 160.9, 152.8, 152.5, 146.6, 140.8, 137.2, 135.6, 131.9, 130.6, 129.1, 128.7, 120.9, 119.7, 114.2, 113.0, 55.6.

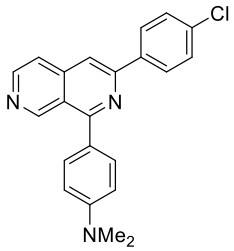
MS (EI, 70 eV): *m/z* (%) = 346 (100), 345 (67), 331 (15), 317 (27), 316 (18), 315 (81), 304 (13), 303 (25), 302 (25), 267 (13), 266 (12), 134 (14).

HRMS (EI): *m/z* calc. for [$C_{21}H_{15}ClN_2O$]: 346.0873; found: 346.0870 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3054, 2994, 2832, 1608, 1544, 1514, 1380, 1246, 1176, 1090, 1012, 866, 828.

M.p. (°C): 146.

4-(3-(4-Chlorophenyl)-2,7-naphthyridin-1-yl)-N,N-dimethylaniline (153b)



According to **TP5**, the naphthyridine **151** (82 mg, 0.30 mmol, 1.00 equiv) was added to a solution of $CoCl_2$ (10 mol %) and dry THF (1 mL) at room temperature. Appropriate zinc reagent **152b** (0.45 mmol, 1.50 equiv) was added dropwise over 15 min *via* syringe at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 48 h. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **153b** as a lightly yellow solid (90 mg, 0.25 mmol, 83%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.61 (s, 1H), 8.64 (d, *J* = 5.7 Hz, 1H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.83 (s, 1H), 7.80 (d, *J* = 8.9 Hz, 2H), 7.63 (d, *J* = 5.7 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.07 (s, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 161.6, 153.1, 152.5, 151.5, 146.4, 141.1, 137.4, 135.4, 131.8, 129.0, 128.7, 125.8, 120.8, 119.7, 112.2, 112.0, 40.4.

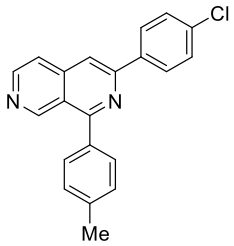
MS (EI, 70 eV): *m/z* (%) = 359 (100), 358 (57), 344 (12), 342 (15), 317 (18), 316 (15), 315 (54), 179 (12).

HRMS (EI): *m/z* calc. for [$C_{22}H_{18}ClN_3$]: 359.1189; found: 359.1183 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2918, 2812, 1608, 1528, 1382, 1196, 1088, 1010, 974, 864, 832.

M.p. (°C): 163.

3-(4-Chlorophenyl)-1-(p-tolyl)-2,7-naphthyridine (153c)



According to **TP5**, the naphthyridine **151** (82 mg, 0.30 mmol, 1.00 equiv) was added to a solution of $CoCl_2$ (10 mol %) and dry THF (1 mL) at room temperature. Appropriate zinc reagent **152c** (0.45 mmol, 1.50 equiv) was added dropwise over 15 min *via* syringe at 0 °C The reaction mixture was allowed to warm up to room temperature and stirred for 48 h. The crude product was purified by column chromatography (EtOAc / MeOH = 9.5:0.5) to give the title compound **153c** as a lightly yellow solid (66 mg, 0.20 mmol, 67%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.54 (s, 1H), 8.69 (d, *J* = 5.7, 1H), 8.18 (d, *J* = 8.5 Hz, 2H), 7.96 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.70 (d, *J* = 5.7 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 7.7 Hz, 2H), 2.50 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 161.7, 153.0, 152.7, 146.7, 140.8, 139.8, 137.2, 135.7, 135.4, 130.5, 129.5, 129.1, 128.8, 121.0, 119.7, 113.4, 21.6.

MS (EI, 70 eV): *m/z* (%) = 330 (79), 329 (62), 317 (31), 316 (22), 315 (100), 146 (10).

HRMS (EI): *m/z* calc. for [$C_{21}H_{15}ClN_2$]: 330.0924; found: 330.0901 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3054, 2922, 1610, 1546, 1494, 1412, 1380, 1330, 1186, 1094, 1014, 976, 830, 788.

M.p. (°C): 150.

3 Directed Zincation or Magnesiation of 2- and 4-Pyrones and their Derivatives

3.1 Starting Materials

2-Pyrone and 4-pyrone were purchased from TCI. Methyl coumalate was purchased from Alfa Aesar. 3,5-Dibromo-2*H*-pyran-2-one was prepared using known procedures.[97a]

3.2 Typical Procedures (TP)

Typical procedure for the magnesation of 2-pyrone (154) using TMPMgCl·LiCl (89) (TP6):

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 2-pyrone (**154**, 1.00 equiv) was dissolved in dry THF (0.50 M solution). After the solution was cooled to –40 °C, TMPMgCl·LiCl (**89**, 1.20 equiv) was added and the mixture was stirred at the same temperature. The completion of the metalation was achieved after 15 min, stated by TLC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF. Subsequent reactions with electrophiles were carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat.aq. NaCl (10 mL) and extracted with Et_2O (3 × 20 mL) if not noted differently. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash-column chromatography.

Typical procedure for the zincation of methyl coumalate (156) using TMPZnCl·LiCl (92) (TP7):

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, methyl coumalate (**156**, 1.00 equiv) was dissolved in dry THF (0.50 M solution). After the solution was cooled to −78 °C, TMPZnCl·LiCl (**92**, 1.20 equiv) was added and the mixture was stirred at the same temperature. The completion of the metalation was achieved after 15 min, stated by TLC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL) if not specifically indicated. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash-column chromatography.

Typical procedure for the zincation of 3,5-dibromo-2*H*-pyran-2-one (157) using TMPZnCl·LiCl (92) (TP8):

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 3,5-dibromo-2*H*-pyran-2-one (**157**, 1.00 equiv) was dissolved in dry THF (0.50 M solution). After the

solution was cooled to −10 °C, TMPZnCl·LiCl (**92**, 1.20 equiv) was added and the mixture was stirred at the same temperature. The completion of the metalation was achieved after 15 min, stated by TLC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL) if not specifically indicated. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by flash-column chromatography.

Typical procedure for the magnesiation of 6-substituted 2-pyrone (159) using TMPMgCl·LiCl (89) (TP9):

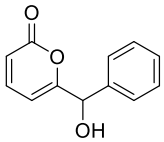
In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 6-substituted 2-pyrone (**159**, 1.00 equiv) was dissolved in dry THF (0.50 M solution). After the solution was cooled to −40 °C, TMPMgCl·LiCl (**89**, 1.20 equiv) was added and the mixture was stirred at the same temperature. The completion of the metalation was achieved after 1 h, stated by TLC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL) if not specifically indicated. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash-column chromatography.

Typical procedure for the zincation of 4-pyrone (155) using $TMP_2Zn·2MgCl_2·2LiCl$ (93) (TP10):

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 4-pyrone (**155**, 1.00 equiv) was dissolved in dry THF (0.50 M solution). After the solution was cooled to −35 °C, $TMP_2Zn·2MgCl_2·2LiCl$ (**93**, 1.20 equiv) was added and the mixture was stirred at the same temperature. The completion of the metalation was achieved after 2 h, stated by TLC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL) if not specifically indicated. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash-column chromatography.

3.3 Reaction of Magnesiated 2-Pyrone with Electrophiles

6-(Hydroxy(phenyl)methyl)-2*H*-pyran-2-one (159a)



According to **TP6**, 2-pyrone (**154**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.54 mL, 0.60 mmol, 1.20 equiv). Benzaldehyde (0.06 mL, 0.60 mmol, 1.20 equiv) was then added dropwise at –40 °C. The reaction mixture was warmed to 25 °C and was stirred until completion of the reaction. The crude product was purified by column chromatography (*i*hex/Et_2O = 5:5) furnishing the compound **159a** as a yellow solid (73 mg, 0.36 mmol, 72%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 7.53–7.46 (m, 3H), 7.40–7.29 (m, 3H), 6.50 (dt, *J* = 6.6, 1.0 Hz, 1H), 6.13–6.09 (m, 1H), 5.52 (d, *J* = 3.8 Hz, 1H), 5.42 (d, *J* = 4.4 Hz, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 167.7, 161.8, 144.9, 141.7, 129.2, 128.9, 127.8, 114.4, 101.9, 73.1.

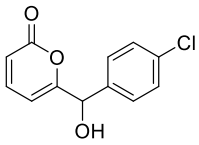
MS (70 eV, EI) m/z (%): 202 (48), 198 (46), 186 (100), 173 (14), 128 (16), 107 (52), 95 (100).

HRMS (EI): *m/z* calc. for [$C_{12}H_{10}O_3$]: 202.0630; found 202.0622 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3072, 1716, 1535, 148, 1398, 1090, 1074, 845, 801.

M.p. (°C): 107–108.

6-((4-Chlorophenyl)(hydroxy)methyl)-2*H*-pyran-2-one (159b)



According to **TP6**, 2-pyrone (**154**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.54 mL, 0.60 mmol, 1.20 equiv). 4-Chlorobenzaldehyde (0.06 mL, 0.60 mmol, 1.20 equiv) was then added dropwise at –40 °C. The reaction mixture was warmed to 25 °C and was stirred until completion of the reaction. The

crude product was purified by flash-column chromatography (*i*hex/Et_2O = 4:6) furnishing the compound **159b** as a yellow oil (71 mg, 0.30 mmol, 60%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 7.54–7.47 (m, 3H), 7.43–7.38 (m, 2H), 6.50 (dt, *J* = 6.6, 0.9 Hz, 1H), 6.12 (dd, *J* = 9.4, 1.2 Hz, 1H), 5.53 (d, *J* = 12.5 Hz, 2H).

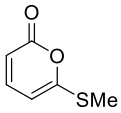
^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 167.0, 161.6, 144.9, 140.7, 134.2, 129.5, 129.3, 114.7, 102.1, 72.4.

MS (70 eV, EI) *m/z* (%): 236 (20), 234 (10), 220 (11), 143 (34), 142 (10), 138 (100), 113 (25), 111 (45), 97 (56), 96 (28), 77 (79), 75 (33), 51 (19), 50 (15).

HRMS (EI): *m/z* calc. for [$C_{12}H_9ClO_3$]: 236.0240; found 236.0243 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3072, 1716, 1535, 1488, 1398, 1090, 1074, 845, 801.

6-(Methylthio)-2*H*-pyran-2-one (159c)



According to **TP6**, 2-pyrone (**154**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.54 mL, 0.60 mmol, 1.20 equiv). Methyl methanethiosulfonate (0.06 mL, 0.60 mmol, 1.20 equiv) was then added dropwise at –40 °C. The reaction mixture was warmed to 25 °C and was stirred until completion of the reaction. The crude product was purified by flash-column chromatography (*i*hex/Et_2O = 4:6) furnishing the compound **159c** as an orange oil (67 mg, 0.47 mmol, 95%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 7.42 (dd, *J* = 9.3, 7.0 Hz, 1H), 6.22 (dd, *J* = 7.0, 0.8 Hz, 1H), 5.99 (dd, *J* = 9.3, 0.8 Hz, 1H), 2.54 (s, 3H).

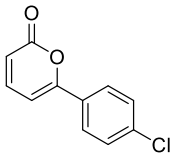
^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ/ppm = 165.7, 161.7, 145.0, 110.1, 102.4, 13.8.

MS (70 eV, EI) *m/z* (%): 142 (42), 114 (12), 95 (100), 43 (13), 39 (37), 28 (22), 18 (20).

HRMS (EI): *m/z* calc. for [$C_6H_6O_2S$]: 142.0089; found 142.0076 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 1724, 1606, 1513, 1435, 1173, 1080, 780.

6-(4-Chlorophenyl)-2*H*-pyran-2-one (159d)



According to **TP6**, 2-pyrone (**154**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.54 mL, 0.60 mmol, 1.20 equiv). The magnesium reagent was transmetalated to zinc in the presence of $ZnCl_2$ (1.00 M solution in THF, 0.75 mL, 0.75 mmol, 1.50 equiv) and stirring for 30 min at −40 °C. The zinc reagent underwent a Negishi cross-coupling reaction in the presence of $Pd(dba)_2$ (11 mg, 8 mol%), $P(2\text{-furyl})_3$ (9.0 mg, 15 mol%) and 1-chloro-4-iodobenzene (143 mg, 0.60 mmol, 1.20 equiv) at 25 °C for 12 h. The crude product was purified by flash-column chromatography (*i*hex/Et_2O = 5:5) furnishing the compound **159d** as a yellowish solid (78 mg, 0.38 mmol, 75%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 7.87–7.83 (m, 2H), 7.58 (dd, J=9.3, 6.8, 1H), 7.53–7.48 (m, 2H), 6.92 (dd, *J* = 6.8, 0.8 Hz, 1H), 6.25 (dd, *J* = 9.3, 0.8 Hz, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 161.3, 160.2, 144.9, 137.0, 131.3, 130.0, 127.9, 115.0, 102.4.

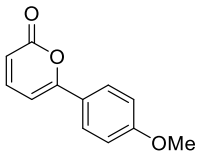
MS (70 eV, EI) *m/z* (%): 206 (53), 180 (31), 179 (11), 178 (100), 149 (16), 139 (10), 115 (30), 111 (14).

HRMS (EI): *m/z* calc. for [$C_{11}H_7ClO_2$]: 206.0135; found 206.0110 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3072, 1716, 1535, 1488, 1398, 1090, 1074, 845, 801.

M.p. (°C): 100–101.

6-(4-Methoxyphenyl)-2*H*-pyran-2-one (159e)



According to **TP6**, 2-pyrone (**154**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.60 mmol, 0.54 mL,

1.20 equiv). The magnesium reagent was transmetalated to zinc in the presence of $ZnCl_2$ (1.00 M solution in THF, 0.75 mmol, 1.50 equiv) and stirring for 30 min at −40 °C. The zinc reagent underwent a Negishi cross-coupling reaction in the presence of $Pd(dba)_2$ (11 mg, 8 mol%), P(2-furyl)$_3$ (9.0 mg, 15 mol%) and 1-iodo-4-methoxybenzene (140 mg, 0.60 mmol, 1.20 equiv) at 25 °C for 12 h. The crude product was purified by flash-column chromatography (*i*hexane/Et_2O = 6:4) furnishing the compound **159e** as a yellowish solid (91 mg, 0.45 mmol, 90%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 7.85–7.80 (m, 2H), 7.55 (dd, *J* = 9.3, 6.9 Hz, 1H), 7.08–7.03 (m, 2H), 6.79 (dd, *J* = 6.9, 0.8 Hz, 1H), 6.16 (dd, *J* = 9.3, 0.8 Hz, 1H), 3.87 (s, 3H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 162.8, 161.8, 161.8, 145.3, 128.0, 125.0, 115.3, 113.2, 100.5, 55.9.

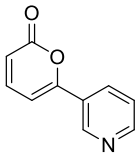
MS (70 eV, EI) *m/z* (%): 202 (44), 174 (100), 131 (40), 103 (16).

HRMS (EI): *m/z* calc. for [$C_{12}H_{10}O_3$]: 202.0630; found 202.0622 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3007, 1719, 1606, 1505, 1415, 1235, 1178, 1021, 835, 787.

M.p. (°C): 137–139.

6-(Pyridin-3-yl)-2*H*-pyran-2-one (159f)



According to **TP6**, 2-pyrone (**154**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.54 mL, 0.60 mmol, 1.20 equiv). The magnesium reagent was transmetalated to zinc in the presence of $ZnCl_2$ (1.00 M solution in THF, 0.75 mmol, 1.50 equiv) and stirring for 30 min at −40 °C. The zinc reagent underwent a Negishi cross-coupling reaction in the presence of $Pd(dba)_2$ (11 mg, 8 mol%), P(2-furyl)$_3$ (9.0 mg, 15 mol%) and 3-iodopyridine (60 mg, 0.60 mmol, 1.20 equiv) at 25 °C for 12 h. The crude product was purified by flash-column chromatography (*i*hexane/Et_2O = 4:6) furnishing the compound **159f** as a yellowish solid (83 mg, 0.48 mmol, 95%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 9.07 (d, *J* = 0.8 Hz, 1H), 8.68 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.22 (ddd, *J* = 8.1, 2.4, 1.6 Hz, 1H), 7.65 (dd, *J* = 9.4, 6.8 Hz, 1H), 7.55–7.50 (m, 1H), 7.05 (dd, *J* = 6.8, 0.8 Hz, 1H), 6.32 (dd, *J* = 9.4, 0.8 Hz, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 161.3, 159.2, 152.2, 147.6, 144.9, 133.5, 128.6, 124.6, 115.6, 103.1.

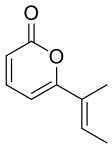
MS (70 eV, EI) *m/z* (%): 173 (45), 145 (100), 117 (11), 95 (17), 78 (16), 57 (12), 55 (10), 50 (12), 43 (13), 43 (16).

HRMS (EI): *m/z* calc. for [$C_{10}H_7NO_2$]: 173.0477; found 173.0472 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2917, 2849, 1726, 1628, 1540, 1476, 1266, 1108, 1069, 841, 793, 695.

M.p. (°C): 96–98.

(*E*)-6-(But-2-en-2-yl)-2*H*-pyran-2-one (159g)



According to **TP6**, 2-pyrone (**154**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.54 mL, 0.60 mmol, 1.20 equiv). The magnesium reagent was transmetalated to zinc in the presence of $ZnCl_2$ (1.00 M solution in THF, 0.75 mmol, 1.50 equiv) and stirring for 30 min at −40 °C. The zinc reagent underwent a Negishi cross-coupling reaction in the presence of PEPPSI-*i*Pr (12 mg, 8 mol%) and (*E*)-2-bromobut-2-ene (60 mg, 0.60 mmol, 1.20 equiv) at 25 °C for 12 h. The crude product was purified by flash-column chromatography (*i*hexane/Et_2O = 4:6) furnishing the compound **159g** as a yellowish solid (72 mg, 0.48 mmol, 95%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 7.48 (dd, *J* = 9.3, 6.9 Hz, 1H), 6.56 (qd, *J* = 7.1, 1.2 Hz, 1H), 6.32 (d, *J* = 6.9 Hz, 1H), 6.12 (d, *J* = 9.3 Hz, 1H), 1.88 (p, *J* = 1.0 Hz, 3H), 1.86–1.82 (m, 3H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 162.6, 161.6, 145.1, 129.4, 128.4, 114.0, 101.3, 14.2, 12.1.

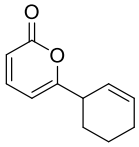
MS (70 eV, EI) *m/z* (%): 150 (94), 122 (100), 121 (13), 107 (71), 93 (18), 91 (13), 79 (49), 77 (21), 55 (28), 53 (17), 43 (25), 41 (11).

HRMS (EI): *m/z* calc. for [$C_9H_{10}O_2$]: calc. 150.0681; found 150.0671 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3075, 2924, 1704, 1638, 1540, 1445, 1093, 1018, 832, 796, 784, 705.

M.p. (°C): 63–66.

6-(Cyclohex-2-en-1-yl)-2*H*-pyran-2-one (159h)



According to **TP6**, 2-pyrone (**154**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.54 mL, 0.60 mmol, 1.20 equiv). The magnesium reagent was treated with CuCN·2LiCl (1.00 M solution in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) for 30 min at −40 °C. A subsequent allylation reaction was performed in the presence of 3-bromocyclohex-1-ene (193 mg, 0.60 mmol, 1.20 equiv) at −40 °C. The reaction mixture was stirred at 25 °C until completion of the reaction. The crude product was purified by flash-column chromatography (*i*hexane/Et_2O = 4:6) furnishing the compound **159h** as a yellow oil (44 mg, 0.25 mmol, 50%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 7.44 (dd, *J* = 9.3, 6.7 Hz, 1H), 6.12–6.08 (m, 2H), 5.93 (dtd, *J* = 9.9, 3.7, 2.3 Hz, 1H), 5.67 (dq, *J* = 10.1, 2.3 Hz, 1H), 3.27 (ddt, *J* = 9.2, 5.8, 2.7 Hz, 1H), 1.97 (m, *J* = 13.4, 8.5, 5.8, 3.1 Hz, 2H), 1.82–1.55 (m, 4H).

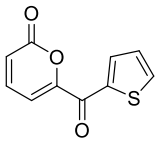
^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 169.3, 162.4, 144.9, 131.2, 125.8, 113.8, 102.9, 40.3, 27.9, 25.4, 20.8.

MS (70 eV, EI) *m/z* (%): 176 (100), 169 (11), 167 (11), 162 (31), 149 (12), 148 (40), 147 (17).

HRMS (EI): *m/z* calc. for [$C_{11}H_{12}O_2$]: 176.0837; found 176.0830 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933, 1732, 1630, 1556, 1448, 1295, 1088, 801.

6-(Thiophene-2-carbonyl)-2*H*-pyran-2-one (159i)



According to **TP6**, 2-pyrone (**154**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.54 mL, 0.60 mmol, 1.20 equiv). The magnesium reagent was treated with CuCN·2LiCl (1.00 M solution in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) for 30 min at −40 °C. Acylation was achieved with thiophene-2-carbonyl chloride (0.06 mL, 0.60 mmol, 1.20 equiv) at −40 °C and warming to −15 °C. The reaction mixture was stirred at −15 °C until completion of the reaction. The crude product was purified by flash-column chromatography (*i*hex/Et_2O 5:5) furnishing the compound **159i** as a yellow solid (45 mg, 0.22 mmol 44%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 8.33 (dd, *J* = 3.9, 1.1 Hz, 1H), 8.10 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.74 (dd, *J* = 9.4, 6.6 Hz, 1H), 7.35 (dd, *J* = 5.0, 3.9 Hz, 1H), 7.20 (dd, *J* = 6.6, 0.9 Hz, 1H), 6.63 (dd, *J* = 9.4, 0.9 Hz, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 176.9, 159.9, 156.6, 144.0, 141.5, 137.5, 137.0, 129.8, 121.1, 109.8.

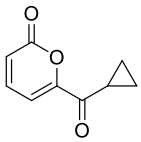
MS (70 eV, EI) *m/z* (%): 206 (39), 111 (100), 95 (60), 39 (26), 28 (12), 18 (13).

HRMS (EI): *m/z* calc. for [$C_{10}H_6O_3S$]: 206.0038; found 206.0045 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3090, 1726, 1636, 1604, 1509, 1410, 1358, 1289, 1077, 858, 811, 734.

M.p. (°C): 143–146.

6-(Cyclopropanecarbonyl)-2*H*-pyran-2-one (159j)



According to **TP6**, 2-pyrone (**154**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.54 mL, 0.60 mmol, 1.20 equiv). The magnesium reagent was treated with CuCN·2LiCl (1.00 M solution in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) for 30 min at −40 °C. Acylation was achieved with cyclopropanecarbonyl chloride (0.05 mL, 0.60 mmol, 1.20 equiv) at −40 °C and warming to −15 °C. The reaction mixture was stirred at −15 °C until completion of the reaction. The crude product was purified by flash-column chromatography (*i*hex/Et_2O = 5:5) furnishing the compound **159j** as a yellow solid (49 mg, 0.30 mmol, 60%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 7.68 (dd, *J* = 9.4, 6.6 Hz, 1H), 7.09 (dd, *J* = 6.6, 1.0 Hz, 1H), 6.59 (dd, *J* = 9.4, 0.9 Hz, 1H), 2.84–2.78 (m, 1H), 1.17–1.07 (m, 4H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 193.7, 160.2, 156.0, 143.8, 121.3, 107.6, 16.7, 12.9.

MS (70 eV, EI) *m/z* (%): 164 (42), 149 (2), 129 (2), 126 (2), 125 (3), 123 (2), 111 (3), 109 (3), 97 (4), 96 (8).

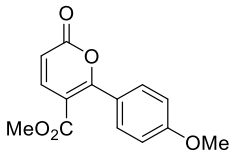
HRMS (EI): *m/z* calc. for [$C_9H_8O_3$]: calc. 164.0473; found 164.0472 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 1718, 1672, 1406, 1244, 1060, 1018, 960, 816.

M.p. (°C): 84–85.

3.4 Reaction of Zincated Methyl Coumalate with Electrophiles

Methyl 6-(4-methoxyphenyl)-2-oxo-2*H*-pyran-5-carboxylate (160a)



According to **TP7**, methyl coumalate (**156**, 72 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –78 °C, using TMPZnCl·LiCl (**92**, 0.95 M in THF, 0.63 mL, 0.60 mmol, 1.20 equiv). The zinc reagent underwent a Negishi cross-coupling reaction in the presence of $Pd(dba)_2$ (11 mg, 8 mol%), $P(2\text{-furyl})_3$ (9.0 mg, 15 mol%) and 1-iodo-4-methoxybenzene (140 mg, 0.60 mmol, 1.20 equiv) at 25 °C for 12 h. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 7:3) furnishing the compound **160a** as an orange solid (59 mg, 0.23 mmol, 45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.81 (d, *J* = 9.7 Hz, 1H), 7.57–7.50 (m, 2H), 6.97–6.91 (m, 2H), 6.24 (d, *J* = 9.7 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 167.2, 165.5, 162.3, 160.6, 144.6, 131.1, 124.3, 113.7, 112.4, 108.6, 55.5, 52.4.

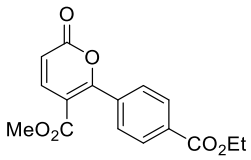
MS (70 eV, EI) *m/z* (%): 260 (40), 232 (76), 201 (26), 135 (100), 77 (16).

HRMS (EI): *m/z* calc. for [$C_{14}H_{12}O_5$]: 260.0685; found 260.0681 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 1723, 1606, 1505, 1436, 1331, 1256, 1178, 1071, 857, 781.

M.p. (°C): 127–129.

Methyl 6-(4-(ethoxycarbonyl)phenyl)-2-oxo-2*H*-pyran-5-carboxylate (160b)



According to **TP7**, methyl coumalate (**156**, 72 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –78 °C, using TMPZnCl·LiCl (**92**, 0.95 M in THF, 0.63 mL, 0.60 mmol, 1.20 equiv). The zinc reagent underwent a Negishi cross-coupling reaction in the presence of $Pd(dba)_2$ (11 mg, 8 mol%), $P(2\text{-furyl})_3$ (9.0 mg, 15 mol%) and ethyl 4-iodobenzoate (0.10 mL, 0.60 mmol, 1.20 equiv) at

25 °C for 12 h. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 7:3) furnishing the compound **160b** as a yellowish liquid (87 mg, 0.29 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 8.11 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 9.7 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 6.35 (d, *J* = 9.7 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H).

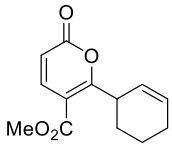
^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 166.1, 165.6, 164.5, 159.7, 143.9, 136.0, 132.7, 129.2, 129.0, 114.0, 110.0, 61.4, 52.4, 14.3.

MS (70 eV, EI) *m/z* (%): 302 (75), 274 (60), 257 (31), 246 (18), 243 (16), 229 (39), 197 (20), 178 (13), 177 (100), 149 (26), 121 (11), 76 (12), 71 (11), 65 (11), 43 (57).

HRMS (EI): *m/z* calc. for [$C_{16}H_{14}O_6$]: 302.0790; found 302.0785 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983, 1752, 1709, 1547, 1269, 1100, 1071, 997, 870, 769, 702.

Methyl 6-(cyclohex-2-en-1-yl)-2-oxo-2*H*-pyran-5-carboxylate (160c)



According to **TP7**, methyl coumalate (**156**, 72 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –78 °C, using TMPZnCl·LiCl (**92**, 0.95 M in THF, 0.63 mL, 0.60 mmol, 1.20 equiv). The magnesium reagent was treated with CuCN·2LiCl (1.00 M solution in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) for 30 min at −78 °C. A subsequent allylation reaction was performed in the presence of 3-bromocyclohex-1-ene (0.07 mL, 0.60 mmol, 1.20 equiv) at −78 °C. The reaction mixture was stirred at 25 °C until completion of the reaction. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 7:3) furnishing the compound **160c** as a white solid (82 mg, 0.35 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.81 (d, *J* = 9.8 Hz, 1H), 6.17 (d, *J* = 9.8 Hz, 1H), 5.93 (ddt, *J* = 9.7, 4.6, 2.7 Hz, 1H), 5.56 (d, *J* = 12.4 Hz, 1H), 4.53 (ddt, *J* = 8.8, 5.9, 2.9 Hz, 1H), 3.87 (s, 3H), 2.21–1.78 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 176.6, 164.5, 160.7, 144.1, 130.2, 124.8, 112.5, 108.4, 52.5, 39.0, 27.4, 24.5, 21.5.

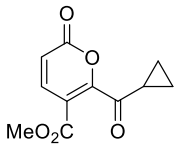
MS (70 eV, EI) *m/z* (%): 234 (94), 230 (62), 225 (40), 217 (4), 215 (100), 209 (24), 202 (100), 174 (72), 108 (52), 79 (76).

HRMS (ESI): *m/z* calc. for [$C_{13}H_{14}O_4$]: 234.0892; found 234.0885 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2947, 1742, 1716, 1622, 1549, 1437, 1290, 1258, 1071, 909, 847, 786.

M.p. (°C): 90–92.

Methyl 6-(cyclopropanecarbonyl)-2-oxo-2*H*-pyran-5-carboxylate (160d)



According to **TP7**, methyl coumalate (**156**, 72 mg, 0.50 mmol) was completely metalated within 15 min at –78 °C, using TMPZnCl·LiCl (**92**, 0.95 M in THF, 0.63 mL, 0.60 mmol, 1.20 equiv). The zinc reagent was treated with CuCN·2LiCl (1.00 M solution in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) for 30 min at −78 °C. Acylation was achieved with cyclopropanecarbonyl chloride (0.05 mL, 0.60 mmol, 1.20 equiv) at −78 °C and warming to −15 °C. The reaction mixture was stirred at 0 °C until completion of the reaction. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 7:3) furnishing the compound **160d** as a yellow oil (44 mg, 0.20 mmol, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.63 (d, *J* = 9.8 Hz, 1H), 6.43 (d, *J* = 9.7 Hz, 1H), 3.83 (s, 3H), 2.45 (tt, *J* = 8.3, 4.5 Hz, 1H), 1.32 (p, *J* = 4.0 Hz, 2H), 1.19 (dq, *J* = 7.8, 3.8 Hz, 2H).

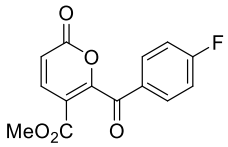
^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 195.1, 164.0, 160.5, 158.5, 142.4, 117.2, 110.3, 53.1, 19.8, 13.9.

MS (70 eV, EI) *m/z* (%): 222 (2), 163 (6), 153 (100), 123 (10), 85 (68), 69 (98).

HRMS (EI): *m/z* calc. for [$C_{11}H_{10}O_5$]: 222.0528; found 222.0521 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 1758, 1727, 1697, 1629, 1440, 1385, 1317, 1199, 1090, 977, 770.

Methyl 6-(4-fluorobenzoyl)-2-oxo-2*H*-pyran-5-carboxylate (160e)



According to **TP7**, methyl coumalate (**156**, 72 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –78 °C, using TMPZnCl·LiCl (**92**, 0.95 M in THF, 0.63 mL, 0.60 mmol, 1.20 equiv). The zinc reagent was treated with CuCN·2LiCl (1.00 M solution in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) for 30 min at −78 °C. Acylation was achieved with 4-fluorobenzoyl chloride (54.0 mL, 0.60 mmol, 1.20 equiv) at −78 °C and warming to −15 °C. The reaction mixture was stirred at 0 °C until completion of the reaction. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 7:3) furnishing the compound **160e** as a yellow oil (77 mg, 0.28 mmol, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.92–7.83 (m, 3H), 7.19 (t, *J* = 8.4 Hz, 2H), 6.42 (d, *J* = 10.2 Hz, 1H), 3.69–3.66 (m, 3H).

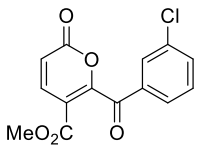
^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 184.6, 166.8 (d, *J* = 258.3 Hz), 163.6, 162.8, 158.2, 142.3, 132.3 (d, *J* = 9.8 Hz), 130.4, 116.6 (d, *J* = 22.4 Hz), 115.7, 109.5, 52.8.

MS (70 eV, EI) *m/z* (%): 245 (20), 232 (34), 217 (100), 203 (16), 189 (16), 175 (24), 153 (16), 123 (100), 85 (10).

HRMS (EI): *m/z* [M + H^+] calc. for [$C_{14}H_{10}FO_5$]: 277.0507; found 277.0504 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 1764, 1723, 1683, 1596, 1437, 1298, 1240, 1156, 1088, 924, 833, 802, 783.

Methyl 6-(3-chlorobenzoyl)-2-oxo-2*H*-pyran-5-carboxylate (160f)



According to **TP7**, methyl coumalate (**156**, 72 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at –78 °C, using TMPZnCl·LiCl (**92**, 0.95 M in THF, 0.63 mL, 0.60 mmol, 1.20 equiv). The zinc reagent was treated with CuCN·2LiCl (1.00 M solution in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) for 30 min at −78 °C. Acylation was achieved with 3-chlorobenzoyl chloride (0.08 mL, 0.60 mmol, 1.20 equiv) at −78 °C and warming to −15 °C. The reaction mixture was stirred at 0 °C

until completion of the reaction. The crude product was purified by flash-column chromatography (*i*hex/EtOAc 7:3) furnishing the compound **160f** as a yellow oil (93 mg, 0.32 mmol, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.90 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.81 (d, *J* = 9.8 Hz, 1H), 7.53 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1H), 7.48–7.39 (m, 2H), 6.41 (d, *J* = 9.8 Hz, 1H), 3.69 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 184.6, 163.3, 163.1, 158.3, 142.7, 134.9, 134.3, 132.9, 132.4, 131.5, 127.4, 115.8, 109.7, 52.9.

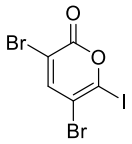
MS (70 eV, EI) *m/z* (%): 292 (8), 250 (10), 203 (40), 153 (33), 140 (27), 139 (100), 111 (25), 85 (17), 75 (17).

HRMS (EI): *m/z* calc. for [$C_{14}H_9ClO_5$]: 292.0139; found 292.0132 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 1756, 1720, 1586, 1434, 1409, 1290, 1232, 1086, 1048, 916, 832, 784, 768, 740.

3.5 Reaction of Zincated 3,5-Dibromo-2*H*-pyran-2-one with Electrophiles

3,5-Dibromo-6-iodo-2H-pyran-2-one (163a)



According to **TP8**, 3,5-dibromo-2*H*-pyran-2-one (**157**, 126 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 1.5 h at −10 °C, using TMPZnCl·LiCl (**92**, 0.95 M in THF, 0.63 mL 0.60 mmol, 1.20 equiv). Iodine (153 mg, 0.60 mmol, 1.20 equiv) was then added at −10°C. The reaction mixture was warmed to 25 °C and was stirred until completion of the reaction. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 9:1) furnishing the compound **163a** as a yellow-brown (120 mg, 0.32 mmol, 64%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 8.03 (s, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 157.1, 146.7, 118.1, 111.6, 111.1.

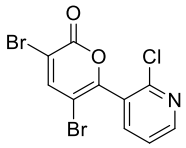
MS (70 eV, EI) *m/z* (%): 379 (45), 338 (24), 255 (47), 253 (100), 251 (51), 227 (25), 224 (49), 223 (26), 199 (26), 127 (12), 118 (20), 116 (21), 53 (6).

HRMS (EI): *m/z* calc. for [$C_5HBr_2IO_2$]: 377.7388; found 377.7382 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921, 2853, 1715, 1574, 1486, 1207, 1055, 983, 902, 885, 733.

M.p. (°C): 97–99.

3,5-Dibromo-6-(2-chloropyridin-3-yl)-2*H*-pyran-2-one (163b)



According to **TP8**, 3,5-dibromo-2*H*-pyran-2-one (**157**, 126 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 1.5 h at −10 °C, using TMPZnCl·LiCl (**92**, 0.95 M in THF, 0.63 mL 0.60 mmol, 1.20 equiv). The zinc reagent reacted in a Negishi cross-coupling reaction in the presence of $Pd(dba)_2$ (11 mg, 8 mol%), P(2-furyl)$_3$ (9.0 mg, 15 mol%) and 2-chloro-3-iodopyridine (143 mg, 0.60 mmol,

1.20 equiv) at 25 °C for 12 h. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 7:3) furnishing the compound **163b** as a yellow oil (107 mg, 0.30 mmol, 60%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 8.62 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.26 (s, 1H), 8.16 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.65 (dd, *J* = 7.6, 4.8 Hz, 1H).

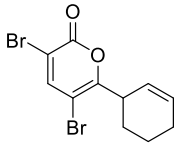
^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 157.2, 154.9, 153.0, 149.9, 148.4, 141.6, 128.7, 124.0, 113.1, 101.6.

MS (70 eV, EI) *m/z* (%): 365 (100), 363 (38), 339 (42), 337 (75), 335 (28), 286 (20), 232 (14), 229 (78), 228 (58), 197 (13), 149 (14), 142 (17), 140 (60), 114 (17), 112 (40), 76 (21), 50 (11), 44 (18), 43 (11).

HRMS (EI): *m/z* calc. for [$C_{10}H_4Br_2ClNO_2$]: 362.8297; found 362.8296 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2922, 2853, 1737, 1716, 1602, 1492, 1409, 1248, 1177, 1055, 1026, 913, 902, 845, 741, 733.

3,5-Dibromo-6-(cyclohex-2-en-1-yl)-2*H*-pyran-2-one (163c)



According to **TP8**, 3,5-dibromo-2*H*-pyran-2-one (**157**, 126 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 1.5 h at −10 °C, using TMPZnCl·LiCl (**92**, 0.95 M in THF, 0.63 mL 0.60 mmol, 1.20 equiv). The zinc reagent was treated with CuCN·2LiCl (1.00 M solution in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) for 30 min at −40 °C. A subsequent allylation reaction was performed in the presence of 3-bromocyclohex-1-ene (0.07 mL, 0.60 mmol, 1.20 equiv) at −40 °C. The reaction mixture was stirred at 25 °C until completion of the reaction. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 7:3) furnishing the compound **163c** as a yellow oil (100 mg, 0.30 mmol, 60%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 8.02 (s, 1H), 6.00–5.86 (m, 1H), 5.65–5.56 (m, 1H), 3.78 (ddp, *J* = 8.5, 5.7, 2.6 Hz, 1H), 2.09 (ddd, *J* = 11.4, 5.7, 2.8 Hz, 2H), 1.99 (dtd, *J* = 11.3, 5.7, 2.7 Hz, 1H), 1.90 (dtt, *J* = 12.1, 5.5, 2.2 Hz, 1H), 1.82–1.72 (m, 1H), 1.71–1.58 (m, 1H).

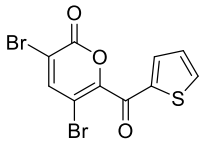
^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 164.8, 157.9, 148.8, 131.0, 125.0, 109.9, 97.9, 40.5, 26.8, 25.0, 21.8.

MS (70 eV, EI) *m/z* (%): 334 (38), 332 (20), 305 (12), 280 (16), 255 (11), 254 (57), 253 (57), 251 (12), 224 (13), 197 (14), 146 (25), 117 (10), 81 (100), 80 (15), 79 (33), 77 (17), 53 (22), 51 (10), 41 (21).

HRMS (EI): *m/z* calc. for [$C_{11}H_{10}Br_2O_2$]: 331.9048; found 331.9033 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2927, 2834, 1719, 1608, 1532, 1287, 1134, 1033, 986, 959, 902, 867, 740, 716.

3,5-Dibromo-6-(thiophene-2-carbonyl)-2*H*-pyran-2-one (163d)



According to **TP8**, 3,5-dibromo-2*H*-pyran-2-one (**157**, 126 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 1.5 h at −10 °C, using TMPZnCl·LiCl (**92**, 0.95 M in THF, 0.63 mL 0.60 mmol, 1.20 equiv). The zinc reagent was treated with CuCN·2LiCl (1 M solution in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) for 30 min at −40 °C. Acylation was achieved with thiophene-2-carbonyl chloride (0.06 mL, 0.60 mmol, 1.20 equiv) at −40 °C and warming to −10 °C. The reaction mixture was stirred at −15 °C until completion of the reaction. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 7:3) furnishing the compound **163d** as a yellow oil (100 mg, 0.28 mmol, 55%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 8.25 (d, *J* = 1.0 Hz, 1H), 8.20–8.15 (m, 2H), 7.34 (ddd, *J* = 4.9, 3.9, 1.0 Hz, 1H).

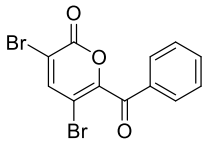
^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 177.6, 155.8, 152.2, 148.9, 141.5, 138.7, 138.3, 130.0, 116.0, 100.7.

MS (70 eV, EI) *m/z* (%): 364 (12), 285 (5), 283 (4), 112 (6), 111 (100), 83 (5).

HRMS (EI): *m/z* calc. for [$C_9H_8O_3$]: 361.8248; found 361.8240 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2922, 2858, 1731, 1638, 1510, 1409, 1354, 1289, 1240, 1062, 1028, 933, 902, 823, 735.

6-Benzoyl-3,5-dibromo-2*H*-pyran-2-one (163e)



According to **TP8**, 3,5-dibromo-2*H*-pyran-2-one (**157**, 126 mg, 0.50 mmol, 1.00 equiv) was completely metalated within 15 min at −10 °C, using TMPZnCl·LiCl (**92**, 0.95 M in THF, 0.63 mL 0.60 mmol, 1.20 equiv). The zinc reagent was treated with CuCN·2LiCl (1.00 M solution in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) for 30 min at −40 °C. Acylation was achieved with benzoyl chloride (0.07 mL, 0.60 mmol, 1.20 equiv) at −40 °C and warming to −10 °C. The reaction mixture was stirred at −10 °C until completion of the reaction. The crude product was purified by flash-column chromatography (*i*hex/EtOAc 7:3) furnishing the compound **163e** as a yellow oil (94 mg, 0.26 mmol, 53%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 8.23 (s, 1H), 8.10–8.04 (m, 2H), 7.80–7.74 (m, 1H), 7.65–7.59 (m, 2H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 186.5, 156.0, 153.0, 148.4, 135.8, 135.0, 130.9, 130.0, 115.5, 100.1.

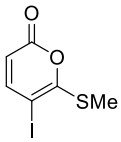
MS (70 eV, EI) *m/z* (%): 359 (9), 355 (5), 106 (6), 105 (100), 77 (28), 50 (2).

HRMS (EI): *m/z* calc. for [$C_{12}H_6Br_2O_3$]: 355.8684; found 355.8678 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 1741, 1668, 1594, 1448, 1272, 1226, 1040, 949, 798, 725, 681.

3.6 Further Functionalization of the 6-Substituted 2-Pyrones

5-Iodo-6-(methylthio)-2*H*-pyran-2-one (165)



According to **TP9**, 6-(methylthio)-2*H*-pyran-2-one (**159c**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 1 h at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.54 mL, 0.60 mmol, 1.20 equiv). Iodine (152 mg, 0.60 mmol, 1.20 equiv) was then added at –40 °C. The reaction mixture was warmed to 25 °C and was stirred until completion of the reaction. The crude product was purified by column chromatography (*i*hex/Et_2O = 4:6) furnishing the compound **165** as a yellow oil (58 mg, 0.22 mmol, 43%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 8.01 (d, *J* = 7.4 Hz, 1H), 6.11 (d, *J* = 7.4 Hz, 1H), 2.56 (s, 3H).

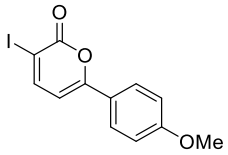
^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 166.7, 158.9, 153.6, 104.3, 77.5, 14.0.

MS (70 eV, EI) *m/z* (%): 267 (64), 39 (13), 220 (100), 192 (17), 85 (13), 55 (10), 44 (11), 43 (10).

HRMS (EI): *m/z* calc. for [$C_6H_5IO_2S$]: 267.9055; found 267.9063 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2927, 2868, 1708, 1590, 1492, 1325, 1237, 1107, 967, 744.

3-Iodo-6-(4-methoxyphenyl)-2*H*-pyran-2-one (167a)



According to **TP9**, 2-pyrone (**159e**, 0.50 M in THF, 1.00 mL, 0.50 mmol) was completely metalated within 1 h at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.54 mL, 0.60 mmol, 1.20 equiv). Iodide (152 mg, 0.60 mmol, 1.20 equiv) was then added at –40 °C. The reaction mixture was warmed to 25 °C and was stirred until completion of the reaction. The crude product was purified by column chromatography (*i*hex/Et_2O = 4:6) furnishing the compound **167a** as a yellow-orange oil (157 mg, 0.48 mmol, 95%).

1H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 8.19 (d, J = 7.4 Hz, 1H), 7.89–7.84 (m, 2H), 7.10–7.05 (m, 2H), 6.68 (d, J = 7.4 Hz, 1H), 3.89 (s, 3H).

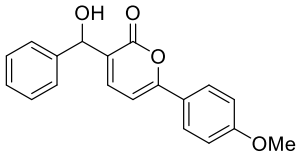
13C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 163.2, 162.4, 159.0, 154.3, 128.2, 124.3, 115.4, 102.2, 81.4, 55.9.

MS (70 eV, EI) m/z (%):327 (61), 299 (21), 201 (10), 146 (11), 145 (100), 135 (19), 130 (10), 102 (23), 92 (10), 77 (11), 76 (8), 63 (9).

HRMS (EI): m/z calc. for [$C_{12}H_9IO_3$]: 327.9600; found 327.9585 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm-1 = 2924, 1708, 1598, 1504, 1458, 1257, 1176, 1107, 1024, 837.

3-(Hydroxy(phenyl)methyl)-6-(4-methoxyphenyl)-2*H*-pyran-2-one (167b)



According to **TP9**, 2-pyrone (**159e**, 0.25 M in THF, 1.00 mL, 0.25 mmol) was completely metalated within 1 h at –40 °C, using TMPMgCl·LiCl (**89**, 1.10 M in THF, 0.27 mL, 0.30 mmol, 1.20 equiv). Benzaldehyde (0.03 mL, 0.30 mmol, 1.20 equiv) was then added at –40 °C. The reaction mixture was warmed to 25 °C and was stirred until completion of the reaction. The crude product was purified by column chromatography (*i*hex/EtOAc = 8:2) furnishing the compound **167b** as a yellow oil (34 mg, 0.11 mmol, 45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.71–7.64 (m, 2H), 7.39 (d, *J* = 7.3 Hz, 2H), 7.34–7.29 (m, 2H), 7.25 (dd, *J* = 8.3, 6.1 Hz, 1H), 7.20–7.14 (m, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.47 (d, *J* = 7.1 Hz, 1H), 5.74 (s, 1H), 3.79 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = δ = 162.6, 161.9, 160.1, 140.8, 140.0, 128.7, 128.2, 127.4, 127.4, 126.8, 123.7, 114.5, 100.0, 72.1, 55.6.

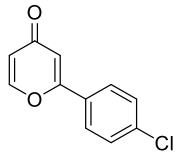
MS (70 eV, EI) m/z (%): 308 (100), 292 (15), 291 (11), 279 (18), 264 (15), 263 (39), 262 (24), 231 (30), 204 (10), 203 (71), 202 (11), 145 (13), 135 (66), 107 (10), 105 (30), 79 (14).

HRMS (EI): m/z calc. for [$C_{19}H_{16}O_4$]: 308.1049; found 308.1043 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2838, 1697, 1694, 1605, 1554, 1510, 1257, 1175, 1026, 806, 700.

3.7 Reaction of Zincated 4-Pyrone with Electrophiles

2-(4-Chlorophenyl)-4*H*-pyran-4-one (169a)



According to **TP10**, 4*H*-pyran-4-one (**155**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 2 h at −35 °C, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.55 M in THF, 0.55 mL, 0.30 mmol, 0.60 equiv). The zinc reagent reacted in a Negishi cross-coupling reaction in the presence of $Pd(dba)_2$ (11 mg, 8 mol%), $P(2\text{-furyl})_3$ (9.0 mg, 15 mol%) and 1-chloro-4-iodobenzene (114 mg, 0.60 mmol, 1.20 equiv) at 25 °C for 12 h. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 7:3) furnishing the compound **169a** as a yellow solid (52 mg, 0.25 mmol, 50%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = δ = 8.11 (d, *J* = 6.1 Hz, 1H), 7.96–7.88 (m, 2H), 7.61–7.54 (m, 2H), 6.81 (d, *J* = 2.4 Hz, 1H), 6.29 (dd, *J* = 5.9, 2.4 Hz, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 178.4, 163.0, 156.4, 137.6, 131.2, 130.1, 128.3, 117.5, 113.1.

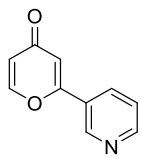
MS (70 eV, EI) *m/z* (%):206 (97), 205 (68), 138 (33), 101 (14), 89 (8).

HRMS (EI): *m/z* calc. for $[C_{11}H_7ClO_2]$: 206.0135; found 206.0123 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2914, 1649, 1539, 1424, 1363, 1201, 1092, 1055, 1029, 836, 798, 720.

M.p. (°C): 124–126.

2-(Pyridin-3-yl)-4*H*-pyran-4-one (169b)



According to **TP10**, 4*H*-pyran-4-one (**155**, 0.50 M in THF, 1.00 mL 0.50 mmol, 1.00 equiv) was completely metalated within 2 h at −35 °C, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.55 M in THF, 0.55 mL,

0.30 mmol, 0.60 equiv). The zinc reagent underwent a Negishi cross-coupling reaction in the presence of $Pd(dba)_2$ (11 mg, 8 mol%), P(2-furyl)$_3$ (9.0 mg, 15 mol%) and 3-iodopyridine (60 mg, 0.60 mmol, 1.20 equiv) at 25 °C for 12 h. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 7:3) furnishing the compound **169b** as a brown solid (74 mg, 0.43 mmol, 86%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 9.09 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.74 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.26 (ddd, *J* = 8.1, 2.4, 1.6 Hz, 1H), 8.15 (dd, *J* = 5.9, 0.3 Hz, 1H), 7.56 (ddd, *J* = 8.1, 4.8, 0.9 Hz, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 6.32 (dd, *J* = 5.9, 2.4 Hz, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 178.3, 162.2, 156.6, 152.8, 147.9, 134.0, 128.4, 124.6, 117.7, 113.8.

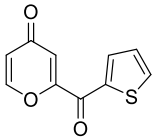
MS (70 eV, EI) *m/z* (%):173 (100), 174 (12), 145 (59), 116 (10), 106 (14), 103 (35), 78 (11), 76 (15), 51 (7), 50 (11).

HRMS (EI): *m/z* calc. for [$C_{10}H_7NO_2$]: 173.0477; found 173.0476 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 1647, 1425, 1368, 1251, 1200, 1125, 1058, 1012, 932, 831, 703.

M.p. (°C): 115–116.

2-(Thiophene-2-carbonyl)-4*H*-pyran-4-one (169c)



According to **TP10**, 4*H*-pyran-4-one (**155**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 2 h at −35 °C, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.55 M in THF, 0.55 mL, 0.30 mmol, 0.60 equiv). The zinc reagent was treated with CuCN·2LiCl (1.00 M solution in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) for 30 min at −35 °C. Acylation was achieved with thiophene-2-carbonyl chloride (0.06 mL, 0.60 mmol, 1.20 equiv) at −35 °C and warming to −5 °C. The reaction mixture was stirred at −5 °C until completion of the reaction. The crude product was purified by flash-column chromatography. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 7:3) furnishing the compound **169c** as a yellow-orange solid (73 mg, 0.35 mmol, 71%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 8.28 (dd, *J* = 3.9, 1.1 Hz, 1H), 8.24 (dd, *J* = 5.9, 0.3 Hz, 1H), 8.14 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.34 (dd, *J* = 5.0, 3.9 Hz, 1H), 6.89 (dd, *J* = 2.6, 0.3 Hz, 1H), 6.46 (dd, *J* = 5.9, 2.6 Hz, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 178.2, 178.2, 159.7, 156.5, 141.2, 138.1, 137.4, 129.9, 119.0, 118.7.

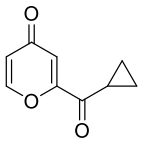
MS (70 eV, EI) *m/z* (%): 206 (31), 178 (22), 110 (100), 82 (7).

HRMS (EI): *m/z* calc. for $[C_{10}H_6O_3S]$: 206.0038; found 206.0037 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3077, 1634, 1409, 1376, 1352, 1279, 1201, 1109, 1057, 940, 833, 798, 720.

M.p. (°C): 128–131.

2-(Cyclopropanecarbonyl)-4*H*-pyran-4-one (169d)



According to **TP10**, 4*H*-pyran-4-one (**155**, 0.50 M in THF, 1.00 mL, 0.50 mmol, 1.00 equiv) was completely metalated within 2 h at −35 °C, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93**, 0.55 M in THF, 0.54 mL, 0.30 mmol, 0.60 equiv). The zinc reagent was treated with CuCN·2LiCl (1.00 M solution in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) for 30 min at −35 °C. Acylation was achieved with cyclopropanecarbonyl chloride (0.05 µL, 0.60 mmol, 1.20 equiv) at −35 °C and warming to −5 °C. The reaction mixture was stirred at −5 °C until completion of the reaction. The crude product was purified by flash-column chromatography. The crude product was purified by flash-column chromatography (*i*hex/EtOAc = 7:3) furnishing the title compound **169d** as a yellow-brown solid (41 mg, 0.25 mmol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.84 (d, *J* = 5.8 Hz, 1H), 6.98 (d, *J* = 2.6 Hz, 1H), 6.44 (dd, *J* = 5.8, 2.6 Hz, 1H), 2.66 (ddd, *J* = 12.4, 7.8, 4.5 Hz, 1H), 1.32–1.26 (m, 2H), 1.16 (dq, *J* = 7.6, 4.2, 3.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 194.1, 179.0, 157.9, 154.9, 118.8, 116.8, 17.0, 13.8.

MS (70 eV, EI) *m/z* (%): 164 (53), 123 (8), 69 (100), 41 (27).

HRMS (EI): *m/z* calc. for [$C_9H_8O_3$]: 164.0473; found 164.0465 (M^+).

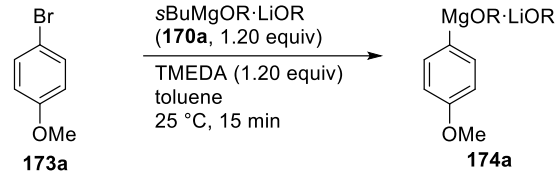
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 1648, 1410, 1367, 1244, 1197, 1178, 1103, 1056, 997, 834, 720.

M.p. (°C): 75–77.

4 Aryl and Heteroaryl Magnesium Reagents in Toluene by Br/Mg- or Cl/Mg-Exchange

4.1 Screening of Magnesium Exchange Reagent

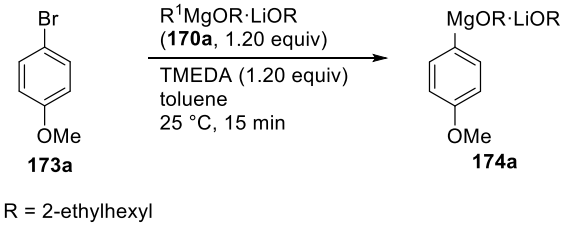
Table 15: Variation of the Alkoxide Residue.



Entry	R^1	Yield (%)[a]
1	$CH(Bu)_2$	0
2	$C(CH_3)(Et)(iPr)$	83
3	CH(Me)Hex	99
4	$CH_2CH(Et)Bu$	99[b]

[a] Yield of **174a** determined by GC-analysis of water quenched reaction aliquots. [b] 2-Ethylhexanol was used instead of 2-octanol because it is commercially available.

Table 16: Variation of the Alkyl Residue.

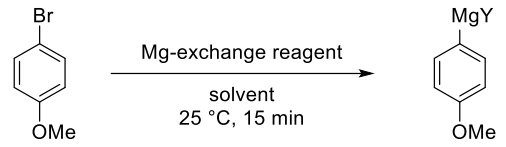


R = 2-ethylhexyl

Entry	R^1	Yield (%)[a]
1	*n*Bu	35
2	*s*Bu	99
3	*t*Bu	49

[a] Yield of **174a** determined by GC-analysis of water quenched reaction aliquots.

Table 17: Bromine-magnesium exchange for 4-bromoanisole (**174a**) using various magnesium-exchange reagents.

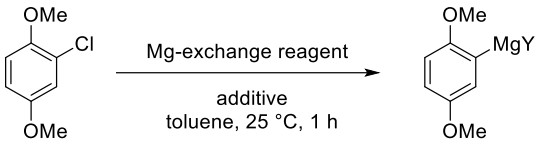


173a **174a**

Entry	Mg-exchange reagent	Equiv	Solvent	Yield(%)[a]
1	*i*PrMgCl·LiCl (**36**)	1.20	THF	1 [0][b]
2	*s*Bu_2Mg·2LiCl (**81**)	0.60	THF	13 [0][b]
3	*n*Bu_3MgLi	0.40	THF	99 [0][b],[d]
4	*s*BuMgOR·LiOR (**170a**)	1.20	toluene	85
5	*s*BuMgOR·LiOR (**170a**)	1.20	toluene	99[c],[e]
6	*s*BuMgOR·LiOR (**170a**)	1.20	THF	14[c]

[a] Yield of **174a** determined by GC-analysis of water quenched reaction aliquots. [b] Yield obtained in toluene. [c] Yield obtained in the presence of TMEDA (1.20 equiv). [d] Decomposition was observed by reaction with various electrophiles. [e] The reactions were also performed in hexane, cyclohexane or cyclopentyl methyl ether (CPME) with the same yield.

Table 18: Chlorine-magnesium exchange on aryl chloride **179a** using various magnesium-exchange reagents.



179a **180a**

Entry	Mg-exchange reagent	Equiv	Additive	Yield (%)[a]
1	*i*PrMgCl·LiCl (**36**)	1.20	PMDTA	0 [0][b]
2	*s*Bu_2Mg·2LiCl (**81**)	0.60	PMDTA	0 [0][b]
3	*n*Bu_3MgLi	0.40	PMDTA	decomposition
4	*s*BuMgOR·LiOR (**170a**)	1.20	PMDTA	0 [0][b]
5	*s*Bu_2Mg·2LiOR (**170b**)	0.60	-	48
6	*s*Bu_2Mg·2LiOR (**170b**)	0.60	TMEDA	59
7	*s*Bu_2Mg·2LiOR(**170b**)	0.60	PMDTA	73 [20][c]

[a] Yield of **180a** determined by GC-analysis of water quenched reaction aliquots. [b] Yield obtained in the presence of TMEDA. [c] Yield obtained in THF.

Lithium tributylmagnesiate is not suitable for a chlorine-magnesium exchange (entry 3). *s*Bu_2Mg·2LiOR (**170b**) is certainly the most powerful exchange reagent to date for performing bromine-magnesium exchanges and is also able to trigger a chlorine-magnesium exchange. *s*BuMgOR·LiOR (**170a**) gave no exchange with aryl chlorides. It was possible to replace *s*BuMgOR·LiOR (**170a**) by *s*Bu_2Mg·2LiOR (**170b**) in the case of 4-bromoanisole. However, the reaction conditions were not improved. In case of halogenated heterocycles, we observed more decomposition by using *s*Bu_2Mg·2LiOR (**170b**) instead of *s*BuMgOR·LiOR (**170a**), due to the too high reactivity of the reagent. Thus, the use of *s*BuMgOR·LiOR (**170a**) compared to *s*Bu_2Mg 2LiOR (**170b**) is beneficial in the performance of bromine-magnesium exchanges, since the aryl- and heteroarylmagnesium alkoxides are more stable in toluene. Furthermore, the storage of *s*BuMgOR·LiOR (**170a**) over several weeks is possible.

4.2 Preparation of *s*BuMgOCH_2CH(Et)Bu·LiOCH_2CH(Et)Bu (170a):

Method A:

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with *n*Bu_2Mg (0.66 M in hexane, 15.0 mL, 9.9 mmol) and the reaction mixture was cooled to 0 °C. Then, 2-ethylhexanol (3.10 mL, 20 mmol) was added dropwise. After 24 h a gelatinous compound was obtained.[111] To the reaction mixture *s*BuLi (1.21 M in hexane, 8.18 mL, 9.9 mmol) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm to room temperature for 2 h. The solvents were removed under vaccum affording a lightly yellow foam. Freshly distilled toluene (9 mL) was added under vigourous stirring at 0 °C. The freshly prepared *s*BuMgOCH_2CH(Et)Bu·LiOCH_2CH(Et)Bu was titrated prior to use at 0 °C by iodometric titration. The *s*BuMgOCH_2CH(Et)Bu·LiOCH_2CH(Et)Bu concentration of the resulting clear solution was 1.00–1.50 M.

Method B:

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with Mg[OCH_2CH(Et)Bu]$_2$[112] (0.85 M in heptane, 15.0 mL, 13 mmol) and was cooled to 0 °C. Then, *s*BuLi (1.21 M in hexane, 10.6 mL, 13 mmol) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm to room temperature for 2 h. The solvents were removed under vaccum affording a lightly yellow foam. Freshly distilled toluene (9 mL) was added under vigourous stirring at 0 °C. The prepared *s*BuMgOCH_2CH(Et)Bu·LiOCH_2CH(Et)Bu was titrated prior to use at 0 °C by iodometric titration. The *s*BuMgOCH_2CH(Et)Bu·LiOCH_2CH(Et)Bu concentration of the resulting clear solution was 1.00–1.50 M.

4.3 Preparation of *s*$Bu_2Mg{\cdot}2LiOCH_2CH(Et)Bu$ (170b):

Method A:

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with *n*Bu_2Mg (0.66 M in hexane, 15.0 mL, 9.9 mmol) and the reaction mixture was cooled to 0 °C. Then, 2-ethylhexanol (3.10 mL, 20 mmol) was added dropwise. After 24 h a gelatinous compound was obtained. To the reaction mixture *s*BuLi (1.21 M in hexane, 16.4 mL, 20 mmol) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm to room temperature for 2 h. The solvents were removed under vaccum affording a lightly yellow foam. Freshly distilled toluene (9 mL) was added under vigourous stirring at 0 °C. The prepared *s*$Bu_2Mg{\cdot}2LiOCH_2CH(Et)Bu$ was titrated prior to use at 0 °C by iodometric titration. The *s*$Bu_2Mg{\cdot}2LiOCH_2CH(Et)Bu$ concentration of the resulting clear solution was 0.60–0.85 M.

Method B:

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with $Mg[OCH_2CH(Et)Bu]_2$ (0.85 M in heptane, 15.0 mL, 13 mmol) and was cooled to 0 °C. Then, *s*BuLi (1.21 M in hexane, 21.2 mL, 26 mmol) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm to room temperature for 2 h. The solvents were removed under vaccum affording a lightly yellow foam. Freshly distilled toluene (9 mL) was added under vigourous stirring at 0 °C. The freshly prepared *s*$Bu_2Mg{\cdot}2LiOCH_2CH(Et)Bu$ was titrated prior to use at 0 °C by iodometric titration. The *s*$Bu_2Mg{\cdot}2LiOCH_2CH(Et)Bu$ concentration of the resulting clear solution was 0.60–0.85 M.

4.4 Titration Using Iodine[128]

A dry flask was charged with accurately weighed I_2 (0.25 mmol), fitted with a rubber septum, and flushed with argon. THF (3–5 mL) was added and stirring was started. After the iodine was completely dissolved, the resulting brown solution was cooled to 0 °C in an ice bath and the organomagnesium reagent was added dropwise *via* a 1.00 mL syringe (0.01 mL graduations) until the brown color disappeared. The amount consumed contains 1.00 equiv of the organometallic reagent relative to iodine in the case of monoorganometallic reagents and 0.50 equiv for diorganometallic reagents.

4.5 Typical Procedures

Typical Procedure for the Preparation of Arylmagnesium Alkoxides *via* a Bromine-Magnesium Exchange using 170a (TP11):

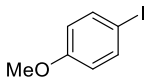
A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with the corresponding aryl bromide (1.00 equiv) in dry toluene (0.50–1.0 M solution) and TMEDA (1.20 equiv) was added. The resulting solution was stirred at indicated temperature and *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.20 equiv) was added dropwise. The completion of the bromine-magnesium exchange was checked by GC-analysis of reaction aliquots quenched with water, using tetradecane as internal standard. Subsequent reactions with electrophiles were carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl solution or aq. $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated.

Typical Procedure for the Preparation of Arylmagnesium Alkoxides *via* a Chlorine-Magnesium Exchange using 170b (TP12):

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with the corresponding aryl chloride (1.00 equiv) in dry toluene (0.50–1.0 M solution) and TMEDA (1.20 equiv) was added. The resulting solution was stirred at 25 °C and *s*BuMg$_2$·LiOCH$_2$CH(Et)Bu (**170b**, 1.20 equiv) was added dropwise. The completion of the chlorine-magnesium- exchange was checked by GC-analysis of reaction aliquots quenched with water, using tetradecane as internal standard. Subsequent reactions with electrophiles were carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl solution or aq. $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated.

4.6 Aryl Magnesium Reagents in Toluene by Br/Mg-Exchange

4-Iodoanisole (175a)



According to **TP11**, to a mixture of 4-bromoanisole (**173a**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, iodine (152 mg, 0.60 mmol, 1.20 equiv, in 1.00 mL THF) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded title compound **175a** as a white solid (81 mg, 0.35 mmol, 70%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.63–7.49 (d, 2H), 6.76–6.61 (d, 2H), 3.78 (s, 3H).

^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 159.6, 138.3, 116.5, 82.8, 55.5.

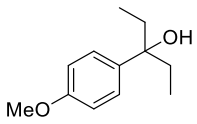
MS (EI, 70 eV): *m/z* (%) = 234 (100), 191 (15), 154 (11), 126 (10), 92 (64), 77 (41), 76 (11), 74 (14), 64 (23), 62 (23), 61 (10), 48 (19).

HRMS (EI): *m/z* calc. for [C$_7$H$_7$IO]: 233.9542; found: 233.9540 (M$^+$).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2966, 2837, 1586, 1486, 1287, 1248, 1175, 1028, 833, 813.

M.p. (°C): 52–55.

3-(4-Methoxyphenyl)pentan-3-ol (175b)



According to **TP11**, to a mixture of 4-bromoanisole (**173a**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, 3-pentanone (0.06 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 2 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175b** as a light yellow oil (78 mg, 0.40 mmol, 80%).

^{1}H-NMR (400 MHz, CDCl3): δ / ppm = 7.32–7.24 (d, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 1.92–1.72 (m, 4H), 0.76 (t, *J* = 7.4 Hz, 6H).

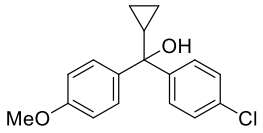
^{13}C-NMR (101 MHz, CDCl3): δ / ppm = 158.2, 138.0, 127.3, 126.8, 113.4, 55.3, 35.0, 8.0.

MS (EI, 70 eV): *m/z* (%) = 194 (2), 176 (11), 165 (100), 57 (19).

HRMS (EI): *m/z* calc. for [$C_{12}H_{18}O_2$]: 194.1307; found: 194.1282 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972, 2837, 1677, 1601, 1510, 1462, 1245, 1174, 1031, 828.

(4-Chlorophenyl)(cyclopropyl)(4-methoxyphenyl)methanol (175c)



According to **TP11**, to a mixture of 4-bromoanisole (**173a**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, (4-chlorophenyl)(cyclopropyl) methanone (0.12 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 2 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175c** as a light yellow oil (124 mg, 0.43 mmol, 86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37–7.31 (m, 4H), 7.28–7.23 (m, 2H), 6.86–6.80 (m, 2H), 3.78 (s, 3H), 1.82 (s, OH), 1.54 (m, *J* = 8.3, 5.5, 1H), 0.62 (m, *J* = 8.0, 5.0, 3.0, 1H), 0.55–0.39 (m, 3H).

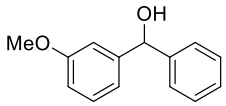
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.9, 146.2, 139.2, 132.8, 128.3, 128.1, 113.5, 76.6, 55.4, 21.8, 2.3, 1.6.

MS (EI, 70 eV): *m/z* (%) = 281 (38), 225 (98), 209 (32), 207 (100), 149 (32), 128 (22), 117 (20), 115 (24), 104 (19), 91 (68), 81 (18), 79 (23), 78 (87), 77 (29), 43 (35).

HRMS (EI): *m/z* calc. for [$C_{17}H_{17}ClO_2$]: 288.0917; found: 288.0909 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1608, 1508, 1246, 1174, 1090, 1034, 1014, 984, 880, 818.

(3-Methoxyphenyl)(phenyl)methanol (175d)



According to **TP11**, to a mixture of 3-bromoanisole (**173b**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, benzaldehyde (0.06 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175d** as a light yellow oil (104 mg, 0.48 mmol, 95%).

^{1}H-NMR (599 MHz, CDCl$_3$): δ / ppm = 7.37–7.30 (m, 4H), 7.27–7.21 (m, 2H), 6.97–6.88 (m, 2H), 6.80 (dd, *J* = 8.2, 2.6 Hz, 1H), 5.71 (s, 1H), 3.74 (s, 3H), 2.82 (s, OH).

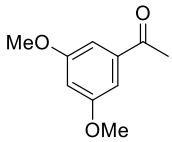
^{13}C-NMR (151 MHz, CDCl$_3$): δ / ppm = 159.7, 145.6, 143.8, 129.5, 128.5, 127.5, 126.6, 119.0, 112.9, 112.1, 76.0, 55.2.

MS (EI, 70 eV): *m/z* (%) = 214 (81), 152 (12), 135 (47), 107 (19), 105 (90), 94 (13), 92 (12), 79 (31), 78 (20), 77 (100), 65 (15), 51 (18).

HRMS (EI): *m/z* calc. for [C$_{14}$H$_{14}$O$_2$]: 214.0994; found: 214.0987 (M$^+$).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2835, 1598, 1488, 1453, 1435, 1258, 1149, 1036, 784, 702.

1-(3,5-Dimethoxyphenyl)ethan-1-on (175e)



According to **TP11**, to a mixture of 1-bromo-3,5-dimethoxybenzene (**173c**, 109 mg, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, *N*-methoxy-*N*-methylacetamide (0.06 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175e** as a light yellow oil (80 mg, 0.44 mmol, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.07 (s, 2H), 6.64 (s, 1H), 3.82 (s, 6H), 2.56 (s, 3H).

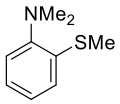
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 197.8, 161.0, 139.2, 106.3, 105.4, 55.7, 26.8.

MS (EI, 70 eV): *m/z* (%) = 180 (74), 165 (100), 137 (25), 122 (31), 77 (12), 63 (10), 24 (24).

HRMS (EI): *m/z* calc. for [$C_{10}H_{12}O_2$]: 180.0786; found: 180.0780 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2938, 1680, 1590, 1356, 1297, 1203, 1152, 1065, 1043, 842, 681.

***N*,*N*-Dimethyl-2-(methylthio)aniline (175f)**



According to **TP11**, to a mixture of 2-bromo-*N*,*N*-dimethylaniline (**173d**, 109 mg, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, *S*-methyl methanesulfonothioate (0.05 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175f** as a light orange oil (70 mg, 0.42 mmol, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.21–7.15 (m, 1H), 6.69–6.64 (m, 2H), 6.58–6.54 (m, 1H), 2.96 (s, 6H), 2.50 (s, 3H).

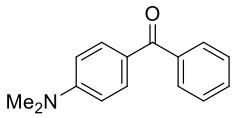
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 150.9, 139.1, 129.5, 114.9, 111.0, 109.9, 40.6, 16.1.

MS (EI, 70 eV): *m/z* (%) = 167 (100), 166 (71), 152 (10), 151 (18), 134 (13), 43 (73).

HRMS (EI): *m/z* calc. for [$C_9H_{13}NS$]: 167.0769; found: 167.0759 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2917, 2799, 1584, 1561, 1490, 1346, 1104, 988, 955, 759, 685.

(4-(Dimethylamino)phenyl)(phenyl)methanone (175g)



According to **TP11**, to a mixture of 2-bromo-*N*,*N*-dimethylaniline (**173e**, 109 mg, 0.50 mmol, 1.00 equiv), TMEDA (0.06 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol 1.20 equiv) at 25 °C. After 4 h, *N*-methoxy-*N*-methylacetamide (0.06 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 2 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175g** as a light orange oil (74 mg, 0.33 mmol, 65%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.43 (m, *J* = 7.7, 1.5, 0.8 Hz, 2H), 7.37–7.22 (m, 5H), 7.13 (m, *J* = 8.3, 6.7, 1.8 Hz, 1H), 7.07 (m, *J* = 7.7, 1.5, 0.8 Hz, 1H), 2.60 (s, 6H).

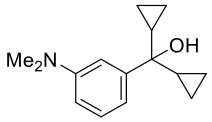
^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 195.2, 153.4, 139.4, 132.8, 131.2, 129.5, 128.1, 124.9, 110.7, 40.2.

MS (EI, 70 eV): *m/z* (%) = 225 (65), 224 (13), 148 (199), 134 (21), 105 (15), 77 (37).

HRMS (EI): *m/z* calc. for [C$_{15}$H$_{15}$NO]: 225.1154; found: 225.1131 (M$^+$).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2945, 2830, 1595, 1485, 1453, 1149, 1033, 1016, 934, 771, 761, 699.

Dicyclopropyl(3-(dimethylamino)phenyl)methanol (175h)



According to **TP11**, to a mixture of 3-bromo-*N*,*N*-dimethylaniline (**173f**, 365 mg, 1.0 mmol, 1.00 equiv), TMEDA (0.18 mL, 1.2 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 1.20 mL, 1.2 mmol 1.20 equiv) at 25 °C. After 1.5 h, dicyclopropyl ketone (0.14 mL, 1.2 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 2 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175h** as a colorless oil (185 mg, 0.80 mmol, 80%).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.25 (t, *J* = 7.9 Hz, 1H), 7.17 (s, 1H), 7.07 (dt, *J* = 7.7, 1.2 Hz, 1H), 6.57 (ddd, *J* = 8.2, 2.6, 0.8 Hz, 1H), 2.63 (s, 6H), 1.10 (tt, *J* = 8.4, 5.5 Hz, 2H), 0.63 (m, *J* = 9.5, 5.5, 4.0 Hz, 2H), 0.50 (m, *J* = 9.5, 5.6, 4.0 Hz, 2H), 0.40–0.32 (m, 2H), 0.24–0.17 (m, 2H).

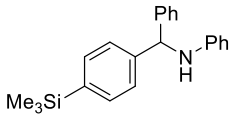
^{13}C-NMR (101 MHz, C_6D_6): δ / ppm = 150.8, 148.9, 128.7, 115.1, 111.6, 111.0, 73.5, 40.6, 21.5, 2.3, 0.6.

MS (EI, 70 eV): *m/z* (%) = 231 (48), 213 (32), 184 (32), 182 (28), 170 (34), 168 (34), 167 (49), 165 (62), 154 (26), 153 (52), 152 (57), 144 (30), 128 (74), 115 (100), 91 (29), 69 (34).

HRMS (EI): *m/z* calc. for [$C_{15}H_{21}NO$]: 231.1623; found: 231.1617 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3004, 2800, 1601, 1578, 1495, 1432, 1347, 1154, 994, 774, 699.

***N*-(Phenyl(4-(trimethylsilyl)phenyl)methyl)aniline (175i)**



According to **TP11**, to a mixture of (4-bromophenyl)trimethylsilane (**173g**, 0.09 mL, 1.0 mmol, 1.00 equiv), TMEDA (0.18 mL, 1.2 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 1.20 mL, 1.2 mmol, 1.20 equiv) at 25 °C. After 15 min, *N*-benzylideneaniline (217 mg, 1.2 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 2 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc/Et$_3$N = 10:0.05:0.05) afforded the title compound **175i** as a colorless oil (285 mg, 0.86 mmol, 86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.39 (d, *J* = 8.0 Hz, 2H), 7.26 (dt, *J* = 15.9, 7.6 Hz, 6H), 7.19–7.15 (m, 1H), 7.06–7.01 (m, 2H), 6.64–6.58 (m, 1H), 6.49–6.43 (m, 2H), 5.40 (s, 1H), 0.16 (s, 9H).

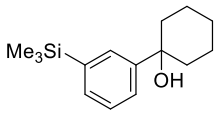
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 147.5, 143.6, 143.0, 139.6, 133.9, 129.3, 128.9, 127.5, 127.5, 126.9, 117.8, 113.6, 63.2, −1.0.

MS (EI, 70 eV): *m/z* (%) = 331 (4), 240 (15), 239 (100), 211 (10), 165 (27), 135 (11), 73 (15).

HRMS (EI): *m/z* calc. for [$C_{22}H_{25}NSi$]: 331.1756; found: 331.1752 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3410, 2953, 1599, 1500, 1425, 1312, 1246, 1107, 832, 746, 689,

1-(3-(Trimethylsilyl)phenyl)cyclohexan-1-ol (175j)



According to **TP11**, to a mixture of (3-bromophenyl)trimethylsilane (**173h**, 0.09 mL, 1.0 mmol, 1.00 equiv), TMEDA (0.18 mL, 1.2 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 1.20 mL, 1.2 mmol, 1.20 equiv) at 25 °C. After 15 min, cyclohexanone (0.12 mL, 1.2 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 2 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175j** as a colorless oil (186 mg, 0.75 mmol, 75%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.71 (s, 1H), 7.51 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 1.92–1.75 (m, 7H), 1.70–1.64 (m, 3H), 0.30 (s, 9H).

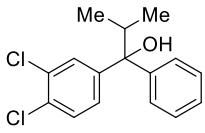
^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 148.6, 140.4, 131.9, 129.3, 127.7, 125.3, 73.4, 39.0, 25.6, 22.3, −0.9.

MS (EI, 70 eV): *m/z* (%) = 230 (50), 216 (13), 215 (100), 157 (29), 156 (27), 129 (10), 128 (14), 75 (32), 73 (17).

HRMS (EI): *m/z* calc. for [C$_{15}$H$_{24}$OSi]: 248.1596; found: 248.1590 (M$^+$).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936, 2856, 2247, 1448, 1248, 1121, 969, 906, 836, 729.

1-(3,4-Dichlorophenyl)-2-methyl-1-phenylpropan-1-ol (175k)



According to **TP11**, to a mixture of 4-bromo-1,2-dichlorobenzene (**173i**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, 2-methyl-1-phenylpropan-1-one (0.09 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 2 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175k** as a white solid (106 mg, 0.36 mmol, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.63 (d, *J* = 2.1 Hz, 1H), 7.47 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.31 (m, *J* = 8.4, 3.4 Hz, 4H), 7.23–7.18 (m, 1H), 2.84 (hept, *J* = 6.7 Hz, 1H), 2.05 (s, OH), 0.89 (dd, *J* = 14.5, 6.7 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 147.3, 145.9, 132.4, 130.4, 130.1, 128.6, 128.0, 127.1, 125.7, 125.4, 80.1, 35.1, 17.1.

MS (EI, 70 eV): *m/z* (%) = 251 (100), 175 (52), 173 (83), 105 (27), 77 (12).

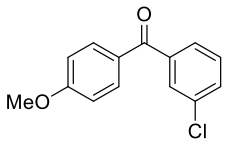
HRMS (EI): *m/z* calc. for [$C_{13}H_9Cl_2O$]: 251.0030; found: 251.0023 (M − *i*Pr).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972, 2876, 1468, 1378, 1168, 1028, 976, 818, 748, 708.

M.p. (°C): 85–90.

4.7 Aryl Magnesium Reagents in Toluene by Br/Mg-Exchange and Subsequent Copper-Catalyzed Reactions

(3-Chlorophenyl)(4-methoxyphenyl)methanone (175l)



According to **TP11**, to a mixture of 4-bromoanisole (**173a**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, CuI (9.0 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C. 3-Chloro-benzoyl chloride (0.08 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175l** as a white solid (118 mg, 0.48 mmol, 95%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.81 (d, *J* = 9.0 Hz, 2H), 7.73 (s, 1H), 7.66–7.60 (m, 1H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.90 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 194.1, 163.7, 140.2, 134.6, 132.7, 132.0, 129.8, 129.7, 129.7, 127.9, 113.9, 55.7.

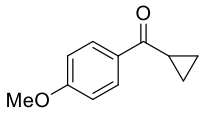
MS (EI, 70 eV): *m/z* (%) = 246 (28), 136 (9), 135 (100), 77 (7).

HRMS (EI): *m/z* calc. for [$C_{14}H_{11}ClO_2$]: 246.0448; found: 246.0441 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 1728, 1644, 1602, 1506, 1418, 1254, 1028, 838, 768, 756.

M.p. (°C): 67–68.

Cyclopropyl(4-methoxyphenyl)methanone (175m)



According to **TP11**, to a mixture of 4-bromoanisole (**173a**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, CuI (9.0 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C. Cyclopropanecarbonyl chloride (0.05 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175m** as a colorless oil (53 mg, 0.30 mmol, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05–7.98 (m, 2H), 7.00–6.93 (m, 2H), 3.88 (s, 3H), 2.64 (m, *J* = 7.9, 4.6 Hz, 1H), 1.25–1.17 (m, 2H), 1.00 (dq, *J* = 7.1, 3.5 Hz, 2H).

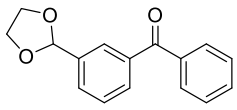
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 199.2, 163.4, 131.2, 130.4, 113.8, 55.6, 16.8, 11.3.

MS (EI, 70 eV): *m/z* (%) = 176 (22), 175 (8), 135 (100), 77 (8).

HRMS (EI): *m/z* calc. for [$C_{11}H_{12}O_2$]: 176.0837; found: 176.0830 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1656, 1594, 1384, 1224, 1166, 1022, 990, 834, 756, 692.

(3-(1,3-Dioxolan-2-yl)phenyl)(phenyl)methanone (175n)



According to **TP11**, to a mixture of 2-(3-bromophenyl)-1,3-dioxolane (**173j**, 0.15 mL, 1.0 mmol, 1.00 equiv), TMEDA (0.18 mL, 1.2 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 1.20 mL, 1.2 mmol, 1.20 equiv) at 25 °C. After 15 min, CuI (9.0 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C.

Benzoyl chloride (0.14 mL, 1.2 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175n** as a colorless oil (178 mg, 0.70 mmol, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.93 (t, *J* = 1.7 Hz, 1H), 7.82–7.77 (m, 3H), 7.72 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.62–7.56 (m, 1H), 7.53–7.45 (m, 3H), 5.86 (s, 1H), 4.16–4.02 (m, 4H).

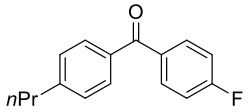
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.5, 138.5, 137.8, 137.6, 132.6, 131.0, 130.6, 130.2, 128.5, 128.4, 128.3, 103.3, 65.5.

MS (EI, 70 eV): *m/z* (%) = 254 (15), 253 (95), 209 (18), 209 (69), 195 (21), 192 (13), 183 (13), 182 (89), 181 (90), 177 (12), 166 (37), 165 (45), 153 (8), 152 (17), 149 (19), 105 (100), 77 (53), 76 (10), 73 (43).

HRMS (EI): *m/z* calc. for [$C_{16}H_{14}O_3$]: 254.0943; found: 254.0889 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2888, 1657, 1597, 1447, 1275, 1075, 940, 786, 712, 697, 641.

(4-Fluorophenyl)(4-propylphenyl)methanone (175o)



According to **TP11**, to a mixture of 1-bromo-4-propylbenzene (**173k**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, CuI (9.0 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C. 4-Fluorobenzoyl chloride (0.07 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175o** as a colorless oil (76 mg, 0.32 mmol, 64%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 (ddd, *J* = 8.2, 5.2, 2.4 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.19–7.12 (m, 2H), 2.71–2.65 (m, 2H), 1.69 (h, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

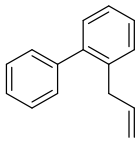
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.2, 165.4 (d, *J* = 253.7 Hz), 148.2, 135.2, 134.3, 132.7 (d, *J* = 9.1 Hz), 130.3, 128.6, 115.5 (d, *J* = 21.8 Hz), 38.2, 24.4, 13.9.

MS (EI, 70 eV): *m/z* (%) = 242 (41), 213 (11), 199 (49), 148 (10), 147 (100), 123 (31), 91 (11).

HRMS (EI): *m/z* calc. for [$C_{16}H_{15}FO$]: 242.1107; found: 242.1101 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1646, 1594, 1500, 1298, 1218, 1154, 930, 852, 758, 684.

2-Allyl-1,1'-biphenyl (175p)



According to **TP11**, to a mixture of 2-bromo-1,1'-biphenyl (**173l**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol 1.20 equiv) at 25 °C. After 15 min, CuI (9.0 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C. Allyl bromide (0.05 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175p** as a light yellow oil (89 mg, 0.46 mmol, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.45–7.27 (m, 9H), 5.92 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 1H), 5.04 (dq, *J* = 10.1, 1.4 Hz, 1H), 4.95 (dq, *J* = 17.0, 1.6 Hz, 1H), 3.37 (dt, *J* = 6.3, 1.4 Hz, 2H).

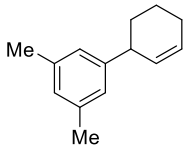
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.1, 141.8, 137.9, 137.3, 130.2, 129.8, 129.4, 128.1, 127.5, 127.0, 126.2, 115.9, 37.6.

MS (EI, 70 eV): *m/z* (%) = 194 (13), 180 (15), 179 (100), 178 (50), 165 (28), 152 (11).

HRMS (EI): *m/z* calc. for [$C_{15}H_{14}$]: 194.1096; found: 194.1089 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2984, 1736, 1448, 1372, 1234, 1110, 1044, 938, 846, 786.

3',5'-Dimethyl-1,2,3,4-tetrahydro-1,1'-biphenyl (175q)



According to **TP11**, to a mixture of 1-bromo-3,5-dimethylbenzene (**173m**, 0.07 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv)

at 25 °C. After 15 min, CuI (9.0 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C. 3-Bromocyclohexene (0.07 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex) afforded the title compound **175q** as a colorless oil (84 mg, 0.45 mmol, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.90 (s, 3H), 5.93 (m, *J* = 9.8, 3.4 Hz, 1H), 5.76 (dd, *J* = 10.1, 2.1 Hz, 1H), 3.39 (m, *J* = 7.8, 5.1, 2.6 Hz, 1H), 2.36 (s, 6H), 2.15 (m, *J* = 7.9, 2.6 Hz, 2H), 2.10–2.01 (m, 1H), 1.81 (m, *J* = 14.5, 4.4 Hz, 1H), 1.74–1.54 (m, 2H).

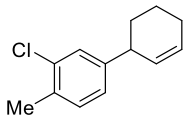
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 146.8, 137.9, 130.7, 128.2, 127.8, 125.7, 42.0, 32.8, 25.2, 21.5, 21.5.

MS (EI, 70 eV): *m/z* (%) = 186 (91), 182 (35), 171 (59), 167 (23), 165 (24), 157 (26), 143 (86), 141 (27), 128 (43), 115 (26), 91 (20), 79 (31), 44 (100).

HRMS (EI): *m/z* calc. for [$C_{14}H_{18}$]: 186.1409; found: 186.1402 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2984, 1737, 1446, 1372, 1235, 1044, 938, 847, 608.

3'-Chloro-4'-methyl-1,2,3,4-tetrahydro-1,1'-biphenyl (175r)



According to **TP11**, to a mixture of 4-bromo-2-chlorotoluene (**173n**, 0.13 mL, 1.0 mmol, 1.00 equiv), TMEDA (0.18 mL, 1.0 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 1.20 mL, 1.2 mmol 1.20 equiv) at 25 °C. After 15 min, CuI (18 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C. 3-Bromocyclohexene (0.14 mL, 1.2 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex) afforded the title compound **175r** as a colorless oil (183 mg, 0.89 mmol, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.23 (s, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 5.98–5.87 (m, 1H), 5.69 (dd, *J* = 10.1, 2.0 Hz, 1H), 3.37 (ddt, *J* = 7.7, 5.1, 2.5 Hz, 1H), 2.37 (s, 3H), 2.11 (m, *J* = 5.4, 3.6, 2.2 Hz, 2H), 2.05–1.98 (m, 1H), 1.79–1.71 (m, 1H), 1.69–1.50 (m, 2H).

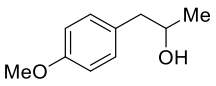
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 146.1, 134.3, 133.5, 130.9, 129.7, 128.9, 128.4, 126.2, 41.3, 32.6, 25.1, 21.1, 19.7.

MS (EI, 70 eV): *m/z* (%) = 206 (100), 291 (30), 171 (73), 156 (17), 143 (100), 141 (18), 129 (15), 128 (47), 115 (19).

HRMS (EI): *m/z* calc. for [$C_{13}H_{15}Cl$]: 206.0862; found: 206.0855 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 1574, 1564, 1494, 1445, 1248, 1049, 994, 875, 815, 707, 698.

1-(4-Methoxyphenyl)propan-2-ol (175s)



According to **TP11**, to a mixture of 4-bromoanisole (**173a**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, CuI (9.0 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C. Propylene oxide (0.04 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 4 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175s** as a colorless oil (89 mg, 0.46 mmol, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.13 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 3.97 (dt, *J* = 12.8, 6.1 Hz, 1H), 3.79 (s, 3H), 2.73 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.62 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.66 (s, OH), 1.23 (d, *J* = 6.2 Hz, 3H).

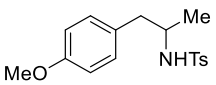
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.4, 130.6, 130.4, 114.1, 69.1, 55.4, 45.0, 22.8.

MS (EI, 70 eV): *m/z* (%) = 166 (12), 122 (68), 121 (100), 107 (15), 91 (13), 77 (8).

HRMS (EI): *m/z* calc. for [$C_{10}H_{14}O_2$]: 166.0994; found: 166.0988 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2937, 1512, 1448, 1320, 1247, 1159, 1093, 983, 815, 661.

***N*-(1,3-Diphenylpropan-2-yl)-4-methylbenzenesulfonamide (175t)**



According to **TP11**, to a mixture of 4-bromoanisole (**173a**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added

*s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol 1.20 equiv) at 25 °C. After 15 min, CuI (9.0 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C. 2-Methyl-1-tosylaziridine (127 mg, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 10 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175t** as a light yellow oil (118 mg, 0.37 mmol, 73%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.61 (d, *J* = 8.3, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.94–6.89 (m, 2H), 6.76–6.72 (m, 2H), 4.25 (d, *J* = 7.2 Hz, NH), 3.78 (s, 3H), 3.47 (hept, *J* = 6.7 Hz, 1H), 2.66–2.56 (m, 2H), 2.41 (s, 3H), 1.09 (d, *J* = 6.5 Hz, 3H).

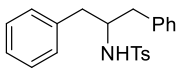
^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 158.6, 143.2, 137.8, 130.4, 129.7, 129.1, 127.1, 114.1, 55.4, 51.1, 42.6, 21.7, 21.5.

MS (EI, 70 eV): *m/z* (%) = 319 (1), 198 (94), 155 (100), 122 (31), 121 (30), 91 (58).

HRMS (EI): *m/z* calc. for [C$_{17}$H$_{21}$NO$_3$S]: 319.1242; found: 319.1240 (M$^+$).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3268, 1454, 1290, 1146, 1088, 980, 816, 758, 704, 656.

***N*-(1,3-Diphenylpropan-2-yl)-4-methylbenzenesulfonamide (175u)**



According to **TP11**, to a mixture of brombenzene (**173o**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, CuI (9.0 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C. 2-Benzyl-1-tosylaziridine (172 mg, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 10 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175u** as a white solid (175 mg, 0.48 mmol, 95%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.42–7.37 (m, 2H), 7.20 (dt, *J* = 4.5, 2.2, 6H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.06–7.00 (m, 4H), 4.26 (d, *J* = 6.8, NH), 3.61 (h, *J* = 6.6, 1H), 2.81 (dd, *J* = 13.8, 6.3, 2H), 2.72 (dd, *J* = 13.8, 6.7, 2H), 2.38 (s, 3H).

^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 143.0, 137.2, 136.9, 129.6, 129.6, 128.7, 127.0, 126.8, 56.3, 40.9, 21.6.

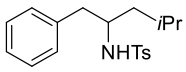
MS (EI, 70 eV): *m/z* (%) = 366 (1), 156 (15), 119 (16), 118 (20), 92 (27), 65 (18).

HRMS (EI): *m/z* calc. for [$C_{22}H_{24}NO_2S$]: 366.1522; found: 366.1518 (M^+ + H).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3268, 1454, 1290, 1146, 1088, 980, 816, 758, 704, 656.

M.p. (°C): 99–101.

4-Methyl-N-(4-methyl-1-phenylpentan-2-yl)benzenesulfonamide (175v)



According to **TP11**, to a mixture of brombenzene (**173o**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at 25 °C. After 15 min, CuI (9.0 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C. 2-Isobutyl-1-tosylaziridine (152 mg, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 10 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc 9:1) afforded the title compound **175v** as a light yellow oil (89 mg, 0.46 mmol, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.69 (d, *J* = 8.3 Hz, 2H), 7.26–7.17 (m, 5H), 7.03–6.99 (m, 2H), 4.18 (s, NH), 3.51 (dq, *J* = 14.2, 6.4 Hz, 1H), 2.74–2.63 (m, 2H), 2.41 (s, 3H), 1.56 (m, *J* = 6.4, 6.0 Hz, 1H), 1.24–1.18 (m, 2H), 0.80 (d, *J* = 6.7 Hz, 3H), 0.66 (d, *J* = 6.5, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 143.3, 138.1, 137.1, 129.8, 129.7, 128.6, 127.2, 126.7, 53.0, 44.0, 41.7, 24.5, 23.0, 21.9, 21.7.

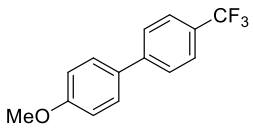
MS (EI, 70 eV): *m/z* (%) = 166 (12), 122 (68), 121 (100), 107 (15), 91 (13), 77 (8).

HRMS (EI): *m/z* calc. for [$C_{10}H_{14}O_2$]: 166.0994; found: 166.0988 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3278, 2954, 1320, 1156, 1088, 1032, 814, 746, 700, 662.

4.8 Aryl Magnesium Reagents in Toluene by Br/Mg-Exchange and Subsequent Palladium-Catalyzed Cross-Couplings

4-Methoxy-4'-(trifluoromethyl)-1,1'-biphenyl (175w)



According to **TP11**, to a mixture of 4-bromoanisole (**173a**, 0.07 mL, 0.60 mmol, 1.20 equiv), TMEDA (0.10 mL, 0.72 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.78 mL, 0.72 mmol 1.20 equiv) at 25 °C. After 15 min, using a syringe-pump, the magnesium-species was then added dropwise to a solution of Pd(OAc)$_2$ (3.4 mg, 3 mol%), SPhos (8.2 mg, 4 mol%) and 1-chloro-4-(trifluoromethyl)benzene (0.06 mL, 0.50 mmol, 1.00 equiv) in toluene (1 mL) over 1 h at room temperature. The resulting mixture was further stirred for 1 h. The reaction mixture was quenched with sat. aq. NH$_4$Cl solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175w** as a light brown solid (89 mg, 0.36 mmol, 70%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.71–7.64 (m, 4H), 7.58–7.53 (m, 2H), 7.05–7.00 (m, 2H), 3.88 (s, 3H).

^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 160.0, 144.4 (q, *J* = 1.3 Hz), 132.3, 128.8 (d, *J* = 32.4 Hz, 2C), 128.5, 127.0, 125.8 (q, J = 3.8 Hz, 2C), 124.5 (d, *J* = 271.8 Hz), 114.6, 55.5.

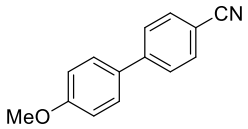
MS (EI, 70 eV): *m/z* (%) = 252 (100), 237 (43), 209 (63), 188 (10), 183 (14), 139 (10).

HRMS (EI): *m/z* calc. for [C$_{14}$H$_{11}$F$_3$O]: 252.0762; found: 252.0757 (M$^+$).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2966, 1602, 1568, 1532, 1460, 1444, 1402, 1326, 1296, 1276, 1202, 1182, 1076, 1036, 960, 828, 746.

M.p. (°C): 115–117.

4'-Methoxy-[1,1'-biphenyl]-4-carbonitrile (175x)



According to **TP11**, to a mixture of 4-bromoanisole (**173a**, 0.07 mL, 0.60 mmol, 1.00 equiv), TMEDA (0.10 mL, 0.72 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.78 mL, 0.72 mmol 1.20 equiv) at 25 °C. After 15 min, Zn(OPiv) (160 mg, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 30 min. PEPPSI-*i*Pr (14 mg, 4 mol%) and 4-bromobenzonitrile (109 mg, 0.60 mmol, 1.00 equiv) was added at 25 °C and the resulting mixture was further stirred overnight. The reaction mixture was quenched with sat. aq. NH$_4$Cl solution (10 mL), extracted with EtOAc(3 × 20 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **175x** as a light brown solid (76 mg, 0.36 mmol, 72%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.73–7.61 (m, 4H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H).

^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 160.3, 145.4, 132.7, 131.7, 128.5, 127.3, 119.3, 114.7, 110.2, 55.6.

MS (EI, 70 eV): *m/z* (%) = 209 (100), 194 (50), 166 (55), 140 (30), 139 (10).

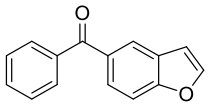
HRMS (EI): *m/z* calc. for [C$_{14}$H$_{11}$ON]: 209.0841; found: 209.0834 (M$^+$).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961, 2221, 1603, 1492, 1445, 1294, 1239, 1176, 1036, 1000, 822.

M.p. (°C): 101–103.

4.9 Heteroaryl Magnesium Reagents in Toluene by Br/Mg-Exchange

Benzofuran-5-yl(phenyl)methanone (178a)



According to **TP11**, to a mixture of 5-bromobenzofuran (**176a**, 0.08 mL, 0.20 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol 1.20 equiv) at 25 °C. After 15 min, CuI (9.0 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C. Benzoyl chloride (0.07 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **178a** as yellow oil (78 mg, 0.35 mmol, 70%).

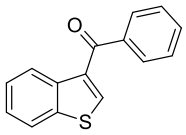
^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.09 (d, *J* = 1.5 Hz, 1H), 7.83 (m, *J* = 12.2, 8.5, 1.6 Hz, 3H), 7.72 (d, *J* = 2.2 Hz, 1H), 7.63–7.57 (m, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 6.86 (dd, *J* = 2.2, 0.9 Hz, 1H).

^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 196.7, 157.4, 146.5, 138.4, 133.0, 132.3, 130.1, 128.4, 127.4, 127.0, 124.6, 111.5, 107.4.

MS (EI, 70 eV): *m/z* (%) = 222 (54), 221 (15), 145 (13), 145 (100), 89 (11).

HRMS (EI): *m/z* calc. for [C$_{15}$H$_{10}$O$_2$]: 222.0681; found: 222.0674 (M$^+$).

Benzofuran-5-yl(4-fluorophenyl)methanol (178b)



According to **TP11**, to a mixture of 3-bromobenzothiophen (**176b**, 108 mg, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol 1.20 equiv) at −10 °C. After 15 min, *N*-methoxy-*N*-methylacetamide (0.06 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **178b** as a yellow oil (79 mg, 0.33 mmol, 65%).

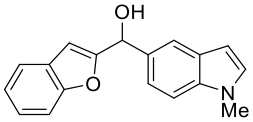
^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.85–7.81 (m, 3H), 7.63–7.59 (m, 1H), 7.54 (d, *J* = 5.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 5.4 Hz, 1H).

13C NMR (101 MHz, $CDCl_3$) δ / ppm = 196.9, 144.0, 139.2, 138.2, 134.1, 132.4, 130.2, 128.5, 128.0, 126.4, 125.5, 124.7, 122.6.

MS (EI, 70 eV): *m/z* (%) = 238 (61), 237 (17), 161 (15), 161 (100), 133 (12), 89 (12).

HRMS (EI): *m/z* calc. for [$C_{15}H_{10}OS$]: 238.0452; found: 238.0447 (M^+).

Benzofuran-2-yl(1-methyl-1*H*-indol-5-yl)methanol (178c)



According to **TP11**, to a mixture of 5-bromo-1-methyl-1*H*-indole (**176c**, 104 mg, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol 1.20 equiv) at 25 °C. After 15 min, benzofuran-2-carbaldehyde (0.07 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **178c** as an orange oil (86 mg, 0.31 mmol, 62%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.75 (s, 1H), 7.55–7.51 (m, 1H), 7.48–7.44 (m, 1H), 7.39–7.31 (m, 2H), 7.29–7.19 (m, 2H), 7.09 (d, *J* = 3.1 Hz, 1H), 6.57 (s, 1H), 6.51 (d, *J* = 3.1 Hz, 1H), 6.05 (s, 1H), 3.79 (s, 3H), 2.64 (s, OH).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.6, 155.2, 136.8, 131.7, 129.7, 128.5, 128.3, 124.1, 122.8, 121.1, 120.8, 119.7, 111.4, 109.5, 103.8, 101.4, 71.6, 33.0.

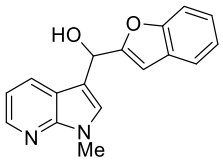
MS (EI, 70 eV): *m/z* (%) = 277 (100), 261 (22), 260 (96), 158 (48), 144 (19), 132 (23), 130 (20).

HRMS (EI): *m/z* calc. for [$C_{18}H_{15}NO_2$]: 277.1103; found: 277.1106 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3033, 1581, 1488, 1452, 1376, 1252, 1146, 1007, 957, 800, 739, 720.

M.p. (°C): 180

Benzofuran-2-yl(1-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methanol (178d)



According to **TP11**, to a mixture of 3-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**176d**, 105 mg, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol 1.20 equiv) at 25 °C. After 15 min, benzofuran-2-carbaldehyde (0.07 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **178d** as an orange oil (97 mg, 0.35 mmol, 70%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 8.37 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.01 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.60–7.56 (m, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.34–7.23 (m, 3H), 7.08 (dd, *J* = 7.9, 4.7 Hz, 1H), 6.71 (s, 1H), 6.26 (s, 1H), 3.89 (s, 3H).

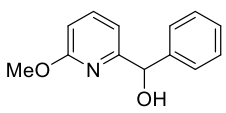
^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 158.4, 155.1, 148.2, 143.6, 128.3, 128.2, 127.7, 124.4, 123.0, 121.3, 118.7, 115.9, 113.1, 111.5, 103.8, 64.9, 31.4.

MS (EI, 70 eV): *m/z* (%) = 276 (41), 275 (13), 225 (24), 207 (39), 160 (10), 159 (100), 131 (18), 43 (24).

HRMS (EI): *m/z* calc. for [$C_{17}H_{12}N_2O_2$]: 276.0895; found: 276.0895(M^+ − 2H).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 1690, 1600, 1556, 1454, 1409, 1300, 1255, 1126, 948, 774, 751.

(6-Methoxypyridin-2-yl)(phenyl)methanol (178e)



According to **TP11**, to a mixture of 2-bromo-6-methoxypyridine (**176e**, 0.06 mL, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol, 1.20 equiv) at −30 °C. After 15 min, benzaldehyde (0.06 mL, 0.60 mmol, 1.20 equiv) was added and the reaction

mixture was stirred for 1 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **178e** as colorless oil (77 mg, 0.36 mmol, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.50 (t, *J* = 7.8 Hz, 1H), 7.43–7.39 (m, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.67 (dd, *J* = 7.8 Hz, 2H), 5.69 (d, *J* = 4.5 Hz, 1H), 4.94 (d, *J* = 4.6 Hz, OH), 4.00 (s, 3H).

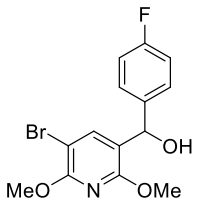
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.3, 158.9, 143.3, 139.6, 128.5, 127.8, 127.0, 113.8, 109.3, 77.2, 76.8, 74.8, 53.5.

MS (EI, 70 eV): *m/z* (%) = 215 (66), 214 (19), 154 (17), 138 (100), 124 (12), 110 (54), 109 (69), 108 (31), 105 (13), 104 (11), 94 (15), 93 (12), 91 (18), 80 (23), 79 (20), 78 (13), 77 (35).

HRMS (EI): *m/z* calc. for [$C_{13}H_{13}NO_2$]: 215.0946; found: 215.0939 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3410, 2952, 1600, 1508, 1468, 1416, 1292, 1186, 1098, 1028, 990, 882, 810, 736, 654.

(5-Bromo-2,6-dimethoxypyridin-3-yl)(4-fluorophenyl)methanol (178f)



According to **TP11**, to a mixture of 3,5-dibromo-2,6-dimethoxypyridine (**176f**, 148 mg, 0.50 mmol, 1.00 equiv), TMEDA (0.09 mL, 0.60 mmol, 1.20 equiv) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 0.60 mL, 0.60 mmol 1.20 equiv) at −30 °C. After 15 min, 4-fluorobenzaldehyde (0.06 mL, 0.60 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 1 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **178f** as colorless oil (115 mg, 0.34 mmol, 68%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.62 (s, 1H), 7.32 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.01 (t, *J* = 8.7 Hz, 2H), 5.88 (d, *J* = 4.0 Hz, 1H), 3.98 (s, 3H), 3.93 (s, 3H).

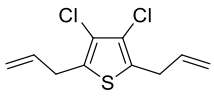
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.3 (d, *J* = 245.8 Hz), 158.3, 157.8, 141.5, 138.3 (d, *J* = 3.1 Hz), 128.2 (d, *J* = 8.1 Hz, 2C), 119.0, 115.4 (d, *J* = 21.4 Hz, 2C), 95.7, 69.8, 54.5, 53.9.

MS (EI, 70 eV): *m/z* (%) = 341 (99), 340 (11), 325 (31), 324 (30), 248 (55), 247 (12), 246 (70), 244 (16), 220 (11), 218 (15), 125 (23), 123 (48), 95 (11).

HRMS (EI): *m/z* calc. for [$C_{14}H_{13}BrFNO_3$]: 341.0063; found: 341.0051 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3328, 2952, 1592, 1578, 1472, 1420, 1400, 1384, 1306, 1268, 1192, 1058, 1016, 830, 788, 726.

2,5-Diallyl-3,4-dichlorothiophene (178g)



According to **TP11**, to a mixture of tetrachlorothiophene (**176g**, 111 mg, 0.50 mmol, 1.00 equiv), TMEDA (0.19 mL, 1.30 mmol) and toluene (1 mL) was added *s*BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**170a**, 1.00 M in toluene, 2.60 mL, 2.60 mmol, 2.60 equiv) at 25 °C. After 4 h, CuI (18 mg, 20 mol%) was added and stirring was continued for 1 h at 0 °C. Allyl bromide (0.11 mL, 1.3 mmol, 2.60 equiv) was added and the reaction mixture was stirred for 1 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **178g** as a colorless oil (70 mg, 0.30 mmol, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 5.89 (ddt, *J* = 16.6, 10.0, 6.6 Hz, 2H), 5.27–5.09 (m, 4H), 3.51 (dt, *J* = 6.5, 1.3 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 134.1, 132.9, 120.9, 117.6, 32.8.

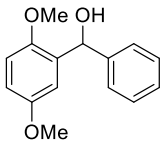
MS (EI, 70 eV): *m/z* (%) = 232 (65), 206 (18), 205 (27), 199 (32), 197 (93), 196 (10), 171 (18), 169 (54), 163 (10), 162 (100), 161 (51), 156 (22), 155 (12), 147 (16), 135 (26), 134 (64, 130 (20, 129 (26), 128 (43), 121 (23), 115 (13).

HRMS (EI): *m/z* calc. for [$C_4H_2Cl_2S$]: 231.9880; found: 231.9874 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3082, 2982, 1670, 1540, 1486, 1426, 1296, 1228, 1164, 1088, 1058, 988, 918, 772, 732, 686.

4.10 Aryl Magnesium Reagents in Toluene by Cl/Mg-Exchange

(2,5-Dimethoxyphenyl)(phenyl)methanol (181a)



According to **TP12**, to a mixture of 2-chloro-1,4-dimethoxybenzene (**179a**, 0.14 mL, 1.0 mmol, 1.00 equiv), PMDTA (0.12 mL, 0.60 mmol, 0.60 equiv) and toluene (1 mL) was added *s*$Bu_2Mg{\cdot}2LiOCH_2CH(Et)Bu$ (**170b**, 0.70 M in toluene, 0.86 mL, 0.60 mmol, 0.60 equiv) at 25 °C. After 1 h, benzaldehyde (0.15 mL, 1.5 mmol, 1.50 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **181a** as a light yellow oil (149 mg, 0.61 mmol, 61%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.45–7.41 (m, 2H), 7.38–7.33 (m, 2H), 7.31–7.27 (m, 1H), 6.89 (d, *J* = 2.9, 1H), 6.86–6.78 (m, 2H), 6.05 (d, *J* = 4.1 Hz, 1H), 3.77 (d, *J* = 3.6 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 153.9, 151.0, 143.2, 133.2, 128.3, 127.3, 126.6, 114.2, 112.9, 112.0, 72.3, 56.1, 55.8.

MS (EI, 70 eV): *m/z* (%) = 244 (100), 226 (11), 167 (13), 165 (15), 139 (45), 105 (30), 91

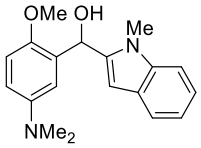
(14), 79 (12), 77 (28), 43 (37).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}O_3$]: 244.1099; found: 244.1095 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2938, 2834, 1591, 1492, 1452, 1276, 1212, 1177, 1037,

831.

(5-(Dimethylamino)-2-methoxyphenyl)(1-methyl-1H-indol-2-yl)methanol (181b)



According to **TP12**, to a mixture of 1,3-dichloro-2-methoxybenzene (**179b**, 185 mg, 1.0 mmol, 1.00 equiv), PMDTA (0.12 mL, 0.60 mmol, 0.60 equiv) and toluene (1 mL) was added *s*$Bu_2Mg{\cdot}2LiOCH_2CH(Et)Bu$ (**170b**, 0.70 M in toluene, 0.86 mL, 0.60 mmol 0.60 equiv) at 25 °C. After

1 h, 1-methyl-1*H*-indole-2-carbaldehyde (239 mg, 1.5 mmol, 1.50 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **181b** as a light yellow solid (217 mg, 0.70 mmol, 70%).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.04 (dd, *J* = 6.8, 1.5, 1H), 7.25–7.17 (m, 3H), 6.99 (d, *J* = 7.2, 1H), 6.71–6.58 (m, 4H), 3.30 (s, 3H), 2.83 (s, 3H), 2.57 (s, 6H).

^{13}C-NMR (101 MHz, C_6D_6): δ / ppm = 149.8, 146.2, 137.9, 133.8, 127.4, 121.9, 120.9, 119.6, 119.0, 114.5, 112.9, 112.1, 109.4, 67.0, 55.6, 41.4, 31.8.

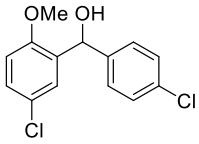
MS (EI, 70 eV): *m/z* (%) = 294 (100), 280 (10), 279 (55), 263 (13), 234 (15), 144 (36), 139 (18), 131 (11).

HRMS (EI): *m/z* calc. for [$C_{19}H_{22}N_2O_2$]: 310.1681; found: 310.1672 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2827, 1505, 1448, 1421, 1317, 1240, 1234, 1034, 997, 782, 739, 684.

M.p. (°C): 109–110.

(5-Chloro-2-methoxyphenyl)(4-chlorophenyl)methanol (181c)



According to **TP12**, to a mixture of 2,4-dichloro-1-methoxybenzene (**179c**, 0.14 mL, 1.0 mmol, 1.00 equiv), PMDTA (0.12 mL, 0.60 mmol, 0.60 equiv) and toluene (1 mL) was added sBu$_2$Mg·2LiOCH$_2$CH(Et)Bu (**170b**, 0.70 M in toluene, 0.86 mL, 0.60 mmol, 0.60 equiv) at 25 °C. After 1 h, 4-chlorobenzaldehyde (211 mg, 1.5 mmol, 1.50 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **181c** as a light yellow oil (141 mg, 0.50 mmol, 50 %).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.51 (d, *J* = 2.6 Hz, 1H), 7.09–7.03 (m, 4H), 7.01 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.13 (d, *J* = 8.7 Hz, 1H), 5.75 (d, *J* = 4.2 Hz, 1H), 3.03 (s, 3H), 2.72 (d, *J* = 4.5 Hz, OH).

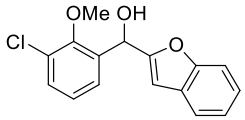
^{13}C-NMR (101 MHz, C_6D_6): δ / ppm = 155.0, 142.2, 134.3, 133.3, 128.6, 128.4, 127.8, 127.4, 126.3, 112.1, 70.3, 55.1.

MS (EI, 70 eV): *m/z* (%) = 282 (78), 266 (38), 264 (61), 247 (34), 229 (44), 201 (30), 194 (39), 171 (31), 169 (100), 165 (24), 154 (32), 143 (30), 141 (33), 138 (56), 125 (25).

HRMS (EI): *m/z* calc. for [$C_{14}H_{12}Cl_2O_2$]: 282.0214; found: 282.0206 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2945, 2839, 1596, 1485, 1408, 1246, 1180, 1127, 1090, 1031, 1013, 902, 809.

Benzofuran-2-yl(3-chloro-2-methoxyphenyl)methanol (181d)



According to **TP12**, to a mixture of 1,3-dichloro-2-methoxybenzene (**179d**, 0.14 mL, 1.0 mmol, 1.00 equiv), PMDTA (0.12 mL, 0.60 mmol, 0.60 equiv) and toluene (1 mL) was added *s*$Bu_2Mg{\cdot}2LiOCH_2CH(Et)Bu$ (**170b**, 0.70 M in toluene, 0.86 mL, 0.60 mmol, 0.60 equiv) at 25 °C. After 1 h, benzofuran-2-carbaldehyde (0.18 mL, 1.5 mmol, 1.50 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **181d** as a light yellow oil (202 mg, 0.70 mmol, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.53 (dd, *J* = 7.1, 1.4 Hz, 1H), 7.46–7.42 (m, 2H), 7.37 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.30–7.20 (m, 2H), 7.09 (t, *J* = 7.9 Hz, 1H), 6.57 (s, 1H), 6.24 (d, *J* = 4.1 Hz, 1H), 3.81 (s, 3H), 3.60 (s, OH).

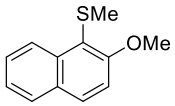
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.3, 155.0, 153.6, 135.7, 130.6, 128.1, 127.7, 127.0, 125.2, 124.4, 122.9, 121.2, 111.4, 104.0, 65.9, 61.5.

MS (EI, 70 eV): *m/z* (%) = 288 (100), 271 (20), 171 (24), 169 (71), 165 (21), 155 (44), 147 (42), 145 (20), 131(41), 119 (20), 118 (33), 91 (33), 89 (22).

HRMS (EI): *m/z* calc. for [$C_{16}H_{13}ClO_3$]: 288.0553; found: 288.0546 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2945, 1465, 1454, 1425, 1254, 1234, 1134, 999, 791, 751.

(2-Methoxynaphthalen-1-yl)(methyl)sulfane (181e)



According to **TP12**, to a mixture of 1-chloro-2-methoxynaphthalene (**179e**, 96 mg, 0.50 mmol, 1.00 equiv), PMDTA (0.06 mL, 0.30 mmol, 0.60 equiv) and toluene (1 mL) was added *s*$Bu_2Mg{\cdot}2LiOCH_2CH(Et)Bu$ (**170b**, 0.70 M in toluene, 0.43 mL, 0.30 mmol 0.60 equiv) at 25 °C. After 1 h, *S*-methyl methanesulfonothioate (0.08 mL, 0.75 mmol, 1.50 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **181e** as a light yellow oil (63 mg, 0.31 mmol, 62%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.62 (d, *J* = 8.6 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.56 (m, *J* = 8.5, 6.8, 1.3 Hz, 1H), 7.38 (m, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 4.06 (s, 3H), 2.39 (s, 3H).

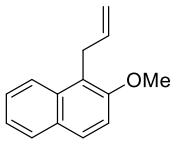
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.3, 135.8, 130.5, 129.5, 128.4, 127.3, 125.6, 124.0, 118.1, 113.3, 56.9, 18.6.

MS (EI, 70 eV): *m/z* (%) = 204 (100), 189 (35), 171 (23), 161 (15), 128 (19), 115 (25).

HRMS (EI): *m/z* calc. for [$C_{12}H_{12}OS$]: 204.0609; found: 204.0603 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921, 2839, 1590, 1504, 1462, 1326, 1264, 1244, 1068, 969, 806, 748, 654.

(2-Methoxynaphthalen-1-yl)(methyl)sulfane (181f)



According to **TP12**, to a mixture of 1-chloro-2-methoxynaphthalene (**179e**, 96 mg, 0.50 mmol, 1.00 equiv), PMDTA (0.06 mL, 0.30 mmol, 0.60 equiv) and toluene (1 mL) was added *s*$Bu_2Mg{\cdot}2LiOCH_2CH(Et)Bu$ (**170b**, 0.70 M in toluene, 0.43 µL, 0.30 mmol 0.60 equiv) at 25 °C. After 1 h, CuI (9.0 mg, 10 mol%) was added and stirring was continued for 1 h at 0 °C. Allyl bromide (0.06 mL, 1.5 mmol, 1.50 equiv) was added and the reaction mixture was stirred for 1 h at 0 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc = 9:1) afforded the title compound **181f** as a light yellow oil (75 mg, 0.38 mmol, 75%).

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 7.94 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.47 (m, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.34 (m, *J* = 8.0, 6.8, 1.0 Hz, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 6.09–6.01 (m, 1H), 5.02–4.96 (m, 2H), 3.96 (s, 3H), 3.87 (dt, *J* = 5.8, 1.6 Hz, 2H).

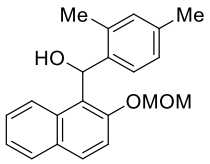
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 154.6, 136.9, 133.3, 129.4, 128.6, 128.2, 126.4, 123.7, 123.4, 121.1, 115.1, 113.8, 56.9, 29.2.

MS (EI, 70 eV): *m/z* (%) = 198 (100), 197 (15), 183 (45), 167 (61), 166 (11), 165 (73), 155 (13), 153 (32), 152 (29), 141 (21), 139 (12), 128 (19), 115 (21).

HRMS (EI): *m/z* calc. for [$C_{14}H_{14}O$]: 198.1045; found: 198.1037 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3074, 2933, 2837, 1625, 1595, 1513, 1262, 1251, 1080, 910, 805, 745.

(2,4-Dimethylphenyl)(2-(methoxymethoxy)naphthalen-1-yl)methanol (181g)



According to **TP12**, to a mixture of 1-chloro-2-(methoxymethoxy)naphthalene (**179f**, 222 mg, 1.0 mmol, 1.00 equiv), PMDTA (0.12 µL, 0.60 mmol, 0.60 equiv) and toluene (1 mL) was added *s*Bu_2Mg·2$LiOCH_2CH$(Et)Bu (**170b**, 0.70 M in toluene, 0.86 mL, 0.60 mmol 0.60 equiv) at 25 °C. After 15 min, 2,4-dimethylbenzaldehyde (0.21 mL, 1.5 mmol, 1.50 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. Purification of the crude product by flash column chromatography (*i*hex/EtOAc/ Et_3N = 9:0.05:0.05) afforded the title compound **181g** as a light yellow oil (255 mg, 0.79 mmol, 79%).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.19 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 11.3, 8.5 Hz, 2H), 7.34 (dd, *J* = 12.1, 8.5 Hz, 2H), 7.13–7.09 (m, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.89 (s, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 4.71 (s, 2H), 3.73 (d, *J* = 7.7 Hz, 1H), 3.00 (s, 3H), 2.47 (s, 3H), 2.09 (s, 3H).

^{13}C-NMR (101 MHz, C_6D_6): δ / ppm = 153.1, 138.5, 136.8, 136.5, 132.6, 131.7, 130.3, 129.7, 128.4, 127.2, 126.4, 126.1, 124.6, 124.5, 124.0, 116.2, 94.8, 69.0, 55.6, 20.6, 19.6.

MS (EI, 70 eV): *m/z* (%) = 322 (3), 260 (8), 259 (12), 246 (34), 215 (6), 115 (6), 45 (15).

HRMS (EI): *m/z* calc. for [$C_{21}H_{22}O_3$]: 322.1569; found: 322.1563 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2920, 1709, 1596, 1510, 1465, 1235, 1149, 1012, 923, 811.

5 Crystallographic Data

Single Crystal X-Ray Diffraction Studies

Single crystals of compound **141a**, **159a** and **163a**, suitable for X-ray diffraction, were obtained by slow evaporation of a DCM solutions. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).
Data collection was performed with the CrysAlis CCD software; [132] CrysAlis RED software[133] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method[134] was applied. The structures were solved with SHELXS-97, [135] refined with SHELXL-97[136] and finally checked using PLATON. [137]

[132] CrysAlis CCD, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).
[133] CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).
[134] SCALE3 ABSPACK – An Oxford Diffraction Program (1.0.4, gui:1.0.3) (C), Oxford Diffraction, Ltd., 2005.
[135] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen,Germany.
[136] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[137] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

3-Iodo-2-((2-methoxyethoxy)methyl)-2,7-naphthyridin-1(2*H*)-one (141a)

CCDC-1565047 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

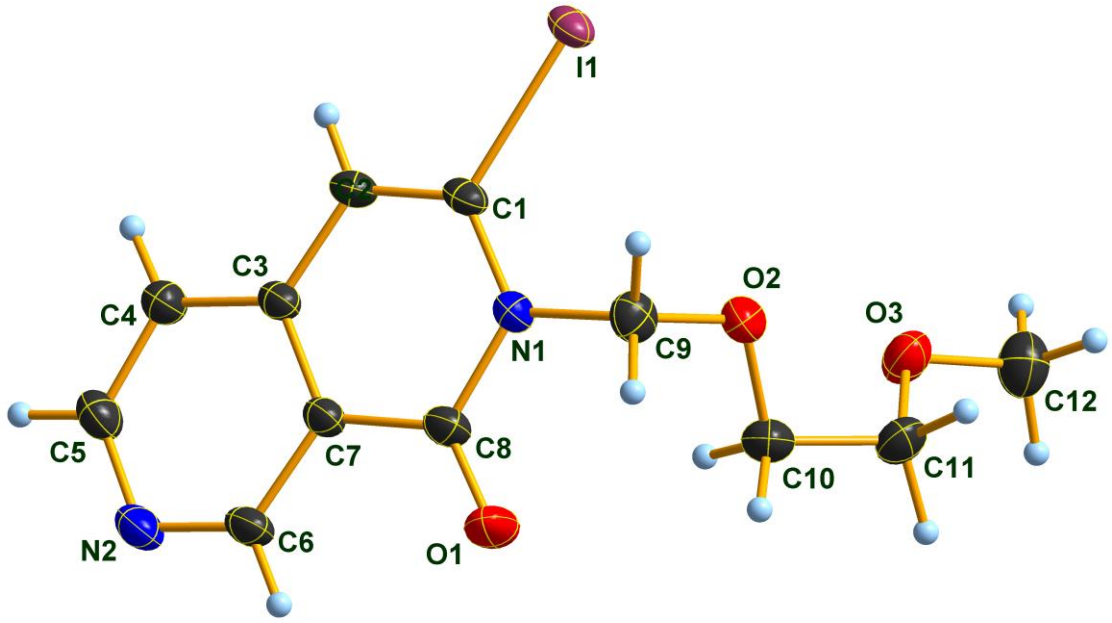


Figure 5: Molecular structure of compound **141a** in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50% probability level.

Table 19: Details for X-ray data collection and structure refinement for compound **141a**.

	141a
Empirical formula	$C_{12}H_{13}IN_2O_3$
Formula mass	360.14
T[K]	173(2)
Crystal size [mm]	0.42 × 0.17 × 0.11
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*-1
a [Å]	8.5985(2)
b [Å]	8.9813(2)
c [Å]	10.1508(2)
α [°]	113.998(2)
β [°]	91.780(2)
γ [°]	111.582(2)
V [Å ^{3}]	650.70(3)
Z	2
$\rho_{calc.}$ [g cm^{-3}]	1.838
μ [mm^{-1}]	2.463
F(000)	352
Θ range [°]	4.15–25.24
Index ranges	$-12 \leq h \leq 12$
	$-12 \leq k \leq 12$
	$-14 \leq l \leq 14$
Reflns. collected	12980
Reflns. obsd.	3629
Reflns. unique	3946
	(R_{int} = 0.0320)
R_1, wR_2 (2σ data)	0.0214, 0.0480
R_1, wR_2 (all data)	0.0253, 0.0499
GOOF on F^2	1.041
Peak/hole [e Å^{-3}]	0.526 / −0.759

Table 20: Selected bond lengths (Å) of compound **141a**.

I1–C1	2.114(2)	N2–C5	1.356(3)
C1–C2	1.339(2)	C11–C10	1.501(3)
C1–N1	1.394(2)	C4–C5	1.370(3)
O2–C9	1.402(2)	C7–C3	1.403(2)
O2–C10	1.435(2)	C7–C8	1.460(3)
N1–C8	1.405(2)	C3–C4	1.403(3)
N1–C9	1.468(2)	C3–C2	1.426(2)

O3–C12	1.411(3)	O1–C8	1.228(2)
O3–C11	1.413(3)	N2–C6	1.324(3)
C7–C6	1.402(3)		

Table 21: Selected bond angles (°) of compound **141a**.

C2–C1–N1	122.6(2)	C5–C4–C3	119.3(2)
C2–C1–I1	117.0(1)	O1–C8–N1	120.7(2)
N1–C1–I1	120.4(1)	O1–C8–C7	123.6(2)
C9–O2–C10	114.1(2)	N1–C8–C7	115.7(2)
C1–N1–C8	121.5(2)	O2–C9–N1	113.6(2)
C1–N1–C9	121.5(2)	N2–C5–C4	123.9(2)
C8–N1–C9	116.9(2)	O2–C10–C11	109.0(2)
C12–O3–C11	113.1(2)	C4–C3–C2	124.0(2)
C6–C7–C3	118.8(2)	C6–N2–C5	117.0(2)
C6–C7–C8	119.8(2)	O3–C11–C10	109.6(2)
C3–C7–C8	121.4(2)	N2–C6–C7	123.7(2)
C7–C3–C4	117.2(2)	C1–C2–C3	119.9(2)
C7–C3–C2	118.8(2)		

Table 22: Selected torsion angles (°) of compound **141a**.

C2–C1–N1–C8	−0.5(3)	C2–C3–C4–C5	−179.5(2)
I1–C1–N1–C8	−178.4(1)	C1–N1–C8–O1	178.9(2)
C2–C1–N1–C9	−177.3(2)	C9–N1–C8–O1	−4.2(3)
I1–C1–N1–C9	4.9(2)	C1–N1–C8–C7	−0.7(2)
C6–C7–C3–C4	−3.0(3)	C9–N1–C8–C7	176.2(2)
C8–C7–C3–C4	176.1(2)	C6–C7–C8–O1	1.8(3)
C6–C7–C3–C2	178.2(2)	C3–C7–C8–O1	−177.3(2)
C8–C7–C3–C2	−2.7(3)	C6–C7–C8–N1	−178.6(2)
C12–O3–C11–C10	−171.8(2)	C3–C7–C8–N1	2.4(3)
C5–N2–C6–C7	0.6(3)	C10–O2–C9–N1	−76.2(2)
C3–C7–C6–N2	1.8(3)	C1–N1–C9–O2	−83.2(2)
C8–C7–C6–N2	−177.2(2)	C8–N1–C9–O2	99.9(2)
N1–C1–C2–C3	0.2(3)	C6–N2–C5–C4	−1.9(3)
I1–C1–C2–C3	178.1(1)	C3–C4–C5–N2	0.6(3)
C7–C3–C2–C1	1.4(3)	C9–O2–C10–C11	−167.4(2)
C4–C3–C2–C1	−177.3(2)	O3–C11–C10–O2	−69.2(2)
C7–C3–C4–C5	1.8(3)		

6-(Hydroxy(phenyl)methyl)-2*H*-pyran-2-one (159a)

CCDC-1847973 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

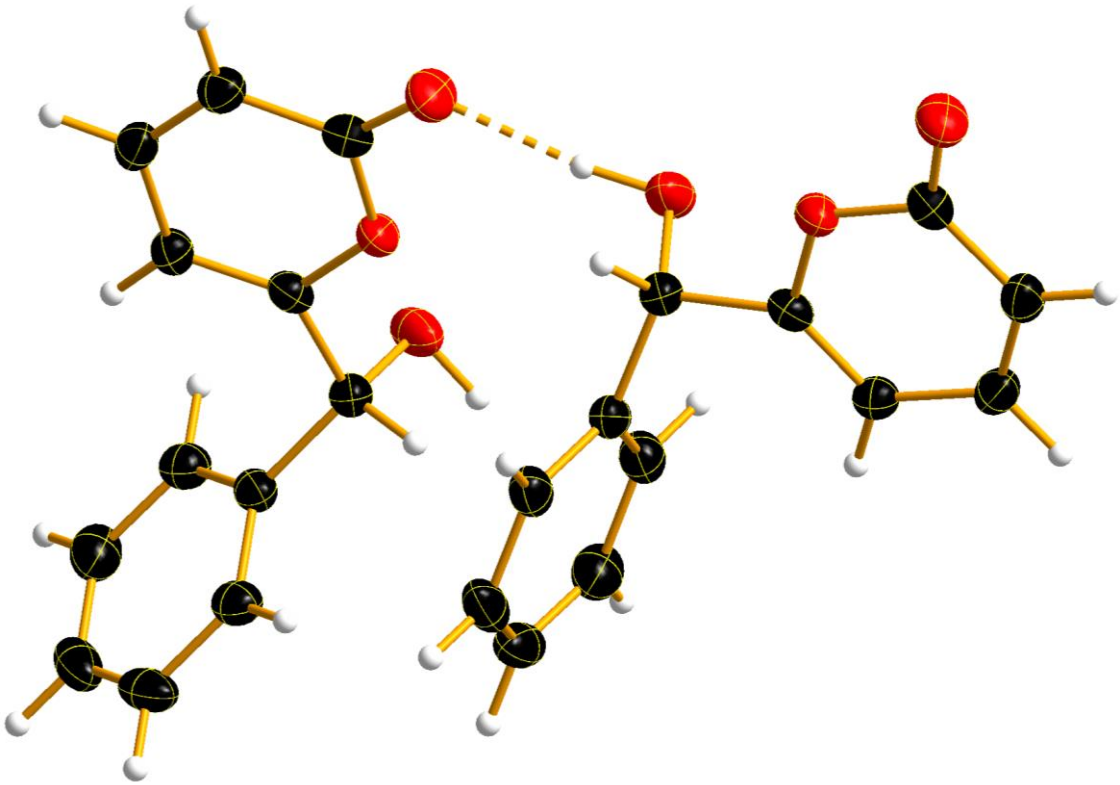


Figure 6: Molecular structure of compound **159a** in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50% probability level. Symmetry code: *i*: x, 0.5−y, −0.5+z.

Table 23: Details for X-ray data collection and structure refinement for compound **159a**.

	159a
Empirical formula	$C_{12}H_{10}O_3$
Formula mass	202.20
T[K]	173(2)
Crystal size [mm]	0.34 × 0.21 × 0.04
Crystal description	colorless platelet
Crystal system	monoclinic
Space group	*Ia*
a [Å]	6.7309(4)
b [Å]	13.6616(8)
c [Å]	10.5298(6)
α [°]	90
β [°]	98.991(5)
γ [°]	90
V [Å ^{3}]	956.37(10)
Z	4
$\rho_{calc.}$ [g cm^{-3}]	1.404
μ [mm^{-1}]	0.101
F(000)	424
Θ range [°]	4.50–25.24
Index ranges	$-6 \leq h \leq 8$
	$-17 \leq k \leq 18$
	$-14 \leq l \leq 10$
Reflns. collected	2910
Reflns. obsd.	1390
Reflns. unique	1546 (R_{int} = 0.0286)
R_1, wR_2 (2σ data)	0.0336, 0.0668
R_1, wR_2 (all data)	0.0395, 0.0699
GOOF on F^2	1.039
Peak/hole [e Å^{-3}]	0.166 / –0.157

Table 24: Selected bond lengths (Å) of compound **159a**.

O1–C1	1.218(3)	C6–C7	1.522(3)
O2–C1	1.373(3)	C7–C8	1.384(3)
O2–C5	1.378(3)	C7–C12	1.389(3)
O3–C6	1.428(3)	C8–C9	1.390(3)
C1–C2	1.431(3)	C9–C10	1.377(4)
C2–C3	1.343(3)	C10–C11	1.378(4)
C3–C4	1.431(3)	C11–C12	1.391(3)
C4–C5	1.332(3)	C5–C6	1.502(3)

Table 25: Selected bond angles (°) of compound **159a**.

C1–O2–C5	122.2(2)	C8–C7–C12	119.4(2)
O1–C1–O2	116.6(2)	C8–C7–C6	121.5(2)
O1–C1–C2	126.7(2)	C12–C7–C6	119.1(2)
O2–C1–C2	116.7(2)	C7–C8–C9	120.4(2)
C3–C2–C1	121.1(2)	C10–C9–C8	119.8(2)
C2–C3–C4	119.7(2)	C9–C10–C11	120.4(2)
C5–C4–C3	119.4(2)	C10–C11–C12	119.9(2)
C4–C5–O2	120.8(2)	C7–C12–C11	120.1(2)
C4–C5–C6	128.8(2)	O3–C6–C7	112.7(2)
O2–C5–C6	110.4(2)	C5–C6–C7	112.0(2)
O3–C6–C5	106.0(2)		

Table 26: Selected torsion angles (°) of compound **159a**.

C5–O2–C1–O1	177.6(2)	O2–C5–C6–C7	159.3(2)
C5–O2–C1–C2	−2.6(3)	O3–C6–C7–C8	−37.9(3)
O1–C1–C2–C3	−177.3(2)	C5–C6–C7–C8	81.6(3)
O2–C1–C2–C3	2.9(3)	O3–C6–C7–C12	143.4(2)
C1–C2–C3–C4	−1.1(3)	C5–C6–C7–C12	−97.2(2)
C2–C3–C4–C5	−1.1(3)	C12–C7–C8–C9	0.8(3)
C3–C4–C5–O2	1.4(3)	C6–C7–C8–C9	−177.9(2)
C3–C4–C5–C6	−176.1(2)	C7–C8–C9–C10	−0.8(4)
C1–O2–C5–C4	0.5(3)	C8–C9–C10–C11	0.2(4)
C1–O2–C5–C6	178.4(2)	C9–C10–C11–C12	0.3(4)
C4–C5–C6–O3	100.3(3)	C8–C7–C12–C11	−0.3(3)
O2–C5–C6–O3	−77.4(2)	C6–C7–C12–C11	178.5(2)
C4–C5–C6–C7	−23.0(3)	C10–C11–C12–C7	−0.3(3)

Table 27: Hydrogen bond data of compound **159a**; angles in (°), distances in (Å).

D–H ⋯ A	D–H	H ⋯ A	D ⋯ A	D–H ⋯ A
$O3^{i}$–$H3^{i}$ ⋯ O1	0.997(10)	1.783(10)	2.773(2)	171.6(12)

3,5-Dibromo-6-iodo-2*H*-pyran-2-one (163a)

CCDC-1851127 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

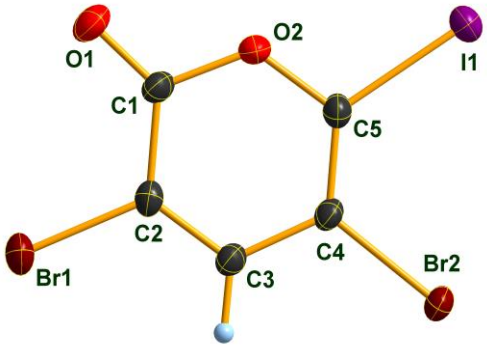


Figure 7: Molecular structure of compound **163a** in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50% probability level.

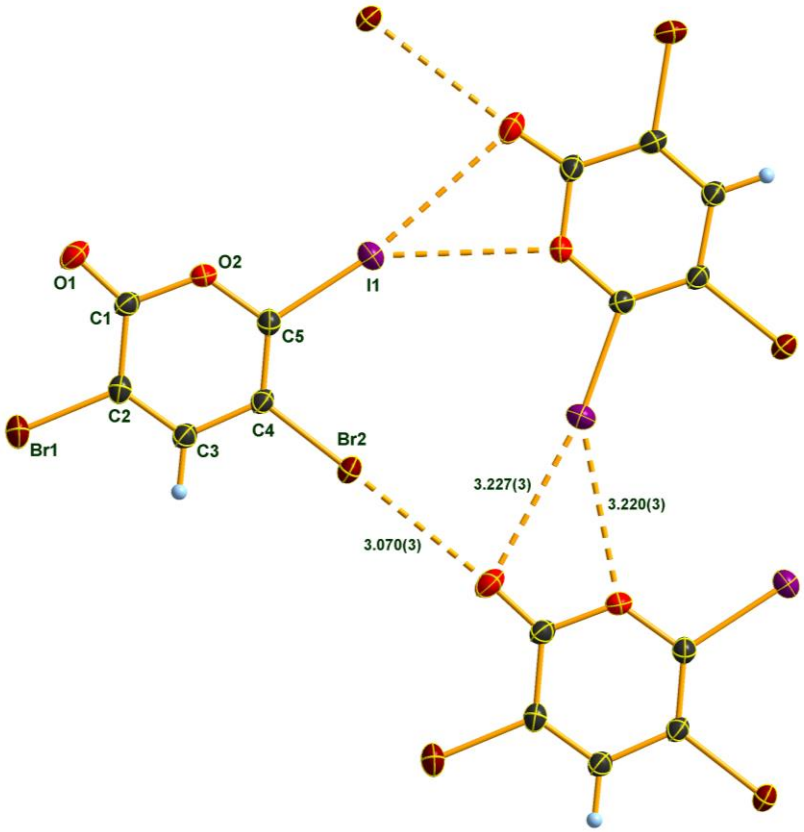


Figure 8: Halogen bonding in the crystal structure of compound **163a**, DIAMOND representation; thermal ellipsoids are drawn at 50% probability level. Symmetry codes: upper unlabeled molecule: 0.5-x, −0.5+y, 1.5−z; lower unlabeled molecule: x, −1+y, z; isolated bromine atom: 0.5−x, 0.5+y, 1.5−z. Sum of the van der Waals radii: Br/O: 337 pm, I/O: 350 pm.

Table 28: Details for X-ray data collection and structure refinement for compound **163a**.

	163a
Empirical formula	$C_5HBr_2IO_2$
Formula mass	379.78
T[K]	143(2)
Crystal size [mm]	0.30 × 0.10 × 0.05
Crystal description	dark yellow block
Crystal system	monoclinic
Space group	*P*21/*n*
a [Å]	8.0015(3)
b [Å]	8.9288(3)
c [Å]	11.3513(5)
α [°]	90
β [°]	92.236(4)
γ [°]	90
V [Å ^{3}]	810.36(5)
Z	4
$\rho_{calc.}$ [g cm^{-3}]	3.113
μ [mm^{-1}]	13.748
F(000)	680
Θ range [°]	4.26–25.24
Index ranges	$-11 \leq h \leq 11$
	$-12 \leq k \leq 12$
	$-16 \leq l \leq 16$
Reflns. collected	16311
Reflns. obsd.	2068
Reflns. unique	2469 (R_{int} = 0.0457)
R_1, wR_2 (2σ data)	0.0269, 0.0557
R_1, wR_2 (all data)	0.0367, 0.0597
GOOF on F^2	1.024
Peak/hole [e Å^{-3}]	1.206 / −1.036

Table 29: Selected bond lengths (Å) of compound **163a**.

I1–C5	2.066(3)	O2–C1	1.379(4)
Br2–C4	1.875(3)	O1–C1	1.218(4)
Br1–C2	1.873(3)	C1–C2	1.445(5)
C4–C5	1.342(5)	C3–C2	1.350(4)
C4–C3	1.436(4)	O2–C5	1.366(4)

Table 30: Selected bond angles (°) of compound **163a**.

C5–C4–C3	118.8(3)	C3–C2–C1	120.9(3)
C5–C4–Br2	122.9(3)	C3–C2–Br1	121.8(3)
C3–C4–Br2	118.2(2)	C1–C2–Br1	117.3(2)
C5–O2–C1	123.9(3)	C4–C5–O2	120.5(3)
O1–C1–O2	116.8(3)	C4–C5–I1	127.8(2)
O1–C1–C2	127.8(3)	O2–C5–I1	111.6(2)
O2–C1–C2	115.4(3)	C2–C3–C4	120.3(3)

Table 31: Selected torsion angles (°) of compound **163a**.

C5–O2–C1–O1	−179.2(3)	O1–C1–C2–Br1	3.1(5)
C5–O2–C1–C2	3.8(5)	O2–C1–C2–Br1	179.8(2)
C5–C4–C3–C2	0.7(5)	C3–C4–C5–O2	2.7(5)
Br2–C4–C3–C2	−177.7(3)	Br2–C4–C5–O2	−179.0(2)
C4–C3–C2–C1	−1.9(5)	C3–C4–C5–I1	−177.1(2)
C4–C3–C2–Br1	178.1(2)	Br2–C4–C5–I1	1.2(5)
O1–C1–C2–C3	−176.9(4)	C1–O2–C5–C4	−5.1(5)
O2–C1–C2–C3	−0.3(5)	C1–O2–C5vI1	174.7(2)