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

Synthesis, Functionalization and Polymerization of Heterocycles Using Frustrated Lewis Pairs, Boron, Magnesium and Zinc Reagents.

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aus Heidelberg

München 2010

Erklärung

Diese Dissertation wurde im Sinne von § 13 Abs. 3 bzw. 4 der Promotionsordnung vom 29. Januar 1998 von Prof. Dr. Paul Knochel betreut.

Ehrenwörtliche Versicherung

Diese Dissertation wurde selbstständig und ohne unerlaubte Hilfe erarbeitet.

München, den 14.12.2010

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Benjamin Alexander Haag

Dissertation eingereicht am	14.12.2010
1. Gutachter:	Prof. Dr. Paul Knochel
2. Gutachter:	Prof. Dr. Thomas Carell
Mündliche Prüfung am	14.01.2011

This work was carried out from March 2007 until October 2010 under the supervision of Prof. Dr. Paul Knochel at the Department of Chemistry of the Ludwig-Maximilians-University Munich.

First of all, I would like to express my gratitude to Prof. Dr. Paul Knochel for giving me the great opportunity doing my Ph.D. in his group. Furthermore, I sincerely thank him for his inspiring guidance, fruitful discussions and support throughout my scientific research.

At the same time, I am also very grateful to Prof. Dr. T. Carell for agreeing to be second reviewer, as well as Prof. Dr. Konstantin Karaghiosoff, Prof. Dr. Heinz Langhals, Prof. Dr. Manfred Heuschmann and Prof. Dr. Rudolf Knorr for the interest shown in this doctoral thesis by accepting to be co-reviewers.

Furthermore, I would like to thank Dr. Coura Diene, Tobias Blümke, Matthias Schade, Sebastian Bernhardt and Andreas Wagner for the careful correction of this manuscript.

In particular, I would like to thank Prof. Dr. Konstantin Karaghiosoff for his efforts and time spent with me investigating the "frustrated Lewis pairs". In this respect, I also would like to thank Prof. Dr. Hendrik Zipse for fruitful discussions on theoretical investigations of "frustrated Lewis pairs" and diastereoselective cross-couplings.

In addition, I would like to thank Zhi-Guang Zhang for the collaboration on the preparation of polyfunctional indoles. My thanks go to Zhihua Peng for the cooperative work on the indazole and the triazine scaffold. For the successful cooperation in the field of "frustrated Lewis pairs", I would like to thank Milica Jaric and Andreas Unsinn. Furthermore, I would like to thank "my Nachbar", Tobias Thaler, for the excellent collaboration investigating the diastereoselective cross-coupling. In addition, I would like to thank Stefan Wunderlich, Andreas Unsinn, Fabian Piller, Matthias Schade, Albrecht Metzger and Andrej Gavryushin for the fruitful collaboration on metalation and magnesium insertion reactions. Special thanks go to Sebastian Bernhardt and Christoph Sämann for an excellent collaboration and for continuing the work on organoborate compounds.

I thank all past and present co-workers I have met in the Knochel group for their kindness and help. Special thanks go to my labmates Matthias Schade, Dr. Christoph Rohbogner, Dr. Marc Mosrin, Dr. Christina Despotopulou, Estelle Durantie, Zhi-Guang Zhang, Timo Hohl, Tomke Bresser, Klaus Groll and Dr. Rick Bauer for the fantastic atmosphere and the time we spent.

In addition, I would like to thank Theresa Soltner, Dr. Sabine Schneider, Dr. Francois Crestey, Veronika Werner, Dr. Coura Diene, Gabriel Monzon, Sebastian Bernhardt, Dr. Armin Stoll, Christoph Sämann, Andreas Wagner, Tobias Thaler, Dr. Matthew Helm, Prof. Giuliano Clososki, Xavier Mollat du Jourdin, Dr. Nadège Boudet, Dr. Christian Rauhut, Dr. Fabian Piller and Dr. Andrej Gavryushin for the great atmosphere during and after scientific research.

I would like to thank Tobias Blümke and Matthias Schade particularly for invaluable and joyful late-night discussions about important matters of general significance.

I would like to thank Renate Schröder, Beatrix Cammelade, Christine Schliski, Vladimir Malakhov, Simon Matthe and Yulia Tsvik for organizing everyday life in the lab. Special thanks also go to the analytical team of the faculty for their precise work.

Furthermore, I would like to thank Doro Fried and Timo Hohl for their contribution to this work in the course of their internships. In particular, I would like to thank Zhi-Guang and Simon Matthe for their efforts spent contributing to this work.

Moreover, I would like to thank my parents and my brother for financial and enduring support.

“Find a job you love and you'll never work a day in your life.“

Confucius

Für meine Eltern und meinen Bruder.

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

PUBLICATIONS

1. Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P.* "Preparation of Polyfunctional Arylmagnesium, Arylzinc, and Benzylic Zinc Reagents by Using Magnesium in the Presence of LiCl" *Chem. Eur. J*. **2009**, *15*, 7192–7202.
2. Haag, B.; Peng, Z.; Knochel, P.* "Preparation of Polyfunctional Indazoles and Heteroarylazo Compounds Using Highly Functionalized Zinc Reagents" *Org. Lett.* **2009**, *11*, 4270–4273.
3. Thaler, T.; Haag, B.; Gavryushin, A.; Schober, K.; Hartmann, E.; Gschwind, R.; Zipse, H.; Knochel, P.* "Highly Diastereoselective Csp^3-Csp^2-Negishi Cross-Coupling with Cycloalkylzinc Compounds" *Nature Chem*. **2010**, *2*, 125.
4. *Designated "Hot Paper"*: Jaric, M.; Haag, B.; Unsinn, A.; Karaghiosoff, K.; Knochel, P.* "Highly Selective Metalations of Pyridines and Related Heterocycles Using New Frustrated Lewis Pairs or tmp-Zinc and tmp-Magnesium Bases with $BF_3 \cdot OEt_2$" *Angew. Chem, Int. Ed.* **2010**, *49*, 5451–5455.
5. Peng, Z.; Haag, B.; Knochel, P.* "Preparation of 2-Magnesiated 1,3,5-Triazines via an Iodine-Magnesium Exchange" *Org. Lett.* **2010**, *12*, 5398–5401.
6. *Designated "Hot Paper"*: Haag, B.; Zhang, Z.-G.; Li, J.-S.; Knochel, P. "Fischer Indole Synthesis with Organozinc Reagents" *Angew. Chem.* **2010**, *122*, 9703-9706; *Angew. Chem. Int. Ed.* **2010**, *49*, 9513–9516.
7. Zhang, Z.-G.; Haag, B.; Li, J.-S.; Knochel, P. "Efficient Preparation of Polyfunctional Indoles via a Zinc Organometallic Variation of the Fischer Indole Synthesis" *Synthesis* **2011**, 23-29.
8. Jaric, M.; Haag, B.; Manolikakes, S.; Knochel, P. "Selective and Multiple Functionalization of Complex Pyridines and Alkaloids via Mg- and Zn-Organometallic Intermediates" **2011**, *submitted*.

REVIEWS AND PATENTS

1. Haag, B.; Mosrin, M.; Hiriyakkanavar, I.; Malakhov, V.; Knochel, P. "Regio- and Chemoselective Metalations of Arenes and Heteroarenes Using TMP Metal Amides" *Angew. Chem. Int. Ed.* **2011**, *submitted*.
2. Knochel, P.; Haag, B. "Process for the Preparation of Highly Regioselective Hal/Mg-exchange Reagents and their Application in Functionalization and Regioregular Polymerization Reactions" **2010**, *patent pending*.
3. Knochel, P.; Haag, B. "Metallic Amidoborates for Efficient Functionalization of Substituted Organic Compounds" **2010**, *patent pending*.
4. Knochel, P.; Haag, B. "Low-Cost One-Step Synthesis of Polyfunctional Organoborates" **2010**, *patent pending*.

Table of Contents:

Abbreviations:

Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonane
BDMAEE	bis[2-(dimethylamino)ethyl]ether
BDMAMA	bis[2-(dimethylamino)ethyl]methylamine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
calc.	calculated
chloranil	tetrachloro-*para*-benzoquinone
corr.	corrected
d	day
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	*trans*,*trans*-dibenzylideneacetone
DFT	density functional theory
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,2-bis(diphenylphosphino)propane
Eq.	equation
equiv	equivalent
EI	electron-ionization
Et	ethyl
EtOAc	ethyl acetate
exp	experimental
FG	functional group
FLP	frustrated Lewis pair
GC	gas chromatography
h	hour
HRMS	high resolution mass spectrometry
Hex	hexyl

HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HMQC	heteronuclear multiple quantum correlation
HT	head-to-tail
*i*Pr	*iso*-propyl
IR	infrared
ITO	indium tin oxide
J	spin-spin coupling constant (NMR)
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
M	molarity
m	meta
Me	methyl
min	minute
m.p.	melting point
MS	mass spectrometry
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	ortho
Oct	octyl
p	para
P3AT	poly(3-alkylthiophene)
PCBM	1-(3-methoxycarbonyl)propyl-1-phenyl[6.6]C_{61}
PEPPSI	pyridine, enhanced, precatalyst, preparation, stabilization, and initiation
Ph	phenyl
Piv	pivaloyl
PT	polythiophene
R	organic moiety
rr	regioregular
rflx	reflux
*s*Bu	*sec*-butyl
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
*t*Bu	*tert*-butyl

tfp	tris(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
TP	typical procedure
Ts	4-toluenesulfonyl
TTMPP	tris(trimethoxyphenyl)phosphine
X	halogen (F, Cl, Br, I)

A. General Introduction

1. Overview

Heterocycles constitute the largest group of organic compounds and are becoming ever more significant in all aspects of pure and applied chemistry.[1] Heterocycles are important, not only because of their chemical, biological and technical significance. In addition, many natural products or biologically active compounds contain heterocyclic scaffolds, such as vitamins, antibiotics, alkaloids, pharmaceuticals, herbicides or dyes, to name a few. In particular, their extraordinary structural diversity, multiplicity and unique reactivity patterns are crucial challenges for synthetic chemists. In order to meet these challenges successfully, the use of organometallic compounds as key intermediates is essential. However, the nature of the metal center in the organometallic reagent predominantly determines its reactivity and chemoselectivity in the reaction with an electrophile. This nature can readily be modulated by numerous parameters, such as choice of ligands or solvents. The right adjustments will result in the desired reactivity of the organometallic reagent in reactions with organic substrates. Furthermore, choosing the right organometallic compound and tuning the ligand sphere for any given organic transformation will reward the synthetic chemist with high yields, regio- and chemoselectivity. With respect to thermal stability and reactivity, in particular functionalized heterocyclic organometallics involve great challenges to organic chemists.

1.1 Organolithium Reagents

In organometallic chemistry, organolithium compounds are among the most versatile reagents. The halogen-lithium exchange reaction discovered by Wittig *et al.*[2] and Gilman *et al.*[3] allows the preparation of a broad range of organolithium compounds. Seminal work has been done by Schlenk and Holtz, especially with their developments of inert-gas techniques, enabling the handling of these reactive compounds.[4] Due to the strongly polarized lithium–carbon bond, organolithium compounds are generally used as highly reactive nucleophiles and strong bases. Their applications range from simple deprotonation and anionic

[1] a) A. F. Pozharskii, A. T. Soldatenkov, A. R. Katritzky, in *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry and Biochemistry and the Role of Heterocycles in Science, Technology, Medicine and Agriculture*, Wiley-VCH, Weinheim, **1997**; b) T. Eicher, S. Hauptmann, in *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, 2. Ed., Wiley-VCH, Weinheim, **2003**; c) A. R. Katritzky, in *Advances in Heterocyclic Chemistry*, Academic Press, Oxford, Vol. 82, **2002**.
[2] G. Wittig, U. Pockels, H. Droge, *Chem. Ber.* **1938**, *71*, 1903.
[3] a) R. G. Jones, H. Gilman, *Org. React.* **1951**, *6*, 339; b) H. Gilman,W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106.
[4] W. Schlenk, J. Holtz, *Ber. Dtsch. Chem. Ges.* **1917**, *50*, 262.

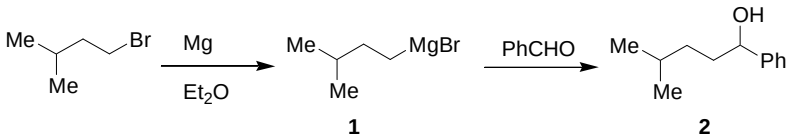
polymerization reactions to carbolithiations, as well as asymmetric syntheses. Thereby, adducts between organolithiums and Lewis bases, primarily ether molecules and nitrogen bases, play an essential role.[5] In recent years, developments in ligand design have led to many applications and new types of reactions, such as asymmetric deprotonation or addition reactions.[6] Developments in cryogenic techniques in the 1990s constitute a crucial progress with organolithium reagents, facilitating the handling of these highly reactive and pyrophoric compounds.[7] Henceforward, organolithium nucleophiles are versatile reagents for carbon-carbon and carbon-heteroatom bond formations via alkylations, additions to carbon heteroatom double bonds, aldol condensations, opening of epoxides, or conjugate additions. Among the versatile preparation methods of organolithium reagents, the most common and practical are enolization, halogen-lithium exchange, direct deprotonation with organic lithium reagents, transmetallation reactions, carbon-heteroatom bond cleavage and carbolithiation of multiple carbon-carbon bonds.[8] Moreover, *in situ* generated lithium "ate" complexes have also become popular reagents in organic syntheses.[9] Due to the commercial availability of the most frequently and widely used organolithium reagents, such as lithium diisopropylamide (LDA) or butyllithium (BuLi), the scope of applications of these reagents is still expanding.

1.2 Organomagnesium Reagents

In comparison to organolithium reagents, the corresponding magnesium derivatives are highly advantageous with respect to functional group tolerance, thermal stability and handling.[10] Since the discovery and first preparation of soluble organomagnesium reagents[11] by Victor Grignard in 1901, these organometallics have played a key role in organic synthesis in academia, as well as in large-scale preparations in industry.[12] In 1912, Victor Grignard was awarded the Nobel Prize for his key discovery. Grignard demonstrated already in his first report the facile preparation of alkylmagnesium reagents, such as isoamylmagnesium bromide

[5] T. Stey, D. Stalke in *The Chemistry of Organolithium Compounds* (Eds.: Z. Rappoport, I. Marek), Wiley, New York, **2004**, pp. 47.
[6] For examples, see: a) D. Hoppe, F. Hintze, P. Tebben, *Angew. Chem. Int. Ed.* **1990**, *29*, 1422; b) S. T. Kerrick, P. Beak, *J. Am. Chem. Soc.* **1991**, *113*, 9708; c) M. C. Whisler, P. Beak, *J. Org. Chem.* **2003**, *68*, 1207; d) I. Coldham, R. C. B. Copley, T. F. N. Haxell, S. Howard, *Org. Biomol. Chem.* **2003**, *1*, 1532; e) C. Metallinos, H. Szillat, N. J. Taylor, V. Snieckus, *Adv. Synth. Catal.* **2003**, *345*, 370; f) E.-U. Würthwein, K. Behrens, D. Hoppe, *Chem. Eur. J.* **1999**, *5*, 3459; g) K. B. Wiberg, W. F. Bailey, *Tetrahedron Lett.* **2000**, *41*, 9365; h) P. H. Martinz, K. C. Hueltzsch, F. Hampel, *Chem. Commun.* **2006**, 2221; i) B. Goldfuss, *Synthesis* **2005**, 2271.
[7] First structure determinations of organolithium compounds: a) H. Dietrich, *Acta Crystallogr.* **1963**, *16*, 681; b) E. A. C. Lucken, E. Weiss, *J. Organomet. Chem.* **1964**, *2*, 197.
[8] J. Clayden, in *Organolithiums: Selectivity for Synthesis*; Pergamon Press: Oxford, U.K., **2002**; pp 273.
[9] R. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802.
[10] *Handbook of Functionalized Organometallics*, Vol. 1 (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.
[11] V. Grignard, *Ann. Chim.* **1901**, *24*, 433.
[12] F. R. Bush, D. M. De Antonis, in *Grignard Reagents- New Developments* (Ed.: H. G. Richey, Jr.); Wiley, New York, **2000**, pp.165.

(**1**), by direct metal insertion and its addition to benzaldehyde leading to the corresponding carbinol **2** (Scheme 1).

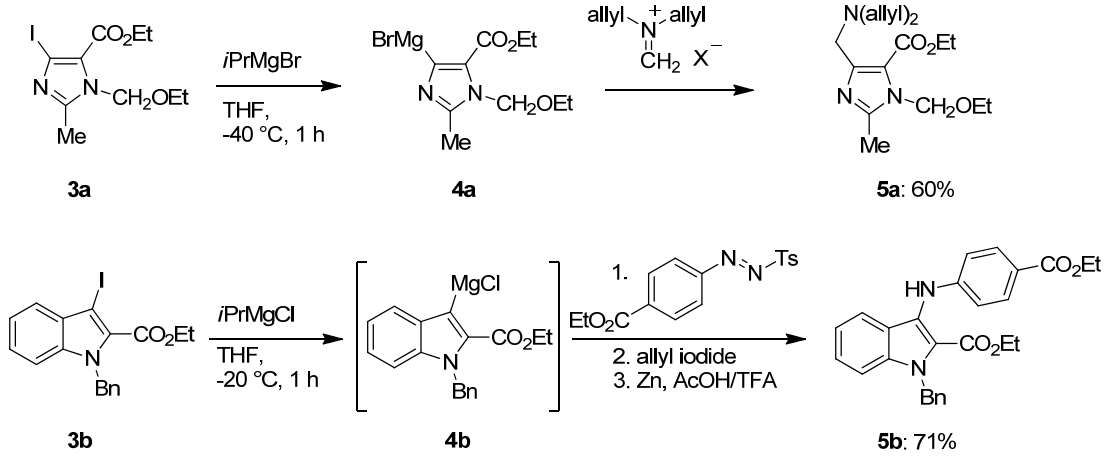


Scheme 1. Early example for the preparation of isoamylmagnesium bromide (**1**) followed by the addition to benzaldehyde.

Thereafter, the so-called Grignard reagents have become very popular nucleophilic reagents. In particular, these reagents are characterized by their convenient synthesis, thermal stability, excellent chemoselectivity and good reactivity towards a broad range of electrophiles. The reactivity of the carbon-magnesium bond can readily be tuned by appropriate transmetalation with many metallic salts, broadening its utilizability in synthesis dramatically.[10] Organomagnesium reagents have a broad spectrum of chemoselective reaction patterns, such as addition to carbonyl functions, addition to nitro groups, carboxylation with carbon dioxide, or numerous reaction possibilities after transmetalation to noble metals.[10] At the same time, the carbon-magnesium bond possesses an intrinsic reactivity that is compatible with the presence of many important organic functional groups in the same molecule. Recently, practical methods for the preparation of polyfunctional aryl and heteroaryl magnesium compounds bearing sensitive functions have become available, which further increases the scope of Grignard reagents in organic synthesis.[13] The direct magnesium insertion into organic halides is still the most common method for the preparation of organomagnesium compounds. The first example of a Br/Mg-exchange reaction was briefly reported in 1931 by Prévost.[14] Thereafter, important contributions were made by Villiéras,[15] Tamborski and Moore.[16] Furukawa *et al.* demonstrated the synthetic potential of I/Mg-exchange reagents such as EtMgBr generating heteroarylmagnesium iodides.[17] Thereafter, these exchange reagents have become of increased importance in modern organic synthesis.[18] In particular,

[13] a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4415; b) C. Najera, M. Yus, *Recent Res. Dev. Org. Chem.* **1997**, *1*, 67.
[14] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[15] a) J. Villiéras, *Bull. Soc. Chim. Fr.* **1967**, *5*, 1520; b) J. Villiéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Soc. Chim. Fr.* **1986**, 470.
[16] C. Tamborski, G. J. Moore, *J. Organomet. Chem.* **1971**, *26*, 153.
[17] N. Furukawa, T. Shibutani, H. Fujihara, *Tetrahedron Lett.* **1987**, *28*, 5845.
[18] For other examples of halogen–magnesium exchange reactions, see: a) H. H. Paradies, M. Görbing, *Angew. Chem. Int. Ed.* **1969**, *8*, 279; b) G. Cahiez, D. Bernard, J. F. Normant, *J. Organomet. Chem.* **1976**, *113*, 107;

Knochel *et al.* intensively explored the usability of I/Mg-exchange reagents, like *i*PrMgCl, for the preparation of functionalized aryl and heteroarylmagnesium halides.[19] In particular, the methods for the generation of polyfunctional heteroarylmagnesium reagents proved to be exceptionally mild while tolerating a broad range of sensitive functions such as ester, nitrile, keto, amide, or nitro groups.[20] In addition, functionalized heterocycles such as **3a** could be converted to the magnesium derivative **4a** using *i*PrMgBr leading after addition to an iminium salt to the fully substituted imidazole **5a** in 60% yield (Scheme 2). Moreover, ester-substituted indoles like **3b** were functionalized via the corresponding indol-3-ylmagnesium chloride **4b** leading to the 2,3-disubstituted indole **5b** in 71% yield (Scheme 2).[21]



Scheme 2. Functionalization of heterocycles via heteroarylmagnesium reagents **3b** and **5b**.

Remarkably, Knochel *et al.* also developed and extensively explored the synthetic potential of novel Hal/Mg-exchange reagents such as *i*PrMgCl·LiCl.[22] In comparison to the "naked" *i*PrMgCl, the LiCl-complexed alkylmagnesium reagent is more efficient and higher reaction rates were observed. Knochel *et al.* clearly illustrated the supremacy of LiCl-complexed *i*PrMgCl over the uncomplexed reagent by comparative Br/Mg-exchange reactions. Thus, 2,6-dibromopyridine (**3c**) was converted to the pyridylmagnesium halide **4c** which was added to benzaldehyde leading to the α-pyridylalcohol **5c** in 42% and 89% yield, respectively (Scheme 3).[22]

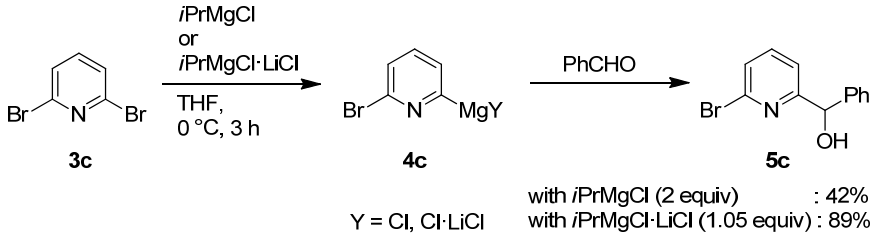
c) D. Seyferth, R. L. Lambert, *J. Organomet. Chem.* **1973**, *54*, 123; d) H. Nishiyama, K. Isaka, K. Itoh, K. Ohno, H. Nagase, K. Matsumoto, H. Yoshiwara, *J. Org. Chem.* **1992**, *57*, 407; e) C. Bolm, D. Pupowicz, *Tetrahedron Lett.* **1997**, *38*, 7349.

[19] L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.

[20] 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.

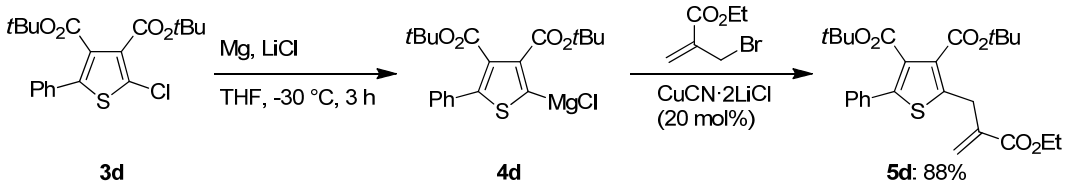
[21] I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 897.

[22] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed*. **2004**, *43*, 3333.



Scheme 3. Functionalization of **3c** via its heteroarylmagnesium reagent.

Furthermore, encouraged by such organomagnesium reagents possessing exceptional functional group tolerance,[20] Knochel and co-workers further explored the direct magnesium insertion. In several reports, Knochel *et al.* demonstrated an atom economical direct magnesium insertion,[23] avoiding harsh reaction conditions or low reaction temperatures, as in the case of Rieke´s method.[24] LiCl as solubilizing and accelerating additive proved to be essential for magnesium insertion with broad functional group tolerance. Thereby, polyfunctional heterocycles such as the ester-substituted thiophene **3d** were successfully converted to the thienylmagnesium reagent **4d** (–30 °C, 3 h) followed by a copper-catalyzed allylation affording the fully substituted thiophene derivative **5d** in 88% yield (Scheme 4).[23]

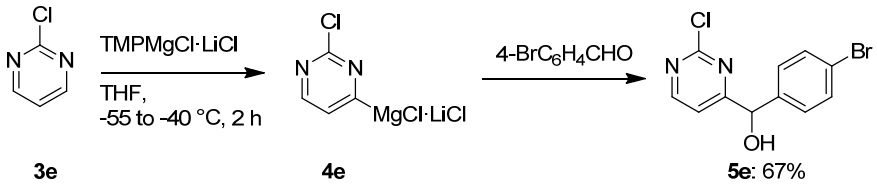


Scheme 4. Direct magnesium insertion with functionalized heterocycles.

Besides the direct magnesium insertion and Hal/Mg-exchange reactions, the deprotonative metalation has become an important tool towards functionalized organomagnesium intermediates. After the first report of magnesium amides as metalating reagents by Hauser *et al.*[25] in 1947, Eaton *et al.* firstly demonstrated their synthetic potential in directed *ortho*-metalations of aromatics.[26] However, these metal amides have only recently emerged as a distinct class of metalating reagents and a useful tool for regioselective functionalizations of various arenes and heteroarenes.[27] In this respect, important contributions were made by Schlecker and Mulzer,[28] as well as by Kondo and Sakamoto.[29,30] However, Knochel *et al.*

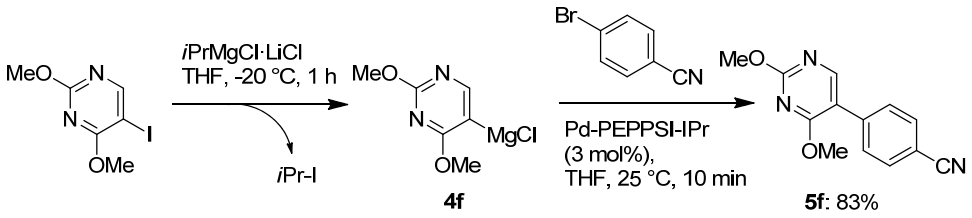
[23] F. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.
[24] a) R. D. Rieke, *Science* **1989**, *246*, 1260; b) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925.
[25] a) R. Hauser, H. G. Walker, Jr., *J. Am. Chem. Soc.* **1947**, *69*, 295; b) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350; c) L. Meunier, C. R. Hebd. *Seances Acad. Sci.* **1903**, *136*, 758.
[26] P. E. Eaton, C-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016.
[27] R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802.
[28] a) A. W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414 ; b) A. Huth, E. Ottow, J. Mulzer, *Justus Liebigs Ann. Chem.* **1995**, 1441.
[29] Y. Kondo, A. Yoshida, T. Sakamoto, *J. Chem. Soc., Perkin Trans 1* **1996**, 2331.

demonstrated the use of highly soluble LiCl-complexed magnesium TMP-amides, such as TMPMgCl·LiCl, possessing high kinetic activity (TMP = 2,2,6,6-tetramethylpiperidyl).[31] Thus, sensitive heterocycles like 2-chloropyrimidine were efficiently magnesiated and subsequently added to 4-bromobenzaldehyde producing the carbinol **5e** in 67% yield (Scheme 5).



Scheme 5. Regioselective magnesiation and functionalization of 2-chloropyrimidine.

Since polyfunctional aryl and heteroarylmagnesium reagents have become readily available, the scope of their use in organic synthesis has further been extended; in particular, beyond simple addition reactions to carbonyl functions. Nowadays, organomagnesium derivatives have found numerous applications, such as in Kumada-type cross-couplings, in which these reagents are frequently used.[32] Despite numerous reports about Kumada cross-coupling reactions,[33] Knochel *et al.* discovered an accelerated variation of this type of cross-coupling. Hereby, *iso*-propyl iodide generated by the I/Mg-exchange reaction accelerates subsequent Kumada-type cross-coupling reactions.[34] Thus, the pyrimidinylmagnesium halide **4f** furnished after Pd-catalyzed cross-coupling (Pd-PEPPSI-IPr (3 mol%), 25 °C, 10 min) the substituted pyrimidine **5f** in 83% yield (Scheme 6).

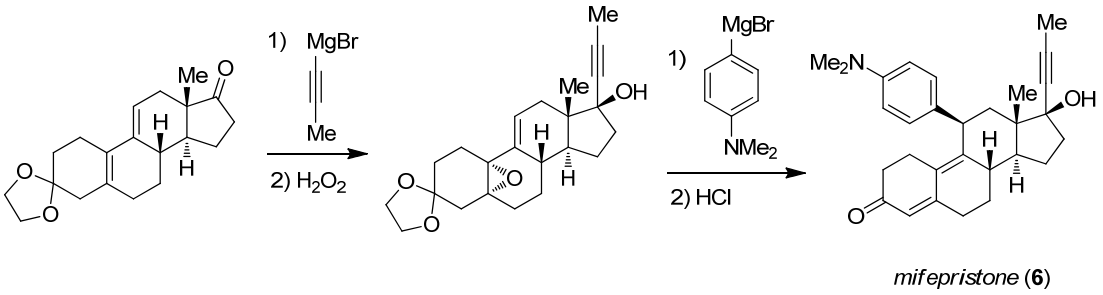


Scheme 6. Kumada cross-coupling using a heterocyclic Grignard reagent.

Moreover, the low price and low toxicity of magnesium metal make these compounds suitable intermediates for large scale applications in industry. The pharmaceutical industry has particular interest in the use of organomagnesium reagents, since they often offer convenient

[30] a) M.-X. Zhang, P. E. Eaton, *Angew. Chem. Int. Ed.* **2002**, *41*, 2169; b) Y. Kondo, Y. Akihiro, T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2331; c) P. E. Eaton, C. H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016; d) P. E. Eaton, M.-X. Zhang, N. Komiya, C.-G. Yang, I. Steele, R. Gilardi, *Synlett* **2003**, *9*, 1275; e) P. E. Eaton, R. M. Martin, *J. Org. Chem.* **1988**, *53*, 2728; f) M. Shilai, Y. Kondo, T. Sakamoto, *J. Chem. Soc. Perkin Trans. 1* **2001**, 442.
[31] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
[32] M. Kumada, *Pure Appl. Chem.* **1980**, *52*, 669.
[33] J. Adrio, J. C. Carretero, *ChemCatChem* **2010**, *2*, 1384.
[34] G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 205.

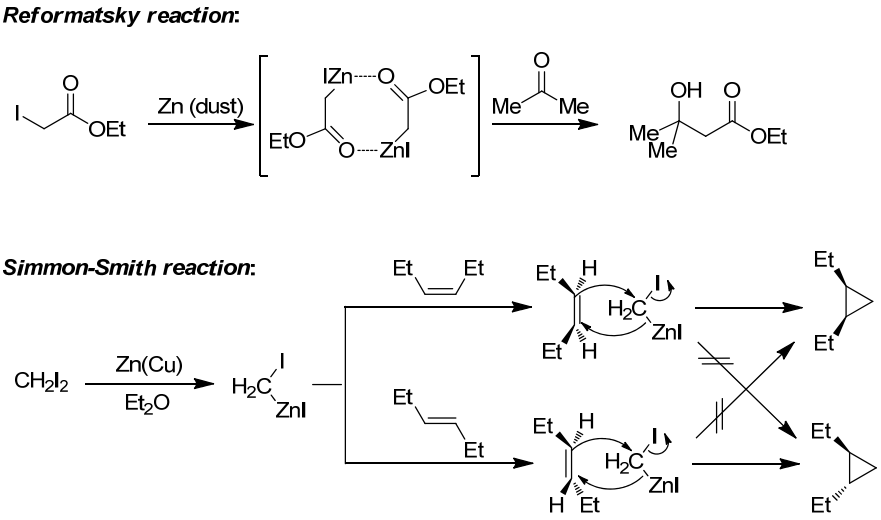
and concise synthetic routes to complex structures, e.g. the synthesis of the contraceptive *mifepristone* (**6**; Scheme 7).



Scheme 7. Industrial preparation of *mifepristone* (**6**).

1.3 Organozinc Reagents

The highly reactive nature of many organometallics often precludes the presence of sensitive functional groups in these reagents.[35] However, Frankland discovered in 1849, even before the discovery of soluble organomagnesium reagents, that heating ethyl iodide with elemental zinc produces highly pyrophoric diethylzinc.[36] Thereafter, named reactions using such organozinc intermediates (R_2Zn or RZnX) were discovered, e.g. the Reformatsky[37] or the Simmons-Smith[38] reaction. Henceforward, these organic transformations have been frequently applied in synthetic chemistry (Scheme 8).[38]

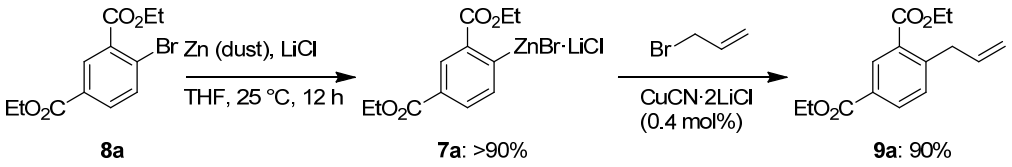


Scheme 8. Early examples of the Reformatsky and the Simmon-Smith reaction.

In comparison to the corresponding more reactive organomagnesium reagents, major characteristics of organozinc compounds are thermal stability and often higher selectivity,

[35] P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.
[36] a) E. Frankland, *J. Chem. Soc.* **1850**, *2*, 263; b) E. Frankland, *Justus Liebigs Ann. Chem.* **1849**, *71*, 171 and 213; c) C. Elschenbroich, A. Salzer, in *Organometallics: a concise introduction*; Wiley-VCH, Weinheim, **1989**.
[37] S. Reformatsky, *Chem. Ber.* **1887**, *20*, 1210.
[38] H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 4256.

accompanied by high tolerance towards various functional groups, as shown at an early stage by Hunsdiecker[39]. Additionally, the highly covalent character of the carbon-zinc bond affords in the absence of salts, configurationally stable organozincs,[40] whereas, at the same temperature, organomagnesium or lithium reagents undergo racemisation. The direct zinc insertion into organic halides is the most attractive and simplest method for the preparation of functionalized organozinc halides.[41] The preparation of arylzinc iodides could only be achieved using Rieke-zinc,[41a,42] or required the presence of electron-withdrawing substituents in *ortho*-position as well as elevated temperatures.[43] Remarkably, Knochel el al. reported a LiCl-mediated direct zinc insertion into aryl and heteroaryl iodides and even bromides using commercially available and inexpensive zinc dust.[44] Thus, the functionalized arylzinc reagent **7a** was formed in the presence of LiCl and zinc dust (25 °C, 12 h) starting from diethyl 4-bromoisophthalate (**18a**). Subsequent copper-catalyzed allylation provided the substituted diester **9a** in 90% yield (Scheme 9).[44]



Scheme 9. LiCl-mediated zinc insertion into an aryl bromide followed by allylation.

Besides transmetalation, organozinc reagents are readily prepared via I/Zn-exchange. However, I/Zn-exchange reactions have only been applicable to primary and secondary alkyl iodides and failed with aryl iodides.[45,46] Therefore, Knochel and co-workers recently reported a Li(acac)-catalyzed iodine-zinc-exchange reaction resolving the aforementioned problems.[47] Furthermore, pioneering work by Zakharin and Okhlobystin,[48] and Thiele *et al.*[49] promoted a

[39] H. Hunsdiecker, H. Erlbach, E. Vogt, *Ger. Off.* 722467, **1942;** *Chem. Abstr.* **1943**,*37*, P 5080.
[40] E. Hupe, P. Knochel, *Org. Lett.* **2001**, *3*, 127.
[41] a) *Polyfunctional Zinc Organometallics for Organic Synthesis*: P. Knochel, H. Leuser, L.-Z. Gong, S. Perrone, F. F. Kneisel, in *Handbook of Functionalized Organometallics*, Vol. 1 (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**, p. 251; b) *Organozinc Reagents* (Eds.: P. Knochel, P. Jones), Oxford University Press, New York, **1999**.
[42] a) R. D. Rieke, P. T. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323; b) R. T. Arnold, S. T. Kulenovic, *Synth. Commun.* **1977**, *7*, 223.
[43] R. Ikegami, A. Koresawa, T. Shibata, K. Takagi, *J. Org. Chem.* **2003**, *68*, 2195.
[44] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.
[45] a) L. Micouin, P. Knochel, *Synlett* **1997**, 327; b) M. Uchiyama, M. Koike, M. Kameda, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1996**, *118*, 8733.
[46] For a cobalt-catalyzed synthesis of organozinc reagents with zinc metal, see: a) H. Fillon, C. Gosmini, J. Perichon, *J. Am. Chem. Soc.* **2003**, *125*, 3867; b) for the use of activated zinc, see: R. D. Rieke, *Science* **1989**, *246*, 1260; c) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445.
[47] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.
[48] L. I. Zakharin, O. Y. Okhloystin, *Z. Obshch. Chim.* **1960**, *30*, 2134; Engl. Trans., p. 2109; *Chem. Abstr.* **1961**, *55*, 9319a.
[49] a) K.-H. Thiele, P. Zdunneck, *J. Organomet. Chem.* **1965**, *4*, 10; b) K.-H. Thiele, G. Engelhardt, J. Köhler, M. Armstedt, *J. Organomet. Chem.* **1967**, *9*, 385.

general method for the preparation of versatile diorganozinc reagents via boron-zinc exchange.[50] Additionally, organozinc reagents are also accessible via direct metalation using zincates.[51] Based on previously mentioned developments in the field of metal amide bases,[52] Kondo, Uchiyama, Mulvey, Hevia and Knochel recently reported various TMP-derived zinc bases, such as $R_2Zn(TMP)Li$, $(TMP)ZnLiCl_2$, $(TMP)_2Zn(MgCl_2)_2(LiCl)_2$ or $R_2Zn(TMP)Li$/Na-TMEDA.[51,53,54,55] In particular, Knochel *et al.* described highly regio- and chemoselective zincation reactions with functionalized aromatics and heteroaromatics using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[54] and $TMPZnCl{\cdot}LiCl$[55]. Thus, electron-poor *N*-heterocycles, such as 2-chloro-3-nitropyridine, were efficiently zincated by $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (–40 °C, 1.5 h) affording bispyridylzinc derivative **7b**. Subsequent allylation with 3-bromocyclohexene furnished the trisubstituted pyridine **9b** in 80% yield (Scheme 10).[54] Moreover, $TMPZnCl{\cdot}LiCl$ smoothly converts (25 °C, 30 min) sensitive heterocycles like 3,6-dichloropyridazine to the heteroarylzinc halide **7c** leading to the substituted ketone **9c** in 96% yield (Scheme 10).[55]

[50] a) F. Langer, J. Waas, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 5261; b) F. Langer, L. Schwink, A. Devasagayaraj, P.-Y. Chavant, P. Knochel, *J. Org. Chem.* **1996**, *61*, 8229; c) M. Srebnik, *Tetrahedron Lett.* **1991**, *32*, 2449; d) W. Oppolzer, R. N. Radinov, *Helv. Chim. Acta* **1992**, *75*, 170; e) W. Oppolzer, R. N. Radinov, *J. Am. Chem. Soc.* **1993**, *115*, 1593.

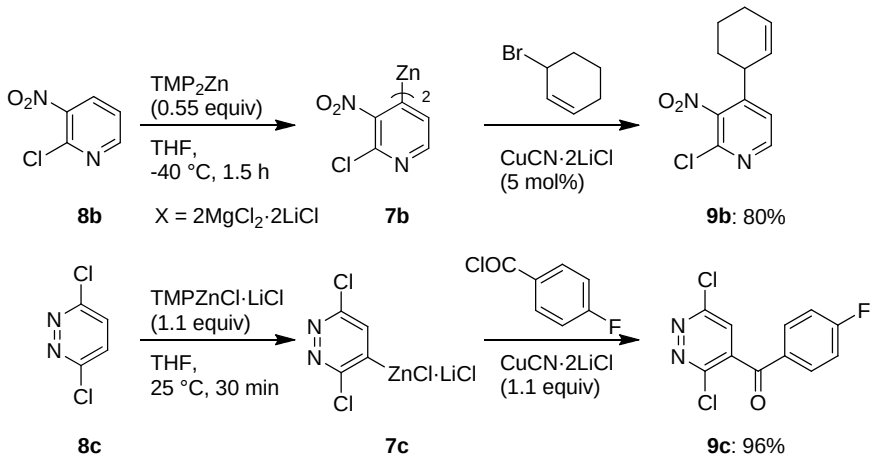
[51] a) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539; b) W. Clegg, S. H. Dale, R. W. Harrington, E. Hevia, G. H. Honeyman, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2006**, *45*, 2374.

[52] For reviews; see: a) H. W. Gschward, H. R. Rodriguez, *Organic Reactions* **1979**, *26*, 1; b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; c) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed*. **2004**, *43*, 2206; d) M. Schlosser, *Angew Chem. Int. Ed.* **2006**, *45*, 5432; e) M. Schlosser, *Angew Chem. Int. Ed.* **2005**, *44*, 376; f) M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3975; g) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827; h) R. Chinchilla, C. Najera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667; i) A. Turck, N. Ple, F. Mongin, G. Queguiner, *Tetrahedron* **2001**, *57*, 4059; j) F. Mongin, G. Queguiner, *Tetrahedron* **2001**, *57*, 4489; k) M. Schlosser, F. Mongin, *Chem. Soc. Rev.* **2007**, *36*, 1161; l) F. Chevallier, F. Mongin, *Chem. Soc. Rev.* **2008**, 37, 595; m) M. Vieth, S. Wieczorek, K. Fries, V. Huch *Z. Anorg. Allg. Chem.* **2000**, *626*, 1237; n) J. Claydon, in *Organolithium: Selectivity for Syntheses* (Eds: J. E. Baldwin, R. M. Williams), Elsvier, Amsterdam, **2002**; o) F. Leroux, M. Schlosser, E. Zohar, I. Marek, in *Chemistry of Organolithium Compounds* (Eds: Z. Rappoport, I. Marek) Wiley, New York, **2004,** Chapt. 1, p. 435; p) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802; q) R. E. Mulvey, *Acc. Chem. Res.* **2009**, *42*, 743; r) R. E. Mulvey, *Organometallics* **2006**, *25*, 1060; d) M. Westerhausen, *Dalton Trans 2* **2006**, 4755.

[53] a) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514; b) H. R. L. Barley, W. Clegg, S. H. Dale, E. Hevia, G. W. Honeyman, A. R. Kennedy, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2005**, *44*, 6018; c) W. Clegg, S. H. Dale, E. Hevia, G. W. Honeyman, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2006**, *45*, 2370; d) W. Clegg, S. H. Dale, A. M. Drummond, E. Hevia, G. W. Honeyman, R. E. Mulvey, *J. Am. Chem. Soc.* **2006**, *128*, 7434; e) M. Uchiyama, Y. Kobayashi, T. Furuyama, S. Nakamura, Y. Kajihara, T. Miyoshi, T. Sakamoto, Y. Kondo, K. Morokuma, *J. Am. Chem. Soc.* **2008**, *130*, 472; f) W. Clegg, B. Conway, E. Hevia, M. D. Mccalla, L. Russo, R. E. Mulvey, *J. Am. Chem. Soc.* **2009**, *131*, 2375.

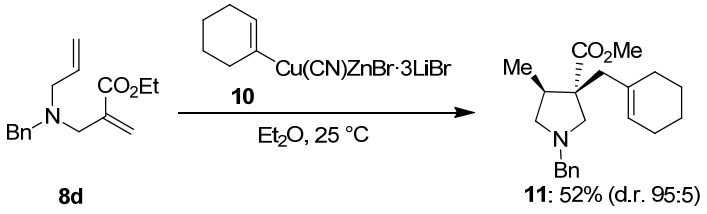
[54] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.

[55] M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837.



Scheme 10. Preparation of heteroarylzinc reagents using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ or $TMPZnCl \cdot LiCl$.

As described, numerous methods for the preparation of organozinc reagents have been reported over the last decades. Hence, reports about their applications are numerous, as well. Especially, the tendency of organozinc reagents to allow fast transmetalation reactions with noble metals is of particular interest. The generated highly reactive organometallic species, e. g. organocuprates,[56] offer a broad spectrum of versatile reactivities. Thereof, so-called "Knochel-cuprates"[57] of the general formula RCu(CN)ZnX are widely used reagents in modern organic chemistry, e.g. for acylation, 1,4-addition, carbocupration, allylic substitution, or allylation reactions. Thus, the cyclohexenyl cuprate **10** added to the Michael-acceptor **8d** leading to the substituted pyrrolidine **11** in 52% yield (Scheme 11).[58]

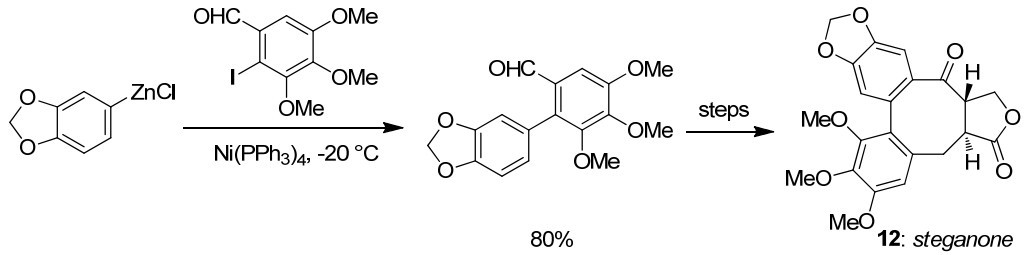


Scheme 11. 1,4-addition of a "Knochel-cuprate" (**10**).

Furthermore, Negishi *et al.* reported in 1976 a novel type of C-C bond formation taking advantage of the fast transmetalation tendency of organozincs to palladium or nickel complexes, known as Negishi cross-coupling.[59] Due to high reaction rates and efficiency, these types of reactions have soon after become widely used, e. g. in the natural product synthesis of *steganone* (**12**; Scheme 12).[60] Over the last decades, this type of reaction has been

[56] a) T. Thaler, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 645; b) *The Chemistry of Organocopper Compounds* (Eds.: Z. Rappoport, I. Marek), John Wiley & Sons: Chichester, **2009**.
[57] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[58] A. W. Hird, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2003**, *42*, 1276.
[59] a) E.-I. Negishi, S. Baba, *J. Chem. Soc., Chem. Commun.* **1976**, 596; b) S. Baba, E. Negishi, *J. Am. Chem. Soc.* **1976**, *98*, 6729; c) E.-I. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[60] E. R. Larson, R. A. Raphael, *Tetrahedron Lett.* **1979**, 5041.

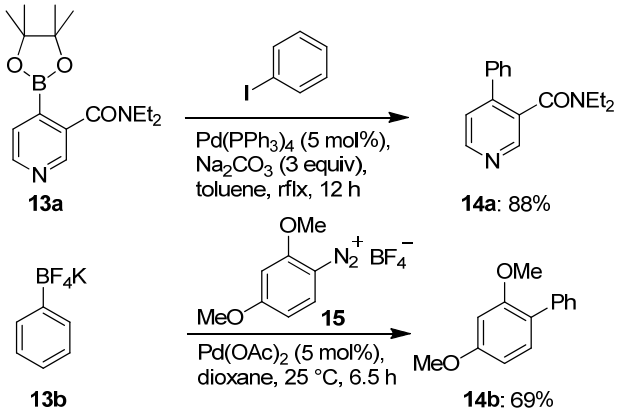
intensively developed and studied in detail. Nowadays, it is one of the most frequently applied cross-coupling reactions.



Scheme 12. Ni-catalyzed Negishi cross-coupling for the total synthesis of *steganone.*

1.4 Organoboron Reagents

In 1860, Frankland[61] reported the first isolation of an organoboronic acid.[62] Later, Brown *et al.* intensively explored the preparation and application of boron-containing compounds in organic synthesis.[63] For his pioneering work and development, H. C. Brown was rewarded with the Nobel Prize in 1979. In the same year, Suzuki and Miyaura[64] enhanced the use of boronic acids by the discovery of its transition metal catalyzed cross-coupling reaction with organic halides. Few reactions have influenced organic synthesis as greatly as the Suzuki-Miyaura reaction.[65] Thus, the pyridylboronic pinacolate **13a** readily reacts with iodobenzene in the presence of a Pd-catalyst ($Pd(PPh_3)_4$, 5 mol%) and base (Na_2CO_3, 3 equiv) leading to 3-phenylpyridine derivative **14a** in 88% yield (Scheme 13).[66]

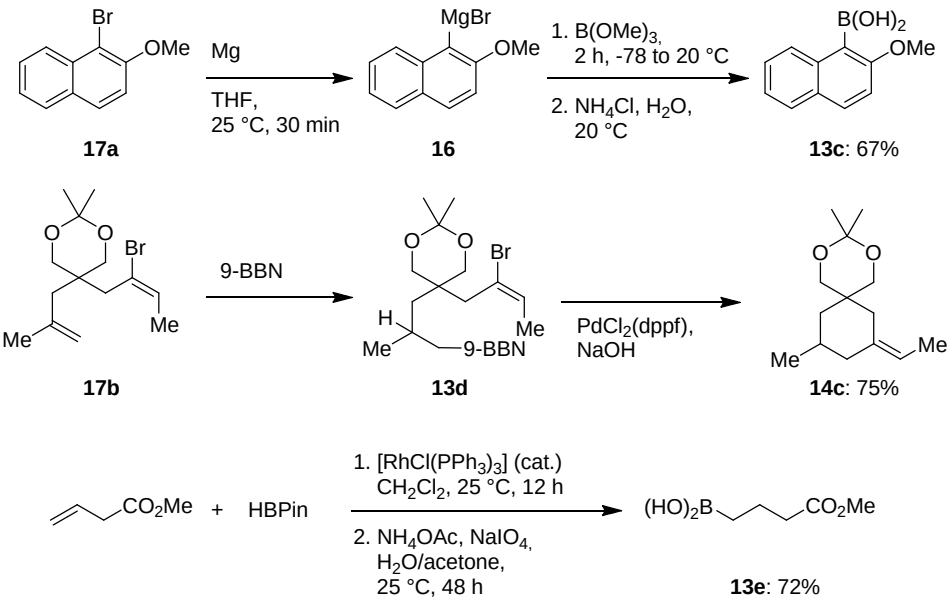


Scheme 13. Suzuki cross-couplings using organoboronic compounds of type **13**.

[61] a) E. Frankland, B. Duppa, *Proc. Royal Soc.* **1860**, *10*, 568; b) E. Frankland, *J. Chem. Soc.* **1862**, *15*, 363.
[62] *Boronic Acids (Ed.:* D. G. Hall*),* Wiley-VCH*,* Weinheim, **2005**.
[63] a) H. C. Brown, in *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, **1972**; b) A. Pelter, K. Smith, H. C. Brown, in *Borane Reagents*, Academic Press, New York, **1988**; c) D. S. Matteson, in *Stereodirected Synthesis with Organoboranes*, Springer, New York, **1995**; d) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; e) T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2000**, *611*, 392; f) E. Tyrell, P. Brookes, *Synthesis* **2003**, 469; g) T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2003**, *680*, 3.
[64] N. Miyaura, A. Suzuki, *J. Chem. Soc., Chem. Commun.* **1979**, 866.
[65] G. A. Molander, B. Canturk, *Angew. Chem. Int. Ed.* **2009**, *48*, 9240.
[66] M. Alessi*,* A. L. Larkin*,* K. A. Ogilvie*,* L. A. Green*,* S. Lai*,* S. Lopez*,* V. Snieckus*, J. Org. Chem.* **2007***, 72,* 1588.

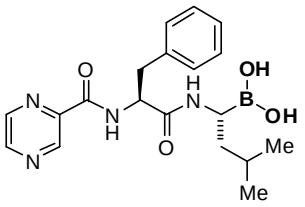
Based on the work of Vedejs *et al.*[67] and the first report of organotrifluoroborates in C-C bond formations by Gênet and co-workers,[68] aryltrifluoroborates, such as potassium phenyltrifluoroborate (**13b**), readily react with aryldiazonium salts like **15** producing under Pd-catalysis the biphenyl **14b** in 69% yield. Thereafter, major contributions in this field were made by Molander, Buchwald, Hartwig, Fu and others.[65] One of the most significant reasons for the extensive use of organoboron compounds in modern organic synthesis is the highly covalent character of the carbon-boron bond and their high compatibility with a broad range of functional groups,[69] water stability and relatively low toxicity.[63] Hence, these reagents have emerged to a versatile class of synthons in organic chemistry.[63,70] Therefore, numerous highly functionalized boron derivatives can be prepared by various synthetic methods, such as hydroboration, transmetalation, or transition metal-catalyzed borylation.[10] Thus, transmetalation from the methoxy-substituted naphthylmagnesium bromide (**16**) with $B(OMe)_3$ and subsequent hydrolysis furnished 2-methoxynaphthylboronic acid (**13c**) in 67% yield (Scheme 14).[71] The hydroboration of diene **17b** with 9-BBN afforded the boron compound **13d**. Subsequent intramolecular C-C-bond formation gave **14c** in 75% yield (Scheme 14).[72] Rh-catalyzed hydroboration, firstly reported by Männig and Nöth,[73] also offers access to boronic acids such as **13e** using Wilkinson´s catalyst ($[RhCl(PPh_3)_3]$; Scheme 14).[65,74]

[67] E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin, M. R. Schrimpf, *J. Org. Chem.* **1995**, *60,* 3020.
[68] a) S. Darses, J.-P. Gênet, J.-L. Brayer, J.-P. Demoute, *Tetrahedron Lett.* **1997**, *38,* 4393; b) S. Darses, G. Michaud, J.-P. Gênet, *Eur. J. Org. Chem.* **1999**, 1875.
[69] a) S. Darses, T. Jeffery, J.-P. Gênet, J.-L. Brayer, J.-P. Demoute, *Tetrahedron Lett.* **1996**, *37*, 3857; b) D. Willis, R. M. Strongin, *Tetrahedron Lett.* **2000**, *41*, 6271; c) G. Manickam, A. D. Schluter, *Synthesis* **2000**, 442; d) J. W. Goodby, M. Hird, R. A. Lewis, K. J. Toyne, *J. Chem. Soc., Chem. Commun.* **1996**, 2719; e) B. U. Maes, Lemiere, R. Dommisse, K. Augustyns, A. Haemers, *Tetrahedron* **2000**, *56*, 1777; f) D. Ren, R. A. McClelland, *Can. J. Chem.* **1998**, *76*, 78.
[70] a) A. Suzuki, in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, pp. 49; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; c) S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263; d) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; e) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544; f) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176; g) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633; h) A. Suzuki, *J. Organomet. Chem.* **2002**, *653*, 83; i) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.
[71] a) S. Vyskocil, L. Meca, I. Tislerova, I. Cisarova, M. Polasek, S. R. Harutyunyan, Y. N. Belokon, R. M. J. Stead, L. Farrugia, P. Miroslav, H. R. Syuzanna, Y. N. Belokon, R. M. J. Stead, L. Farrugia, S. C. Lockhart,W. L. Mitchell, P. Kocovsky, *Chem. Eur. J*. **2002**, *8*, 4633.
[72] N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, A. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 314.
[73] D. Männing, H. Nöth, *Angew. Chem. Int. Ed.* **1985**, *24*, 878.
[74] D. A. Evans, G. C. Fu, A. H. Hoveyda, *J. Am. Chem. Soc.* **1988**, *110*, 6917.



Scheme 14. Preparation of organoboron compounds.

The synthetic utility of organoboranes is further enhanced by many more versatile applications, e. g. allylation and propargylation of aldehydes with allylic and allenic boronic esters, migratory rearrangement, as well as asymmetric reduction, Diels-Alder reactions and others.[62] Furthermore, boronic acids have even proven their unique value in medicinal chemistry such as the commercialization of Velcade®, the first boronic acid drug in human health therapy. *Bortezomib* (Velcade®) is a very promising therapeutic for the treatment of cancer and inflammatory diseases.



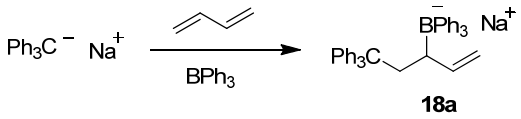
bortezomib

1.5 The Concept of Frustrated Lewis Pairs

In 1923, Lewis[75] put forth a description of acids and bases categorizing molecules as electron pair donors or acceptors, which is central to our understanding of main group and transition metal chemistry. Generally, the combination of Lewis acids and bases results in the formation of simple Lewis acid-base adducts, widely known and applied in transition metal coordination chemistry. A classic demonstration of this concept is the formation of an ammonia-borane adduct, NH_3-BH_3, upon combination of the Lewis acid borane (BH_3) with the Lewis base

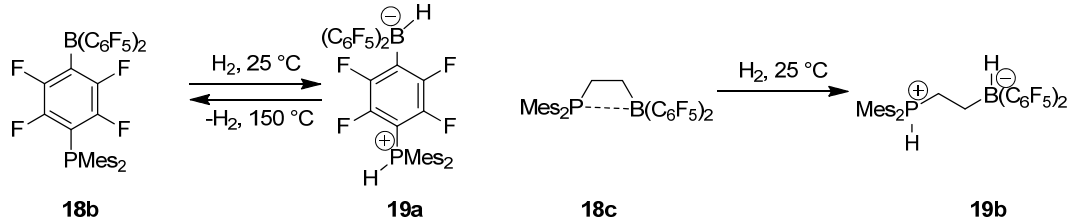
[75] G. N. Lewis, in *Valence and the Structure of Atoms and Molecules*, Chemical Catalogue Company, Inc., New York, **1923**.

ammonia. Based on pioneering work by Brown *et al.*,[76] Wittig and Benz,[77a] the "frustrated Lewis pairs" (FLP) are generally understood by the combination of sterically demanding Lewis donors and acceptors. Their steric hindrance precludes formation of simple Lewis acid-base adducts and remaining "unquenched" reactivity. This unique type of reactivity allows subsequent actions of both Lewis acids and bases on other molecules. Wittig, Benz and Tochtermann used this exceptional property for synthetic applications, such as the addition of the FLP tritylsodium and triphenylborane to butadiene leading to the borate species **18a** (Scheme 15).[77]



Scheme 15. Early "frustrated Lewis pair" (FLP) and its addition to butadiene.

However, Stephan and Erker have extended this concept of FLPs in order to demonstrate new reactivity, ultimately leading to new approaches in catalysis.[78] Remarkably, B-P-containing compounds such as **18b** and **18c** reversibly absorb hydrogen leading to the zwitterionic species like **19a** and **19b** (Scheme 16).

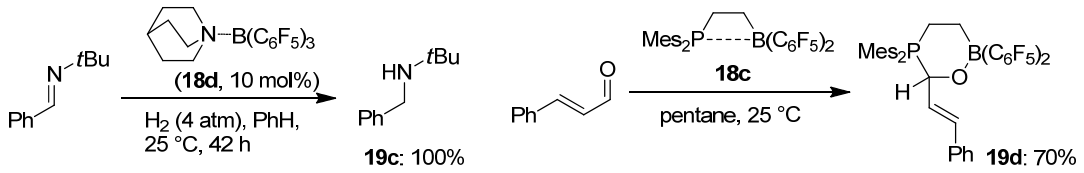


Scheme 16. Activation of hydrogen by FLPs of type **18b** and **18c**.

These investigations resulted in various new synthetic applications, e.g. metal-free catalytic hydrogenation activation or addition reactions.[79] Thus, Soós *et al.* showed the formation of FLPs like **18d** using $B(C_6F_5)_3$ and sterically less hindered amines such as DABCO.[79e,79f] These amine derived FLPs, like **18d**, were applied in catalytic hydrogenations with imines leading to the corresponding secondary amines of type **19c** in excellent yield (Scheme 17).[79e]

[76] H. C. Brown, H. I. Schlesinger, S. Z. Cardon, *J. Am. Chem. Soc.* **1942**, *64*, 325.
[77] a) G. Wittig, E. Benz, *Chem. Ber.* **1959**, *92*, 1999–2013; b) W. Tochtermann, *Angew. Chem. Int. Ed.* **1966**, *5*, 351.
[78] a) G. C. Welch, D. W. Stephan, *J. Am. Chem. Soc.* **2007**, *129*, 1880; b) G. C. Welch, R. R. S. Juan, J. D. Masuda, D. W. Stephan, *Science* **2006**, 314, 1124; c) P. Spies, G. Erker, G. Kehr, K. Bergander, R. Frohlich, S. Grimme, D. W. Stephan, *Chem. Commun.* **2007**, 5072.
[79] a) J. S. McCahill, G. C. Welch, D. W. Stephan, *Angew. Chem. Int. Ed.* **2007**, *46*, 4968; b) S. Grimme, H. Kruse, L. Goerigk, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 1402; c) T. A. Rokob, A. Hamza, A. Stirling, T. Soós, I. Pápai, *Angew. Chem. Int. Ed.* **2008**, *47*, 2435; d) P. A. Chase, G. C. Welch, T. Jurca, D. W. Stephan, *Angew. Chem. Int. Ed.* **2007**, *46*, 8050; e) G. Erős, H. Mehdi, I. Pápai, T. Rokob, P. Király, G. Tárkányi, T. Soós, *Angew. Chem. Int. Ed.* **2010**, *49*, 6559; f) P. A. Chase, T. Jurca, D. W. Stephan, *Chem. Commun.* **2008**, 1701.

Furthermore, Erker and co-workers demonstrated selective 1,2-additions of FLPs like **18c** to cinnamylaldehyde producing the six-membered adduct **19d** in 70% yield (Scheme 17).[80]



Scheme 17. Metal-free catalytic hydrogenation and addition of FLPs like **18c** and **18d**.

The concept of "frustrated Lewis Pairs" (FLPs) is rooted in the early observations of Brown, Wittig, and Tochtermann. However, during the last few years, FLPs have developed from chemical curiosities to a new strategy for the activation of small molecules.

1.6 Conducting Organic Polymers

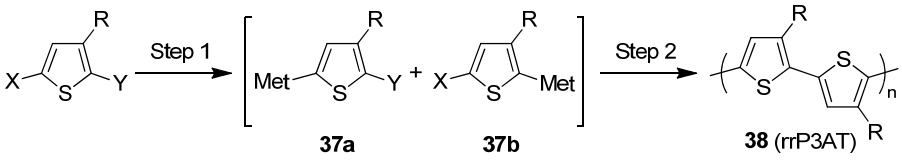
In the late 1970s, conjugated polymers were proclaimed as futuristic new materials that would lead to next generation of electronic and optical devices.[81,82,83,84,85,86] Polythiophenes are an important representative class of conjugated polymers forming some of the most environmentally and thermally stable materials.[87] The synthesis and study of regioregular polythiophenes has produced conjugated polymers that self-assemble into well-defined superstructures and has extended the application of these materials.[88] Formation of ordered supermolecular structures in these regioregular materials correlates strongly with their excellent electrical conductivity. One of the first chemical preparations of unsubstituted polythiophene (PT) was reported in 1980 by Yamamoto,[89] and Dudek.[90] Due to strong limitations of these polymers, such as low solubility and consequently low molecular weight, Elsenbaumer and co-workers synthesized soluble and processable polyalkylthiophenes

[80] C. M. Mömming, S. Frömel, G. Kehr, R. Fröhlich, S. Grimme and Gerhard Erker, *J. Am. Chem. Soc.* **2009**, *131*, 12280.
[81] a) J. H. Burroughes, D. D. C. Bradley, A. R. Brown, R. N. Marks, K. Mackay, R. H. Friend, P. L Burns, A. B. Holmes, *Nature* **1990**, *347*, 539; b) H. E. Katz, *J. Mater. Chem.* **1997**, *7*, 369.
[82] J. Liu, E. Heina, T. Kowalewski, R. D. McCullough, *Angew. Chem. Int. Ed.* **2002**, *41*, 329.
[83] J. H. Burroughes, D. D. C. Bradley, A. R. Brown, R. N. Marks, K. Mackay, R. H. Friend, P. L. Burns, A. R. Holmes, *Nature* **1990**, *347*, 539.
[84] a) A. Bao, A. Dodabalapur, A. J. Lovinger, *Appl. Phys. Lett.* **1996**, *69*, 4108; b) Z. Bao, A. J. Lovinger, *Chem. Mater.* **1999**, *11*, 2607; c) G. H. Gelinck, T. C. T. Geuns, D. M. de Leeuw, *Appl. Phys. Lett.* **2000**, *77*, 1487.
[85] a) H. Sirringhaus, N. Tessler, R. H. Friend, *Science* **1998**, *280*, 1741; b) C. J. Drury, C. M. J. Mutsaers, C. M. Hart, M. Matters, D. M. de Leeuw, *Appl. Phys. Lett.* **1998**, *73*, 108.
[86] A. Dodabalapur, Z. Bao, A. Makhija, J. G. Laquindanum, V. R. Raju, Y. Feng, H. E. Katz, J. Rogers, *Appl. Phys. Lett.* **1998**, *73*, 142.
[87] *Handbook of Conducting Polymers*, 2nd ed. (Eds: T. Skotheim, J. Reynolds, R. Elsenbamer), Marcel Dekker, New York **1998**.
[88] R. D. McCullough, *Adv. Mater.* **1998**, *10*, 1. b) R. D. McCullough, P. C. Ewbank, in *Handbook of Conducting Polymers*, 2nd ed., Marcel Dekker, New York, **1998**, chap. 9, p. 225.
[89] T. Yamamoto, K. Sanechika, A. Yamamoto, *J. Polym. Sci., Polym Lett. Ed.* **1980**, *18*, 9.
[90] J. W. P. Lin, L. P. Dudek, *J. Polym. Sci., Polym. Chem. Ed.* **1980**, *18*, 2869.

(PATs) in 1985.[91] However, the first methods generated irregular PATs, namely randomly polymerized head-to-tail (HT), head-to-head (HH) and tail-to-tail (TT) monomers, which are so-called defective PATs.[92] Unfavourable HH causes a sterically driven twist of thiophene backbone, resulting in a loss of conjugation. On the other hand, regioregular, head-to-tail (HT) poly(3-substitutedthiophene) can easily access a low energy planar conformation, leading to highly conjugated polymers.[93] McCullough *et al.*[94] and shortly thereafter Rieke *et al.*[95] developed methods for the preparation of regioregular HT poly(3-alkylthiophene)s (rrP3AT). McCullough´s method provided rrP3ATs with a HT regioregularity of >98% and was later modified toward the GRIM method (Grignard Metathesis).[96] The key to McCullough´s method is the regiospecific generation of the 2-bromo-3-alkylthien-5-ylmagnesium reagent of type **20a** by lithiation with LDA (–78 °C, 40 min) followed by transmetallation with $MgBr_2$ (Table 1, entry 1). Polymerization is conducted via Kumada-type cross-couplings with catalytic amounts of Ni(dppp)Cl_2 leading to rrP3ATs in 44-66% yield with typical molecular weights (M_n) of 20,000–40,000 and polydispersities (PDI) of around 1.4.[97] Rieke´s method, treating 2,5-dibromothiophene with highly reactive "Rieke zinc" (Zn*) affords a regioisomeric mixture of the organozinc intermediates **20a** and **20b** in a ratio of 90:10 (Table 1, entry 2). Subsequent polymerization by addition of Ni(dppe)Cl_2 gives rrP3ATs in ca. 75% yield (M_n = 24,000–34,000; PDI = 1.4).[95] In comparison to other methods, the Grignard metathesis (GRIM) is essentially advantageous and highly attractive for industries, since cryogenic temperatures and highly reactive metals are unnecessary.[96] Using Br/Mg-exchange reaction, 2,5-dibromothiophene is converted into a regioisomeric mixture of **20a** and **20b** in a ratio of 85:15 to 75:25 (Table 1, entry 3).[98] Polymerization by transition metal-catalyzed cross-coupling furnishes rrP3ATs with high regioregularity (M_n = 20,000–35,000; PDI = 1.2–1.4).

[91] a) K. Y. Jen, R. Oboodi, R. L. Elsenbaumer, *Polym. Mater. Sci. Eng.***1985**, *53*, 79; b) R. L. Elsenbaumer, K.-Y. Jen, R. Oboodi, *Synth. Met.* **1986**, *15*, 169; c) G. G. Miller, R. L. Elsenbaumer, *J. Chem. Soc., Chem. Commun.* **1986**, 1346.
[92] R. D. McCullough, *Adv. Mater.* **1998**, *12*, 93.
[93] R. L. Elsenbaumer, K-Y. Jen, G. G. Miller, H. Eckhardt, L. W. Shacklette, R. Jow, in *Electronic Properties of Conjugated Polymers* (Eds: H. Kuzmany, M. Mehring, S. Roth), Springer Series in Solid State Sciences, Vol. 76, Springer, Berlin, **1987**, p. 400.
[94] R. D. McCullough, R. D. Lowe, *J. Chem. Soc., Chem. Commun.* **1992**, *1*, 70.
[95] T. A. Chen, R. D. Rieke, *J. Am. Chem. Soc.* **1992**, *114*, 10087.
[96] a) R. S. Loewe, S. M. Khersonsky, R. D. McCullough, *Adv. Mater.* **1999**, *11*, 250; b) R. C. Hiorns, A. Khoukh, B. Gourdet, C. Dargon-Lartigau, *Polym. Int.* **2006**, *55*, 608.
[97] I. Osaka, R. D. McCullough, *Acc. Chem. Res.* **2008**, *41*, 1202.
[98] R. S. Loewe, E. C. Ewbank, J. Liu, L. Zhai, R. D. McCullough, *Macromolecules* **2001**, *34*, 4324.

Table 1. Typical methods for the synthesis of regioregular poly(3-alkylthiophene)s (rrP3ATs).



Method	X, Y	Step 1	Met ratio **37a** : **37b**	Step 2	Regio- regularity
McCullough	H, Br	i) LDA/THF, –40 °C, 40 min ii) $MgBr_2 \cdot OEt_2$ ($ZnCl_2$), –60 to –40 °C, 40 min	MgBr (ZnCl) ~98 : ~2	$Ni(dppp)Cl_2$ –5 to 25 °C, 18 h	98–100%
Rieke	Br, Br	Zn*/THF, –78 to 25 °C, 4 h	ZnBr 90 : 10	$Ni(dppe)Cl_2$ 0 to 25 °C, 24 h	97–100%
GRIM	Br, Br	R'MgX'/THF, rt or rflx, 1 h	MgX' ~85 : ~15	$Ni(dppp)Cl_2$ 25 °C or rflux, < 1 h	>99%

[b] R' = alkyl; X' = Br, Cl

Other methods, involving Suzuki-, and Stille-type cross-couplings, have also successfully been applied in regioregular polymerization reactions.[99]

For the application in polymer solar cells, thiophene-based conjugated polymers, especially poly(3-hexylthiophene) (P3HT), have attracted enormous attention due to their good film-forming, strong absorption, and high hole-transportation properties.[100,101] The process of converting light into electricity by an organic solar cell can be schematically described by a cascade reaction.[102] First of all, the absorption of a photon forms an excited state or exciton (bound electron-hole pair), followed by its diffusion to a place where it can dissociate (charge separation). Subsequently, charge transport occurs within the organic semiconductor to the respective electrodes.[102,100] Generally, rrP3ATs are used in so-called blended "P3AT:PCBM bulk heterojunction" solar cells. Thereby, the organic semiconductor acts as electron donor, absorbing the photon, diffusing the exciton to the heterojunction with the electron acceptor, where the exciton can dissociate, also called "charge separation". The fullerene PCBM [1-(3-methoxycarbonyl)propyl-1-phenyl[6.6]C_{61}], acting as electron acceptor, absorbs the

[99] a) A. Iraqi, G. Barker, *J. Mater. Chem.* **1998**, *8*, 25; b) S. Guillerez, G. Bidan, *Synth. Met.* **1998**, *93*, 123.
[100] S. Günes, H. Neugebauer, N. S. Sariciftci, *Chem. Rev.* **2007**, *107*, 1324.
[101] L. Huo, Y. Zhou, Y. Li, *Macromol. Rapid Commun.* **2009**, *30*, 925.
[102] J. M. Nunzi, *C. R. Physique* **2002**, *3*, 523.

electron which is transported via multiple layers to the electrode.[103] After charge separation, the rrP3AT transfers the "hole" to the Ca/Al electrode (Figure 1).

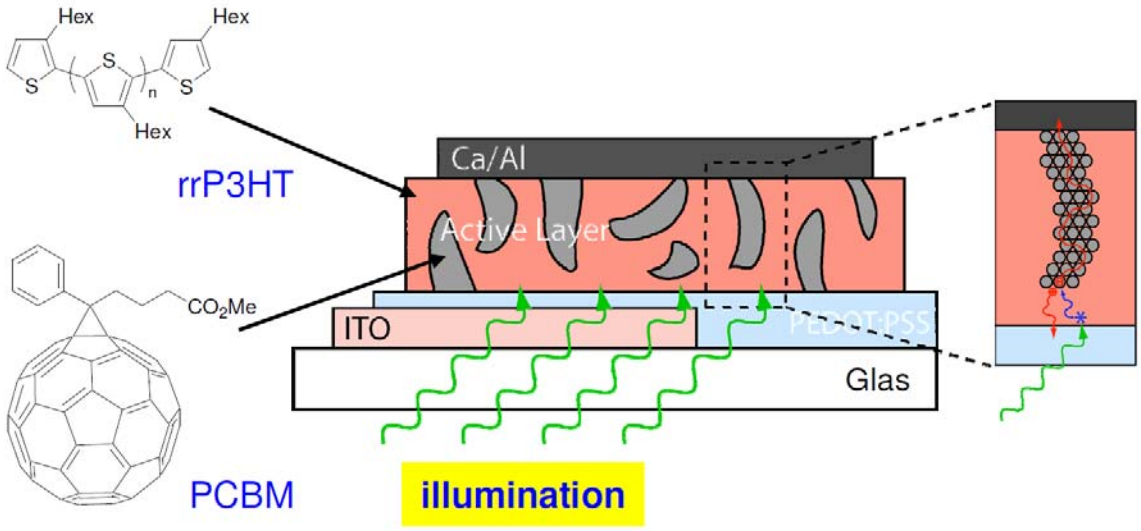


Figure 1. Typical layout of a "P3AT:PCBM bulk heterojunction" solar cell.

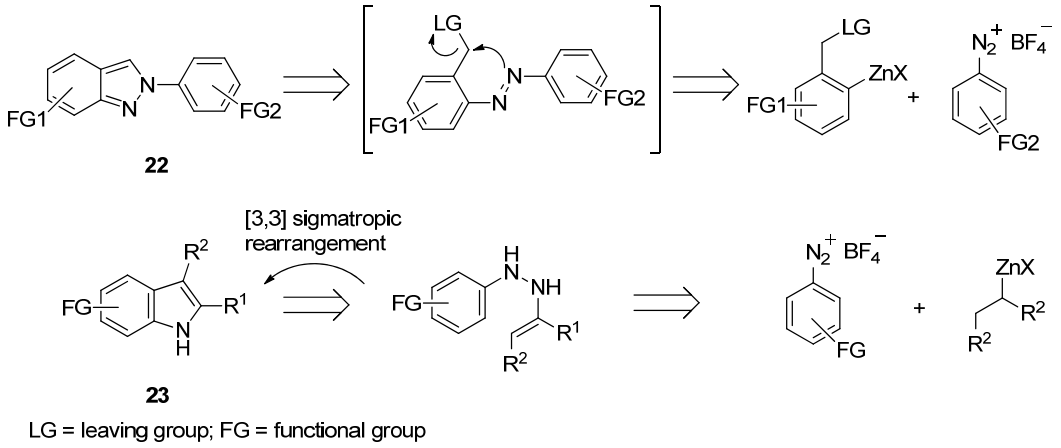
Due to the constant quest for higher efficiencies in organic photovoltaics, this field is constantly evolving, marked by numerous reports in recent time about further improvements.[104]

[103] R. R. Reyes, K. Kim, D. L. Carroll, *Appl. Phys. Lett.* **2005**, *87*, 083506.
[104] a) G. Dennler, M. C. Scharber, C. J. Brabec, *Adv. Mater.* **2009**, *21*, 1323; b) L.-M. Chen, Z. Hong, G. Li, Y. Yan, *Adv. Mater.* **2009**, *21*, 1434; c) A. Gadisa, W. D. Oosterbaan, K. Vandewal, J.-C. Bolseé, S. Bertho, J. D'Haen, L. Lutsen, D. Vanderzande, J. V. Manca, *Adv. Funct. Mater.* **2009**, *19*,1.

2. Objectives

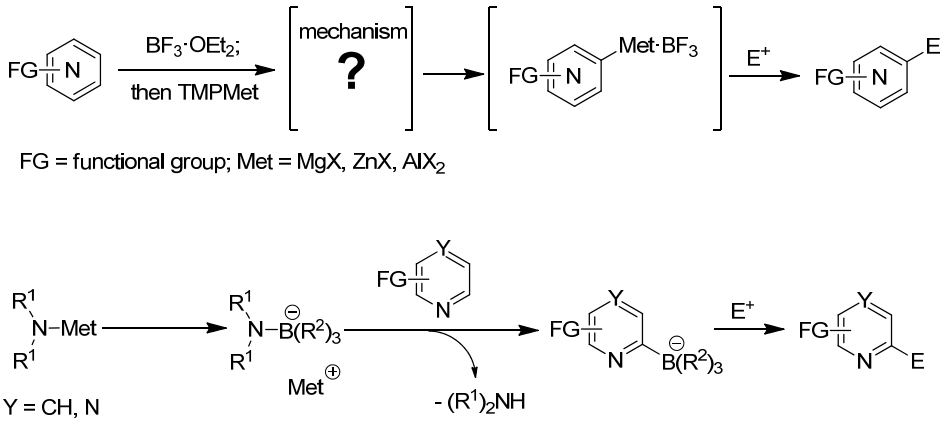
In this work, we envisioned the development of new methods for the concise preparation of indazoles and indoles using organozinc reagents. Furthermore, our goal was the efficient functionalization of heterocycles by means of organometallics, like boron, magnesium, and zinc derivatives. In addition, a regioselective halogen-magnesium exchange reagent should be developed for the preparation of heteroarylmagnesium halides and subsequent polymerization.

In particular, we envisioned the use of polyfunctional organozinc reagents in the preparation of functionalized 2-aryl-2*H*-indazoles of type **22** and indoles of type **23**. Known procedures for the synthesis of heterocycles often require harsh reaction conditions, along with long reaction times and high temperatures. Sensitive functionalities often are not compatible with such reaction conditions. In order to avoid complicated multi-step syntheses, we planned the reaction of substituted arylzinc reagents with functionalized aryldiazonium salts affording the corresponding arylazo compounds. Subsequent intramolecular substitution of the leaving group and re-aromatization was expected to give 2-aryl-2*H*-indazoles of type **22** (Scheme 18). Furthermore, alkylzinc reagents were expected to add to aryldiazonium salts providing after isomerization substituted arylhydrazines. Thereafter, a [3,3]-sigmatropic rearrangement of the substituted arylhydrazines should furnish polyfunctional indoles of type **23** (Scheme 18).



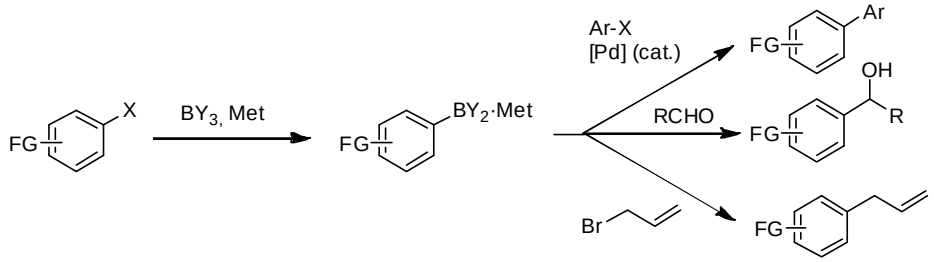
Scheme 18. Preparation of polyfunctional 2-aryl-2*H*-indazoles (**22**) and indoles (**23**) using functionalized organozinc reagents.

Inspired by Kessar´s smooth and fast lithiation reactions[105] in the presence of $BF_3 \cdot OEt_2$, our target was to use boron reagents for the direct and regioselective metalation and subsequent functionalization of sensitive heterocycles using TMP-derived metal amide bases (Scheme 19). In addition, the effect of boron reagents should be explored in particular on substituted *N*-heterocycles, which are generally difficult to metalate or functionalize. Furthermore, the mode of action of boron additives like BF_3 should be thoroughly investigated using density functional theory (DFT) methods and NMR techniques. Based on these results, we planned to extend the scope by preparing thermally stable amidoborate bases showing the same accelerated and high rates in metalation reactions with arenes and heteroarenes (Scheme 19).



Scheme 19. Metalation of *N*-heterocycles using $BF_3 \cdot OEt_2$ and TMP-derived metal amide bases; mechanistic investigation of the metalation process.

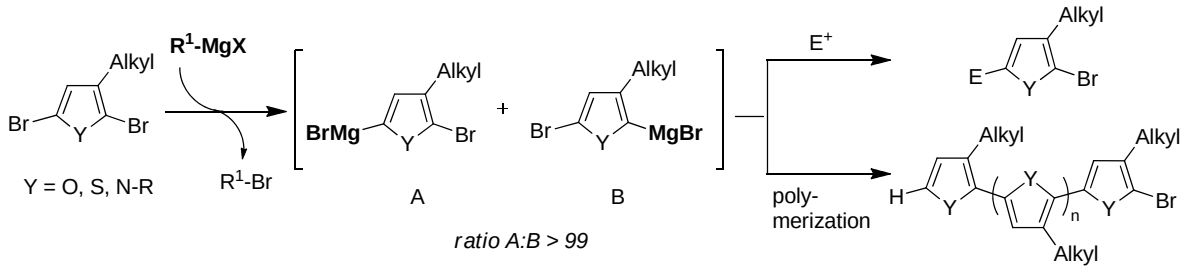
Another project aimed at novel *in situ* methods for the inexpensive and fast preparation of organoboron compounds using low-cost starting materials and avoiding high-priced cryogenic temperatures. Furthermore, the reactivity of such *in situ* prepared organoborates should be explored in detail and readily available organic halides like bromides or chlorides should be used for cross-coupling reactions (Scheme 20).



Scheme 20. *In situ* preparation of functionalized organoboron reagents using oxidizable metals followed by trapping with electrophiles.

[105] a) S. V. Kessar, P. Singh, R. Vohra, N. Kaur, K. Singh, *J. Chem. Soc., Chem. Commun.* **1991**, 568; b) S. V. Kessar, P. Singh, K. N. Singh, P. Venugopalan, A. Kaur, P. Bharatam, A. Sharma, *J. Am. Chem. Soc.* **2007**, *129*, 4506; c) S. V. Kessar, P. Singh, K. N. Singh, P. V. Bharatam, A. K. Sharma, S. Lata, A. Kaur, *Angew. Chem. Int. Ed.* **2008**, *47*, 4703.

Due to valuable properties of soluble organic polymers, we have been interested in the highly regioselective preparation of organometallic 5-membered heterocycles with respect to subsequent polymerization. Generally, the pendant alkyl chains improve solubility of the organic polymers. Hence, we focused the research on Hal/Mg-exchange reagents achieving high regioselectivity via discrimination by steric interactions. This method should not only enable us to selectively functionalize 5-membered heteroarenes, but also enhance the regioregularity of organic polymers after regioregular head-to-tail polymerization reactions (Scheme 21).



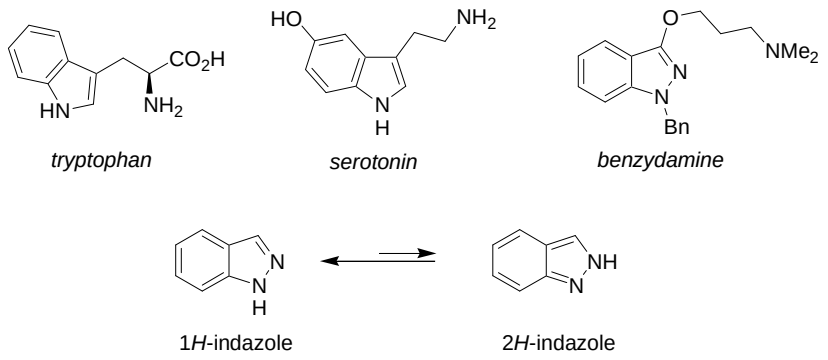
Scheme 21. Regioselective functionalization and regioregular polymerization of 5-membered heteroarenes via Br/Mg-exchange reagents.

B. Results and Discussion

1. Preparation of Polyfunctional Heterocycles

1.1 Introduction

Azaheterocycles constitute an important class of biologically active compounds. Thereof, indoles and structurally similar indazoles are present in various natural products. For instance, tryptophan, an essential amino acid, is one of nature´s most frequently used building blocks. Even its metabolic forms, like the neurotransmitter serotonin, are also biologically active compounds. Similarly, various indazole structures also proved their biological activity, e.g. *benzydamine* acting as an analgesic, anti-inflammatory and antipyretic drug. However, the selective substitution and functionalization of indazoles so far remain challenging, due to the tautomeric equilibrium between 1*H*- and *2H*-indazole (Scheme 22).



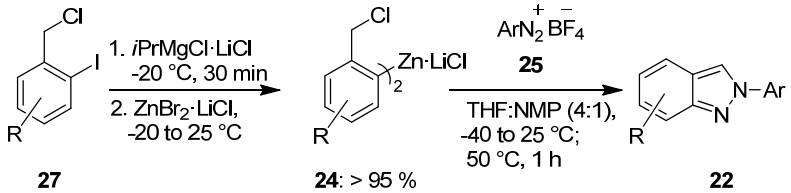
Scheme 22. Biologically active indole and indazole structures; 1*H*- and 2*H*-indazole tautomers.

1.2 Preparation of Functionalized 2-Aryl-2*H*-indazoles using Substituted Arylzinc Reagents and Aryldiazonium Tetrafluoroborates

Heterocyclic compounds, and in particular indazoles, have found numerous applications as pharmaceuticals, agrochemicals and polymers.[106,107] Some indazoles act as dopamine antagonists, anti-inflammatory, analgesic or antipyretic agents.[107a,108] The use of organometallics for the preparation of complex heterocycles as key intermediates has proven

[106] a) A. Schmidt, A. Beutler, B. Snovydovych, *Eur. J. Org. Chem.* **2008**, 4073; b) W. Stadlbauer, Indazole and its Derivatives, in *Science of Synthesis: Methods of Molecular Transformations* (Houben-Weyl), Vol. 12, George Thieme Verlag, Stuttgart, **2002**, 227.
[107] a) H. Cerecetto, A. Gerpe, M. González, V. Arán, C. Ochoa de Ocáriz, *Mini-Rev. Med. Chem.* **2005**, *5*, 869; b) V. Minkin, D. Garnovskii, J. Elguero, A. Katritzky, O. Denisko, *Adv. Heterocycl. Chem.* **2000**, *76*, 157; c) J. van Ooijen, J. Reedijk, *J. Magn. Magn. Mater.* **1979**, *12*, 4; d) G. Sagi, K. Szucs, L. Otvos, *J. Med. Chem.* **1992**, *35*, 4549; e) O. Dann, P. Nickel, *Liebigs Ann. Chem.* **1963**, *667*,101.
[108] M. De Angelis, F. Stossi, K. Carlson, B. Katzenellenbogen, J. Katzenellenbogen, *J. Med. Chem.* **2005**, *48*, 1132.

to be very useful.[109] Especially, organozinc compounds are of high importance due to their exceptional functional group tolerance and satisfactory reactivity in the presence of appropriate catalysts.[110] The compatibility of organozinc compounds with nitrogen functionalities at high oxidation states such as nitro groups, azides and triazenes is a remarkable feature.[111] Diphenylzinc has been reported to react with diazonium salts providing azo compounds.[112] Thus, we envisioned the reaction of functionalized 2-chloromethylarylzinc reagents of type **24** with various aryldiazonium tetrafluoroborate salts of type **25** leading to a new general synthesis of 2-aryl-2*H*-indazoles of type **22** (Scheme 23).[113,114]



27 **24**: > 95 % **22**

Scheme 23. Synthesis of aryl-2*H*-indazole derivatives of type **22**.

Treatment of 2-iodobenzyl chloride (**27a**) with *i*PrMgCl·LiCl (1.05 equiv, –20 °C, 30 min) furnishes 2-chloromethylphenylmagnesium chloride.[115] Transmetalation with $ZnBr_2$·LiCl (0.55 equiv, –20 °C to 25 °C, 20 min) provided the diarylzinc **24a**.[116] This zinc reagent was then added to benzenediazonium tetrafluoroborate in a 1:1 THF:NMP mixture (NMP = *N*-methyl-2-pyrrolidone) at –40 °C.[114c] After stirring the reaction mixture at 25 °C (30 min) and

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[110] a) *Organozinc Reagents - A Practical Approach*; (Eds.: P. Knochel, P. Jones); Oxford University Press: Oxford, **1999**; b) P. Knochel, in *Handbook of Functionalized Organometallics*, Vol. 1, Wiley-VCH, Weinheim, **2005**, pp. 251; c) G. Manolikakes, C. Munoz Hernandez, M. Schade, A. Metzger, P. Knochel, *J. Org. Chem.* **2008**, *73*, 8422; d) P. Knochel, M. I. Calaza, E. Hupe, *Carbon-Carbon Bond-Forming Reactions Mediated by Organozinc Reagents*, in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed., (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, **2004**, *2*, 619.

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[112] D. Curtin, J. Tveteen, *J. Org. Chem.* **1961**, *26*, 1764.

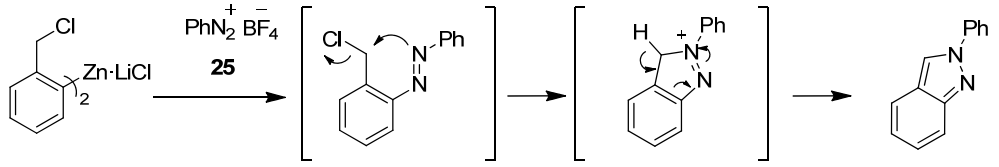
[113] B. A. Haag, Z. Peng, P. Knochel, *Org. Lett.* **2009**, *11*, 4270.

[114] a) D. Varughese, M. Manhas, A. Bose, *Tetrahedron Lett.* **2006**, *47*, 6795; b) M. Peters, R. Stoll, R. Goddard, G. Buth, S. Hecht, *J. Org. Chem*. **2006**, *71*, 7840; c) I. Sapountzis, P. Knochel, *Angew. Chem., Int. Ed*. **2004**, *43*, 897.

[115] T. Delacroix, L. Bérillon, G. Cahiez, P. Knochel, *J. Org. Chem.* **2000**, *65*, 8108.

[116] The use of the mixed $ZnBr_2$·LiCl has a beneficial effect on the reactivity of zinc reagents **1** with aryldiazonium salts.

warming the solution to 50 °C for 1 h, 2-phenyl-2*H*-indazole (**22a**) was isolated in 98% yield (Table 2, entry 1).



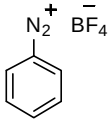
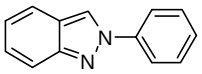
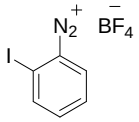
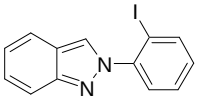
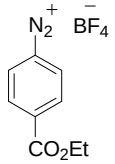
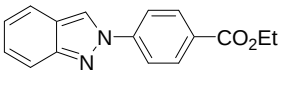
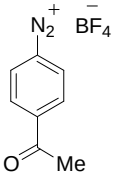
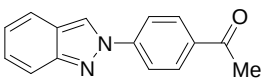
24 **28** **29** **22**

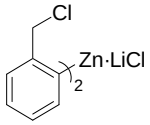
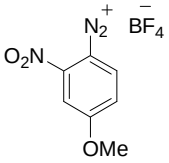
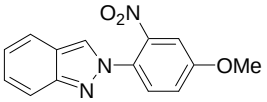
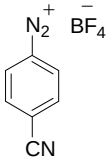
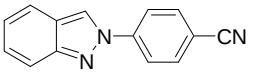
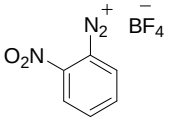
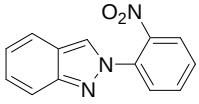
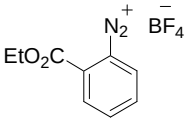
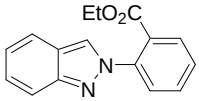
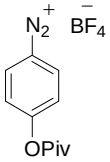
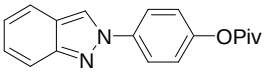
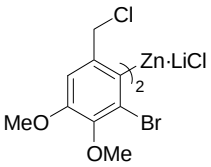
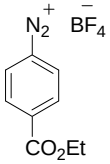
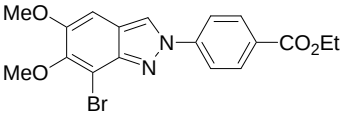
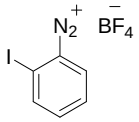
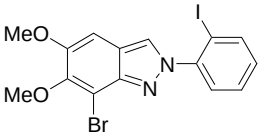
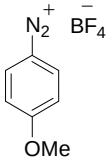
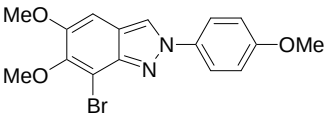
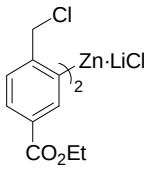
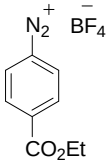
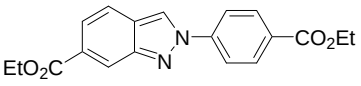
Scheme 24. Tentative mechanism of the indazole synthesis.

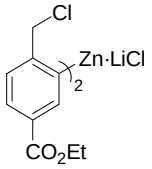
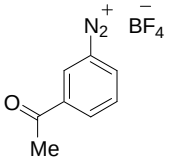
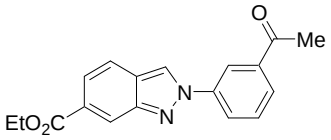
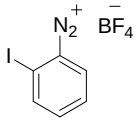
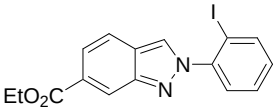
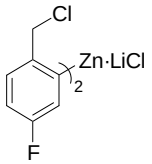
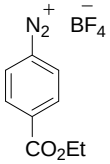
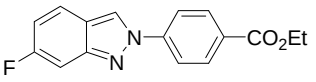
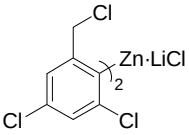
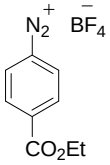
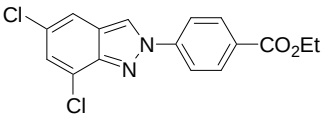
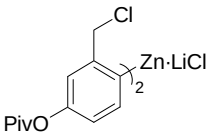
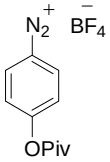
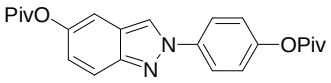
Furthermore, we envisioned that the diarylzinc reagent **24** chemoselectively adds to the diazonium salt **25** yielding the 2-chloromethylarylazo compound **28**. Intramolecular nucleophilic substitution at the benzylic carbon leads to the cyclic intermediate **29**. Subsequent proton abstraction furnishes indazole **22** (Scheme 24).

This reaction displays a remarkable functional group tolerance. Thus, a great variety of diazonium tetrafluoroborate salts and di(2-chloromethylaryl)zinc reagents can be prepared and used for the synthesis of 2-aryl-2*H*-indazole derivatives (**22a**–**r**) bearing sensitive functional groups such as ester, keto, cyano, or nitro groups (Table 2).

Table 2. Aryl-2H-indazole synthesis by the reaction of di(2-chloromethylaryl)zinc with aryldiazonium tetrafluoroborate.

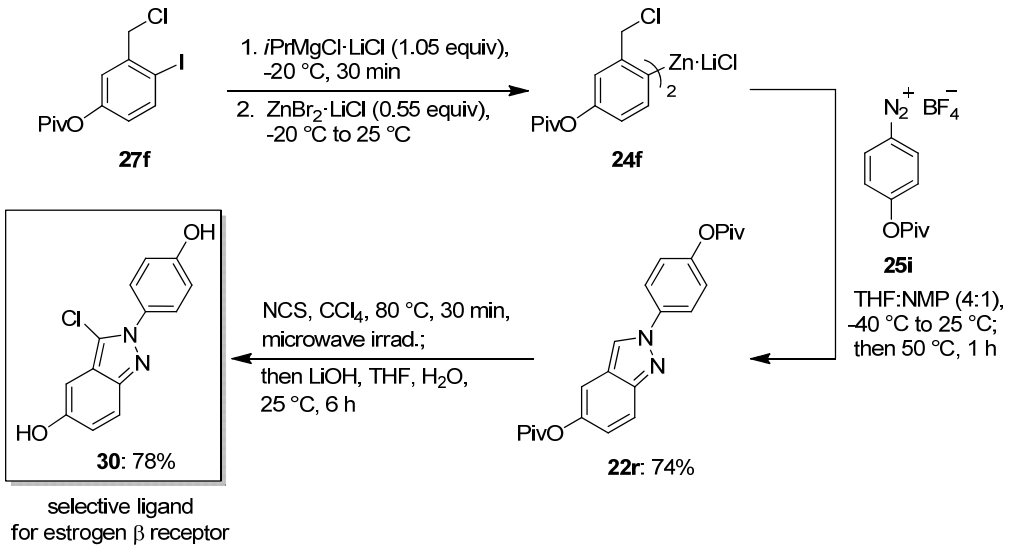
Entry	Zinc reagent[b]	Aryldiazonium salt	Product, Yield[a]
			
1	**24a**	**25a**	**22a**: 98%
			
2	**24a**	**25b**	**22b**: 83%
			
3	**24a**	**25c**	**22c**: 97%
			
4	**24a**	**25d**	**22d**: 84%

Entry	Zinc reagent[b]	Aryldiazonium salt	Product, Yield[a]
5	 **24a**	 **25e**	 **22e**: 96%
6	**24a**	 **25f**	 **22f**: 82%
7	**24a**	 **25g**	 **22g**: 63%
8	**24a**	 **25h**	 **22h**: 77%
9	**24a**	 **25i**	 **22i**: 76%
10	 **24b**	 **25c**	 **22j**: 76%
11	**24b**	 **25b**	 **22k**: 68%
12	**24b**	 **25j**	 **22l**: 69%
13	 **24c**	 **25c**	 **22m**: 71%

Entry	Zinc reagent[b]	Aryldiazonium salt	Product, Yield[a]
14	 **24c**	 **25k**	 **22n**: 68%
15	**24c**	 **25b**	 **22o**: 90%
16	 **24d**	 **25c**	 **22p**: 75%
17	 **24e**	 **25c**	 **22q**: 66%
18	 **24f**	 **25i**	 **22r**: 74%

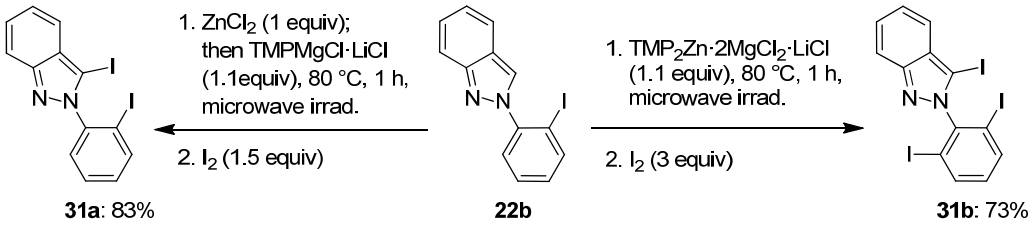
[a] Yield of isolated, analytically pure product as determined by ^{1}H NMR. [b] With $ZnBr_2 \cdot LiCl$ (0.55 equiv) a transmetalation was performed.

As an application, a highly selective ligand for the estrogen receptor β (**30**) was prepared.[108] In the key step, the diarylzinc reagent **24f** reacted with the diazonium salt **25i** affording the indazole derivative **22r**. Selective chlorination of **22r** with *N*-chlorosuccinimide (NCS) using microwave irradiation and subsequent deprotection of the hydroxyl groups furnished the indazole derivative **30** in 78% yield (Scheme 25). Further functionalization of the indazole scaffold can be achieved by using TMP-derived bases.[117-119]



Scheme 25. Synthesis of a selective ligand for estrogen receptor β (**30**). Aryl-2*H*-indazole synthesis by the reaction of di(2-chloromethylaryl)zinc with aryldiazonium tetrafluoroborate.

Selective zincation of the indazole **22b** was achieved using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.[117b] Subsequent trapping with iodine furnished 2-(2,6-diiodophenyl)-3-iodo-2*H*-indazole (**31b**) in 73% yield (Scheme 26). Also, the treatment of **22b** with $ZnCl_2$ (1.0 equiv) followed by the addition of TMPMgCl·LiCl (1.1 equiv) is leading to a selective monozincated indazole.[118,119] After iodolysis, the diiodoindazole **31a** is obtained in 83% yield.



Scheme 26. Direct *mono*- and *bis*-zincation of indazole **3b**.

Polycyclic heteroaromatics bearing an indazole unit were prepared using domino cross-coupling[120] (Scheme 27). Thus, Pd-catalyzed cross-coupling ($Pd(PPh_3)_4$ (4 mol %), THF,

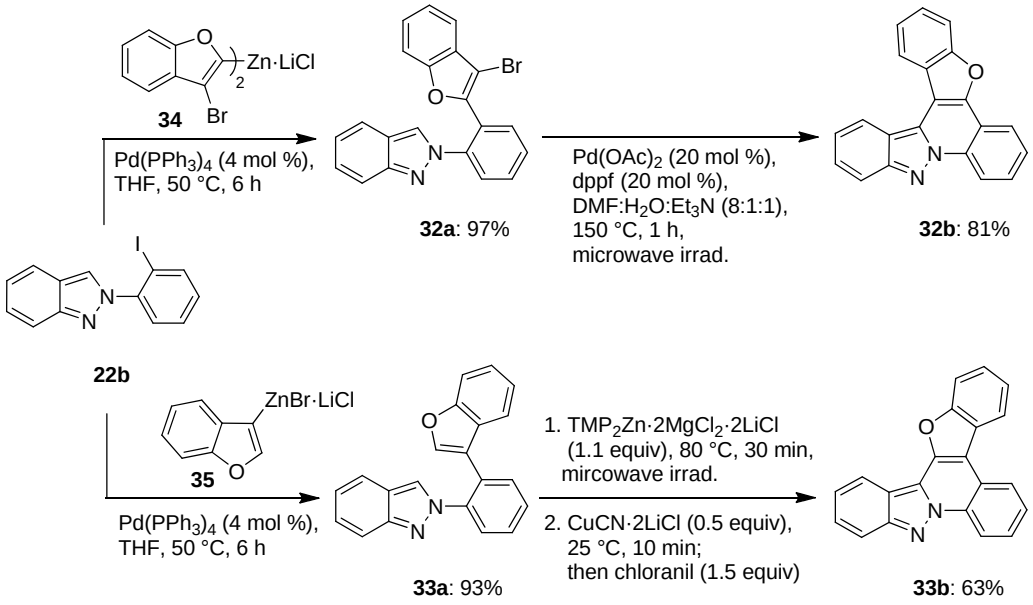
[117] a) S. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705; b) S. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed*. **2007**, *46*, 7685; c) N. Østergaard, N. Skjærbæk, M. Begtrup, P. Vedsø, *J. Chem. Soc., Perkin Trans. 1* **2002**, 428; d) C. James, V. Snieckus, *J. Org. Chem.* **2009**, *74*, 4080; e) G. Bentabed-Ababsa, F. Blanco, A. Derdour, F. Mongin, F. Trécourt, G. Quéguiner, R. Ballesteros, B. Abarca, *J. Org. Chem*. **2009**, *74*, 163.

[118] a) Z. Dong, G. Clososki, S. Wunderlich, A. Unsinn, J. Li, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 457; b) J.-M. L'Helgoual'ch, A. Seggio, F. Chevallier, M. Yonehara, E. Jeanneau, M. Uchiyama, F. Mongin, *J. Org. Chem*. **2008**, *73*, 177.

[119] a) O. Baron, W. Lin, *Org. Lett*. **2006**, *8*, 5673; b) G. Clososki, C. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681.

[120] a) J.-X. Wang, J. McCubbin, M. Jin, R. Laufer, Y. Mao, A. Crew, M. Mulvihill, V. Snieckus, *Org. Lett.* **2008**, *10*, 2923; b) A. de Meijere, P. von Zezschwitz, S. Braese, *Acc. Chem. Res*. **2005**, *38*, 413; c) K. Albrecht, O. Reiser, M. Weber, B. Knieriem, A. de Meijere, *Tetrahedron* **1994**, *50*, 383; d) E. Negishi, A. King, N.

50 °C, 6 h) with 2- and 3-zincated benzofuran derivatives (**34**, **35**) give in almost quantitative yields the structures **32a** and **33a**. Treatment of indazole **32a** with $Pd(OAc)_2$ (20 mol %) and dppf (20 mol%) in a 8:1:1 DMF:H_2O:Et_3N mixture at 150 °C for 1 h provided the cyclized indazole **32b**.[121] Bismetalation of indazole **33a** with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (1.1 equiv, 80 °C, 30 min, microwave irradiation) followed by transmetalation with CuCN·2LiCl and addition of chloranil furnished the isomeric polycyclic heterocycle **33b** in 63% yield (Scheme 27).[117a,122]



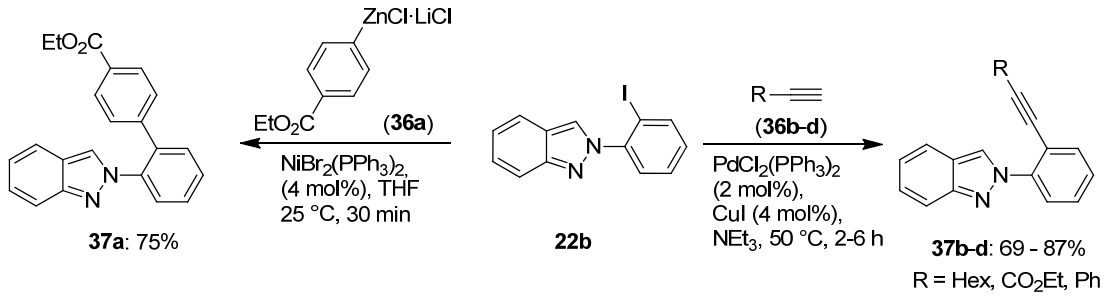
Scheme 27. Domino-cross-coupling en route to the formation of heterocyclic isomeric indazoles of type **32b** and **33b**.

Furthermore, the iodoindazole **22b** was functionalized via a Ni-catalyzed cross-coupling ($NiBr_2(PPh_3)_2$ (4 mol%), 25 °C, 30 min) using an ester-substituted arylzinc halide like **36a** leading to the indazole derivative **37a** in 75% yield (Scheme 28). In addition, Sonogashira-type cross-coupling reactions with **22b** and various alkynes (**36b**–**d**) afforded the corresponding substituted indazoles **37b**–**d** in 69–87% yield (Scheme 28).

Okukado, *J. Org. Chem.* **1977**, *42*, 1821; e) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; f) Ø. Rist, M. Begtrup, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1566; g) C. James, A. Coelho, M. Gevaert, P. Forgione, V. Snieckus, *J. Org. Chem.* **2009**, *74*, 4094; h) Z. Zhao, A. Jaworski, I. Piel, V. Snieckus, *Org. Lett.* **2008**, *10*, 2617.

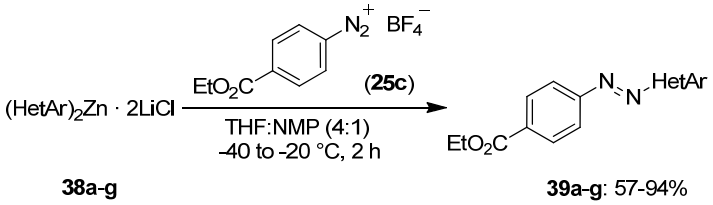
[121] The crystal structure of **32b** shows high symmetry in alignment of molecules in long chains via intermolecular H-bonding; see Supporting Information.

[122] a) V. del Amo, S. Dubbaka, A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 7838; b) M. Kienle, S. R. Dubbaka, K. Brade, P. Knochel, *Eur. J. Org. Chem*. **2007**, *25*, 4166.



Scheme 28. Functionalization of **22b** via transition metal catalyzed cross-coupling reactions.

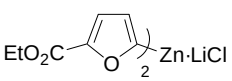
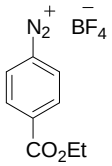
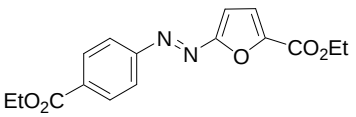
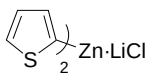
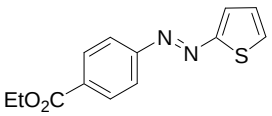
Additionally, we have examined the synthesis of heterocyclic azo compounds, since they are not easily accessible by conventional methods. Thus, the reaction of heteroarylzincs of type **38** with aryldiazonium tetrafluoroborate **25c** leads to various functionalized azo compounds (Scheme 29).

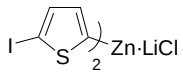
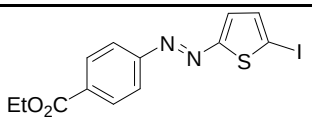
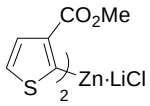
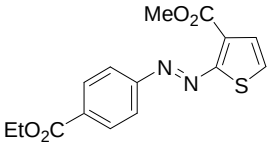
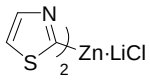
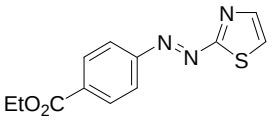
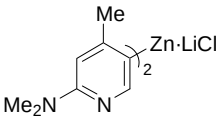
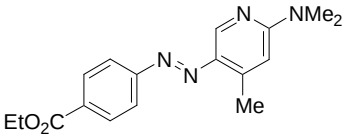
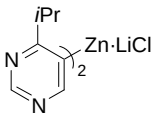
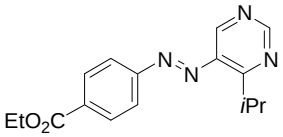


Scheme 29. Heterocyclic organozinc mediated azo-coupling.

The required diarylzincs (**38a**–**g**) were obtained by halogen/magnesium-exchange from the corresponding heteroaryl iodides or bromides followed by transmetalation with $ZnBr_2 \cdot LiCl$ (–20 to 25 °C, 20 min). Reaction of these zinc organometallics with aryldiazonium tetrafluoroborate salt **25c** in THF:NMP mixture (4:1) from –40 to –20 °C for 2 h furnished the azo compounds (**39a**–**g**) in 57–94% yield (Table 3).

Table 3. Reaction of heterocyclic diarylzinc with aryldiazonium tetrafluoroborate salt leading to heteroarylazo compounds.

Entry	Zinc reagent[b]	Aryldiazonium salt	Product, Yield[a]
1	 **38a**	 **25c**	 **39a**: 89%
2	 **38b**	**25c**	 **39b**: 83%

Entry	Zinc reagent[b]	Aryldiazonium salt	Product, Yield[a]
3	 **38c**	**25c**	 **39c**: 94%
4	 **38d**	**25c**	 **39d**: 83%
5	 **38e**	**25c**	 **39e**: 83%
6	 **38f**	**25c**	 **39f**: 65%
7	 **38g**	**25c**	 **39g**: 59%

[a] Yield of isolated, analytically pure product as determined by ^{1}H NMR. [b] With $ZnBr_2 \cdot LiCl$ (0.55 equiv) a transmetalation was performed.

As demonstrated above, we have developed a short and convenient synthetic route to 2-aryl-2*H*-indazoles using highly functionalized arylzinc reagents. Thus, readily available 2-chloromethylarylzinc reagents react with functionalized aryldiazonium tetrafluoroborates providing polyfunctional indazoles. As an application, we have prepared a highly selective binding ligand for the estrogen receptor β (**30**). Furthermore, new heterocyclic azo compounds were also prepared. Selective metalations of these 2-aryl-2*H*-indazoles afford new polycyclic aromatics. The performance of a chemoselective addition of diheteroarylzincs to aryldiazonium salts allows an efficient preparation of new heterocyclic azo compounds.

1.3 Organometallic Variation of the Fischer Indole Synthesis

Indoles (**23**) are an important class of *N*-heterocycles present in many natural products or pharmaceuticals.[123] Their synthesis presents a great challenge, and a range of new synthetic approaches to indoles has been reported in recent years.[124] Metal-catalyzed or -mediated methods have proven to be especially useful.[125] The classical Fischer indole synthesis[126] starting from aryl hydrazines[127,128] **40** and ketones **41** is still extensively used, although this method suffers from several drawbacks.[129,130] The highly acidic reaction conditions combined with moderate functional group compatibility and the poor availability of aryl hydrazines **40** strongly limit this method. Furthermore, unsymmetrical ketones result in regioisomeric mixtures of indoles.[129] Since organozinc reagents are readily available, inexpensive and compatible with numerous functional groups,[131] we envisioned a new retrosynthetic pathway of the Fischer indole synthesis, in which the key intermediates **42A** and **42B** would not be

[123] a) R. J. Sundberg, in *Comprehensive Heterocyclic Chemistry II*, Vol. 2 (Eds: A. R: Katritzky, C. W. Ress, E. F. V. Scriven, C. W. Bird), Pergamon Press, Oxford, **1996,** p 119;. b) A. Joule, Indole and its Derivatives, in *Science of Synthesis: Methods of Molecular Transformations (Houben-Weyl)*, Cat. 2, Vol. 10 (Ed: E. J. Thomas), George Thieme Verlag, Stuttgart, **2000**, Chapter 10.13; c) T. Eicher, S. Hauptmann, in *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, Wiley-VCH, Weinheim, 2 Ed., **2003**.

[124] a) N. Okamoto, Y. Miwa, H. Minami, K. Takeda, R. Yanada, *Angew. Chem. Int. Ed.* **2009**, *48*, 9693; b) D. Solé, O. Serrano, *J. Org. Chem.* **2008**, *73*, 2476; c) P. S. Baran, C. A. Guerrero, N. B. Ambhaikar, B. D. Hafensteiner, *Angew. Chem. Int. Ed.* **2005**, *44*, 606; d) M. P. Kumar, R.-S. Liu, *J. Org. Chem.* **2006**, *71*, 4951; e) K. Alex, A. Tillack, N. Schwarz, M. Beller, *Angew. Chem. Int. Ed.* **2008**, *47*, 2304; f) T. Pei, C.-y. Chen, P. G. Dormer, I. W. Davies, *Angew. Chem. Int. Ed.* **2008**, *47*, 4231; g) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui, N. Jiao, *Angew. Chem. Int. Ed.* **2009**, *48*, 4572; h) J. Barluenga, A. Jiménez-Aquino, F. Aznar, C. Valdés, *J. Am. Chem. Soc.* **2009**, *131*, 4031; i) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585; j) M. Nazaré, C. Schneider, A. Lindenschmidt, D. W. Will, *Angew. Chem. Int. Ed.* **2004**, *43*, 4526; k) P. Kothandaraman, W. Rao, S. J. Foo, P. W. H. Chan, *Angew. Chem. Int. Ed.* **2010**, *49*, 4619.

[125] a) S. Kirchberg, R. Fröhlich, A. Studer, *Angew. Chem. Int. Ed.* **2009**, *48*, 4235; b) H. Tokuyama, Y. Kaburagi, X. Chen, T. Fukuyama, *J. Am. Chem. Soc.* **1999**, *121*, 3791; c) S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 6621; d) L. S. Hegedus, G. F. Allen, E. L. Waterman, *J. Am. Chem. Soc.* **1976**, *98*, 2674; e) G. Bartoli, R. Leardini, A. Medici, D. Rosini, *J. Chem. Soc., Perkin Trans. 1* **1978**, 692; f) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689; g) C. E. Castro, E. J. Gaughan, D. C. Owsley, *J. Org. Chem*. **1966**, *31*, 4071; h) M. Mori, K. Chiba, Y. Ban, *Tetrahedron Lett.* **1977**, *18*, 1037; i) P .G. Gassman, T. J. van Bergen, D. P. Gilbert, B. W. Cue, *J. Am. Chem. Soc.* **1974**, *96*, 5495; j) A. D. Batcho, W. Leimgruber, US Patent **1973**, No. 3732245; k) D. Zhang, L. Liebeskind, *J. Org. Chem.* **1996**, *61*, 2594; l) H. Hemetsberger, D. Knittel, *Monatsh. Chem.* **1972**, *103*, 194; m) D. Taber, W. Tian, *J. Am. Chem. Soc.* **2005**, *128*, 1058; n) A. Reissert, *Chem. Ber.* **1897**, *30*, 1030; o) T. Sugasawa, M. Adachi, K. Sasakura, A. Kitagawa, *J. Org. Chem.* **1978**, *44*, 578; p) J. Dunetz, R. Danheiser, *J. Am. Chem. Soc.* **2005**, *127*, 5776; q) K. Campos, J. Woo, S. Lee, R. Tillyer, *Org. Lett.* **2004**, *6*, 79.

[126] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241; b) B. Robinson, in *The Fischer Indole Synthesis*, Wiley-Interscience, New York, **1982**.

[127] For the preparation of functionalized aryl hydrazines, see: R. J. Lundgren, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 8686.

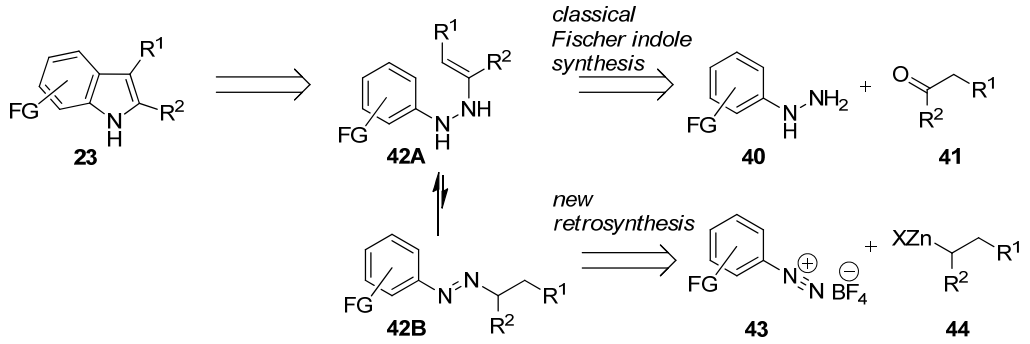
[128] R. J. Lundgren, B. D. Peters, P. G. Alsabeh, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 4071.

[129] For recent reviews, see: a) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed*. **2009**, 48, 9608; b) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875; c) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285; d) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; e) T. L. Gilchrist, *J. Chem. Soc., Perkin Trans 1* **2001**, 2491; f) G. Gribble, *J. Chem. Soc., Perkin Trans 1* **2000**, 1045.

[130] For a review of the Japp-Klingemann reaction, see: R. R. Phillips, *Org. React.* **1959**, *10*, 143.

[131] a) P. Knochel, in *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, **2005**; b) A. Leprêtre, A. Turck, N. Plé, P. Knochel, G. Quéguiner, *Tetrahedron* **2000**, *56*, 265.

obtained from **40** and **41**, but rather from the reaction of readily available aryldiazonium salts of type **43** and functionalized alkylzinc reagents of type **44** (Scheme 30).[132,133]

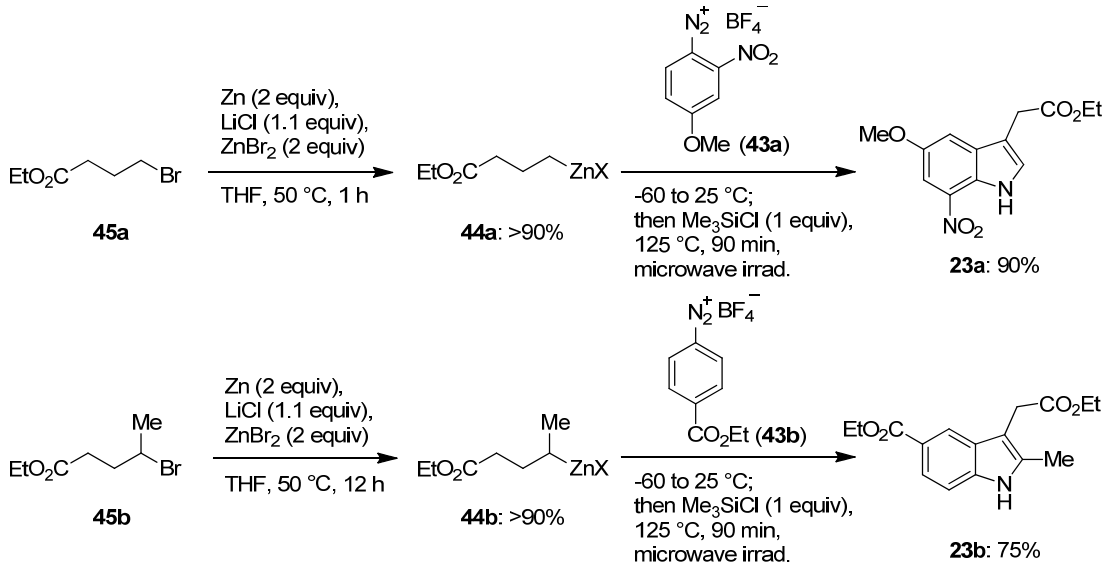


Scheme 30. Alternative retrosynthetic analysis of the Fischer indole synthesis.

This approach proved to be very fruitful, since many functional groups such as ester, cyano, nitro or keto groups, are well tolerated, and unexpectedly the issue of regioselectivity mentioned above is resolved.[134] Thus, the reaction of ethyl 4-bromobutanoate **45a** (1.1 equiv) with zinc dust (2 equiv), $ZnBr_2$ (2 equiv)[135] and LiCl (1.1 equiv) in THF produces the expected alkylzinc halide (**44a**) in 90% yield (50 °C, 1 h).[136] The addition of a THF solution of **44a** (1 equiv) to the functionalized aryldiazonium tetrafluoroborate (**43a**; 1.25 equiv, –60 °C to 25 °C) produces tentatively an azo compound of type **42B** which isomerizes to the unsaturated hydrazine **42A**. Addition of Me_3SiCl (1 equiv) followed by heating the reaction mixture using microwave irradiation (125 °C, 90 min) furnished after standard work-up the polyfunctional indole **23a** in 90% isolated yield.[137] Similarly, a secondary alkylzinc halide such as **44b** (90% yield) was prepared from the corresponding secondary alkyl bromide **45b** (1.1 equiv; Zn, LiCl, $ZnBr_2$, 50 °C, 12 h). Its addition to the ester-substituted diazonium salt **43b**[132a,135] from –60 to 25 °C followed by addition of Me_3SiCl and microwave irradiation (125 °C, 90 min) furnishes *regioselectively* the trisubstituted indole **23b** in 75% yield (Scheme 31). No regioisomer was detected. The presence of additional $ZnBr_2$ (2.0 equiv) proved to be essential to ensure a selective reaction with the diazonium salt in the next

[132] For the reaction of *aryl*zinc reagents with diazonium salts, see: a) B. A. Haag, Z. Peng, P. Knochel, *Org. Lett.* **2009**, *11*, 4270; b) D. Curtin, J. Tveteen, *J. Org. Chem.* **1961**, *26*, 1764.
[133] E. Yasui, M. Wada, N. Takamura, *Tetrahedron* **2009**, *65*, 461.
[134] B. Haag, Z.-G. Zhang, J.-S. Li, P. Knochel, *Angew. Chem.* **2010**, *122*, 9703–9706; *Angew. Chem. Int. Ed.* **2010**, *49*, 9513–9516.
[135] The additional presence of $ZnBr_2$ (2.0 equiv) proved to be essential to ensure a selective reaction with the diazonium salt in the next reaction step. In the absence of $ZnBr_2$, double addition products to diazonium salts have been detected.
[136] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; c) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.
[137] The addition of Me_3SiCl (1 equiv) was found to accelerate the cyclization reaction.

reaction step. In the absence of $ZnBr_2$, double addition products to diazonium salts were detected.

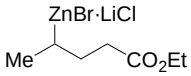
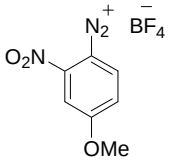
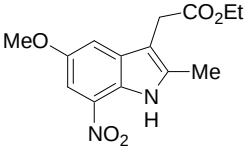
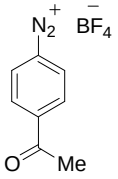
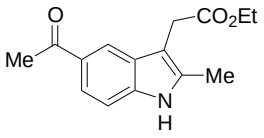
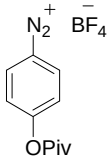
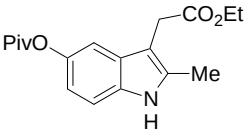
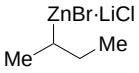
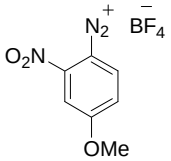
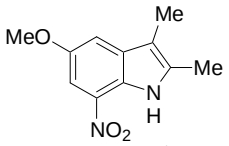
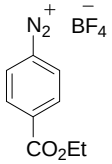
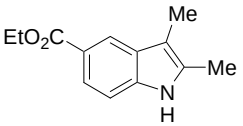
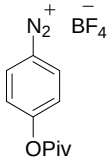
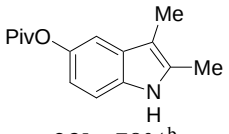
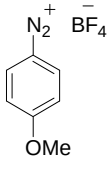
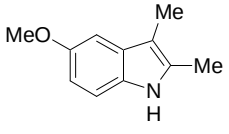
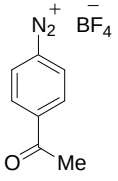
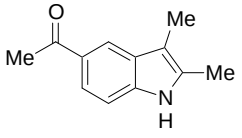


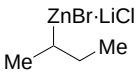
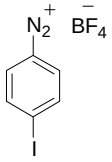
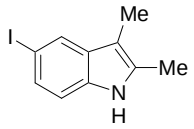
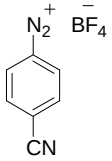
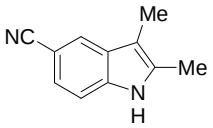
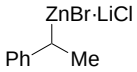
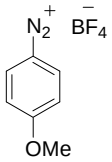
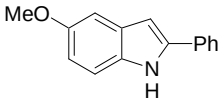
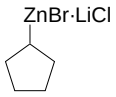
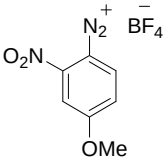
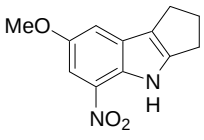
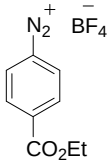
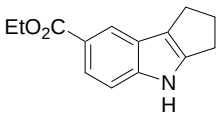
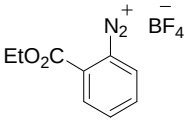
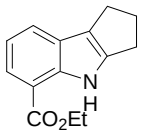
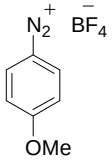
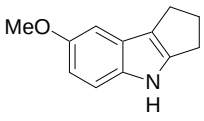
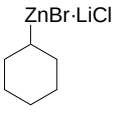
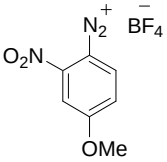
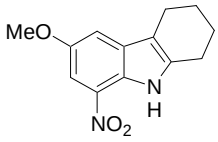
Scheme 31. Preparation of polyfunctional indoles **23a** and **23b**.

The alkylzinc reagent **44b** also reacted with various substituted aryldiazonium salts (**43a**, **43c**–**d**) providing the functionalized indole derivatives (**23c**–**e**) in 65–73% yield (Table 4, entries 1–3). By applying the same procedure to *s*BuZnBr[135] (**44c**) and to several functionalized aryldiazonium tetrafluoroborates (**43a**–**g**)[132a,135,138] polyfunctional 2,3-dimethylindoles (**23f**–**l**) were *regioselectively* produced in 78–85% yield (Table 4, entries 4–10). None of the regioisomeric 3-ethylindoles was observed. The benzylic zinc reagent **44d**[139] reacted with 4-methoxybenzenediazonium tetrafluoroborate (**43e**) providing after microwave irradiation (125 °C, 90 min) the expected 2-phenylindole derivative **23m** in 46% yield (Table 4, entry 11). Secondary cycloalkylzinc halides such as **44e**–**g**[136,135] also added to functionalized aryldiazonium salts (**43a**–**i**, **43k**) furnishing after microwave irradiation (125 °C, 0.5–2 h) the polysubstituted indole derivatives **23n–z** and **23aa–ad** in 52–92% yield (Table 4, entries 12–28). Instead of microwave irradiation, conventional heating was also successful in the cases of electron-rich substrates, however requiring longer reaction times in the cyclization-step to the indole derivatives.

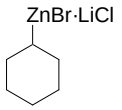
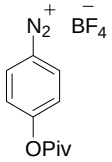
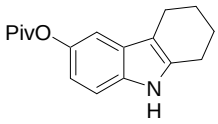
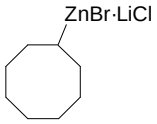
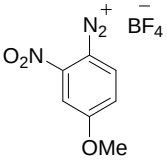
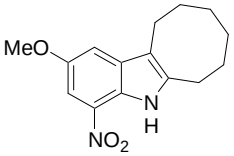
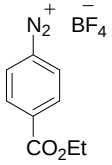
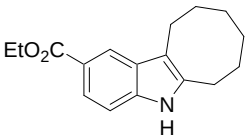
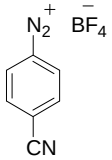
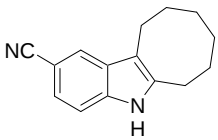
[138] I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 897.
[139] A. Metzger, C. Argyo, P. Knochel, *Synthesis* **2010**, 882.

Table 4. Preparation of polyfunctional indoles of type **23** via addition of alkylzinc reagents of type **44** to aryldiazonium tetrafluoroborates of type **43**.

Entry	Zinc reagent	Aryldiazonium salt	Product, Yield[a]
1	 **44b**	 **43a**	 **23c**: 69%
2	**44b**	 **43c**	 **23d**: 73%
3	**44b**	 **43d**	 **23e**: 65%
4	 **44c**	 **43a**	 **23f**: 81%[b]
5	**44c**	 **43b**	 **23g**: 75%
6	**44c**	 **43d**	 **23h**: 78%[b]
7	**44c**	 **43e**	 **23i**: 84%[b]
8	**44c**	 **43c**	 **23j**: 81%

Entry	Zinc reagent	Aryldiazonium salt	Product, Yield[a]
9	 **44c**	 **43f**	 **23k**: 85%
10	**44c**	 **43g**	 **23l**: 78%
11	 **44d**	 **43e**	 **23m**: 46%
12	 **44e**	 **43a**	 **23n**: 68%
13	**44e**	 **43b**	 **23o**: 78%
14	**44e**	 **43k**	 **23p**: 52%
15	**44e**	 **43e**	 **23q**: 67%
16	 **44f**	 **43a**	 **23r**: 89%[b]

Entry	Zinc reagent	Aryldiazonium salt	Product, Yield[a]
17	**44f**	**43b**	**23s**: 81%
18	**44f**	**43g**	**23t**: 81%
19	**44f**	**43c**	**23u**: 88%
20	**44f**	**43k**	**23v**: 46%
21	**44f**	**43h**	**23w**: 63%
22	**44f**	**43i**	**23x**: 56%
23	**44f**	**43f**	**23y**: 56%
24	**44f**	**43e**	**23z**: 83%

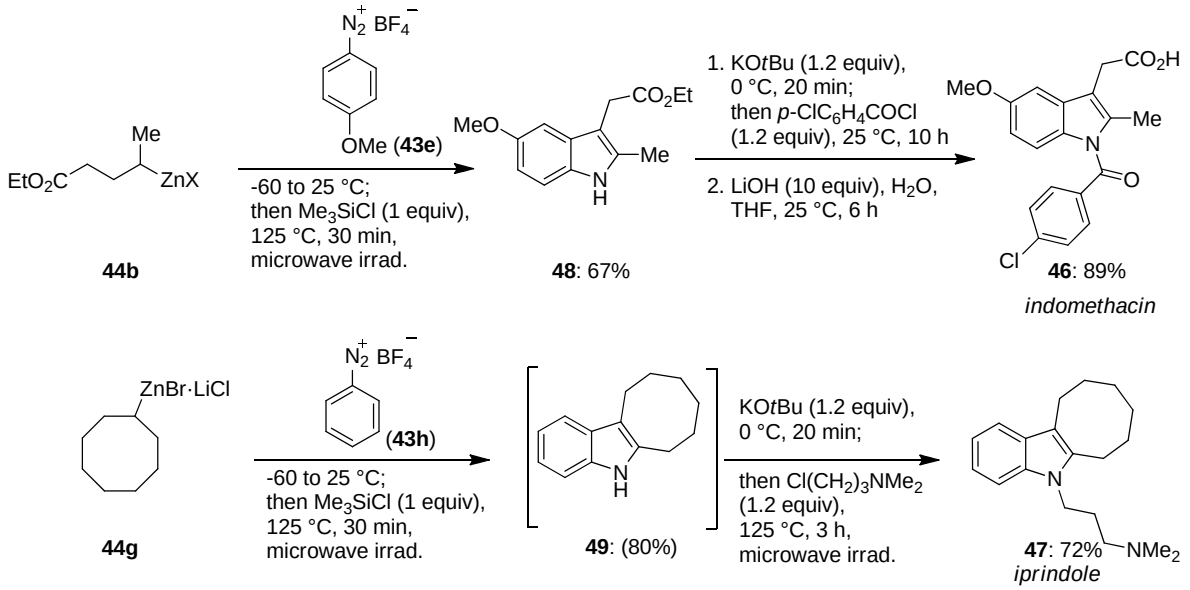
Entry	Zinc reagent	Aryldiazonium salt	Product, Yield[a]
25	 **44f**	 **43d**	 **23aa**: 77%
26	 **44g**	 **43a**	 **23ab**: 86%[b]
27	**44g**	 **43b**	 **23ac**: 89%
28	**44g**	 **43g**	 **23ad**: 92%

[a] Yield of isolated, analytically pure product as determined by ^{1}H NMR. [b] No Me_3SiCl was added.

We have applied this organometallic variation of the Fischer indole synthesis to a short preparation of *indomethacin* (**46**), an anti-inflammatory drug,[140] and of *iprindole* (**47**)[141], an anti-depressant. Thus, the reaction of the zinc reagent **44b** with the aryldiazonium salt **43e** produces under standard conditions the indole **48** in 67% yield which was converted in two steps to *indomethacin* **46** in 89% yield (Scheme 32). Similarly, cyclooctylzinc bromide (**44g**) adds to PhN_2BF_4 (**43h**) and provides after microwave irradiation the indole **49** which was *N*-alkylated leading to *iprindole* **47** in 72% yield (Scheme 32).

[140] a) K.-J. Hwang, S.-J. Lee, B.-T. Kim, S. Raucher, *Bull. Korean Chem. Soc.* **2006**, *27*, 933; b) T. Y. Shen, T. B. Windholz, A. Rosegay, B. E. Witzel, A. N. Wilson, J. D. Willett, W. J. Holtz, R. L. Ellis, A. R. Matzuk, S. Lucas, C. H. Stammer, F. W. Holly, L. H. Sarett, E. A. Risley, G. W. Nuss, C. A. Winter, *J. Am. Chem. Soc.* **1963**, *85*, 488; c) K. R. Campos, J. C. S. Woo, S. Lee, R. D. Tillyer, *Org. Lett.* **2004**, *6*, 79; d) C. Mukai, Y. Takahashi, *Org. Lett.* **2005**, *7*, 5793; e) I. V. Magedov, S. A. Maklakov, Yu. I. Smushkevich, *Chem. Heterocycl. Comp.* **2005**, *41*, 449.

[141] a) L. M. Rice, E. Hertz, M. E. Freed, *J. Med. Chem.* **1964**, *7*, 313; b) B. L. Baxter, M. I. Gluckman, *Nature* **1969**, *223*, 750.



Scheme 32. Preparation of indomethacin (**46**) and iprindole (**47**).

Due to the good availability of functionalized organozincs,[142] the efficiency, and practicability of this new methodology, we developed large scale procedures affording various polyfunctional indole derivatives in 10–20 mmol.[143]

Thus, the primary alkylzinc bromide **44a** reacted with the aryldiazonium salt **43a** (–60 to 25 °C) providing after microwave irradiation (Me_3SiCl (1 equiv), 125 °C, 90 min) the indole **23a** in 90% yield (Table 5, entry 1). Furthermore, the secondary alkylzinc bromide **44b** obtained after direct zinc insertion[144] with the alkyl bromide **45b** (Zn (2 equiv), LiCl (1.1 equiv), $ZnBr_2$ (2 equiv), 50 °C, 12 h) added smoothly to a substituted aryldiazonium salt[145] such as **43e** (–60 to 25 °C) leading after addition of Me_3SiCl (1 equiv) and heating by microwave irradiation (125 °C, 30 min) regioselectively to the polyfunctional indole **48** in 67% yield as single regioisomer (Table 5, entry 2). Moreover, the ester-substituted secondary alkylzinc bromide **44b** added to the aryldiazonium tetrafluoroborate **43d** furnishing under our standard conditions the 3-substituted indole **23e** in 63% yield (Table 5, entry 3). Similarly, *s*BuZnBr·LiCl (**44c**) added to various polyfunctional aryldiazonium salts (**43a**, **43c** and **43i**–**j**) affording regioselectively the functionalized 2,3-dimethylindole derivatives **23f**, **23j** and **23ae**–**af** in 68–82% yield (Table 5, entries 4–7). Under the same reaction conditions, cyclopentylzinc bromide (**44e**) and substituted aryldiazonium salts such as **43a** and **43c–d** led

[142] E. Erdik, in *Organozinc Reagents in Organic Synthesis*; CRC-Press: Boca Raton, FL, **1996**; b) Z. Dong, G. Manolikakes, J. Li, P. Knochel, *Synthesis* **2009**, 681; c) C. Despotopoulou, C. Gignoux, D. McConnell, P. Knochel, *Synthesis* **2009**, 3661; d) G. Monzon, P. Knochel, *Synlett* **2010**, 304; e) A. Metzger, C. Argyo, P. Knochel, *Synthesis* **2010**, 882.

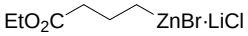
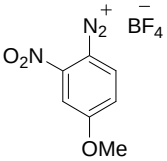
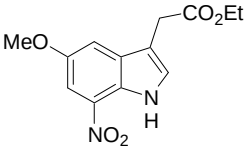
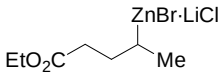
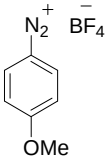
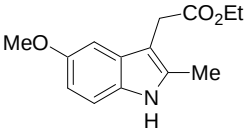
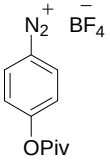
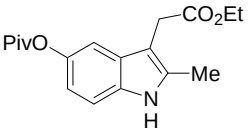
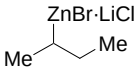
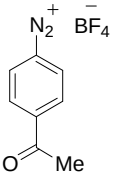
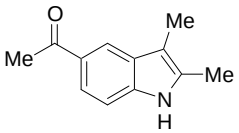
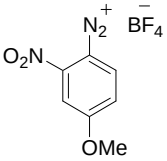
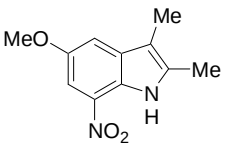
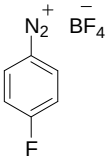
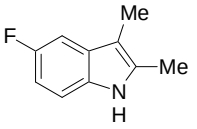
[143] Z.-G. Zhang, B. Haag, J.-S. Li, P. Knochel, *Synthesis* **2010**, 23-29.

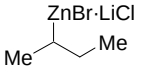
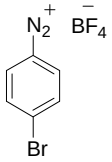
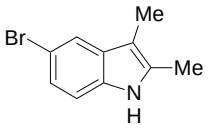
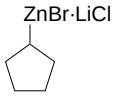
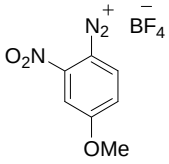
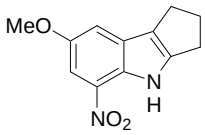
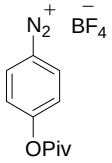
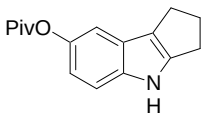
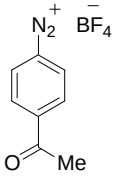
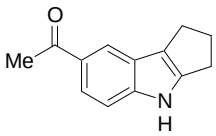
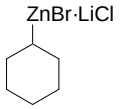
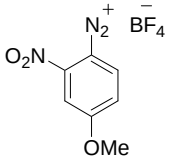
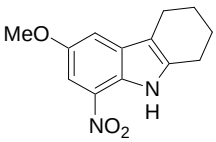
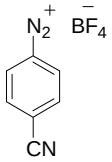
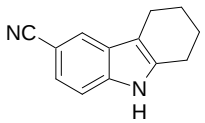
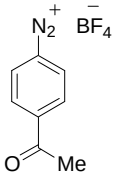
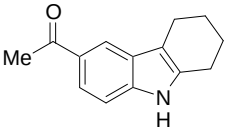
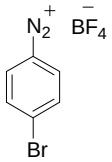
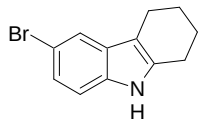
[144] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

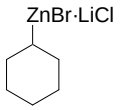
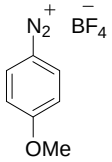
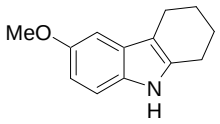
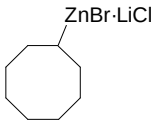
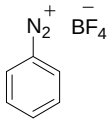
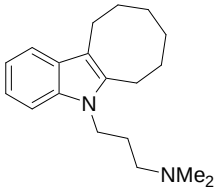
[145] a) B. Haag, Z. Peng, P. Knochel, P. *Org. Lett.* **2009**, *11*, 4270; b) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 897.

to the corresponding indoles **23n**, **23ag–ah** in 68–76% yield (Table 5, entries 8–10). The secondary alkylzinc reagent *c*HexZnBr·LiCl (**44e**) added to readily available functionalized aryldiazonium tetrafluoroborates (**43a**, **43c**, **43g**, **43j** and **43e**) and provided polyfunctional tetrahydro-1*H*-carbazoles **23r**, **23t**–**u** and **23ai**–**aj** in 73–91% yield (Table 5, entries 11–15). As in small scale experiments, instead of microwave irradiation, conventional heating was also successfully used in the case of electron-rich substrates, yet requiring longer reaction times for the cyclization-step to the corresponding indole derivatives.

Table 5. 10–20 mmol scale preparations of polyfunctional indoles of type **23** via the addition of alkylzinc reagents of type **44** to aryldiazonium tetrafluoroborates of type **43**.

Entry	Zinc reagent	Aryldiazonium salt	Product, Yield[a]
1	 **44a**	 **43a**	 **23a**: 90%
2	 **44b**	 **43e**	 **48**: 67%
3	**44b**	 **43d**	 **23e**: 63%
4	 **44c**	 **43c**	 **23j**: 80%
5	**44c**	 **43a**	 **23f**: 80%
6	**44c**	 **43i**	 **23ae**: 68%

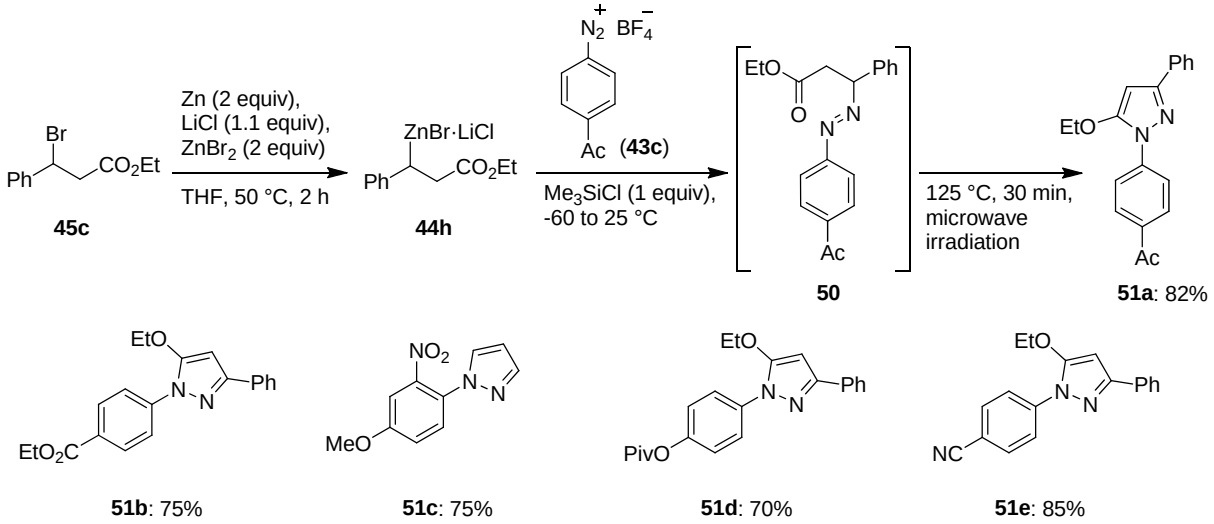
Entry	Zinc reagent	Aryldiazonium salt	Product, Yield[a]
7	 **44c**	 **43j**	 **23af**: 80%
8	 **44e**	 **43a**	 **23u**: 68%
9	**44e**	 **43d**	 **23ag**: 72%
10	**44e**	 **43c**	 **23ah**: 76%
11	 **44f**	 **43a**	 **23r**: 91%
12	**44f**	 **43g**	 **23t**: 80%
13	**44f**	 **43c**	 **23u**: 73%
14	**44f**	 **43j**	 **23ai**: 80%

Entry	Zinc reagent	Aryldiazonium salt	Product, Yield[a]
15	 **44f**	 **43e**	 **23aj**: 80%
16	 **44g**	 **43h**	 **47**: 72%[b]

[a] Yield of isolated, analytically pure product as determined by 1H NMR. [b] After indole formation, the reaction mixture was treated with KO*t*Bu (1.2 equiv, 0 °C, 20 min), then with $Cl(CH_2)_3NMe_2$ (1.2 equiv, 125 °C, 3 h, microwave irradiation).

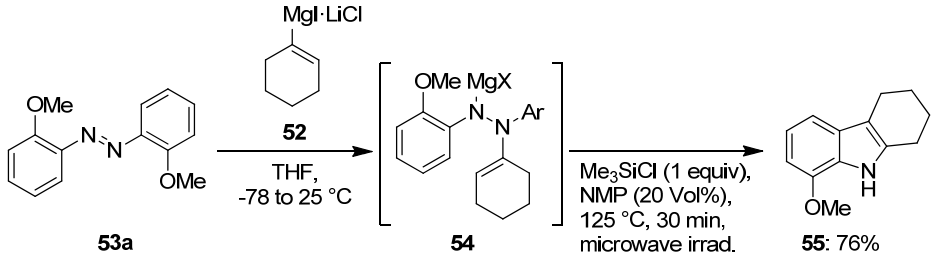
Furthermore, we have applied the large scale procedure to the preparation of the anti-depressant *iprindole* (**47**) on a four-gram-scale. In a one-pot procedure on a 20 mmol scale, cyclooctylzinc bromide (**44g**) added smoothly to benzenediazonium tetrafluoroborate (**43h**; –60 to 25 °C) leading after microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1 equiv) to the indole derivative. Subsequent *N*-alkylation of this intermediate (KO*t*Bu (1.2 equiv), 0 °C, 20 min; then $Cl(CH_2)_3NMe_2$ (1.2 equiv), 125 °C, 3 h) provided *iprindole* (**47**) in 72% yield (Table 5, entry 16).

Surprisingly, β-substituted alkylzinc halides like **44h** did not provide, after addition to aryldiazonium salts **43b**–**d** or **43g** and subsequent heating, the corresponding functionalized indoles. In contrast, addition of **44h** to a functionalized aryldiazonium tetrafluoroborates like **43c** led tentatively to an intermediate azo compound of type **50**. Heating by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1 equiv) afforded the substituted pyrazole **51a** in 82% yield (Scheme 33). In addition, the pyrazole derivatives **51b**–**e** could be prepared from various aryldiazonium salts (**43a**–**b**, **43d** and **43g**) in 70–85% yield using these standard conditions (Scheme 33).



Scheme 33. Preparation of substituted pyrazoles of type **51**.

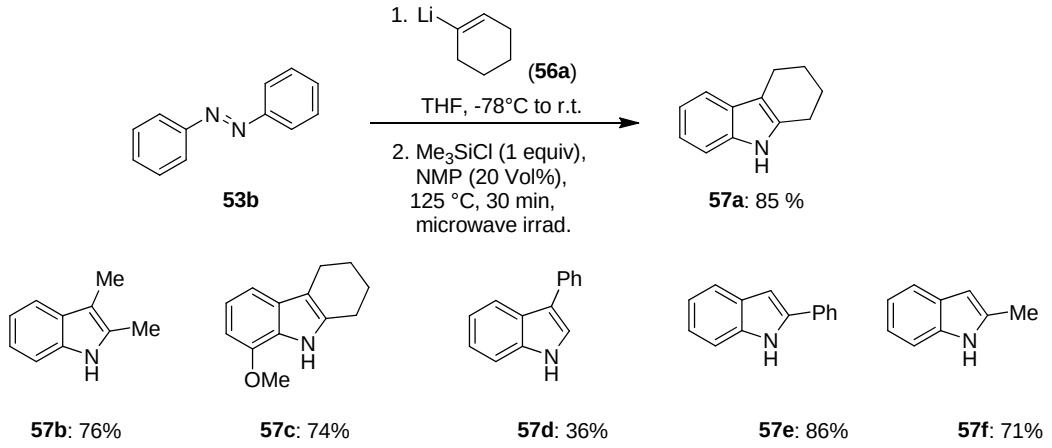
In the course of our studies, we found that the key hydrazine intermediate of type **42A** can also be obtained by the addition of an alkenylmagnesium reagent such as cyclohexenylmagnesium iodide (**52**)[146] to a methoxy-substituted azobenzene like **53a** leading to the magnesiated hydrazine **54** which after addition of Me_3SiCl and microwave irradiation produces the carbazole **55** (Scheme 34).



Scheme 34. Preparation of substituted tetrahydrocarbazole **55a** via the addition of alkenylmagnesium reagent **52** to the azobenzene derivative **53a**.

Furthermore, alkenyllithium reagents, such as cyclohexen-1-yllithium (**56a**), readily react with azobenzene (–78 to 25 °C) leading after addition of Me_3SiCl (1 equiv) and heating by microwave irradiation (125 °C, 30 min) to 1,2,3,4-tetrahydrocarbazole (**57a**) in 85% yield (Scheme 35). Similarly, various alkenyllithium reagents (**56a**–**e**) also add to azobenzene derivatives (**53a**–**b**) providing after microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1 equiv) the expected indoles (**57b**–**f**) in 36–86% yield (Scheme 35).

[146] H. E. Ramsden, J. R. Leebrick, S. D. Rosenberg, E. H. Miller, J. J. Walburn, A. E. Balint, R. Cserr, *J. Org. Chem.* **1957**, *22*, 1602.



Scheme 35. Preparation of indoles of type **57** via the addition of alkenyllithium reagents of type **56a** to the azobenzene derivatives.

We have described a new organometallic variation of the Fischer indole synthesis allowing the preparation of various polyfunctional indoles from readily available aryldiazonium tetrafluoroborates and functionalized primary and secondary alkylzinc halides. High regioselectivity in the indole ring formation was observed. This variation enhances the scope of the original Fischer indole synthesis tolerating a broad range of functionalities and displaying a remarkable regioselectivity. As an application of this method, the antidepressant iprindole and the anti-inflammatory drug indomethacin were efficiently prepared. Additionally, we have extended the scope and improved the reaction conditions for the preparation of polyfunctional indoles on a larger scale. In the course of our study, we have also developed an alternative preparation of indole derivatives via addition of alkenylmagnesium or lithium reagents to azo compounds.

2. Preparation of Organometallics via Direct Metal Insertion or Hal/Mg-Exchange Reaction in the Presence of LiCl

2.1 Introduction

Organoboron compounds have proven to be powerful tools in synthetic chemistry and are thus widely used reagents for C-C bond formations. In general, their preparation via transmetalation from the corresponding organolithium or magnesium reagents is one of the most common, highly regioselective methods.[10] However, the high reactivity of organolithium reagents mostly precludes the synthesis of polyfunctional organoboron reagents. On the other hand, versatile polyfunctional as well as heterocyclic Mg-organometallics reagents are readily available.[147] Based on Grignard´s discovery[11] and major contributions of Rieke *et al.*[24], the direct magnesium insertion has emerged to an important method for the preparation of organomagnesium reagents.[10] First described by Prévost,[14] Knochel *et al.* extensively contributed in the field of Hal/Mg-exchange reactions over the last decade.[20,148] In particular, the development of LiCl-complexed exchange reagents, such as *i*PrMgCl·LiCl,[22] has tremendously effected modern organometallic chemistry. The reagent *i*PrMgCl·LiCl proved to be an efficient exchange reagent for the generation of aryl- and heteroarylmagnesium reagents bearing sensitive functions, like ester or cyano groups. Despite numerous major developments, great efforts are still directed toward the preparation of organometallic reagents.

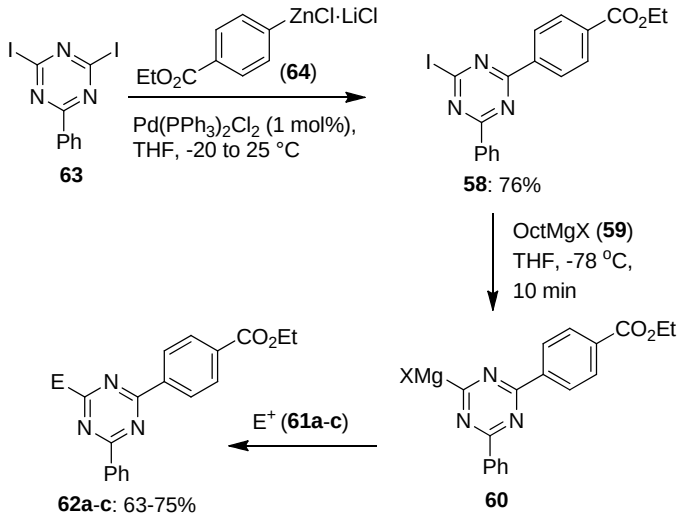
2.2 1,3,5-Triazinylmagnesium Reagents via an I/Mg-exchange Reaction

Heterocycles gained increased significance in modern chemistry.[149] Among *N*-containing heterocycles, 1,3,5-triazine derivatives[150,151] have found numerous industrial applications as

[147] 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.
[148] a) H. Ila, O. Baron, A. J. Wagner, P. Knochel, *Chem. Commun*. **2006**, 583; b) P. Knochel, W. Dohle, N. Gommermann, F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed*. **2003**, *42*, 4302; c) M. Abarbri, P. Knochel, *Synlett* **1999**, 1577; d) F. Dehmel, M. Abarbri, P. Knochel, *Synlett* **2000**, 345; e) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed*. **2004**, *43*, 3333; f) F. Cresty, P. Knochel, *Synthesis* **2010**, 1097; g) L. Melzig, C. Rauhut, P. Knochel, *Synthesis* **2009**, 1041.
[149] a) A. F. Pozharskii, A. T. Soldatenkov, A. R. Katritzky, in *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry and Biochemistry and the Role of Heterocycles in Science, Technology, Medicine and Agriculture*, Wiley-VCH, Weinheim, **1997**; b) T. Eicher, S. Hauptmann, in *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, 2. Ed., Wiley-VCH, Weinheim, **2003**; c) A. R. Katritzky, in *Advances in Heterocyclic Chemistry*, Academic Press, Oxford, Vol. 82, **2002**.
[150] For reviews, see: a) A. V. Angerer, in *Science of Synthesis* (Ed.: S. M. Weinreb), **2003**, Vol. 17, p 449; b) G. Giacomelli, A. Porcheddu, in *Comprehensive Heterocyclic Chemistry III* (Ed.: K. Turnbull), **2008**, 9, 197; c) Blotny, G. *Tetrahedron* **2006**, *62*, 9507.

pharmaceuticals,[152] liquid crystals,[153] reactive dyes[154] and organic light-emitting diodes (OLED).[155] However, the efficient syntheses of polyfunctional 1,3,5-triazines remain a synthetic challenge. Metalated heterocyclic intermediates have proven to possess great potential for the concise synthesis of functionalized heterocycles.[156] In particular, polyfunctionalized organomagnesium compounds show a high tolerance towards a wide range of functional groups and are easily accessible, e.g. via Br/Mg- or I/Mg-exchange reaction.[157] It has been reported that the reaction of 2-chloro-4,6-dimethoxy-1,3,5-triazine with ketones using lithium powder and substoichiometric amounts of naphthalene involving a lithiated 1,3,5-triazine intermediate, affords the corresponding alcohols in 13–50% yield.[158] However, we envisioned a straightforward and practical preparation of fully substituted 1,3,5-triazines via magnesiated triazines.[159] Thus, various functionalized iodotriazine derivatives of type **58** underwent a smooth I/Mg-exchange reaction using OctMgBr (**59**; 1.1 equiv, –78 °C, 10 min) affording the corresponding 2-magnesiated 1,3,5-triazines of type **60**. Subsequent reactions of the triazinylmagnesium reagents **60** with various electrophiles (E^+; **61a**–**c**) led to substituted triazines of type **62** in 59–75% yield (Scheme 36 and Table 6).

[151] C. Grundmann, *Angew. Chem.* **1963**, *75*, 393.
[152] a) A. Dhainaut, G. Regnier, A. Tizot, A. Pierre, S. Leonce, N. Guilbaud, L. Kraus-Berthier, G. Atassi, *J. Med. Chem*. **1996**, *39*, 4099; b) S. Ronchi, D. Prosperi, F. Compostella, L. Panza, *Synlett*, **2004**, 1007.
[153] a) A. Kohlmeier, D. Janietz, S. Diele, *Chem. Mater.* **2006**, *18*, 1483; b) H. C. Holst, T. Pakula, H. Meier, *Tetrahedron* **2004**, *60*, 6765; c) E. Beckel, N. Cramer, A. Harant, C. Bowman, *Liq. Cryst.* **2003**, *30*, 1343.
[154] K. Xie, Y. Sun, A. Hou, *J. Appl. Polym. Sci.* **2007**, *103*, 2166.
[155] a) A. Kulkarni, C. Tonzola, A. Babel, S. Jenekhe, *Chem. Mater.* **2004**, *16*, 4556; b) J.-W. Kang, D.-S. Lee, H.-D. Park, Y.-S. Park, J. W. Kim, W.-I. Jeong, K.-M. Yoo, K. Go, S.-H. Kim, J.-J. Kim, *J. Mater. Chem.* **2007**, *17*, 3714; c) T.-Y. Chu, M.-H. Ho, J.-F. Chen, C. H. Chen, *Chem. Phys. Lett.* **2005**, *415*, 137; d) H. Inomata, K. Goushi, T. Masuko, T. Konno, T. Imai, H. Sasabe, J. Brown, C. Adachi, *Chem. Mater.* **2004**, *16*, 1285; e) J. Pang, Y. Tao, S. Freiberg, X.-P. Yang, M. D'Iorio, S. Wang, *J. Mater. Chem.* **2002**, *12*, 206.
[156] a) T. Delacroix, L. Bérillon, G. Cahiez, P. Knochel, *J. Org. Chem.* **2000**, 65, 8108; b) M. Poirier, F. Chen, C. Bernard, Y.-S. Wong, G. Wu, *Org. Lett*. **2001**, *3*, 3795; c) W. Dohle, A. Staubitz, P. Knochel, *Chem. Eur. J*. **2003**, *9*, 5323; d) V. Anh Vu, I. Marek, K. Polborn, P. Knochel, *Angew. Chem. Int. Ed.*, **2002**, *41*, 351; e) M. Mosrin, M. Petrera, P. Knochel, *Synthesis* **2008**, 3697; f) G. Monzon, P. Knochel, *Synlett* **2010**, 304.
[157] a) H. Ila, O. Baron, A. J. Wagner, P. Knochel, *Chem. Commun*. **2006**, 583; b) P. Knochel, W. Dohle, N. Gommermann, F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed*. **2003**, *42*, 4302; c) M. Abarbri, P. Knochel, *Synlett* **1999**, 1577; d) F. Dehmel, M. Abarbri, P. Knochel, *Synlett* **2000**, 345; e) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed*. **2004**, *43*, 3333; f) F. Cresty, P. Knochel, *Synthesis* **2010**, 1097.
[158] I. Gómez, E. Alonso, D. J. Ramón, M. Yus, *Tetrahedron* **2000**, *56*, 4043.
[159] Z. Peng, B. Haag, P. Knochel, *Org. Lett.* **2010**, *12*, 5398–5401.



Scheme 36. Preparation of functionalized 1,3,5-triazinylmagnesium reagents **60** followed by functionalization with various electrophiles.

In comparison to well-established Hal/Mg-exchange reagents such as *i*PrMgCl,[160] the Grignard reagent OctMgBr (**59**) is less nucleophilic and more selective, avoiding undesired substitution products. Due to its long alkyl chain, OctMgBr (**59**) proved to be highly soluble at low temperatures (−78 °C) displaying an excellent reactivity in Hal/Mg-exchange reactions. The substrate for the exchange reaction, namely the iodotriazine **58**, was prepared from 2,4-diiodo-6-phenyl-1,3,5-triazine[161] (**63**) using a Negishi-type cross-coupling[162] with the ester-substituted arylzinc chloride (**64**) in the presence of $Pd(PPh_3)_2Cl_2$ (1 mol%) in 76% yield (Scheme 36). Thus, the 1,3,5-triazine-based Grignard reagent **60** bearing an electron-withdrawing functional group in *para*-position of the phenyl substitutent was prepared via a rapid I/Mg-exchange with OctMgBr (**59**; 1.1 equiv, −78 °C, 10 min) from the corresponding 2-iodo-1,3,5-triazine **58**. OctMgBr (**59**) in particular avoids side-products due to a nucleophilic substitution of the triazine ring. Thus, the 1,3,5-triazinylmagnesium reagent **60** afforded after addition of PhCHO (**61a**) or *p*-NC-C_6H_4-CHO (**61b**), the functionalized 1,3,5-triazinyl alcohols **62a**–**b** in 63−75% yield (Table 6, entries 1 and 2). Similarly, a copper-

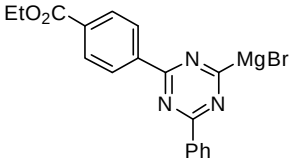
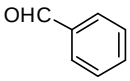
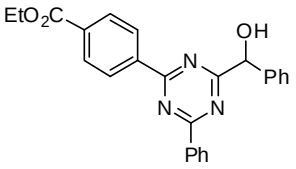
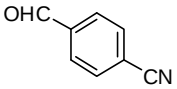
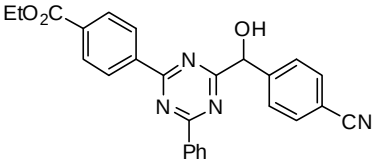
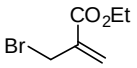
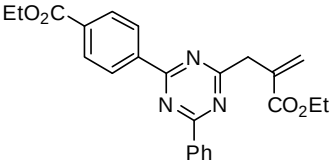
[160] a) P. Knochel, in *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, **2005**; b) A. Leprêtre, A. Turck, N. Plé, P. Knochel, G. Quéguiner, *Tetrahedron* **2000**, *56*, 265; c) C. Rauhut, C. Cervino, A. Krasovskiy, P. Knochel, *Synlett* **2009**, 67.

[161] Obtained after treatment of 2,4-dichloro-6-phenyl-1,3,5-triazine with HI. See: G. Vlád, I. T. Horváth, J. *Org. Chem.* **2002**, *67*, 6550.

[162] a) J.-X. Wang, J. McCubbin, M. Jin, R. Laufer, Y. Mao, A. Crew, M. Mulvihill, V. Snieckus, *Org. Lett.* **2008**, *10*, 2923; b) A. de Meijere, P. von Zezschwitz, S. Braese, *Acc. Chem. Res.* **2005**, *38*, 413; c) K. Albrecht, O. Reiser, M. Weber, B. Knieriem, A. de Meijere, *Tetrahedron* **1994**, *50*, 383; d) E. Negishi, A. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; e) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; f) Ø. Rist, M. Begtrup, *J. Chem. Soc., Perkin Trans.* **2001**, *1*, 1566; g) C. James, A. Coelho, M. Gevaert, P. Forgione, V. Snieckus, *J. Org. Chem.* **2009**, *74*, 4094; h) Z. Zhao, A. Jaworski, I. Piel, V. Snieckus, *Org. Lett.* **2008**, *10*, 2617; i) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; j) X. Zeng, M. Quian, Q. Hu, E. Negishi, *Angew. Chem. Int. Ed.* **2004**, *43*, 2259; g) G. Manolikakes, M. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765; h) Z. Dong, G. Manolikakes, J. Li, P. Knochel, *Synthesis* **2009**, 681.

catalyzed allylation[163] of **60** with ethyl (2-bromomethyl)acrylate[164] (**61c**) provided the triazinyl-substituted acrylate **62c** in 71% yield (Table 6, entry 3).

Table 6. Functionalized 1,3,5-triazine derivatives of type **62** obtained by I/Mg-exchange and subsequent quenching with an electrophile (**61a**–**c**).

Entry	Magnesium reagent	Electrophile	Product, Yield[a]
1	 **60**[b]	 **61a**	 **62a**: 51%
2	**60**[b]	 **61b**	 **62b**: 63%
3	**60**[b]	 **61c**	 **62c**: 71%[c]

[a] Yield of isolated, analytically pure product as determined by 1H NMR. [b] Obtained after I/Mg-exchange with OctMgBr (**59**; −78 °C, 10 min). [c] Obtained after addition of CuCN·2LiCl (20 mol%); then ethyl (2-bromomethyl)acrylate (**61c**; 1.2 equiv; –40 to 25 °C, 12 h).

Therefore, we have developed a new method for the preparation of stable 1,3,5-triazinylmagnesium reagents which react with aldehydes, acid chlorides and allylic halides furnishing a range of new functionalized fully-substituted 1,3,5-triazine derivatives.

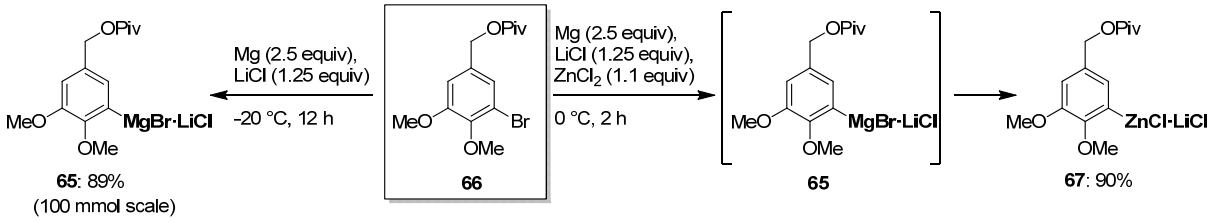
[163] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[164] M. Rambaud, J. Villieras, *Synthesis* **1984**, 406.

2.3 Direct Magnesium Insertion in the Presence of $ZnCl_2$ and LiCl

Organomagnesium regents are key organometallics in organic synthesis. They display an excellent reactivity towards a range of important electrophiles,[165] but are also found to be compatible with a number of common functional groups, like an ester, an aryl ketone or a nitrile.[166] The major drawback for the use of polyfunctional aryl- and heteroaryl-magnesium species was the lack of convenient preparation methods for such reagents. The iodine-magnesium exchange-reaction was found to be a practical method for preparing functionalized magnesium reagents, but it had some important drawbacks, such as the use of expensive aryl iodides as substrates. The corresponding Br/Mg-exchange was often too slow to be of practical use.[167] However, it was found that the halogen-metal exchange reaction[167] could be catalyzed by the addition of lithium salts such as Li(acac)[168] or LiCl.[169] These discoveries led to the development of a convenient mixed lithium and magnesium reagent *i*PrMgCl·LiCl for the preparation of polyfunctional magnesium reagents. The large-scale synthesis of this commercially available reagent[170] led to the observation that the formation rate of *i*PrMgCl·LiCl from *i*PrCl, Mg and LiCl is greatly accelerated by LiCl.[171] It turns out that this rate acceleration occurs with numerous metals and a detailed report for the LiCl-accelerated preparation of polyfunctional zinc[172] and indium[173] compounds has already been published. Recently, Knochel and co-workers reported the use of magnesium in the presence of LiCl for preparing various aryl- and heteroarylmagnesium reagents from the corresponding

[165] a) *Handbook of Grignard Reagents* (Eds.: G. S. Silverman, P. E. Rakita), CRC Press, New York, **1996**; b) *Grignard Reagents, New Developments* (Ed.: H. G. Richey Jr.) Wiley VCH, New York, **2000**, p. 185.
[166] a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; b) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.
[167] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, 37, 1701; b) K. Oshima, *J. Organomet. Chem.* **1999**, 575, 1; c) K. Kitagawa, A. Inoue, H. Shinokubo, K. Oshima, *Angew. Chem. Int. Ed.* **2000**, *39*, 2481; d) A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2001**, *66*, 4333; e) R. I. Yousef, T. Rüffer, H. Schmidt, D. Steinborn, *J. Organomet. Chem.* **2002**, *655*, 111; f) A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *Tetrahedron* **2000**, *56*, 9601.
[168] a) F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017; b) L.-Z. Gong, P. Knochel, *Synlett*, **2005**, 267.
[169] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; b) A. Krasovskiy, B. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159; c) H. Ren, A. Krasovskiy, P. Knochel, *Org. Lett.* **2004**, *23*, 4215; d) H. Ren, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2005**, 543; e) F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, 2288; f) F. Kopp, P. Knochel, *Org. Lett*. **2007**, **9**, 1639; g) F. Kopp, S. Wunderlich, P. Knochel, *Chem. Commun.* **2007**, 2075.
[170] *i*PrMgCl·LiCl is commercially available from Aldrich and Chemetall GmbH (Frankfurt, Germany).
[171] P. Knochel, A. Gavryushin, V. Malakhov, A. Krasovskiy, *Ger. Offen*. **2007**, DE 102006015378 A1 20071004.
[172] 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.
[173] 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*, 7648.

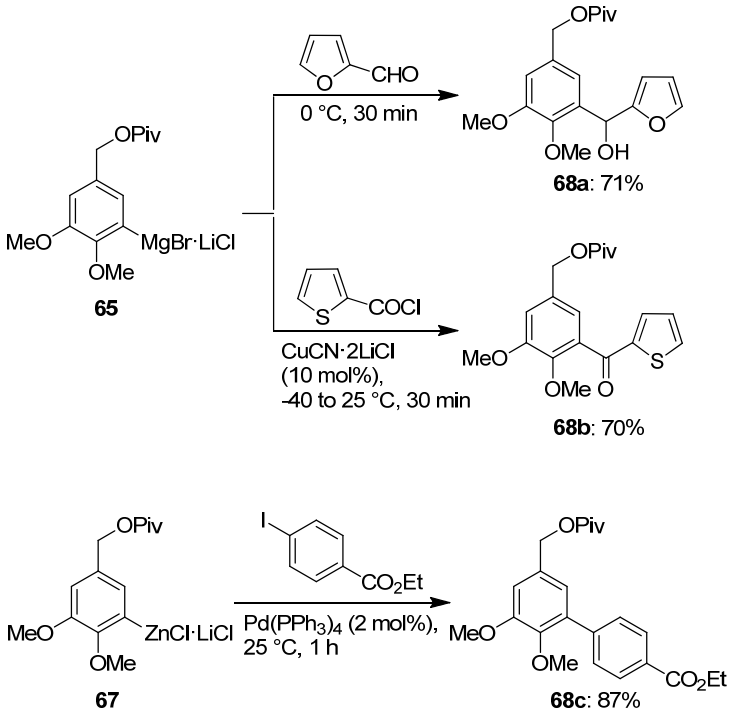
organic chlorides or bromides.[174] The described method tolerates sensitive functional groups. Thus, the scale-up of this procedure was successfully achieved producing functionalized arylmagnesium reagents such as **65** on a 100 mmol scale. The procedure uses the accelerated direct magnesium insertion (Mg (2.5 equiv), LiCl (1.25 equiv), –20 °C, 12 h) starting from the corresponding aryl bromide **66** in 89% yield[175] (Scheme 37). This procedure complements the pioneering contributions of Rieke using highly reactive magnesium powder prepared by the reduction of $MgCl_2$ with lithium in the presence of naphthalene (20 mol%).[176] Although the present method does not reach the insertion rates observed with Rieke-magnesium, it allows the preparation of several new classes of functionalized organomagnesium reagents using practical and economical reaction conditions. In the case of arenes and heteroarenes bearing sensitive functional groups, we developed an alternative procedure in which the organic halide **66** was treated with Mg/LiCl (2.5 equiv/1.25 equiv) in the presence of $ZnCl_2$ (1 equiv, 0 °C, 2 h). Under these conditions, the thermally unstable magnesium intermediate **65** is transmetallated *in situ* to the corresponding polyfunctional zinc derivative[174,177] **67** in 90% yield. The latter possesses an improved chemical stability (Scheme 37). This procedure is of special interest, since such electron-rich aryl bromides do not directly react with Zn, even in the presence of LiCl. The strong reduction potential of Mg compared to Zn ensures, however, a rapid formation of the organometallic species.



Scheme 37. LiCl-mediated preparation of functionalized Mg- and Zn-organometallics.

[174] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.
[175] Determined by titration with iodine.
[176] a) R. D. Rieke, *Science* **1989**, *246*, 1260; b) R. D. Rieke, P. M. Hudnall, *J. Am. Chem. Soc.* **1972**, *94*, 7178; c) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925; d) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem*. **2000**, *65*, 5428; e) R. D. Rieke, *Top. Curr. Chem*. **1975**, *59*, 1; f) R. D. Rieke, *Acc. Chem. Res*. **1977**, *10*, 301; g) T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 3674; h) R. D. Rieke, *Aldrichim. Acta* **2000**, *33*, 52; i) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem*. **2000**, *65*, 5428; j) T.-A. Chen, X. Wu, R. D. Rieke, *J. Am. Chem. Soc.* **1995**, *117*, 233.
[177] A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824.

Furthermore, the arylmagnesium reagent **65** was added to furfural (0 °C, 30 min) leading to the polyfunctional alcohol **68a** in 71 % yield (Scheme 38). A Cu(I)-catalyzed acylation (CuCN·2LiCl (10 mol%), –40 to 25 °C, 30 min) of **65** with 2-thiophenecarbonyl chloride produced the ketone **68b** in 70% yield. The substituted arylzinc chloride **67** was functionalized via a Negishi cross-coupling[178] ($Pd(PPh_3)_4$ (2 mol%), 25 °C, 1 h) affording the expected biphenyl derivative **68b** in 87% yield (Scheme 38).



Scheme 38. Preparation of polyfunctional pivalates (**68a**–**c**) via the functionalized arylzinc halide **67** or arylmagnesium halide **65**.

We applied the direct Mg insertion in the presence of LiCl with and without *in situ* trapping with $ZnCl_2$ towards the preparation of functionalized organometallic reagents leading to polyfunctional aromatics.

[178] E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc*. **1980**, *102*, 3298; X. Zeng, M. Quian, Q. Hu, E. Negishi, *Angew. Chem., Int. Ed.* **2004**, *43*, 2259; G. Manolikakes, M. A. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765.

2.4 Cycloalkylzincs via LiCl-Mediated Direct Zinc Insertion and their Diastereoselective Csp^2-Csp^3 Cross-Couplings

Organozinc or magnesium reagents are an important class of organometallics. These reagents are frequently used in Pd-catalyzed cross-coupling reactions for preparing complex organic molecules,[179] including stereoselective C-C bond formations.[180,181] In their pioneering work, T. Hayashi and M. Kumada have shown that secondary alkylmagnesium and zinc reagents allow the preparation of chiral cross-coupling products.[181l-o] The Zn- or Mg-organometallics used in these reactions are configurationally labile and subject to rapid epimerization. Inspired by a recent report by Duthie *et al.* about diastereoselective reactions using menthylmagnesium halides,[182] we envisioned that their corresponding zinc derivatives might also undergo stereoselective C-C bond formations. Thus, P. Knochel and T. Thaler developed a highly diastereoselective Negishi cross-couplings,[183] as well as an unexpected generalization of this stereocontrol to various substituted cycloalkylzinc reagents. Initially, menthylzinc halides of type **69** were prepared either by treating menthylmagnesium chloride **70** with $ZnCl_2$ (1.1 equiv, THF, 25 °C, 10 min) or by the reaction of neomenthyl iodide **71**[184] with zinc dust and

[179] a) A. Rudolph, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, 2656; b) J. Terao, N. Kambe, *Acc. Chem. Res.* **2008**, *41*, 1545; c) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544; d) Corbet, G. Mignani *Chem. Rev.* **2006**, *106*, 2651; e) A.-M. Chacko, W. Qu, H. F. Kung, *J. Org. Chem.* **2008**, *73*, 4874; f) B. Ines, I. Moreno, R. SanMartin, E. Dominguez, *J. Org. Chem.* **2008**, *73*, 8448; g) C. Valente, S. Baglione, D. Candito, C. J. O'Brien, M. G. Organ, *Chem. Commun.* **2008**, 735; h) J. Liqun, Y. Zhao, H. Wang, A. Lei, *Synthesis* **2008**, 649; i) Y. Zhao, H. Wang, X. Hou, Y. Hu, A. Lei, H. Zhang, L. Zhu, *J. Am. Chem. Soc.* **2006**, *128*, 15048. j) N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. J. Organ, *Org. Lett.* **2005**, *7*, 3805; k) K. Menzel, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 3718; l) N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, A. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 314; m) Y. Hoshino, T. Ishiyama, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1988**, *29*, 3983; n) J. Uenishi, J.-M. Beau, R. W. Armstrong, Y. Kishi, *J. Am. Chem. Soc.* **1987**, *109*, 4756; o) N. Miyaura, T. Ishiyama, M. Ishikawa, A. Suzuki, *Tetrahedron Lett.* **1986**, *27*, 6369.

[180] a) C. Studte, B. Breit, *Angew. Chem. Int. Ed.* **2008**, *47*, 5451; b) N. Rodriguez, C. Ramirez de Arellano, G. Asensio, M. Medio-Simon, *Chem. Eur. J.* **2007**, *13*, 4223; c) N. Rodriguez, A. Cuenca, C. Ramirez De Arellano, M. Medio-Simon, D. Peine, G. Asensio, *J. Org. Chem.* **2004**, *69*, 8070; d) B. Hölzer, R. W. Hoffmann, *Chem. Commun.* **2003**, 732.

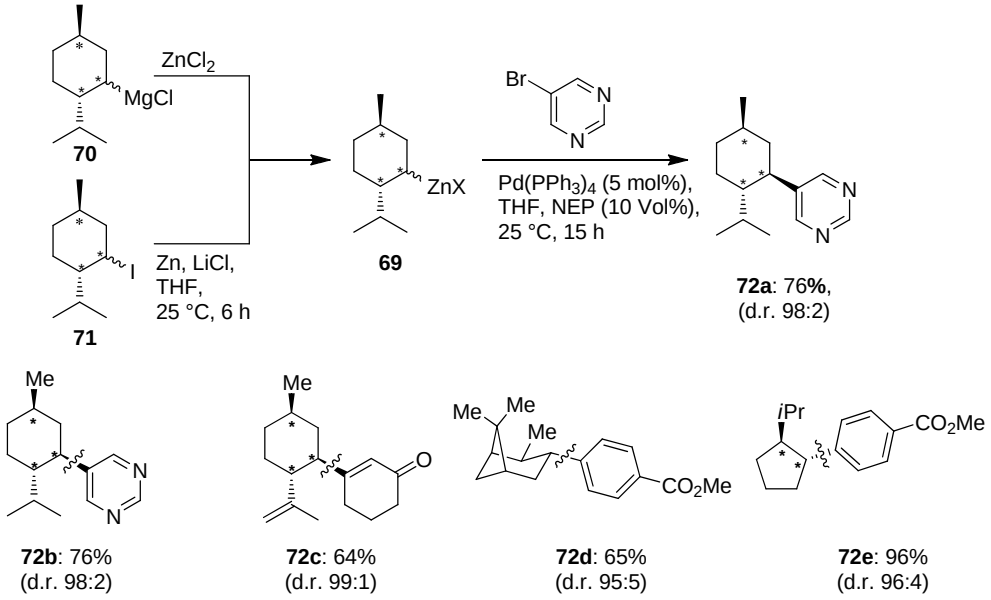
[181] a) F. Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 8347; b) T. Hayashi, *J. Organomet. Chem.* **2002**, *653*, 41; c) G. Cross, B. K., Vriesema, G. Boven, R. M. Kellogg, F. Van Bolhuis, *J. Organomet. Chem.* **1989**, *370*, 357; d) T. Hayashi, T. Hagihara, Y. Katsuro, M. Kumada, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 363; e) T. Hayashi, M. Konishi, H. Ito, M. Kumada, *J. Am. Chem. Soc.* **1982**, *104*, 4962; f) P. M. Lundin, J. Esquivias, G. C. Fu, *Angew. Chem. Int. Ed.* **2009**, *48*, 154; g) S. W. Smith, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 12645; h) S. Son, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 2756; i) J. Caeiro, J. Perez Sestolo, L. A. Sarandeses, *Chem. Eur. J.* **2008**, *14*, 741; j) C. Fischer, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 4594; k) K.-G. Chung, Y. Miyake, S. Uemura, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2725; p) K.-G. Chung, Y. Miyake, S. Uemura, *J. Chem. Soc., Perkin Trans. 1* **2000**, 15; l) T. Hayashi, M. Konishi, M. Fukushima, K. Kanehira, T. Hioki, M. Kumada, *J. Org. Chem.* **1983**, *48*, 2195; m) T. Hayashi, M. Konishi, T. Hioki, M. Kumada, A. Ratajczak, H. Niedbala, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3615; n) T. Hayashi, K. Kanehira, T. Hioki, M. Kumada, *Tetrahedron Lett.* **1981**, *22*, 137; o) T. Hayashi, M. Tajika, K. Tamao, M. Kumada, *J. Am. Chem. Soc.* **1976**, *98*, 3718.

[182] J. Beckmann, D. Dakternieks, M. Dräger, A. Duthie, *Angew. Chem. Int. Ed.* **2006**, *45*, 6509.

[183] a) E.-I. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; b) E.-I. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.

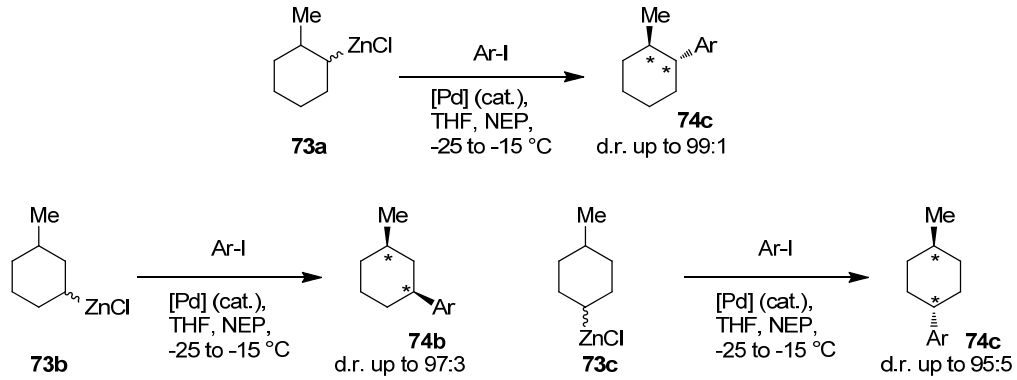
[184] R. Joseph, P. S. Pallan, A. Sudalai, T. Ravindranathan, *Tetrahedron Lett.* **1995**, *36*, 609.

LiCl[185] (THF, 25 °C, 6 h, 78%; Scheme 39). The resulting menthylzinc reagents of type **69** were then subjected to Pd-catalyzed cross-couplings with aryl halides at room temperature. Much to our delight, the *trans*-cross-coupling products were obtained with high diastereomeric purities (d.r. 96:4 to ≥99:1) and 63–81% yields (Scheme 39).[186] Furthermore, various cycloalkylzinc halides also furnished cross-coupling products of type **72** with equally high diastereoselectivities (Scheme 39).[187]



Scheme 39. Preparation and cross-coupling reaction of substituted cyclohexylzinc halides.

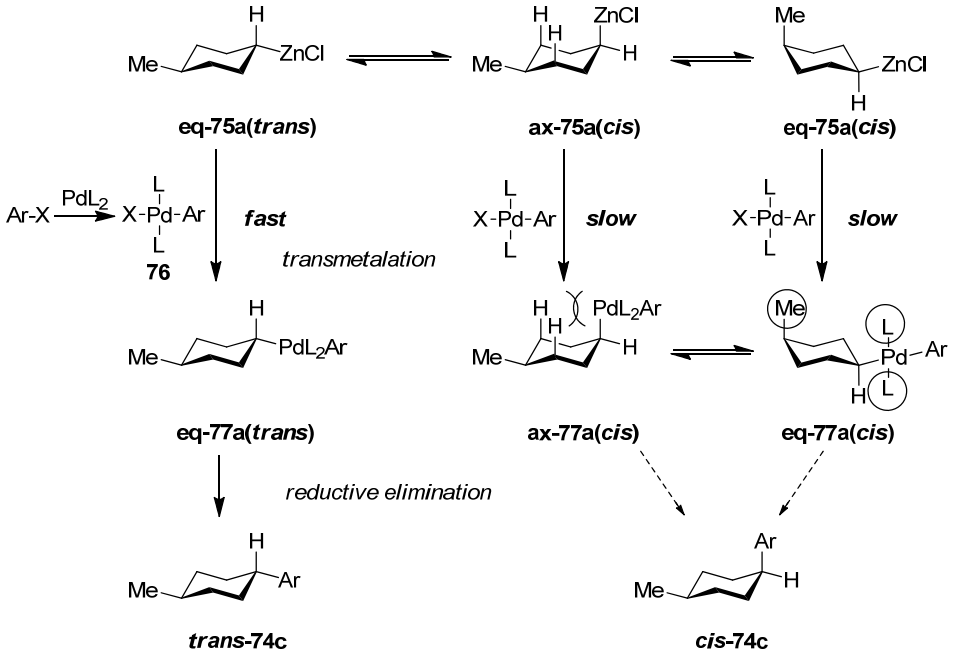
Moreover, similar stereoselectivities were observed with cyclohexylzinc reagents **73a–c** bearing substituents at position 2, 3 and even at position 4 such as **73c** (Scheme 40). In particular, with 4-substituted cyclohexylzinc reagents, a large steric effect was not expected due to the remoteness of the substituents. However, the cross-coupling products of type **74c** were obtained with a high diastereomeric ratio (up to 95:5) (Scheme 40).



Scheme 40. Cross-coupling products obtained with 2-, 3- and 4-substituted cyclohexylzinc reagents.

[185] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.
[186] These examples were prepared by T. Thaler and A. Grayvushin and have been included for the sake of completeness. For experimental details, please see: T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. Gschwind, H. Zipse, P. Knochel, *Nature Chem*. **2010**, *2*, 125.

Remarkably, these diastereoselective Negishi cross-coupling reactions could be extended to various cyclic systems, including cyclopentanes, bicyclic compounds and steroids.[187] Furthermore, the experimental results indicate that the diastereoselectivities were not affected by the sterics or the nature of the ring substituents. In order to explain the origin of the observed diastereoselectivities, we focused our investigations on quantum chemical calculations. Thus, we propose a tentative mechanism in which the conformers and both diastereoisomers of the cyclohexylzinc complex (**eq-75a(*trans*)**, **ax-75a(*cis*)** and **eq-75a(*cis*)**) are in equilibrium (Scheme 41).[188]



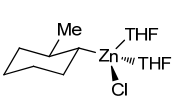
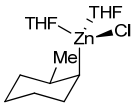
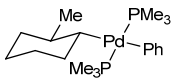
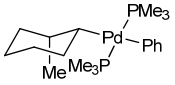
Scheme 41. Mechanistic proposal for the diastereoselective cross-coupling of substituted cycloalkylzinc reagents with aryl iodides.

Although the carbon-zinc bond is reported to be configurationally stable,[189] it was shown that the presence of metallic salts facilitates its epimerization[190] and the presence of PdX_2, MgX_2, ZnX_2 or LiCl in the reaction mixture may be responsible for this fast equilibration. The transmetalation of the zinc reagent **eq-75a(*trans*)** with $ArPdL_2X$ (**76**), obtained by Pd(0)-insertion into an aryl halide (Ar-X), preferentially led to the palladium intermediate **eq-77a(*trans*)** provided that the transmetallation occurred with retention of the

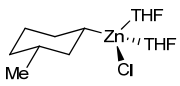
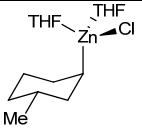
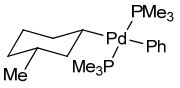
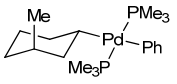
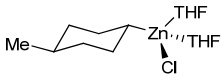
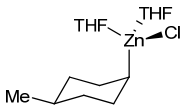
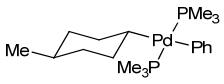
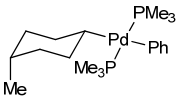
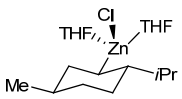
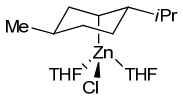
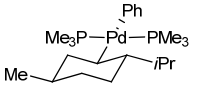
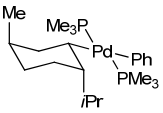
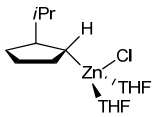
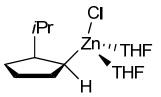
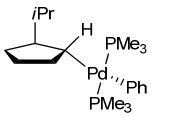
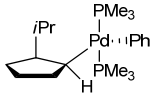
[187] T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. Gschwind, H. Zipse, P. Knochel, *Nature Chem*. **2010**, *2*, 125.
[188] The ax/eq notation describes the position of the metal substituent and the cis/trans notation describes the relative stereochemistry of the metal and the methyl substituents on the cyclohexyl ring.
[189] a) A. Guijarro, R. D. Rieke, *Angew. Chem. Int. Ed.* **2000**, *39*, 1475; b) L. Micouin, M. Oestreich, P. Knochel, *Angew. Chem. Int. Ed.* **1997**, *36*, 245.
[190] A. Boudier, C. Darcel, F. Flachsmann, L. Micouin, M. Oestreich, P. Knochel, *Chem. Eur. J.* **2000**, *6*, 2748.

configuration[191]. The alternative formation of the palladium intermediates **ax-77a(*cis*)** and **eq-77a(*cis*)** is disfavoured for steric reasons. In both of these conformers, either the palladium moiety or the methyl group occupies the axial position. This results in repulsive interactions with the bulky phosphine ligands on the palladium, as shown by density functional theory (DFT) calculations[192] (see below). After reductive elimination, the *trans*-product ***trans*-74c** was obtained selectively from **eq-74c(*trans*)** (Scheme 41). In order to gain insight into the energetic differences between the palladium intermediates of type **74c** and to verify our mechanistic proposal, we used DFT-methods to carry out a conformational analysis on the respective organozinc and organopalladium complexes. Comparison of the energetically lowest conformers showed that only small and insignificant thermodynamic differences exist between the diastereomeric cycloalkylzinc complexes (less than 0.77 kcal mol^{-1} in free energy for zinc complexes **75a–e**; Table 7). However, the corresponding organopalladium complexes (**77a**–**e**) show a significant change in thermodynamic energies that favour the diastereoisomers with all substituents in equatorial positions. The calculations demonstrate that considerable repulsive interactions between the substituents on the cycloalkyl moiety and the phosphine ligands on palladium increase the energy gap between the diastereomeric complexes up to 9.84 kcal·mol^{-1} in free energy (Table 7). This energy increase becomes experimentally significant and accounts for the diastereoselective control observed in the cross-coupling reactions.

Table 7. Conformational analysis of the diastereomeric zinc and palladium complexes based on DFT calculations.

Entry	Organozinc complexes		Organopalladium complexes	
	$\Delta G_{298,(eq\text{-}ax)}$, $\Delta E_{0,(eq\text{-}ax)}$ [kcal·mol^{-1}][a]		$\Delta G_{298,(eq\text{-}ax)}$, $\Delta E_{0,(eq\text{-}ax)}$ [kcal·mol^{-1}][a]	
				
	eq-75b	**ax-75b**	**eq-77b**	**ax-77b**
1	–0.55, –1.29		–4.85, –5.02	

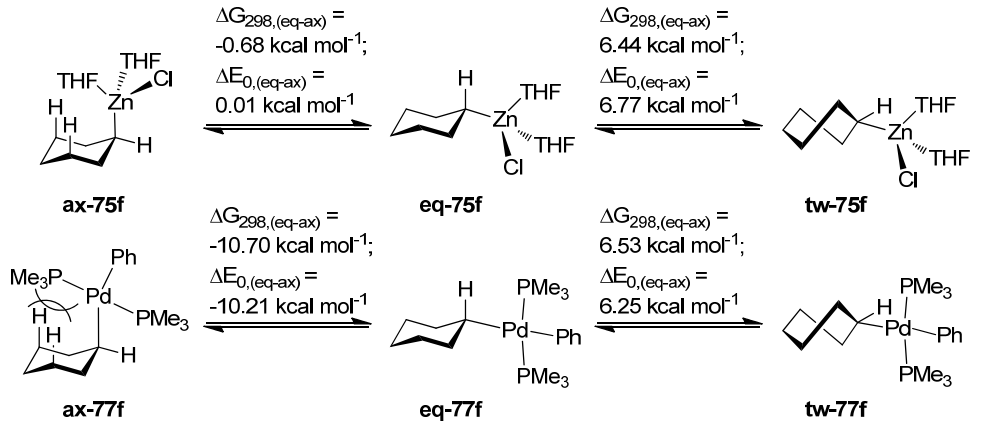
[191] K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer, C.-y. Chen, *J. Am. Chem. Soc.* **2006**, *128*, 3538.
[192] DFT calculations were carried out using the Gaussian03 Rev.B.04 program package with the non-local hybrid B3LYP exchange-correlation functionals. The basis set, denoted as 631SVP, consists of the Ahlrich def2-SVP all-electron basis set for zinc atoms, all-electron and ECP for palladium atoms and the 6-31G(d,p) basis set for other atoms. Please, see Experimental Section 4.3 for full details of the computational study.

Entry	Organozinc complexes		Organopalladium complexes	
	$\Delta G_{298,(eq\text{-}ax)}$, $\Delta E_{0,(eq\text{-}ax)}$ [kcal·mol^{-1}][a]		$\Delta G_{298,(eq\text{-}ax)}$, $\Delta E_{0,(eq\text{-}ax)}$ [kcal·mol^{-1}][a]	
				
	eq-75c	**ax-75c**	**eq-77c**	**ax-77c**
2	–0.68, 0.10		–2.88, –2.59	
				
	eq-75a	**ax-75a**	**eq-77a**	**ax-77a**
3	–0.51, –0.04		–2.08, –2.37	
				
	eq-75d	**ax-75d**	**eq-77d**	**ax-77d**
4	–0.77, –0.36		–9.84, –10.08	
				
	***trans*-75e**	***cis*-75e**	***trans*-77e**	***cis*-77e**
5	–0.43, 0.10		–5.54, –5.03	

[a] Calculated energetic difference (B3LYP/631SVP// B3LYP/631SVP) between the thermodynamically lowest conformers of the two diastereoisomers.

Furthermore, DFT calculations[192] on the cyclohexylmetal complexes of type **75f** and **77f** revealed remarkable differences in energy between the equatorial (*eq*) and axial (*ax*) position of the metal center, as well as the twisted (*tw*) conformation of the cyclohexyl ring (Scheme 42). The cyclohexylzinc chloride complexes thermodynamically favor the equatorial position **eq-75f** only to a small extent ($\Delta G_{298,(eq\text{-}ax)}$ = –0.68 kcal·mol^{-1}). In comparison, the twisted conformation of the cyclohexyl moiety in the zinc reagent **tw-75f** is highly disfavoured ($\Delta G_{298,(eq\text{-}ax)}$ = 6.44 kcal·mol^{-1}). In contrast, the Pd-complex **eq-77f** bearing the metal center in equatorial position is energetically favored ($\Delta G_{298,(eq\text{-}ax)}$ = –10.70 kcal·mol^{-1}), compared to complex **ax-77f** with the Pd in axial position. In addition, the Pd-complex **tw-**

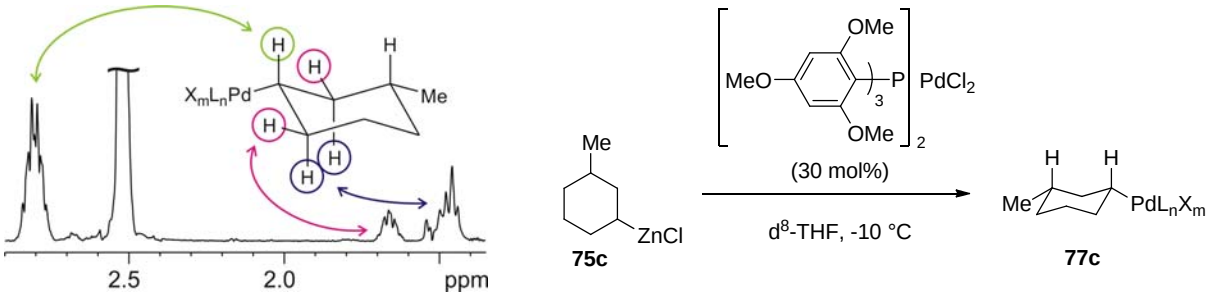
77f, bearing the twisted conformation of cyclohexyl moiety, is thermodynamically higher in energy ($\Delta G_{298,(eq\text{-}ax)}$ = 6.53 kcal·mol^{-1}; Scheme 42).



Scheme 42. Conformational analysis of the cyclohexylzinc and palladium complexes based on DFT calculations (given energies refer to relative Gibbs free energies at 298 K and to relative zero-point corrected electronic energies).

Based on this conformational analysis using DFT-calculations (B3LYP/631SVP //B3LYP/631SVP), we could identify the significant diasteromeric conformations of the cyclohexylzinc and palladium complexes. Furthermore, we could exclude the twisted conformation of cyclohexyl for both organometallic species using this analysis.

In order to substantiate the results from the theoretical calculations suggesting that the diastereoselectivity originates from a fast transmetalation of the cycloalkylzinc reagent to the palladium complex, Gschwind *et al.* carried out NMR studies on the reaction of 3-methylcyclohexylzinc chloride (**75c**) with $(TMPP)_2PdCl_2$ in d8-THF (0.3 M) at −10 °C (Figure 2). Many signals of several zinc species (**75c** and aggregates) and palladium complexes were detected in the NMR spectra. However, using ^{1}H–^{31}P heteronuclear multiple bond correlation (HMBC) analysis, only one ^{31}P chemical shift simultaneously displayed cross-signals with the cyclohexyl and aromatic ^{1}H-signals. This shows that only one palladium intermediate was present in a detectable amount. Spin-spin coupling between the proton signals in the cyclohexyl ring identified the intermediate as a structure of type **77c** (Figure 2), in which the palladium occupies the equatorial position ($^{3}J_{HH}$-coupling was detected at 11 Hz, which corresponds to a coupling of axial protons). These results confirm the conformational preferences suggested in the tentative mechanism in Scheme 41.



a) cross-section of the ^{1}H–^{31}P-HMBC spectrum b) transmetalation step

Figure 2. NMR studies on the transmetallation of 3-methylcyclohexylzinc chloride (**75c**) to $(TTMPP)_2PdCl_2$.

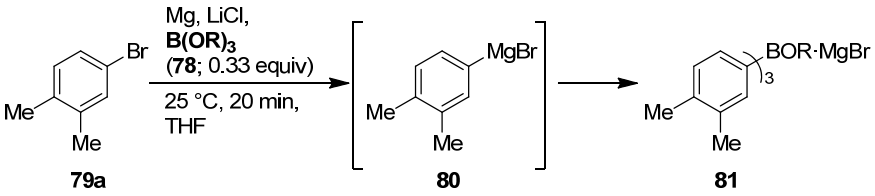
In summary, we have shown that Csp^3-Csp^2 cross-coupling reactions of variously substituted six- and five-membered cycloalkylzinc reagents proceed with high diastereoselectivities. This was best rationalized by assuming an equilibration of the zinc reagents and the preferential formation of the most stable **eq**-Pd-intermediate. This mechanistic picture is strongly supported by intensive investigations using DFT-calculations and NMR experiments.

2.5 One-Step Synthesis of Functionalized Organoborates via Accelerated Direct Metal Insertion in the Presence of $B(OBu)_3$

Organometallic reagents are of increasing importance in organic chemistry, especially as key intermediates for the synthesis of biologically active compounds as well as natural products.[193] In particular, transition metal catalyzed cross-couplings using organometallic intermediates have become widely used synthetic tools. [194,195] Negishi-,[196] Stille-,[197] Heck-,[198] and Suzuki-Miyaura-types[199,194b] of reaction allow the concise construction of polyfunctional aromatics and heteroaromatics. The latter has especially proven to be outstandingly practical and has been extensively used in straightforward C-C bond formations.[200,201] Moreover, the applied organoboron compounds, such as boronic acids, boronic esters as well as organotrifluoroborates generally display great tolerance toward functional groups and possess reasonable thermal stability.[200] However, the known methods for preparation of these reagents suffer from major drawbacks,[200] such as multi-step syntheses, low atom-economy, expensive transition-metal catalysis or low tolerance towards functional groups.[202,203] Sparked by

[193] a) I. Omae, in *Applications of Organometallic Compounds*, John Wiley and Sons: Chichester, **1998**; b) P. Knochel, in *Handbook of Functionalized Organometallics*, Wiley-VCH: Weinheim, **2005**.
[194] For reviews on Miyaura-Suzuki cross-coupling reactions, see: a) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; c) G. A. Molander, B. Canturk, *Angew. Chem. Int. Ed.* **2009**, *48*, 9240; d) A. Suzuki, *Heterocycles* **2010**, *80*, 15; e) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.
[195] a) K. L. Billingsley, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2008**, *47*, 4695; b) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302; c) J. Monot, M. Makhlouf Brahmi, S.-H. Ueng, C. Robert, M. Desage-El Murr, D. P. Curran, M. Malacria, L. Fensterbank, E. Lacôte, *Org. Lett.* **2009**, *11*, 4914; d) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716; e) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc*. **2009**, 131, 6961; f) Y. Yamamoto, M. Takizawa, X.-Q. Yu, N. Miyaura, *Angew. Chem. Int. Ed.* **2008**, *47*, 928; g) S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2008**, *47*, 1473; h) Z. Lu, G. Fu, *Angew. Chem. Int. Ed.* **2010**, *49*, 6676; i) M. Butters, J. N. Harves, J. Jover, A. J. J. Lennox, G. C. Lloyd-Jones, P. M. Murray, *Angew. Chem. Int. Ed.* **2010**, *49*, 5156; j) C. S. Cho, *Cat. Commun.* **2008**, *9*, 2261.
[196] E.-I. Negishi, F. Liu, in *Metal-Catalyzed Cross-Coupling Reactions*, (F. Diederich, P. J. Stang, eds.), Wiley–VCH, Weinheim, Germany, **1998**, pp 1.
[197] a) J. K. Stille, *Angew. Chem. Int. Ed.* **1986**, *25*, 508; b) T. N. Mitchell, *Synthesis* **1992**, 803.
[198] F. Diederich, P. J. Stang, in *Metal-catalyzed Cross-coupling Reactions*, Wiley-VCH, Weinheim, **1998**.
[199] A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147.
[200] Reviews on the preparation of organoboron compounds, see: a) A. Pelter, K. Smith, H. C. Brown, in *Borane Reagents*, Academic Press: London, **1988**; b) D. S. Matteson, in *Reactivity and Structure Concept in Organic Synthesis: Stereodirected Synthesis with Organoboranes*, Springer: New York, **1994**; Vol. 32; c) M. Vaultier, B. Carboni, in *Comprehensive Organometallic Chemistry*, G. Wilkinson, F. G. Stone, E. W. Abel, Eds., Pergamon: New York, **1995**; Vol. 11, p 191; d) K. Smith, A. Pelter, in *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming Eds., Pergamon: New York, **1991**; Vol. 8, p 703; e) M. Zaidlewicz, M. Krzeminski, *Science of Synthesis*, **2004**, *6*, 1097; f) M. M. Midland, *Chem. Rev.* **1989**, *89*, 1553; g) C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415; h) V. Darmency, P. Renaud, *Top. Curr. Chem.* **2006**, *263*, 71.
[201] For reviews on organotrifluoroborates, see: a) A. Darses, J.-P. Genet, *Chem. Rev.* **2008**, *108*, 288; b) G. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275.
[202] K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, 103, 169.
[203] P. Merino, T. Tejero, *Angew. Chem. Int. Ed.* **2010**, *49*, 7164.

Brown's report,[204] we envisioned a direct, facile, atom-economic and inexpensive route to polyfunctional and heterocyclic organoborates via direct metal insertion compensating the drawbacks mentioned above. In contrast to Brown's method,[204] we investigated a milder and more convenient method for the preparation of organoborates via direct magnesium insertion and *in situ* trapping with trialkylborates of type **78** displaying low Lewis acidity. Based on a recent publication by Knochel *et al.*, we also utilized the accelerating effect of LiCl-additive in direct metal insertions allowing the presence of a broad range of sensitive functional groups in the organometallic reagent.[205,206,207] Initially, we explored various borate sources for the *in situ* trapping of the generated organomagnesium intermediate. Thus, the reaction of an aryl bromide such as 4-bromoxylene (**79a**) with magnesium turnings (1.6 equiv) in the presence of LiCl (1.1 equiv) and a borate of type **78** (0.33 equiv) produces (25 °C, 20 min) tentatively the intermediate arylmagnesium bromide **80**. This intermediate is immediately trapped by **78** generating an aryl borate of type **81** (Scheme 43).



Scheme 43. Preparation of aryl borate of type **81** via direct magnesium insertion in the presence of a boron source and LiCl.

Remarkably, the comparison of the conversion of the aryl bromide to the magnesium reagent in the presence and the absence of boron source clearly indicates slower rate of reaction in the latter case (Table 8, entry 1). Interestingly, various boron compounds of type **78**, such as $B(OMe)_3$ (**78a**), $B(OEt)_3$ (**78b**), $B(O\textit{i}Pr)_3$ (**78c**), $B(OBu)_3$ (**78d**), $B(OAc)_3$ (**78e**), and even $NaB(OMe)_4$ (**78f**) or $LiB(OMe)_4$ (**78g**), are feasible for *in situ* trapping of the magnesium reagent forming the trisarylborate **2b** (Table 8, entries 2–8). However, the highest rates of reaction were observed with $B(OBu)_3$. In conclusion, the insertion was accelerated, not only by the presence of LiCl, but also by the borate additive. For a general applicability, a fast substitution on the boron center, along with non-activating properties of sensitive functional groups induced by high Lewis acidity, is essential to avoid the formation of side products.

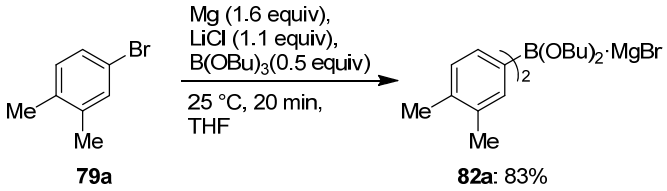
[204] a) H. C. Brown, U. S. Racherla, *Organometallics* **1986**, *5*, 391-393; b) H. C. Brown, U. S. Racherla, *J. Org. Chem.* **1986**, 51, 427.
[205] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; c) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett*. **2008**, *10*, 1107.
[206] 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*, 7648.
[207] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

Table 8. Preparation of organoborates of type **2b** using various borate sources after 20 min at 25 °C.

entry	borate	yield[a] of $Ar_3BOR{\cdot}MgBr$	yield[a] of Ar-MgBr[a]
1	-	-	54%
2	$B(OMe)_3$	33%	60%
3	$B(OEt)_3$	49%	39%
4	$B(OiPr)_3$	51%	41%
5	$B(OBu)_3$	64%	20%
6	$B(OAc)_3$	43%	27%
7	$NaB(OMe)_4$	28%	34%
8	$LiB(OMe)_4$	41%	42%

[a] Determined by GC-analysis of an iodolyzed reaction aliquot.

Furthermore, an optimum ratio of $B(OBu)_3$ to aryl bromide of 2:1 ($ArBr:B(OBu)_3$) was found that allows sufficiently fast reaction times, while using only minimal amount of $B(OBu)_3$. Thus, 4-bromoxylene (**79a**) reacted with Mg (1.6 equiv; 25 °C, 20 min) in the presence of LiCl (1.1 equiv) and $B(OBu)_3$ (0.5 equiv) producing the aryl borate **82a** in 83% yield (Scheme 44).

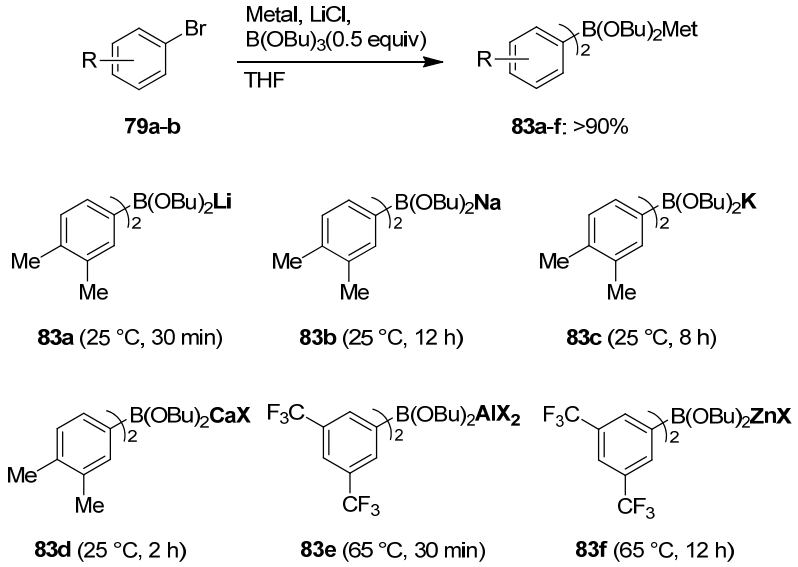


79a **82a**: 83%

Scheme 44. Preparation of the aryl borate **82a** using 0.5 equivalent of $B(OBu)_3$.

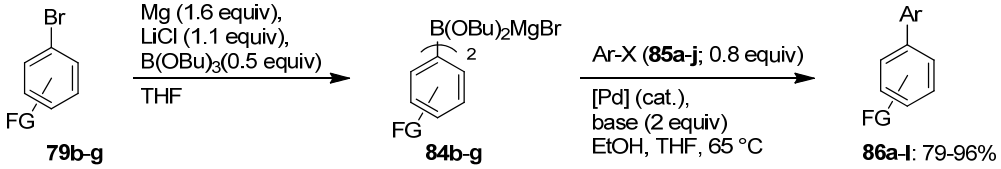
Besides elemental magnesium, other metal sources are also feasible for the preparation of arylborates of type **83** using unactivated aryl bromides. Thus, oxidizable metals, such as Li, Na, or K, readily react with 4-bromoxylene (**79a**; 25 °C, 0.5–12 h) in the presence of LiCl (1.1 equiv) and $B(OBu)_3$ (0.5 equiv) generating the expected aryl borates **83a**–**c** in more than 90% yield (Scheme 45). Interestingly, using the same conditions with 4-bromoxylene (**79a**; 25 °C, 2 h), calcium turnings also furnished the desired organoborate **83b** (Scheme 45). Due to a thick impenetrable oxide surface, calcium turnings generally are inert in direct metal insertion reactions with aryl halides.[208] Remarkably, due to the accelerating effect of $B(OBu)_3$, activated aryl bromides such as 1-bromo-bis(trifluoromethyl)-benzene (**79b**) also react with rather unreactive, but inexpensive, metal sources, such as Al or Zn, leading to the corresponding arylborates **83e**–**f** (Scheme 45).

[208] S. Krieck, H. Görls, L. Yu, M. Reiher, M. Westerhausen, *J. Am. Chem. Soc.* **2009**, *131*, 2977.



Scheme 45. Preparation of organoborates of type **5** using various metal sources.

In contrast to Negishi-[196] and Kumada-Corriu-type[209] cross-couplings, the organometallic boron intermediates are readily isolated as well as stored displaying thermal stability also in protic or aqueous media. Hence, we investigated its use and reactivity especially in Suzuki-type cross-coupling reactions. We could show that a broad range of polyfunctional aromatics and heteroaromatics bearing sensitive or relatively acidic functional groups could be prepared without protective groups. Thus, the functionalized aryl bromides **79a**–**e** were readily reacted with Mg-turnings (1.6 equiv) in the presence of $B(OBu)_3$ (0.5 equiv) and LiCl (1.1 equiv) providing the corresponding arylborates **84b**–**g** in ca. 90% yield (Scheme 46). Subsequent Suzuki-type cross-couplings with aryl halides, like chlorides, bromides and iodides, furnished the polyfunctional aromatics **86a**–**l** in 79–96% yield (Scheme 46).



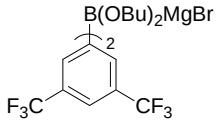
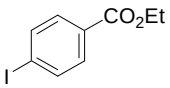
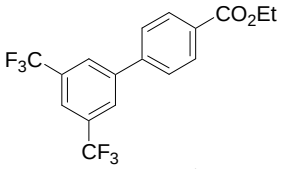
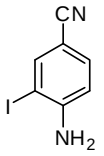
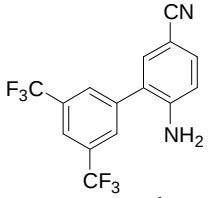
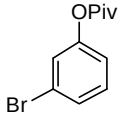
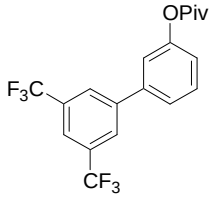
Scheme 46. Preparation of organoborates of type **84** followed by Suzuki-type cross-coupling reactions with aryl halides (FG = functional group).

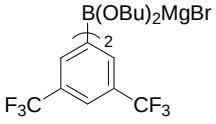
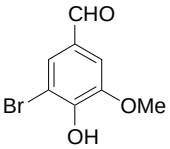
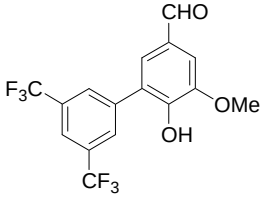
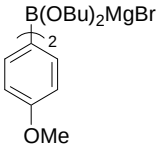
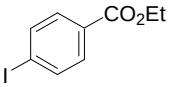
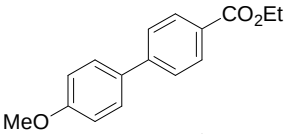
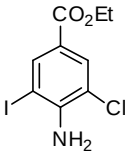
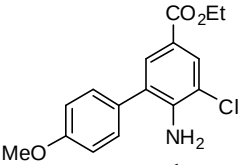
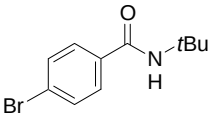
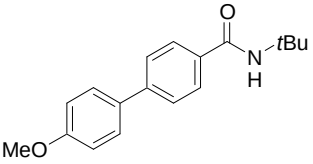
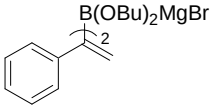
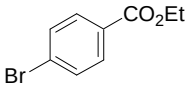
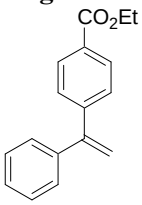
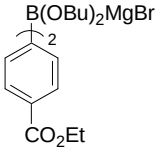
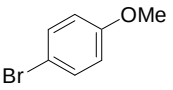
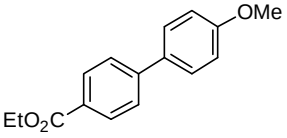
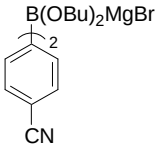
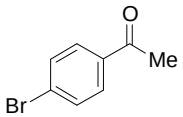
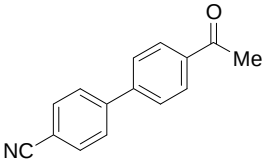
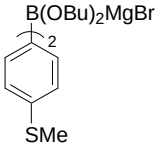
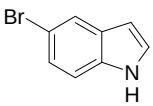
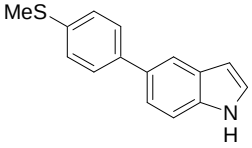
In particular, 1-bromo-bis(trifluoromethyl)-benzene (**79b**) was efficiently converted into the diarylborate **84b** via the direct magnesium insertion (Mg (1.6 equiv), LiCl (1.1 equiv)) in the presence of trisbutylborate ($B(OBu)_3$ (0.5 equiv), 25 °C, 15 min). Subsequent Suzuki cross-coupling[201b] with the aryl bromides or iodides **85a**–**c** furnished the substituted biphenyls **86a**–**c** in 79–91% yield (Table 9, entries 1–3). Additionally, a Suzuki-type cross-coupling of

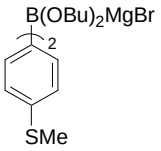
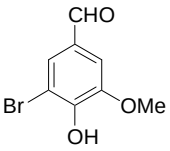
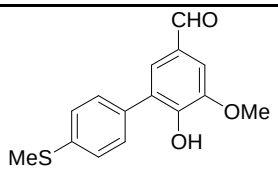
[209] a) R. J. P. Corriu, J. P. Masse, *J. Chem. Soc. Chem. Commun.* **1972**, 144; b) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374.

84b with 5-bromovanillin (**85d**) bearing an aldehyde- and a hydroxy-function produced successfully the substituted vanillin **86d** in 83% yield (Table 9, entry 4). Furthermore, using the same conditions, the dianisylborate **84c** prepared from 4-bromoanisole (**79c**) readily furnished after the Pd-catalyzed cross-coupling the amino-, amido-, or ester-substituted biphenyls **86e**–**g** in 79–96% yield (Table 9, entries 5–7). Similarly, direct insertion of *alpha*-bromostyrene (**79d**; 0 °C, 30 min) using Mg turnings (1.6 equiv) in the presence of LiCl (1.1 equiv) and $B(OBu)_3$ (0.5 equiv) efficiently generated the distyrylborate **84d** leading after Suzuki cross-coupling with ethyl 4-bromobenzoate (**85g**) to the ester-substituted 1,2-diphenylethylene 8**6h** in 95% yield (Table 9, entry 8). Additionally, functionalized diarylborates such as **84e** and **84f** prepared from the corresponding aryl bromides **79e** and **79f** furnished after Pd-catalyzed cross-coupling with **85h** or **85i** functionalized biphenyls **86i** or **86j** in 82–83% yield (Table 9, entries 9 and 10). Similarly, the diarylborate **84g** afforded after Suzuki cross-coupling reactions with 5-bromoindole (**85j**) or 5-bromovanillin (**85d**) the substituted indole **86k** in 92% yield or the polyfunctional vanillin derivative **86l** in 87% yield (Table 9, entries 11 and 12).

Table 9. Preparation of functionalized aromatics of type **86** via direct magnesium insertion in the presence of LiCl and $B(OBu)_3$ with aryl bromides of type **79** followed by Suzuki-type cross-coupling.

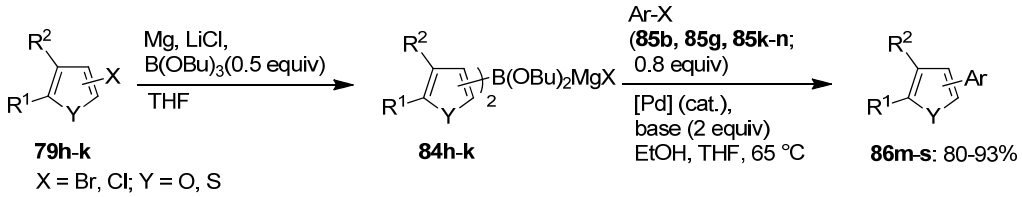
Entry	$Ar_2B(OBu)_2MgBr$ (conditions [T, t])	Electrophile	Product, Yield[a]
1	 **84b** (25 °C, 15 min)	 **85a**	 **86a**: 91%[b]
2	**84b**	 **85b**	 **86b**: 87%[b]
3	**84b**	 **85c**	 **86c**: 79%[c]

Entry	$Ar_2B(OBu)_2MgBr$ (conditions [T, t])	Electrophile	Product, Yield[a]
4	 **84b**	 **85d**	 **86d**: 83%[c]
5	 **84c** (25 °C, 1 h)	 **85a**	 **86e**: 96%[d]
6	 **84c**	**85e**	 **86f**: 93%[d]
7	 **84c**	**85f**	 **86g**: 79%[e]
8	 **84d** (0 °C, 30 min)	 **85g**	 **86h**: 95%[e]
9	 **84e** (25 °C, 1 h)	 **85h**	 **86i**: 83%[c]
10	 **84f** (25 °C, 1 h)	 **85i**	 **86j**: 82%[c]
11	 **84g** (25 °C, 1 h)	 **85j**	 **86k**: 92%[e]

Entry	$Ar_2B(OBu)_2MgBr$ (conditions [T, t])	Electrophile	Product, Yield[a]
12	 **5g**	 **85d**	 **86l**: 87%[e]

[a] Yield of isolated, analytically pure product as determined by 1H NMR. [b] Obtained after Pd-catalyzed cross-coupling ($Pd(PPh_3)_4$ (4 mol%), Cs_2CO_3 (1 equiv), THF/EtOH (1:1), 65 °C, 2 h). [c] Obtained after Pd-catalyzed cross-coupling ($PdCl_2$(dppf) (4 mol%), Cs_2CO_3 (2 equiv), THF/EtOH (1:1), DMF, 65 °C, 12 h). [d] Obtained after Pd-catalyzed cross-coupling ($PdCl_2$ (4 mol%), K_3PO_4 (2 equiv), THF/EtOH (1:1), 65 °C, 2 h). [e] Obtained after Pd-catalyzed cross-coupling ($PdCl_2$(dppf) (4 mol%), Cs_2CO_3 (2 equiv), THF/EtOH (1:1), 65 °C, 6 h). dppf = 1,1´-bis(diphenylphosphino)ferrocene.

Remarkably, functionalized heteroaryl bromides as well as chlorides (**79h-k**) or benzyl chlorides (**79l** and **79m**) readily afford the corresponding diheteroaryl- or dibenzylborates using the direct Mg-insertion in the presence of $B(OBu)_3$ and LiCl. Subsequent cross-coupling reactions with substituted aryl halides (chlorides, bromides, iodides; **85b**, **85g**, **85k**–**n**) furnished the expected polyfunctional aromatics and heteroaromatics **86m-s** in 80–93% yield (Scheme 47).

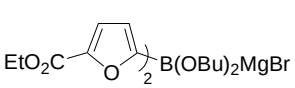
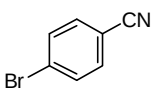
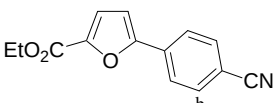


Scheme 47. Preparation of heterocyclic organoborates of type **84** followed by Suzuki-type cross-coupling reactions with aryl halides (FG = functional group).

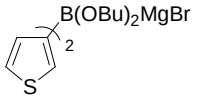
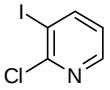
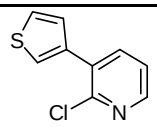
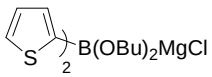
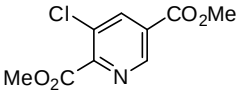
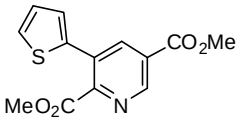
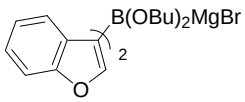
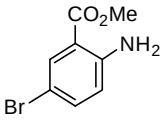
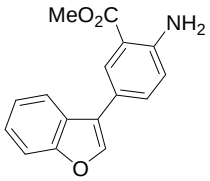
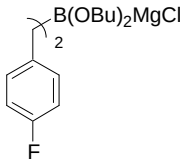
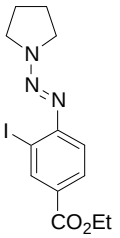
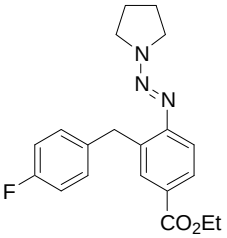
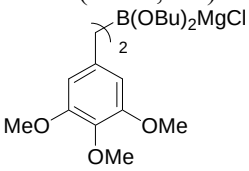
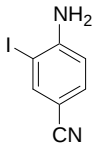
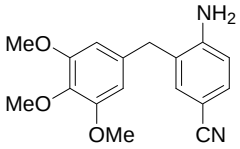
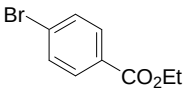
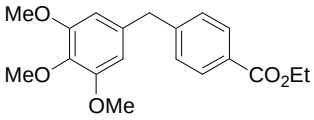
Thus, treatment of ethyl 5-bromofuroate (**79h**) furnished the functionalized difurylborate **84h** (25 °C, 1 h) leading after a Pd-catalyzed cross-coupling with 4-bromobenzonitrile (**85k**) to the disubstituted furan **86m** in 80% yield (Table 10, entry 1). Furthermore, 3-bromothiophene (**79i**) or 2-chlorothiophene (**79j**) provided after borylation (Mg (1.6 equiv), LiCl (1.1 equiv), $B(OBu)_3$ (0.5 equiv), 25 °C, 30 min) the corresponding thiophenylborates **84i** and **84j**. Suzuki-type cross-couplings of **84i–j** with substituted 3-iodo- or 3-chloropyridines (**85l**–**m**) the functionalized pyridines **86n–o** in 86–93% yield (Table 10, entries 2 and 3). Similarly, 3-bromobenzo[*b*]furan (**79k**) reacted with Mg/LiCl/$B(OBu)_3$ (1.6 equiv/ 1.1 equiv/ 0.5 equiv) via direct Mg-insertion (25 °C, 30 min) producing the corresponding heteroarylborate **84k**. Subsequent Pd-catalyzed cross-coupling reaction with methyl 4-bromoanthranilate (**85n**)

afforded functionalized benzofuran **86p** in 84% yield (Table 10, entry 4). In contrast, the direct magnesium insertion into benzylic carbon-halogen bonds predominantly generates dimers, via the Wurtz-Fittig pathway.[210] The outstandingly high reactivity of such benzylmagnesium intermediates serves as explanation. However, the direct magnesium insertion in the presence of borate resolves this synthetic problem. Moreover, in comparison to the alternative direct zinc insertion with benzyl chlorides, higher rates of reaction could be observed with magnesium, taking advantage of the greater oxidation potential. For instance, the direct Mg-insertion (1.6 equiv, LiCl (1.1 equiv), 25 °C, 1 h) in the presence of $B(OBu)_3$ (0.5 equiv) with 4-fluorobenzyl chloride (**79l**) leading to the benzylborate **84l** is approximately 12 times faster than the direct zinc insertion[207,211] in the absence of borate (25 °C, 12 h). Furthermore, the generated benzylborate by *in situ* trapping is water-stable. From a practical point of view, subsequent cross-coupling reactions are more convenient. Remarkably, using the *in situ* generation of benzylborates, such as **84l**, only negligible amounts of dimeric homocoupling product were observed. Thus, the 4-fluorobenzylborate derivative **84l** provided after Pd-catalyzed cross-coupling the expected functionalized arene **86q** in 88% yield (Table 10, entry 5). Similarly, 3,4,5-trimethoxybenzyl chloride **79m** also reacted smoothly with Mg/LiCl/$B(OBu)_3$ (1.6 equiv/ 1.1 equiv/ 0.5 equiv) via direct Mg-insertion (25 °C, 1 h) affording the methoxy-substituted benzylborate **84m**. Subsequent Suzuki cross-coupling with aryl halides, such as the iodoaniline **85b** and ethyl 4-bromobenzoate (**85g**), led to the corresponding aniline derivative **86r** and the substituted benzoate **86s** in 84–89% yield (Table 10, entry 6 and 7).

Table 10. Preparation of polyfunctional heteroaryl- or benzylborate derivatives of type **84** via direct magnesium insertion in the presence of LiCl and $B(OBu)_3$ from the corresponding heteroaryl bromides or chlorides as well as benzyl chlorides and subsequent Suzuki-type cross-coupling with organic halides of type **85**.

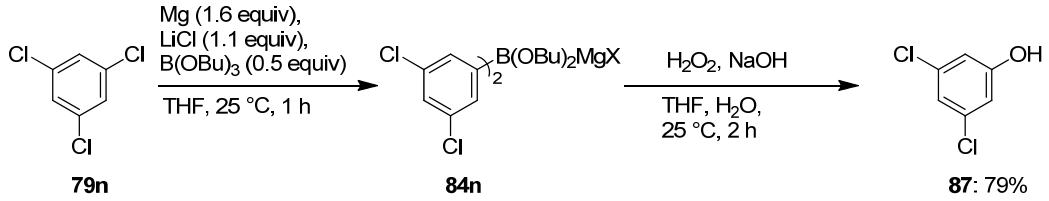
Entry	$R_2B(OBu)_2MgBr$ (conditions [T, t])	Electrophile	Product, Yield[a]
1	 **84h** (25 °C, 1 h)	 **85k**	 **86m**: 80%[b]

[210] R. Fittig, J. König, *Justus Liebigs Annal. Chem.* **1867**, *144*, 277.
[211] A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.

Entry	$R_2B(OBu)_2MgBr$ (conditions [T, t])	Electrophile	Product, Yield[a]
2	 **84i** (25 °C, 30 min)	 **85l**	 **86n**: 93%[c]
3	 **84k** (25 °C, 30 min)	 **85m**	 **86o**: 86%[e]
4	 **84i** (25 °C, 30 min)	 **85n**	 **86p**: 84%[e]
5	 **84l** (25 °C, 1 h)	 **85o**	 **86q**: 88%[d]
6	 **84m** (25 °C, 1 h)	 **85b**	 **86r**: 89%[e]
7	**84m**	 **85g**	 **86s**: 84%[e]

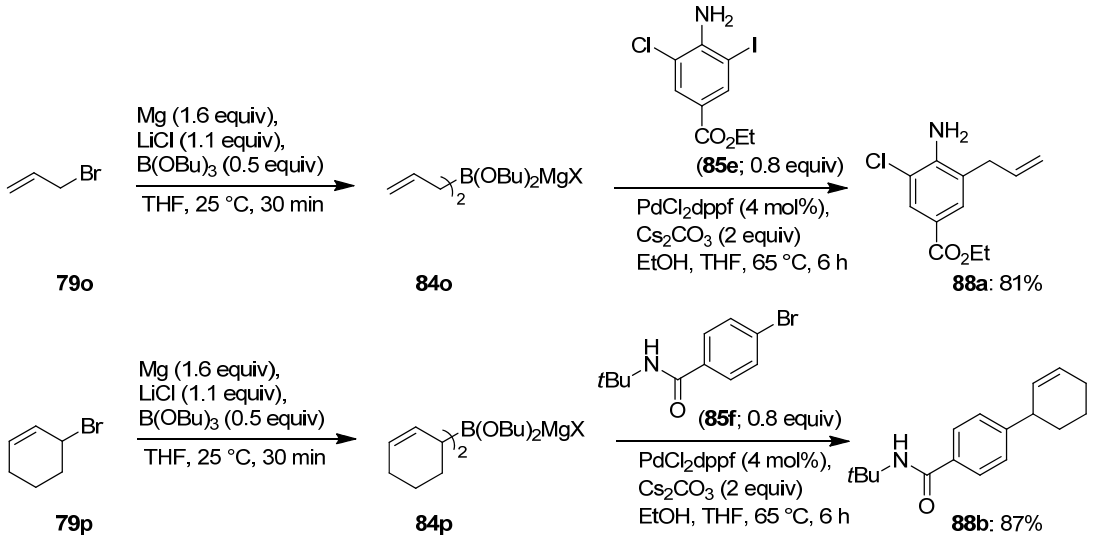
[a] Yield of isolated, analytically pure product as determined by 1H NMR. [b] Obtained after Pd-catalyzed cross-coupling ($PdCl_2$(dppf) (4 mol%), Cs_2CO_3 (2 equiv), THF/EtOH (1:1), DMF, 65 °C, 12 h). [c] Obtained after Pd-catalyzed cross-coupling ($PdCl_2$(dppf) (4 mol%), Cs_2CO_3 (2 equiv), THF/EtOH (1:1), DMF, 65 °C, 1 h). [d] Obtained after Pd-catalyzed cross-coupling ($Pd(PPh_3)_4$ (4 mol%), K_3PO_4 (2 equiv), THF/EtOH (1:1), 65 °C, 2 h). [e] Obtained after Pd-catalyzed cross-coupling ($PdCl_2$(dppf) (4 mol%), Cs_2CO_3 (2 equiv), THF/EtOH (1:1), 65 °C, 6 h). dppf = 1,1´-bis(diphenylphosphino)ferrocene.

Among organometallic reagents, organoboron compounds have the remarkable ability to undergo oxidation reactions with oxidizing reagents such as H_2O_2 providing the corresponding alcohols. Thus, 1,3,5-trichlorobenzene (**79n**) efficiently reacted via magnesium insertion in the presence of borate (Mg (1.6 equiv), LiCl (1.1 equiv), $B(OBu)_3$ (0.5 equiv), 25 °C, 1 h) affording the borate **84n**. Oxidation using H_2O_2 and aq. NaOH (25 °C, 2 h) furnished 3,5-dichlorophenol (**87**) in 79% yield (Scheme 48).



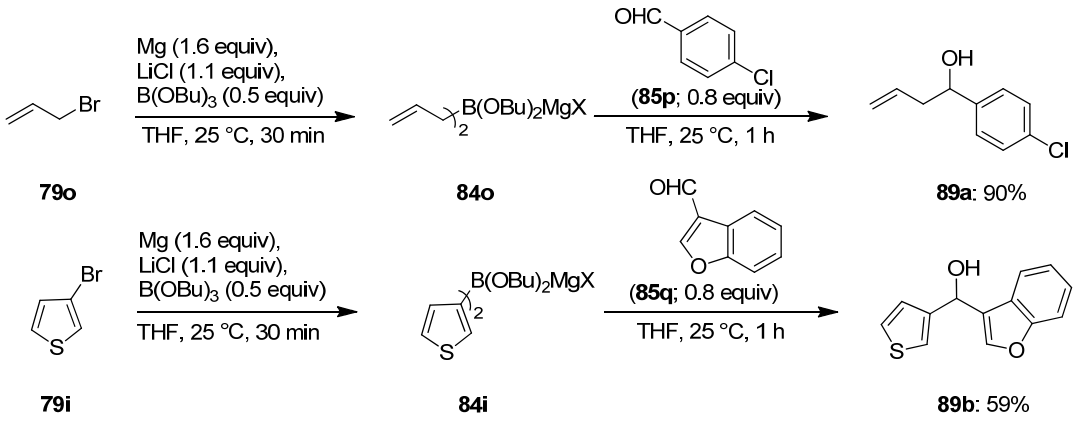
Scheme 48. Preparation of the diarylborate **84n** followed by oxidation leading to the phenol **87**.

Remarkably, primary and secondary alkyl bromides such as allyl bromide (**79o**) or 3-bromocyclohexene (**79p**) efficiently react with Mg/LiCl/$B(OBu)_3$ affording smoothly the dialkylborates **84o** or **84p** (Scheme 49). Similar to Mg-insertion reactions with benzyl chlorides or bromides, dimeric homo-coupling products were avoided due to the *in situ* trapping with $B(OBu)_3$. Subsequent Pd-catalyzed cross-couplings ($PdCl_2$(dppf) (4 mol%, Cs_2CO_3 (2 equiv), EtOH, THF, 65 °C, 6 h) with the aniline derivative **85e** or the benzamide **85f** furnished the expected substituted arenes **88a** and **88b** in 81–87% yield (Scheme 49).



Scheme 49. Preparation of allylborates like **84o** and **84p** leading after Pd-catalyzed cross-coupling to the functionalized arenes of type **88**.

Furthermore, the diallylborate **84o** prepared from allyl bromide (**79o**) added smoothly to 4-chlorobenzaldehyde (**85p**; 25 °C, 1 h) providing the substituted allylalcohol **89a** in 90% yield (Scheme 50). Generally, arylboron compounds only add to aldehydes via transition metal catalysis, preferable using Rh-catalysts.[212] However, the *in situ* generated heteroarylborate **84i**, which includes stoichiometric amounts of Lewis acidic magnesium salts, provided with benzofuran-2-carbaldehyde (**85q**), in the absence of transition metals, the corresponding carbinol **89b** in 59% yield (Scheme 50).

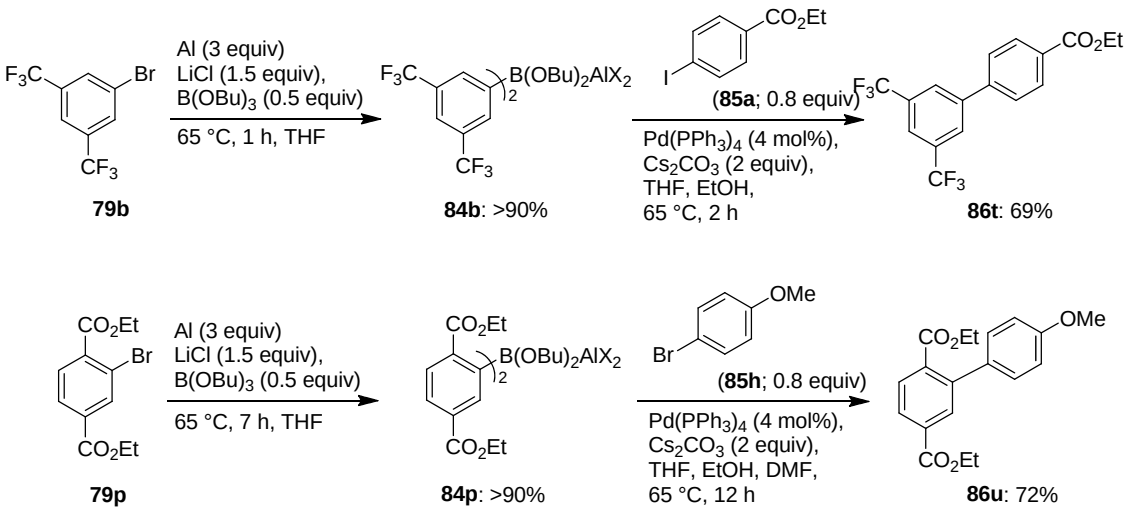


Scheme 50. Preparation of a secondary alcohols of type **89** using the organoborates **84o** or **84i**.

Besides magnesium, as mentioned above, various oxidizable metals are feasible in the described method for the *in situ* preparation of organoborates. Hence, we further explored the use of aluminium in the direct metal insertion in the presence of borates. Remarkably, Knochel *et al.* recently reported the preparation of aluminium reagents for the first time via direct metal insertion.[213] Aluminium metal is inexpensive and the waste products are generally non-toxic as well as non-corrosive. However, merely heavy transition metals or heavy main group elements enable the direct metal insertion of aluminium into carbon-halogen bonds. Nevertheless, we could show that borates such as $B(OBu)_3$ also permit the direct aluminium insertion into carbon-halogen bonds of various aryl bromides like 1-bromo-bis(trifluoromethyl)benzene (**79b**; 65 °C, 1 h) affording the arylborate **84b**. Subsequent Suzuki-type catalyzed cross-coupling ($Pd(PPh_3)_4$ (4 mol%), Cs_2CO_3 (2 equiv), THF, EtOH, 65 °C, 2 h) with ethyl 4-iodobenzoate (**85a**) produced the polysubstituted biphenyl **86t** in 69% yield (Scheme 51). Similarly, the bromo-terephthalate **79p** furnished via direct insertion reaction with aluminium (3 equiv, 65 °C, 7 h) in the presence of $B(OBu)_3$ (0.5 equiv) the functionalized arylborate **84p**. Thereafter, the Pd-catalyzed cross-coupling ($Pd(PPh_3)_4$

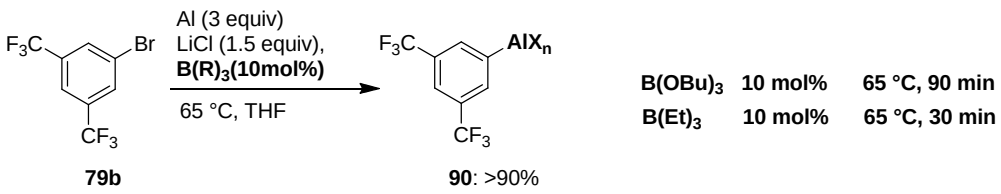
[212] K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169.
[213] T. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nature Chem.* **2010**, *2*, 313.

(4 mol%), Cs_2CO_3 (2 equiv), THF, EtOH, DMF, 65 °C, 12 h) with 4-bromoanisole (**85h**; furnishes the polyfunctional biphenyl **86u** in 72% yield (Scheme 51).



Scheme 51. Preparation of polysubstituted arylborates **84b** und **84p** via direct aluminium insertion in the presence of $B(OBu)_3$ followed by Pd-catalyzed cross-coupling reactions.

Remarkably, we could clearly demonstrate the accelerating effect of borates in direct aluminium insertion using merely catalytic amounts of borate leading to the corresponding organoaluminium reagents. Thus, $B(OBu)_3$ or BEt_3 applied in catalytic amounts (10 mol%) proved to enable the direct aluminium insertion with the activated aryl bromide **79b** affording the substituted arylaluminium reagent **90** in ca. 90% yield (Scheme 52). Compared to the reaction times using substoichiometric amounts of borate ($B(OBu)_3$ (0.5 equiv), Scheme 51), the direct aluminium insertion reaction (Al (3 equiv), LiCl (1.5 equiv), BR_3 (10 mol%)) proceeded with similar rates ($B(OBu)_3$: 65 °C, 90 min; BEt_3: 65 °C, 30 min). Moreover, using the same reaction conditions, no direct aluminium insertion with **79b** was observed after 24 h at 65 °C in the absence of borates or LiCl.



Scheme 52. Preparation of substituted aluminium reagent **90** via the direct metal insertion, catalyzed by $B(OBu)_3$ (10 mol%) or BEt_3 (10 mol%).

In summary, we have demonstrated an efficient and low-cost one-step synthesis of polyfunctional borates via accelerated direct metal insertion tolerating a wide range of functional groups. The method proved to be highly flexible and fast by means of the

accelerating effect of $B(OBu)_3$ and LiCl during the direct metal insertion allowing the conversion of functionalized primary and secondary alkyl, alkenyl, benzyl or aryl as well as heteroaryl bromides into the corresponding organoborates. Furthermore, we demonstrated the practicability of the prepared organoborates bearing sensitive functional groups in the uncatalyzed addition to aldehydes and in Suzuki-type cross-couplings. In addition, the substantial accelerating effect of $B(OBu)_3$ has been demonstrated in the direct metal insertion with aryl bromides using less reactive metals, such as Al, Ca, and Zn. Moreover, we could show that Li, K and Na are also feasible for the in situ preparation of organoborates via direct metal insertion.

3. Functionalization of Pyridines and Related Heterocycles Using Frustrated Lewis Pairs

3.1 Introduction

The directed *ortho*-metalation of aromatic and heterocyclic compounds is an efficient method for the functionalization of these scaffolds.[214] Besides conventional lithium bases, a range of new bimetallic ate-bases have been introduced by Kondo, Mulvey, Mongin and Uchiyama.[215] These bases allow a smooth metalation of a number of unsaturated systems due to synergetic effects between the two metals. Recently, Knochel and co-workers reported highly soluble LiCl-complexed metal amides, such as TMPMgCl·LiCl (**91**),[216] (TMP = 2,2,6,6-tetramethylpiperidyl), $TMP_2Mg·2LiCl$ (**92**),[217] TMPZnCl·LiCl (**93a**),[218] $TMP_2Zn·2MgCl_2·2LiCl$ (**93b**),[219] and $TMP_3Al·3LiCl$ (**93a**).[220] These reagents allow smooth, chemo- and regioselective metalations of various aromatics and heterocycles with a broad functional group compatibility.[217-220]

[214] a) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376; b) C. Heiss, E. Marzi, F. Mongin, M. Schlosser, *Eur. J. Org. Chem.* **2007**, 669; c) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489; d) M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3975; e) D. M. Hodgson, C. D. Bray, N. D. Kindon, *Org. Lett.* **2005**, *7*, 2305; f) M. Yus, F. Foubelo, *Handbook of Functionalized Organometallics*, P. Knochel Ed., Wiley-VCH: Weinheim, Germany **2005**; Vol. 1, pp. 7; g) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; i) J. Clayden, C. C. Stimson, M. Keenan, *Chem. Commun.* **2006**, 1393; j) P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016; k) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc.* **1993**, *115*, 11370; l) P. Beak, V. Snieckus, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.

[215] a) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc*. **1999**, *121*, 3539; b) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc*. **2002**, *124*, 8514; c) H. Naka, M. Uchiyama, Y. Matsumoto, A. E. H. Wheatley, M. McPartlin, J. V. Morey, Y. Kondo, *J. Am. Chem. Soc*. **2007**, *129*, 1921; d) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802; e) M. Uchiyama, Y. Kobayashi, T. Furuyama, S. Nakamura, Z. Kajihara, T. Miyoshi, T. Sakamoto, Y. Kondo, K. Morokuma, *J. Am. Chem. Soc*. **2008**, *130*, 472 f) F. Chevallier, F. Mongin, *Chem. Soc. Rev.* **2008**, *37*, 595; g) A. Seggio, F. Chevallier, M. Vaultier, F. Mongin, *J. Org. Chem*. **2007**, *72*, 6602; h) W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, C. T. O'Hara, L. Russo, *Angew. Chem. Int. Ed.* **2008**, *47*, 731; i) P. Alborés, L. Carrella, W. Clegg, P. García-Álvarez, A. R. Kennedy, J. Klett, R. E. Mulvey, E. Rentschler, L. Russo, *Angew. Chem. Int. Ed.* **2009**, *48*, 3317; j) V. L. Blair, L. M. Carrella, W. Clegg, J. Klett, R. E. Mulvey, E. Rentschler, L. Russo, *Chem. Eur. J*. **2009**, *15*, 856.

[216] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; b) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; c) N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525; d) N. Boudet, S. R. Dubbaka, P. Knochel, *Org. Lett.* **2008**, *10*, 1715; e) A. H. Stoll, P. Knochel, *Org. Lett.* **2008**, *10*, 113; f) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497.

[217] a) G. C. Clososki, C. J. Rohbogner; P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681; b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503.

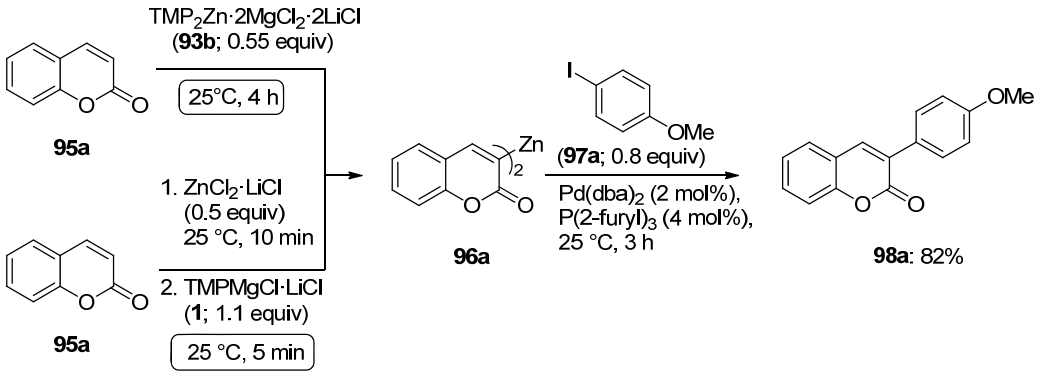
[218] M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837.

[219] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705.

[220] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 1501.

3.2 *In situ* Metalation with TMPMgCl·LiCl in the Presence of $ZnCl_2$

Moreover, Knochel *et al.* described an additional procedure involving a complexation of some organic substrates with $ZnCl_2$ prior to the addition of $TMP_2Mg·2LiCl$ (**92**) which led to improved metalation yields.[221] In light of the drawbacks of this method, such as the thermal stability of $TMP_2Mg·2LiCl$ (**92**), we developed a similar procedure using $ZnCl_2$-precomplexed substrates for the metalation with TMPMgCl·LiCl (**91**; 1.1 equiv). Compared to $TMP_2Zn·2MgCl_2·2LiCl$ (**93b**), unprecedented rate accelerations were observed. Hence, complete zincation of coumarin (**95a**) is achieved with $TMP_2Zn·2MgCl_2·2LiCl$ (**93b**) within 4 h at 25 °C, whereas treatment of **95a** with $ZnCl_2·LiCl$ (0.5 equiv) followed by the addition of TMPMgCl·LiCl (**91**; 1.1 equiv) leads to the zincated species **96a** *within 5 min at 25 °C*. After a Pd-catalyzed cross-coupling[222] with 4-iodoanisole (**97a**), the expected coumarin derivative **98a** is obtained in 82% yield (Scheme 53).[223,224]

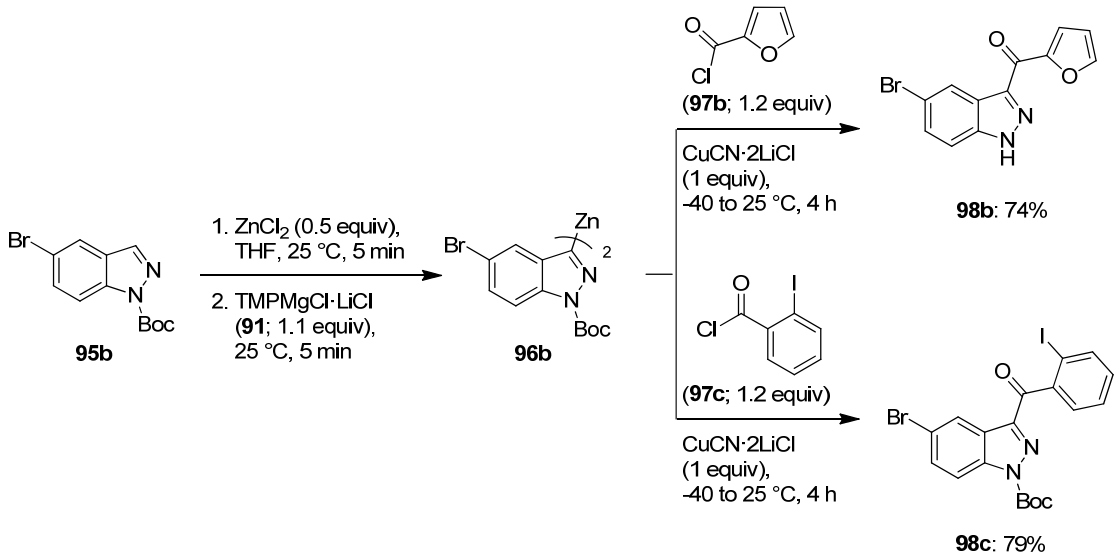


Scheme 53. Dramatic acceleration of the metalation of coumarin (**95a**) and subsequent Pd-catalyzed cross-coupling.

Thus, treatment of sensitive heterocycles, like the 1*H*-indazole **95b**, with $ZnCl_2$ (0.5 equiv) followed by addition of TMPMgCl·LiCl (**91**; 1.1 equiv, 25 °C, 15 min) furnished the diorganozinc **96b** (Scheme 54). In contrast, metalation using TMPMgCl·LiCl (**91**; 25 °C, 5 min) in the absence of $ZnCl_2$ led to immediate and complete decomposition of the indazole ring. Cu(I)-mediated acylation (CuCN·2LiCl (1 equiv), –40 to 25 °C, 4 h) of zinc reagent **96b**

[221] Z. Dong, G. Clososki, S. Wunderlich, A. Unsinn, J. Li, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 457.
[222] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[223] Interestingly, attempts to generate the highly reactive base in stoichiometric amounts (addition of TMPMgCl·LiCl (**91**; 3.0 equiv) to $ZnCl_2$ (1.0 equiv)) did not lead to optimum results due to various side reactions and variable metalation rates.
[224] Compound **98a** was prepared by A. Unsinn and has been included for sake of completeness.

with 2-furoyl chloride (**97b**) or 2-iodobenzoyl chloride (**97c**) afforded the corresponding ketones **98b** and **98c** in 74–79% yield (Scheme 54).



Scheme 54. Preparation of substituted diheteroarylzinc reagent **96b** followed by Cu(I)-mediated acylation reactions.

3.3 Highly Selective Metalations of Pyridines and Related Heterocycles Using New Frustrated Lewis Pairs or TMP-Zn and TMP-Mg Bases with or without $BF_3 \cdot OEt_2$

The functionalization of pyridines and quinolines is a major synthetic goal, since many of these heterocycles have important biological properties[225] or are of interest as new materials.[226] The regioselective functionalization of these heterocyclic scaffolds has been achieved by directed metalations[227] or metal-catalyzed C-H activations.[228] The stoichiometric

[225] a) K. C. Nicolaou, R. Scarpelli, B. Bollbuck, B. Werschkun, M. M. A. Pereira, M. Wartmann, K.-H. Altmann, D. Zaharevitz, R. Gussio, P. Giannakakou, *Chem. Biol.* **2000**, *7*, 593; b) B. Oliva, K. Miller, N. Caggiano, A. J. O´Neill, G. D. Cuny, M. Z. Hoemann, J. R. Hauske, I. Chopra, *Antimicrob. Agents Chemother.* **2003**, *47*, 458; c) A. Bouillon, A. S. Voisin, A. Robic, J.-C. Lancelot, V. Collot, S. Rault, *J. Org. Chem.* **2003**, *68*, 10178; d) E. M. Nolan, J. Jaworski, K.-I. Okamoto, Y. Hayashi, M. Sheng, S. J. Lippard, *J. Am. Chem. Soc.* **2005**, *127*, 16812; e) A. Hayashi, M. Arai, M. Fujita, M. Kobayashi, *Biol. Pharm. Bull.* **2009**, *32*, 1261; f) J. Quiroga, J. Trilleras, B. Insuasty, R. Abonia, M. Nogueras, A. Marchal, J. Cobo, *Tetrahedron Lett.* **2010**, *51*, 1107.

[226] a) A. Yokoyama, I. Nishiyama, A. Yoshizawa, *Ferroelectrics* **1993**, 148, 139; b) Y. G. Skrypnik, T. F. Doroshenko, *Mater. Sci.* **1996**, *32*, 537; c) H. Tsutsumi, K. Okada, T. Oishi, *Electrochim. Acta* **1996**, *41*, 2657; d) C. G. Bangcuyo, M. E. Rampey-Vaughn, L. T. Quan, S. M. Angel, M. D. Smith, U. H. F. Bunz, *Macromolecules* **2002**, *35*, 1563; e) M. Vetrichelvan, S. Valiyaveettil, *Chem. Eur. J.* **2005**, *11*, 5889.

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[228] a) S. Murai, in *Activation of Unreactive Bonds and Organic Synthesis,* Springer, **1999**; b) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439.

lithiation of unactivated pyridines is often complicated due to Tchitchibabin-type dimerizations.[229] An elegant solution has been proposed by Kessar *et al.* who showed that a complexation of pyridine with BF_3 allows a low temperature α-lithiation of pyridine[230] as well as some other amino derivatives.[231] Michl *et al.* described also the BF_3-assisted metalation of 3-alkylpyridines with $BF_3 \cdot OEt_2$ using lithium TMP-zincates.[232] However, attempts to magnesiate, zincate or aluminate unactivated pyridines with using highly chemoselective LiCl-complexd TMP metal amide bases proved to be unsatisfactory. Thus, using TMPMgCl·LiCl (**91**; 1.1 equiv, 25 °C) only a partial magnesiation was observed (less than 40%). This led us to consider metalations with the TMP-bases **91–94** in the presence of $BF_3 \cdot OEt_2$. We developed a convenient regioselective C-H activation of various polyfunctional pyridines and related heterocycles by a stepwise BF_3-activation followed by metalation with the appropriate TMP-base as well as an unexpected alternative metalation method involving new frustrated Lewis pairs[233,234] such as TMPMgCl·BF_3·LiCl (**99**) derived from the strong TMP-Lewis base and the strong Lewis acid $BF_3 \cdot OEt_2$.[235] Thus, the complexation of 4-phenylpyridine (**95c**) with $BF_3 \cdot OEt_2$ (1.1 equiv, 0 °C, 15 min) to **100** followed by the addition of TMPMgCl·LiCl (**91**; 1.1 equiv, –40 °C, 20 min) generates a metalated pyridine which after transmetalation with $ZnCl_2$ and a subsequent Negishi cross-coupling[236] with ethyl 4-iodobenzoate (**97d**) affords the 2-arylated pyridine **98d** in 84% yield. In order to clarify the nature of the generated organometallic intermediate, we have performed an alternative experiment, in which 4-phenylpyridine (**95c**) was treated with a *premixed* solution of $BF_3 \cdot OEt_2$ (1.1 equiv) and TMPMgCl·LiCl (**91**; 1.1 equiv, –40 °C, 10 min) tentatively written as TMPMgCl·BF_3·LiCl (**99**; Scheme 55).

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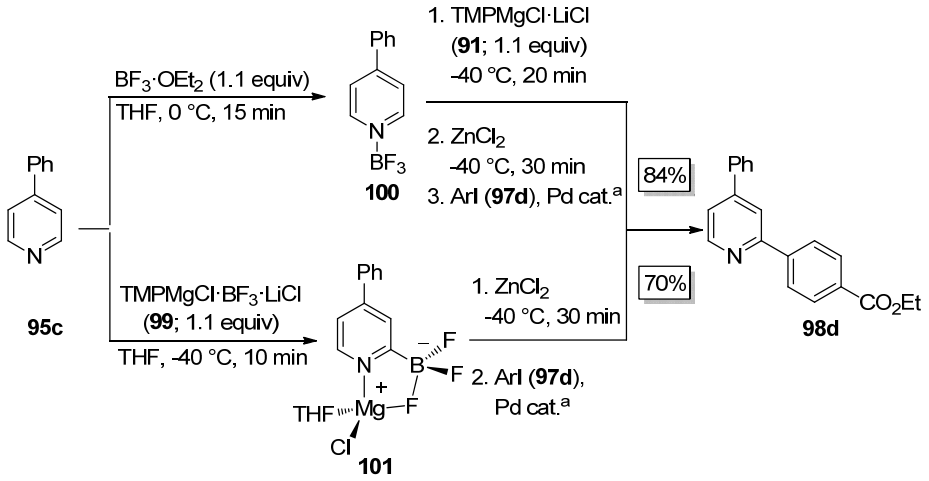
[229] a) A. J. Clarke, S. McNamara, O. Meth-Cohn, *Tetrahedron Lett*. **1974**, *15*, 2373; b) P. Gros, Y. Fort, P. Caubère, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3597.
[230] S. V. Kessar, P. Singh, K. N. Singh, M. Dutt, *J. Chem. Soc., Chem. Commun*. **1991**, 570.
[231] a) S. V. Kessar, P. Singh, R. Vohra, N. Kaur, K. Singh, *J. Chem. Soc., Chem. Commun.* **1991**, 568; b) S. V. Kessar, P. Singh, K. N. Singh, P. Venugopalan, A. Kaur, P. Bharatam, A. Sharma, *J. Am. Chem. Soc.* **2007**, *129*, 4506; c) S. V. Kessar, P. Singh, K. N. Singh, P. V. Bharatam, A. K. Sharma, S. Lata, A. Kaur, *Angew. Chem. Int. Ed.* **2008**, *47*, 4703.
[232] a) P. Schwab, F. Fleischer, J. Michl, *J. Org. Chem.* **2002**, *67*, 443; b) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539.
[233] For an excellent review, see: D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46.
[234] a) S. Bontemps, H. Gornitzka, G. Bouhadir, K. Miqueu, D. Bourissou, *Angew. Chem. Int. Ed.* **2006**, *45*, 1611; b) G. C. Welch, L. Cabrera, P. A. Chase, E. Hollink; J. D. Masuda, P. Wei, D. W. Stephan, *Dalton Trans.* **2007**, 3407; c) J. S. J. Mc Cahill, G. C. Welch, D. W. Stephan, *Angew. Chem. Int. Ed.* **2007**, *46*, 4968; d) T. A. Rokob, A. Hamza, A. Stirling, T. Soós, I. Pápai, *Angew. Chem. Int. Ed.* **2008**, *47*, 2435; e) D. W. Stephan, *Dalton Trans.* **2009**, 3129; f) S. Grimme, H. Kruse, L. Goerigk, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 1402.
[235] M. Jaric, B. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem, Int. Ed.* **2010**, *49*, 5451.
[236] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.



Scheme 55. BF_3-triggered accelerated metalations. ArI: *p*-$IC_6H_4CO_2Et$ (**97d**); [a] Pd cat.: [$Pd(dba)_2$] (5 mol%); $P(2\text{-furyl})_3$ (10 mol%), –40 to 25 °C, 12 h.

Surprisingly, an efficient metalation with reagent **99** occurs within 10 min at –40 °C. Transmetalation with $ZnCl_2$[237] and a Negishi cross-coupling[236] with the aryl iodide **97d** provides product **98d** in comparable yield (70%). This result implies that the new frustrated Lewis pair ($TMPMgCl{\cdot}BF_3{\cdot}LiCl$ (**99**)) is unexpectedly reactive in the metalation of pyridines.[233,234] We have examined the mechanism and scope of this reaction in more detail. ^{11}B-NMR, ^{19}F-NMR, ^{13}C-NMR measurements clearly indicate that the intermediate organometallic species **101** bears a carbon-boron bond as depicted in Scheme 55.[238,239] Thus, the low temperature NMR-experiments (–60 °C) of intermediate **101** showed the expected quartet signal (J = 14.8 Hz) for the carbon-fluorine coupling at 210 ppm in the ^{19}F-coupled ^{13}C NMR spectrum ($^{13}C\{^1H\}$-NMR; Figure 3). Furthermore, a ^1H-coupled ^{13}C NMR experiment ($^{13}C\{^{19}F\}$ NMR) displays as expected a doublet (J = 13.8 Hz) for a carbon-hydrogen coupling of this quaternary carbon (Figure 4). Additionally, HMBC and HMQC measurements clearly supported that this carbon belongs to the pyridyl moiety. Moreover, all carbons in the pyridyl ring have been assigned and a coordination of BF_3 at the nitrogen of the pyridine could be precluded.

[237] This cross-coupling proceeds less efficiently in the absence of $ZnCl_2$. For details on stability and cross-coupling of potassium α-pyridyltrifluoroborates, see: a) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302; b) K. Billingsley, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 4695.
[238] For further details see Experimental Section 5.4.
[239] R. A. Oliveira, R. O. Silva, G. A. Molander, P. H. Menezes, *Magn. Reson. Chem.* **2009**, *47*, 873.

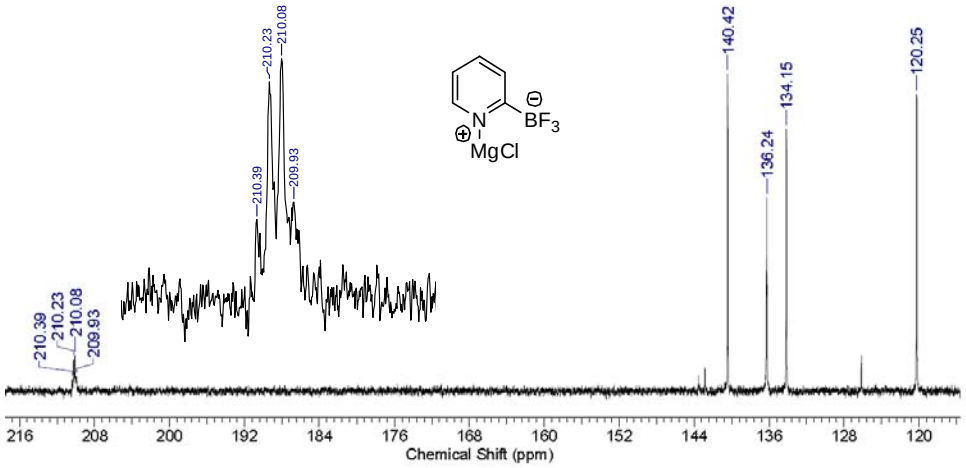


Figure 3. $^{13}C\{^{1}H\}$ NMR spectrum (^{19}F-coupled).

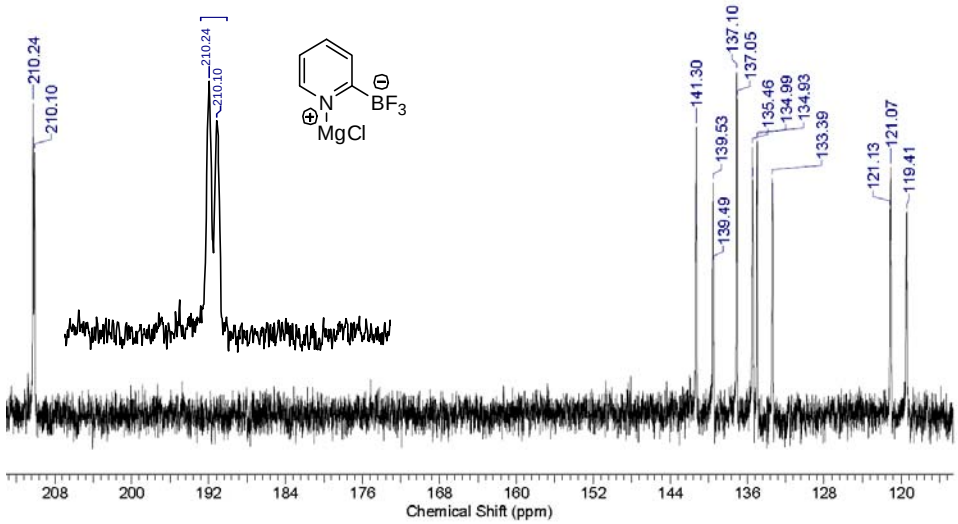


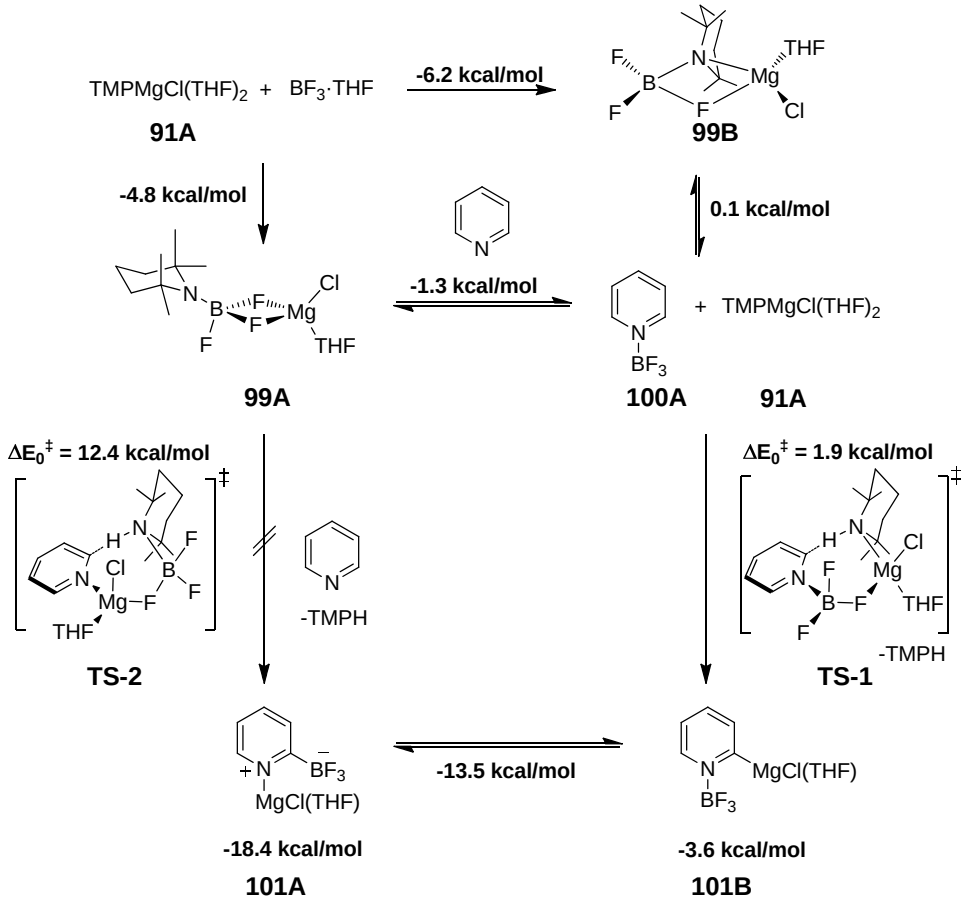
Figure 4. $^{13}C\{^{19}F\}$ NMR spectrum (^{1}H-coupled).

The structure bearing a carbon-boron bond has also been supported by DFT-calculations.[240] Computational thermodynamical analysis shows that structure **101A** (bearing a C-B bond) is by 13.5 kcal/mol thermodynamically more stable than the isomeric structure **101B** (bearing a C-Mg bond; Scheme 56). This indicates that the pyridyltrifluoroborates which are otherwise difficult to prepare can be readily obtained in a one-pot procedure via highly regioselective C-H activations.[237,241,242] The exact structure of the reagent **99** could not be clearly assigned

[240] DFT calculations were carried out using the Gaussian03 Rev.B.04 program package with the nonlocal hybrid B3LYP exchange correlation functionals and the Møller-Plesset second-order correlation energy correction (MP2). The basis set denoted as 631SVP consists of the Ahlrich def2-SVP all electron basis set for Mg atoms and the 6-31G(d,p) basis set for other atoms. Unless otherwise stated energies refer to relative zero-point corrected electronic energies (MP2/631SVP//B3LYP/631SVP). For full details on the computational study and full citations, see Experimental Section.

[241] The pyridyl-2-trifluoroborate (**101**) was also prepared in an alternative way: an I/Mg-exchange of 2-iodo-4-phenylpyridine followed by a transmetalation with BF_3 and $ZnCl_2$ furnished also the product **98d** in 65% yield.

despite numerous NMR-studies. However, DFT-calculations led to the tentative structures **99A** and **99B** showing that both are energetically favoured.[238] NMR-studies confirm that several species for **99** exist in solution. The reaction pathways of **99A** and **99B** with pyridine have been modeled by DFT-calculations revealing that **99A** or **99B** may dissociate in the presence of pyridine furnishing a Py·BF_3 complex (**100A**) as well as TMPMgCl(THF)$_2$ (**91A**). The reaction of **100A** with **91A** proceeds thereafter via **TS–1** with a particularly low activation barrier (1.9 kcal/mol) affording eventually the magnesium chloride pyridyl-2-trifluoroborate complex (**101A**).[243] The alternative pathway implying a direct metalation of pyridine with **99A** or **99B** (no prior dissociation) proceeding via **TS–2** has a comparably much higher activation energy (12.4 kcal/mol).



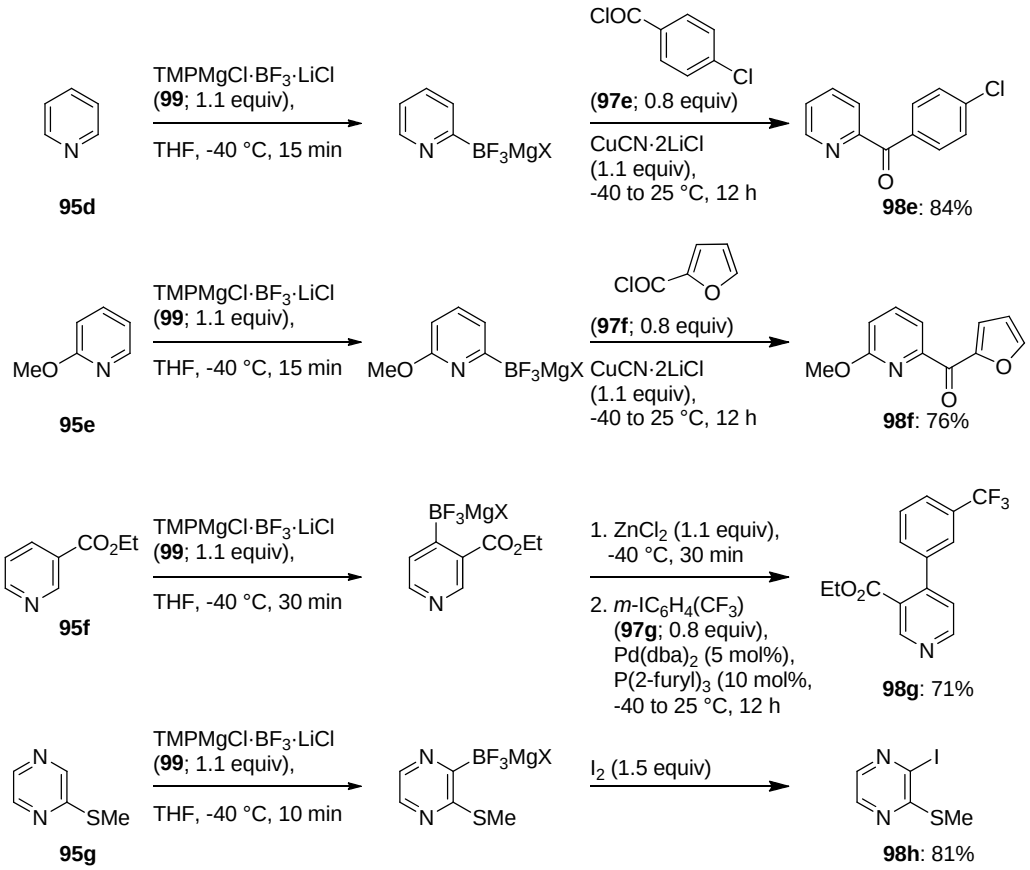
Scheme 56. Structure and reactivity of frustrated Lewis pairs (**99**).

These calculations depict the frustrated Lewis pair character of **99** showing the facile reversibility of its formation in the presence of an appropriate substrate such as pyridine and led us to examine the synthetic utility and reaction scope of this new class of reagents.

[242] For an excellent review, see: G. A. Molander, B. Canturk, *Angew. Chem. Int. Ed.* **2009**, *48*, 9240.
[243] The reaction of pyridine with TMPMgCl(THF)$_2$ has also been modelled and is described in the Experimental Section 5.4.

Pyridine (**95d**) similarly reacts with TMPMgCl·BF_3·LiCl (**99**; 1.1 equiv, –40 °C, 15 min) and furnishes after transmetalation with CuCN·2LiCl[244] and a subsequent acylation reaction with 4-chlorobenzoyl chloride (**97e**; 0.8 equiv, –40 °C to 25 °C, 12 h) the pyridyl ketone **98e** in 84% yield (Scheme 57).[245] The lithiation of 2-methoxypyridine (**95e**) with lithium superbases produces a mixture of products, unless a large excess of base is added.[246] However, by using the frustrated Lewis pair TMPMgCl·BF_3·LiCl (**99**), regioselective metalation can be achieved producing after acylation with 2-furoyl chloride (**97f**) the 2,6-disubstituted pyridine (**98f**) in 76% yield.[245] The metalation of electron-poor pyridines such as **95f** cannot be performed with any conventional lithium base due to extensive decomposition.[247] The new reagent **99** efficiently resolves this synthetic problem. Thus, the treatment of ethyl nicotinate (**95f**) with TMPMgCl·BF_3·LiCl (**99**; 1.5 equiv, –40 °C, 30 min) furnishes an organometallic intermediate which undergoes a smooth Negishi cross-coupling[236] with 1-iodo-3-(trifluoromethyl)-benzene (**97g**) leading to the functionalized pyridine **98g** in 71% yield.[245] Other related sensitive heterocycles such as 2-(methylthio)-pyrazine (**95g**) are metalated with **99** (1.1 equiv, –40 °C, 10 min) leading after iodolysis to 2-iodo-3-(methylthio)pyrazine (**98h**) in 81% yield (Scheme 57).

[244] a) P. Knochel, M. Yeh, S. Berk, J. Talbert, *J. Org. Chem*. **1988**, *53*, 2390; b) P. Knochel, S. A. Rao*, J. Am. Chem. Soc.* **1990**, *112*, 6146.
[245] This example was prepared by M. Jaric and has been included for sake of completeness.
[246] a) P. Gros, Y. Fort, G. Quéguiner, P. Caubère, *Tetrahedron Lett.* **1995**, *36*, 4791 ; b) P. Gros, Y. Fort, P. Caubère, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3071.
[247] G. Bentabed-Ababsa, S. Cheikh Sid Ely, S. Hesse, E. Nassar, F. Chevallier, T. Tai Nguyen, A. Derdour, F. Mongin, *J. Org. Chem.* **2010**, *75*, 839.

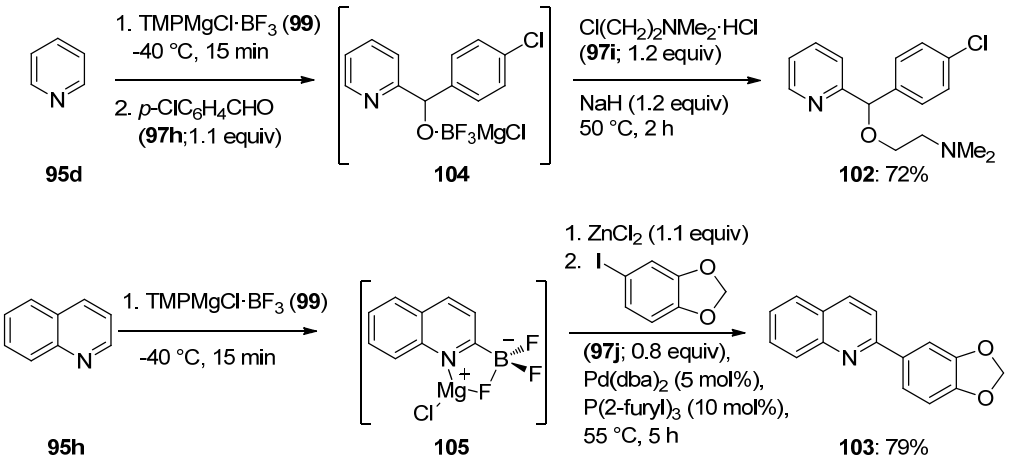


Scheme 57. Regioselective metalation of *N*-heterocycles with the frustrated Lewis pair (**99**).

To demonstrate the synthetic potential of the reagent **99**, we have prepared two biologically active molecules: an antihistaminic drug, carbinoxamine (**102**)[248] and the haplophyllum alkaloid, dubamine (**103**),[249,245] in two one-pot procedures (Scheme 58).

Thus, the treatment of pyridine (**95d**) with TMPMgCl·BF_3·LiCl (**99**; 1.1 equiv, –40 °C, 15 min) followed by the addition of 4-chlorobenzaldehyde (**97h**) leads to the alcoholate **104** which was in situ reacted with $Cl(CH_2)_2NMe_2$·HCl (**97i**; 1.2 equiv) and NaH (1.2 equiv, 50 °C, 2 h) providing carbinoxamine (**102**) in 72% yield. Similarly, the reaction of quinoline (**95h**) with TMPMgCl·BF_3·LiCl (**99**; 1.1 equiv, –40 °C, 15 min) furnishes the magnesium chloride quinolinyltrifluoroborate (**105**). Transmetalation with $ZnCl_2$ and subsequent Negishi cross-coupling[236] with the aryl iodide **97j** affords dubamine (**103**) in 79% yield (Scheme 58).

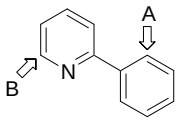
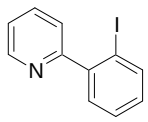
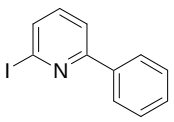
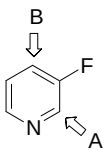
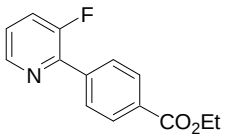
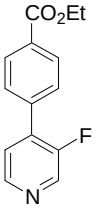
[248] a) B. Garat, C. Landa, O. Rossi Richeri, R. Tracchia, *J. Allergy* **1956**, *27*, 57; b) E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1996**, *37*, 5675.
[249] C. M. Melendez Gomez, V. V. Kouznetsov, M. A. Sortino, S. L. Alvarez, S. A. Zacchino, *Bioorg. Med. Chem.* **2008**, *16*, 7908.



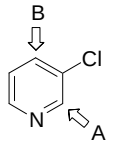
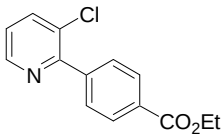
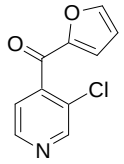
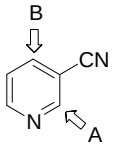
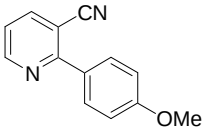
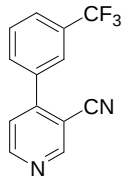
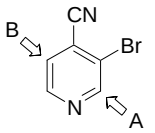
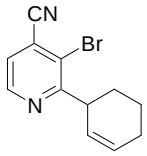
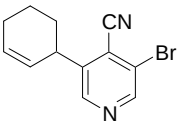
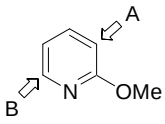
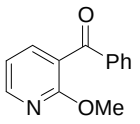
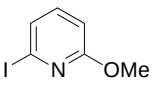
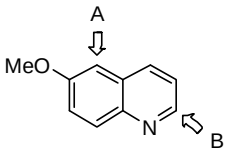
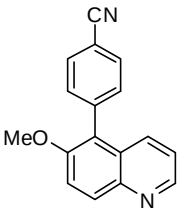
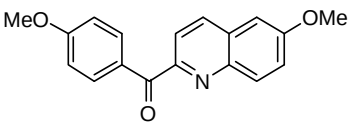
Scheme 58. One-pot preparation of carbinoxamine (**102**) and dubamine (**103**).

During the study of the reaction scope of TMPMgCl·BF_3·LiCl (**99**), we realized that the performance of a two-step metalation with precomplexation with BF_3·OEt_2 and subsequent addition of TMPMgCl·LiCl (**91**), TMP_2Zn·$2MgCl_2$·LiCl (**93b**) or [(*t*Bu)NCH(*i*Pr)(*t*Bu)]$_3$Al·3LiCl (**94b**) in a second step, proves to be more flexible and often results in higher yields.[250] This two-step metalation allows in a number of cases, a complete switch of regioselectivity by using either TMP-derived bases **91–94** without BF_3·OEt_2 (metalation procedure A) or metalation of BF_3-precomplexed *N*-heterocycles (metalation procedure B; Table 11).

Table 11. Switchable, regioselective metalations of *N*-heterocycles with TMP-bases in the presence or absence of BF_3·OEt_2.

Entry	Substrate	TMP-base metalation (procedure A)[a]	BF_3-triggered metalation (procedure B)[a]
1	 **95i**	 **106a**: 85%[b]	 **107a**: 83%[c]
2	 **95j**	 **106b**: 72%[d,e]	 **107b**: 74%[d,e]

[250] Although TMPMgCl·BF_3·LiCl (**99**) is conveniently prepared within 5 min at –40 °C, a study of its stability reveals that it decomposes slowly in the absence of a substrate within a few hours at –20 °C.

Entry	Substrate	TMP-base metalation (procedure A)[a]	BF_3-triggered metalation (procedure B)[a]
3	 **95k**	 **106c**: 75%[f,e]	 **107c**: 78%[f,g]
4	 **95l**	 **106d**: 85%[h,e]	 **107d**: 78%[i,e]
5	 **95m**	 **106e**: 65%[j]	 **107e**: 63%[k,g]
6	 **95n**	 **106f**: 80%[l,g]	 **107f**: 75%[m]
7	 **95o**	 **106g**: 68%[n,e]	 **107g**: 94%[o,g]

[a] Yield of analytically pure isolated product as determined by ^{1}H NMR. [b] TMPMgCl·LiCl (**91**; 55 °C, 30 h). [c] TMPMgCl·LiCl (**91**; 0 °C, 30 h). [d] TMPMgCl·LiCl (**91**; –78 °C, 30 min). [e] Obtained by a palladium-catalyzed cross-coupling with $[Pd(dba)_2]$ (5 mol%) and P(2-furyl)$_3$ (10 mol%) at 25 °C for 12 h. [f] TMPMgCl·LiCl (**91**; –78 °C, 45 min). [g] Obtained after transmetalation with CuCN·2LiCl (1.1 equiv). [h] $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93b**; 25 °C, 12 h). [i] $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93b**; –30 °C, 30 min). [j] TMPMgCl·LiCl (**91**; –78 °C, 1 h). [k] $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93b**; –78 °C, 1 h). [l]

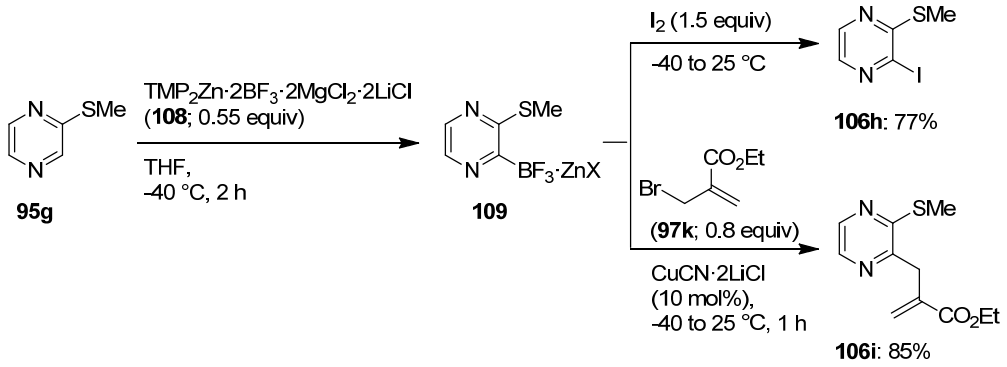
[(*t*Bu)NCH(*i*Pr)(*t*Bu)]$_3$Al·3LiCl (**94b**; 25 °C, 2 h). [m] TMPMgCl·LiCl (**91**; 0 °C, 60 h). [n] [(*t*Bu)NCH(*i*Pr)(*t*Bu)]$_3$Al·3LiCl (**94b**; –78 °C, 1 h). [o] TMPMgCl·LiCl (**91**; 0 °C, 1 h).

Thus, 2-phenylpyridine (**95i**) is selectively magnesiated with TMPMgCl·LiCl (**91**; 2 equiv, 55 °C, 30 h) in the *ortho*-position of the phenyl substituent leading after iodolysis to the aryl iodide **106a** (85% yield). In contrast, precomplexation with BF_3·OEt_2 (1.1 equiv, 0 °C, 15 min) followed by the addition of TMPMgCl·LiCl (**91**; 1.5 equiv, 0 °C, 30 h) leads to a selective metalation in position 6 affording after iodolysis the 2-iodopyridine derivative **107a** (83% yield). A number of substituted pyridines (**95j–n**; entries 2–6) display this remarkable switch in selectivity. Thus, 3-fluoropyridine (**95j**) is magnesiated with TMPMgCl·LiCl (**91**; 1.1 equiv, –78 °C, 30 min) in position 2. After transmetalation with $ZnCl_2$ and a Negishi cross-coupling[236] with ethyl 4-iodobenzoate (**97d**), the 2,3-disubstituted pyridine **106b** is obtained in 72% yield (entry 2). Precomplexation with BF_3·OEt_2 and metalation with TMPMgCl·LiCl (**91**; 1.1 equiv, –78 °C, 30 min) provides the 4-metalated pyridine which after cross-coupling with the aryl iodide **97d** furnished the 3,4-disubstituted pyridine **107b** (74% yield; entry 2). This complementary functionalization is observed for 3-chloropyridine (**95k**) and 3-cyanopyridine (**95l**) as well leading after similar reaction sequences to the 2,3-disubstituted pyridines **106c** and **106d** (75–85% yield) and to the 3,4-disubstituted pyridines **107c** and **107d** (78% yield). The metalation of the electron-poor pyridine **95l** is especially remarkable, since such sensitive heterocycles are prone to polymerization during metalations. Thus, nicotinonitrile (**95l**) is selectively metalated in position 2 using TMP_2Zn·$2MgCl_2$·2LiCl (**93b**) furnishing after a Negishi cross-coupling[236] the 2,3-disubstituted pyridine **106d** in 85% yield whereas a precomplexation with BF_3·OEt_2 and zincation with **93b** (–30 °C, 30 min) provides after cross-coupling the 3,4-disubstituted product **107d** (79% yield; entry 4). For electron-deficient disubstituted pyridines like 3-bromo-4-cyanopyridine (**95m**), the metalation is performed with TMPMgCl·LiCl (**91**; 1.1 equiv, –78 °C, 1 h) affording after copper-mediated allylation[251] with 3-bromocyclohexene (**97j**) the 1,2,3-trisubstituted pyridine **106e** (65% yield; entry 5). In contrast, after precomplexation with BF_3·OEt_2 (1.1 equiv, 0 °C, 15 min) and subsequent reaction with TMP_2Zn·$2MgCl_2$·2LiCl (**93b**), a selective zincation occurs in position 4 providing after allylation the 3,4,5-trisubstituted pyridine **107e** (63% yield; entry 5). Electron-rich pyridines such as 2-methoxypyridine (**95n**) can also be regioselectively deprotonated using in this case the aluminium base [(*t*Bu)NCH(*i*Pr)(*t*Bu)]$_3$Al·3LiCl (**94b**) which, in the

[251] F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

absence of $BF_3 \cdot OEt_2$, is leading after acylation to the 2,3-substituted pyridine **106f** (80% yield; entry 6). Precomplexation with $BF_3 \cdot OEt_2$ followed by a metalation with TMPMgCl·LiCl (**91**) and iodolysis provides 2-iodo-6-methoxypyridine (**107f**; 75% yield; entry 6). This regioselectivity has been extended to functionalized quinoline derivatives. Thus, 6-methoxyquinoline (**95o**) is aluminated with $[(t\text{Bu})\text{NCH}(i\text{Pr})(t\text{Bu})]_3\text{Al} \cdot 3\text{LiCl}$ (**94b**) in position 5[252] affording after transmetalation with $ZnCl_2$ and a subsequent Negishi cross-coupling[236] the 5,6-disubstituted quinoline **106g** in 68% yield, whereas a precomplexation with $BF_3 \cdot OEt_2$ using TMPMgCl·LiCl (**91**) leads after a copper-mediated acylation to the 2,6-disubstituted quinoline **107g** (94% yield; entry 7).[253] The regioselectivity of the metalation in the presence of BF_3 may be best explained by assuming in the case of 3-substituted pyridines that the BF_3-complexation at the pyridine-nitrogen leads to a substantial steric hindrance at position 2, hence favouring position 4 for metalation.

In addition, an even milder frustrated Lewis pair than **99**, such as $TMP_2Zn \cdot 2BF_3 \cdot 2MgCl_2 \cdot 2LiCl$ (**108**), proved to be highly useful in metalation reactions with sensitive heterocycles. Thus, 2-(methylthio)pyrazine (**95g**) reacted smoothly (–40 °C, 2 h) with $TMP_2Zn \cdot 2BF_3 \cdot 2MgCl_2 \cdot 2LiCl$ (**108**) providing the heteroaryltrifluoroborate **109**. Iodolysis or Cu(I)-catalyzed allylation of **109** with ethyl 2-(bromomethyl)acrylate (**97k**; –40 to 25 °C, 1 h) furnished the disubstituted pyrazines **106h**–**i** in 77–85% yield (Scheme 59).



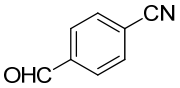
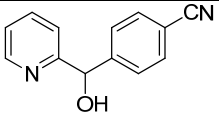
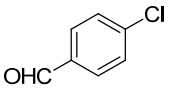
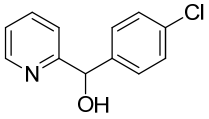
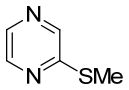
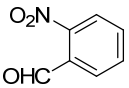
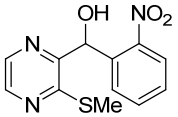
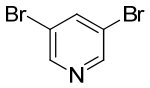
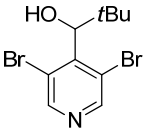
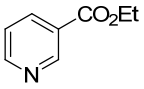
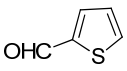
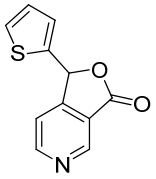
Scheme 59. Regioselective metalation of sensitive *N*-heterocycles with the frustrated Lewis pair **108**.

Classical organoboron reagents generally only add via transition metal catalysis, preferably via Rh-catalysis,[254] to aldehyde functions. In contrast, the generated heteroarylborates of type **101** added to functionalized aldehydes, such as **97h** and **97l–o**, leading to the corresponding carbinols **106k**–**o** in 56–79% yield (Table 12). Thus, $TMPMgCl \cdot BF_3 \cdot LiCl$ (**99**) efficiently metalated pyridine (**95d**) with (–40 °C, 10 min) leading after addition to

[252] The use of an Al-base is essential. A mixture of metalated regioisomers is obtained by using TMPMgCl·LiCl.
[253] These examples were prepared by A. Unsinn and have been included for a more complete understanding.
[254] K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169.

4-cyanobenzaldehyde (**97l**) or 4-chlorobenzaldehyde (**97h**; –40 to 25 °C, 1 h) to the α-pyridyl alcohols **106k–l** in 68–73% yield (Table 12, entries 1 and 2). Furthermore, metalation of 2-(methylthio)pyrazine (**95q**) with **99** (1.1 equiv, –40 °C, 10 min), followed by addition to 2-nitrobenzaldehyde (**97m**; –40 to 25 °C, 1 h), provided the polyfunctional pyrazine **106m** in 56% yield (Table 12, entry 3). Moreover, electron-poor pyridines, such as **95r** or **95f**, afforded after metalation with TMPMgCl·BF_3·LiCl (**99**; –40 °C, 30 min) and subsequent addition to aldehydes **97n** or **97o**, the polysubstituted pyridines **106n–o** in 70–79% yield (Table 12, entries 4 and 5).

Table 12. Regioselective metalation of *N*-heterocycles with frustrated Lewis pair **99** followed by addition to aldehydes.

Entry	Substrate	Aldehyde	Product, Yield[a]
1	 **95d**[b]	 **97l**	 **106k**: 73%
2	**95d**[b]	 **97h**	 **106l**: 68%
3	 **95q**[b]	 **97m**	 **106m**: 56%
4	 **95r**[c]	 **97n**	 **106n**: 79%
5	 **95f**[c]	 **97o**	 **106o**: 70%

[a] Yield of isolated, analytically pure isolated product as determined by ^{1}H NMR. [b] TMPMgCl·BF_3·LiCl (**99**; –40 °C, 10 min). [c] TMPMgCl·BF_3·LiCl (**99**; –40 °C, 30 min).

In summary, we have developed a new class of frustrated Lewis pairs based on BF_3·OEt_2 and LiCl-complexed Mg or Zn TMP-amides allowing an efficient, regioselective metalation of

various *N*-heterocycles. This approach constitutes an expeditive preparation of versatile magnesium chloride heteroaryl trifluoroborates expanding the work of Molander *et al.*[237,239,242] Furthermore, using DFT-calculations, we could theoretically rationalize the experimentally observed acceleration during the metalation reactions. The metalation of various *N*-heterocycles with or without $BF_3 \cdot OEt_2$ using hindered Mg-, Zn- or Al-bases allows a complementary regioselective functionalization leading to a range of new polyfunctional *N*-heterocycles.

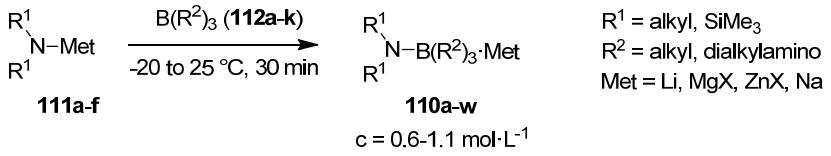
3.4 Direct Preparation of Functionalized Organoborates via Accelerated C-H Activation Using Amidoborates

Recently, we have reported the efficient and regioselective metalation of pyridines and related *N*-heterocycles using frustrated Lewis pairs, such as TMPMgCl·BF_3·LiCl (**99**).[255] In comparison to the corresponding metal amide bases, these reagents displayed unprecedented rates of metalation with functionalized heterocycles. Although the frustrated Lewis pair **99** is conveniently prepared within 5 min at –40 °C, a study of its stability revealed that it decomposes slowly in the absence of a substrate within a few hours at –20 °C. Therefore, we envisioned the preparation of frustrated Lewis pairs showing high reactivity in metalation reactions together with thermal stability in common solvents and also stability in the absence of substrate.

For this purpose, we developed a facile preparation of metalating borate reagents, such as **110a**–**w** using inexpensive metal amide bases.[256,257] Thus, these borate bases are derived from highly soluble metal amide bases, such as TMPMgCl·LiCl (**111a**), TMPLi (**111b**), (HMDS)MgCl (**111c**; HMDS = hexamethyldisilazide), (HMDS)Li (**111d**), (*i*Pr_2N)MgCl·LiCl (**111e**), (*i*Pr_2N)MgCl (**111f**) and (*i*Pr_2N)Li (**111g**; LDA) using trialkylboranes (**112a**–**i**) leading to the corresponding trialkylamidoborates (**110a**–**p)** at low temperature (–20 °C) (Scheme 60). Similarly, magnesium and lithium amides form in the presence of fluoro-*bis*[di(trimethylsilyl)amino]borane (**112j**) or tris(diisopropylamino)borane (**112k**) the

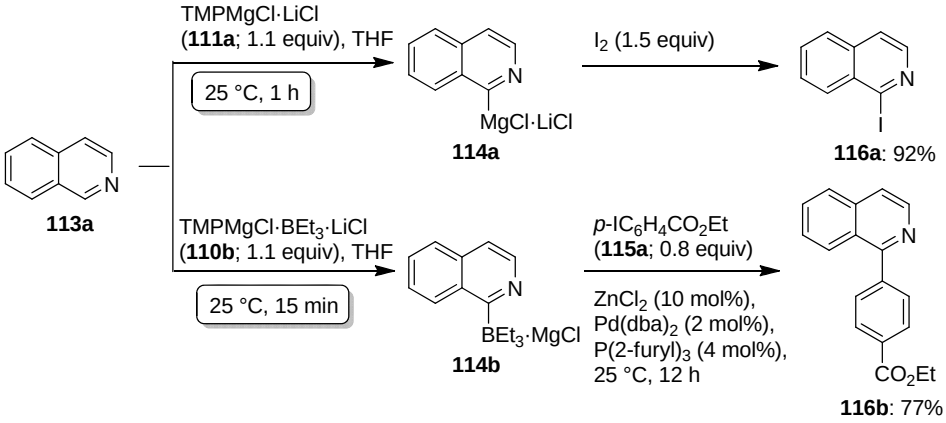
[255] M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.
[256] For review on metal amide bases, see: a) M. Schlosser, *Angew. Chem., Int. Ed.* **2005**, *44*, 376; b) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem., Int. Ed.* **2007**, *46*, 3802; c) R. E. Mulvey, *Acc. Chem. Res.* **2009**, *42*, 743.
[257] a) A. Krasovsky, V. Krasovskaya, P. Knochel, *Angew. Chem., Int. Ed.* **2006**, *45*, 2958; b) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem., Int. Ed.* **2007**, *46*, 7681; c) C. J. Rohbogner, S. H. Wunderlich, G. C. Clososki, P. Knochel, *Eur. J. Org. Chem.* **2009**, 1781.

corresponding amidoborates (**110q–w**) which also prove to be highly valuable metalating reagents (Scheme 60).



Scheme 60. Preparation of amidoborates of type **110**.

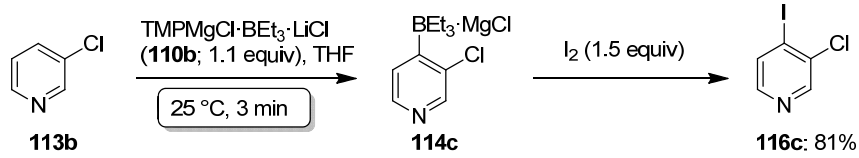
The new borate bases of type **110** allow the convenient and direct syntheses of structurally versatile organoborates, which are particularly known for their thermal stability, in contrast to frustrated Lewis pair adducts derived from metal amides and $BF_3 \cdot OEt_2$.[255] These generated amidoborate bases (**110a**–**w**) display high stability towards decomposition and no significant decrease in concentration. Thus, complete magnesiation of isoquinoline (**113a**) with TMPMgCl·LiCl (**111a**) requires 1 h at 25 °C, whereas the treatment of **113a** with TMPMgCl·BEt_3·LiCl (**110b**; 1.1 equiv) leads to organoboron species **114a** *within 15 min at 25 °C*. After iodolysis or a Pd-catalyzed cross-coupling[258,259] ($ZnCl_2$ (10 mol%), $Pd(dba)_2$ (2 mol%), P(2-furyl)$_3$ (4 mol%), 25 °C, 12 h) with ethyl 4-iodobenzoate (**115a**), the expected isoquinoline derivatives **116a**[260] and **116b** were obtained in 77–92% yield (Scheme 61).



Scheme 61. Dramatic acceleration of the metalation of isoquinoline (**113a**) and subsequent iodolysis or Pd-catalyzed cross-coupling.

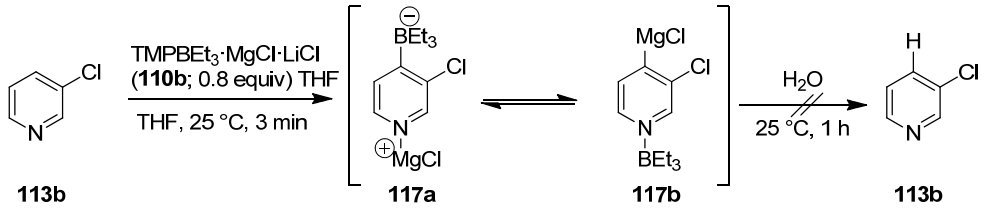
Furthermore, metalation of electron-poor pyridines like 3-chloropyridine (**113b**) were efficiently metalated using TMPMgCl·BEt_3·LiCl (**110b**; 1.1 equiv, 25 °C, 3 min), whereas magnesiation with TMPMgCl·LiCl (**111a**) only affords decomposition. Iodolysis of **114c** provided 3-chloro-4-iodopyridine (**116c**) in 81% yield (Scheme 62).

[258] F. Diederich, P. J. Stang, in *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH: Weinheim, **1998**.
[259] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[260] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.



Scheme 62. Efficient metalation of 3-chloropyridine (**113b**) using TMPMgCl·BEt_3·LiCl (**110b**).

In order to clarify the nature of the generated organometallic species, we examined the reaction mixture using mass spectroscopy (Figure 5). Because organoborates are stable in protic solvents, as well as in mineral acids, the 3-chloropyridylborate of type **117** was stirred in water (25 °C, 1 h; Scheme 63).



Scheme 63. Stability of pyridyltrialkylborates of type **117** in water.

Before and after treatment with water, the mixture was subjected to mass spectroscopic analysis showing that the organoborate of type **117** was not hydrolyzed (Figure 5a and 5b). Due to high sensitivity of organomagnesium reagents towards moisture, the magnesium derivative **117b** would immediately have been hydrolyzed. This result precludes the existence of **117b** as the organometallic intermediate.

a) b)

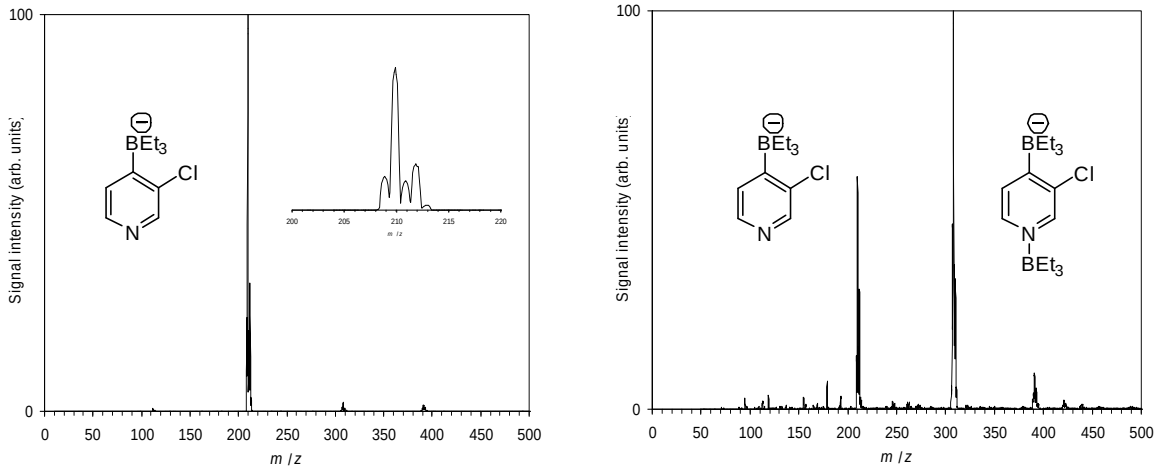
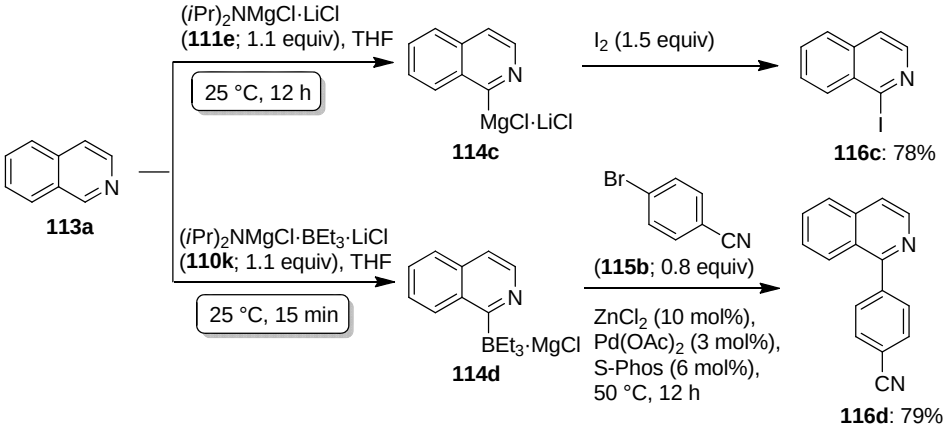


Figure 5. Mass spectroscopic analysis of the organoborate of type **8** in the absence (a) and in the presence (b) of water.

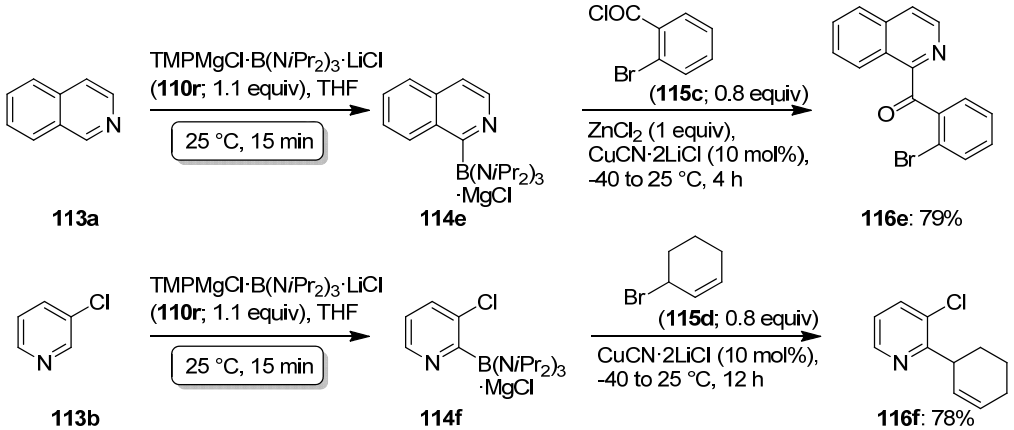
In addition, a more dramatic change in rate of metalation was observed with (*i*Pr)$_2$NMgCl·BEt_3·LiCl (**110k**). Thus, the magnesiation of isoquinoline (**113a**) with (*i*Pr)$_2$NMgCl·LiCl (**111e**) required 12 h at 25 °C. However, using (*i*Pr)$_2$NMgCl·BEt_3·LiCl (**110k**) provided complete metalation only after *15 min at 25 °C*. Iodolysis of **114c** or Pd-

catalyzed cross-coupling with 4-bromobenzonitrile (**115b**; $ZnCl_2$ (10 mol%), $Pd(OAc)_2$ (3 mol%), S-Phos (6 mol%), 50 °C, 12 h) afforded the substituted isoquinoline derivatives **116c**[260] and **116d** in 78–79% yield (Scheme 64).



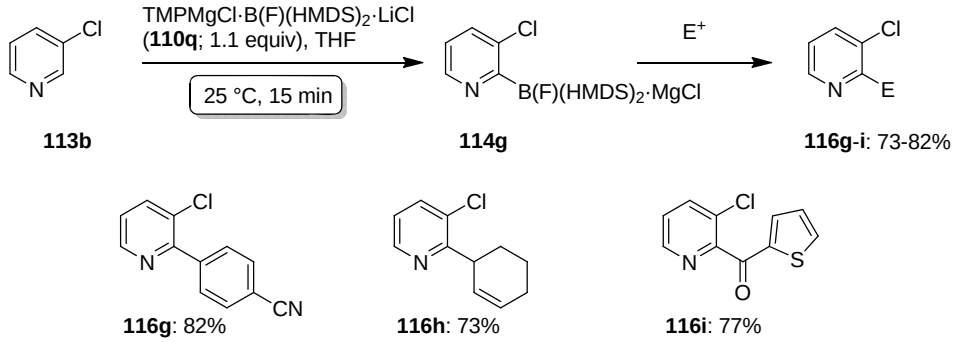
Scheme 64. Accelerated metalation of isoquinoline (**113a**) using (iPr)$_2$NMgCl·BEt$_3$·LiCl (**110k**).

Interestingly, using various aminoboranes such as B(F)(HMDS)$_2$ (**112j**) or B(NiPr$_2$)$_3$ (**112k**) together with TMPMgCl·LiCl (**111a**) also formed stable amidoborates like TMPMgCl·B(NiPr$_2$)$_3$·LiCl (**110r**) or TMPMgCl·B(F)(HMDS)$_2$·LiCl (**110q**). The generated frustrated Lewis pairs of type **110** proved to be highly efficient in metalation reaction with *N*-heterocycles. Thus, treatment of isoquinoline (**113a**) with TMPMgCl·B(NiPr$_2$)$_3$·LiCl (**110r**) furnished (25 °C, 15 min) the organoborate **8c** leading after Cu(I)-catalyzed acylation ($ZnCl_2$ (1 equiv), CuCN·2LiCl (10 mol%), –40 to 25 °C, 4 h) with 2-bromobenzoyl chloride (**115c**; 0.8 equiv) the expected ketone **116e** in 79% yield (Scheme 65). In addition, 3-chloropyridine (**113b**) was functionalized in position 2 using **110r** (25 °C, 15 min) followed by copper-catalyzed allylation with 3-bromocyclohexene (**115d**; 0.8 equiv) providing the alkylated pyridine **116f** in 78% yield (Scheme 65).



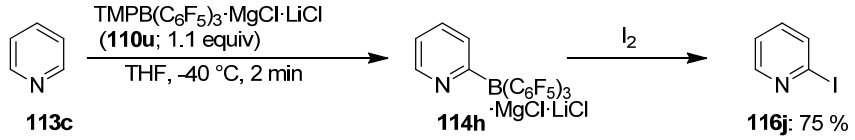
Scheme 65. Functionalization of *N*-heterocycles **113a** and **113b** via accelerated metalation using TMPMgCl·B(NiPr$_2$)$_3$·LiCl (**110r**).

Similarly, 3-chloropyridine (**113b**) was smoothly metalated with TMPMgCl·B(F)(HMDS)$_2$·LiCl (**110q**) providing the heteroarylborate **114g** which reacted with various electrophiles producing the functionalized pyridines **116g–i** in 73–82% yield. Thus, a Pd-catalyzed cross-coupling ($ZnCl_2$ (10 mol%), $Pd(dba)_2$ (2 mol%), P(2-furyl)$_3$ (4 mol%), 25 °C, 12 h) with 4-iodobenzonitrile (0.8 equiv) afforded the substituted 2-arylpyridine **116g** in 82% yield (Scheme 66). Additionally, Cu(I)-catalyzed allylation or acylation with 3-bromocyclohexene (0.8 equiv) or 2-thiophenecarbonyl chloride (0.8 equiv) led to substituted pyridines **116h**–**i** in 73–77% yield (Scheme 66).



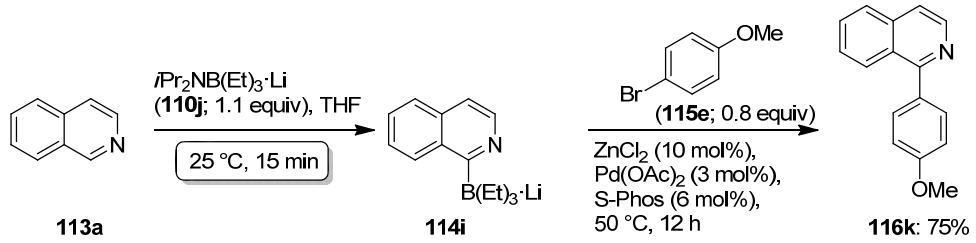
Scheme 66. Preparation of the pyridylborate **113b** using TMPMgCl·B(N*i*Pr$_2$)$_3$·LiCl (**110q**) and subsequent trapping with electrophiles.

Remarkably, the highest reactivity observed in the metalation of *N*-heterocycles with amidoborate bases was observed during the reaction of pyridine (**113c**) with TMPB(C$_6$F$_5$)$_3$·MgCl·LiCl (**110u**; Scheme 67). Treatment of **113c** with **110u** (–40 °C, 2 min) led to the metalated pyridine **114h**. 2-Iodopyridine (**116j**) was obtained in 75 % yield after iodolysis of **114h** (Scheme 67).



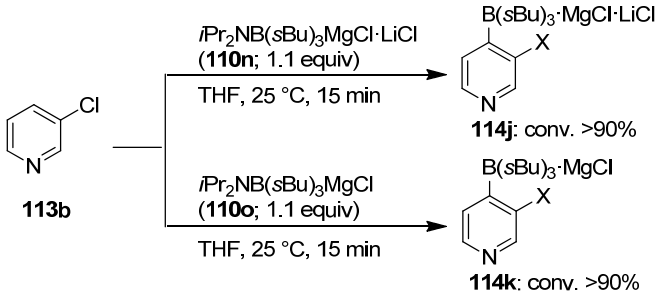
Scheme 67. Instant metalation of pyridine using TMPB(C$_6$F$_5$)$_3$·MgCl·LiCl (**110u**).

In addition, isoquinoline (**113a**) reacted with *i*Pr$_2$NBEt$_3$·Li (**110j**; 25 °C, 15 min) furnishing the heteroarylborate **114i**. A Pd-catalyzed cross-coupling ($ZnCl_2$ (10 mol%), $Pd(OAc)_2$ (3 mol%), S-Phos (6 mol%), 50 °C, 12 h) with 4-bromoanisole (**115e**) provided the substituted isoquinoline **116k** in 75% yield (Scheme 68).



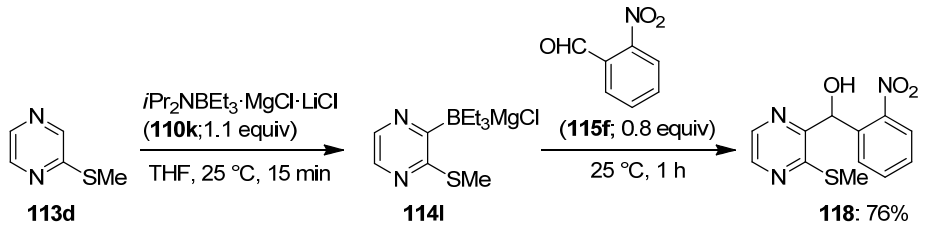
Scheme 68. Preparation of heteroarylborate **114i** using *i*Pr$_2$NBEt$_3$·Li (**110j**) followed by a Pd-catalyzed cross-coupling.

Furthermore, we investigated the influence of LiCl. Based on our experience with metal amide bases, LiCl-complexed metal amide bases generally displayed better solubility in common organic solvents than LiCl-free amides. However, the amidoborate bases with and without LiCl, like *i*Pr$_2$NB(*s*Bu)$_3$·MgCl·LiCl (**110n**) and *i*Pr$_2$NB(*s*Bu)$_3$·MgCl (**110o**), had similar concentrations in THF (c ~ 0.7 mol·L^{-1}) and showed comparable rates of metalation (25 °C, 15 min) with 3-chloropyridine (**113b**) (Scheme 69). These results indicate that lithium chloride additive does not play an essential role in the accelerated metalation process. In order to maintain good solubility of the borate bases, long alkyl moieties on the boron center are highly beneficial.



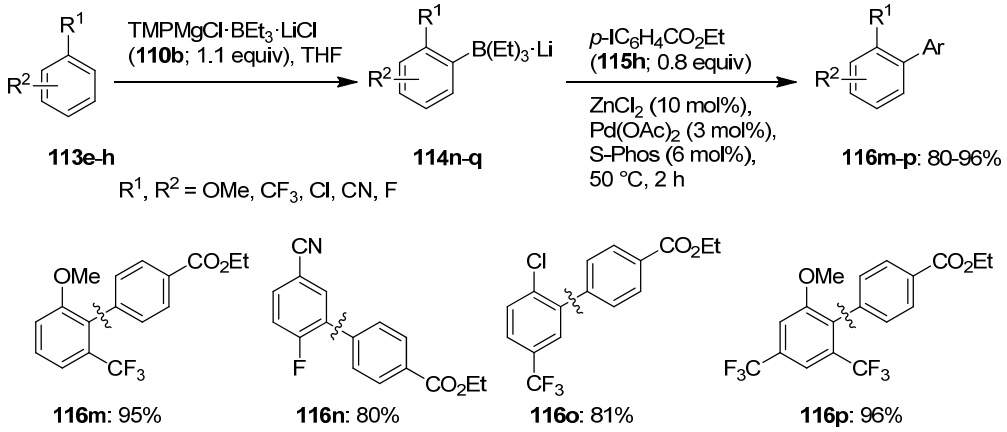
Scheme 69. Metalation of *N*-heterocycles via direct C-H activation using amidoborate bases with and without LiCl like **110n** and **110o**.

As mentioned above, organoborates only react in transition metal catalysis, preferably Rh-catalyzed,[212] with aldehydes. Remarkably, organoborates such as **114l** smoothly added in the absence of transition metals to aldehyde functions. Thus, 2-(methylthio)pyrazine (**113d**) was metalated using *i*Pr$_2$NBEt$_3$·MgCl·LiCl (**110k**; 25 °C, 15 min) affording the organoborate **114l**. Subsequent addition to 2-nitrobenzaldehyde (**115f**) provided the carbinol **118** in 76% yield (Scheme 70).



Scheme 70. Addition of heteroarylborates like **114l** to 2-nitrobenzaldehyde (**115f**).

Moreover, frustrated Lewis pairs like the amidoborates **110b** also proved to be highly efficient metalating reagents with carbocycles. We could use the generated arylborates such as **114m–p** in Pd-catalyzed cross-coupling reactions affording the corresponding biphenyls. Thus, 3-(trifluoromethyl)anisole (**113e**) was metalated using TMPBEt$_3$·MgCl·LiCl (**110b**; 1.1 equiv, 25 °C, 1 h) furnishing after a Suzuki-type cross-coupling ($ZnCl_2$ (10 mol%), $Pd(OAc)_2$ (3 mol%), S-Phos (6 mol%), 65 °C, 2 h) with ethyl 4-iodobenzoate (**115g**; 0.8 equiv) the functionalized biphenyl **116l** in 95% yield (Scheme 71). Similarly, 4-fluorobenzonitrile (**113f**) reacted with **110b** (25 °C, 30 min) affording the arylborate **114n** leading, after a Pd-catalyzed cross-coupling ($ZnCl_2$ (10 mol%), $Pd(OAc)_2$ (3 mol%), S-Phos (6 mol%), 65 °C, 2 h) with **115g** (0.8 equiv) substituted anisole **116m** in 80% yield (Scheme 71). Using TMPBEt$_3$·MgCl·LiCl (**110b**; 25 °C, 12 h), 4-chloro-(trifluoromethyl)benzene (**113g**) produced after a Pd-catalyzed cross-coupling with **115g** (0.8 equiv) the functionalized biphenyl **116n** in 81% yield (Scheme 71). Furthermore, TMPBEt$_3$·MgCl·LiCl (**110b**; 25 °C, 30 min) reacted with 3,5-bis(trifluoromethyl)anisole (**113h**) providing the substituted arylborate **114p** leading after a Suzuki-type cross-coupling to the polysubstituted biaryl **116o** in 96% yield (Scheme 71).



Scheme 71. Functionalization of substituted carbocycles via direct C-H activation using TMPBEt$_3$·MgCl·LiCl (**110b**).

In summary, a new class of thermally stable frustrated Lewis pairs was readily prepared and applied in the direct and accelerated synthesis of functionalized organoborates. Furthermore, these organoboron reagents smoothly react in uncatalyzed addition to aldehydes or in Suzuki-type cross-coupling reactions.

3.5 Calculation of C-H Acidities in Polysubstituted Aromatics and Heteroaromatics

As indicated by the increasing numbers of publications addressing the regioselective C-H activation reactions, such methods have emerged as important tools for direct functionalizations of polysubstituted arenes and heteroarenes.[214] However, the prediction of regioselectivity in metalation reactions is still difficult, since electronic and steric effects as well as coordination play important roles in such reactions.[215] Moreover, the determination of the most acidic position in substituted arenes or heteroarenes is difficult, since their pK_a-values are often not available experimentally. Thus, we envisioned developing a relatively fast as well as reasonably accurate model emitting pK_a values for six-membered polysubstituted aromatics and heterocycles using DFT-methods (density functional theory).[261] Thus, before starting calculations of solution-phase acidities for C-H bonds in aromatic heterocycles, it is important to ascertain that the gas-phase acidity can be accurately calculated for the same bond, defined as the relative free energy (Scheme 72).

Scheme 72. Gas-phase acidity of an heteroaromatic C-H bond.

Thus, eleven compounds (**119a**–**k**) were included in a test-set having reported and experimentally determined relative Gibbs free energies.[262] Various post-HF (post Hartree-Fock) and DFT methods in combination with various basis sets were investigated. It could be shown that the hybride density functional B3LYP using the 6-311+G(2df,2p) basis set fit the best to experimental values (Table 13).[263]

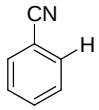
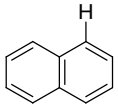
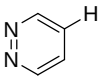
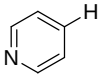
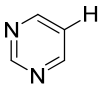
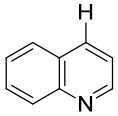
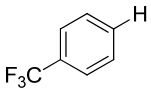
Table 13. Experimental and theoretical gas-phase acidities for 11 arenes and heteroarenes of C-H bonds (B3LYP/6-311++G(2df,2p)//B3LYP/6-31+G**).

Entry	Compound	ΔG^0_{298} (exp) [kcal·mol^{-1}]	ΔG^0_{298} (calc) [kcal·mol^{-1}]
1	 **119a**	392.9	393.6

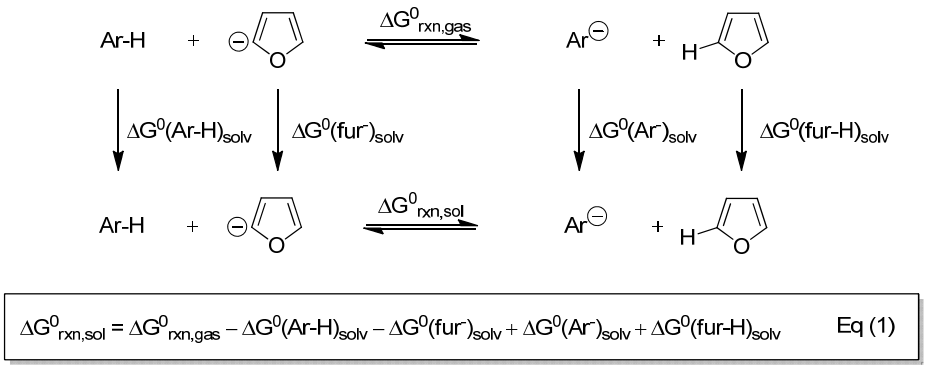
[261] K. Shen, Y. Fu, J.-N. Li, L. Liu, Q.-X. Guo, *Tetrahedron* **2007**, *63*, 1568.

[262] Gas-phase acidities of aromatic heterocycles: a) C. H. DePuy, S. R. Kass, G. P. Bean, *J. Org. Chem.* **1988**, *53*, 4427; b) M. Meot-Ner, J. F. Liebman, S. A. Kafafi, *J. Am. Chem. Soc.* **1988**, *110*, 5937; c) M. Meot-Ner, S. A. Kafafi, *J. Am. Chem. Soc.* **1988**, *110*, 6297; d) G. E. Davico, V. M. Bierbaum, C. H. Depuy, G. B. Ellison, R. R. Squires, *J. Am. Chem. Soc.* **1995**, *117*, 2590; e) D. R. Reed, S. R. Kass, *J. Mass Spectrom.* **2000**, *35*, 534.

[263] DFT calculations were carried out using the Gaussian03 Rev.B.04 program package with the nonlocal hybrid B3LYP exchange correlation functionals in combination with the 6-311++G(2df,2p) basis set for all atoms. Unless otherwise stated energies refer to relative Gibbs free energies (ΔG^0_{298}). For full details on the computational study and full citations, see Experimental Section.

Entry	Compound	ΔG^0_{298} (exp) [kcal·mol^{-1}]	ΔG^0_{298} (calc) [kcal·mol^{-1}]
			
2	**119b**	374.6	375.4
			
3	**119c**	380.0	382.9
			
4	**119d**	383.8	386.9
			
5	**119e**	373.4	374.7
			
6	**119f**	383.1	384.4
			
7	**119g**	384.0	384.1
			
8	**119h**	376.9	378.0
			
9	**119i**	376.9	378.5
			
10	**119j**	373.0	376.9
			
11	**119k**	378.6	381.6

As the calculated gas-phase acidities show (Table 13), DFT methods tend to systematically overestimate this chemical property. Thus, in order to preclude systematic errors and to improve accuracy, we based our model on an isodesmic reaction of the arene Ar-H with a furyl anion affording the aryl (Ar^-) anion and furan (Scheme 73).



Scheme 73. Isodesmic reaction for the pKa value calculations in solution and its equation.

A new test-set of ten heterocyclic compounds (**120a**–**j**) with reported experimental pK_a values[264,266] in solution-phase (DMSO[265] and THF)[266] was theoretically explored to find the optimum method-basis-set combination and solvation model for the calculation of the most accurate pK_a values via Eq (2) (Figure 6).[261]

$$pK_a\,(\text{HetAr-H}) = 35.0 + \frac{\Delta G^0_{rxn,sol}}{2.303 \cdot RT} \qquad \text{Eq (2)}$$

Figure 6. Calculation of pK_a values via calculated relative Gibbs free energies ($\Delta G^0_{rxn,sol}$) in Eq (2) for the isodesmic reaction of Scheme 73 (experimental pK_a (furan) = 35.0).

Thus, we examined various polarized continuum models (PCM), such as IEFPCM (integral equation formalism model), CPCM (polarized conductor calculation model), and IPCM (static isodensity surface polarized continuum model). The best fit and hence the most accurate results were observed using the Hartree-Fock method (RHF) in combination with the aug-CC-pVDZ basis set and the IEFPCM (IEFPCM/RHF/aug-CC-pVDZ//B3LYP/6-311++G(2df,2p)). In particular, the IEFPCM/bondi model (TSNUM=60; TSARE = 0.4; alpha = 1.20) was found to be the most accurate for calculating pK_a values of the C-H bonds in arenes and heteroarenes of the test-set (**120a**–**j**).[267] Due to over- or underestimating of chemical properties by quantum chemical methods, we applied a correction term in order to get higher degrees of accuracy. Hereby, the correlation coefficient between the experimental

[264] pK_a of aromatic heterocycles: F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456 and references therein.
[265] Despite the various solvents utilized in pK_a determination, there is a linear relationship among these different acidity scales, see: A. Streitwieser, D. Z. Wang, M. Stratakis, A. Facchetti, R. Gareyev, A. Abbotto, J. Krom, K. V. Kilway, *Can. J. Chem.* **1998**, *76*, 765.
[266] R. R. Fraser, T. S. Mansour, S. Savard, *Can. J. Chem.* **1985**, *63*, 3505.
[267] The theoretical calculations were conducted with the Gaussian03 Rev.B.04 package. HF, B3LYP, and MP2(FC) methods with various basis sets (i.e. 6-31+G(2d,2p), G3MP2large, 6-311++G(2df,2p), or aug-CC-pVDZ), different solvation models (i.e. IEFPCM, CPCM, IPCM) and varying cavity models (i.e UA0, bondi) and electrostatic scaling factors (0.9-1.30) were systematically utilized and compared. Finally, the gas-phase energy calculations were conducted using the B3LYP/6-311++G(2df,2p)//B3LYP/6-311++G(2df,2p) method. The PCM solvation model was used in its integral equation formalism (IEFPCM) calculating the solvation free energies in DMSO and converted via its linear correlation to THF solvent. All IEFPCM calculations were performed at RHF/aug-CC-pVDZ level (TSNUM=60; TSARE = 0.4; alpha = 1.20).

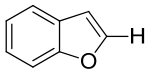
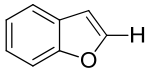
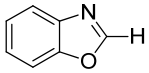
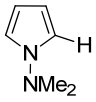
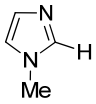
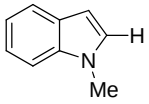
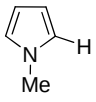
pK_a values and the calculated results provided by IEFPCM/bondi method is as high as 1.011. The mean error is 1.7 pk_a units (Figure 7).

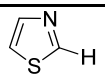
$$pK_a\,(exp) = 1.011 \cdot pK_a(calc) - 1.7 \qquad \text{Eq (3)}$$

Figure 7. Correlation between the experimental and theoretical pKa values for 10 aromatic heterocycles (**120a**–**j**).

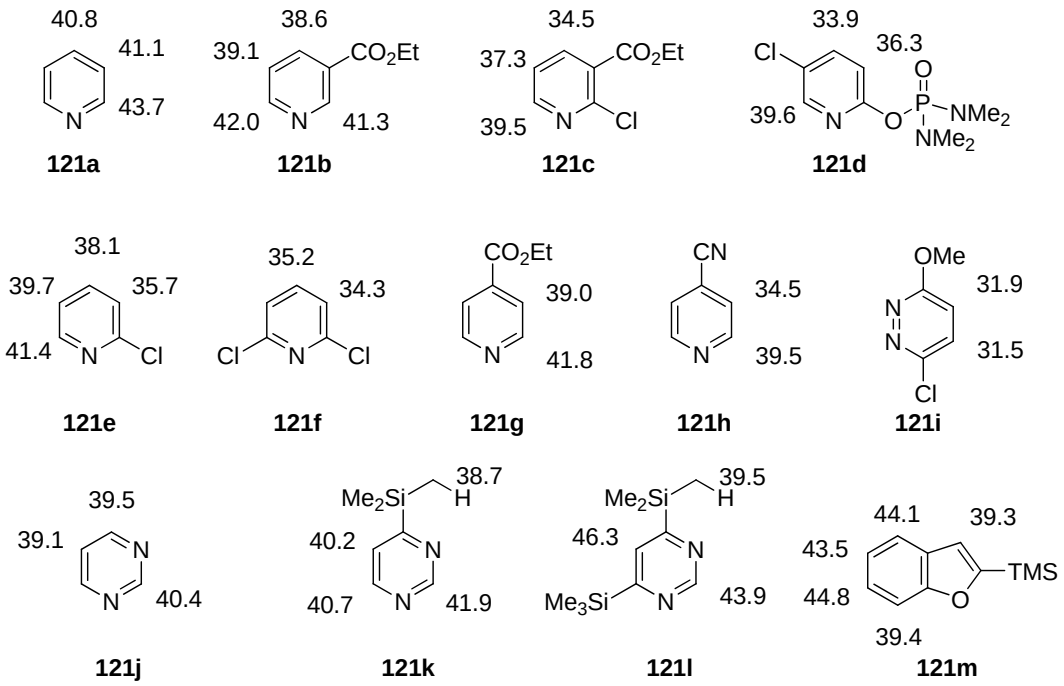
Correction of the calculated pK_a values gives an improved rmse (root mean squared error) of 1.0 pK_a units (Table 14).

Table 14. Experimental, theoretical, and corrected pK_a values in THF for C-H bonds of heteroarenes (**2a**-**j**).

Entry	Compound	pK_a (exp)	pK_a (calc)	pK_a (corr)
1	 **120a**	33.2	34.2	32.5
2	 **120b**	33.5	33.3	31.6
3	 **120c**	24.5	26.9	25.2
4	 **120d**	37.1	39.8	38.1
5	 **120e**	35.6	35.6	33.9
6	 **120f**	33.7	36.2	34.5
7	 **120g**	38.1	38.8	37.1
8	 **120h**	39.5	40.8	39.1

Entry	Compound	pK_a (exp)	pK_a (calc)	pK_a (corr)
9	 **120i**	29.7	31.4	29.7
10	 **120j**	33.0	34.7	33.0

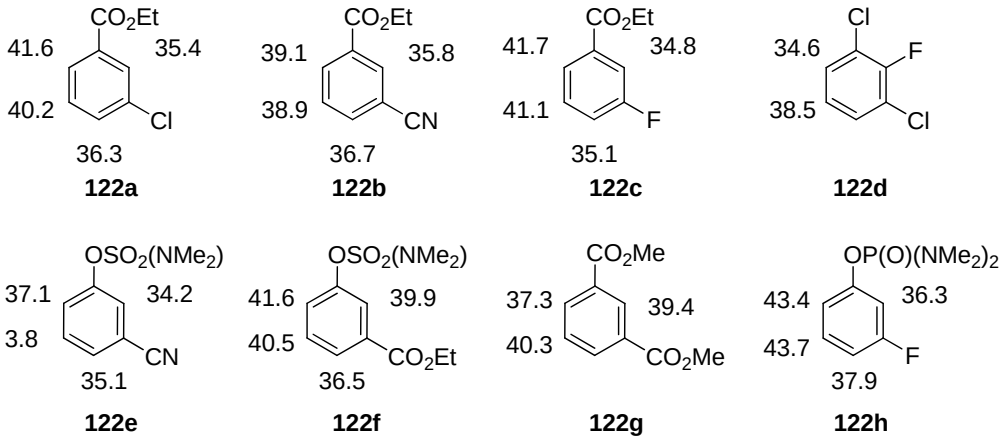
The developed calculation model enabled us to estimate pK_a values of various substituted aromatics and heteroaromatics. Thus, the C-H acidities of substituted and unsubstituted heterocycles (**121a**–**m**), such as pyridine, pyrimidine, pyrazine or benzofuran, which are experimentally not accessible, were obtained (Scheme 74). In conclusion, position 4 is the most acidic C-H bond of unsubstituted pyridine (**121a**) or pyridines bearing an electron-withdrawing group in position 3 (**121b**–**d**). Furthermore, 2-halo-pyridines (**121e**–**f**) are highly acidic *ortho* to the substitutent, namely in position 3 (Scheme 74). The normal acidity of unsubstituted pyrimidine (**121j**) can be shifted by electron-donating silicon-substituent from position 5 to position 2.



Scheme 74. Calculated solution-phase pK_a values in THF of various substituted heteroaromatics (**121a**–**m**).

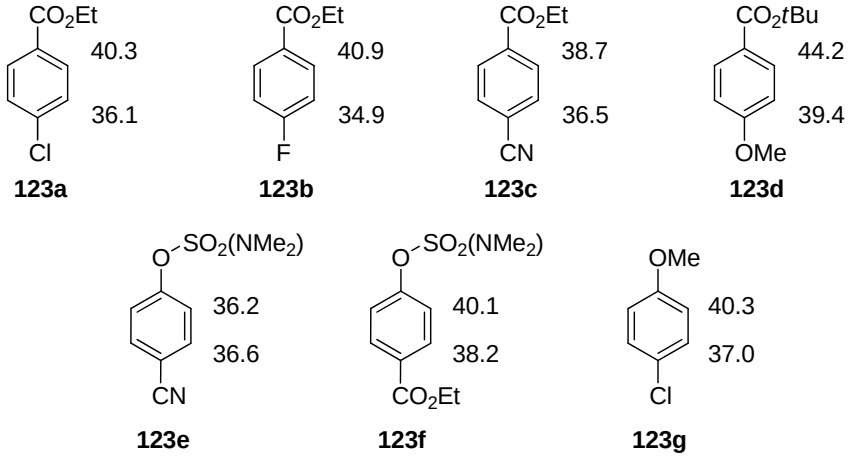
Furthermore, pK_a values of 1,3-disubsituted arenes (**122a**–**h**), like benzoates, sulfamates or phophinates, were calculated using the described method. We could demonstrate that electron-poor 1,3-disubstituted benzoates (**122a**–**c**, **122g**), sulfamates (**122e–f**) or a

phosphinate (**122h**) display the most acidic C-H bond between the two substitutents (Scheme 75).



Scheme 75. Calculated solution-phase pK_a values in THF of 1,3-disubstituted benzene derivatives (**122a**–**h**).

Similarly, the solution-phase pK_a values in THF of *para*-disubstituted aromatics (**123a**–**g**) bearing ester, cyano, sulfamoyloxy, or methoxy groups were calculated (Scheme 76). Thereby, the positions *ortho* to halogen-substituents are generally the most acidic C-H bonds.



Scheme 76. Calculated solution-phase pK_a values in THF of 1,4-disubstituted benzene derivatives (**123a**–**g**).

In conclusion, we developed a model for the calculation of pKa values of various functionalized arenes and heteroaromatics, which are experimentally not accessible. Thereby, we could identify the electronic effects responsible for the shift of C-H acidity in substituted aromatics and heteroaromatics.

4. Regioselective Preparation of Heteroarylmagnesium Reagents and its Applications in Functionalization and Regioregular Polymerization Reactions

4.1 Introduction

Applications of conjugated organic polymers in novel electronic devices are as numerous as versatile.[268] In particular, poly(3-alkylthiophenes) (P3ATs), and predominantly poly(3-hexylthiophene) (P3HT), proved to be especially valuable in organic photovoltaics.[269] Such polymers show good solubility in common organic solvents, processability, and environmental stability.[270] In order to adopt planar conformations, which consequently result in highly ordered two- and three-dimensional polymer architectures, high regioregularity and narrow polydispersity of poly(3-alkylthiophenes) are essential for these physical properties.[271] Regioregular P3ATs were first synthesized using McCullough´s method.[272] A similar method was developed shortly thereafter by Rieke.[273] Triggered by intensive studies on Hal/Mg-exchange reactions,[274] the McCullough method was modified and has been known as Grignard metathesis (GRIM).[272e] However, McCullough´s method suffers from several drawbacks, such as the demand of highly purified starting materials. In contrast, Rieke´s method uses easy-to-purify starting materials. Nevertheless, Rieke´s method involves highly active zinc (Zn*, Rieke-Zn), generated via an extensive preparation. In general, both methods require low temperatures and long reaction times. Although the GRIM method combines

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[269] a) A. Gadisa, W. D. Oosterbaan, K. Vandewal, J.-C. Boslee, S. Bertho, J. D'Haen, L. Lutsen, D. Vanderzande, J. V. Manca, *Adv. Funct. Mater.* **2009**, *19*, 1; b) R. D. McCullough, S. Tristam-Nagle, S. P. Williams, R. D. Lowe, M. Jayaraman, *J. Am. Chem. Soc.* **1993**, *115*, 4910; c) R. D. McCullough, S. Williams, *J. Am. Chem. Soc.* **1993**, *115*, 11608.

[270] a) T.-A. Chen, X. Wu, R. Rieke, *J. Am. Chem. Soc.* **1995**, *117*, 233; b) A. Patil, A. J. Heeger, F. Wudl, *Chem. Rev.* **1988**, *88*, 183; c) D. Cotts, Z. Reyes, in *Electrically Conductive Organic Polymers for Advanced Applications*; Noyes Data Corp.: Park Ridge, NJ, **1986**; d) *Science and Applications of Conducting Polymers*; (Eds.: W. R. Salaneck, D. T. Clark, E. J. Samuelsen); IOP Publications Ltd.: Bristol, UK, **1990**, p 1.

[271] a) M. Urien, L. Bailly, L. Vignau, E. Cloutet, A. de Cuendias, G. Wantz, H. Cramail, L. Hirsch, J.-P. Parneix, *Polym. Int.* **2008**, *57*, 764; b) R. Miyakoshi, A. Yokoyama, T. Yokozawa, *Macromol. Rapid. Commun.* **2004**, *25*, 1663.

[272] a) R. S. Loewe, P. C. Ewbank, J. Liu, L. Zhai, R. D. McCullough, *Macromolecules* **2001**, *34*, 4324; b) R. D. McCullough, R. D. Lowe, *J. Chem. Soc., Chem. Commun.* **1992**, 70; b) R. D. McCullough, R. Lowe, M. Jayaraman, D. L. Anderson, *J. Org. Chem.* **1993**, *58*, 904; c) R. D. McCullough, R. D. Lowe, M. Jayaraman, P. C. Ewbank, D. L. Anderson, S. Tristram-Nagle, *Synth. Met.* **1993**, *55*, 1198; d) R. D. McCullough, S. P. Williams, S. Tristram-Nagle, M. Jayaraman, P. C. Ewbank, L. Miller, *Synth. Met.* **1995**, *67*, 279; e) R. S. Loewe, S. M. Khersonsky, R. D. McCullough, *Adv. Mater.* **1999**, *11*, 250.

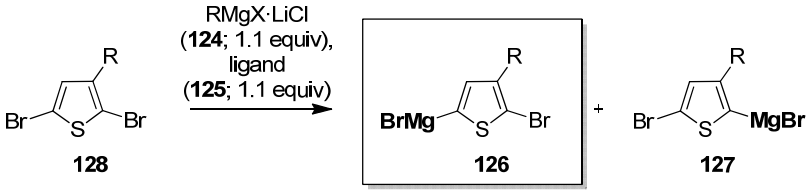
[273] a) T.-A. Chen, R. D. Rieke, *J. Am. Chem. Soc.* **1992**, *114*, 10087; b) T.-A. Chen, R. D. Rieke, *Synth. Met.* **1993**, *60*, 175; c) T.-A. Chen, R. A. O'Brien, R. D. Rieke, *Macromolecules* **1993**, *26*, 3462; d) T.-A. Chen, X. Wu, R. D. Rieke, *J. Am. Chem. Soc.* **1995**, *117*, 233.

[274] L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem., Int. Ed.* **1998**, *37*, 1701.

advantages of both methods, this procedure also generates significant amounts of undesired regioisomeric thiophenylmagnesium derivatives.

4.2 Regioselective Br/Mg-Exchange Reagents

Thus, we envisioned convenient Hal/Mg-exchange reagents (**124**) involving bulky ligands of type **125** in order to achieve high regioselectivity via steric discrimination. Furthermore, our target was to improve the scope in order to provide single regioisomers of substituted five-membered heterocycles of type **126** prior to polymerization reactions (Scheme 77).

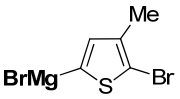
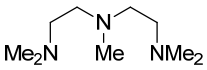
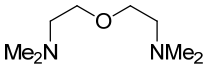
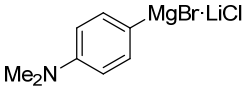
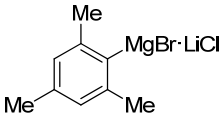
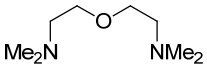
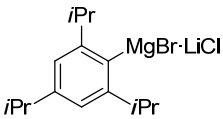
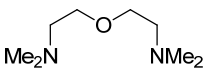


Scheme 77. Regioselective Br/Mg-exchange using ligand-complexed magnesium reagents.

Efficient and regioselective Br/Mg-exchange was achieved using 2,5-dibromo-3-methylthiophene (**128a**) and various magnesium reagents (**124a**–**d**). Thus, treatment of **128a** with *i*PrMgCl·LiCl (**124a**; 1.1 equiv) furnished a regioisomeric mixture of the thiophenylmagnesium derivatives **126a** and **127a** in a ratio of 80:20 (Table 15, entry 1). Additive ligands such as TMEDA (*N*,*N*,*N*',*N*'-tetramethylethan-1,2-diamine), DABCO (1,4-diazabicyclo[2.2.2]octan), or NEt_3, did not show any influence on the Br/Mg-exchange reaction. However, prior addition of a ligand, like BDMAMA (**125a**; bis[2-dimethylamin)ethyl]methylamine) or BDMAEE (**125b**; bis[2-dimethylamin)ethyl]-ether), significantly improved the regioisomeric ratio of the obtained organomagnesium reagent in favour of **126a** (85:15 and 87:13; Table 15, entries 2 and 3). Moreover, conducting the exchange reaction of **128a** with **124a** and **125b** at lower temperatures (–60 °C, 1 h) proved to be beneficial with respect to the regioisomeric ration (Table 15, entry 4). In comparison to secondary alkylmagnesium reagents, the arylmagnesium derivatives, such as **124b** or **124c**, displayed lower exchange reactions rates and only a small increase of regioselectivity (Table 15, entry 5 and 6). Remarkably, using ligand **125b** with mesitylmagnesium bromide (**124c**) in the Br/Mg-exchange reaction with **128a** displayed a regioisomeric ratio of 97:3 in favour of **126a** (Table 15, entry 7). Moreover, increasing steric hindrance of the exchange reagent, e.g. using LiCl-complexed triisopropylphenylmagnesium bromide (**124d**; TIPMgBr·LiCl), furnished already in the absence of any ligand a regioisomeric ratio of 96:4 (Table 15, entry 8). Furthermore, addition of ligand **125b** gave an excellent regioisomeric ratio of >99:1 after the Br/Mg-exchange with **124d** (Table 15, entry 9). Thereby, no

regioisomer like **127a** was observed in ^{1}H NMR measurements of the hydrolyzed (HOAc, 10 equiv) crude reaction mixture.

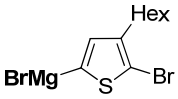
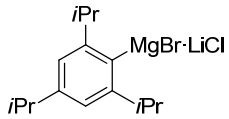
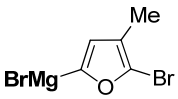
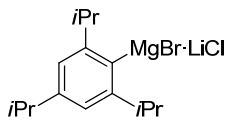
Table 15. Regioselective Br/Mg-exchange with 2,5-dibromo-3-methylthiophene (**128a**) using various complexed and uncomplexed exchange reagents of type **124**.

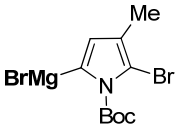
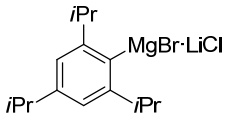
Entry	RMgX·LiCl	Ligand	Conditions (T, t)[a]	Regioisomeric ratio[b] of **126** to **127**
	*i*PrMgCl·LiCl			
1	**124a**	-	–20 °C, 20 min	**126a** (80 : 20)[c]
				
2	**124a**	**125a**	–20 °C, 20 min	**126a** (85 : 15)
				
3	**124a**	**125b**	–20 °C, 20 min	**126a** (87 : 13)
4	**124a**	**125b**	–60 °C, 1 h	**126a** (90 : 10)
				
5	**124b**	-	–20 °C, 3 h[d]	**126a** (82 : 18)
				
6	**124c**	-	–20 °C, 12 h[d]	**126a** (84 : 16)
				
7	**124c**	**125b**	–20 °C, 12 h	**126a** (97 : 3)
				
8	**124d**	-	–20 °C, 12 h[d]	**126a** (96 : 4)
				
9	**124d**	**125b**	–20 °C, 16 h	**126a** (>99 : 1)[e]

[a] Complete conversion as determined by GC-analysis of an iodolyzed reaction aliquot. [b] Determined by ^{1}H NMR of the hydrolyzed (HOAc) crude reaction mixture. [c] Ligands such as TMEDA, DABCO, or NEt_3 did not influence the ratio of regioisomers after Br/Mg-exchange. [d] In the absence of LiCl, conversions of < 10% was observed. [e] Regioisomer **127a** was not observed in ^{1}H NMR measurements of the hydrolyzed crude reaction mixture.

In addition, complexation with $(Me_2NCH_2CH_2)_2O$ (**125b**; BDMAEE) also proved to be highly beneficial in Br/Mg-exchange reactions with various five-membered dibromoheterocycles (**128b**–**d**). Thus, the reaction of 2,5-dibromo-3-hexylthiophene (**128b**) with *i*PrMgCl·LiCl (**124a**; 1.1 equiv, –20 °C, 20 min) in the presence of BDMAEE (**125b**; 1.1 equiv) afforded a ratio of regioisomers of 85:15 in favour of thiophen-5-ylmagnesium bromide **126b** (Table 16, entry 1). Similarly, triisopropylphenylmagnesium bromide (**124d**; TIPMgBr·LiCl; 1.1 equiv, –20 °C, 16 h) in the presence of **125b** provided the single regioisomer **3b** (>99:1) (Table 16, entry 2). Furthermore, 2,5-dibromo-3-methylfuran (**128c**) furnished after Br/Mg-exchange with *i*PrMgCl·LiCl/BDMAE (1.1 equiv/1.1 equiv, –10 °C, 6 h) or with TIPMgBr·LiCl/BDMAE (1.1 equiv/1.1 equiv, –10 °C, 16 h) the furylmagnesium derivative **126c** in a ratio of 80:20, and 95:5 respectively (Table 16, entries 3 and 4). Interestingly, pyrrolylmagnesium derivatives like **126d** could be regioselectively prepared via a Br/Mg-exchange using *i*PrMgCl·LiCl/BDMAE (1.1 equiv/1.1 equiv, –10 °C, 6 h) or TIPMgBr·LiCl/BDMAE (1.1 equiv/1.1 equiv, –10 °C, 16 h) from the corresponding pyrrol derivative **128d** affording ratios of 75:25 and 91:9 (Table 16, entries 5 and 6).

Table 16. Regioselective preparation of organomagnesium reagents (**126b**–**d**) from trisubstituted five-membered heterocycles using various **125b**–compelxed organomagnesium derivatives like **124a** and **124d**.

Entry	RMgX·LiCl, ligand	Conditions (T, t)[a]	Organomagnesium reagent, regioisomeric ratio (**126**:**127**)[b]
1	*i*PrMgCl·LiCl, $(Me_2NCH_2CH_2)_2O$ **124a**, **125b**	–20 °C, 20 min	 **126b** (85 : 15)
2	 $(Me_2NCH_2CH_2)_2O$ **124d**, **125b**	–20 °C, 16 h	**126b** (>99 : 1)[c]
3	*i*PrMgCl·LiCl, $(Me_2NCH_2CH_2)_2O$ **124a**, **125b**	–10 °C, 6 h	 **126c** (80 : 20)
4	 $(Me_2NCH_2CH_2)_2O$ **124d**, **125b**	–10 °C, 16 h	**126c** (95 : 5)

Entry	RMgX·LiCl, Ligand	Conditions (t, T)[a]	Organomagnesium reagent, regioisomeric ratio (**126**:**127**)[b]
5	*i*PrMgCl·LiCl, $(Me_2NCH_2CH_2)_2O$ **124a**, **125b**	–10 °C, 6 h	 **126d** (75 : 25)
6	 $(Me_2NCH_2CH_2)_2O$ **124d**, **125b**	–10 °C, 16 h	**126d** (91 : 9)

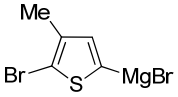
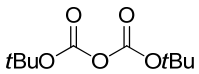
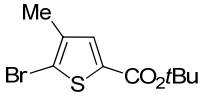
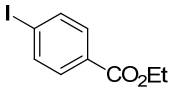
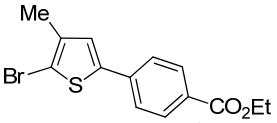
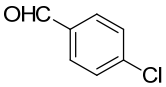
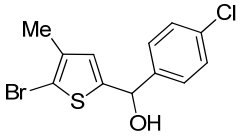
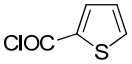
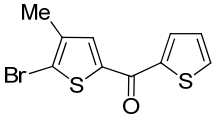
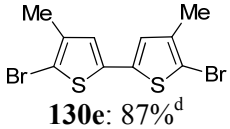
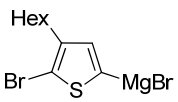
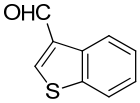
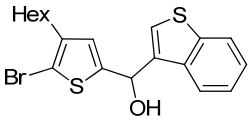
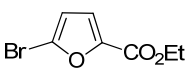
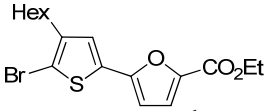
[a] Complete conversion as determined by GC-analysis of an iodolyzed reaction aliquot. [b] Determined by ^{1}H NMR of the hydrolyzed (HOAc) crude reaction mixture. [c] Regioisomer **127b** was not observed in ^{1}H NMR measurements of the hydrolyzed crude reaction mixture.

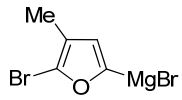
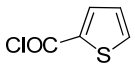
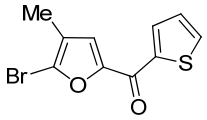
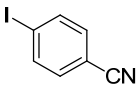
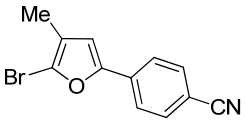
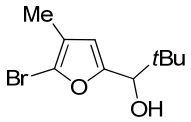
4.3 Functionalization of Regioselectively Generated Heteroarylmagnesium Derivatives

The highly regioselective Br/Mg-exchange reaction with five-membered heterocycles enabled us to selectively functionalize these scaffold. Thus, **126a** lead after transmetalation with $ZnCl_2$ (1 equiv, –20 °C, 10 min) followed by a Cu(I)-catalyzed acylation (CuCN·2LiCl (10 mol%), –40 to 25 °C, 4 h) with di-*tert*-butyl dicarbonate (**129a**; 1.2 equiv) to the functionalized thiophene **130a** in 83% yield (Table 17, entry 1). Furthermore, a Negishi cross-coupling ($Pd(PPh_3)_4$ (4 mol%), 25 °C, 1 h) of **126a** (1 equiv) with ethyl 4-iodobenzoate (**129b**; 1.2 equiv) afforded, after previous transmetalation with $ZnCl_2$ (1 equiv), the substituted benzoate **130b** in 86% yield (Table 17, entry 2). Moreover, addition of the thiophenylmagnesium derivative **126a** to 4-chlorobenzaldehyde (**129c**; 1.2 equiv, 0 °C, 1 h) provided the functionalized carbinol **130c** in 94% yield (Table 17, entry 3). In addition, transmetalation of **126a** (1 equiv) with $ZnCl_2$ (1 equiv, –20 °C, 10 min) followed by a Cu(I)-catalyzed acylation (CuCN·2LiCl (10 mol%), –40 to 25 °C, 4 h) with thiophene-2-carbonyl chloride (**129d**; 1.2 equiv) to the functionalized ketone **130d** in 85% yield (Table 17, entry 4). Similarly, transmetalation of **126a** (1 equiv) with $ZnCl_2$ (0.5 equiv, –40 °C, 10 min) and CuCN·2LiCl (0.5 equiv, –40 °C, 10 min) followed by addition of chloranil (1.5 equiv, 0 to 25 °C, 1 h) generated the substituted thiophenyldimer **130e** in 87% yield (Table 17, entry 5). The

hexyl-substituted thiophenylmagnesium derivative **126b** was functionalized via its addition to 1-benzothiophen-3-carbaldehyde (**129e**; 1.2 equiv, 0 °C, 1 h) producing the corresponding alcohol **130f** in 83% yield (Table 17, entry 6). Also, transmetalation of **126b** with $ZnCl_2$ (1 equiv, –20 C, 10 min) and subsequent Pd-catalyzed cross-coupling ($Pd(PPh_3)_4$ (4 mol%), 25 °C, 1 h) with ethyl 5-bromo-2-furoate (**129f**) lead to the expected diheteroaryl **130g** in 79% yield (Table 17, entry 6). The substituted furylmagnesium derivative **126c** was functionalized via Cu(I)-catalyzed acylation using thiophene-2-carbonyl chloride (**129d**) or via a Negishi cross-coupling ($ZnCl_2$ (1 equiv), –20 °C, 10 min ; then $Pd(PPh_3)_4$ (4 mol%), 25 °C, 1 h) with 4-iodobenzonitrile (**129g**) leading to the polysubstituted furans **130h–i** in 78–79% yield (Table 17, entries 8 and 9). Similarly, addition of **126c** to pivaldehyde (**129h**; 1.2 equiv, 0 °C, 1 h) provided the corresponding alcohol **130j** in 73% yield (Table 17, entry 10).

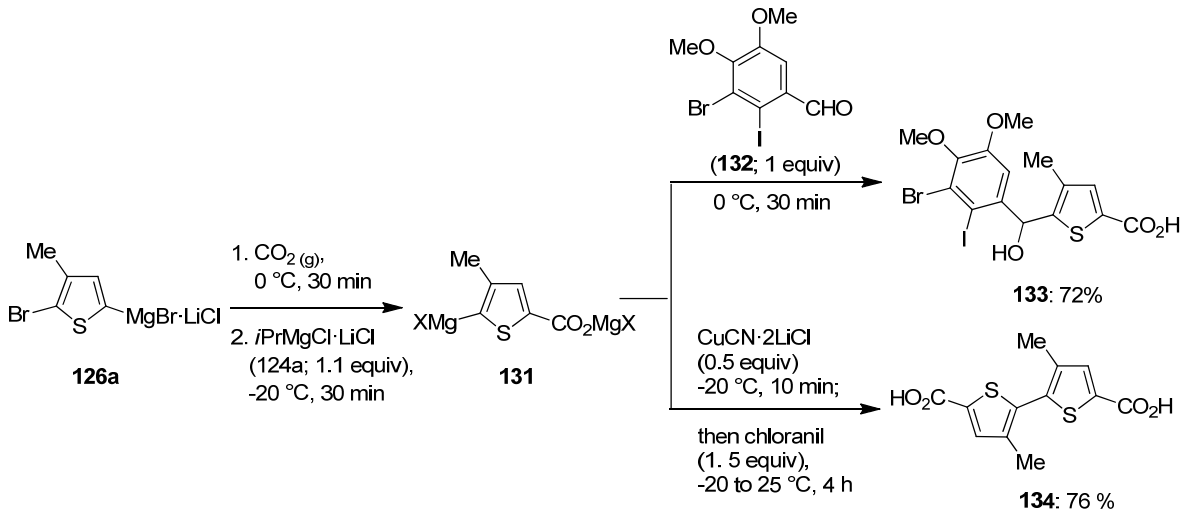
Table 17. Preparation of functionalized five-membered heterocycles of type **130** via regioselectively generated heteroarylmagnesium reagents of type **126**.

Entry	Magnesium reagent	Electrophile	Product, Yield[a]
1	 **126a**	 **129a**	 **130a**: 83%[c]
2	**126a**	 **129b**	 **130b**: 86%[b]
3	**126a**	 **129c**	 **130c**: 94%
4	**126a**	 **129d**	 **130d**: 85%[c]
5	**126a**	-	 **130e**: 87%[d]
6	 **126b**	 **129e**	 **130f**: 83%
7	**126b**	 **129f**	 **130g**: 79%[b]

Entry	Magnesium reagent	Electrophile	Product, Yield[a]
8	 **126c**	 **129d**	 **130h**: 79%[c]
9	**126c**	 **129g**	 **130i**: 78%[b]
10	**126c**	 **129h**	 **130j**: 73%

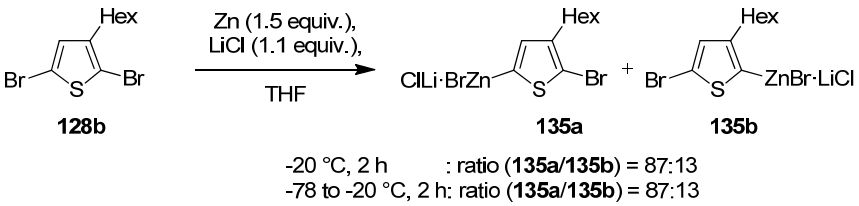
[a] Yield of analytically pure isolated product as determined by ^{1}H NMR. [b] Obtained after a Negishi cross-coupling ($ZnCl_2$ (1 equiv); then $Pd(PPh_3)_4$ (4 mol%)) with Ar-X (1.2 equiv). [c] Obtained after transmetalation with $ZnCl_2$ (1 equiv) followed by a Cu(I)-catalyzed acylation with ArCOCl (1.2 equiv). [d] Obtained after transmetalation with $ZnCl_2$ (0.5 equiv) and a copper-mediated oxidative dimerization (CuCN·2LiCl (0.5 equiv); then addition of chloranil (1.5 equiv)).

Interestingly, using the described method for the regioselective preparation of heteroarylmagnesium derivatives via Br/Mg-exchange, we could selectively *bis*functionalize 2,5-dibromo-3-methylthiophene (**128a**) in two one-pot procedures. Thus, the thiophenylmagnesium derivative **126a** added smoothly to CO_2 (0 °C, 30 min) leading to the corresponding thiophenylcarboxylate derivative. Subsequent treatment with *i*PrMgCl·LiCl (1.1 equiv, –20 °C, 30 min) generated the Grignard reagent **131** via Br/Mg-exchange. Addition of the heteroarylmagnesium compound **131** to the substituted vanillin **132** afforded the corresponding alcohol **133** in 72% yield (Scheme 78). Additionally, oxidative coupling of **131** via transmetalation with CuCN·2LiCl (0.5 equiv, –20 °C, 10 min) followed by addition of chloranil (1.5 equiv, –20 to 25 °C, 4 h) afforded the dithiophene **134** in 76% yield (Scheme 78).



Scheme 78. Regioselective *bis*functionalization of 2,5-dibromo-3-methylthiophene (**128a**) producing the thiophenecarboxylates **133** and **134**.

Inspired by Rieke´s method[273] using active zinc (Zn*), prepared from $ZnCl_2$ and lithium naphthalide, we applied Knochel´s method,[275] the direct metal insertion in the presence of LiCl, to the preparation of thiophenylzinc halides of type **135**. Thus, 2,5-dibromo-3-hexylthiophene (**128b**) reacted with zinc dust (1.5 equiv, LiCl (1.1 equiv), –20 °C, 2 h) leading to a mixture of thiophenylzinc compounds **135a** and **135b** in a ratio of 87:13 (Scheme 79). We could also show that the direct zinc insertion with **128b** at lower temperatures (–78 to 20 °C, 2 h) provides the same ratio of regioisomers (Scheme 79).



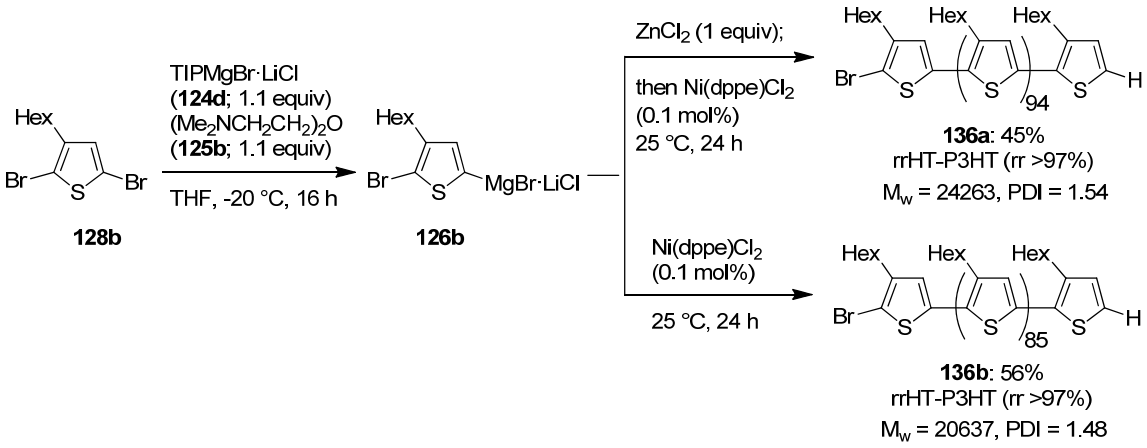
Scheme 79. Regioselective direct zinc insertion in the presence of LiCl with 2,5-dibromo-3-hexylthiophene (**128b**).

4.4 Preparation of 3-Substituted Polythiophenes

We applied the ligand-complexed Br/Mg-exchange reagent **124d** with **125b** in the preparation of poly(3-hexyl)thiophene **136a**. Treatment of 2,5-dibromo-3-hexylthiophene (**128b**) with TIPMgBr·LiCl/$(Me_2NCH_2CH_2)_2O$ (**124d**/**125b**; 1.1 equiv/1.1 equiv, –20 °C, 16 h) furnished the thiophenylmagnesium derivative **126b** in excellent regioselectivity (>99:1). Subsequent

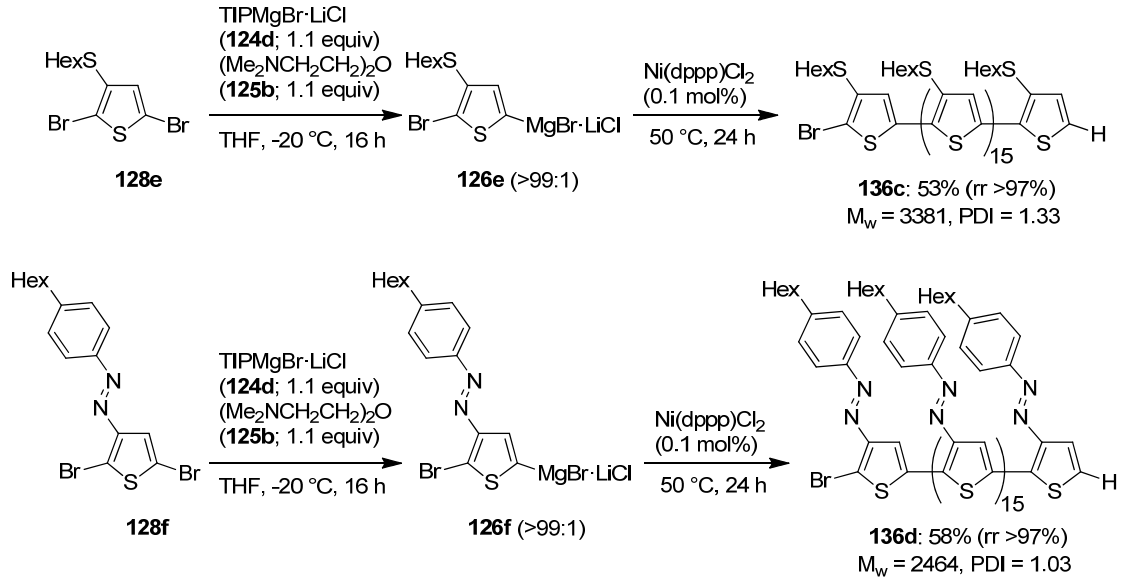
[275] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

addition of $ZnCl_2$ (1 equiv) and Ni-catalyst initiated the cross-coupling polymerization ($Ni(dppe)Cl_2$ (0.1 mol%), 25 °C, 24 h) leading to the regioregular Head-to-Tail-poly(3-hexylthiophene) **136a** (rrHT-P3HT; M_w=24263) in 45% yield with a polydispersity (PDI) of 1.54 (Scheme 80). Similarly, the magnesium reagent **126b** reacted directly in a Ni-catalyzed Kumada-type cross-coupling ($Ni(dppe)Cl_2$ (0.1 mol%), 25 °C, 24 h) to the thiophene-polymer **136b** (rrHT-P3HT; M_w=24263) in 56% yield with a polydispersity (PDI) of 1.48 (Scheme 80).



Scheme 80. Regioselective preparation of 2-bromo-3-hexylthiophenylmagnesium reagent (**126b**) followed by a Ni-catalyzed polymerization to rrHT-P3HT such as **136a** and **136b**.

Interestingly, using TIPMgBr·LiCl/$(Me_2NCH_2CH_2)_2O$ (**124d**, **125b**; 1.1 equiv/1.1 equiv, –20 °C, 16 h) thiohexyl-substituted dibromothiophenes such as **128e** could efficiently be converted to the corresponding heteroarylmagnesium reagent **126e** with complete regioselectivity. Subsequent polymerization via Ni-catalyzed cross-couplings ($Ni(dppp)Cl_2$ (0.1 mol%), 50 °C, 24 h) furnished the oligomer **136c** in 53% yield with a polydispersity (PDI) of 1.33 (Scheme 81). In addition, preparation of a phenylazo-substituted thiophenylmagnesium reagent, like **126f,** was achieved using TIPMgBr·LiCl/$(Me_2NCH_2CH_2)_2O$ (**124d**, **125b**; 1.1 equiv/1.1 equiv, –20 °C, 16 h) leading after a Kumada-type cross-coupling polymerization ($Ni(dppe)Cl_2$ (0.1 mol%), 50 °C, 24 h) to the oligomer **136d** in 58% yield with an excellent polydispersity (PDI) of 1.03 (Scheme 81).



Scheme 81 Regioselective preparation of substituted thiophenylmagnesium reagents such as **126e** and **126f** followed by Ni-catalyzed polymerization to the corresponding oligomers like **136c** and **136d**.

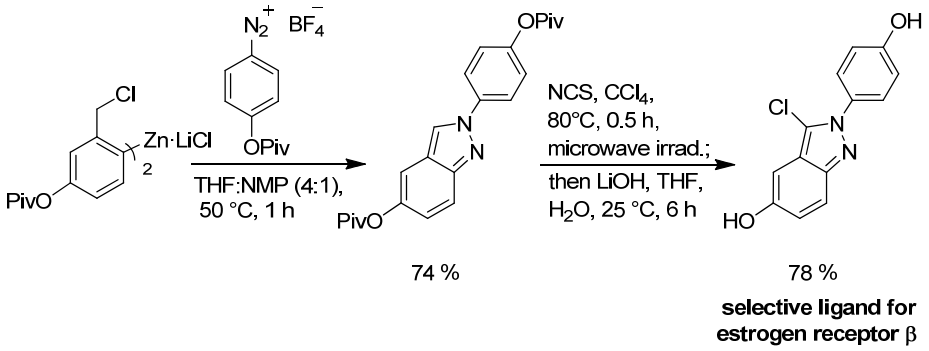
In summary, we have demonstrated the highly regioselective preparation of five-membered heteroarylmagnesium derivatives via efficient ligand-complexed Br/Mg-exchange reagents, such as TIPMgBr·LiCl in combination with $(Me_2NCH_2CH_2)_2O$. The described method offered access to the selective *mono*- and *bis*-functionalization of these scaffolds. Furthermore, we applied the regioselectively prepared heteroarylmagnesium reagents in regioregular cross-coupling polymerizations leading to HT-poly(3-hexylthiophene)s and various substituted thiophene-oligomers.

5. Summary and Outlook

This work was focused on the development of novel methods for the preparation of indazole and indole heterocycles using aryl and alkylzinc reagents. In the course of our studies investigating the direct metal insertion, we explored a rationale for a diastereoselective Negishi cross-coupling using DFT-methods. Furthermore, we developed a novel method for the facile and efficient preparation of organoboron reagents via accelerated direct metal insertion in the presence of borates and LiCl. Moreover, we explored the mechanism and the synthetic use of BF_3-derived frustrated Lewis pairs. In particular, we developed thermally stable frustrated Lewis pairs, such as amidoborates, for the direct preparation of organoboron reagents and subsequent functionalization reactions. Additionally, a regioselective Br/Mg-exchange reagent complexed by a tridentate ligand was developed and employed in the regioregular polymerization of HT-poly- and oligothiophenes.

5.1 Preparation of Polyfunctional 2-Aryl-2*H*-indazoles

In summary, we have developed a short and convenient synthetic route to 2-aryl-2*H*-indazoles using highly functionalized arylzinc reagents. Thus, readily available 2-chloromethylarylzinc reagents react with functionalized aryldiazonium tetrafluoroborates providing polyfunctional indazoles. As an application, we have prepared a highly selective binding ligand for the estrogen receptor β. Furthermore, new heterocyclic azo compounds were also prepared. Selective metalations of these 2-aryl-2*H*-indazoles afford new polycyclic aromatics. The performance of a chemoselective addition of diheteroarylzincs to aryldiazonium salts allows an efficient preparation of new heterocyclic azo compounds.

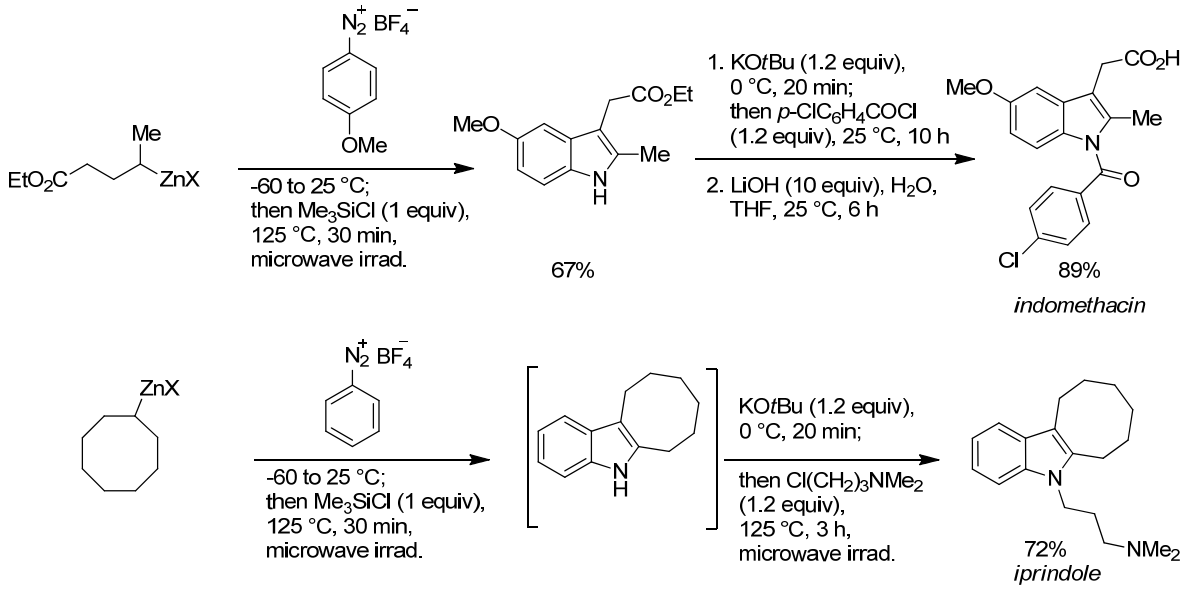


Scheme 82. Preparation of a selective ligand for estrogen receptor β via addition of diarylzinc to aryldiazonium tetrafluoroborate.

The direct synthesis of polyfunctional indazoles has proven to be difficult so far, due to harsh reaction conditions precluding the presence of sensitive functions. However, the described method offers a concise route to such scaffolds. Since many functionalized indazoles display biological activity, further extensions might be directed to the preparation of various polyfunctional indazoles and their use as biologically active drugs.

5.2 Fischer Indole Synthesis using Functionalized Organozinc Reagents

We have described a new organometallic variation of the Fischer indole synthesis allowing the preparation of various polyfunctional indoles from readily available aryldiazonium tetrafluoroborates and functionalized primary and secondary alkylzinc halides. High regioselectivity in the indole ring formation was observed. This variation enhances the scope of the classical Fischer indole synthesis tolerating a broad range of functionalities and displaying a remarkable regioselectivity. As an application of this method, the antidepressant *iprindole* and the anti-inflammatory drug *indomethacin* were efficiently prepared. Additionally, we have extended the scope and improved the reaction conditions for the preparation of polyfunctional indoles on a larger scale. In the course of our study, we have also developed an alternative preparation of indole derivatives via addition of alkenylmagensium or lithium reagents to azo compounds.

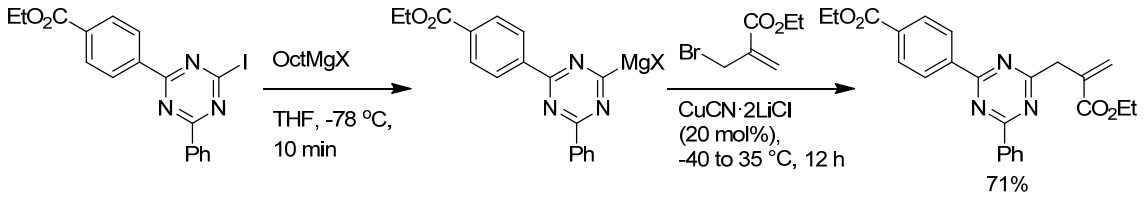


Scheme 83. Preparation of *indomethacin* and *iprindole* via addition of functionalized alkylzinc reagents to aryldiazonium salts.

The indole scaffold is present in many natural products. Since we have successfully developed and implemented a novel methodology to the synthesis of this scaffold, many indole-containing natural products might become available via organometallic total synthesis employing organozinc reagents.

5.3 Preparation of 1,3,5-Triazinylmagnesium Reagents via an I/Mg-exchange

We have developed a novel method for the preparation of stable 1,3,5-triazinylmagnesium reagents which readily react with aldehydes, acid chlorides and allylic halides furnishing a range of new functionalized fully-substituted 1,3,5-triazine derivatives.



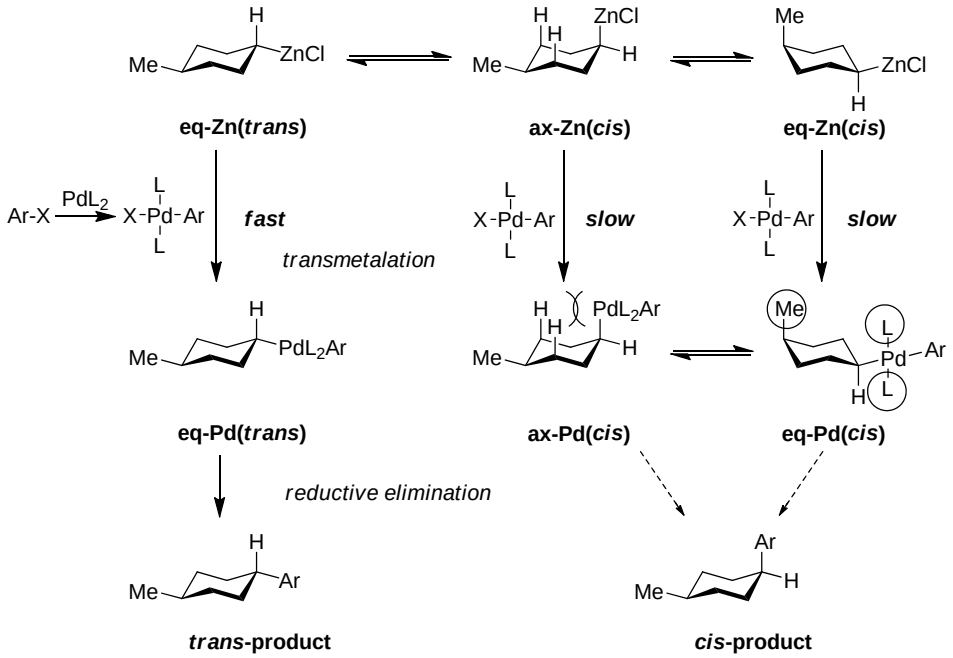
Scheme 84. Preparation of a functionalized 1,3,5-triazinylmagnesium derivative followed by Cu-catalyzed allylation.

The facile preparation of functionalized triazinylmagnesium reagents offers a new access to a wide range of functionalization reactions. Thus, readily functionalized triazines are highly likely to find further applications in opto-electronic devices, due to their unique electronic properties.

5.4 Preparation of Functionalized organometallics via Direct Metal Insertion in the Presence of LiCl

We applied the direct Mg insertion in the presence of LiCl with and without *in situ* trapping with $ZnCl_2$ towards the preparation of functionalized organometallic reagents leading to polyfunctional aromatics. Several sensitive functional groups are well tolerated by this method. Furthermore, we applied the direct zinc insertion for the preparation of substituted cycloalkylzinc reagents. Thereby, we investigated in detail the mechanism of a subsequent diastereoselective Csp^3-Csp^2 cross-coupling using DFT-methods and NMR-techniques. Via thermodynamical analysis of the organometallic intermediates, we developed a hypothesis for the origin of the high diastereoselectivities. This was best rationalized by assuming an

equilibration of the zinc reagents and the preferential formation of the most stable equatorial-Pd-intermediate, as supported not only by DFT-calculations, but also by NMR experiments.

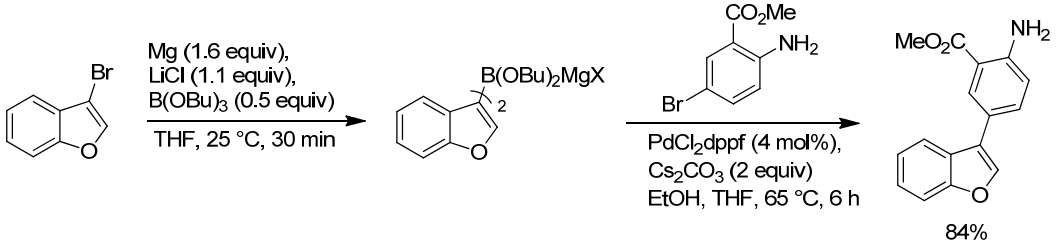


Scheme 85. Mechanistic proposal for the diastereoselective Csp^3-Csp^2 cross-coupling of substituted reagents with aryl iodides.

Based on our proposed mechanism for the diastereoselective Csp^3-Csp^2 cross-coupling and its generality, further extensions might be focused on diastereoselective C-C bond formations of saturated heterocycles or particularly of natural products.

5.5 One-Step Synthesis of Functionalized Organoborates via Accelerated Direct Metal Insertion

Moreover, we have demonstrated an efficient and inexpensive one-step preparation of polyfunctional organoborates via an accelerated direct metal insertion tolerating a wide range of functional groups. The described method proved to be highly flexible and fast using a synergetic effect of $B(OBu)_3$ and LiCl. Furthermore, we demonstrated the practicability of such polyfunctionalized organoborates in uncatalyzed addition reactions to aldehydes and in Suzuki-type cross-couplings.



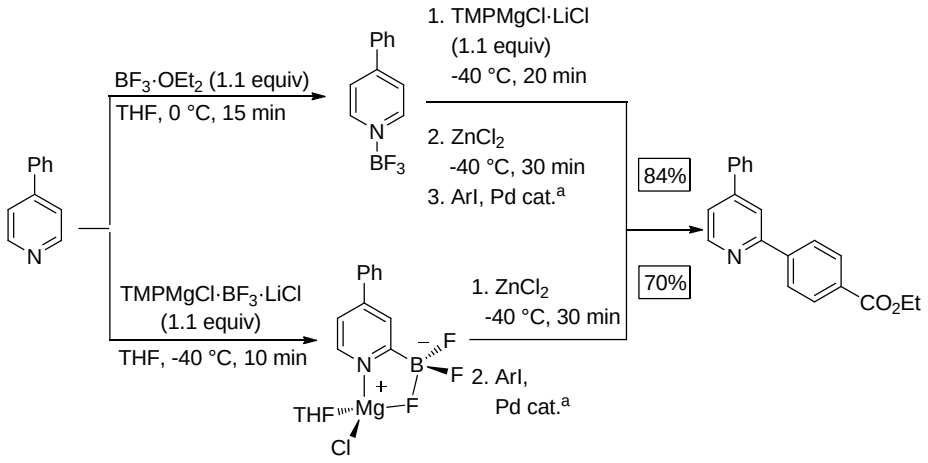
Scheme 86. Preparation of a heteroarylborate via direct magnesium insertion in the presence of LiCl and $B(OBu)_3$ and subsequent Suzuki-type cross-coupling with organic halides.

In addition, the substantial accelerating effect of $B(OBu)_3$ has been demonstrated in the direct metal insertion with aryl bromides using less reactive metals, such as Al, Ca, and Zn. Moreover, we showed that Li, K and Na are also feasible for the *in situ* preparation of organoborates via direct metal insertion.

This method is particularly interesting for the preparation of organoborates in industrial applications, since the direct magnesium insertion in the presence of borates and LiCl avoids expensive cryogenic techniques and toxic waste products. Furthermore, the compatibility of this method with sensitive functional groups is especially remarkable.

5.6 Highly Selective Metalations of Pyridines and Related Heterocycles Using New Frustrated Lewis Pairs

We have developed a new class of frustrated Lewis pairs based on $BF_3{\cdot}OEt_2$ and LiCl-complexed Mg or Zn TMP-amides allowing an efficient, regioselective metalation of various *N*-heterocycles. This approach constitutes an expeditive preparation of versatile magnesium chloride heteroaryl trifluoroborates expanding the work of Molander *et al.* Furthermore, using DFT-calculations, we could theoretically rationalize the experimentally observed acceleration in the metalation reactions. The metalation of various *N*-heterocycles with or without $BF_3{\cdot}OEt_2$ using hindered Mg-, Zn- or Al-bases allows a complementary regioselective functionalization leading to a range of new polyfunctional *N*-heterocycles.

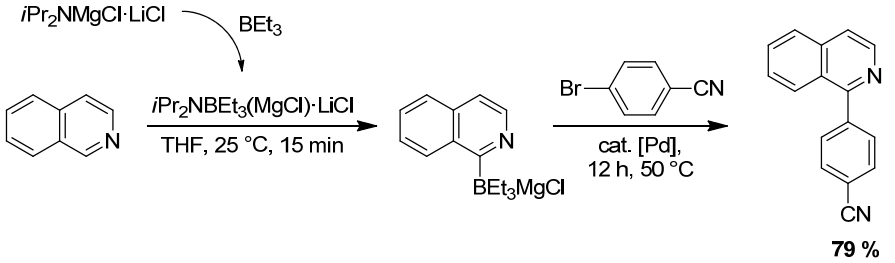


Scheme 87. BF_3-triggered accelerated metalations. ArI: *p*-$IC_6H_4CO_2Et$; [a] Pd cat.: $[Pd(dba)_2]$ (5 mol%); P(2-furyl)$_3$ (10 mol%), –40 to 25 °C, 12 h.

As we could demonstrate, the generated heteroarylborates constitute a new class of frustrated Lewis pairs with unexpected reactivities. Thus, these investigations offer access to novel accelerated metalation reactions and subsequent functionalization reactions. Hence, functionalization of versatile sensitive *N*-heterocycles have become readily available.

5.7 Direct Preparation of Functionalized Organoborates via Accelerated C-H Activation Using Novel Amidoborates

In summary, a new class of thermally stable frustrated Lewis pairs was developed and applied in the direct and accelerated synthesis of functionalized aryl and heteroarylborates via C-H activation. Furthermore, these organoboron reagents readily undergo uncatalyzed addition to aldehydes or Suzuki-type cross-coupling reactions.

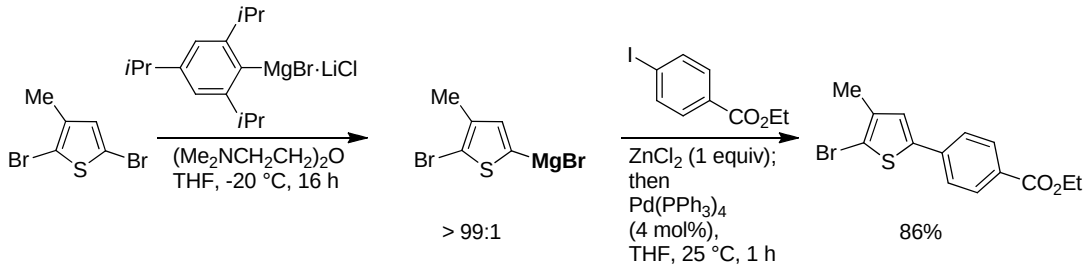


Scheme 88. Direct preparation of organoborates followed by a Suzuki-type cross-coupling.

Furthermore, the development includes a modular concept allowing the preparation of versatile and custom-made amidoborate bases. Based on these developments, various inexpensive metal amide bases have become valuable in functionalization of substituted arenes and heteroarenes.

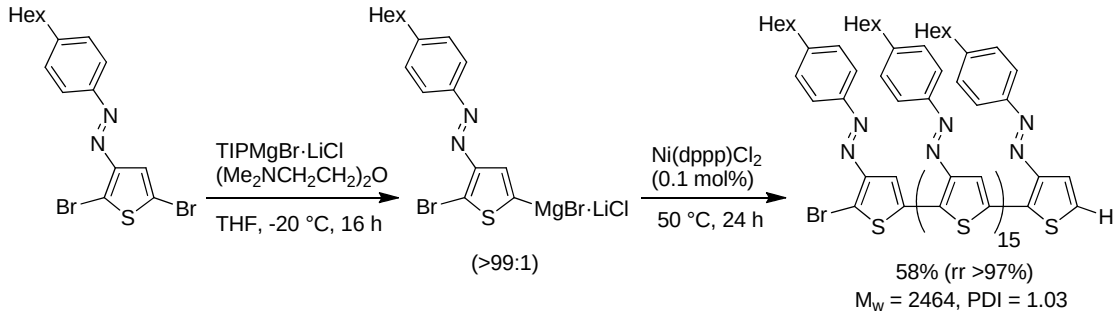
5.8 Highly Regioselective Preparation of Heteroarylmagnesium Reagents and Their Application in Functionalization and Regioregular Polymerization Reactions

In summary, we developed efficient Br/Mg-exchange reagents, such as 2,4,6-triisopropylphenylmagnesium bromide complexed by $(Me_2NCH_2CH_2)_2O$, for the highly regioselective preparation of five-membered heteroaromatics. Furthermore, we applied the generated heteroarylmagnesium reagents in selective *mono*- and *bis*-functionalization reactions.



Scheme 89. Regioselective Br/Mg-exchange using ligand-complexed magnesium reagents followed by a Negishi cross-coupling.

In addition, we could achieve the regioregular polymerization of such organometallics leading to polymers and oligomers comprising 3-subtituted thiophene subunits using this methodology.



Scheme 90. Regioselective preparation of substituted thiophenylmagnesium reagents followed by Ni-catalyzed polymerization to the corresponding oligomers.

The described method proved to be general. Thus, full functionalization of five-membered heteroaromatics has become readily possible leading to novel polyfunctionalized heterocycles. Furthermore, as we could show, substituted regioregular polymers and oligomers of such scaffolds were prepared. Further extensions might include regioregular polymers with finely tuned electronic properties leading to functional materials for applications in organic photovoltaics.

C. Experimental Section

1. General Considerations

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

Solvents

Solvents were dried according to standard procedures by distillation over drying agents as stated below and stored under argon. The solvents used for work-ups and flash column chromatography were distilled at the rotary evaporator.

***Bis*[2-(*N*,*N*-dimethylamino)ethyl]methylamine** was distilled from CaH_2 under nitrogen atmosphere.

***Bis*[2-(*N*,*N*-dimethylamino)ethyl]ether** was distilled from CaH_2 under nitrogen atmosphere.

CH_2Cl_2 or **$CHCl_3$** were pre-dried over $CaCl_2$ and subsequently distilled from CaH_2.

Diethyl ether was pre-dried over calcium hydride and dried with the solvent purification system SPS-400-2 from Innovative Technologies Inc. (Al_2O_3, 1-3 mm, ICN, Eschwege, Germany).

***N*,*N*-dimethylformamide** (DMF) was heated to reflux for 14 h over CaH_2 and then distilled.

Ethanol was treated with phthalic anhydride (25 g/L) and sodium , heated to reflux for 6 h and thereafter distilled.

***N*-methylpyrrolidone** (NMP) was distilled from CaH_2 under nitrogen atmosphere.

Methanol was treated with magnesium turnings (20 g/L) and sodium, heated to reflux for 6 h and thereafter distilled.

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

2,2,6,6-Tetramethylpiperidine was distilled from CaH_2 under nitrogen atmosphere.

Triethylamine was dried over KOH and distilled.

Analytical Data

NMR spectra were recorded on *Bruker* ARX 200, AC 300, WH 400 or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the solvent peak. NMR spectra were recorded in solutions of $CDCl_3$ (residual chloroform: δ 7.25 ppm for ^1H NMR and δ 77.0 ppm for ^{13}C NMR), *d6*-DMSO (residual DMSO: δ 2.49 ppm for ^1H NMR and δ 39.5 ppm for ^{13}C NMR), CD_3OD (residual MeOH: δ 3.34 ppm for ^1H NMR and δ 49.8 ppm for ^{13}C NMR). For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), dd (doublet of a doublet), dt (doublet of triplet), q (quartet), m (multiplet) and br (broad).

Microwave irradiation was performed in a Biotage Initiator™ Unit (Biotage, Uppsala, Sweden) in a closed-vessel system.

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

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

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

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

Chromatography

Flash column chromatography was performed using SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck or Al_2O_3 from Merck (aluminium oxide 90 active, activity grade II-III, , 0.063-0.200 mm, 70–230 mesh ASTM).

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

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

The following substances were prepared according to literature procedures:
128c[276] and **128e**[277].

Reagents

All reagents were purchased from commercial suppliers unless stated otherwise. Reagents of >97% purity were used without further purification. Liquid carboxylic acid chlorides, $BF_3 \cdot OEt_2$, $BF_3 \cdot THF$, aldehydes or allyl bromides were distilled prior to use.

***n*BuLi** was obtained from Chemetall GmbH (Frankfurt, Germany) and titrated[278] prior to use (approx. 2.5 M in hexane).
***s*BuLi** was obtained from Chemetall GmbH (Frankfurt, Germany) and titrated[278] prior to use (approx. 1.5 M in hexane).
***t*BuLi** was obtained from Chemetall GmbH (Frankfurt, Germany) and titrated[278] prior to use (approx. 1.5 M in hexane).
PhMgCl was obtained from Chemetall GmbH (Frankfurt, Germany) and titrated[279] prior to use (1.72 M in THF).
***i*PrMgCl·LiCl** in THF was obtained from Chemetall GmbH (Frankfurt, Germany) and titrated[279] prior to use (1.33 M in THF) or prepared according to the following procedure:
Magnesium turnings (2.64 g, 110 mmol, 1.1 equiv) and anhydrous LiCl (4.20 g, 100 mmol, 1.0 equiv) were placed in an Ar-flushed flask and dried with a heatgun at 450 °C for 10 min *in vacuo*. After cooling to 25 °C and purging with argon, THF (50 mL) was added. A solution of *i*PrCl (7.85 g, 100 mmol, 1.0 equiv) in THF (50 mL) was slowly added at 25 °C. After addition, the reaction mixture was stirred for 12 h at 25 °C. The excess of Mg was removed

[276] J. D. Prugha, A. L. Huitric, W. C. McCarthy, *J. Org. Chem.* **1964**, *29*, 1991.
[277] X. Wu, T.-A. Chen, R. D. Rieke, *Macromol.* **1995**, *28*, 2101.
[278] H.-S. Lin, L. A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[279] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890.

by cannulating the grey solution of *i*PrMgCl·LiCl to a dry and argon-flushed flask. A yield of ca. 95–98% of *i*PrMgCl·LiCl was obtained. The reagent was titrated prior to use by the method of Paquette,[278] or the method developed in our laboratory.[279]

OctMgBr (1 M in THF) was prepared according to the following procedure:

A 1-L three-necked round-bottom flask equipped with a magnetic stirring bar, reflux condenser, addition funnel, and a thermometer was charged with magnesium turnings (14.2 g, 0.584 mol). The flask was gently heated under argon atmosphere (50 °C), while the magnesium turnings were vigorously stirred for 1 h affording activation of the magnesium surface. After cooling to 25 °C and addition of THF (50 mL), ca. 10 mL of a solution of octyl bromide (96.5 g, 0.50 mol) in THF (400 mL) was added to the suspension while continuously stirring. The reaction started after ca. 2-3 min as indicated by a small rise in temperature. Thereafter, the remaining solution of OctBr was added dropwise over a period of 4 h while keeping the temperature below 30 °C. After stirring the reaction mixture for additional 2 h, the supernatant solution was then cannulated into a new dry, argon-flushed Schlenk flask and titrated with iodine affording the concentration of active octylmagnesium bromide (1.0 M).[280]

TIPMgBr·LiCl (124d, 2,4,6-triisopropylphenylmagnesium bromide, 1 M in THF) was prepared according to the following procedure:

Magnesium turnings (3.64 g, 150 mmol, 1.5 equiv) and anhydrous LiCl (4.20 g, 100 mmol, 1.00 equiv) were placed in an Ar-flushed flask and dried with a heatgun at 450 °C for 10 min *in vacuo*. After cooling to 25 °C and purging with argon, THF (50 mL) was added. After addition of THF (60 mL), the magnesium was activated using 1,2-dibromoethane (2 mol%) and Me_3SiCl (5 mol%). Subsequently, a solution of 1-bromo-2,4,6-triisopropylbenzene (28.3 g, 100 mmol) in THF (40 mL) was slowly added at 25 °C. After addition, the reaction mixture was stirred for 12 h at 25 °C. Residual Mg was removed by cannulating the grey solution of 2,4,6-triisopropylmagnesium bromide (**124d**) to a dry and argon-flushed flask. The reagent was titrated prior to use by the method of Paquette,[278] or the method developed in our laboratory.[279]

$ZnBr_2$ (1.0 M in THF) was prepared by drying $ZnBr_2$ (112.7 g, 500 mmol) *in vacuo* for 6 h at 150 °C. After cooling to 25 °C, dry THF (500 mL) was added and stirring was continued until the salt was completely dissolved.

$ZnCl_2$ (1.0 M in THF) was prepared by drying $ZnCl_2$ (68.2 g, 500 mmol) *in vacuo* for 6 h at 150 °C. After cooling to 25 °C, dry THF (500 mL) was added and stirring was continued until the salt was completely dissolved.

[280] C. Tamborskl, G. J. Chen, D. R .Anderson, C. E. Snyder, *Ind. Eng. Chem. Prod. Res. Dev.* **1983**, *22*, 172.

CuCN·2LiCl (1.0 M in THF) was prepared by drying LiCl (6.8 g, 160 mmol) and CuCN (7.2 g, 80 mmol, 99% pure) at 150 °C for 5 h *in vacuo*, cooled to 25 °C and charged with freshly distilled THF (80 mL) under argon with vigorous stirring. The
mixture was stirred for at least 24 h at 25 °C. CuCN·2LiCl (1.0 M in THF) appears as a pale yellow solution.

Preparation of the reagent TMPMgCl·LiCl (91)

A dried and argon-flushed 1-L *Schlenk*-flask, equipped with a magnetic stirring bar and rubber septum, was charged with *i*PrMgCl·LiCl (792 mL, 1.2 m in THF, 950 mmol) then 2,2,6,6-tetramethylpiperidine (141.3 g, 1.00 mol) was added dropwise within 5 min via syringe. The mixture was stirred until gas evolution ceases (24–48 h). Complete formation of the base was checked by GC/MS analysis of reaction aliquots quenched with benzaldehyde. The absence of 2-methyl-1-phenylpropan-1-ol (M^+=150) indicates full conversion. Titration prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator shows a concentration of 1.45 M.

Preparation of the reagent $TMP_2Zn·2MgCl_2·2LiCl$ (93b)

A dried, argon flushed 250 mL *Schlenk*-flask equipped with magnetic stirring bar and rubber septum was charged with $ZnCl_2$ (4.09 g, 30 mmol). The flask was heated to 150 °C *in vacuo* for at least 6 h under vigorous stirring. After cooling to 25 °C, dry THF (10 mL) was added and the resulting slurry was cooled to 0 °C with an ice bath. Then TMPMgCl·LiCl[281] (**91**; 42.9 mL, 1.4 M in THF, 60 mmol) was added via syringe. The mixture was stirred for 12 h until complete dissolution of the salts. Precipitates of the base can easily be redissolved by adding a few mL of dry THF. The freshly prepared $TMP_2Zn·2MgCl_2·2LiCl$ (**93b**) solution was titrated prior to use at 0 °C versus benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.6 M in THF was obtained.

Preparation of the reagent $TMPBEt_3·MgCl·LiCl$ (110b)

A dried, argon flushed 250 mL *Schlenk*-flask equipped with magnetic stirring bar and rubber septum was charged with TMPMgCl·LiCl[281] (**91**; 50 mL, 1.2 M in THF, 60 mmol). At –20 °C, BEt_3 (60 mmol, 5.86 g) was added dropwise via syringe to the vigorously stirred solution. Subsequently, the solution was allowed to slowly warm to 25 °C and continuously

[281] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed*. **2004**, *43*, 3333; b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed*. **2005**, *44*, 159; c) A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497.

stirred for 30 min. The freshly prepared reagent $TMPBEt_3 \cdot MgCl \cdot LiCl$ (**110b**) was titrated prior to use at 0 °C versus benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 1.0 M in THF was obtained.

Determination of the concentration of organomagnesium or zinc reagents

Organomagnesium reagents were directly titrated by adding the respective reagent to a known amount of I_2 in a LiCl-solution in THF (0.50 M). The decolourization of the solution was observed.

Quantum chemical calculations

DFT calculations were carried out using the Gaussian03 Rev.B.04 program package[282] with the nonlocal hybrid B3LYP exchange-correlation functionals[283]. The basis set denoted as 631SVP consists of the Ahlrich def2-SVP all electron basis set[284] for Zn atoms, all electron and ECP for Pd atoms and the 6-31G(d,p) basis set[285]for other atoms. Energy minimizations followed by harmonic vibrational calculations were performed at this level of theory. The absence of imaginary frequencies proved that energy-minimized stationary points correspond well to the local minima of the energy landscape. Vibrational frequencies were also used in determining the isomers' relative Gibbs energies (ΔG^0_{298}) and relative zero-point corrected electronic energies (ΔE^0). Prior to quantum chemical conformational analysis, these structures have been subjected to conformational search using semi-empirical method PM3[286] implemented in the Spartan'08 software package.[287]

[282] M. J. Frisch *et al.* Gaussian 03; Gaussian, Inc., Wallingford CT (**2004**).
[283] a) R. G. Parr, W. Yang, in *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, (1989); b) T. Ziegler, *Chem. Rev*. **1991**, *91*, 651; c) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; d) A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098.
[284] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.
[285] a) P. C. Hariharan, J. A. Pople, *Theoret. Chim. Acta* **1973**, *28*, 213; b) M. M. Francl, W. J. Petro, W. Hehre, J. S. Binkley, M. S. Gordon, D. J. DeFrees, J. A. Pople, *J. Chem. Phys.* **1982**, *77*, 3654; c) V. A. Rassolov, J. A. Pople, M. A. Ratner, T. L. Windus, *J. Chem. Phys*. **1998**, *109*, 1223.
[286] a) J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 209; b) J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 221; c) J. J. P. Stewart, *J. Comput. Chem.* **1991**, *12*, 320; d) J. J. P. Stewart, *J. Mol. Mod.* **2004**, *10*, 155.
[287] Spartan'08 version 1.1.1, Wavefunction, Inc., 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612, USA, **2008**.

2. Typical Procedures

2.1 Typical procedure (TP1) for the preparation of 2-aryl-2*H*-indazole derivatives (22a–r)

To a solution of the 2-iodobenzyl chloride derivative (3.0 mmol) in THF (2 mL) in a dry and argon-flushed Schlenk-flask was added dropwise a solution of *i*PrMgCl·LiCl (3.2 mmol, 1.8 mL, 1.8 M in THF) at –20 °C. The reaction mixture was stirred for 30 min at the same temperature. GC-analysis of a quenched reaction aliquot shows full conversion. $ZnBr_2$ solution (1.6 mL, 1.6 mmol, 1 M in THF) was added to the Grignard reagent at –20 °C and allowed to warm to 25 °C. The solution was stirred for 20 min at the same temperature. To a solution of diazonium salt (2.0 mmol) in NMP/THF (1:1) (4 mL) the diarylzinc species was added dropwise at –40 °C, allowed slowly to warm up to 25 °C and stirred for 30 min at 25 °C. The reaction mixture was then stirred at 50 °C for 1 h. The reaction mixture was diluted with diethyl ether (5 mL) and quenched with sat. NH_4Cl (aq.) (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography to afford the 2-aryl-*2H*-indazole derivative.

2.2 Typical procedure (TP2) for the preparation of aryldiazonium tetrafluoroborates (25a–k, 43a–k)

To a solution of the aniline derivative (50 mmol) in tetrafluoroboric acid (0.4 mol, 35 g, 50 w% in H_2O) was added dropwise a $NaNO_2$ solution (55 mmol, 3.79 g, 4 M in H_2O) under vigorous stirring, while the temperature was kept below –5 °C. The reaction mixture was stirred for additional 30 min at –5 °C. The precipitate was removed by filtration and washed with cold MeOH. The solid was recrystallized from methanol to yield the crystalline aryldiazonium tertrafluoroborate salt.

2.3 Typical procedure (TP3) for the preparation of heterocyclic azo compounds (39a–g)

To a solution of the haloheteroaryl derivative (3.0 mmol) in THF (2 mL) in a dry and argon-flushed Schlenk-flask was added dropwise a solution of *i*PrMgCl·LiCl (3.2 mmol, 1.8 mL, 1.8 M in THF) at –20 °C. The reaction mixture was stirred for 30 min at the same temperature. GC-analysis of a quenched reaction aliquot shows full conversion. $ZnBr_2$ solution (1.6 mL, 1.6 mmol, 1 M in THF) was added to the Grignard reagent at -20 °C and

allowed to warm to 25 °C. The solution was stirred for 20 min at the same temperature. To a solution of diazonium salt (2.0 mmol) in NMP/THF (1:1) (4 mL) the diarylzinc was added dropwise at –40 °C, allowed to slowly warm up to –20 °C and stirred for 2 h at the same temperature. The reaction mixture was diluted with diethyl ether (5 mL) and quenched with sat. NH_4Cl (aq.) (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography to afford the heterocyclic azo compound.

2.4 Typical procedure (TP4) for the preparation of alkylzinc bromides by direct zinc insertion in the presence of LiCl (44a–b)

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with zinc dust (524 mg, 8 mmol) and LiCl (186 mg, 4.4 mmol). The LiCl was dried *in vacuo* with a heatgun (450 °C, 5 min). After addition of THF (2 mL), the zinc was activated with 1,2-dibromoethane (2 mol%) and Me_3SiCl (5 mol%). After stirring for 5 min, alkyl bromide (4.0 mmol) in THF (4 mL) was added at 25 °C to the suspension and the reaction mixture was stirred for the given time at the given temperature. The supernatant solution was then cannulated into a new dry, argon-flushed Schlenk flask and titrated with iodine affording the concentration of active alkylzinc reagent.[288]

2.5 Typical procedure (TP5) for the preparation of alkylzinc bromides by direct magnesium insertion in the presence of $ZnBr_2$ and LiCl (44d–g)

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with magnesium turnings (155 mg, 6.4 mmol) and LiCl (186 mg, 4.4 mmol). The LiCl was dried *in vacuo* with a heatgun (450 °C, 5 min). After addition of THF (2 mL), the magnesium was activated with 1,2-dibromoethane (2 mol%) and Me_3SiCl (5 mol%). After stirring for 5 min, $ZnBr_2$ (4.0 mmol, 4 mL, 1M in THF) was added to the mixture. Thereafter, the suspension was cooled to 0 °C, alkyl bromide (4.0 mmol) in THF (4 mL) was added and the reaction mixture was stirred for the given time at 25 °C. The supernatant solution was then cannulated into a new dry, argon-flushed Schlenk flask and titrated with iodine affording the concentration of active alkylzinc reagent.[289]

[288] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.
[289] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

2.6 Typical procedure (TP6) for the preparation of indole derivatives via alkylzinc bromides and aryldiazonium tetrafluoroborates (23a–aj, 48, 49)

In a flame-dried and argon-flushed Schlenk-flask, the alkylzinc bromide solution (2.0 mmol) was added dropwise to a solution of $ZnBr_2$ (4.0 mmol, 4 mL, 1M in THF) at 25 °C. After stirring at 25 °C for 10 min, the organozinc reagent was transferred slowly to a solution of aryldiazonium tetrafluoroborate (2.5 mmol) in THF (6 mL) at –60 °C. The reaction mixture was allowed to slowly warm to 25 °C. Subsequently, the solvent volume was reduced to half, Me_3SiCl (2.0 mmol, 217 mg) was added, and the reaction mixture was heated by microwave irradiation for the given time at 125 °C. After the reaction mixture had cooled to 25 °C, the resulting solution was diluted with Et_2O (5 mL) and quenched with brine (10 mL). The aqueous layer was extracted with EtOAc (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography afforded the polyfunctional indole.

2.7 Typical procedure (TP7) for the preparation of pyrazole derivatives via alkylzinc bromides and aryldiazonium tetrafluoroborates (51a–e)

In a flame-dried and argon-flushed Schlenk-flask, the alkylzinc bromide solution (2.0 mmol) was added dropwise to a solution of $ZnBr_2$ (4.0 mmol, 4 mL, 1M in THF) at 25 °C. After stirring at 25 °C for 10 min, the organozinc reagent was transferred slowly to a solution of aryldiazonium tetrafluoroborate (2.5 mmol) in THF (6 mL) at –60 °C. The reaction mixture was allowed to slowly warm to 25 °C. Subsequently, the solvent volume was reduced to half, Me_3SiCl (2.0 mmol, 217 mg) was added, and the reaction mixture was heated by microwave irradiation for the given time at 125 °C. After the reaction mixture had cooled to 25 °C, the resulting solution was diluted with Et_2O (5 mL) and quenched with brine (10 mL). The aqueous layer was extracted with EtOAc (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography afforded the polyfunctional pyrazole.

2.8 Typical procedure (TP8) for the preparation of organomagnesium halides via direct magnesium insertion in large scale

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with LiCl (1.25 equiv) and heated under high vacuum using a heat gun (20 min). After cooling to room temperature, magnesium turnings (2.5 equiv) were added followed by THF. The magnesium was activated with *i*Bu2AlH (1 mol%). After 5 min of stirring the aryl chloride or bromide (1 equiv) was added neat or as a solution in THF over the specified time

at the given temperature. The reaction mixture was stirred for the indicated time and then cannulated to a new *Schlenk*-flask for the reaction with an electrophile.

2.9 Typical procedure (TP9) for the preparation of organoborates via direct magnesium insertion in the presence of $B(OBu)_3$

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with magnesium turnings (78 mg, 3.2 mmol) and LiCl (93 mg, 2.2 mmol). LiCl was dried *in vacuo* using a heatgun (450 °C, 5 min). After addition of THF (2 mL), the magnesium was activated with 1,2-dibromoethane (2 mol%) and Me_3SiCl (5 mol%). Stirring for 5 min was followed by addition of $B(OBu)_3$ (230 mg, 1 mmol). Thereafter, a solution of organic halide (2 mmol) in THF (2 mL) was added at the given temperature and stirred for the given time leading to the organoborate.

2.10 Typical procedure (TP10) for the preparation of organoborates via direct aluminium insertion in the presence of $B(OBu)_3$

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with LiCl (127 mg, 6 mmol) and dried in vacuo 450 °C (heatgun, 5 min). Heating was repeated after addition of aluminium dust (162 mg, 6 mmol) magnesium turnings (78 mg, 3.2 mmol). After addition of THF (2 mL), the aluminium was activated with 1,2-dibromoethane (2 mol%) and Me_3SiCl (5 mol%). Stirring for 5 min was followed by addition of $B(OBu)_3$ (230 mg, 1 mmol). Thereafter, a solution of organic halide (2 mmol) in THF (2 mL) was added at 25 °C and the reaction mixture was stirred at the given temperature for the given time leading to the organoborate.

2.11 Typical procedure (TP11) for in situ zincation of functionalized heteroaromatics using TMPMgCl·LiCl in the presence of $ZnCl_2$

A dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with heteroarene (1 equiv) in THF (1 mL) and $ZnCl_2$ (0.5 equiv, 1M in THF). TMPMgCl·LiCl (**91**; 1.1 equiv, 1.2M in THF) was added dropwise and the reaction mixture was stirred at 25 °C for the indicated time. Complete metalation was detected by GC-analysis of an iodolyzed reaction aliquot using tetradecane as internal standard.

2.12 Typical procedure (TP12) for metalation of heteroaromatics using hindered metal amide bases

A dry and argon-flushed Schlenk-tube, equipped with a magnetic stirring bar and a septum, was charged with a solution of heteroarene (1 equiv, 0.2M in THF) and cooled to the indicated temperature. A THF-solution of the given hindered metal amide base, titrated prior to use, was added dropwise and the reaction mixture was stirred at the indicated temperature for the given time. Complete metalation was monitored by GC analysis of iodolyzed reaction aliquots using tetradecane as internal standard.

2.13 Typical procedure (TP13) for BF_3-triggered metalation of heteroaromatics using hindered metal amide bases

A dry and argon-flushed Schlenk-tube, equipped with a magnetic stirring bar and a septum, was charged with a solution of heteroarene (1 equiv, 0.2M in dry THF) and cooled to 0 °C. $BF_3 \cdot OEt_2$ (1.1 equiv) was added dropwise and stirred for 15 min at 0 °C. Subsequently, the reaction mixture was cooled to the given temperature followed by dropwise addition of the indicated hindered metal amide base, titrated prior to use. The mixture was continuously stirred at the indicated temperature for the given time. Complete metalation was monitored by GC analysis of iodolyzed reaction aliquots using tetradecane as internal standard.

2.14 Typical procedure (TP14) for metalation using the frustrated Lewis pair "$TMPBF_3 \cdot MgCl \cdot LiCl$" (99)

A dry and argon-flushed Schlenk-tube, equipped with a magnetic stirring bar and a septum, was charged with TMPMgCl·LiCl (**91**; 1.1 equiv, 1.2M in THF). At –40 °C, $BF_3 \cdot OEt_2$ (1.1 equiv) was added dropwise and the resulting mixture was stirred for 10 min at –40 °C. To this mixture, a solution of heteroarene (1.0 equiv, 0.2M in THF) was added slowly followed by continuous stirring at –40 °C for the indicated time. Complete metalation was monitored by GC-analysis of iodolyzed reaction aliquots using tetradecane as internal standard.

2.15 Typical procedure (TP15) for the preparation of secondary heterocyclic alcohols via metalation using the frustrated Lewis pair "$TMPBF_3 \cdot MgCl \cdot LiCl$" (99)

A dry and argon-flushed Schlenk-tube, equipped with a magnetic stirring bar and a septum, was charged with TMPMgCl·LiCl (**91**; 1.1 equiv, 1.2M in THF). At –40 °C, $BF_3 \cdot OEt_2$ (1.1 equiv) was added dropwise and the resulting mixture was stirred for 10 min at –40 °C.

Then, a solution of heteroarene (1.0 equiv, 2.0M in THF) was added slowly at –40 °C followed by continuous stirring for the indicated time. Complete metalation was monitored by GC-analysis of iodolyzed reaction aliquots using tetradecane as internal standard. Subsequently, a THF solution of an aldehyde (1.1 equiv, 1M in THF) was added dropwise at –40 °C. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 1 h followed by addition of EtOAc (10 mL) and aq. 2M NaOH (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification provided the expected product.

2.16 Typical procedure (TP16) for the metalation of heteroaromatics and aromatics using amidoborates of type 110

A dry and argon-flushed Schlenk-tube, equipped with a magnetic stirring bar and a septum, was charged with a solution of heteroarene (1 equiv, 1.0M in THF). The amidoborate (1.1 equiv) was added dropwise at 25 °C, if not indicated otherwise, and stirred continuously for the given time. Complete conversion was monitored by GC analysis of iodolyzed reaction aliquots using tetradecane as internal standard.

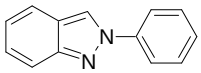
2.17 Typical procedure (TP17) for the regioselective preparation of five-membered heteroarylmagnesium reagents using 124d and 125b

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 2,4,6-triisopropylmagnesium bromide (TIPMgBr·LiCl; **124d**; 1.1 equiv, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 1.1 equiv). After stirring for 10 min at 25 °C, the dibromoheterocycle (1 equiv) was added neat at the given temperature and continuously stirred for the indicated time. Complete Br/Mg-exchange was monitored by GC-analysis of iodolyzed reaction aliquots using tetradecane as internal standard.

3. Preparation of Polyfunctional Heterocycles

3.1 Preparation of Functionalized 2-Aryl-2*H*-indazoles using Substituted Arylzinc Reagents and Aryldiazonium Tetrafluoroborates

Synthesis of 2-phenyl-2*H*-indazole (22a):



According to **TP1** 2-iodobenzyl chloride (**27a**, 757 mg, 3.0 mmol) was converted to the diarylzinc compound **24a** and was reacted with benzenediazonium tetrafluoroborate (**25a**, 383 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded 2-phenyl-2*H*-indazole[290] (**22a**, 380 mg, 98%) as a pale yellow solid.

m.p.: 79.2 – 80.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.38 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 8.4 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H).

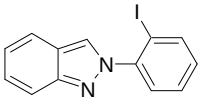
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 149.6, 140.4, 129.5, 127.8, 126.8, 122.7, 122.4, 120.9, 120.4, 120.3, 117.8.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3131, 3054, 1628, 1593, 1519, 1492, 1465, 1456, 1390, 1378, 1312, 1206, 1073, 1046, 950, 905, 780, 747, 683.

MS (EI, 70 eV) *m/z* (%): 195 (14), 194 (M^+, 100), 193 (18), 168 (11), 167 (11), 165 (13), 77 (16), 51 (9).

HRMS (EI): *m/z* calc. for **$C_{13}H_{10}N_2$** (194.0844): 194.0857 (M^+).

Synthesis of 2-(2-iodophenyl)-2*H*-indazole (22b) :



According to **TP1** 2-iodobenzyl chloride (**27a**, 757 mg, 3.2 mmol) was converted to the diarylzinc compound **24a** and was reacted with 2-iodobenzenediazonium tetrafluoroborate (**25b**, 636 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded 2-(2-iodophenyl)-2*H*-indazole (**22b**, 531 mg, 83%) as a pale yellow solid.

[290] A. Reissert, F. Lemmer, *Ber. Chem. Ges., Abt. B* **1926**, *56B*, 351.

m.p.: 118.4 – 119.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.19 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.45 - 7.55 (m, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.10 - 7.29 (m, 2 H).

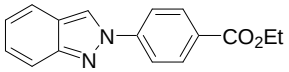
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 149.3, 143.8, 140.0, 130.8, 128.9, 128.3, 126.8, 124.9, 122.4, 121.9, 120.5, 118.0, 94.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3393, 2917, 2850, 1697, 1627, 1443, 1239, 1059, 1021, 948, 816, 748, 738, 702.

MS (EI, 70 eV) *m/z* (%): 321 (14), 320 (M^+, 100), 193 (19), 192 (21), 166 (12).

HRMS (EI): *m/z* calc. for **$C_{13}H_9IN_2$** (319.9810): 319.9806 (M^+).

Synthesis of ethyl 4-(2*H*-indazol-2-yl)benzoate (22c) :



According to **TP1** 2-iodobenzyl chloride (**27a**, 757 mg, 3.0 mmol) was converted to the diarylzinc compound **24a** and was reacted with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**25c**, 528 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded ethyl 4-(2*H*-indazol-2-yl)benzoate [291] (**22c**, 516 mg, 97%) as a pale yellow solid.

m.p.: 144.3 – 145.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 8.18 (d, *J* = 8.7 Hz, 2H), 7.98 (d, *J* = 8.5 Hz, 2 H), 7.77 (d, *J* = 8.7, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.32 (t, *J* = 8.5 Hz, 1H), 7.10 (t, *J* = 8.0 Hz), 4.42 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.7, 150.1, 143.5, 131.1, 129.6, 127.4, 123.0, 122.9, 120.4, 120.5, 120.2, 118.0, 61.2, 14.3.

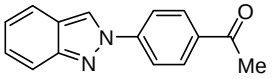
IR (Diamond-ATR, neat) υ (cm^{-1}): 3403, 3138, 3064, 2978, 2902, 1706, 1607, 1522, 1427, 1367, 1270, 1206, 1101, 1037, 856, 749, 684.

MS (EI, 70 eV) *m/z* (%): 267 (17), 266 (M^+, 100), 238 (21), 221 (51), 193 (13), 192 (14), 165 (9).

HRMS (EI): *m/z* calc. for **$C_{16}H_{14}N_2O_2$** (266.1055): 266.1049 (M^+).

Synthesis of 1-[4-(2*H*-indazol-2-yl)phenyl]ethanone (22d) :

[291] M. Armour, J. Cadogan, D. Grace, *J. Chem. Soc., Perk. Trans. 2* **1975**, *11*, 1185.



According to **TP1** 2-iodobenzyl chloride (**27a**, 757 mg, 3.0 mmol) was converted to the diarylzinc compound **24a** and was reacted with 4-acetylbenzenediazonium tetrafluoroborate (**25d**, 468 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded 1-[4-(2*H*-indazol-2-yl)phenyl]ethanone (**22d**, 396 mg, 84%) as an off-white solid.

m.p.: 182.3 – 183.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.44 (s, 1 H), 8.08 (d, *J* = 8.7 Hz, 2), 8.00 (d, *J* = 8.7 Hz, 2 H), 7.76 (d, *J* = 8.9, 1H), 7.67 (d, *J* = 8.5 Hz, 1Hz), 7.32 (t, *J* = 7.3 Hz, 1Hz), 7.10 (t, *J* = 7.3 Hz, 1H), 2.62 (s, 3H).

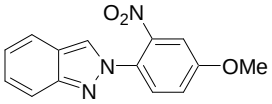
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 196.7, 150.2, 143.5, 136.0, 129.9, 127.5, 123.0, 120.5, 120.4, 120.3, 118.0, 26.6.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3130, 1678, 1602, 1521, 1422, 1381, 1354, 1305, 1259, 1205, 1178, 1116, 1047, 949, 908, 851, 842, 783, 757, 734.

MS (EI, 70 eV) *m/z* (%): 237 (16), 236 (M^+, 94), 222 (13), 221 (100), 193 (20), 192 (22), 166 (11), 110 (12).

HRMS (EI): *m/z* calc. for **$C_{15}H_{12}N_2O$** (236.0950): 236.0921 (M^+).

Synthesis of 2-(4-methoxy-2-nitrophenyl)-2*H*-indazole (22e) :



According to **TP1** 2-iodobenzyl chloride (**27a**, 757 mg, 3.0 mmol) was converted to the diarylzinc compound **24a** and was reacted with 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate (**25e**, 534 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded 2-(4-methoxy-2-nitrophenyl)-2*H*-indazole (**25e**, 516 mg, 96%) as a pale yellow solid.

m.p.: 105.3 – 106.1 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.14 (s, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 2.8, 1H), 7.31 (t, *J* = 8.1 Hz, 1H), 7.21 (dd, *J* = 8.7 Hz, 2.7 Hz, 1H), 7.11 (t, *J* = 8.1 Hz, 1H), 3.91 (s, 3H).

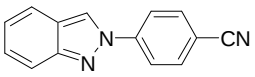
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 159.9, 149.9, 145.7, 129.0, 127.0, 124.1, 122.7, 122.4, 120.3, 118.7, 117.9, 110.1, 56.3.

IR (Diamond-ATR, neat) υ (cm^{-1}): 1628, 1544, 1525, 1357, 1261, 1246, 1226, 1200, 1044, 1024, 900, 826, 797, 792, 761.

MS (EI, 70 eV) *m/z* (%): 269 (M^+, 7), 252 (23), 251 (100), 225 (15), 210 (12), 77 (18), 63 (12), 57 (10), 51 (11).

HRMS (EI): *m/z* calc. for **$C_{14}H_{11}N_3O_3$** (269.0800): 296.0793 (M^+).

Synthesis of 4-(2*H*-indazol-2-yl)benzonitrile (22f) :



According to **TP1** 2-iodobenzyl chloride (**27a**, 757 mg, 3.0 mmol) was converted to the diarylzinc compound **24a** and was reacted with 4-cyanobenzenediazonium tetrafluoroborate (**25f**, 434 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded 4-(2*H*-indazol-2-yl)benzonitrile[291] (**22f**, 359 mg, 82%) as a pale yellow solid.

m.p.: 163.4 – 164.6 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.38 (s, 1H), 7.97 (d, *J* = 8.6 Hz, 2H), 7.70 – 7.74 (m, 3H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.31 (t, *J* = 8.1, 1H), 7.10 (t, *J* = 7.9 Hz, 1H).

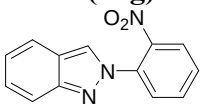
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm):150.1, 143.0, 133.4, 127.7, 123.2, 123.0, 120.5, 120.4, 120.2, 118.0, 117.9, 110.9.

IR (Diamond-ATR, neat) υ (cm^{-1}): 2227, 1629, 1602, 1517, 1423, 1379, 1311, 1208, 1178, 1108, 1041, 951, 838, 820, 783, 758.

MS (EI, 70 eV) *m/z* (%): 220 (15), 219 (M^+, 100), 218 (11), 192 (10), 102 (9).

HRMS (EI): *m/z* calc. for **$C_{14}H_9N_3$** (219.0796): 219.0788 (M^+).

Synthesis of 2-(2-nitrophenyl)-2*H*-indazole (22g) :



According to **TP1** 2-iodobenzyl chloride (**27a**, 757 mg, 3.0 mmol) was converted to the diarylzinc compound **24a** and was reacted with 2-nitrobenzenediazonium tetrafluoroborate (**25g**, 474 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded 2-(2-nitrophenyl)-2*H*-indazole[292] (**22g**, 301 mg, 63%) as a pale yellow solid.

m.p.: 152.3 – 153.8 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.21 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.75 – 7.68 (m, 4H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 8.6 Hz, 1H), 7.13 (t, *J* = 7.1 Hz, 1H).

[292] O. Tsuge, H. Samura, *Org. Prep. Proc. Int.* **1974**, *6*, 161.

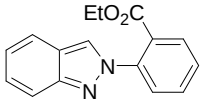
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 150.3, 145.2, 133.1, 129.5, 127.6, 127.3, 125.2, 123.7, 123.0, 122.7, 120.4, 118.1, 114.1.

IR (Diamond-ATR, neat) υ (cm^{-1}): 1692, 1606, 1544, 1524, 1499, 1452, 1380, 1369, 1201, 1096, 1047, 952, 850, 782, 759, 749, 701.

MS (EI, 70 eV) *m/z* (%): 239 (M^+, 16), 223 (15), 222 (100), 105 (9), 77 (21).

HRMS (EI): *m/z* calc. for **$C_{13}H_9N_3O_2$** (239.0695): 239.0680 (M^+).

Synthesis of ethyl 2-(2*H*-indazol-2-yl)benzoate (22h) :



According to **TP1** 2-iodobenzyl chloride (**27a**, 757 mg, 3.0 mmol) was converted to the diarylzinc compound **24a** and was reacted with 2-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**25h**, 528 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded ethyl 2-(2*H*-indazol-2-yl)benzoate (**22h**, 410 mg, 77%) as a pale yellow solid.

m.p.: 140.1 – 141.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.17 (s, 1H), 7.91 (d, *J* = 6.8 Hz, 1H), 7.74 (d, *J* = 8.7, 1H), 7.70 (d, *J* = 8.5, 1H), 7.47-7.65 (m, 3H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 0.84 (t, *J* = 7.05 Hz, 3H).

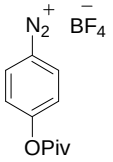
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.2, 149.5, 139.7, 131.9, 130.6, 128.8, 126.6, 126.3, 123.9, 122.3, 122.2, 120.3, 120.1, 117.7, 61.4, 13.5.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3131, 2982, 2957, 2898, 1727, 1689, 1681, 1628, 1606, 1584, 1548, 1519, 1499, 1463, 1451, 1379, 1362, 1351, 1300, 1280, 1245, 1234, 1201, 1151, 1131, 1100, 1050, 1018, 950, 856, 797, 762, 757.

MS (EI, 70 eV) *m/z* (%): 266 (M^+, 42), 221 (32), 195 (16), 194 (100), 165 (12), 77 (10).

HRMS (EI): *m/z* calc. for **$C_{16}H_{14}N_2O_2$** (266.1055): 266.1049 (M^+).

Synthesis of 4-[(2,2-dimethylpropanoyl)oxy]benzenediazonium tetrafluoroborate (25i):



According to **TP2** 4-aminophenyl pivalate (9.65 g, 50.0 mmol) was converted to the diazonium salt. Recrystalization from methanol afforded 4-[(2,2-dimethylpropanoyl)oxy]-benzenediazonium tetrafluoroborate (**25i**, 11.01 g, 76%) as white needles.

m.p.: 125.8 – 133.0 °C.

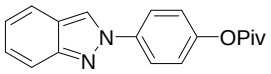
^{1}H-NMR (400 MHz, D6-DMSO) δ (ppm): 8.47 (d, *J* = 9.3 Hz, 2H), 7.20 (d, *J* = 9.3 Hz, 2H), 1.14 (s, 9H).

^{13}C-NMR (100 MHz, D6-DMSO) δ (ppm): 175.2, 169.1, 136.5, 125.0, 100.1, 38.4, 26.7.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3113, 2923, 2854, 2289, 1759, 1576, 1476, 1322, 1237, 1170, 1050, 1027, 890, 854, 796, 752.

HRMS (ESI, 70 eV): *m/z* calc. for **$C_{11}H_{13}N_2O_2$** (205.0977): 205.0971 ([M+H]$^+$).

Synthesis of 4-(2*H*-indazol-2-yl)phenyl pivalate (22i) :



According to **TP1** 2-iodobenzyl chloride (**27a**, 757 mg, 3.0 mmol) was converted to the diarylzinc compound **24a** and was reacted with 4-[(2,2-dimethylpropanoyl)oxy]benzenediazonium tetrafluoroborate (**25i**, 584 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded 4-(2*H*-indazol-2-yl)phenyl pivalate (**22i**, 447 mg, 76%) as an off-white solid.

m.p.: 146.3 – 147.9 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.36 (s, 1H), 7.90 (d, *J* = 9.0 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.11 (t, *J* = 7.9 Hz, 1H), 1.38 (s, 9H).

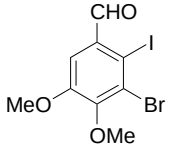
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 176.9, 150.5, 149.8, 137.9, 126.9, 122.8, 122.6, 122.5, 121.9, 120.5, 120.3, 117.9, 39.1, 27.1.

IR (Diamond-ATR, neat) υ (cm^{-1}): 2977, 2959, 2932, 1745, 1520, 1508, 1478, 1457, 1431, 1395, 1382, 1277, 1200, 1165, 1112, 1049, 1027, 1013, 950, 895, 852, 817, 791, 777, 756.

MS (EI, 70 eV) *m/z* (%): 294 (M$^+$, 59), 211 (13), 210 (100), 181 (25), 85 (8), 57 (61).

HRMS (EI): *m/z* calc. for **$C_{18}H_{18}N_2O_2$** (294.1368): 294.1366 (M$^+$).

Synthesis of 3-bromo-2-iodo-4,5-dimethoxybenzaldehyde:



To a solution of 3-bromo-4,5-dimethoxybenzaldehyde (36.75 g, 0.15 mol) in methanol (400 mL) was added silver sulfate (46.77 g, 0.15 mol) and iodine (57.15 g, 0.225 mol) at 25 °C. The reaction mixture was stirred for 24 h at the same temperature, followed by addition of solid $Na_2S_2O_3$ until the solution decolorizes. The solution was filtrated through a

pad of silica and concentrated *in vacuo*. Addition of conc. HCl (30 mL) afforded precipitation of the product which was collected by filtration. Recrystalization from diethyl ether / pentane (1:1) afforded 3-bromo-2-iodo-4,5-dimethoxybenzaldehyde (45.63 g, 82%) as a white solid.

m.p.: 104.8 – 105.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 9.98 (s, 1H), 7.49 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H).

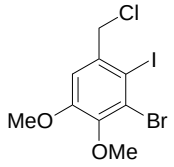
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 196.5, 153.7, 152.1, 133.5, 127.8, 112.4, 99.6, 60.7, 56.3.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3068, 3003, 2942, 2846, 1685, 1572, 1538, 1462, 1419, 1390, 1364, 1298, 1264, 1220, 1193, 1163, 1055, 992, 869, 818, 749, 674.

MS (EI, 70 eV) *m/z* (%): 418 (19), 416 (18), 388 (10), 387 ($[H_2O+M]^+$, 100), 386 (12), 385 ($[H_2O+M]^+$, 96), 372 (M^+, 27), 370 (M^+, 29), 244 (10), 127 (10), 75 (22).

HRMS (EI): *m/z* calc. for **$C_9H_8BrIO_3$** (369.8702): 369.8703 (M^+).

Synthesis of 3-bromo-1-(chloromethyl)-2-iodo-4,5-dimethoxybenzene (27b) :



To a solution of 3-bromo-2-iodo-4,5-dimethoxybenzaldehyde (11.23 g, 30 mmol) in acetonitrile (150 mL) under argon atmosphere sodium borohydride (1.34 g, 30 mmol) was added in small portions at 0 °C. The reaction mixture was allowed to warm up to 25 °C, was stirred for 1 h and slowly poured on 2 M HCl (120 mL). The reaction mixture was extracted with CH_2Cl_2 (3x 100 mL). The combined organic phases were washed with brine (50 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford the crude intermediate. The residue was dissolved in THF (60 mL), followed by addition of NEt_3 (6.66 mL, 48 mmol) and LiCl (3.48 g, 82.5 mmol) at 25 °C. At 0 °C $MeSO_2Cl$ (3.23 mL, 42 mmol) was added dropwise to the vigorous stirring solution. The reaction mixture was allowed to warm up to 25 °C and stirred for 12 h at the same temperature, followed by addition of sat. NH_4Cl (aq.) (50 mL). The aqueous layer was extracted with EtOAc (3x 30 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was subjected to flash column chromatography (pentane / EtOAc = 9:1) to afford 3-bromo-1-(chloromethyl)-2-iodo-4,5-dimethoxybenzene (**27a**, 9.18 g, 85%) as white solid.

m.p.: 119.3 – 120.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.08 (s, 1H), 4.73 (s, 2H), 3.88 (s, 3H), 3.82 (s, 3H).

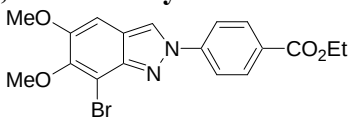
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 153.5, 146.9, 137.7, 127.1, 113.1, 96.2, 60.4, 56.2, 53.3.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3008, 2966, 2934, 2842, 1581, 1544, 1452, 1421, 1366, 1308, 1255, 1198, 1166, 1148, 1054, 993, 970, 914, 858, 817, 790, 711.

MS (EI, 70 eV) *m/z* (%): 394 (11), 392 (51), 390 (M^+, 37), 358 (8), 357 (98), 356 (8), 355 (100).

HRMS (EI): *m/z* calc. for **$C_9H_9BrClIO_2$** (389.8519): 389.8508 (M^+).

Synthesis of ethyl 4-(7-bromo-5,6-dimethoxy-2*H*-indazol-2-yl)benzoate (22j) :



According to **TP1** 3-bromo-1-(chloromethyl)-2-iodo-4,5-dimethoxybenzene (**27b**, 1.17 g, 3.0 mmol) was converted to the diarylzinc compound **24b** and was reacted with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**25c**, 528 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 9:1) afforded 4-(7-bromo-5,6-dimethoxy-2*H*-indazol-2-yl)benzoate (**22j**, 615 mg, 76%) as a pale yellow solid.

m.p.: 125.4 – 126.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.33 (s, 1H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H), 6.83 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H).

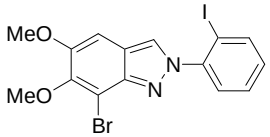
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.6, 151.5, 149.6, 145.6, 143.1, 130.9, 129.2, 120.5, 119.8, 119.4, 104.6, 96.9, 61.2, 60.9, 55.9, 14.2.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3127, 2983, 2946, 2849, 1710, 1608, 1546, 1522, 1482, 1426, 1366, 1342, 1282, 1236, 1170, 1104, 1028, 1000, 955, 924, 856, 820, 766.

MS (EI, 70 eV) *m/z* (%): 407 (25), 406 (M^+, 96), 405 (21), 404 (100, M^+), 391 (13), 360 (14), 310 (18), 185 (12), 120 (28), 43 (17).

HRMS (EI): *m/z* calc. for **$C_{18}H_{17}BrN_2O_4$** (404.0372): 404.0377 (M^+).

Synthesis of 7-bromo-2-(2-iodophenyl)-5,6-dimethoxy-2*H*-indazole (22k) :



According to **TP1** 3-bromo-1-(chloromethyl)-2-iodo-4,5-dimethoxybenzene (**27b**, 1.17 g, 3.0 mmol) was converted to the diarylzinc compound **24b** and was reacted with

2-iodobenzenediazonium tetrafluoroborate (**25b**, 636 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 9:1) afforded 7-bromo-2-2-iodophenyl)-5,6-dimethoxy-2*H*-indazole (**22k**, 624 mg, 68%) as a pale yellow solid.

m.p.: 134.3 – 135.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.12 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.39 - 7.58 (m, 3H), 7.18 (t, *J* = 7.85, 2H), 6.96 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H).

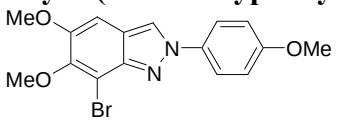
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm):151.2, 149.2, 144.9, 143.4, 139.8, 130.8, 129.0, 128.5, 125.2, 118.1, 104.6, 97.3, 94.4, 60.9, 56.0.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3114, 2982, 2954, 2929, 2824, 1631, 1579, 1544, 1507, 1485, 1467, 1440, 1400, 1342, 1228, 1147, 1043, 1028, 1006, 963, 926, 832, 759, 748, 716, 665.

MS (EI, 70 eV) *m/z* (%): 461 (13), 460 (M^+, 90), 459 (12), 458 (M^+,100), 364 (10), 288 (6).

HRMS (EI): *m/z* calc. for **$C_{15}H_{12}BrIN_2O_2$** (457.9127): 457.9132 (M^+).

Synthesis of 7-bromo-5,6-dimethoxy-2-(4-methoxyphenyl)-2*H*-indazole (22l) :



According to **TP1** 3-bromo-1-(chloromethyl)-2-iodo-4,5-dimethoxybenzene (**27b**, 1.17 g, 3.0 mmol) was converted to the diarylzinc compound **24b** and was reacted with 4-methoxybenzenediazonium tetrafluoroborate (**25j**, 444 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 9:1) afforded 7-bromo-5,6-dimethoxy-2-(4-methoxyphenyl)-2*H*-indazole (**22l**, 501 mg, 69%) as a pale white solid.

m.p.: 116.2 – 117.5 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.17 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.86 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H).

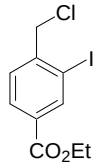
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm):159.0, 150.9, 148.7, 144.8, 133.8, 122.2, 120.6, 118.9, 114.4, 104.5, 97.2, 60.9, 55.9, 55.5.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3138, 3125, 2923, 2905, 1665, 1593, 1538, 1421, 1363, 1291, 1251, 1189, 1172, 1153, 1139, 1086, 1056, 1011, 880, 844, 808, 776, 751, 698, 669.

MS (EI, 70 eV) *m/z* (%): 365 (19), 364 (M^+, 91), 363 (18), 362 (M^+, 100), 348 (29), 347 (27), 268 (16), 253 (11).

HRMS (EI): *m/z* calc. for **$C_{16}H_{15}BrN_2O_3$** (362.0266): 362.0252 (M^+).

Synthesis of 4-chloromethyl-3-iodobenzoic acid ethyl ester (27c):



To a solution of 3-iodo-4-methylbenzoic acid ethyl ester (1.16 g, 4 mmol) in THF (10 mL) was added *N*-bromosuccinimide (783 mg, 4.4 mmol) and dibenzoylperoxide (97 mg, 0.4 mmol). The resulting mixture was refluxed for 9 h. Subsequently, the solvent was concentrated *in vacuo*, filtered through a plug of silica and washed with pentane. The solvent was removed *in vacuo*. In a 50 mL round bottom flask the residue was dissolved in THF (15 mL) and LiCl (433 mg, 10 mmol) was added. The resulting mixture was refluxed for 4 h. Subsequently, the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 100:1) provided 4-chloromethyl-3-iodobenzoic acid ethyl ester (**27c**, 776 mg, 60%) as a white solid.

m.p.: 79.2 – 80.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):8.52 (d, *J* = 1.8 Hz, 1H), 8.04 (dd, *J* = 1.8, 8.1 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 4.70 (s, 2H), 4.41 (q, *J* = 6.9 Hz, 2H), 1.41 (t, *J* = 6.9 Hz, 3H).

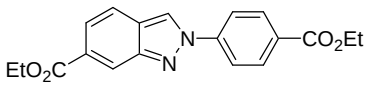
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):164.57, 144.25, 140.73, 131.93, 129.81, 129.77, 98.70, 61.51, 50.32, 14.29.

IR (Diamond-ATR, neat) υ (cm^{-1}): 1708, 1292, 727.

MS (EI, 70 eV) *m/z* (%): 324 (11), 323 (M^+, 19), 288 (100), 123 (13).

HRMS (EI): *m/z* calc. for **$C_{10}H_{10}ClIO_2$** (323.9414): 323.9415 (M^+).

Synthesis of 2-(4-ethoxycarbonyl-phenyl)-2*H*-indazole-6-carboxylic acid ethyl ester (22m):



According to **TP1** 4-Chloromethyl-3-iodo-benzoic acid ethyl ester (**27c**,324 mg, 1 mmol) was converted to the diarylzinc compound **24c** and reacted with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**25c**, 177 mg, 0.67 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1 to 2:1) afforded 2-(4-ethoxycarbonyl-phenyl)-2*H*-indazole-6-carboxylic acid ethyl ester (**22m**, 161 mg, 71%) as a pale yellow solid.

m.p.: 140.6 - 142.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):8.61 (s, 1H), 8.54 (s, 1H), 8.26 (d, *J* = 8.7 Hz, 2H), 8.06 (d, *J* = 8.7 Hz, 2H), 7.70 – 7. 78 (m, 2H), 4.40 – 4.50 (m, 4H), 1.40 – 1.50 (m, 6H).

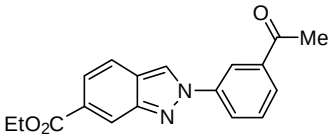
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):166.7, 165.6, 149.4, 143.3, 131.2, 130.2, 129.6, 124.8, 122.5, 121.8, 120.7, 120.4, 61.4, 61.1, 14.3.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3068, 2984, 1697, 1604, 1521, 1363, 1257, 1098, 856, 769, 689.

MS (EI, 70 eV) *m/z* (%): 339 (20), 338 (M^+, 100), 293 (70), 265 (17), 192 (9).

HRMS (EI): *m/z* calc. for **$C_{19}H_{18}N_2O_4$** (338.1267): 338.1242 (M^+).

Synthesis of 2-(3-acetylphenyl)-2*H*-indazole-6-carboxylic acid ethyl ester (22n) :



According to **TP1** 4-chloromethyl-3-iodo-benzoic acid ethyl ester (**27c**, 243 mg, 0.75 mmol) was converted to the diarylzinc compound **24c** and reacted with 3-(acetyl)benzenediazonium tetrafluoroborate[293] (**25k**, 117 mg, 0.5 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1 to 3:1) afforded 2-(3-acetylphenyl)-2*H*-indazole-6-carboxylic acid ethyl ester (**22n**, 104 mg, 68%) as a pale yellow solid.

m.p.: 128.8 – 130.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.61 (s, 1H), 8.55 (s, 1H), 8.51 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.77 (s, 2H), 6.67 (t, *J* = 8.1 Hz, 1H), 4.46 (dd, *J* = 6.9 Hz, 7.2 Hz, 2H), 2.72 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H).

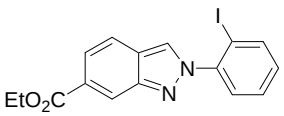
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 196.8, 166.7, 149.2, 140.7, 138.5, 130.1, 129.4, 128.0, 125.3, 124.7, 122.4, 121.7, 120.7, 120.4, 120.3, 61.1, 26.8, 14.3.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3341, 3103, 1707, 1678, 1441, 1368, 1317, 1243, 1060, 795, 741, 592.

MS (EI, 70 eV) *m/z* (%): 309 (14), 308 (M^+, 100), 293 (10), 264 (11), 263 (53), 192 (6).

HRMS (EI): *m/z* calc. for **$C_{18}H_{16}N_2O_3$** (308.1161): 308.1148 (M^+).

Synthesis of 2-(2-iodophenyl)-2*H*-indazole-6-carboxylic acid ethyl ester (22o) :



According to **TP1** 4-chloromethyl-3-iodo-benzoic acid ethyl ester (**27c**, 243 mg, 0.75 mmol) was converted to the diarylzinc compound **24c** and reacted with 2-iodobenzenediazonium tetrafluoroborate (**25b**, 160 mg, 0.5 mmol). Purification by flash column chromatography

[293] S. Sengupta, S. Bhattacharya, *J. Org. Chem*. **1997**, *62*, 3405.

(silica gel, pentane / EtOAc = 5:1) afforded 2-(2-iodo-phenyl)-2*H*-indazole-6-carboxylic acid ethyl ester (**22o**, 177 mg, 90%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.60 (s, 1H), 8.22 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.72 - 7.84 (m, 2H), 7.41 – 7.61 (m, 2H), 7.09 - 7.35 (m, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H).

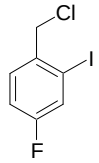
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.9, 148.6, 143.5, 140.1, 131.1, 129.1, 129.0, 128.1, 125.2, 123.8, 122.1, 121.8, 120.5, 94.0, 61.1, 14.3.

IR (Diamond-ATR, neat) υ (cm^{-1}): 2980, 1710, 1504, 1353, 1314, 1224, 1088, 1021, 948, 746.

MS (EI, 70 eV) *m/z* (%): 393 (21), 392 (M^+, 100), 346 (48), 218 (19), 192 (27).

HRMS (EI): *m/z* calc. for **$C_{16}H_{13}N_2O_2I$** (392.0022): 392.0034 (M^+).

Synthesis of 1-chloromethyl-4-fluoro-2-iodo-benzene (27d):



To a solution of 1-fluoro-3-iodo-4-methyl-benzene (2.36 g, 10 mmol) in THF (10 mL) was added N-bromosuccinimide (1.96 g, 11 mmol) and dibenzoylperoxide (242 mg, 1 mmol). The resulting mixture was refluxed for 9 h. Subsequently, the solvent was concentrated *in vacuo*, filtered through a plug of silica and washed with pentane. The solvent was removed *in vacuo*. In a 50 mL round bottom flask the residue was dissolved in THF (15 mL) and LiCl (693 mg, 16 mmol) was added. The resulting mixture was refluxed for 4 h. Subsequently, the solvent was removed *in vacuo*. Purification by flash column chromatography (silica, pentane) provided 4-fluoro-3-chloromethyl-2-iodo-benzene (**27d**, 908 mg, 35%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.60 (dd, *J* = 2.7, 7.7 Hz, 1H), 7.47 (dd, *J* = 6.0, 8.6 Hz, 1H), 7.10 (dt, *J* = 2.7, 16.8 Hz, 1H), 4.68 (s, 2H).

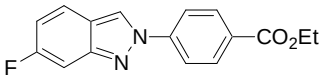
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 163.3 (d, *J* = 251.9 Hz), 136.1 (d, *J* = 3.5 Hz), 131.1 (d, *J* = 8.4 Hz), 126.9 (d, *J* = 23.6 Hz), 116.0 (d, *J* = 20.9 Hz), 99.0 (d, *J* = 8.6 Hz), 50.1 (d, *J* = 0.6 Hz).

IR (Diamond-ATR, neat) υ (cm^{-1}): 1693, 1590, 1225, 863.

MS (EI, 70 eV) *m/z* (%): 269 (M^+, 12), 234 (37), 155 (12).

HRMS (EI): *m/z* calc. for **C_7H_5ClFI** (269.9109): 269.9102 (M^+).

Synthesis of 4-(6-Fluoro-indazol-2-yl)-benzoic acid ethyl ester (22p) :



According to **TP1** 1-chloromethyl-4-fluoro-2-iodobenzene (**27d**, 406 mg, 1.5 mmol) was converted to the diarylzinc compound **24d** and was reacted with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**25c**, 264 mg, 1 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1) afforded 4-(6-fluoro-indazol-2*H*-yl)-benzoic acid ethyl ester (**22p**, 212 mg, 75%) as a pale yellow solid.

m.p.: 159.8-161.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.49 (s, 1H), 8.22 (d, *J* = 9.0 Hz, 2H) , 7.99 (d, *J* = 8.7 Hz, 2H), 7.70 (dd, *J* = 5.4 Hz, 9.2 Hz, 1H), 7.37 (d, *J* = 10.2 Hz, 1H), 6.96 (dt, *J* = 2.1 Hz, 8.7 Hz, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H).

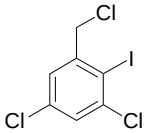
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.7, 162.3 (d, *J* = 244.3 Hz), 150.0 (d, *J* = 13.5 Hz), 143.3, 131.1, 129.7, 122.4 (d, *J* = 10.5 Hz), 121.0 (d, *J* = 1.5 Hz), 120.3, 120.1, 115.0 (d, *J* = 28.6 Hz), 101.0 (d, *J* = 24.0 Hz), 61.35, 14.35.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3073, 2986, 1707, 1639, 1607, 1370, 1270, 1101, 808, 763, 728.

MS (EI, 70 eV) *m/z* (%): 289 (19), 284 (M^+, 100), 239 (74), 210 (18), 192 (8).

HRMS (EI): *m/z* calc. for **$C_{16}H_{13}FN_2O_2$** (284.0961): 284.0955 (M^+).

Synthesis of 1,5-dichloro-3-chloromethyl-2-iodo-benzene (27e) :



To a solution of 1,5-dichloro-2-iodo-3-methyl-benzene (2.3 g, 8 mmol) in THF (10 mL) was added N-bromosuccinimide (1.6 g, 8.8 mmol) and dibenzoylperoxide (194 mg, 0.8 mmol). The resulting mixture was refluxed for 9 h. Subsequently, the solvent was concentrated *in vacuo*, filtered through a plug of silica and washed with pentane. The solvent was removed *in vacuo*. In a 50 mL round bottom flask the residue was dissolved in THF (15 mL) and LiCl (693 mg, 16 mmol) was added. The resulting mixture was refluxed for 4 h. Subsequently, the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, pentane) provided 1,5-dichloro-3-chloromethyl-2-iodo-benzene (**27e**, 716 mg, 54%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.46 (d, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 4.71 (s, 2H).

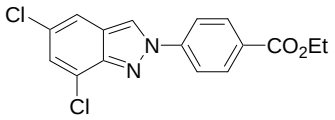
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 143.8, 140.7, 135.1, 128.8, 127.9, 101.4, 51.6.

IR (Diamond-ATR, neat) υ (cm^{-1}): 2362, 1551, 1382, 1266, 1282, 1017, 862, 811.

MS (EI, 70 eV) *m/z* (%): 321 (26), 319 (M^+, 24), 284 (50), 122 (12).

HRMS (EI): *m/z* calc. for **$C_7H_4Cl_3I$** (319.8423): 319.8408 (M^+).

Synthesis of 4-(5,7-dichloro-indazol-2-yl)-benzoic acid ethyl ester (22q) :



According to **TP1** 1,5-dichloro-3-chloromethyl-2-iodo-benzene (**27e**, 482 mg, 1.5 mmol) was converted to the diarylzinc compound **24e** and was reacted with 4-(ethoxycarbonyl)-benzenediazonium tetrafluoroborate (**25c**, 264 mg, 1 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1) afforded 4-(5,7-dichloro-indazol-2*H*-yl)-benzoic acid ethyl ester (**22q**, 219 mg, 66%) as a pale yellow solid.

m.p.: 139.6-141.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.50 (s, 1H), 8.23 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.37 (d, *J* = 1.8 Hz, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H).

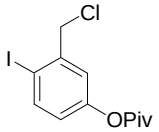
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.5, 146.2, 142.9, 131.2, 130.4, 128.0, 127.7, 124.5, 123.8, 121.3, 120.6, 118.0, 61.4, 14.3.

IR (Diamond-ATR, neat) υ (cm^{-1}): 2987, 1701, 1606, 1517, 1365, 1276, 850, 765.

MS (EI, 70 eV) *m/z* (%): 335 (18), 334 (M^+, 100), 288 (41), 226 (14), 191 (5).

HRMS (EI): *m/z* calc. for **$C_{16}H_{12}Cl_2N_2O_2$** (334.0276): 334.0280 (M^+).

Synthesis of 3-(chloromethyl)-4-iodophenyl pivalate (27f):



To a suspension of 3-(hydroxymethyl)-4-iodophenol (30 mmol, 7.50 g) in THF (125 ml) was added sodium hydride (30 mmol, 1.20 g, 60w% in mineral oil) at 0 °C and stirred for 30 min at the same temperature. Trimethylacetic anhydride (30 mmol, 5.58 g) in THF (50 mL) was added dropwise to the reaction mixture at 0 °C. After stirring the mixture for 3 h at 25 °C, the reaction was quenched with sat. NH_4Cl (aq.) (30 mL). The aqueous layer was extracted with EtOAc (4x 30 mL). The combined organic phases were dried over Na_2SO_4 and the solvent

was removed *in vacuo*. The residue was dissolved in THF (100 mL) and NEt_3 (48 mmol, 6.7 mL), LiCl (82.5 mmol, 3.50 g) were added. At 0 °C, $MeSO_2Cl$ (42 mmol, 3.25 mL) were added dropwise to the stirring solution. The reaction mixture was warmed up to 25 °C and stirred for 12 h at the same temperature, followed by addition of sat. NH_4Cl (aq.) (30 mL). The aqueous layer was extracted with EtOAc(3x 30 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (silica gel, pentane / diethyl ether = 199:1) to afford 3-(chloromethyl)-4-iodophenyl pivalate (**27f**, 8.59 g, 88%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.85 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 6.81 (dd, *J* = 8.4 Hz, 1H), 4.65 (s, 2H), 1.38 (s, 9H).

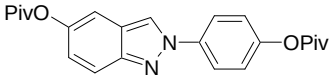
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 176.4, 151.5, 140.9, 140.2, 123.4, 123.3, 94.4, 50.4, 39.0, 27.0.

IR (Diamond-ATR, neat) υ (cm^{-1}): 2973, 2935, 2907, 2873, 1751, 1573, 1465, 1396, 1366, 1268, 1223, 1162, 1102, 1015, 942, 899, 827, 794, 732, 680.

MS (EI, 70 eV) *m/z* (%): 352 (M^+, 10), 270 (17), 268 (47), 233 (35), 97 (13), 85 (35), 83 (16), 77 (12), 71 (13), 69 (15), 57 (100), 56 (10), 55 (19), 44 (14), 43 (16).

HRMS (EI): *m/z* calc. for **$C_{12}H_{14}ClIO_2$** (351.9727): 351.9729 (M^+).

Syntheisi of 4-{5-[(2,2-dimethylpropanoyl)oxy]-2*H*-indazol-2-yl}phenyl pivalate (22r) :



According to **TP1** 3-(chloromethyl)-4-iodophenyl pivalate (**27f**, 1.06 g, 3.0 mmol) was converted to the diarylzinc compound **24f** and was reacted with 4-[(2,2-dimethylpropanoyl)oxy]benzenediazonium tetrafluoroborate (**25i**, 584 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded 4-{5-[(2,2-dimethylpropanoyl)oxy]-2*H*-indazol-2-yl}phenyl pivalate (**22r**, 575 mg, 73%) as a pale pink solid.

m.p.: 118.3 – 120.6.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.33 (s, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 9.3 Hz, 1H), 7.36 (d, *J* = 1.65 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.01 (dd, *J* = 9.2 Hz, 2.1 Hz, 1H), 1.38 (s, 9 H), 1.37 (s, 9 H).

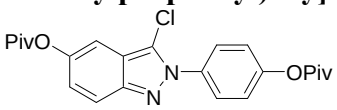
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 177.4, 176.8, 150.6, 148.0, 146.3, 137.8, 123.2, 122.7, 122.3, 121.8, 120.7, 119.1, 110.7, 39.2, 39.1, 27.2, 27.1.

IR (Diamond-ATR, neat) υ (cm^{-1}): 2964, 2933, 2872, 1740, 1604, 1523, 1477, 1459, 1393, 1366, 1280, 1200, 1150, 1110, 1029, 946, 902, 890, 837, 786, 760, 727.

MS (EI, 70 eV) *m/z* (%): 394 (M^+, 36), 311 (12), 310 (63), 226 (54), 85 (11), 57 (100).

HRMS (EI): *m/z* calc. for **$C_{23}H_{26}N_2O_4$** (394.1893): 394.1892 (M^+).

Synthesis of 4-{3-chloro-5-[(2,2-dimethylpropanoyl)oxy]-2*H*-indazol-2-yl}phenyl pivalate



In an argon-flushed microwave tube was added N-chlorosuccinimide (2 mmol, 267 mg) to a solution of **3r** (2 mmol, 788 mg) in CCl_4 (4 mL) at 25 °C. The reaction mixture was heated under microwave irradiation at 80 °C (100 W): *m/z* calc. for 30 min. After cooling down to 25 °C, sat. aqueous NH_4Cl-solution (20 mL) was added to the reaction mixture. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (silica gel, pentane / EtOAc = 95:5) to afford 4-{3-chloro-5-[(2,2-dimethylpropanoyl)oxy]-2*H*-indazol-2-yl}phenyl pivalate as a pale pink solid (706 mg, 83%).

m.p.: 138.4 – 139.2.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.70 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 9.2 Hz, 1H), 7.29 (d, *J* = 1.6 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.03 (dd, *J* = 9.1 Hz, 2.2 Hz, 1H), 1.39 (s, 9H), 1.38 (s, 9H).

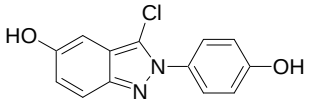
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm):177.3, 176.6, 151.5, 146.7, 146.6, 135.6, 126.6, 124.1, 122.3, 119.8, 119.5, 119.5, 109.5, 39.2, 39.1, 27.2, 27.1.

IR (Diamond-ATR, neat) υ (cm^{-1}): 2969, 2933, 2905, 2873, 1751, 1519, 1478, 1460, 1394, 1368, 1317, 1276, 1204, 1157, 1104, 1030, 1008, 895, 855, 813, 793, 757.

MS (EI, 70 eV) *m/z* (%): 430 (13), 429 (10), 428 (M^+, 33), 345 (22), 344 (14), 343 (68), 262 (15), 260 (49), 225 (16), 85 (13), 57 (100).

HRMS (EI): *m/z* calc. for **$C_{23}H_{25}ClN_2O_4$** (428.1503): 428.1494 (M^+).

Synthesis of 3-chloro-2-(4-hydroxyphenyl)-2*H*-indazol-5-ol (30) :



To a solution of **22r** (5 mmol, 1.97 g) in CCl_4 (10 mL) in an argon-flushed microwave tube was added N-chlorosuccinimide (5 mmol, 667 mg) at 25 °C. The reaction mixture was heated under microwave irradiation at 80 °C (100 W): *m/z* calc. for 30 min. After cooling down to 25 °C, sat. aqueous NH_4Cl-solution (20 mL) was added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organic phases were dried over

Na_2SO_4, the solvent was removed *in vacuo*. The residue was dissolved in 20 mL THF/H_2O mixture (2:1) and $LiOH \cdot H_2O$ (50 mmol, 2.10 g) was added and stirred for 12 h at 25 °C. Subsequently, 2M HCl (30 mL) was added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (silica gel, pentane / EtOAc = 1:1) to afford 3-chloro-2-(4-hydroxyphenyl)-2*H*-indazol-5-ol[294] as a pink solid (**30**, 1.00 g, 78%).

m.p.: 205.8 – 207.0.

^{1}H-NMR (400 MHz, CD_3OD) δ (ppm): 7.47 (d, *J* = 9.2 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 6.99 (dd, *J* = 9.2 Hz, 2.1 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 1.9 Hz, 1H).

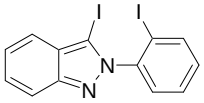
^{13}C-NMR (100 MHz, CD_3OD) δ (ppm): 157.7, 152.2, 144.3, 129.9, 126.7, 122.1, 119.6, 118.4, 118.0, 115.3, 97.9.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3344, 2926, 1734, 1700, 1640, 1599, 1570, 1527, 1516, 1468, 1428, 1386, 1305, 1281, 1240, 1205, 1116, 1100, 1026, 1010, 942, 839, 821, 805.

MS (EI, 70 eV) *m/z* (%): 262 (31), 261 (16), 260 (M^+, 100), 231 (12), 226 (11), 225 (66), 197 (19), 169 (3).

HRMS (EI): *m/z* calc. for **$C_{13}H_9ClN_2O_2$** (260.0353): 260.0343 (M^+).

Synthesis of 3-iodo-2-(2-iodophenyl)-2*H*-indazole (31a) :



To a solution of **22b** (2 mmol, 640 mg) in $ZnCl_2$ solution (2.0 mmol, 2 mL, 1M in THF) in a dry and argon-flushed microwave tube was added TMPMgCl·LiCl (2.2 mmol, 2.2 mL, 1 M in THF) at 25 °C. The reaction mixture was heated under microwave irradiation at 80 °C (100 W): *m/z* calc. for 1 h. After cooling to 25 °C, iodine (3 mmol, 762 mg) in THF (3 mL) was added. Subsequently, sat. aqueous NH_4Cl-solution (10 mL) was added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were washed with sat. $Na_2S_2O_3$ (aq.) (5 mL) and dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (silica gel, pentane / EtOAc = 95:5) to afford 3-iodo-2-(2-iodophenyl)-2*H*-indazole as a pale yellow solid (**31a**, 735 mg, 83%).

m.p.: 150.1 – 151.6.

[294] M. De Angelis, F. Stossi, K. Carlson, B. Katzenellenbogen, J. Katzenellenbogen, *J. Med. Chem.* **2005**, *48*, 1132.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm):8.03 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 1 H), 7.49 - 7.62 (m, 2H), 7.38 - 7.47 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 8.1 Hz, 1H).

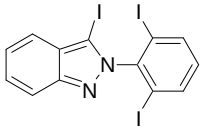
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm):150.0, 143.4, 139.6, 132.7, 131.5, 129.2, 128.9, 127.6, 123.2, 120.9, 118.5, 97.2, 78.4.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3055, 1736, 1721, 1622, 1579, 1552, 1541, 1508, 1483, 1427, 1368, 1350, 1266, 1250, 1215, 1148, 1096, 1040, 1020, 996, 980, 918, 816, 763, 736, 714, 693.

MS (EI, 70 eV) *m/z* (%): 446 (13), 445 (M^+, 100), 202 (12), 191 (42), 95 (6), 76 (10).

HRMS (EI): *m/z* calc. for **$C_{13}H_8I_2N_2$** (445.8777): 445.8766 (M^+).

Synthesis of 2-(2,6-diiodophenyl)-3-iodo-2*H*-indazole (31b) :



To $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ solution (1.1 mmol, 2.75 mL, 0.4 M in THF) in a dry and argon-flushed microwave tube was added **22b** (1 mmol, 320 mg) and $ZnCl_2$ solution (2.0 mmol, 2 mL, 1M in THF) in THF (1 mL) was added at 25 °C. The reaction mixture was heated under microwave irradiation at 80 °C (100 W): *m/z* calc. for 1 h. After cooling to 25 °C, iodine (3 mmol, 762 mg) in THF (5 mL) was added. Subsequently, sat. aqueous NH_4Cl-solution (10 mL) was added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were washed with sat. $Na_2S_2O_3$ (aq.) (5 mL) and dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (silica gel, pentane / EtOAc = 95:5) to afford 2-(2,6-diiodophenyl)-3-iodo-2*H*-indazole as a pale yellow solid (**31b**, 417 mg, 73%).

m.p.: 156.4 – 158.1.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.96 (d, *J* = 7.85 Hz, 2H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.41 (t, *J* = 6.5 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.91 (t, *J* = 7.9 Hz, 1H).

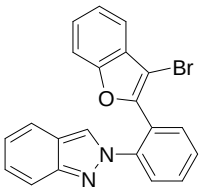
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm):150.2, 144.8, 139.3, 132.7, 127.8, 127.6, 123.4, 121.0, 118.8, 97.4, 77.8.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3130, 3054, 3041, 1628, 1593, 1518, 1493, 1465, 1456, 1389, 1377, 1312, 1233, 1205, 1128, 1101, 1073, 1045, 950, 905, 802, 780, 746, 683.

MS (EI, 70 eV) *m/z* (%): 571 (M^+, 100), 329 (10), 318 (32), 191 (21), 75 (8).

HRMS (EI): *m/z* calc. for **$C_{13}H_7I_3N_2$** (572.7822): 572.7826 (M^+).

Synthesis of 2-[2-(3-bromo-1-benzofuran-2-yl)phenyl]-2*H*-indazole (32a) :



A dry and argon flushed microwave tube, equipped with a magnetic stirring bar, was charged with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (4.95 mmol, 12.34 mL) and 3-bromobenzofuran (9 mmol, 1.77 g) at 25 °C. The reaction mixture was heated under microwave irradiation at 80 °C (100 W): *m/z* calc. for 20 min. After cooling to 25 °C, the di(3-bromobenzofuran-2-yl)zinc was added dropwise to a solution of **22b** (6 mmol, 1.92 g) and $Pd(PPh_3)_4$ (0.24 mmol, 277 mg) at 25 °C. The mixture was heated at 50 °C for 6 h. After cooling down the reaction mixture to 25 °C, sat. aqueous NH_4Cl-solution (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (silica gel, pentane / EtOAc = 9:1) to afford 2-[2-(3-bromo-1-benzofuran-2-yl)phenyl]-2*H*-indazole as a pale yellow solid (**32a**, 2.27 g, 97%).

m.p.: 67.9 – 68.7.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.81 - 7.90 (m, 3H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.45 (t, *J* = 4.3 Hz, 1H), 7.21 - 7.28 (m, 3H), 7.18 (t, *J* = 4.7 Hz, 1H), 6.99 (t, *J* = 8.1 Hz, 1H).

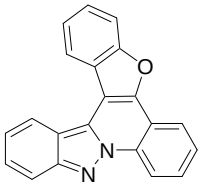
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm):153.7, 149.5, 148.9, 139.6, 131.8, 130.8, 128.4, 128.2, 127.1, 126.6, 125.8, 123.9, 123.8, 123.5, 122.5, 122.0, 120.4, 120.0, 117.9, 111.5, 97.5.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3058, 1628, 1590, 1518, 1489, 1447, 1387, 1347, 1259, 1244, 1195, 1145, 1112, 1082, 1068, 1047, 986, 952, 930, 908, 892, 824, 797, 742.

MS (EI, 70 eV) *m/z* (%): 310 (19), 309 (100), 308 (18), 281 (12), 154 (9).

HRMS (EI): *m/z* calc. for **$C_{21}H_{13}BrN_2O$** (388.0211): 388.0202 (M^+).

Synthesis of [1]benzofuro[3,2-*c*]indazolo[2,3-*a*]quinoline (32b) :



A dry and argon flushed microwave tube, equipped with a magnetic stirring bar, was charged with **32a** (1 mmol, 389 mg), $Pd(OAc)_2$ (0.2 mmol, 44 mg), 1,1'-bis(diphenylphosphino)ferrocene (0.2 mmol, 74 mg), tetrabutylammonium iodide (1 mmol, 369 mg) in DMF:H_2O:NEt_3 mixture (8:1:1) (5 mL) at 25 °C. The reaction mixture was

heated under microwave irradiation at 150 °C (100 W): *m/z* calc. for 1 h. After cooling down to 25 °C, the reaction mixture was diluted with diethyl ether (5 mL). The precipitate was removed by filtration and washed with methanol. The solid was dissolved in chloroform and filtered through a short plug of silica. Evaporation of the solvent afforded [1]benzofuro[3,2-*c*]indazolo[2,3-*a*]quinoline as a yellow solid (**32b**, 256 mg, 83%).

m.p.: 305.8 – 306.7.

^{1}H-NMR (600 MHz, CD_2Cl_2) δ (ppm): 9.02 (d, *J* = 8.3 Hz, 1H), 8.60 (d, *J* = 8.5 Hz, 1H), 8.54 (d, *J* = 5.8 Hz, 1H), 8.46 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.88 (t, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 7.0 Hz, 1H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.54 - 7.64 (m, 3H), 7.34 (t, *J* = 7.4 Hz, 1H).

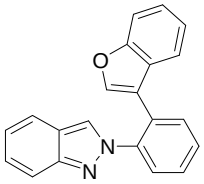
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 151.6, 145.0, 143.9, 129.2, 125.4, 124.5, 123.4, 122.3, 122.1, 119.6, 118.9, 118.1, 117.5, 117.1, 116.2, 113.8, 112.4, 111.7, 110.6, 107.7, 106.4.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3060, 3012, 1631, 1622, 1594, 1556, 1538, 1457, 1396, 1360, 1328, 1309, 1294, 1273, 1218, 1200, 1144, 1121, 1108, 1077, 1069, 1020, 930, 899, 838, 809, 758, 737, 701, 677, 654.

MS (EI, 70 eV) *m/z* (%): 309 (22), 308 (M^+, 100), 307 (8), 278 (8), 154 (17), 126 (6), 117 (7), 91 (7).

HRMS (EI): *m/z* calc. for **$C_{21}H_{12}N_2O$** (308.0950): 308.0943(M^+).

Synthesis of 2-[2-(1-benzofuran-3-yl)phenyl]-2*H*-indazole (33a) :



A dry and argon flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with Mg (14.4 mmol, 350 mg) in THF (10 mL) which was activated with 3 drops of 1,2-dibromoethane and 3 drops of Me_3SiCl. Then, $ZnCl_2$·LiCl solution (10.2 mmol, 10.2 mL, 1M in THF) and 3-bromobenzofuran (9 mmol, 1.77 g) were added at 25 °C, followed by stirring for 1 h at the same temperature. To a solution of **22b** (6 mmol, 1.92 g) and $Pd(PPh_3)_4$ (0.24 mmol, 277 mg) in THF (12 mL) was added dropwise the arylzinc reagent at 25 °C. The reaction mixture was stirred for 6 h at 50 °C. After cooling to 25 °C, sat. aqueous NH_4Cl-solution (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo* and the

residue was subjected to flash column chromatography (silica gel, pentane / EtOAc = 9:1) to afford 2-[2-(1-benzofuran-3-yl)phenyl]-2*H*-indazole as a yellow solid (**33a**, 1.73 g, 93%).

m.p.: 132.5 – 133.5.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.82 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 5.2 Hz, 1H), 7.23 (s, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.1 Hz, 1H).

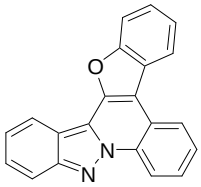
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 155.0, 149.1, 142.4, 139.3, 130.7, 129.3, 128.5, 127.8, 127.6, 126.5, 126.4, 124.9, 124.6, 123.0, 122.1, 122.0, 120.3, 119.6, 117.8, 117.7, 111.5.

IR (Diamond-ATR, neat) υ (cm^{-1}): 2928, 1627, 1606, 1569, 1518, 1497, 1477, 1450, 1384, 1268, 1213, 1191, 1145, 1103, 1091, 1052, 857, 822, 787, 768, 756, 742, 710, 656.

MS (EI, 70 eV) *m/z* (%): 310 (M^+, 100), 309 (31), 281 (35), 279 (6), 181 (11), 140 (8).

HRMS (EI): *m/z* calc. for **$C_{21}H_{14}N_2O$** (310.1106): 310.1097 (M^+).

Synthesis of [1]benzofuro[2,3-*c*]indazolo[2,3-*a*]quinoline (33b) :



A dry and argon flushed microwave tube, equipped with a magnetic stirring bar, was charged with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (1.2 mmol, 3.0 mL) and **33a** (1 mmol, 310 mg) at 25 °C. The reaction mixture was heated under microwave irradiation at 80 °C (150 W): *m/z* calc. for 1 h. After cooling to 25 °C, $CuCN{\cdot}2LiCl$[295] (1 mmol, 1 mL, 1M in THF) was added dropwise to the zinc reagent and further stirred for 10 min at 25 °C. To a solution of chloranil (1.5 mmol, 368 mg) in THF (5 mL) the copper reagent was added dropwise at 25 °C, followed by stirring for 1 h at the same temperature. The reaction mixture was quenched with 2 M aqueous NH_4OH (50 mL) solution. The aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organic phases were washed with 2 M HCl (50 mL) and dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (silica gel, pentane / EtOAc = 9:1 with 0.5 % NEt_3) to afford [1]benzofuro[2,3-*c*]indazolo [2,3-*a*]quinoline as a yellow solid (**33b**, 232 mg, 75%).

m.p.: 259.6 – 260.3.

[295] V. del Amo, S. Dubbaka, A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 7838.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 9.08 (d, *J* = 8.5 Hz, 1H), 8.58 (d, *J* = 7.6 Hz, 1H), 8.48 (d, *J* = 8.1 Hz, 1H), 8.31 (d, *J* = 7.1 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 7.1 Hz, 1H), 7.76 (t, *J* = 7.3 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 6.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H).

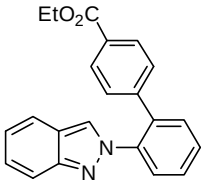
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm):156.4, 149.1, 146.1, 132.1, 128.3, 127.6, 126.8, 126.2, 124.4, 124.2, 124.0, 123.7, 121.8, 121.4, 121.2, 120.8, 118.3, 116.7, 115.4, 112.4, 112.4.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3053, 2925, 2852, 1689, 1678, 1650, 1613, 1570, 1539, 1496, 1462, 1448, 1429, 1381, 1356, 1310, 1270, 1230, 1208, 1178, 1107, 1080, 1055, 1023, 992, 946, 937, 883, 806, 771, 739, 712, 698.

MS (EI, 70 eV) *m/z* (%): 309 (24), 308 (M^+, 100), 307 (8), 154 (14), 44 (16).

HRMS (EI): *m/z* calc. for **$C_{21}H_{12}N_2O$** (308.0950): 308.0933(M^+).

Synthesis of ethyl 2'-(2*H*-indazol-2-yl)biphenyl-4-carboxylate (37a) :



To a solution of ethyl 4-iodobenzoate (1.5 mmol, 414 mg) in THF (2 mL) was added *i*PrMgCl·LiCl (1.55 mmol, 0.86 mL, 1.80 M in THF) at –20 °C. After stirring for 30 min, $ZnBr_2$ (1.5 mmol, 1.5 mL, 1 M in THF) was added dropwise at –20 °C followed by continuous stirring for 10 min. Subsequently, the arylzinc reagent was added dropwise to a solution of **22b** (1 mmol, 320 mg) and $NiBr_2(PPh_3)_2$ (4 mol%, 33 mg) in THF (2 mL) at 25 °C and stirred for 30 min followed by addition of sat. aq. NH_4Cl-solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (silica gel, pentane / EtOAc = 8:2) affording ethyl 2'-(2*H*-indazol-2-yl)biphenyl-4-carboxylate as a pale yellow solid (**37a**, 255 mg, 75%).

m.p.: 123.4 – 124.8.

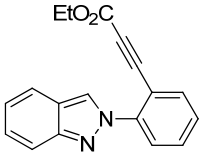
^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm):7.88 (d, *J*=8.2Hz, 2H), 7.75 (d, *J*=8.6Hz, 1H), 7.71-7.74 (m, 1H), 7.61 (s, 1H), 7.51-7.58 (m, 3H), 7.49 (d, *J*=8.4Hz, 1H), 7.30 (t, *J*=7.1Hz, 1H), 7.16 (d, *J*=8.2Hz, 2H), 7.04 (t, *J*=7.8Hz, 1H), 4.32 (q, *J*=7.1Hz, 2H), 1.34 (t, *J*=7.1Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm):166.2, 149.0, 142.5, 138.7, 136.1, 130.9, 129.7, 129.6, 129.3, 129.0, 128.3, 127.5, 126.7, 125.3, 122.1, 122.0, 120.4, 117.7, 61.0, 14.2.

MS (EI, 70 eV) *m/z* (%): 342 (60), 341 (M^+, 100), 313 (38), 269 (12), 268 (17), 267 (11).

HRMS (EI): *m/z* calc. for **$C_{22}H_{18}N_2O_2$** (342.1368): 341.1289 (M^+).

Synthesis of ethyl 3-[2-(2*H*-indazol-2-yl)phenyl]prop-2-ynoate (37b) :



To a solution of **22b** (1 mmol, 320 mg) in NEt_3 (4 mL) was added CuI (4 mol%, 8 mg), $PdCl_2$ (2 mol%, 3.5 mg), PPh_3 (4 mol%, 10.5 mg), and ethyl propiolate (1.5 mmol, 147 mg). The reaction mixture was stirred for 6 h at 50 °C followed by addition of sat. aq. NH_4Cl-solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (silica gel, pentane / EtOAc = 8:2) affording ethyl 3-[2-(2*H*-indazol-2-yl)phenyl]prop-2-ynoate as a pale yellow oil (**37b**, 200 mg, 69%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.93 (d, *J*=8.4Hz, 1H), 8.73 (d, *J*=8.6Hz, 1H), 8.28 (s, 1H), 7.95 (d, *J*=8.8Hz, 1H), 7.91 (d, *J*=7.9Hz, 1H), 7.82 (t, *J*=7.5Hz, 1H), 7.52–7.61 (m, 2H), 7.27 (t, *J*=6.9Hz, 1H), 4.57 (q, *J*=7.1Hz, 2H), 1.52 (t, *J*=7.1Hz, 3H).

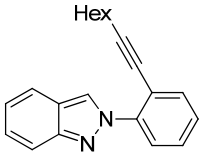
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 165.0, 149.7, 135.2, 131.6, 129.6, 129.4, 128.1, 127.9, 126.4, 124.1, 123.1, 122.0, 121.3, 117.5, 116.4, 116.4, 61.8, 14.3.

IR (Diamond-ATR, neat) υ (cm^{-1}): 2925, 1727, 1610, 1558, 1454, 1362, 1303, 1243, 1214, 1076, 1032, 780, 748, 736.

MS (EI, 70 eV) *m/z* (%): 291 (16), 290 (M^+, 100), 263 (12), 262 (84), 217 (11), 190 (6).

HRMS (EI): *m/z* calc. for **$C_{18}H_{14}N_2O_2$** (290.1055): 290.1040 (M^+).

Synthesis of 2-(2-oct-1-yn-1-ylphenyl)-2*H*-indazole (37c) :



To a solution of **22b** (1 mmol, 320 mg) in NEt_3 (4 mL) was added CuI (4 mol%, 8 mg), $PdCl_2$ (2 mol%, 3.5 mg), PPh_3 (4 mol%, 10.5 mg), and octyne (1.5 mmol, 165 mg). The reaction mixture was stirred for 6 h at 50 °C followed by addition of sat. aq. NH_4Cl-solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (silica gel, pentane / EtOAc = 95:5) affording 2-(2-oct-1-yn-1-ylphenyl)-2*H*-indazole as a yellow oil (**37c**, 208 mg, 69%).

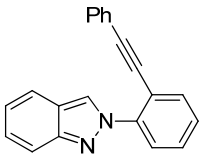
^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.68 (s, 1H), 7.80 (d, *J*=8.0Hz, 2H), 7.71 (d, *J*=8.4Hz, 1H), 7.57 (d, *J*=7.9Hz, 1H), 7.42 (t, *J*=7.8Hz, 1H), 7.30–7.37 (m, 2H), 7.11 (t, *J*=6.9Hz, 1H), 2.32 (t, *J*=6.9Hz, 2H), 1.23–1.32 (m, 4H), 1.13–1.23 (m, 4H), 0.84 (t, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 149.1, 141.3, 133.6, 129.5, 128.5, 127.9, 126.7, 125.8, 122.4, 120.9, 120.4, 118.3, 117.8, 96.3, 77.5, 31.2, 28.5, 28.1, 22.4, 19.5, 14.0.

MS (EI, 70 eV) *m/z* (%): 303 (12), 302 (M^+, 52), 273 (35), 245 (60), 233 (64), 232 (100), 219 (41), 204 (14).

HRMS (EI): *m/z* calc. for **$C_{21}H_{22}N_2$** (302.1783): 302.1773 (M^+).

Synthesis of 2-[2-(phenylethynyl)phenyl]-2*H*-indazole (37d) :



To a solution of **22b** (1 mmol, 320 mg) in NEt_3 (4 mL) was added CuI (4 mol%, 8 mg), $PdCl_2$ (2 mol%, 3.5 mg), PPh_3 (4 mol%, 10.5 mg), and phenylacetylene (1.2 mmol, 123 mg). The reaction mixture was stirred for 2 h at 50 °C followed by addition of sat. aq. NH_4Cl-solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (silica gel, pentane / EtOAc = 9:1) affording 2-[2-(phenylethynyl)phenyl]-2*H*-indazole as a yellow oil (**37d**, 254 mg, 87%).

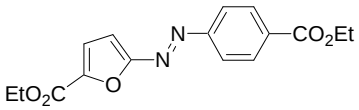
^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.78 (s, 1H), 7.89 (d, *J*=8.0Hz, 1H), 7.85 (d, *J*=8.8Hz, 1H), 7.75 (d, *J*=8.4Hz, 1H), 7.71 (d, *J*=7.7Hz, 1H), 7.50 (t, *J*=7.8Hz, 1H), 7.41 (t, *J*=7.6Hz, 1H), 7.34–7.38 (m, 3H), 7.26–7.32 (m, 3H), 7.14 (t, *J*=7.5Hz, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 149.3, 141.3, 133.4, 131.3, 129.3, 128.7, 128.3, 128.0, 126.8, 125.8, 124.5, 122.4, 122.2, 122.0, 120.5, 117.8, 117.5, 94.5, 85.8.

MS (EI, 70 eV) *m/z* (%): 295 (18), 294 (M^+, 81), 293 (100), 292 (42), 147 (11), 146 (11).

HRMS (EI): *m/z* calc. for **$C_{21}H_{14}N_2$** (294.1157): 294.1130 (M^+).

Synthesis of ethyl 5-{(*E*)-[4-(ethoxycarbonyl)phenyl]diazenyl}-2-furoate (39a) :



According to **TP3** ethyl 5-bromo-2-furoate (657 mg, 3.0 mmol) was converted to the diarylzinc compound **38a** and was reacted with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**25c**, 528 mg, 2.0 mmol). Purification by flash column chromatography

(silica gel, pentane / EtOAc = 95:5) afforded ethyl 5-{(*E*)-[4-(ethoxycarbonyl)phenyl]diazenyl}-2-furoate (**39a**, 562 mg, 89%) as a red solid.

m.p.: 110.3 – 111.6.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.16 (d, *J* = 8.3 Hz, 2H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 3.6 Hz, 1H), 7.11 (d, *J* = 3.5 Hz, 1H), 4.38 - 4.43 (m, 4H), 1.38 - 1.43 (m, 6H).

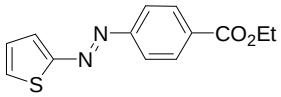
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 165.8, 161.6, 158.5, 155.2, 144.7, 132.9, 130.6, 122.9, 120.0, 110.8, 61.7, 61.3, 14.3.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3136, 3100, 2982, 2938, 2905, 1724, 1702, 1471, 1269, 1245, 1158, 1101, 966, 761, 700.

MS (EI, 70 eV) *m/z* (%): 316 (M^+, 100), 271 (10), 167 (11), 163 (15), 149 (23), 135 (14), 117 (7).

HRMS (EI): *m/z* calc. for **$C_{16}H_{16}N_2O_5$** (316.1059): 316.1054 (M^+).

Synthesis of ethyl 4-[(*E*)-2-thienyldiazenyl]benzoate (39b) :



According to **TP3** 2-iodothiophene (630 mg, 3.0 mmol) was converted to the diarylzinc compound **38b** and was reacted with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**25c**, 528 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded ethyl 4-[(*E*)-2-thienyldiazenyl]benzoate (**39b**, 431 mg, 83%) as a red solid.

m.p.: 115.6 – 117.1.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.15 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 4.6 Hz, 1H), 7.46 (d, *J* = 5.3 Hz, 1H), 7.17 (t, *J* = 4.6 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

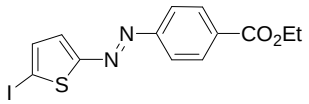
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.0, 160.2, 154.6, 133.1, 131.9, 130.5, 129.7, 127.7, 122.5, 61.2, 14.3.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3407, 3090, 3075, 2998, 2980, 2962, 2939, 1957, 1820, 1714, 1413, 1376, 1269, 1096, 1008, 774, 704.

MS (EI, 70 eV) *m/z* (%): 260 (M^+, 78), 215 (12), 149 (26), 111 (100), 83 (31), 65 (10).

HRMS (EI): *m/z* calc. for **$C_{13}H_{12}N_2O_2S$** (260.0619): 260.0617 (M^+).

Synthesis of ethyl 4-[(*E*)-(5-iodo-2-thienyl)diazenyl]benzoate (39c) :



According to **TP3** 2,5-diiodothiophene (1.00 g, 3.0 mmol) was converted to the diarylzinc compound **38c** and was reacted with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**25c**, 528 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded ethyl 4-[(*E*)-(5-iodo-2-thienyl)diazenyl]benzoate (**39c**, 726 mg, 94%) as a red solid.

m.p.: 140.1 – 141.0.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.13 (d, *J* = 8.6 Hz, 2H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 3.9 Hz, 1H), 7.39 (d, *J* = 3.9 Hz, 1H), 4.39 (q, *J* = 7.0 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

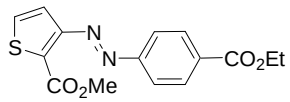
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.9, 164.2, 154.3, 137.6, 133.3, 133.1, 132.1, 130.5, 122.6, 122.5, 83.3, 61.2, 14.3.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3396, 3096, 2989, 2972, 2930, 1707, 1599, 1410, 1361, 1266, 1096, 1042, 1008, 804, 772, 695.

MS (EI, 70 eV) *m/z* (%): 386 (M^+, 100), 260 (46), 237 (32), 209 (15), 149 (45), 111 (44), 103 (14), 82 (13).

HRMS (EI): *m/z* calc. for **$C_{13}H_{11}IN_2O_2S$** (385.9586): 385.9565 (M^+).

Synthesis of methyl 3-{(*E*)-[4-(ethoxycarbonyl)phenyl]diazenyl}thiophene-2-carboxylate (39d) :



According to **TP3** methyl 3-bromothiophene-2-carboxylate (663 mg, 3.0 mmol) was converted to the diarylzinc compound **38d** and was reacted with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**25c**, 528 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded methyl 3-{(*E*)-[4-(ethoxycarbonyl)phenyl]diazenyl}-thiophene-2-carboxylate (**14d**, 528 mg, 83%) as a red solid.

m.p.: 103.2 – 104.3.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.17 (d, *J* = 8.3 Hz, 2H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.43 - 7.49 (m, 2H), 4.40 (q, *J* = 7.0 Hz, 2H), 3.97 (s, 3H), 1.41 (t, *J* = 7.0 Hz, 3H).

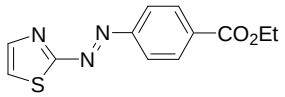
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 165.9, 161.5, 156.3, 155.2, 132.7, 131.5, 130.6, 130.0, 123.0, 118.4, 61.3, 52.5, 14.3.

IR (Diamond-ATR, neat**)**: υ (cm^{-1}): 3427, 3401, 3100, 3000, 2954, 2905, 1721, 1709, 1436, 1278, 1247, 1224, 1097, 1027, 871, 784, 698, 645.

MS (EI, 70 eV): *m/z* (%): 318 (M^+, 100), 273 (11), 169 (80), 149 (73), 125 (39), 103 (16).

HRMS (EI): *m/z* calc. for **$C_{15}H_{14}N_2O_4S$** (318.0674): 318.0660 (M^+).

Synthesis of ethyl 4-[(*E*)-1,3-thiazol-2-yldiazenyl]benzoate (39e) :



According to **TP3** 2-bromothiazole (492 mg, 3.0 mmol) was converted to the diarylzinc compound **38e** and was reacted with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**25c**, 528 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5) afforded ethyl 4-[(*E*)-1,3-thiazol-2-yldiazenyl]benzoate (**39e**, 491 mg, 94%) as a brown solid.

m.p.: 121.9 – 123.1.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm):8.17 (d, *J* = 7.6 Hz, 2H), 8.06 (d, *J* = 2.7 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 3.1 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

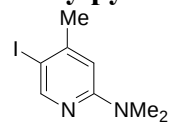
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm):176.6, 165.6, 153.8, 144.3, 133.7, 130.6, 123.5, 122.2, 61.4, 14.2.

IR (Diamond-ATR, neat) υ (cm^{-1}): 3094, 3080, 2978, 2902, 1707, 1601, 1578, 1484, 1450, 1409, 1368, 1322, 1279, 1233, 1192, 1174, 1139, 1122, 1107, 1080, 1022, 1007, 898, 873, 768, 693.

MS (EI, 70 eV) *m/z* (%): 261 (M^+, 34), 233 (31), 215 (32), 187 (83), 150 (29), 121 (88), 104 (32), 76 (56), 65 (100).

HRMS (EI): *m/z* calc. for **$C_{12}H_{11}N_3O_2S$** (261.0572): 261.0569 (M^+).

Synthesis of 2-amine-5-iodo-*N*,*N*,4-trimethylpyridine :



2-Amino-5-iodo-4-methylpyridine (7.4 mmol, 1.70 g) was added to a mixture of formaldehyde solution (30 mL, 0.40 mol, 37 w% in water) and formic acid (0.78 mol, 30 mL). The reaction mixture was refluxed for 18 h. Then, the solution was neutralized with 2 M aqueous NaOH solution. The aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (silica gel, pentane / EtOAc = 95:5) to afford **5-**iodo-2-amino-*N*,*N*,4-trimethylpyridin as a white solid (1.32 g, 68 %).

m.p.: 35.1 – 36.0.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.31 (s, 1H), 6.42 (s, 1H), 3.03 (s, 6H), 2.29 (s, 3H).

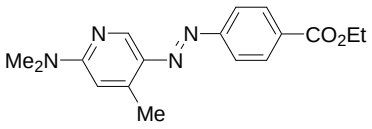
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 159.23, 154.34, 149.94, 107.47, 83.22, 38.13, 27.48.

IR (Diamond-ATR, neat) υ (cm^{-1}): 2920, 2853, 2792, 1584, 1526, 1494, 1432, 1396, 1376, 1338, 1286, 1265, 1228, 1204, 1166, 1065, 1033, 970, 921, 877, 827, 730.

MS (EI, 70 eV) *m/z* (%): 261 (M^+, 88), 246 (44), 232 (73), 149 (100), 107 (27), 92 (35), 79 (19), 65 (23).

HRMS (EI): *m/z* calc. for **$C_8H_{11}IN_2$** (261.9967): 261.9953 (M^+).

Synthesis of ethyl 4-{(*E*)-[6-(dimethylamino)-4-methylpyridin-3-yl]diazenyl}benzoate (39f) :



According to **TP3** 2-amino-5-iodo-*N*,*N*,4-trimethylpyridine (786 mg, 3.0 mmol) was converted to the dipyridylzinc compound **38f** and was reacted with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**2c**, 528 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5 with 0.5 % NEt_3) afforded ethyl 4-{(*E*)-[6-(dimethylamino)-4-methylpyridin-3-yl]diazenyl}benzoate (**39f**, 406 mg, 65%) as a red solid.

m.p.: 140.6 – 142.1.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.61 (s, 1H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.82 (d, *J* = 8.6 Hz, 2H), 6.35 (s, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 3.16 (s, 6H), 2.62 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H).

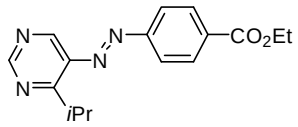
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 166.2, 159.8, 155.9, 147.7, 139.0, 138.5, 130.7, 130.4, 122.1, 105.9, 61.0, 38.2, 18.4, 14.3.

IR (Diamond-ATR, neat) υ (cm^{-1}): 2982, 2931, 2868, 1709, 1657, 1597, 1518, 1477, 1428, 1398, 1350, 1304, 1272, 1229, 1190, 1125, 1098, 1061, 1021, 968, 950, 868, 827, 774, 747, 727, 699.

MS (EI, 70 eV) *m/z* (%): 313 (18), 312 (M^+, 100), 283 (11), 239 (13), 163 (14), 135 (56), 108 (92), 93 (13).

HRMS (EI): *m/z* calc. for **$C_{17}H_{20}N_4O_2$** (312.1586): 312.1578 (M^+).

Synthesis of ethyl 4-{(*E*)-[4-(1-methylethyl)pyrimidin-5-yl]diazenyl}benzoate (39g) :



To a solution of 5-bromopyridine (3 mmol, 477 mg) in THF (4 mL) was added dropwise *i*PrMgCl·LiCl (3.2 mmol, 2.6 mL, 1.23 M in THF) at –60 °C followed by continuous stirring

for 1 h. After addition of $ZnBr_2$ (1.7 mmol, 1.7 mL, 1 M in THF) at –60 °C, the reaction mixture was allowed to slowly warm to 25 °C. According to **TP3** the dipyrimidylzinc compound **38g** reacted with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**25c**, 528 mg, 2.0 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 95:5 with 0.5 % NEt_3) afforded ethyl 4-{(*E*)-[4-(1-methylethyl)pyrimidin-5-yl]diazenyl}benzoate (**39f**, 346 mg, 59%) as a red solid.

m.p.: 145.9 – 147.1.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 9.19 (s, 1H), 8.78 (s, 1H), 8.20 (d, *J*=8.5Hz, 2H), 7.95 (d, *J*=8.5Hz, 2H), 4.40 (q, *J*=7.0Hz, 2H), 4.07 (sep, *J*=6.9Hz, 1H), 1.34–1.45 (m, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 173.0, 165.7, 160.0, 154.8, 143.9, 142.4, 133.2, 130.6, 123.0, 61.4, 30.2, 21.4, 14.3.

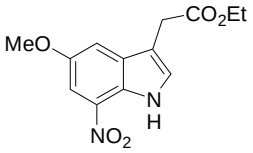
IR (Diamond-ATR, neat) υ (cm^{-1}): 3042, 2974, 2966, 2872, 1709, 1604, 1567, 1545, 1472, 1444, 1272, 1105, 1095, 1023, 869, 770, 691, 586.

MS (EI, 70 eV) *m/z* (%): 298 (M^+, 5), 284 (15), 283 (100), 255 (14), 253 (7), 134 (35), 120 (7), 103 (6).

HRMS (EI): *m/z* calc. for **$C_{16}H_{18}N_4O_2$** (298.1430): 298.1436 (M^+).

3.2 Organometallic Variation of the Fischer Indole Synthesis

Synthesis of ethyl (5-methoxy-7-nitro-1*H*-indol-3-yl)acetate (23a):



According to **TP6**, (4-ethoxy-4-oxobutyl)zinc bromide (**44a**; 2 mmol, 2.7 mL, 0.74M in THF), prepared from ethyl 4-bromobutanoate (**45a**; 2.0 mmol) via **TP4** (50 °C, 1 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate (**43a**; 2.5 mmol, 667 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 90 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3, Al_2O_3; pentane:EtOAc:MeOH = 95:5:0.3) to give **23a** as a red solid (500 mg, 90%).

m.p.: 121.6-122.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.65 (br s, 1H), 7.77 (d, *J*= 2.3Hz, 1H), 7.51 (d, *J*= 2.1Hz, 1H), 7.35 (d, *J*= 1.7Hz, 1H), 4.19 (q, *J*= 7.0Hz, 2H), 3.92 (s, 3H), 3.76 (s, 2H), 1.28 (t, *J*= 7.0Hz, 3H).

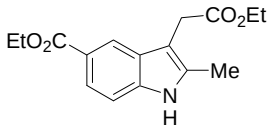
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.3, 153.0, 132.4, 131.5, 126.4, 125.3, 112.2, 109.5, 106.5, 61.0, 56.4, 31.1, 14.2.

MS (70 eV, EI) *m/z* (%): 278 (M^+, 29), 206 (11), 205 (100), 159 (17).

IR (ATR) υ (cm^{-1}): 3390, 2940, 2854, 1708, 1584, 1562, 1512, 1476, 1440, 1410, 1362, 1308, 1266, 1208, 1192, 1130, 1090, 1040, 1022, 948, 932, 842.

HRMS (EI): *m/z* calc. for **$C_{13}H_{14}N_2O_5$** (278.0903): 278.0895.

Synthesis of ethyl 3-(2-ethoxy-2-oxoethyl)-2-methyl-1*H*-indole-5-carboxylate (23b):



According to **TP6**, 2-(4-ethoxy-1-methyl-4-oxobutyl)zinc bromide (**44b**; 2 mmol, 2.2 mL, 0.90M in THF), prepared from ethyl 4-bromopentanoate (**45b**) via **TP4** (50 °C, 12 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-ethoxycarbonylbenzenediazonium tetrafluoroborate (**43b**; 2.5 mmol, 660 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 90 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 92:8:0.2) to give **23b** as a pale yellow solid (434 mg, 75%).

m.p.: 107.2-107.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.34 (br s, 1H), 8.28 (s, 1H), 7.81 (d, *J*=8.4 Hz, 1H), 7.17 (d, *J*= 8.4Hz, 1H), 4.38 (q, *J*= 7.0Hz, 2H), 4.14 (q, *J*= 7.0Hz, 2H), 3.69 (s, 2H), 2.31 (s, 3H), 1.40 (t, *J*= 7.1Hz, 3H), 1.25 (t, *J*= 7.1Hz, 3H).

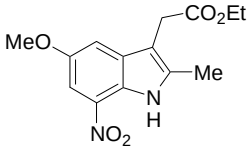
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.9, 167.9, 137.8, 134.2, 128.1, 122.7, 121.7, 120.8, 109.9, 105.8, 60.8, 60.5, 30.2, 14.4, 14.2, 11.6.

MS (70 eV, EI) *m/z* (%): 290 (7), 289 (M^+,41), 244 (12), 217 (18), 216 (100), 188 (22), 142 (12), 57 (8).

IR (ATR) υ (cm^{-1}): 3328, 2986, 1726, 1678, 1622, 1462, 1368, 1274, 1226, 1170, 1132, 1030, 768, 740, 652.

HRMS (EI): *m/z* calc. for **$C_{16}H_{19}NO_4$** (289.1314): 289.1309.

Synthesis of ethyl (5-methoxy-2-methyl-7-nitro-1*H*-indol-3-yl)acetate (23c):



According to **TP6**, 2-(4-ethoxy-1-methyl-4-oxobutyl)zinc bromide (**44b**; 2 mmol, 2.2 mL, 0.90M in THF), prepared from ethyl 4-bromopentanoate (**45b**) via **TP4** (50 °C, 12 h), and

$ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate (**43a**; 2.5 mmol, 667 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 90 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 94:6:0.3) to give **23c** as a orange solid (403 mg, 69%).

m.p.: 126.0-126.8 °C.

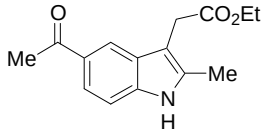
^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.44 (br s, 1H), 7.63 (d, *J*= 1.6Hz, 1H), 7.39 (d, *J*= 1.8Hz, 1H), 4.13 (q, *J*= 7.0Hz, 2H), 3.88 (s, 3H), 3.64 (s, 2H), 2.45 (s, 3H), 1.23 (t, *J*= 7.1Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.0, 152.8, 136.5, 132.5, 131.4, 124.4, 111.6, 105.4, 104.4, 60.7, 56.2, 30.0, 14.0, 11.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3440, 3084, 2982, 2926, 2842, 1720, 1600, 1508, 1478, 1438, 1410, 1364, 1318, 1296, 1234, 1176, 1114, 1042, 926, 862, 648 , 612.

HRMS (ESI, 70 eV): *m/z* calc. for **$C_{14}H_{15}N_2O_5$** (291.0981): 291.0984 ($[M-H]^-$).

Synthesis of ethyl (5-acetyl-2-methyl-1*H*-indol-3-yl)acetate (23d):



According to **TP6**, 2-(4-ethoxy-1-methyl-4-oxobutyl)zinc bromide (**44b**; 2 mmol, 2.2 mL, 0.90M in THF), prepared from ethyl 4-bromopentanoate (**45b**) via **TP4** (50 °C, 12 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-acetylbenzenediazonium tetrafluoroborate (**43c**; 2.5 mmol, 585 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 60 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 95:5:0.2) to give **23d** as a pale yellow solid (379 mg, 73%).

m.p.: 112.3-113.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.40 (br s, 1H), 8.19 (s, 1H), 7.77 (d, *J*= 8.6Hz, 1H), 7.21 (d, *J*= 8.6Hz, 1H), 4.14 (q, *J*= 7.1Hz, 2H), 3.70 (s, 2H), 2.65 (s, 3H), 2.36 (s, 3H), 1.25 (t, *J*= 7.1Hz, 3H).

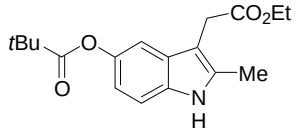
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 198.5, 171.8, 138.0, 134.5, 129.6, 128.1, 121.8, 120.1, 110.1, 106.1, 60.9, 30.2, 26.6, 14.2, 11.7.

MS (70 eV, EI) *m/z* (%): 259 (M^+, 30), 187 (14), 186 (100), 143 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3332, 2992, 2912, 1726, 1658, 1618, 1580, 1456, 1356, 1336, 1264, 1220, 1174, 1036, 792, 670, 646.

HRMS (EI): *m/z* calc. for **$C_{15}H_{17}NO_3$** (259.1208): 259.1203

Synthesis of 3-(2-ethoxy-2-oxoethyl)-2-methyl-1*H*-indol-5-yl pivalate (23e):



According to **TP6**, 2-(4-ethoxy-1-methyl-4-oxobutyl)zinc bromide (**44b**; 2 mmol, 2.2 mL, 0.90M in THF), prepared from ethyl 4-bromopentanoate (**45b**) via **TP4** (50 °C, 12 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-[(2,2-dimethylpropanoyl)oxy]-benzenediazonium tetrafluoroborate (**43d**; 2.5 mmol, 730 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 90 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 90:10:0.5) to give **23e** as a pale yellow solid (412 mg, 65%).

m.p.: >250 °C (decomposition).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.17 (br s, 1H), 7.14 (s, 1H), 6.92 (d, *J*= 8.6Hz, 1H), 6.68 (d, *J*= 8.6Hz, 1H), 4.11 (q, J= 7.1Hz, 2H), 3.59 (s, 2H), 2.22 (s, 3H), 1.39 (s, 9H), 1.22 (t, *J*= 7.1Hz, 3H).

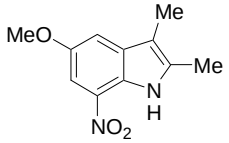
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.2, 172.0, 144.4, 134.3, 132.8, 128.6, 114.6, 110.6, 109.8, 104.3, 60.6, 38.9, 30.4, 27.2, 14.1, 11.4.

MS (70 eV, EI) *m/z* (%): 317 (M^+, 24), 244 (15), 233 (32), 161 (9), 160 (100), 159 (10), 131 (6), 57 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3372, 2976, 2936, 1728, 1590, 1480, 1458, 1368, 1278, 1170, 1122, 1030, 900, 786.

HRMS (EI): *m/z* calc. for **$C_{18}H_{23}NO_4$** (317.1627): 317.1622.

Synthesis of 5-methoxy-2,3-dimethyl-7-nitro-1*H*-indole (23f):



*s*BuZnBr (**44c**; 2 mmol, 7.6 mL, 0.26M in THF) was prepared via addition of *s*BuLi (2 mmol, 1.66 mL, 1.2M in hexane) to a solution of $ZnBr_2$ (6 mmol, 6 mL, 1M in THF) at 0 °C and continuous stirring for 10 min. The resulting alkylzinc reagent reacted according to **TP6** with 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate (**43a**; 2.5 mmol, 667 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min). The crude

product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 96:4:0.5) to give **23f** as a red solid (376 mg, 81%).

m.p.: 153.0-154.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.25 (br s, 1H), 7.61 (d, *J*= 2.2Hz, 1H), 7.30 (d, *J*= 2.2Hz, 1H), 3.89 (s, 3H), 2.39 (s, 3H), 2.19 (s, 3H).

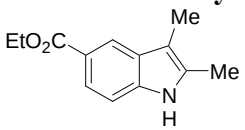
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 152.6, 134.8, 133.8, 131.3, 124.8, 111.8, 107.9, 103.9, 56.4, 11.6, 8.3.

MS (70 eV, EI) *m/z* (%): 221 (13), 220 (M^+,100), 219 (20), 205 (24), 174 (17), 159 (39), 131 (14), 130 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3420, 3370, 3110, 3024, 2914, 2836, 1604, 1576, 1502, 1474, 1458, 1388, 1364, 1330, 1288, 1192, 1178, 1140, 1082, 1044, 966, 878, 834, 756, 700, 606.

HRMS (EI): *m/z* calc. for **$C_{11}H_{12}N_2O_3$** (220.0848): 220.0834.

Synthesis of ethyl 2,3-dimethyl-1*H*-indole-5-carboxylate (23g):



*s*BuZnBr (**44c**; 2 mmol, 7.6 mL, 0.26M in THF) was prepared via addition of *s*BuLi (2 mmol, 1.66 mL, 1.2M in hexane) to a solution of $ZnBr_2$ (6 mmol, 6 mL, 1M in THF) at 0 °C and continuous stirring for 10 min. The resulting alkylzinc reagent reacted according to **TP6** with 4-ethoxycarbonylbenzenediazonium tetrafluoroborate (**43b**; 2.5 mmol, 660 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 2 h) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 96:4:0.5) to give **23g** as a pale yellow solid (325 mg, 75%).

m.p.: 116.0-117.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.24 (s, 1H), 8.02 (br s, 1H), 7.83 (d, *J*= 8.4Hz, 1H), 7.22 (d, *J*= 8.4Hz, 1H), 4.40 (q, *J*= 7.1Hz, 2H), 2.33 (s, 3H), 2.26 (s, 3H), 1.42 (t, *J*= 7.1Hz, 3H).

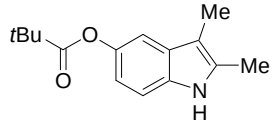
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 168.1, 137.9, 132.0, 129.1, 122.4, 121.2, 120.8, 109.5, 108.5, 60.5, 14.5, 11.5, 8.4.

MS (70 eV, EI) *m/z* (%): 218 (15), 217 (M^+, 100), 216 (12), 189 (18), 188 (29), 174 (12), 173 (11), 172 (72), 144 (30), 143 (18), 115 (8), 78 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3310, 2980, 2906, 2858, 1680, 1620, 1462, 1366, 1270, 1230, 1102, 1022, 768, 742, 674.

HRMS (EI): *m/z* calc. for **$C_{13}H_{15}NO_2$** (217.1103): 217.1099.

Synthesis of 2,3-dimethyl-1*H*-indol-5-yl pivalate (23h):



*s*BuZnBr (**44c**; 2 mmol, 7.6 mL, 0.26M in THF) was prepared via addition of *s*BuLi (2 mmol, 1.66 mL, 1.2M in hexane) to a solution of $ZnBr_2$ (6 mmol, 6 mL, 1M in THF) at 0 °C and continuous stirring for 10 min. The resulting alkylzinc reagent reacted according to **TP6** with 4-[(2,2-dimethylpropanoyl)oxy]benzenediazonium tetrafluoroborate (**43d**; 2.5 mmol, 730 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 2 h). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 90:10:0.5) to give **23h** as a white solid (383 mg, 78%).

m.p.: 127.0-129.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.72 (br s, 1H), 7.07-7.15 (m, 2H), 6.74 (d, *J*= 8.5Hz, 1H), 2.30 (s, 3H), 2.16 (s, 3H), 1.39 (s, 9H).

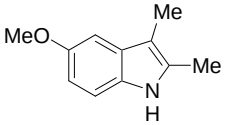
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.1, 144.2, 132.9, 132.1, 129.8, 114.4, 110.3, 109.9, 107.3, 39.0, 27.3, 11.5, 8.4.

MS (70 eV, EI) *m/z* (%): 245 (M^+, 41), 244 (10), 177 (16), 175 (17), 162 (15), 161 (100), 160 (39), 159 (10), 151 (11), 146 (16), 81 (11), 71 (15), 69 (23), 57 (81), 55 (22), 43 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3372, 2968, 2912, 2872, 1724, 1480, 1458, 1282, 1234, 1166, 1140, 1114, 1028, 900, 786, 614.

HRMS (EI): *m/z* calc. for **$C_{15}H_{19}NO_2$** (245.1416): 245.1402.

Synthesis of 5-methoxy-2,3-dimethyl-1*H*-indole (23i):



*s*BuZnBr (**44c**; 2 mmol, 7.6 mL, 0.26M in THF) was prepared via addition of *s*BuLi (2 mmol, 1.66 mL, 1.2M in hexane) to a solution of $ZnBr_2$ (6 mmol, 6 mL, 1M in THF) at 0 °C and continuous stirring for 10 min. The resulting alkylzinc reagent reacted according to **TP6** with 4-methoxybenzenediazonium tetrafluoroborate (**43e**; 2.5 mmol, 555 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 2 h). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 96:4:0.5) to give **23i** as a white solid (294 mg, 84%).

m.p.: 109.0-113.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.55 (br s, 1H), 7.13 (d, *J*= 8.6Hz, 1H), 6.94 (d, *J*= 2.4Hz, 1H), 6.77 (dd, *J*= 8.7Hz, 2.3Hz, 1H), 3.87 (s, 3H), 2.33 (s, 3H), 2.20 (s, 3H).

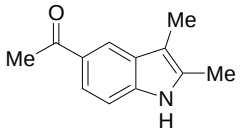
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 153.8, 131.7, 130.3, 129.8, 110.7, 110.5, 106.9, 100.5, 56.0, 11.6, 8.5.

MS (70 eV, EI) *m/z* (%): 175 (M^+, 100), 174 (33), 160 (59), 132 (61), 131 (21), 130 (13), 117 (18), 77 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3376, 2998, 2914, 1590, 1480, 1452, 1426, 1216, 1116, 1056, 1026, 830, 802, 612.

HRMS (EI): *m/z* calc. for **$C_{11}H_{13}NO$** (175.0997): 175.1010.

Synthesis of 1-(2,3-dimethyl-1*H*-indol-5-yl)ethanone (23j):



*s*BuZnBr (**44c**; 2 mmol, 7.6 mL, 0.26M in THF) was prepared via addition of *s*BuLi (2 mmol, 1.66 mL, 1.2M in hexane) to a solution of $ZnBr_2$ (6 mmol, 6 mL, 1M in THF) at 0 °C and continuous stirring for 10 min. The resulting alkylzinc reagent reacted according to **TP6** with 4-acetylbenzenediazonium tetrafluoroborate (**43c**; 2.5 mmol, 585 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 95:5:0.5) to give **23j** as a pale yellow solid (303 mg, 81%).

m.p.: 179.0-181.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.27 (br s, 1H), 8.14 (s, 1H), 7.77 (d, *J*= 8.4Hz, 1H), 7.24 (d, *J*= 8.4Hz, 1H), 2.67 (s, 3H), 2.33 (s, 3H), 2.25 (s, 3H).

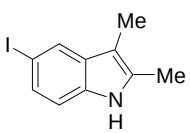
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 198.7, 138.1, 132.4, 129.0, 129.0, 121.5, 119.9, 109.8, 108.7, 26.6, 11.5, 8.3.

MS (70 eV, EI) *m/z* (%): 188 (16), 187 (M^+, 87), 186 (20), 173 (14), 172 (100), 144 (51), 143 (20), 85 (13), 83 (12), 77 (14), 71 (27), 57 (36), 55 (23), 43 (32).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3286, 1654, 1612, 1578, 1458, 1356, 1264, 1232, 1142, 970, 898, 794, 692, 648.

HRMS (EI): *m/z* calc. for **$C_{12}H_{13}NO$** (187.0997): 187.0990.

Synthesis of 5-iodo-2,3-dimethyl-1*H*-indole (23k):



*s*BuZnBr (**44c**; 2 mmol, 7.6 mL, 0.26M in THF) was prepared via addition of *s*BuLi (2 mmol, 1.66 mL, 1.2M in hexane) to a solution of $ZnBr_2$ (6 mmol, 6 mL, 1M in THF) at 0 °C and continuous stirring for 10 min. The resulting alkylzinc reagent reacted according to **TP6** with 4-iodobenzenediazonium tetrafluoroborate (**43f**; 2.5 mmol, 795 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 2 h) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 98:2:0.3) to give **23k** as a pale yellow solid (461 mg, 85%).

m.p.: 133.0-135.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.78 (s, 1H), 7.65 (br s, 1H), 7.34 (d, *J*= 8.4Hz, 1H), 7.00 (d, *J*= 8.4Hz, 1H), 6.99 (s, 3H), 2.33 (s, 3H).

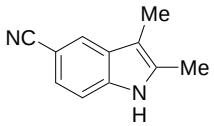
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 134.2, 132.1, 131.7, 129.0, 126.9, 111.9, 106.7, 82.4, 11.5, 8.3.

MS (70 eV, EI) *m/z* (%):272 (15), 271 (M^+, 100), 270 (36), 256 (16), 144 (17), 143 (29), 97 (11), 85 (18), 71 (26), 57 (42), 55 (13), 43 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3390, 1464, 1428, 1300, 1278, 1238, 1002, 968, 892, 868, 792, 738.

HRMS (EI): *m/z* calc. for **$C_{10}H_{10}IN$** (270.9858): 270.9845.

Synthesis of 5-cyano-2,3-dimethyl-1*H*-indole (23l):



*s*BuZnBr (**44c**; 2 mmol, 7.6 mL, 0.26M in THF) was prepared via addition of *s*BuLi (2 mmol, 1.66 mL, 1.2M in hexane) to a solution of $ZnBr_2$ (6 mmol, 6 mL, 1M in THF) at 0 °C and continuous stirring for 10 min. The resulting alkylzinc reagent reacted according to **TP6** with 4-cyanobenzenediazonium tetrafluoroborate (**43g**; 2.5 mmol, 542 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 92:8:0.5) to give **23l** as a pale yellow solid (266 mg, 78%).

m.p.: 137.0-139.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.22 (br s, 1H), 7.76 (s, 1H), 7.22-7.34 (m, 2H), 2.36 (s, 3H), 2.19 (s, 3H).

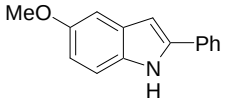
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.9, 133.3, 129.3, 123.9, 123.3, 121.2, 110.7, 107.9, 101.6, 11.5, 8.2.

MS (70 eV, EI) *m/z* (%): 171 (10), 170 (M^+, 81), 168 (12), 155 (49), 85 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3316, 2916, 2860, 2218, 1606, 1524, 1476, 1358, 1318, 1240, 1172, 1106, 928, 874, 800, 618.

HRMS (EI): *m/z* calc. for $\mathbf{C_{11}H_{10}N_2}$ (170.0844): 170.0823.

Synthesis of 5-methoxy-2-phenyl-1*H*-indole (23m):



According to **TP6**, 1-phenylethylzinc bromide (**44d**; 2 mmol, 2.5 mL, 0.80M in THF), prepared from ethyl 1-bromo-1-phenylethane via **TP4** (50 °C, 6 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-methoxybenzenediazonium tetrafluoroborate (**43e**; 2.5 mmol, 555 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 90 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 98:2:0.5) to give **23m** as a pale yellow solid (205 mg, 46%).

m.p.: 168.4-169.8 °C.

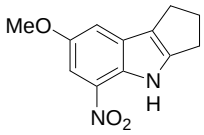
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.26 (br s, 1H), 7.64 (d, *J*= 7.1Hz, 2H), 7.43 (t, *J*= 7.3Hz, 2H), 7.25-7.36 (m, 2H), 7.10 (d, *J*= 2.4Hz, 1H), 6.87 (dd, *J*= 8.7Hz, 2.3Hz, 1H), 6.76 (s, 1H), 3.87 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 154.5, 138.6, 132.4, 132.0, 129.7, 129.0, 127.6, 125.0, 112.6, 111.6, 102.3, 99.8, 55.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3426, 3000, 2926, 2842, 1620, 1588, 1476, 1448, 1214, 1150, 1028, 944, 840, 800, 764, 692.

HRMS (ESI, 70 eV): *m/z* calc. for $\mathbf{C_{15}H_{14}NO}$ (224.1075): 224.1071 ($[M+H]^+$).

Synthesis of 7-methoxy-5-nitro-1,2,3,4-tetrahydrocyclopenta[*b*]indole (23n):



According to **TP6**, cyclopentylzinc bromide (**44e**; 2 mmol, 5.55 mL, 0.36M in THF), prepared from cyclopentyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate (**43a**; 2.5 mmol, 667 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 60 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual

work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 95:5:0.5) to give **23n** as a red solid (316 mg, 68%).

m.p.: 138.0-139.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.45 (br s, 1H), 7.61 (d, *J*= 2.2Hz, 1H), 7.27 (d, *J*= 2.1Hz, 1H), 3.88 (s, 3H), 2.85-2.99 (m, 2H), 2.72-2.85 (m, 2H), 2.46-2.69 (m, 2H).

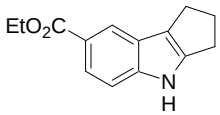
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 152.8, 147.8, 132.0, 130.0, 128.6, 120.4, 112.1, 103.7, 56.4, 28.7, 25.9, 24.1.

MS (70 eV, EI) *m/z* (%): 233 (14), 232 (M^+, 100), 231 (38), 186 (14), 185 (11), 171 (18), 143 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3472, 2960, 2932, 2856, 1570, 1510, 1464, 1372, 1326, 1274, 1194, 1178, 1154, 1088, 1032, 836, 758.

HRMS (EI): *m/z* calc. for **$C_{12}H_{12}N_2O_3$** (232.0848): 232.0864 (M^+).

Synthesis of ethyl 1,2,3,4-tetrahydrocyclopenta[b]indole-7-carboxylate (23o):



According to **TP6**, cyclopentylzinc bromide (**44e**; 2 mmol, 5.55 mL, 0.36M in THF), prepared from cyclopentyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-ethoxycarbonylbenzenediazonium tetrafluoroborate (**43b**; 2.5 mmol, 660 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 60 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 96:4:0.5) to give **23o** as a pale yellow solid (358 mg, 78%).

m.p.: 153.0-155.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.19 (s, 1H), 8.14 (br s, 1H), 7.81 (d, *J*= 8.6Hz, 1H), 7.27 (d, *J*= 8.6Hz, 1H), 4.39 (q, *J*= 7.2Hz, 2H), 2.73-2.94 (m, 4H), 2.40-2.65 (m, 2H), 1.41 (t, *J*= 7.1Hz, 3H).

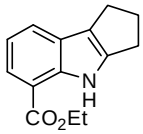
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 168.0, 145.1, 143.6, 124.2, 122.0, 121.7, 121.2, 121.0, 110.8, 60.5, 28.6, 25.9, 24.4, 14.5.

MS (70 eV, EI) *m/z* (%): 230 (17), 229 (M^+, 100), 228 (28), 201 (18), 200 (22), 184 (40), 156 (22), 154 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3290, 2904, 2852, 1678, 1616, 1472, 1276, 1228, 1130, 1064, 1024, 764, 740, 672.

HRMS (EI): *m/z* calc. for **$C_{14}H_{15}NO_2$** (229.1103): 229.1107 (M^+).

Synthesis of ethyl 1,2,3,4-tetrahydrocyclopenta[b]indole-9-carboxylate (23p):



According to **TP6**, cyclopentylzinc bromide (**44e**; 2 mmol, 5.55 mL, 0.36M in THF), prepared from cyclopentyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 2-ethoxycarbonylbenzenediazonium tetrafluoroborate (**43k**; 2.5 mmol, 660 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 60 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 96:4:0.5) to give **23o** as a pale yellow solid (239 mg, 52%).

m.p.: 115.2-116.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.67 (br s, 1H), 7.83 (d, *J*=7.6Hz, 1H), 7.66 (d, *J*=7.8Hz, 1H), 7.12 (t, *J*=7.7Hz, 1H), 4.47 (q, *J*=7.2Hz, 2H), 2.92 (t, *J*=8.0Hz, 2H), 2.86 (t, *J*=6.6Hz, 2H), 2.53–2.62 (m, 2H), 1.47 (t, *J*=7.2Hz, 3H).

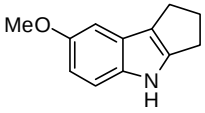
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 167.6, 145.0, 140.8, 125.6, 123.8, 122.4, 119.4, 118.4, 112.6, 60.6, 28.7, 25.8, 24.3, 14.4.

MS (70 eV, EI) *m/z* (%): 230 (10), 229 (M^+, 57), 184 (23), 183 (100), 182 (41), 156 (15), 155 (41), 154 (32), 128 (14), 127 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3402, 2952, 2916, 2906, 2860, 1670, 1586, 1574, 1464, 1264, 1204, 1150, 1066, 1046, 748, 740, 674.

HRMS (EI): *m/z* calc. for **$C_{14}H_{15}NO_2$** (229.1103): 229.1100 (M^+).

Synthesis of 7-methoxy-1,2,3,4-tetrahydrocyclopenta[*b*]indole (23q):



According to **TP6**, cyclopentylzinc bromide (**44e**; 2 mmol, 5.55 mL, 0.36M in THF), prepared from cyclopentyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-methoxybenzenediazonium tetrafluoroborate (**43e**; 2.5 mmol, 555 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 60 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 96:4:0.5) to give **23o** as a pale yellow solid (250 mg, 67%).

m.p.: 122.0-123.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.78 (br s, 1H), 7.18 (d, *J*=8.6Hz, 1H), 6.95 (d, *J*=2.4Hz, 1H), 6.77 (dd, *J*=8.7Hz, 2.5Hz, 1H), 3.87 (s, 3H), 2.76-2.90 (m, 4H), 2.47-2.64 (m, 2H).

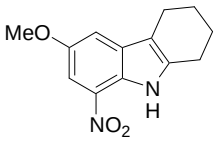
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 153.9, 144.7, 136.0, 125.0, 119.5, 111.8, 109.9, 100.9, 55.9, 28.6, 25.8, 24.3.

MS (70 eV, EI) *m/z* (%): 188 (11), 187 (M^+, 100), 186 (45), 172 (25), 144 (16), 143 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3314, 2938, 2900, 2854, 1670, 1628, 1582, 1482, 1454, 1434, 1300, 1208, 1170, 1086, 1028, 848, 788, 676, 626.

HRMS (EI): *m/z* calc. for **$C_{12}H_{13}NO$** (187,0997): 187.0996 (M^+).

Synthesis of 6-methoxy-8-nitro-2,3,4,9-tetrahydro-1*H*-carbazole (23r):



According to **TP6**, cyclohexylzinc bromide (**44f**; 2 mmol, 5.4 mL, 0.37M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate (**43a**; 2.5 mmol, 667 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 95:5:0.5) to give **23r** as a red solid (438 mg, 89%).

m.p.: 137.1-138.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.27 (br s, 1H), 7.62 (d, *J*= 2.1Hz, 1H), 7.29 (d, *J*= 2.1Hz, 1H), 3.89 (s, 3H), 2.77 (t, *J*= 5.9Hz, 2H), 2.65 (t, *J*= 5.9Hz, 2H), 1.89-2.00 (m, 2H), 1.80-1.89 (m, 2H).

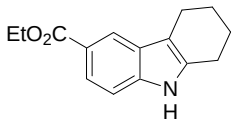
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 152.7, 138.1, 132.3, 131.5, 125.3, 111.7, 110.9, 103.9, 56.4, 23.2, 22.9, 22.8, 20.6.

MS (70 eV, EI) *m/z* (%): 246 (10), 247 (M+, 78), 245 (11), 219 (11), 218 (100), 203 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3424, 2934, 2844, 1734, 1604, 1574, 1508, 1466, 1440, 1382, 1278, 1194, 1134, 1036, 834, 758, 648, 606.

HRMS (EI): *m/z* calc. for **$C_{13}H_{14}N_2O_3$** (246.1004): 246.0997 (M^+).

Synthesis of ethyl 2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxylate (1s):



According to **TP6**, cyclohexylzinc bromide (**44f**; 2 mmol, 5.4 mL, 0.37M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-ethoxycarbonylbenzenediazonium tetrafluoroborate (**43b**; 2.5 mmol, 660 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 96:4:1) to give **23s** as a pale yellow solid (394 mg, 81%).

m.p.: 114.0-116.0 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.25 (s, 1H), 8.18 (br s, 1H), 7.85 (d, *J*=8.4Hz, 1H), 7.24 (d, *J*=8.4Hz, 1H), 4.42 (q, *J*=7.1Hz, 2H), 2.70-2.74 (m, 4H), 1.86-1.93 (m, 4H), 1.43 (t, *J*=7.1Hz, 3H).

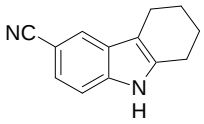
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 168.2, 138.4, 135.6, 127.5, 122.5, 121.2, 120.5, 111.4, 109.9, 60.5, 23.1, 23.1, 23.0, 20.8, 14.5.

MS (70 eV, EI) *m/z* (%): 244 (14), 243 (M^+, 100), 214 (50), 197 (12), 186 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3326, 2926, 1682, 1474, 1444, 1368, 1310, 1232, 1120, 1092, 770, 750.

HRMS (EI): *m/z* calc. for **$C_{15}H_{17}NO_2$** (243.1259): 243.1262 (M^+).

Synthesis of 2,3,4,9-tetrahydro-1*H*-carbazole-6-carbonitrile (23t):



According to **TP6**, cyclohexylzinc bromide (**44f**; 2 mmol, 5.4 mL, 0.37M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-cyanobenzenediazonium tetrafluoroborate (**43g**; 2.5 mmol, 542 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 94:6:1) to give **23t** as a pale yellow solid (318 mg, 81%).

m.p.: 124.0-125.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.13 (br s, 1H), 7.76 (s, 1H), 7.19-7.49 (m, 2H), 2.74 (t, *J*= 5.7Hz, 2H), 2.67 (t, *J*= 5.8Hz, 2H), 1.75-2.03 (m, 4H).

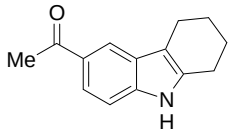
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 137.4, 136.6, 127.7, 124.1, 123.1, 121.2, 111.0, 111.0, 101.7, 23.1, 22.9, 22.8, 20.6.

MS (70 eV, EI) *m/z* (%): 197 (11), 196 (M^+, 79), 195 (17), 169 (12), 168 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3314, 2926, 2846, 2216, 1686, 1622, 1478, 1318, 1236, 1180, 872, 806, 798, 626.

HRMS (EI): *m/z* calc. for **$C_{13}H_{12}N_2$** (196.1000): 196.0997 (M^+).

Synthesis of 1-(2,3,4,9-tetrahydro-1*H*-carbazol-6-yl)ethanone (23u):



According to **TP6**, cyclohexylzinc bromide (**44f**; 2 mmol, 5.4 mL, 0.37M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-acetylbenzenediazonium tetrafluoroborate (**43c**; 2.5 mmol, 585 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 96:4:0.5) to give **23u** as a pale yellow solid (375 mg, 88%).

m.p.: 122.5-124.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.12 (s, 1H), 8.09 (br s, 1H), 7.78 (d, *J*= 8.5Hz, 1H), 7.26 (d, *J*= 8.2Hz, 1H), 2.73 (t, *J*= 5.9Hz, 4H), 2.65 (s, 3H), 1.78-2.01 (m, 4H).

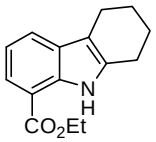
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 198.5, 138.5, 135.8, 129.2, 127.5, 121.7, 119.7, 111.8, 110.0, 62.7, 26.6, 23.2, 23.0, 20.8.

MS (70 eV, EI) *m/z* (%): 214 (19), 213 (M^+, 100), 212 (11), 198 (51), 185 (42), 170 (18), 142 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3286, 2926, 2854, 1652, 1614, 1578, 1460, 1354, 1232, 1122, 812, 798, 686, 648.

HRMS (EI): *m/z* calc. for **$C_{14}H_{15}NO$** (213.1154): 213.1151 (M^+).

Synthesis of ethyl 2,3,4,9-tetrahydro-1*H*-carbazole-8-carboxylate (23v):



According to **TP6**, cyclohexylzinc bromide (**44f**; 2 mmol, 5.4 mL, 0.37M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 2-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**43k**; 2.5 mmol, 660 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 97:3:0.5) to give **23v** as a white solid (224 mg, 46%).

m.p.: 75.5-77.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.43 (br s, 1H), 7.82 (d, *J*=7.7Hz, 1H), 7.67 (d, *J*=7.9Hz, 1H), 7.11 (t, *J*=7.7Hz, 1H), 4.46 (q, *J*=7.1Hz, 2H), 2.69-2.86 (m, 4H), 1.80-2.04 (m, 4H), 1.46 (t, *J*=7.1Hz, 3H).

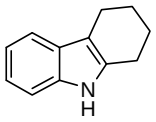
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 167.7, 135.8, 135.3, 129.0, 123.1, 122.9, 118.1, 111.8, 109.9, 60.5, 23.2, 23.2, 23.1, 20.8, 14.4.

MS (70 eV, EI) *m/z* (%): 244 (16), 243 (M^+, 100), 214 (32), 198 (16), 197 (46), 196 (21), 170 (13), 169 (97), 168 (16), 140 (16), 114 (15), 71 (13), 57 (18), 43 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3400, 2988, 2930, 2848, 1674, 1582, 1476, 1374, 1266, 1204, 1142, 1050, 750, 740.

HRMS (EI): *m/z* calc. for **$C_{15}H_{17}NO_2$** (243.1259): 243.1246 (M^+).

Synthesis of 2,3,4,9-tetrahydro-1*H*-carbazole (23w):



According to **TP6**, cyclohexylzinc bromide (**44f**; 2 mmol, 5.4 mL, 0.37M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with benzenediazonium tetrafluoroborate (**43h**; 2.5 mmol, 480 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 96:4:0.5) to give **23w** as a pale yellow solid (216 mg, 63%).

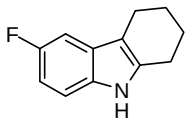
m.p.: 118.6-120.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.65 (br s, 1H), 7.52 (d, *J*=7.3Hz, 1H), 7.28 (d, *J*=7.7Hz, 1H), 7.05-7.24 (m, 2H), 2.75 (q, *J*=6.2Hz, 4H), 1.81-2.07 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 135.6, 134.1, 127.7, 120.9, 119.0, 117.6, 110.3, 110.0, 23.3, 23.2, 20.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3396, 2926, 2848, 1660, 1620, 1590, 1468, 1450, 1440, 1326, 1304, 1234, 1144, 1010, 736, 636.

Synthesis of 6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazole (23x):



According to **TP6**, cyclohexylzinc bromide (**44f**; 2 mmol, 5.4 mL, 0.37M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-fluorobenzenediazonium tetrafluoroborate (**43i**; 2.5 mmol, 525 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 97:3:0.5) to give **23x** as a white solid (212 mg, 56%).

m.p.: 101.0-103.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.65 (bs, 1H), 7.15 (dd, *J*= 8.8Hz, 4.4Hz, 1H), 7.09 (dd, *J*= 9.6Hz, 2.3Hz, 1H), 6.84 (dt, *J*= 9.2Hz, 2.4Hz, 1H), 2.71 (t, *J*= 5.5Hz, 2H), 2.66 (t, *J*= 5.3Hz, 2H), 1.84-1.95 (m, 4H).

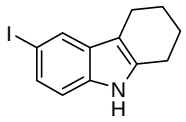
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 157.7 (d, *J*= 233Hz), 136.1, 132.0, 128.2 (d, *J*= 9.5Hz), 110.6 (d, *J*= 9.5Hz), 110.4 (d, *J*= 4.5Hz), 108.7 (d, *J*= 26.0 Hz), 102.8 (d, *J*=23.2Hz), 23.3, 23.1, 23.0, 20.8.

MS (70 eV, EI) *m/z* (%): 190 (15), 189 (M^+, 65), 188 (27), 186 (13), 176 (17), 164 (25), 162 (19), 161 (100), 133 (23), 120 (30), 107 (41), 94 (32), 85 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3404, 2932, 2850, 1582, 1480, 1446, 1318, 1232, 1180, 1128, 920, 854, 794, 702.

HRMS (EI): *m/z* calc. for **$C_{12}H_{12}FN$** (189.0954): 189.0960 (M^+).

Synthesis of 6-iodo-2,3,4,9-tetrahydro-1*H*-carbazole (23y):



According to **TP6**, cyclohexylzinc bromide (**44f**; 2 mmol, 5.4 mL, 0.37M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-iodobenzenediazonium tetrafluoroborate (**43f**; 2.5 mmol, 795 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by

flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 97:3:0.5) to give **23y** as a pale yellow solid (333 mg, 56%).

m.p.: 148.0-150.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.76 (s, 1H), 7.68 (bs, 1H), 7.34 (d, *J*= 8.4Hz, 1H), 7.03 (d, *J*= 8.4Hz, 1H), 2.70 (t, *J*= 5.4Hz, 2H), 2.63 (t, J= 5.4Hz, 2H), 1.75-2.05 (m, 4H).

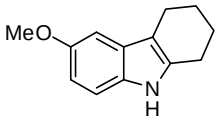
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 135.1, 134.7, 130.5, 129.1, 126.7, 112.2, 109.7, 82.5, 23.1, 23.1, 23.0, 20.7

MS (70 eV, EI) *m/z* (%): 298 (11), 297 (M^+, 100), 295 (7), 268 (52), 141 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3398, 2938, 2904, 2848, 2838, 1574, 1466, 1432, 1308, 1234, 956, 892, 864, 794, 734, 634.

HRMS (EI): *m/z* calc. for **$C_{12}H_{12}IN$** (297.0014): 297.0004 (M^+).

Synthesis of 6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazole (23z):



According to **TP6**, cyclohexylzinc bromide (**44f**; 2 mmol, 5.4 mL, 0.37M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-methoxybenzenediazonium tetrafluoroborate (**43e**; 2.5 mmol, 555 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 95:5:0.5) to give **23z** as a pale yellow solid (334 mg, 83%).

m.p.: 107.9-109.8 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.54 (bs, 1H), 7.15 (d, *J*=8.8Hz, 6.95 (d, *J*=2.2, 1H), 6.78 (dd, *J*=8.7, 2.3Hz, 1H), 3.87 (s, 3H), 2.70 (q, *J*=5.7Hz, 4H), 1.90 (m, 4H).

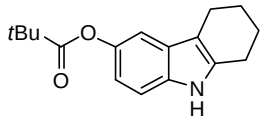
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 153.8, 135.1, 130.7, 128.2, 110.9, 110.5, 110.0, 100.3, 56.0, 23.3, 23.3, 23.2, 20.9.

MS (70 eV, EI) *m/z* (%): 202 (17), 201 (M^+, 100), 174 (11), 173 (57), 157 (18), 71 (9), 57 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3386, 2914, 2850, 1590, 1486, 1450, 1430, 1218, 1136, 1028, 954, 830, 798, 610.

HRMS (EI): *m/z* calc. for **$C_{13}H_{15}NO$** (201.1154): 201.1146 (M^+).

Synthesis of 6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazole (23aa):



According to **TP6**, cyclohexylzinc bromide (**44f**; 2 mmol, 5.4 mL, 0.37M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-(pivaloyloxy)benzenediazonium tetrafluoroborate (**43d**; 2.5 mmol, 730 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 95:5:0.5) to give **23aa** as a pale yellow solid (418 mg, 77%).

m.p.: 140.6-142.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74 (bs, 1H), 7.13 (d, *J*= 8.6Hz, 1H), 7.09 (d, *J*= 2.1Hz, 1H), 6.74 (dd, *J*= 8.6Hz, 2.1Hz, 1H), 2.65 (m, 4H), 1.86 (m, 4H), 1.39 (s, 9H).

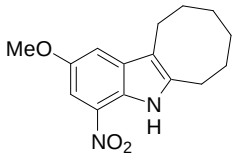
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 178.1, 144.3, 135.6, 133.4, 128.1, 114.4, 110.5, 109.7, 39.0, 27.2, 23.2, 23.2, 23.1, 20.8.

MS (70 eV, EI) *m/z* (%): 272 (10), 271 (M^+, 49), 188 (15), 187 (100), 186 (20), 159 (52), 158 (11), 57 (29), 41 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3392, 2926, 2854, 1730, 1588, 1474, 1394, 1290, 1150, 1030, 1000, 904, 854, 784.

HRMS (EI): *m/z* calc. for **$C_{17}H_{21}NO_2$** (271.1572): 271.1570 (M^+).

Synthesis of 2-methoxy-4-nitro-6,7,8,9,10,11-hexahydro-5*H*-cycloocta[*b*]indole (23ab):



According to **TP6**, cyclooctylzinc bromide (**44g**; 2 mmol, 5.7 mL, 0.35M in THF), prepared from cyclooctyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate (**43a**; 2.5 mmol, 667 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 98:2:0.2) to give **23t** as a red solid (471 mg, 86%).

m.p.: 145.0-146.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.28 (br s, 1H), 7.63 (d, *J*= 1.9Hz, 1H), 7.33 (d, *J*= 1.9Hz, 1H), 3.89 (s, 3H), 2.89 (t, *J*= 6.2Hz, 2H), 2.81 (t, *J*= 6.2Hz, 2H), 1.645-1.87 (m, 4H), 1.36-1.55 (m, 4H).

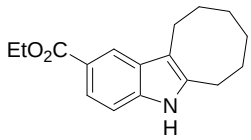
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 152.7, 139.7, 133.0, 131.6, 124.7, 112.5, 111.6, 103.8, 56.4, 29.4, 29.1, 25.9, 25.8, 25.7, 22.0.

MS (70 eV, EI) *m/z* (%): 275 (18), 274 (M^+, 100), 273 (14), 246 (51), 231 (70), 219 (41), 218 (30), 205 (20), 85 (12), 71 (14), 57 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3310, 2922, 2848, 1684, 1614, 1454, 1278, 1240, 1104, 1032, 768, 740, 628.

HRMS (EI): *m/z* calc. for **$C_{15}H_{18}N_2O_3$** (274.1317): 274.1301 (M^+).

Synthesis of ethyl 6,7,8,9,10,11-hexahydro-5*H*-cycloocta[*b*]indole-2-carboxylate (23ac):



According to **TP6**, cyclooctylzinc bromide (**44g**; 2 mmol, 5.7 mL, 0.35M in THF), prepared from cyclooctyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-ethoxycarbonylbenzenediazonium tetrafluoroborate (**43b**; 2.5 mmol, 660 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 60 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 97:3:0.3) to give **23ac** as a brown solid (483 mg, 89%).

m.p.: 111.9-113.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.26 (s, 1H), 8.07 (br s, 1H), 7.82 (d, *J*= 8.5Hz, 1H), 7.25 (d, *J*= 8.6Hz, 1H), 4.40 (q, *J*= 7.1Hz, 2H), 2.69-3.01 (m, 4H), 1.60-1.92 (m, 4H), 1.19-1.57 (m, 7H).

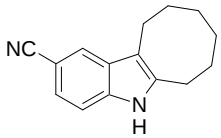
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 168.1, 137.7, 137.0, 128.2, 122.1, 121.2, 120.5, 113.0, 109.8, 60.4, 29.6, 29.2, 25.9, 25.9, 25.7, 22.1, 14.5.

MS (70 eV, EI) *m/z* (%): 272 (19), 217 (M^+, 100), 243 (18), 242 (26), 229 (11), 228 (43), 226 (25), 216 (29), 215 (25), 202 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3414, 2922, 2846, 1576, 1508, 1474, 1288, 1172, 1126, 1032, 836, 622.

HRMS (EI): *m/z* calc. for **$C_{17}H_{21}NO_2$** (271.1572): 271.1557 (M^+).

Synthesis of 6,7,8,9,10,11-hexahydro-5*H*-cycloocta[*b*]indole-2-carbonitrile (23ad):



According to **TP6**, cyclooctylzinc bromide (**44g**; 2 mmol, 5.7 mL, 0.35M in THF), prepared from cyclooctyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-cyanobenzenediazonium tetrafluoroborate (**43g**; 2.5 mmol, 542 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 2 h) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 97:3:0.5) to give **23ad** as a white crystalline solid (412 mg, 92%).

m.p.: 110.4-111.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.22 (br s, 1H), 7.80 (s, 1H), 7.26-7.41 (m, 2H), 2.67-2.96 (m, 4H), 1.60-1.91 (m, 4H), 1.26-1.57 (m, 4H).

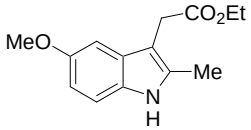
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 138.3, 136.8, 128.4, 123.7, 123.1, 121.3, 112.5, 111.1, 101.7, 29.5, 29.2, 25.9, 25.8, 25.7, 22.0.

MS (70 eV, EI) *m/z* (%): 225 (19), 224 (M^+, 98), 223 (22), 196 (36), 195 (45), 182 (27), 181 (100), 170 (13), 169 (64), 168 (69), 156 (44), 140 (14), 71 (19), 57 (29), 55 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3334, 2942, 2920, 2904, 2844, 2218, 1618, 1472, 1454, 1440, 1304, 1184, 872, 802, 644.

HRMS (EI): *m/z* calc. for **$C_{15}H_{16}N_2$** (224.1313): 224.1308 (M^+).

Synthesis of ethyl (5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (48):



According to **TP6**, 2-(4-ethoxy-1-methyl-4-oxobutyl)zinc bromide (**44b**; 2 mmol, 2.2 mL, 0.90M in THF), prepared from ethyl 4-bromopentanoate via **TP4** (50 °C, 12 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with 4-methoxybenzenediazonium tetrafluoroborate (**43e**; 2.5 mmol, 555 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2 mmol, 217 mg). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; isohexane:EtOAc:MeOH = 94:6:0.3) to give **48** as a pale yellow solid (331 mg, 67%).

m.p.: 69.0-70.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.81 (br s, 1H), 7.10 (d, *J*= 8.6Hz, 1H), 7.00 (d, *J*= 2.2Hz, 1H), 6.76 (dd, *J*= 8.8Hz, 2.4Hz, 1H), 4.12 (q, *J*=7.1Hz, 2H), 3.82 (s, 3H), 3.63 (s, 2H), 2.35 (s, 3H), 1.24 (t, *J*= 7.1Hz, 3H).

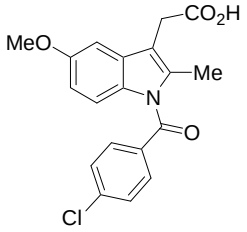
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.0, 154.1, 133.5, 130.1, 128.9, 110.9, 110.8, 104.5, 100.5, 60.6, 55.9, 30.6, 14.2, 11.7.

MS (70 eV, EI) *m/z* (%): 247 (27), 175 (10), 174 (100), 131 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3314, 2976, 2924, 2832, 1708, 1588, 1486, 1454, 1370, 1320, 1264, 1216, 1172, 1124, 1102, 1030, 790, 686, 632.

HRMS (EI): *m/z* calc. for **$C_{14}H_{17}NO_3$** (247.1208): 247.1204 (M^+).

Synthesis of [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid (46, *indomethacin*):



To a solution of the indole **48** (2 mmol, 494 mg) in dry THF (4 mL), KO*t*Bu (2.4 mmol, 229 mg) was added at 0 °C and continuously stirred for 20 min. 4-chlorobenzoyl chloride (2.4 mmol, 420 mg) was added to the resulting dark solution. After stirring for 10 h at 25 °C, $LiOH \cdot H_2O$ (20 mmol, 838 mg) in H_2O (4 mL) was added and continuously stirred for 6 h at 25 °C followed by extraction of the organic phase with 2M aq. NH_3 (2x 5 mL). The aqueous phase was washed with CH_2Cl_2 (10 mL). Addition of conc. HCl (10 mL) resulted in precipitation of the product which was filtered off and washed with water. The product was dissolved in a mixture of $MeOH/CH_2Cl_2$ (50 mL), dried over Na_2SO_4. Filtration and evaporation of the solvent afforded *indomethacin* (**46**; 657mg)[296] as a pale white solid in 92% yield.

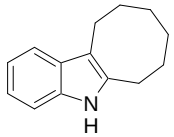
^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.93 (d, *J*= 8.63Hz, 2H), 7.55 (d, *J*= 8.6Hz, 2H), 7.11 (d, *J*= 8.6Hz, 1H), 6.88 (d, *J*= 2.2Hz, 1H), 6.62 (dd, *J*= 8.7Hz, 2.4Hz, 1H), 3.71 (s, 3H), 3.51 (s, 2H), 2.28 (s, 3H).

^{1}C NMR (75 MHz, DMSO-d_6) δ (ppm): 173.1, 166.4, 153.0, 137.8, 133.7, 131.1, 130.1, 129.6, 128.7, 128.7, 110.9, 109.5, 103.8, 100.1, 55.3, 29.9, 11.4.

[296] a) K.-J. Hwang, S.-J. Lee, B.-T. Kim, S. Raucher, *Bull. Korean Chem. Soc.* **2006**, *27*, 933; b) T. Y. Shen, T. B. Windholz, A. Rosegay, B. E. Witzel, A. N. Wilson, J. D. Willett, W. J. Holtz, R. L. Ellis, A. R. Matzuk, S. Lucas, C. H. Stammer, F. W. Holly, L. H. Sarett, E. A. Risley, G. W. Nuss, C. A. Winter, *J. Am. Chem. Soc.* **1963**, *85*, 488; c) K. R. Campos, J. C. S. Woo, S. Lee, R. D. Tillyer, *Org. Lett.* **2004**, *6*, 79; d) C. Mukai, Y. Takahashi, *Org. Lett.* **2005**, *7*, 5793; e) I. V. Magedov, S. A. Maklakov, Yu. I. Smushkevich, *Chem. Heterocycl. Compd.* **2005**, *41*, 449.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3392, 2830, 2538, 1678, 1590, 1422, 1282, 1214, 1176, 1090, 1014, 924, 852, 808, 760, 682.

Synthesis of 6,7,8,9,10,11-hexahydro-5*H*-cycloocta[*b*]indole (49):



According to **TP6**, cyclooctylzinc bromide (**44g**; 2 mmol, 5.7 mL, 0.35M in THF), prepared from cyclooctyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with benzenediazonium tetrafluoroborate (**43h**; 2.5 mmol, 480 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane) to give **49** as a pale yellow solid (318 mg, 80%).

m.p.: 71.0-72.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.66 (br s, 1H), 7.43-7.55 (m, 1H), 7.21-7.34 (m, 1H), 7.00-7.15 (m, 2H), 2.75-2.98 (m, 4H), 1.63-1.88 (m, 4H), 1.31-1.59 (m, 4H).

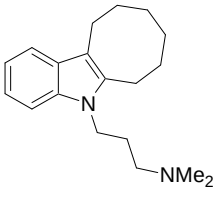
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 135.6, 135.0, 128.5, 120.5, 118.8, 117.6, 111.5, 110.2, 29.5, 29.4, 25.9, 25.8, 25.7, 22.1.

MS (70 eV, EI) *m/z* (%): 200 (12), 199 (M^+, 100), 198 (19), 171 (18), 170 (30), 157 (13), 156 (76), 144 (42), 143 (49), 131 (30).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3400, 3302, 2922, 2850, 1686, 1628, 1522, 1456, 1442, 1338, 1240, 740, 686.

HRMS (EI): *m/z* calc. for **$C_{14}H_{17}N$** (199.1361): 199.1351 (M^+).

Synthesis of [3-(6,7,8,9,10,11-hexahydro-5*H*-cycloocta[*b*]indol-5-yl)propyl]dimethyl-amine (47, *iprindole*): **One-Pot-Procedure**



iprindole

According to **TP6**, cyclooctylzinc bromide (**44g**; 2 mmol, 5.7 mL, 0.35M in THF), prepared from cyclooctyl bromide via **TP5** (25 °C, 2 h), and $ZnBr_2$ (4 mmol, 4 mL, 1M in THF) reacted with benzenediazonium tetrafluoroborate (**43h**; 2.5 mmol, 480 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min). After cooling to 0 °C,

KO*t*Bu (2.4 mmol, 229 mg) was slowly added. The reaction mixture was stirred for 20 min at 0 °C followed by addition of (3-chloropropyl)-dimethylamine (2.4 mmol, 292 mg). The resulting solution was heated by microwave irradiation (125 °C, 3 h) and quenched with brine (10 mL). The aqueous phase was extracted with EtOAc (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 97:3:0.3) to give iprindole (**47**)[297] as a yellow oil (409 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.50 (d, *J*= 7.3Hz, 1H), 7.29 (d, *J*= 7.8Hz, 1H), 7.10 (t, *J*= 7.9Hz, 1H), 7.01-7.08 (m, 1H), 4.12 (t, *J*= 7.6Hz, 2H), 2.79-2.95 (m, 4H), 2.30 (t, *J*= 6.9Hz, 2H), 2.23 (s, 6H), 1.83-1.97 (m, 2H), 1.64-1.78 (m, 4H), 1.35-1.47 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.6, 136.0, 127.5, 120.1, 118.4, 117.6, 111.8, 108.9, 56.8, 45.4, 40.9, 30.4, 29.3, 28.7, 26.1, 25.9, 23.0, 22.9.

MS (70 eV, EI) *m/z* (%): 284 (M+, 57), 213 (33), 212 (20), 198 (20), 185 (21), 184 (20), 171 (21), 170 (73), 157 (21), 156 (26), 145 (22), 144 (24), 71 (15), 58 (100), 43 (58), 41 (48).

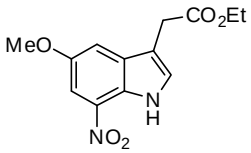
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3050, 2920, 2848, 2814, 2764, 1464, 1370, 1338, 1316, 1180, 1040, 734, 696.

HRMS (EI): *m/z* calc. for **$C_{19}H_{28}N_2$** (284.2252): 284.2246 (M^+).

[297] a) L. M. Rice, E. Hertz, M. E. Freed, *J. Med. Chem.* **1964**, *7*, 313; b) B. L. Baxter, M. I. Gluckman, *Nature* **1969**, *223*, 750.

Preparations of indole derivatives on a 10-20 mmol scale

Synthesis of ethyl 5-methoxy-7-nitro-1*H*-indol-3yl acetate (23a):



In a flame-dried and argon-flushed Schlenk-flask, a solution of **44a** (10 mmol, 13.5 mL, 0.74 M in THF) prepared via **TP4** from ethyl 4-bromobutanoate (**45a**) was added dropwise to a solution of $ZnBr_2$ (20 mmol, 20 mL, 1M in THF) at 25 °C. After stirring at 25 °C for 10 min, the organozinc reagent was transferred slowly to a solution of 4-methoxy-2-nitrobenzene-diazonium tetrafluoroborate (**43a**, 3.34 g, 12.5 mmol) in THF (50 mL) at –60 °C. The reaction mixture was allowed to slowly warm to 25°C. Subsequently, the solvent volume was reduced by half, Me_3SiCl (1.08 g, 10 mmol) was added, and the reaction mixture was heated by microwave irradiation for 90 min at 125 °C. After the reaction mixture had cooled to 25 °C, the resulting solution was diluted with Et_2O (20 mL) and quenched with brine (50 mL). The aqueous layer was extracted with EtOAc (3x 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (Al_2O_3; pentane-EtOAc-MeOH, 95:5:0.3) afforded **23a** as a red solid (2.50 g, 90%).

m.p.: 121.6-122.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.65 (br s, 1 H), 7.77 (d, J = 2.3 Hz, 1 H), 7.51 (d, J = 2.1 Hz, 1 H), 7.35 (d, J = 1.7 Hz, 1 H), 4.19 (q, J = 7.0 Hz, 2 H), 3.92 (s, 3 H), 3.76 (s, 2 H), 1.28 (t, J = 7.0 Hz, 3 H).

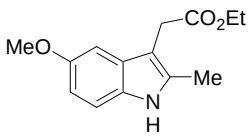
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.3, 153.0, 132.4, 131.5, 126.4, 125.3, 112.2, 109.5, 106.5, 61.0, 56.4, 31.1, 14.2.

IR (ATR) υ (cm^{-1}): 3390, 2940, 2854, 1708, 1584, 1562, 1512, 1476, 1440, 1410, 1362, 1308, 1266, 1208, 1192, 1130, 1090, 1040, 1022, 948, 932, 842.

MS (70 eV, EI): *m/z* (%): 278 (M^+, 29), 206 (11), 205 (100), 159 (17).

HRMS (EI): *m/z* calc. for **$C_{13}H_{14}N_2O_5$** (278.0903): 278.0895 (M^+).

Synthesis of ethyl (5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (48):



According to **TP6**, 2-(4-ethoxy-1-methyl-4-oxobutyl)zinc bromide (**44b**; 10 mmol, 11.1 mL, 0.90 M in THF), prepared from ethyl 4-bromopentanoate (**45b**) via **TP4** (50 °C, 12 h), and $ZnBr_2$ (20 mmol, 20 mL, 1M in THF) reacted with 4-methoxy-benzenediazonium tetrafluoroborate (**43e**; 12.5 mmol, 2.77 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 1 h) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane-EtOAc-MeOH = 90:10:0.5) to give **48** as a pale yellow solid (1.65 g, 67%);

m.p.: 69.0-70.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.81 (br s, 1H), 7.10 (d, *J*= 8.6Hz, 1H), 7.00 (d, *J*= 2.2Hz, 1H), 6.76 (dd, *J*= 8.8Hz, 2.4Hz, 1H), 4.12 (q, *J*=7.1Hz, 2H), 3.82 (s, 3H), 3.63 (s, 2H), 2.35 (s, 3H), 1.24 (t, *J*= 7.1Hz, 3H).

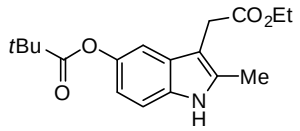
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.0, 154.1, 133.5, 130.1, 128.9, 110.9, 110.8, 104.5, 100.5, 60.6, 55.9, 30.6, 14.2, 11.7.

MS (70 eV, EI) *m/z* (%): 247 (27), 175 (10), 174 (100), 131 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3314, 2976, 2924, 2832, 1708, 1588, 1486, 1454, 1370, 1320, 1264, 1216, 1172, 1124, 1102, 1030, 790, 686, 632.

HRMS (EI): *m/z* calc. for **$C_{14}H_{17}NO_3$** (247.1208): 247.1204 (M^+).

Synthesis of 3-(2-ethoxy-2-oxoethyl)-2-methyl-1*H*-indol-5-yl pivalate (23e):



According to **TP6**, 2-(4-ethoxy-1-methyl-4-oxobutyl)zinc bromide (**44b**; 10 mmol, 11.1 mL, 0.90 M in THF), prepared from ethyl 4-bromopentanoate (**45b**) via **TP4** (50 °C, 12 h), and $ZnBr_2$ (20 mmol, 20 mL, 1M in THF) reacted with 4-[(2,2-dimethylpropanoyl)oxy]-benzenediazonium tetrafluoroborate (**43d**; 12.5 mmol, 3.65 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 1 h) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane-EtOAc-MeOH = 90:10:0.5) to give **23e** as a pale yellow solid (2.00 g, 63%); decomposition > 250 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.17 (br s, 1 H), 7.14 (s, 1 H), 6.92 (d, *J* = 8.6 Hz, 1 H), 6.68 (d, *J* = 8.6 Hz, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 3.59 (s, 2 H), 2.22 (s, 3 H), 1.39 (s, 9 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

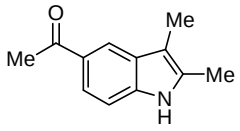
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.2, 172.0, 144.4, 134.3, 132.8, 128.6, 114.6, 110.6, 109.8, 104.3, 60.6, 38.9, 30.4, 27.2, 14.1, 11.4.

IR (ATR) υ (cm^{-1}): 3372, 2976, 2936, 1728, 1590, 1480, 1458, 1368, 1278, 1170, 1122, 1030, 900, 786.

MS (70 eV, EI): *m/z* (%): 317 (M^+, 24), 244 (15), 233 (32), 161 (9), 160 (100), 159 (10), 131 (6), 57 (18).

HRMS (EI): *m/z* calc. for **$C_{18}H_{23}NO_4$** (317.1627): 317.1622 (M^+).

Synthesis of 1-(2,3-Dimethyl-1*H*-indol-5-yl)ethanone (23j):



*s*BuZnBr (**44c**; 10 mmol, 38.5 mL, 0.26 M in THF) was prepared via addition of *s*BuLi (10 mmol, 8.33 mL, 1.2M in hexane) to a solution of $ZnBr_2$ (30 mmol, 30 mL, 1M in THF) at 0 °C and continuous stirring for 10 min. Following the **TP6**, the resulting alkylzinc reagent reacted with 4-acetylbenzenediazonium tetrafluoroborate (**43c**; 12.5 mmol, 2.92 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane-EtOAc-MeOH, 95:5:0.3) to give **23j** as a pale yellow solid (1.49 g, 80%).

m.p.: 179.0-181.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.27 (br s, 1 H), 8.14 (s, 1 H), 7.77 (d, J = 8.4 Hz, 1 H), 7.24 (d, J = 8.4 Hz, 1 H), 2.67 (s, 3 H), 2.33 (s, 3 H), 2.25 (s, 3 H).

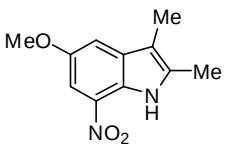
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 198.7, 138.1, 132.4, 129.0, 129.0, 121.5, 119.9, 109.8, 108.7, 26.6, 11.5, 8.3.

IR (ATR) υ (cm^{-1}): 3286, 1654, 1612, 1578, 1458, 1356, 1264, 1232, 1142, 970, 898, 794, 692, 648.

MS (70 eV, EI): *m/z* (%): 188 (16), 187 (M^+, 87), 186 (20), 173 (14), 172 (100), 144 (51), 143 (20), 85 (13), 83 (12), 77 (14), 71 (27), 57 (36), 55 (23), 43 (32).

HRMS (EI): *m/z* calc. for **$C_{12}H_{13}NO$** (187.0997): 187.0990 (M^+).

Synthesis of 5-methoxy-2,3-dimethyl-7-nitro-1*H*-indole (23f):



*s*BuZnBr (**44c**; 10 mmol, 38.6 mL, 0.26 M in THF) was prepared via addition of *s*BuLi (10 mmol, 8.3 mL, 1.2 M in hexane) to a solution of $ZnBr_2$ (30 mmol, 30 mL, 1 M in THF) at

0 °C and continuously stirring for 10 min. The resulting alkylzinc reagent reacted according **TP6** with 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate (**43a**; 12.5 mmol, 3.33 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 2 h). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane-EtOAc-MeOH = 96:4:0.5) to give **23f** as a red solid (1.77 g, 80%).

m.p.: 153.0-154.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.25 (br s, 1 H), 7.61 (d, J = 2.2 Hz, 1 H), 7.30 (d, J = 2.2 Hz, 1 H), 3.89 (s, 3 H), 2.39 (s, 3 H), 2.19 (s, 3 H).

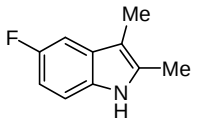
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 152.6, 134.8, 133.8, 131.3, 124.8, 111.8, 107.9, 103.9, 56.4, 11.6, 8.3.

IR (ATR) υ (cm^{-1}): 3420, 3370, 3110, 3024, 2914, 2836, 1604, 1576, 1502, 1474, 1458, 1388, 1364, 1330, 1288, 1192, 1178, 1140, 1082, 1044, 966, 878, 834, 756, 700, 606.

MS (70 eV, EI): *m/z* (%): 221 (13), 220 (M^+,100), 219 (20), 205 (24), 174 (17), 159 (39), 131 (14), 130 (10).

HRMS (EI): *m/z* calc. for **$C_{11}H_{12}N_2O_3$** (220.0848): 220.0834 (M^+).

Synthesis of 5-fluoro-2,3-dimethyl-1*H*-indole (23ae):



*s*BuZnBr (**44c**; 10 mmol, 38.6 mL, 0.26 M in THF) was prepared via addition of *s*BuLi (10 mmol, 8.3 mL, 1.2 M in hexane) to a solution of $ZnBr_2$ (30 mmol, 30 mL, 1 M in THF) at 0 °C and continuously stirring for 10 min. The resulting alkylzinc reagent reacted according to **TP6** with 4-fluorobenzenediazonium tetrafluoroborate (**43i**; 12.5 mmol, 2.62 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 90 min). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane-EtOAc-MeOH = 96:4:0.2) to give **23ae** as a pale yellow solid (1.11 g, 68%).

m.p.: 98.2-99.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.64 (br s, 1 H), 7.06-7.17 (m, 2 H), 6.83 (dd, J = 8.8 Hz, 2.6 Hz, 1H), 2.35 (s, 3 H), 2.17 (s, 3 H).

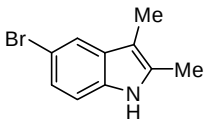
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 157.7 (d, J = 233.4 Hz), 132.7, 131.5, 129.9 (d, J = 9.5 Hz), 110.4 (d, J = 9.8 Hz), 108.8 (d, J = 26.1 Hz), 107.5, 103.0 (d, J = 23.3 Hz), 11.6, 8.4.

IR (ATR) υ (cm^{-1}): 3408, 2916, 2862, 1628, 1586, 1482, 1442, 1386, 1288, 1228, 1184, 1130, 944, 792, 702.

MS (70 eV, EI): *m/z* (%): 163 (M^+, 18), 162 (24), 148 (15), 71 (54), 70 (18), 57 (75), 65 (38), 55 (26), 44 (32), 43 (100).

HRMS (EI): *m/z* calc. for **$C_{10}H_{10}FN$** (163.0797): 163.0796 (M^+).

Synthesis of 5-bromo-2,3-dimethyl-1*H*-indole (32af):



*s*BuZnBr (**44c**; 10 mmol, 38.6 mL, 0.26 M in THF) was prepared via addition of *s*BuLi (10 mmol, 8.3 mL, 1.2 M in hexane) to a solution of $ZnBr_2$ (30 mmol, 30 mL, 1 M in THF) at 0 °C and continuously stirring for 10 min. The resulting alkylzinc reagent reacted according to **TP6** with 4-bromobenzenediazonium tetrafluoroborate (**43j**; 12.5 mmol, 3.38 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 90 min). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; *iso*hexane-EtOAc-MeOH = 95:5:0.5) to give **32af** as a pale yellow solid (1.79 g, 80%).

m.p.: 152.6-154.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.62 (br s, 1 H), 7.59 (d, J = 1.7 Hz, 1H), 7.19 (dd, J = 8.6 Hz, 1.7 Hz, 1 H), 7.07 (d, J = 8.3 Hz, 1 H), 2.33 (s, 3 H), 2.18 (s, 3 H).

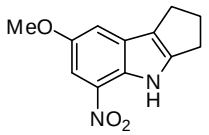
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 133.7, 132.2, 131.2, 123.4, 120.5, 112.2, 111.4, 106.9, 11.5, 8.3.

IR (ATR) υ (cm^{-1}): 3396, 2914, 1572, 1466, 1426, 1386, 1302, 1274, 1238, 1044, 1002, 966, 898, 864, 798, 744, 668.

MS (70 eV, EI): *m/z* (%): 226 (24), 225 (M^+, 65), 224 (95), 223 (M^+, 81), 222 (69), 210 (42), 208 (45), 143 (62), 115 (26), 89 (17), 75 (22), 71 (56), 57 (42), 44 (32), 43 (100).

HRMS (EI): *m/z* calc. for **$C_{10}H_{10}{}^{79}BrN$** (222.9997): 222.9974 (M^+).

Synthesis of 7-methoxy-5-nitro-1,2,3,4-tetrahydrocyclo-penta[*b*]indole (23u):



According to **TP6**, cyclopentylzinc bromide (**44e**; 10 mmol, 27.7 mL, 0.36 M in THF), prepared from cyclopentyl bromide (**45e**) via **TP5** (25 °C, 4 h), and $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF) reacted with 4-methoxy-2-nitro-benzenediazonium tetrafluoroborate (**43a**; 12.5 mmol, 3.33 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 90 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was

purified after the usual work-up by flash column chromatography (Al_2O_3; pentane-EtOAc-MeOH, 96:4:0.2) to give **23u** as a red solid (1.56 g, 68%).

m.p.:138.0-139.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.45 (br s, 1 H), 7.61 (d, J = 2.2 Hz, 1 H), 7.27 (d, J = 2.1 Hz, 1 H), 3.88 (s, 3 H), 2.85-2.99 (m, 2 H), 2.72-2.85 (m, 2 H), 2.46-2.69 (m, 2 H).

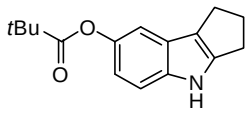
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 152.8, 147.8, 132.0, 130.0, 128.6, 120.4, 112.1, 103.7, 56.4, 28.7, 25.9, 24.1.

IR (ATR) υ (cm^{-1}): 3472, 2960, 2932, 2856, 1570, 1510, 1464, 1372, 1326, 1274, 1194, 1178, 1154, 1088, 1032, 836, 758.

MS (70 eV, EI): *m/z* (%): 233 (14), 232 (M^+, 100), 231 (38), 186 (14), 185 (11), 171 (18), 143 (9).

HRMS (EI): *m/z* calc. for **$C_{12}H_{12}N_2O_3$** (232.0848): 232.0864 (M^+).

Synthesis of 1,2,3,4-tetrahydrocyclopenta[*b*]indol-7-yl pivalate (23ag):



According to **TP6**, cyclopentylzinc bromide (**44e**; 10 mmol, 27.7 mL, 0.36 M in THF), prepared from cyclopentyl bromide (**45e**) via **TP5** (25 °C, 4 h), and $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF) reacted with 4-[(2,2-dimethyl-propanoyl)oxy]benzenediazonium tetrafluoroborate (**43d**; 12.5 mmol, 3.64 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 60 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane-EtOAc-MeOH, 96:4:0.2) to give **23ag** as a white powder (1.86 g, 72%).

m.p.: 141.5-142.9 °C.

^{1}H NMR (300 MHz) δ (ppm): 7.89 (br s, 1 H), 7.15 (d, J = 8.7 Hz, 1 H), 7.08 (d, J = 2.4 Hz, 1H), 6.73 (dd, J = 5.7 Hz, 2.4 Hz, 1 H), 2.84-2.75 (m, 4 H), 2.55-2.46 (m, 2 H), 1.40 (s, 9 H).

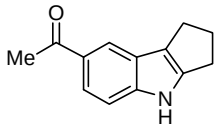
^{13}C NMR (75 MHz) δ (ppm): 178.15, 145.27, 144.51, 138.75, 124.94, 119.87, 113.98, 111.46, 110.51, 39.03, 28.59, 27.29, 25.86, 24.35.

IR (ATR) υ (cm^{-1}): 3392, 2950, 2851, 1730, 1623, 1580, 1475, 1461, 1162, 1137, 1112, 786, 625.

MS (70 eV, EI): *m/z* (%): 257 (M^+, 32), 174 (14), 173 (100), 172 (42).

HRMS (EI): *m/z* calc. for **$C_{16}H_{19}NO_2$** (257.1416): 257.1412 (M^+).

Synthesis of 7-acetyl-1,2,3,4-tetrahydrocyclo-penta[*b*]indole (23ah):



According to **TP6**, cyclopentylzinc bromide (**44e**; 10 mmol, 27.7 mL, 0.36 M in THF), prepared from cyclopentyl bromide (**45e**) via **TP5** (25 °C, 4 h), and $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF) reacted with 4-acetylbenzenediazonium tetrafluoroborate (**43c**; 12.5 mmol, 2.92 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 60 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane-EtOAc-MeOH, 92:8:0.5) to give **23ah** as a pale yellow solid (1.93 g, 76%).

m.p.: 168.4-170.7 °C.

^{1}H NMR (300 MHz) δ (ppm): 8.24 (br s, 1H), 8.12 (s, 1H), 7.78 (d, *J*=8.6Hz, 1H), 7.31 (d, *J*=8.6Hz, 1H), 2.81-2.96 (m, 4H), 2.67 (s, 3H), 2.48-2.62 (m, 2H).

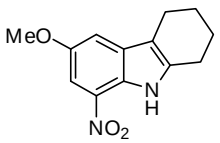
^{13}C NMR (75 MHz) δ (ppm): 198.6, 145.4, 143.7, 129.6, 124.2, 121.3, 121.0, 120.5, 111.0, 28.6, 26.6, 25.9, 24.4.

IR (ATR) υ (cm^{-1}): 3234, 2944, 2908, 2852, 1652, 1598, 1470, 1360, 1272, 1246, 1124, 1096, 952, 872, 810, 700, 644.

MS (70 eV, EI): *m/z* (%): 199 (M^+, 60), 198 (24), 188 (21), 184 (86), 156 (41), 154 (28), 85 (30), 57 (85), 55 (35), 43 (100).

HRMS (EI): *m/z* calc. for **$C_{13}H_{13}NO$** (199.0997): 199.0992 (M^+).

Synthesis of 6-methoxy-8-nitro-2,3,4,9-tetrahydro-1*H*-carbazole (23r):



According to **TP6**, cyclohexylzinc bromide (**44f**; 10 mmol, 27 mL, 0.37 M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 4 h), and $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF) reacted with 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate (**43a**; 12.5 mmol, 3.33 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane-EtOAc-MeOH = 95:4:0.5) to give **23r** as a red solid (2.25 g, 91%).

m.p.: 137.1-138.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.27 (br s, 1 H), 7.62 (d, J = 2.1 Hz, 1 H), 7.29 (d, J = 2.1 Hz, 1 H), 3.89 (s, 3 H), 2.77 (t, J= 5.9 Hz, 2 H), 2.65 (t, J = 5.9 Hz, 2 H), 1.89-2.00 (m, 2 H), 1.80-1.89 (m, 2 H).

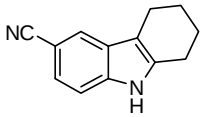
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 152.7, 138.1, 132.3, 131.5, 125.3, 111.7, 110.9, 103.9, 56.4, 23.2, 22.9, 22.8, 20.6.

IR (ATR) υ (cm^{-1}): 3424, 2934, 2844, 1734, 1604, 1574, 1508, 1466, 1440, 1382, 1278, 1194, 1134, 1036, 834, 758, 648, 606.

MS (70 eV, EI): *m/z* (%): 246 (10), 247 (M+, 78), 245 (11), 219 (11), 218 (100), 203 (8).

HRMS (EI): *m/z* calc. for **$C_{13}H_{14}N_2O_3$** (246.1004): 246.0997 (M^+).

Synthesis of 2,3,4,9-Tetrahydro-1*H*-carbazole-6-carbonitrile (23t):



According to **TP6**, cyclohexylzinc bromide (**44f**; 10 mmol, 27 mL, 0.37 M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 4 h), and $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF) reacted with 4-cyanobenzenediazonium tetrafluoroborate (**43g**; 12.5 mmol, 2.71 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; *iso*hexane-EtOAc-MeOH = 95:6:1) to give **23t** as a pale yellow solid (1.56 g, 80%).

m.p.: 124.0-125.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.13 (br s, 1 H), 7.76 (s, 1 H), 7.19-7.49 (m, 2 H), 2.74 (t, J = 5.7 Hz, 2 H), 2.67 (t, J = 5.8 Hz, 2 H), 1.75-2.03 (m, 4 H).

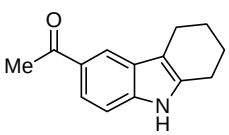
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 137.4, 136.6, 127.7, 124.1, 123.1, 121.2, 111.0, 111.0, 101.7, 23.1, 22.9, 22.8, 20.6.

MS (70 eV, EI): *m/z* (%): 197 (11), 196 (M^+, 79), 195 (17), 169 (12), 168 (100).

IR (ATR) υ (cm^{-1}): 3314, 2926, 2846, 2216, 1686, 1622, 1478, 1318, 1236, 1180, 872, 806, 798, 626.

HRMS (EI): *m/z* calc. for **$C_{13}H_{12}N_2$** (196.1000): 196.0997 (M^+).

Synthesis of 1-(2,3,4,9-tetrahydro-1*H*-carbazol-6-yl)ethanone (23u):



According to **TP6**, cyclohexylzinc bromide (**44f**; 10 mmol, 27 mL, 0.37 M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 4 h), and $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF) reacted with 4-acetylbenzenediazonium tetrafluoroborate (**43c**; 12.5 mmol, 2.92 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane-EtOAc-MeOH = 90:10:0.5) to give **23u** as a pale yellow (1.56 g, 73%).

m.p.: 122.5-124.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.12 (s, 1 H), 8.09 (br s, 1 H), 7.78 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1 H), 2.73 (t, J = 5.9 Hz, 4 H), 2.65 (s, 3 H), 1.78-2.01 (m, 4 H).

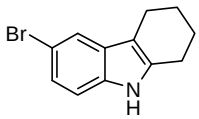
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 198.5, 138.5, 135.8, 129.2, 127.5, 121.7, 119.7, 111.8, 110.0, 62.7, 26.6, 23.2, 23.0, 20.8.

IR (ATR) υ (cm^{-1}): 3286, 2926, 2854, 1652, 1614, 1578, 1460, 1354, 1232, 1122, 812, 798, 686, 648.

MS (70 eV, EI): *m/z* (%): 214 (19), 213 (M^+, 100), 212 (11), 198 (51), 185 (42), 170 (18), 142 (8).

HRMS (EI): *m/z* calc. for **$C_{14}H_{15}NO$** (213.1154): 213.1151 (M^+).

Synthesis of 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazole (23ai):



According to **TP6**, cyclohexylzinc bromide (**44f**; 10 mmol, 27 mL, 0.37 M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 4 h), and $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF) reacted with 4-bromobenzenediazonium tetrafluoroborate (**43j**; 12.5 mmol, 3.38 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; *iso*hexane-EtOAc-MeOH = 95:5:0.5) to give **23ai** as a pale yellow solid (2.00 g, 80%).

m.p.: 152.6-154.1 °C.

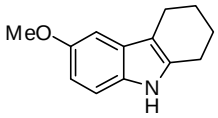
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.63 (br s, 1 H), 7.58 (d, J = 1.8 Hz, 1 H), 7.19 (dd, J = 8.4 Hz, 1.8 Hz, 1 H), 7.11 (d, J = 8.4 Hz, 1 H), 2.73-2.64 (m, 4 H), 1.95-1.84 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 135.60, 134.26, 129.68, 123.59, 120.42, 112.32, 111.71, 110.01, 23.22, 23.14, 23.06, 20.76.

IR (ATR) υ (cm^{-1}): 3400, 2938, 2906, 2848, 1578, 1434, 1310, 1232, 1046, 974, 862, 796.

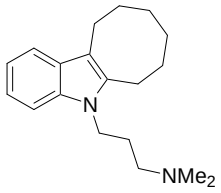
MS (70 eV, EI): *m/z* (%): 252 (10), 251 (M^+, 76), 250 (26), 249 (M^+, 81), 248 (16), 224 (12), 223 (98), 221 (100), 168 (19), 167 (15), 142 (11), 115 (12).
HRMS (EI): *m/z* calc. for **$C_{12}H_{12}{}^{79}BrN$** (249.0153): 249.0137 (M^+).

Synthesis of 6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazole (23aj):



According to **TP6**, cyclohexylzinc bromide (**44f**; 10 mmol, 27 mL, 0.37 M in THF), prepared from cyclohexyl bromide via **TP5** (25 °C, 4 h), and $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF) reacted with 4-methoxy-benzenediazonium tetrafluoroborate (**43e**; 12.5 mmol, 2.77 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; pentane-EtOAc-MeOH = 95:4:0.5) to give **23aj**[298] as a pale yellow solid (2.25 g, 80%).
m.p.: 107.9-109.8 °C.
^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.56 (br s, 1 H), 7.15 (d, J = 8.6 Hz, 1 H), 6.95 (d, J = 2.4 Hz, 1 H), 6.88 (dd, J = 8.6 Hz, 2.4 Hz, 1 H), 3.87 (s, 3 H), 2.73-2.69 (m, 4 H), 2.67-1.89 (m, 4 H).

Synthesis of [3-(6,7,8,9,10,11-hexahydro-5*H*-cycloocta[*b*]indol-5-yl)propyl]dimethyl-amine (47, *iprindole*):



iprindole

According to **TP6**, cyclooctylzinc bromide (**44g**; 20 mmol, 57 mL, 0.35 M in THF), prepared from cyclooctyl bromide via **TP5** (25 °C, 4 h), and $ZnBr_2$ (40 mmol, 40 mL, 1 M in THF) reacted with benzenediazonium tetrafluoroborate (**43h**; 25 mmol, 4.80 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2.17 g, 20 mmol). After cooling to 0 °C, KO*t*Bu (24 mmol, 2.29 g) was slowly added. The reaction mixture was stirred for 20 min at 0 °C followed by addition of (3-chloropropyl)-dimethylamine (24 mmol, 2.92 g). The resulting solution was heated by

[298] J. Chen, Y. Hu, *Synth. Commun.* **2006**, *36*, 1485.

microwave irradiation (125 °C, 3 h) and quenched with brine (50 mL). The aqueous phase was extracted with EtOAc (3x 50 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (Al_2O_3; pentane:EtOAc:MeOH = 97:3:0.3) to give iprindole (**47**) as a yellow oil (4.09 g, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.50 (d, *J* = 7.3 Hz, 1 H), 7.29 (d, *J* = 7.8 Hz, 1 H), 7.10 (t, *J* = 7.9 Hz, 1 H), 7.01-7.08 (m, 1 H), 4.12 (t, *J* = 7.6 Hz, 2 H), 2.79-2.95 (m, 4 H), 2.30 (t, *J* = 6.9 Hz, 2 H), 2.23 (s, 6 H), 1.83-1.97 (m, 2 H), 1.64-1.78 (m, 4 H), 1.35-1.47 (m, 4 H).

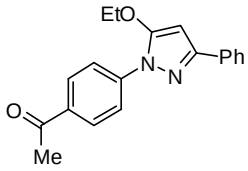
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.6, 136.0, 127.5, 120.1, 118.4, 117.6, 111.8, 108.9, 56.8, 45.4, 40.9, 30.4, 29.3, 28.7, 26.1, 25.9, 23.0, 22.9.

IR (ATR) υ (cm^{-1}): 3050, 2920, 2848, 2814, 2764, 1464, 1370, 1338, 1316, 1180, 1040, 734, 696.

MS (70 eV, EI): *m/z* (%): 284 (M+, 57), 213 (33), 212 (20), 198 (20), 185 (21), 184 (20), 171 (21), 170 (73), 157 (21), 156 (26), 145 (22), 144 (24), 71 (15), 58 (100), 43 (58), 41 (48).

HRMS (EI): *m/z* calc. for **$C_{19}H_{28}N_2$** (284.2252): 284.2246 (M^+).

Synthesis of 1-[4-(5-ethoxy-3-phenyl-1*H*-pyrazol-1-yl)phenyl]ethanone (51a):



According to **TP7**, (3-ethoxy-3-oxo-1-phenylpropyl)zinc bromide (**44h**; 2 mmol, 2.27 mL, 0.88M in THF), prepared from ethyl 3-bromo-3-phenylpropanoate via **TP4** (50 °C, 6 h), and $ZnBr_2$ (4 mmol, 4 mL, 1 M in THF) reacted with 4-acetylbenzenediazonium tetrafluoroborate (**43c**; 2.5 mmol, 585 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (217 mg, 2 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; *iso*hexane-EtOAc-MeOH = 96:4:0.5) to give **51a** as a pale yellow solid (502 mg, 82%).

m.p.: 131.1-131.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.98-8.09 (m, 4H), 7.88 (dd, *J*=8.3Hz, 1.4Hz, 2H), 7.32-7.52 (m, 3H), 6.02 (s, 1H), 4.28 (q, *J*=7.0Hz, 2H), 2.63 (s, 3H), 1.53 (t, *J*=7.0Hz, 3H).

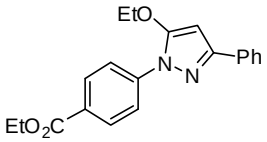
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 197.0, 155.9, 151.3, 142.8, 134.0, 133.0, 129.3, 128.6, 128.3, 125.5, 120.6, 84.3, 68.3, 26.5, 14.6.

IR (ATR) υ (cm^{-1}): 3128, 3108, 2978, 1670, 1590, 1560, 1512, 1472, 1396, 1374, 1364, 1266, 1148, 1046, 946, 834, 760, 694, 674.

MS (70 eV, EI): *m/z* (%): 307 (23), 306 (M^+, 100), 278 (34), 277 (36), 263 (63), 249 (11), 236 (24), 235 (20), 207 (12), 102 (21), 91 (13), 77 (14), 43 (25).

HRMS (EI): *m/z* calc. for **$C_{19}H_{18}N_2O_2$** (306.1368): 306.1360 (M^+).

Synthesis of ethyl 4-(5-ethoxy-3-phenyl-1*H*-pyrazol-1-yl)benzoate (51b):



According to **TP7**, (3-ethoxy-3-oxo-1-phenylpropyl)zinc bromide (**44h**; 2 mmol, 2.27 mL, 0.88M in THF), prepared from ethyl 3-bromo-3-phenylpropanoate via **TP4** (50 °C, 6 h), and $ZnBr_2$ (4 mmol, 4 mL, 1 M in THF) reacted with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**43b**; 2.5 mmol, 660 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (217 mg, 2 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; *iso*hexane-EtOAc-MeOH = 96:4:0.5) to give **51b** as a pale yellow solid (504 mg, 75%).

m.p.: 125.3-126.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.12 (d, *J*=8.8Hz, 2H), 7.98 (d, *J*=8.8Hz, 2H), 7.86 (d, *J*=7.3Hz, 2H), 7.29-7.47 (m, 3H), 5.99 (s, 1H), 4.39 (q, *J*=7.1Hz, 2H), 4.24 (q, *J*=7.0Hz, 2H), 1.50 (t, *J*=7.1Hz, 3H), 1.40 (t, *J*=7.1Hz, 3H).

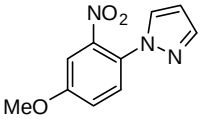
^{13}C NMR (75 MHz, $CDCl_3$ δ (ppm): 166.1, 155.8, 151.2, 142.6, 133.1, 130.4, 128.5, 128.2, 127.3, 125.5, 120.5, 84.2, 68.3, 60.9, 14.6, 14.3.

IR (ATR) υ (cm^{-1}): 2984, 2974, 2900, 1712, 1606, 1590, 1560, 1512, 1394, 1376, 1360, 1276, 1152, 1110, 1044, 1024, 948, 852, 764, 730, 694, 674.

MS (70 eV, EI): *m/z* (%): 337 (21), 336 (M^+, 100), 308 (38), 307 (32), 263 (11), 235 (16), 102 (13).

HRMS (EI): *m/z* calc. for **$C_{20}H_{20}N_2O_3$** (336.1474): 336.1468 (M^+).

Synthesis of 1-(4-methoxy-2-nitrophenyl)-1*H*-pyrazole (51c):



According to **TP7**, [2-(1,3-dioxolan-2-yl)ethyl]zinc bromide (**44h**; 2 mmol, 2.5 mL, 0.80M in THF), prepared from 2-(2-bromoethyl)-1,3-dioxolane via **TP4** (50 °C, 6 h), and $ZnBr_2$ (4 mmol, 4 mL, 1 M in THF) reacted with 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate (**43a**; 2.5 mmol, 666 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (217 mg, 2 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; *iso*hexane-EtOAc-MeOH = 96:4:0.5) to give **51c** as a pale yellow solid (329 mg, 75%).

m.p.: 102.7-104.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.71 (d, *J*=1.3Hz, 1H), 7.65 (d, *J*=1.9Hz, 1H), 7.48 (d, *J*=8.8Hz, 1H), 7.40 (d, *J*=2.8Hz, 1H), 7.19 (dd, *J*=8.9Hz, 2.9Hz, 1H), 6.43-6.53 (m, 1H), 3.92 (s, 3H).

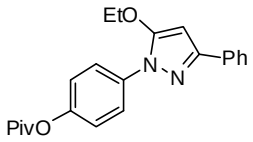
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 158.8, 143.3,141.3, 129.8, 127.7, 123.5, 118.4, 109.4, 107.2, 55.8.

IR (ATR) υ (cm^{-1}): 3388, 3142, 3118, 3012, 2940, 2860, 1524, 1454, 1400, 1362, 1312, 1272, 1234, 1112, 1034, 942, 868, 830, 804, 770, 648, 620.

MS (70 eV, EI): *m/z* (%): 219 (M^+, 33), 202 (11), 162 (31), 150 (14), 146 (17), 143 (10), 136 (18), 134 (15), 93 (17), 91 (45), 85 (14), 73 (77), 71 (95), 56 (13), 55 (100), 43 (47), 42 (27), 41 (35).

HRMS (EI): *m/z* calc. for **$C_{10}H_9N_3O_3$** (219.0644): 219.0634 (M^+).

Synthesis of 4-(5-ethoxy-3-phenyl-1*H*-pyrazol-1-yl)phenyl 2,2-dimethylpropanoate (51d):



According to **TP7**, (3-ethoxy-3-oxo-1-phenylpropyl)zinc bromide (**44h**; 2 mmol, 2.27 mL, 0.88M in THF), prepared from ethyl 3-bromo-3-phenylpropanoate via **TP4** (50 °C, 6 h), and $ZnBr_2$ (4 mmol, 4 mL, 1 M in THF) reacted with 4-[(2,2-dimethyl-propanoyl)oxy]-benzenediazonium tetrafluoroborate (**43d**; 2.5 mmol, 728 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (217 mg, 2 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; *iso*hexane) to give **51d** as a white powder (510 mg, 70%).

Mp 119.8-120.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.79-7.96 (m, 4H), 7.43 (t, *J*=7.4Hz, 2H), 7.35 (t, *J*=7.1Hz, 1H), 7.16 (d, *J*=9.0Hz, 2H), 5.97 (s, 1H), 4.16 (q, *J*=7.1Hz, 2H), 1.35-1.53 (m, 10H).

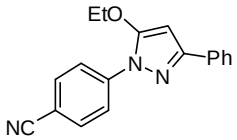
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 176.8, 155.1, 150.3, 148.7, 136.3, 133.3, 128.3, 127.8, 125.3, 122.5, 121.6, 83.5, 67.9, 38.9, 27.0, 14.4.

IR (ATR) υ (cm^{-1}): 2980, 1722, 1602, 1560, 1510, 1456, 1416, 1394, 1378, 1344, 1286, 1222, 1190, 1150, 1116, 1052, 952, 758, 698.

MS (70 eV, EI): *m/z* (%): 365 (21), 364 (M^+, 78), 281 (21), 280 (100), 252 (43), 251 (44), 223 (22), 144 (15), 102 (17), 57 (74), 41 (12).

HRMS (EI): *m/z* calc. for **$C_{22}H_{24}N_2O_3$** (364.1787): 364.1772 (M^+).

Synthesis of 4-(5-ethoxy-3-phenyl-1*H*-pyrazol-1-yl)benzonitrile (51e):



According to **TP7**, (3-ethoxy-3-oxo-1-phenylpropyl)zinc bromide (**44h**; 2 mmol, 2.27 mL, 0.88M in THF), prepared from ethyl 3-bromo-3-phenylpropanoate via **TP4** (50 °C, 6 h), and $ZnBr_2$ (4 mmol, 4 mL, 1 M in THF) reacted with 4-cyanobenzenediazonium tetrafluoroborate (**43g**; 2.5 mmol, 542 mg). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (217 mg, 2 mmol). The crude product was purified after the usual work-up by flash column chromatography (Al_2O_3; *iso*hexane) to give **51e** as a white powder (492 mg, 85%).

Mp 134.5-135.2 °C.

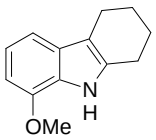
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.07 (d, *J*=8.8Hz, 2H), 7.85 (d, *J*=6.9Hz, 2H), 7.69 (d, *J*=8.8Hz, 2H), 7.29-7.51 (m, 3H), 6.00 (s, 1H), 4.27 (q, *J*=7.1Hz, 2H), 1.52 (t, *J*=7.1Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 156.0, 151.7, 142.5, 132.9, 132.8, 128.6, 128.5, 125.5, 120.9, 118.8, 108.5, 84.5, 68.5, 14.6.

IR (ATR) υ (cm^{-1}): 3136, 3058, 2984, 2226, 1604, 1590, 1556, 1510, 1468, 1458, 1416, 1390, 1376, 1364, 1148, 1024, 948, 894, 830, 764, 690.

HRMS (ESI): *m/z* calc. for **$C_{18}H_{16}N_3O$** (290.1293): 290.1286 ($[M+H]^+$).

Synthesis of 8-methoxy-2,3,4,9-tetrahydro-1*H*-carbazole (55a):



A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with magnesium turnings (98 mg, 4 mmol). LiCl (2.75 mL, 2.75 mmol, 1M in THF) was added and the magnesium was activated with 1,2-dibromoethane (2 mol%) and Me_3SiCl (5 mol%). After stirring for 5 min, the suspension was cooled to 0 °C, cyclohexenyl iodide (2.5 mmol, 520 mg) was added and the reaction mixture was stirred for 1 h at 0 °C. The supernatant solution was added dropwise to a solution of 2,2′-dimethoxyazobenzene (2.0 mmol, 484 mg) in THF (4 mL) at 0°C followed by warming to 25 °C and continuous stirring for 1 h at 25 °C. After addition of Me_3SiCl (2.0 mmol, 217 mg) and NMP (= *N*-methylpyrrolidone; 2 mL), the resulting solution was heated to 125 °C for 30 min using microwave irradiation. After cooling to 25 °C, the reaction mixture was diluted with Et_2O (5 mL) and quenched with 2M aq. HCl (5 mL). The aqueous layer was extracted with EtOAc (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (silica gel; pentane:EtOAc = 9:1) furnished the indole **55a** as a yellow oil in 76% yield (306 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.91 (br s, 1H), 7.09 (d, *J*= 7.9Hz, 1H), 7.00 (t, *J*= 7.8Hz, 1H), 6.61 (d, *J*= 7.7Hz, 1H), 3.95 (s, 3H), 2.66-2.78 (m, 4H), 1.82-1.96 (m, 4H).

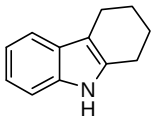
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 145.6, 133.6, 129.1, 125.7, 119.4, 110.8, 110.6, 101.5, 55.3, 23.3, 23.2, 23.1, 21.1.

MS (70 eV, EI) *m/z* (%): 202 (15), 201 (M^+, 98), 200 (23), 174 (12), 173 (100), 158 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3423, 3404, 3062, 2926, 2854, 1572, 1467, 1345, 1224, 774, 686, 650.

HRMS (EI): *m/z* calc. for **$C_{13}H_{15}NO$** (201.1154): 201.1135 (M^+).

Synthesis of 2,3,4,9-tetrahydro-1*H*-carbazole (57a):



A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with *t*BuLi (5 mmol, 3.33 mL, 1.5 M in hexane) in THF (3 mL) at −78 °C. Cyclohexenyl iodide (2.5 mmol, 520 mg) in THF (2 mL) was added and the reaction mixture was stirred for 2 h at −78 °C followed by addition of a solution of azobenzene (**53b**, 2.0 mmol, 364 mg) in THF (4 mL) at −78 °C. The reaction mixture was allowed to slowly warm to 25 °C and was continuously stirred for 1 h at 25 °C. After addition of Me_3SiCl (2.0

mmol, 217 mg) and NMP (*N*-methylpyrrolidone; 2 mL), the resulting solution was heated to 125 °C for 30 min using microwave irradiation. After cooling to 25 °C, the reaction mixture was diluted with Et_2O (5 mL) and quenched with 2M aq. HCl (5 mL). The aqueous layer was extracted with EtOAc (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (SiO_2; pentane:EtOAc = 9:1) furnished the indole **57a** as a pale yellow solid (292 mg, 85%).

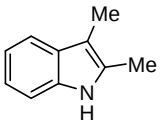
m.p.: 118.6-120.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.65 (br s, 1H), 7.52 (d, *J*=7.3Hz, 1H), 7.28 (d, *J*=7.7Hz, 1H), 7.05-7.24 (m, 2H), 2.75 (q, *J*=6.2Hz, 4H), 1.81-2.07 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 135.6, 134.1, 127.7, 120.9, 119.0, 117.6, 110.3, 110.0, 23.3, 23.2, 20.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3396, 2926, 2848, 1660, 1620, 1590, 1468, 1450, 1440, 1326, 1304, 1234, 1144, 1010, 736, 636.

Synthesis of 2,3-dimethyl-1*H*-indole (57b):



A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with *t*BuLi (5 mmol, 3.33 mL, 1.5 M in hexane) in THF (3 mL) at −78 °C. 2-Bromo-but-2-ene (2.5 mmol, 338 mg) in THF (2 mL) was added and the reaction mixture was stirred for 2 h at −78 °C followed by addition of a solution of azobenzene (**53b**, 2.0 mmol, 364 mg) in THF (4 mL) at −78 °C. The reaction mixture was allowed to slowly warm to 25 °C and was continuously stirred for 1 h at 25 °C. After addition of Me_3SiCl (2.0 mmol, 217 mg) and NMP (*N*-methylpyrrolidone; 2 mL), the resulting solution was heated to 125 °C for 30 min using microwave irradiation. After cooling to 25 °C, the reaction mixture was diluted with Et_2O (5 mL) and quenched with 2M aq. HCl (5 mL). The aqueous layer was extracted with EtOAc (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (SiO_2; pentane:EtOAc = 95:5) furnished the indole **57b** as a pale yellow solid (224 mg, 76%).

m.p.: 104.8-106.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.47-7.68 (m, 2H), 7.04-7.34 (m, 3H), 2.37 (s, 3H), 2.31 (s, 3H).

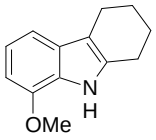
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 135.3, 130.8, 129.2, 120.9, 119.1, 118.0, 110.2, 107.1, 11.5, 8.5.

MS (70 eV, EI) *m/z* (%): 146 (9), 145 (M^+, 75), 144 (100), 143 (15), 130 (40), 77 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3400, 3105, 1476, 1267, 1238, 742, 650.

HRMS (EI): *m/z* calc. for **$C_{10}H_{11}N$** (145.0891): 145.0878 (M^+).

Synthesis of 8-methoxy-2,3,4,9-tetrahydro-1*H*-carbazole (57c):

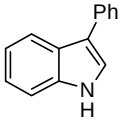


A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with *t*BuLi (5 mmol, 3.33 mL, 1.5 M in hexane) in THF (3 mL) at −78 °C. Cyclohexenyl iodide (2.5 mmol, 520 mg) in THF (2 mL) was added and the reaction mixture was stirred for 2 h at −78 °C followed by addition of a solution of 2,2´-dimethoxyazobenzene (**53a**, 2.0 mmol, 484 mg) in THF (4 mL) at −78 °C. The reaction mixture was allowed to slowly warm to 25 °C and was continuously stirred for 1 h at 25 °C. After addition of Me_3SiCl (2.0 mmol, 217 mg) and 2 mL NMP (*N*-methylpyrrolidone), the resulting solution was heated to 125 °C for 30 min using microwave irradiation. After cooling to 25 °C, the reaction mixture was diluted with Et_2O (5 mL) and quenched with 2M aq. HCl (5 mL). The aqueous layer was extracted with EtOAc (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (SiO_2; pentane:EtOAc = 9:1) furnished the indole **57c** as a yellow oil (298 mg, 74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.91 (br s, 1H), 7.09 (d, *J*= 7.9Hz, 1H), 7.00 (t, *J*= 7.8Hz, 1H), 6.61 (d, *J*= 7.7Hz, 1H), 3.95 (s, 3H), 2.66-2.78 (m, 4H), 1.82-1.96 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 145.6, 133.6, 129.1, 125.7, 119.4, 110.8, 110.6, 101.5, 55.3, 23.3, 23.2, 21.1.

Synthesis of 3-phenyl-1*H*-indole (57d):



A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with *t*BuLi (5 mmol, 3.33 mL, 1.5 M in hexane) in THF (3 mL) at −78 °C. *Beta*-bromostyrene (2.5 mmol, 458 mg) in THF (2 mL) was added and the reaction mixture was stirred for 2 h at −78 °C followed by addition of a solution of azobenzene (**53b**, 2.0 mmol,

364 mg) in THF (4 mL) at −78 °C. The reaction mixture was allowed to slowly warm to 25 °C and was continuously stirred for 1 h at 25 °C. After addition of Me_3SiCl (2.0 mmol, 217 mg) and NMP (*N*-methylpyrrolidone; 2 mL), the resulting solution was heated to 125 °C for 30 min using microwave irradiation. After cooling to 25 °C, the reaction mixture was diluted with Et_2O (5 mL) and quenched with 2M aq. HCl (5 mL). The aqueous layer was extracted with EtOAc (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (SiO_2; pentane:EtOAc = 9:1) furnished the indole **57d** as a pale yellow solid (139 mg, 36%).

m.p.: 89.1-91.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.10-8.40 (br s, 1H), 8.00 (d, *J*= 7.8Hz, 1H), 7.72 (d, *J*= 7.3Hz, 1H), 7.42-7.55 (m, 3H), 7.19-7.41 (m, 5H).

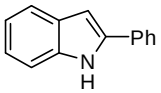
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.7, 135.5, 128.7, 127.5, 125.9, 125.4,122.4, 121.7, 120.3, 119.8, 118.3, 111.4.

MS (70 eV, EI) *m/z* (%): 194 (16), 193 (M^+, 100), 165 (26), 111 (22), 105 (38), 85 (40), 83 (35), 77 (38), 71 (58), 69 (41), 67 (16), 57 (93), 56 (21), 55 (48), 43 (57).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3400, 3011, 1573, 1539, 737.

HRMS (EI): *m/z* calc. for **$C_{14}H_{11}N$** (193.0891): 193.0893 (M^+).

Synthesis of 2-phenyl-1*H*-indole (57e):



A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with *t*BuLi (5 mmol, 3.33 mL, 1.5 M in hexane) in THF (3 mL) at −78 °C. *Alpha*-bromostyrene (2.5 mmol, 458 mg) in THF (2 mL) was added and the reaction mixture was stirred for 2 h at −78 °C followed by addition of a solution of azobenzene (**53b**, 2.0 mmol, 364 mg) in THF (4 mL) at −78 °C. The reaction mixture was allowed to slowly warm to 25 °C and was continuously stirred for 1 h at 25 °C. After addition of Me_3SiCl (2.0 mmol, 217 mg) and NMP (*N*-methylpyrrolidone; 2 mL), the resulting solution was heated to 125 °C for 30 min using microwave irradiation. After cooling to 25 °C, the reaction mixture was diluted with Et_2O (5 mL) and quenched with 2M aq. HCl (5 mL). The aqueous layer was extracted with EtOAc (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (SiO_2; pentane:EtOAc = 9:1) furnished the indole **57e** as a pale yellow solid (332 mg, 86%).

m.p.: 191.2-194.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.32 (br s, 1H), 7.58-7.72 (m, 3H), 7.37-7.50 (m, 3H), 7.32 (t, *J*= 7.5Hz, 1H), 7.20 (dt, *J*= 7.0Hz, 1.2Hz, 1H), 7.13 (dt, *J*= 7.8Hz, 1.2Hz, 1H), 6.83 (dd, *J*= 2.2Hz, 1.0Hz, 1H).

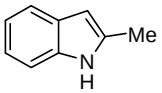
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 137.9, 136.8, 132.4, 129.3, 129.0, 127.7, 125.1, 122.3, 120.6, 120.3, 110.9, 100.0.

MS (70 eV, EI) *m/z* (%): 194 (16), 193 (M^+, 100), 192 (10), 165 (17), 97 (12), 85 (15), 83 (12), 77 (12), 71 (21), 69 (13), 57 (30), 55 (14), 43 (18), 41 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3430, 3023, 1479, 1387, 741.

HRMS (EI): *m/z* calc. for **$C_{14}H_{11}N$** (193.0891): 193.0876 (M^+).

Synthesis of 2-methyl-1*H*-indole (57f):



A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with *t*BuLi (5 mmol, 3.33 mL, 1.5 M in hexane) in THF (3 mL) at −78 °C. 2-Bromo-propene (2.5 mmol, 303 mg) in THF (2 mL) was added and the reaction mixture was stirred for 2 h at −78 °C followed by addition of a solution of azobenzene (**53b**, 2.0 mmol, 364 mg) in THF (4 mL) at −78 °C. The reaction mixture was allowed to slowly warm to 25 °C and was continuously stirred for 1 h at 25 °C. After addition of Me_3SiCl (2.0 mmol, 217 mg) and NMP (*N*-methylpyrrolidone; 2 mL), the resulting solution was heated to 125 °C for 30 min using microwave irradiation. After cooling to 25 °C, the reaction mixture was diluted with Et_2O (5 mL) and quenched with 2M aq. HCl (5 mL). The aqueous layer was extracted with EtOAc (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (SiO_2; pentane:EtOAc = 95:5) furnished the indole **57f** as a pale yellow solid (206 mg, 71%).

m.p.: 60.3-61.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.57-7.62 (m, 2H), 7.27 (dd, *J*= 7.5Hz, 1.7Hz, 1H), 7.12-7.23 (m, 2H), 6.28 (s, 1H), 2.42 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.0, 135.1, 129.0, 120.8, 120.0, 119.5, 110.2, 100.2, 13.5.

MS (70 eV, EI) *m/z* (%): 132 (8), 131 (M^+, 74), 130 (100), 103 (9), 77 (10), 69 (10).

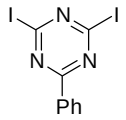
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3400, 3113, 1456, 1278, 793, 749, 650.

HRMS (EI): *m/z* calc. for **C_9H_9N** (131.0735): 131.0752 (M^+).

4. Preparation of Organometallics via Direct Metal Insertion or Hal/Mg-Exchange Reaction in the Presence of LiCl

4.1 1,3,5-Triazinylmagnesium Reagents via an I/Mg-exchange Reaction

Synthesis of 2,4-diiodo-6-phenyl-1,3,5-triazine (63):



A 50 mL round-bottom flask was charged with HI (57 w% solution, 20 mL). The solution was cooled to 5 °C and 2,4-dichloro-6-phenyl-1,3,5-triazine (4.52 g, 20 mmol) was added at the same temperature. The reaction mixture was allowed to slowly warm to 25 °C and stirred for 12 h at 25 °C. The mixture was carefully neutralized with K_2CO_3, and decolorized with sat. Na_2SO_3 (aq.) (ca. 5 mL). Water was added until all solid residues dissolved. The aqueous layer was extracted with CH_2Cl_2 (3x 50 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/EtOAc = 50:1) afforded 2,4-diiodo-6-phenyl-1,3,5-triazine (**63**, 5.5 g, 67%) as a white solid.

m. p.: 188.5-190.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.49-8.42 (m, 2H), 7.68-7.48 (m, 3H).

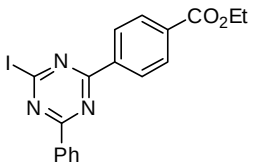
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 170.2, 139.6, 134.4, 132.3, 129.8, 128.9.

IR (Diamond-ATR, neat) ν (cm^{-1}): 3065 (W), 2924 (W), 1469 (S), 1369 (M), 1237 (W), 1205 (M), 1170 (M), 1084 (W), 802 (W), 759 (S), 688 (M), 640 (W).

MS (EI, 70 eV) *m/z* (%): 408 (M^+, 46), 282 (5), 281 (45), 230 (1), 229 (12), 178 (11). 130 (8), 129 (100), 128 (1), 103 (12), 77 (11).

HRMS (EI) calc. $[C_9H_5I_2N_3]^+$: 408.8573): 408.8567 (M^+).

Synthesis of ethyl 4-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzoate (58):



To a solution of 2,4-diiodo-6-phenyl-1,3,5-triazine (**63**, 820 mg, 2 mmol) and $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol) in THF (20 mL) in a dry and argon-flushed Schlenk-flask was added dropwise a solution of (4-(ethoxycarbonyl)phenyl)zinc iodide (0.72 M in THF, 3.4 mL,

2.4 mmol) in THF prepared according to literature procedure[299] at −10 °C followed by continously stirring for 2 h. After stirring for 13 h at 25 °C, the reaction mixture was quenched with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/EtOAc = 20:1) afforded **58** (440 mg, 51%) as a white solid.

m. p.: 172.3-174.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.68-8.57 (m, 4H), 8.22-8.17 (m, 2H), 7.68-7.51 (m, 3H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H),

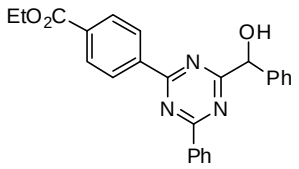
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.2, 170.1, 165.9, 142.7, 138.0, 134.6, 133.9, 133.6, 129.8, 129.4, 129.2, 128.8, 61.4, 14.3.

IR (Diamond-ATR, neat) ν (cm^{-1}): 3054 (VW), 2981 (VW), 1709 (S), 1482 (VS), 1353 (M), 1271 (S), 1221 (S), 1069 (M), 1018 (W), 827 (W), 797 (M), 754 (S), 688 (M), 647 (W).

MS (EI, 70 eV) *m/z* (%): 432 (100), 322 (6), 217 (13), 145 (1).

HRMS (ESI) calc. $[C_{18}H_{14}IN_3O_2 + H]^+$: 432.0209): 432.0200 ($[M+H]^+$).

Synthesis of 4-[4-(hydroxy-phenyl-methyl)-6-phenyl-[1,3,5]triazin-2-yl]-benzoic acid ethyl ester (62a):



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with iodo-1,3,5-triazine derivative **58** (1 mmol, 431 mg) in THF (1 mL) followed by dropwise addition of a solution of OctMgBr (1.1 mmol, 1.1 mL, 1 M in THF) at −78 °C and stirring for 10 min. After addition of benzaldehyde (**61a**, 117 mg, 1.1 mmol), the reaction mixture was allowed to warm to 25 °C and continuously stirred for 1 h. The mixture was quenched with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/EtOAc = 10:1) afforded **62a** (309 mg, 75%) as a white solid.

m. p.:144.7-146.3 °C.

[299] A. Krasoviskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.71 (d, *J* = 8.3 Hz, 2H), 8.67 (d, *J* = 7.1 Hz, 2H), 8.22 (d, *J* = 8.3 Hz, 2H), 7.74-7.54 (m, 5H), 7.47-7.25 (m, 3H), 5.97 (s, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H).

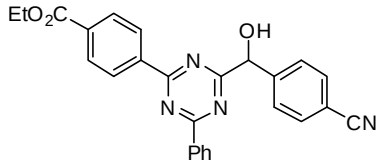
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.7, 171.6, 170.6, 166.0, 140.9, 139.1, 134.9, 134.2, 133.3, 129.8, 129.2, 128.9, 128.8, 128.5, 128.1, 126.7, 75.2, 61.4, 14.4.

IR (Diamond-ATR, neat) ν (cm^{-1}): 3467 (M), 3063 (W), 2982 (W), 2929 (W), 1717 (S), 1520 (S), 1372 (S), 1275 (S), 1104 (M), 909 (M), 760 (M), 731 (S), 698 (M).

MS (EI, 70 eV) *m/z* (%): 411 (M^+, 67), 410 (17), 395 (28). 366 (11), 334 (28), 305 (22), 232 (12), 219 (15), 130 (16), 105 (100).

HRMS (EI) calc. $[C_{25}H_{21}N_3O_3]^+$: 411.1583): 411.1573 (M^+).

Synthesis of ethyl 4-{4-[(4-cyanophenyl)(hydroxy)methyl]-6-phenyl-1,3,5-triazin-2-yl} benzoate (62b):



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with iodo-1,3,5-triazine derivative **58** (1 mmol, 431 mg) in THF (1 mL) followed by dropwise addition of a solution of OctMgBr (1.1 mmol, 1.1 mL, 1 M in THF) at −78 °C and stirring for 10 min. After addition of 4-cyanobenzaldehyde (**61b**, 144 mg, 1.1 mmol), the reaction mixture was allowed to warm to 25 °C and continuously stirred for 1 h. The mixture was quenched with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/EtOAc = 9:1) afforded **62b** (275 mg, 75%) as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.54-8.71 (m, 4H), 8.20 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.48-7.72 (m, 5H), 5.97 (d, *J* = 3.7 Hz, 1H), 4.99 (d, *J* = 4.5 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

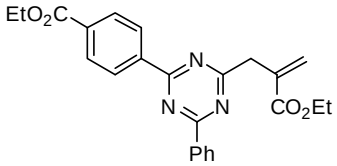
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.5, 171.8, 170.8, 165.9, 146.0, 138.7, 134.6, 134.5, 133.6, 132.2, 129.9, 129.2, 129.0, 128.9, 127.5, 118.7, 112.0, 74.3, 61.5, 14.3.

IR (Diamond-ATR, neat) ν (cm^{-1}): 3454 (VW), 3068 (VW), 2960 (W), 2932 (W), 2872 (VW), 2230 (W), 1716 (S), 1694 (M), 1580 (M), 1514 (VS), 1364 (S), 1270 (VS), 1220 (M), 1102 (S), 1018 (S), 976 (M), 836 (S), 750 (VS), 688 (VS), 650 (S).

MS (EI, 70 eV) *m/z* (%): 437 (33), 436 (M^+, 100), 434 (34), 420 (29), 419 (31), 334 (34), 305 (20), 130 (50), 129 (25), 104 (39), 103 (38), 102 (28).

HRMS (EI) calc. $[C_{26}H_{20}N_4O_3]^+$: 436.1535): 436.1523 (M^+).

Synthesis of ethyl 4-{4-[2-(ethoxycarbonyl)prop-2-en-1-yl]-6-phenyl-1,3,5-triazin-2-yl} benzoate (62c):



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with iodo-1,3,5-triazine derivative **58** (1 mmol, 431 mg) in THF (1 mL) followed by dropwise addition of a solution of OctMgBr (1.1 mmol, 1.1 mL, 1 M in THF) at −78 °C and stirring for 10 min. After addition of CuCN·2LiCl[300] (0.2 mmol, 0.2 mL, 1 M in THF) at −78 °C and stirring for 10 min, ethyl 2-(bromomethyl)acrylate (**61c**, 213 mg, 1.1 mmol) was added dropwise. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 4 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/EtOAc = 9:1) afforded **62c** (296 mg, 71%) as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.50-8.74 (m, 4H), 8.17 (d, *J* = 8.4 Hz, 2H), 7.48-7.66 (m, 3H), 6.40 (d, *J* = 1.0 Hz, 1H), 5.75 (d, *J* = 1.0 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 2.64 (s, 2H), 1.36-1.47 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.7, 172.2, 171.7, 170.7, 167.9, 166.1, 141.5, 139.7, 135.5, 134.5, 133.9, 132.9, 129.8, 128.9, 128.7, 61.6, 61.3, 41.8, 15.3, 14.3.

IR (Diamond-ATR, neat) ν (cm^{-1}): 2982 (W), 2938 (W), 1716 (S), 1580 (W), 1516 (VS), 1450 (M), 1362 (S), 1272 (S), 1242 (S), 1160 (M), 1098 (S), 1018 (S), 834 (S), 774 (S), 686 (VS), 650 (S).

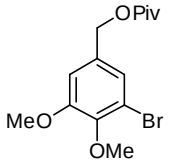
MS (EI, 70 eV) *m/z* (%): 418 (33), 417 (M^+, 77), 388 (40), 372 (36), 345 (67), 344 (100), 104 (37), 103 (28), 94 (23), 71 (33), 57 (46), 55 (24), 43 (32).

HRMS (EI) calc. $[C_{24}H_{23}N_3O_4]^+$: 417.1689): 417.1690 (M^+).

[300] V. del Amo, S. R. Dubbaka, A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 7838.

4.2 Direct Magnesium Insertion in the Presence of $ZnCl_2$ and LiCl

Synthesis of 3-bromo-4,5-dimethoxybenzyl pivalate (66):



To a solution of 3-bromo-4,5-dimethoxy-benzaldehyde (0.444 mol, 108.8 g) in methanol (900 ml) at 0 °C was added sodium borohydride (0.444 mol, 16.78 g) portionwise. The mixture was kept at 0 °C for 30 min. The solvent was removed and the residue was poured on ice (300 g). Thereafter, the mixture was neutralized with 2 M HCl, the aqueous layer was extracted with ethyl acetate (3 x 150 ml) and dried over Na_2SO_4. The residue was dissolved in THF (800 ml) and sodium hydride (0.488 mol, 19.5 g) was added portionwise at 0 °C. The mixture was kept at the same temperature for 10 min, followed by dropwise addition of pivaloyl chloride (0.488 mol, 60 mL) in THF (100 ml) at 0 °C. The reaction mixture was allowed to warm to 25 °C and further stirred for 2 h, followed by addition of saturated $NaHCO_3$ aqueous (150 ml) and was extracted with diethyl ether (3 x 150 ml). The combined organic layers were washed with brine (50 ml) and dried over Na_2SO_4. The solvent was removed and the residue was subjected to flash chromatography (EtOAc:pentane = 1:9) to give **66** as a colorless oil (119.56 g, 82%).

^{1}H-NMR(300 MHz, $CDCl_3$): δ (ppm):7.13 (s, 1H), 6.86 (s, 1H), 5.04 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 1.26 (s, 9H).

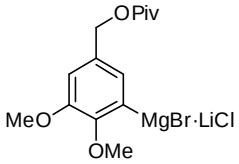
^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm):178.0, 153.6, 146.0, 133.6, 123.8, 117.5, 111.0, 65.0, 60.4, 56.0, 38.7, 27.1.

MS (70 eV, EI): *m/z* (%):330 (34) [M+], 332 (33) [M+], 231 (100), 229 (95), 57 (51).

IR (ATR): $\tilde{\nu}$ (cm^{-1}): 2972, 2936, 1809, 1728, 1570, 1491, 1462, 1278, 1140, 1047, 1001, 844, 821.

HRMS (EI): ($C_{14}H_{19}BrO_4$) calc. 330.0467) 300.0466 (M^+).

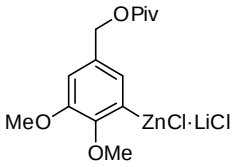
Synthesis of 5-{[(2,2-dimethylpropanoyl)oxy]methyl}-2,3-dimethoxyphenylmagnesium bromide (65):



A dry and argon-flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (5.30 g, 125 mmol) and heated with a heat gun under high vacuum

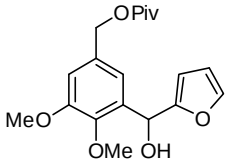
(20 min). Magnesium turnings (6.08 g, 250 mmol) and THF (250 mL) were added and the magnesium was activated with *i*Bu_2AlH (0.14 mL, 114 mg, 0.8 mmol). After 5 min of stirring, the suspension was cooled to –20 °C and 3-bromo-4,5- dimethoxybenzyl pivalate (**66**, 33.10 g, 100 mmol) was added slowly, so that the reaction temperature is kept below –15 °C. After complete addition, the reaction mixture was stirred for additional 1 h at –20 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed *Schlenk*-flask and the yield of the magnesium reagent was determined by iodometric titration (270 mL, 0.33 M, 89.1 mmol, 89 %).

Synthesis of 5-{[(2,2-dimethylpropanoyl)oxy]methyl}-2,3-dimethoxyphenylzinc chloride (67):



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with LiCl (2.54 mg, 60 mmol) and was heated under high vacuum for 5 min. $ZnCl_2$ (4.44 g, 44 mmol) was added and was similarly heated under high vacuum. Magnesium powder (1.56 g, 62 mmol) and 60 mL THF were added and the magnesium powder was activated with *i*Bu_2AlH (4 mL, 0.1 M in THF, 0.4 mmol). After 5 min of stirring, the aryl 3-bromo-4,5-dimethoxybenzyl pivalate (40 mmol, 13. 2 g) was added dropwise in 2 h at 0 °C. The reaction mixture was then cannulated to a new *Schlenk*-flask for the reaction with an electrophile and the yield of the zinc reagent was determined by iodometric titration (77.5 mL, 0.47M, 18.1 mmol, 90%).

Synthesis of 3-[2-furyl(hydroxy)methyl]-4,5-dimethoxybenzyl pivalate (68a):



To a solution of furfural (20 mmol, 1.92 g) in THF (20 mL) at 0 °C the magnesium reagent **65** (20 mmol, 61 mL, 0.33M in THF) was added dropwise. The reaction mixture was stirred for 30 min at 0 °C, followed by addition of saturated NH_4Cl (100 mL) and 2M HCl (10 mL) and extraction with EtOAc (3x100 mL). The combined organic layers were washed with brine

(20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (pentane/EtOAc = 4 : 1) furnished **68a** as a pale yellow oil (4.92 g, 71%).

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.33 (d, *J*=1.4Hz, 1H), 7.01 (d, *J*=2.0Hz, 1H), 6.84 (d, *J*=2.0Hz, 1H), 6.28 (dd, *J*=3.3Hz, 1.8Hz, 1H), 6.13 (d, *J*=3.1Hz, 1H), 6.03 (s, 1H), 5.04 (s, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 1.21 (s, 9H).

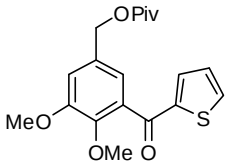
^{13}C NMR (150 MHz, $CDCl_3$,) δ (ppm):178.2, 155.9, 152.2, 145.9, 142.0, 134.6, 132.3, 118.7, 111.3, 110.1, 106.7, 65.8, 65.7, 60.7, 55.6, 38.7, 27.0.

IR (ATR) υ (cm^{-1}) : 3469, 2972, 2939, 1723, 1594, 1492, 1463, 1282, 1143, 1032, 1005, 910, 728.

MS (70 eV, EI) ***m/z*** **(%)**: 349 (20), 348 (M^+, 100), 248 (14), 247 (96), 246 (33), 232 (13), 231 (85), 217 (37), 215 (42), 178 (26), 163 (60).

HRMS (EI): *m/z* calc. for $C_{19}H_{24}O_6$ (348.1573): 348.1569 (M^+).

Synthesis of 3,4-dimethoxy-5-(2-thienylcarbonyl)benzyl pivalate (68b):



To a CuCN·2LiCl solution (2 mmol, 2 mL, 1M in THF), the arylmagnesium reagent **65** (20 mmol, 61 mL, 0.33M in THF) was added dropwise at –40 °C, followed by stirring for 10 min. Subsequently, the reaction mixture was cannulated dropwise to a solution of 2-thiophencarbonyl chloride (20 mmol, 2.93 g) in 20 ml THF at –40 °C. The mixture was stirred for 10 min at the same temperature, allowed to warm to 25 °C and continuously stirred for 30 min, followed by addition of saturated NH_4Cl (100 mL) and extraction with EtOAc (3x 100 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (pentane/EtOAc = 9 : 1) furnished **68b** as a pale yellow oil (5.02, 70%).

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.65 (d, *J*=4.9Hz, 1H), 7.41 (d, *J*=3.1Hz, 1H), 7.03 (t, *J*=4.0Hz, 1H), 6.98 (s, 1H), 6.91 (s, 1H), 5.03 (s, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 1.17 (s, 9H).

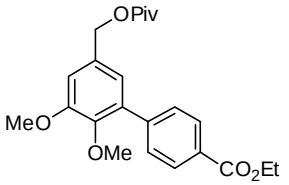
^{13}C NMR (150 MHz, $CDCl_3$,) δ (ppm): 187.3, 177.9, 152.7, 146.2, 144.2, 135.5, 134.8, 133.8, 132.2, 127.9, 119.3, 113.6, 65.2, 61.8, 55.8, 38.6, 27.0.

IR (ATR) υ (cm^{-1}) : 2972, 2938, 2254, 1725, 1646, 1481, 1410, 1270, 1143, 1048, 1001, 910, 725.

MS (70 eV, EI) ***m/z*** **(%)**: 363 (9), 362 (M^+, 35), 262 (19), 261 (100), 163 (17), 110 (24).

HRMS (EI): *m/z* calc. for $C_{19}H_{22}O_5S$ (362.1188): 362.1176 (M^+).

Synthesis of ethyl 5'-{[(2,2-dimethylpropanoyl)oxy]methyl}-2',3'-dimethoxybiphenyl-4-carboxylate (68c):



$Pd(PPh_3)_4$ (462 mg, 2 mol%) and ethyl 4-iodobenzoate (5.52 g, 20 mmol) in THF (40 mL) were added to the freshly prepared zinc reagent **67** (20 mmol, 42.6 mL, 0.47M in THF) and the mixture was stirred 1 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution (100 mL) extracted with EtOAc (3x 100 mL). The combined organic phases were washed with sat. NaCl solution (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica gel, pentane/EtOAc = 95:5) to give **68c** as a yellow oil (6.92 g, 87%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.07 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.1, 2H), 6.90 (s, 1H), 5.08 (s, 2H), 4.37 (q, J = 7.0 Hz, 2H), 3.88 (s, 3H), 3.55 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H), 1.22 (s, 9H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 178.1, 166.4, 153.0, 146.2, 142.5, 134.6, 132.5, 129.3, 129.1, 129.0, 121.5, 111.4, 65.6, 60.8, 60.6, 55.9, 38.7, 27.1, 14.3.

IR (ATR) ν ~ (cm^{-1}): 2974, 2937, 1716, 1588, 1481, 1463, 1270, 1138, 1101, 1020, 1006, 842.

MS (70 eV, EI) *m/z* **(%)**: 400 (56) [M^+], 299 (100), 300 (16).

HRMS (EI): *m/z* calc. for $C_{23}H_{28}O_6$ (400.1886): 400.1875 (M^+).

4.3 Cycloalkylzincs via LiCl-Mediated Direct Zinc Insertion and their Diastereoselective Csp^2-Csp^3 Cross-Couplings

Experimental details of compounds (**69**, **72a–e**) and **XYZ-coordinates** of calculated structures (**eq75a–f**, **ax75a–f**, **eq77a–f**, **ax77a–f**, **trans–74c** and **cis–74c**) are given in supplementary material of the following report:

T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. Gschwind, H. Zipse, P. Knochel, *Nature Chem*. **2010**, *2*, 125.

(http://www.nature.com/nchem/journal/v2/n2/extref/nchem.505-s1.pdf)

DFT calculations

Prior to the DFT calculations, all structures have been pre-optimized by a semiempirical equilibrium conformer search at the PM3 level using the Spartan'08 computational package[301]. In order to validate the semi-empirical search method, a library of possible conformational isomers of 3-methylcyclohexylzinc chloride and 3-methylcyclohexyl-bis(trimethylphosphine)phenyl-palladium were subjected to single point DFT calculations (B3LYP/631SVP). The energetically lowest conformer of the semi-empirical search turned out to be also the energetically lowest conformer determined by the DFT single point calculations. Thus, these pre-optimized complexes were used as guesses for the DFT-based geometry optimizations.

Computational details: DFT calculations were carried out using the Gaussian03 Rev.B.04 program package[302] with the nonlocal hybrid B3LYP exchange-correlation functionals[303]. The basis set denoted as 631SVP consists of the Ahlrich def2-SVP all electron basis set[304] for Zn atoms, all electron and ECP for Pd atoms and the 6-31G(d,p) basis set[305] for other atoms. Energy minimizations followed by harmonic vibrational calculations were performed at this level of theory. The absence of imaginary frequencies proved that energy-minimized stationary points correspond well to the local minima of the energy landscape. Vibrational frequencies were also used in determining the isomers' relative Gibbs energies (ΔG) and relative zero-point corrected electronic energies.

Calculated relative energies of organometallic conformers with an axial substituent

As a result of preliminary calculations, the axial-substituted conformers comprising the lowest energy cannot be guessed *a priori*. Therefore, we performed DFTcalculations on

[301] Spartan'08 version 1.1.1, Wavefunction, Inc., 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612, USA, **2008**.

[302] Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.

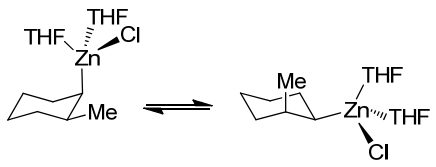
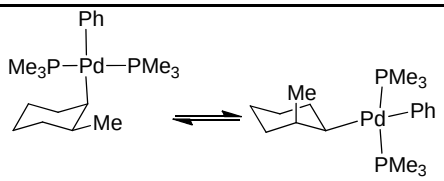
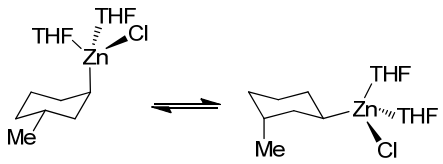
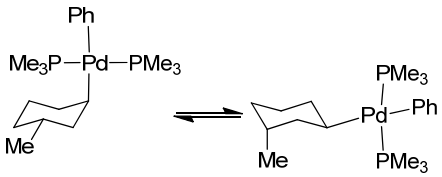
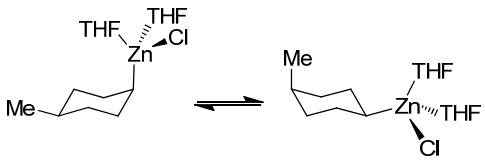
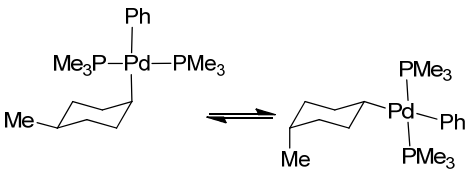
[303] a) R. G. Parr, W. Yang, *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, **1989**; b) T. Ziegler, *Chem. Rev.* **1991**, *91*, 651; c) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; d) A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098.

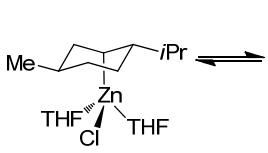
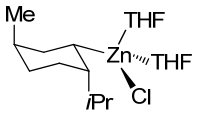
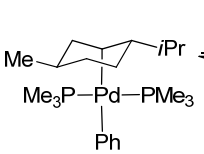
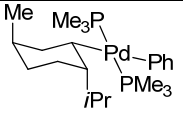
[304] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.

[305] a) P. C. Hariharan, J. A. Pople, *Theoret. Chimica Acta* **1973**, *28*, 213; b) M. M. Francl, W. J. Petro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. DeFrees, J. A. Pople, *J. Chem. Phys.* **1982**, *77*, 3654; c) V. A. Rassolov, J. A. Pople, M. A. Ratner, T. L. Windus, *J. Chem. Phys.* **1998**, *109*, 1223.

conformational isomers of the possible diastereoisomers. During the course of our study, we found that the cycloalkylzinc chloride complexes of type **ax1-75** bearing the substituent in the equatorial and the zinc atom in the axial position are generally favored in energy (Table 18). However, the cyclohexylpalladium complexes bearing the metal-substitutent in the equatorial position are in general energetically favored, due to bulky phosphine-ligands on the Pd center resulting in repulsive interactions. Furthermore, the difference in energy of the conformers of **ax1-77** and **ax2-77** are higher (Table 18). In contrast, the two conformers of (-)-menthyl-phenylbis(trimethylphosphine)palladium (**ax1-77d, ax2-77d**) are energetically equal. In comparison the diasteromeric cyclohexylpalladium complex **eq-77d** bearing the Pd-substituent in equatorial position, the structures **ax1-77d** and **ax2-77d** are equally disfavored.

Table 18. Relative energies of axial conformers of cyclohexylzinc and palladium complexes based on DFT calculations.,

Entry	Organozinc complexes	Organopalladium complexes
	$\Delta G_{298,(ax2\text{-}ax1)}$, $\Delta E_{0,(ax2\text{-}ax1)}$ [kcal·mol^{-1}]^a	$\Delta G_{298,(ax2\text{-}ax1)}$, $\Delta E_{0,(ax2\text{-}ax1)}$ [kcal·mol^{-1}]^a
		
	ax1–75b **ax2–75b**	**ax1–77b** **ax2–77b**
1	1.61, 3.03	–7.18, –6.68
		
	ax1–75c **ax2–75c**	**ax1–77c** **ax2–77c**
2	2.83, 2.26	–5.84, –5.41
		
	ax1–75a **ax2–75a**	**ax1–77a** **ax2–77a**
3	1.96, 2.50	–7.79, –7.60

				
	ax1–75d	**ax2–75d**	**ax1–77d**	**ax2–77d**
4	6.23, 6.67		–0.41, –0.55	

[a] Calculated energetic difference (B3LYP/631SVP// B3LYP/631SVP) between the thermodynamically lowest conformers of the two diastereoisomers.

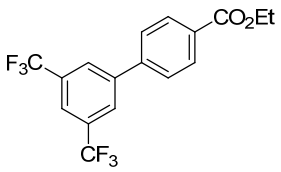
Table 19. Electronic, zero-point-corrected electronic and Gibbs free energies of cyclohexylzinc and palladium complexes based on DFT calculations (B3LYP/631SVP//B3LYP/631SVP).

Entry	Compound	E_e (a.u.)	E_0 (a.u.)	G_{298} (a.u.)
1	**ax1-75a**	-2978.98681821	-2978.56069400	-2978.61869100
2	**ax2-75a**	-2978.98300572	-2978.55671000	-2978.61556600
3	**eq-75a**	-2978.98680215	-2978.56075900	-2978.61950200
4	**ax1-75b**	-2978.98629663	-2978.55977000	-2978.61579600
5	**ax2-75b**	-2978.98146033	-2978.55494700	-2978.61323800
6	**eq-75b**	-2978.98685374	-2978.56065100	-2978.61785900
7	**ax1-75c**	-2978.98672192	-2978.56060600	-2978.61845100
8	**ax2-75c**	-2978.98304348	-2978.55699800	-2978.61394900
9	**eq-75c**	-2978.98650967	-2978.56044600	-2978.61953400
10	**ax1-75d**	-3096.93038388	-3096.41981900	-3096.48286700
11	**ax2-75d**	-3096.91999909	-3096.40919600	-3096.47294500
12	**eq-75d**	-3096.93100331	-3096.42039400	-3096.48409400
13	***trans*-75e**	-3018.29133235	-3017.83794800	-3017.89894300
14	***cis*-75e**	-3018.29189630	-3017.83811100	-3017.89826100
15	**ax-75f**	-2939.66938288	-2939.27097900	-2939.32643600
16	**eq75f**	-2939.66927170	-2939.27099900	-2939.32752200
17	**tw75f**	-2939.65847035	-2939.26021600	-2939.31725900
18	**ax1-75a**	-1556.40869968	-1555.90030400	-1555.96155200
19	**ax2-75a**	-1556.42010018	-1555.91240800	-1555.97396200
20	**eq-75a**	-1556.42409863	-1555.91618200	-1555.97728100
21	**ax1-75b**	-1556.40524548	-1555.89611500	-1555.95495300
22	**ax2-75b**	-1556.41545863	-1555.90675900	-1555.96640000
23	**eq-75b**	-1556.42274985	-1555.91448200	-1555.97440300
24	**ax1-75c**	-1556.41187676	-1555.90337300	-1555.96281900
25	**ax2-75c**	-1556.42034803	-1555.91199000	-1555.97211900

26	**eq-75c**	-1556.42416938	-1555.91612200	-1555.97671500
27	**ax1-75d**	-1674.35033933	-1673.75643700	-1673.82117600
28	**ax2-75d**	-1674.35081335	-1673.75731700	-1673.82182800
29	**eq-75d**	-1674.36665735	-1673.77338700	-1673.83751000
30	***trans*-75e**	-1595.72781345	-1595.19208100	-1595.25502000
31	***cis*-75e**	-1595.71993391	-1595.18407300	-1595.24618800
32	**ax-75f**	-1517.09119212	-1516.61028100	-1516.66885700
33	**eq75f**	-1517.10667215	-1516.62655000	-1516.68591300
34	**tw75f**	-1517.09709084	-1516.61661100	-1516.67550300

4.4 One-Step Synthesis of Functionalized Organoborates via Accelerated Direct Metal Insertion in the Presence of $B(OBu)_3$

Synthesis of ethyl 3',5'-bis(trifluoromethyl)biphenyl-4-carboxylate (86a):



According to **TP9**, 3,5-di(trifluoromethyl)bromobenzene (**79b**, 586 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 15 min) leading to a THF solution of the diarylborate **84b**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with ethyl 4-iodobenzoate (**85a**, 1.6 mmol, 442 mg), $Pd(PPh_3)_4$ (4 mol%, 93 mg), and Cs_2CO_3 (652 mg, 2 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 2 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/ EtOAc = 98:2) affording **86a** as white solid (527 mg, 91%).

m.p.: 98.4-99.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.19 (d, *J*=8.6Hz, 2H), 8.05 (s, 1H), 7.91 (s, 2H), 7.69 (d, *J*=8.6Hz, 2H), 4.44 (t, *J*=7.1Hz, 2H), 1.44 (q, *J*=7.1Hz, 3H).

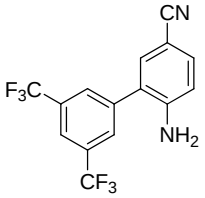
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.0, 142.2, 132.4 (q, *J*=33.4Hz), 130.9, 130.5, 130.4, 127.2-127.7 (m), 127.2, 123.5 (q, *J*=272.9Hz), 121.5-122.0 (m), 61.3, 14.3.

MS (70 eV, EI) *m/z* (%): 362 (M^+, 23), 334 (40), 318 (17), 317 (100), 269 (27), 220 (13).

IR (ATR) υ (cm^{-1}): 3080, 2994, 1714, 1610, 1466, 1382, 1370, 1278, 1258, 1170, 1114, 1054, 896, 772, 704.

HRMS (EI): *m/z* calc. for **$C_{17}H_{12}F_6O_2$** (362.0741): 362.0711 (M^+).

Synthesis of 6-amino-3',5'-bis(trifluoromethyl)biphenyl-3-carbonitrile (86b):



According to **TP9**, 3,5-di(trifluoromethyl)bromobenzene (**79b**, 586 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 15 min) leading to a THF solution of the diarylborate **84b**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 4-amino-3-iodobenzonitrile (**85b**, 1.6 mmol, 391 mg), $Pd(PPh_3)_4$ (4 mol%, 93 mg), and Cs_2CO_3 (652 mg, 2 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 2 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/ EtOAc = 9:1) affording **86b** as white solid (460 mg, 87%).

m.p.: 159.6-161.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.95 (s, 1H), 7.92 (s, 2H), 7.50 (dd, *J*=8.4Hz, 1.9Hz, 1H), 7.41 (d, *J*=1.9Hz, 1H), 6.83 (d, *J*=8.4Hz, 1H), 4.19 (br s, 2H).

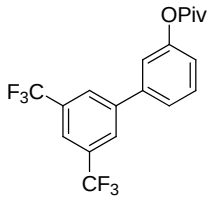
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 146.92, 138.94, 134.06, 133.39, 132.35 (q, *J*=33.7Hz), 128.83 (m), 128.7, 123.66, 121.67 (m), 118.79, 115.41, 100.93.

MS (70 eV, EI) *m/z* (%): 331 (15), 330 (M^+, 100), 309 (23), 241 (33).

IR (ATR) υ (cm^{-1}): 3392, 2216, 1630, 1606, 1504, 1378, 1322, 1280, 1254, 1188, 1170, 1130, 1108, 848, 818, 682.

HRMS (EI): *m/z* calc. for **$C_{15}H_8F_6N_2$** (330.0592): 330.0595 (M^+).

Synthesis of 3',5'-bis(trifluoromethyl)biphenyl-3-yl 2,2-dimethylpropanoate (86c):



According to **TP9**, 3,5-di(trifluoromethyl)bromobenzene (**79b**, 586 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 15 min) leading to a THF solution of the diarylborate **84b**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 3-bromophenyl 2,2-dimethylpropanoate (**85c**, 1.6 mmol, 411 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.3 g, 4 mmol) in EtOH/DMF (5 mL, 4:1) followed by stirring at 65 °C for 12 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 95:5) affording **86c** as pale yellow (493 mg, 79%).

m.p.: 157.7-159.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.87 (s, 1H), 7.84 (s, 2H), 7.31 (d, *J*=8.2Hz, 1H), 6.90-7.00 (m, 2H), 6.77 (dd, *J*=8.0Hz, 1.1Hz, 1H), 0.85 (s, 9H).

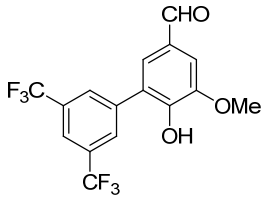
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 216.7, 152.0, 142.6, 136.2, 131.6 (q, *J*=29.5Hz), 129.9, 129.7 (m), 128.8, 124.6, 121.8 (m), 116.4, 45.3, 27.1.

MS (70 eV, EI) *m/z* (%): 390 (M^+, 5), 334 (14), 333 (100), 49 (12).

IR (ATR) υ (cm^{-1}): 3328, 2980, 2362, 2342, 1672, 1580, 1458, 1382, 1276, 1172, 1128, 1116, 1098, 966, 904, 790, 748, 708, 684.

HRMS (EI): *m/z* calc. for **$C_{19}H_{16}F_6O_2$** (390.1054): 390.1031 (M^+).

Synthesis of 6-hydroxy-5-methoxy-3',5'-bis(trifluoromethyl)biphenyl-3-carbaldehyde (86d):



According to **TP9**, 3,5-di(trifluoromethyl)bromobenzene (**79b**, 586 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 15 min) leading to a THF solution of the diarylborate **84b**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 5-bromovanilline (**85d**, 1.6 mmol, 368 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.3 g, 4 mmol) in EtOH/DMF (5 mL, 4:1) followed by stirring at 65 °C for 12 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 8:2) affording **86d** as pale yellow (483 mg, 83%).

m.p.: >275 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.9 (s, 1H), 8.1 (s, 2H), 7.9 (s, 1H), 7.6 (s, 1H), 7.5 (s, 1H), 4.1 (s, 3H).

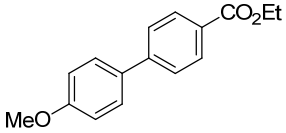
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 190.5, 157.5, 148.7, 147.6, 138.3, 131.7 (q, *J*=33.4Hz), 129.7, 129.1, 128.4, 127.5 (m), 121.5 (m), 108.8, 56.6.

MS (70 eV, EI) *m/z* (%): 364 (M^+, 5), 228 (8), 88 (4), 61 (12), 45 (13), 43 (100).

IR (ATR) υ (cm^{-1}): 3294, 2970, 2360, 1740, 1672, 1500, 1468, 1382, 1362, 1294, 1272, 1180, 1152, 1118, 898, 864, 844, 750, 710, 682.

HRMS (EI): *m/z* calc. for **$C_{16}H_{10}F_6O_3$** (364.0534): 364.0522 (M^+).

Synthesis of ethyl 4'-methoxybiphenyl-4-carboxylate (86e):



According to **TP9**, 4-bromoanisole (**79c**, 374 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 1 h) leading to a THF solution of the diarylborate **84c**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with ethyl 4-iodobenzoate (**85a**, 1.6 mmol, 442 mg), $PdCl_2$ (4 mol%, 14 mg), and K_3PO_4 (848 mg, 4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 2 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The

crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 9:1) affording **86e** as white solid (394 mg, 96%).

m.p.: 104.5-105.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.1 (d, *J*=8.6Hz, 2H), 7.6 (d, *J*=8.6Hz, 2H), 7.6 (d, *J*=8.9Hz, 2H), 7.0 (d, *J* =8.8Hz, 2H), 4.4 (q, *J*=7.2Hz, 2H), 3.9 (s, 3H), 1.4 (t, 3H).

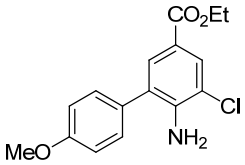
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.5, 159.8, 145.1, 132.4, 130.0, 128.6, 128.3, 126.4, 114.3, 60.9, 55.3, 14.4.

MS (70 eV, EI) *m/z* (%): 257 (15), 256 (100), 228 (25), 212 (11), 211 (71), 183 (9), 168 (10), 139 (15), 85 (15), 71 (23), 57 (29), 55 (10).

IR (ATR) υ (cm^{-1}): 2994, 2904, 2838, 2548, 1704, 1600, 1530, 1494, 1472, 1290, 1270, 1252, 1198, 1108, 1036, 828, 770, 718.

HRMS (EI): *m/z* calc. for **$C_{16}H_{16}O_3$** (256.1099): 256.1090 (M^+).

Synthesis of ethyl 6-amino-5-chloro-4'-methoxybiphenyl-3-carboxylate (86f):



According to **TP9**, 4-bromoanisole (**79c**, 374 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 1 h) leading to a THF solution of the diarylborate **84c**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with ethyl 4-amino-3-chloro-5-iodobenzoate (**85e**, 1.6 mmol, 521 mg), $PdCl_2$ (4 mol%, 14 mg), and K_3PO_4 (848 mg, 4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 2 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 9:1) affording **86f** as brown oil (454 mg, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.96 (d, *J*=2.1Hz, 1H), 7.71 (d, *J*=1.9Hz, 1H), 7.36 (d, *J*=8.8Hz, 2H), 7.01 (d, *J*=8.8Hz, 2H), 4.33 (q, *J*=7.1Hz, 2H), 3.86 (s, 3H), 1.37 (t, *J*=7.2Hz, 3H).

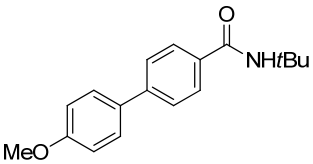
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.9, 159.4, 144.7, 130.5, 130.1, 127.3, 127.2, 120.1, 118.5, 118.5, 114.6, 60.7, 55.4, 14.4.

MS (70 eV, EI) *m/z* (%): 307 (32), 306 (18), 305 (M^+, 100), 291 (31), 277 (23), 262 (25), 261 (12), 260 (67).

IR (ATR) υ (cm^{-1}): 3486, 3370, 2978, 2944, 2916, 2846, 2836, 1702, 1608, 1512, 1474, 1424, 1314, 1238, 1220, 1112, 1024, 914, 836, 816, 764, 690.

HRMS (EI): *m/z* calc. for **$C_{16}H_{16}ClNO_3$** (305.0819): 305.0807 (M^+).

Synthesis of *N-tert*-butyl-4'-methoxybiphenyl-4-carboxamide (86g):



According to **TP9**, 4-bromoanisole (**79c**, 374 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 1 h) leading to a THF solution of the diarylborate **84c**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 4-bromo-*N-tert*-butylbenzamide (**85f**, 1.6 mmol, 410 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.30 g, 4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 6 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 85:15) affording **86g** as white solid (358 mg, 79%).

m.p.: 160.8-161.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.78 (d, *J*=8.4Hz, 2H), 7.59 (d, *J*=8.2Hz, 2H), 7.55 (d, *J*=8.8Hz, 2H), 6.99 (d, *J*=8.8Hz, 2H), 5.99 (br s, 1H), 3.86 (s, 3H), 1.50 (s, 9H).

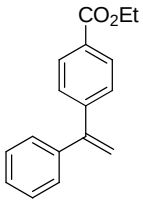
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.6, 159.7, 143.5, 133.9, 132.6, 128.2, 127.2, 126.6, 114.3, 55.4, 51.6, 28.9.

MS (70 eV, EI) *m/z* (%): 284 (12), 283 (M^+, 64), 227 (63), 212 (15), 211 (100), 168 (9).

IR (ATR) υ (cm^{-1}): 3396, 3354, 2962, 2924, 2360, 1634, 1602, 1530, 1514, 1492, 1452, 1292, 1250, 1180, 1038, 826, 770.

HRMS (EI): *m/z* calc. for **$C_{18}H_{21}NO_2$** (283.1572): 283.1572 (M^+).

Synthesis of ethyl 4-(1-phenylvinyl)benzoate (86h):



According to **TP9**, (1-bromovinyl)benzene (**79d**, 366 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 0 °C, 30 min) leading to a THF solution of the diarylborate **84d**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with ethyl 4-bromobenzoate (**85g**, 1.6 mmol, 367 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.30 g, 4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 6 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/Et_2O = 95:5) affording **86h** colorless oil (383 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.01 (d, *J*=8.7Hz, 2H), 7.40 (d, *J*=8.7Hz, 2H), 7.28-7.37 (m, 5H), 5.55 (d, *J*=1.0Hz, 1H), 5.53 (d, *J*=1.0Hz, 1H), 4.39 (q, *J*=7.1Hz, 2H), 1.40 (t, *J*=7.1Hz, 3H).

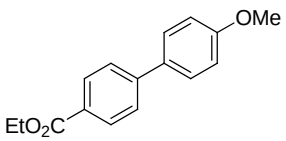
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.4, 149.3, 145.9, 140.8, 129.7, 129.5, 128.3, 128.2, 128.0, 127.8, 115.8, 60.9, 14.3.

MS (70 eV, EI) *m/z* (%): 252 (M^+, 34), 207 (39), 179 (24), 178 (30), 155 (11), 141 (12), 127 (16), 113 (20), 111 (14), 99 (25), 96 (25), 85 (60), 84 (11), 83 (24), 71 (79), 70 (16), 69 (23), 57 (100), 56 (17), 55 (27), 43 (100), 41 (21).

IR (ATR) υ (cm^{-1}): 2982, 1714, 1608, 1494, 1446, 1404, 1366, 1268, 1176, 1102, 1018, 904, 864, 774, 700.

HRMS (EI): *m/z* calc. for **$C_{17}H_{16}O_2$** (252.1150): 252.1150 (M^+).

Synthesis of ethyl 4'-methoxybiphenyl-4-carboxylate (86i):



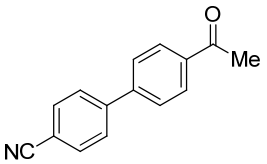
According to **TP9**, ethyl 4-bromobenzoate (**79e**, 458 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 1 h)

leading to a THF solution of the diarylborate **84e**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 4-bromoanisole (**85h**, 1.6 mmol, 299 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.3 g, 4 mmol) in EtOH/DMF (5 mL, 4:1) followed by stirring at 65 °C for 12 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 9:1) affording **86i** as white solid (340 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.1 (d, *J*=8.6Hz, 2H), 7.6 (d, *J*=8.6Hz, 2H), 7.6 (d, *J*=8.9Hz, 2H), 7.0 (d, *J* =8.8Hz, 2H), 4.4 (q, *J*=7.2Hz, 2H), 3.9 (s, 3H), 1.4 (t, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.5, 159.8, 145.1, 132.4, 130.0, 128.6, 128.3, 126.4, 114.3, 60.9, 55.3, 14.4.

Synthesis of 4'-acetylbiphenyl-4-carbonitrile (86j):



According to **TP9**, 4-bromobenzonitrile (**79f**, 364 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 1 h) leading to a THF solution of the diarylborate **84f**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 4-bromoacetophenone (**85i**, 1.6 mmol, 318 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.3 g, 4 mmol) in EtOH/DMF (5 mL, 4:1) followed by stirring at 65 °C for 12 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 9:1) affording **86j** as white solid (290 mg, 82%).

m.p.: 106.2-107.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.08 (d, *J*=8.7Hz, 2H), 7.67-7.81 (m, 6H), 2.66 (s, 3H).

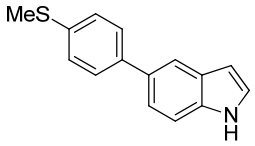
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 197.4, 144.3, 143.5, 136.9, 132.9, 129.1, 127.9, 127.4, 118.6, 111.9, 26.7.

MS (70 eV, EI) *m/z* (%): 222 (5), 221 (M^+, 19), 207 (14), 206 (100), 178 (30), 177 (18), 151 (24).

IR (ATR) υ (cm^{-1}): 3050, 2226, 1682, 1602, 1396, 1358, 1266, 1178, 1116, 1004, 956, 862, 814, 742, 714, 622.

HRMS (EI): *m/z* calc. for **$C_{15}H_{11}NO$** (221.0841): 221.0826 (M^+).

Synthesis of 5-[4-(methylsulfanyl)phenyl]-1*H*-indole (86k):



According to **TP9**, 4-bromothioanisole (**79g**, 406 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 1 h) leading to a THF solution of the diarylborate **84g**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 5-bromo-1*H*-indole (**85j**, 1.6 mmol, 314 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.30 g, 4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 6 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 85:15) affording **86k** as a pale yellow solid (352 mg, 92%).

m.p.: 82.6-83.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.16 (br s, 1H), 7.87 (s, 1H), 7.61 (d, *J*=8.6Hz, 2H), 7.43-7.48 (m, 2H), 7.37 (d, *J*=8.4Hz, 2H), 7.24 (t, *J*=2.4Hz, 1H), 6.59-6.65 (m, 1H), 2.55 (s, 3H).

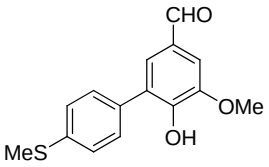
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 139.6, 136.1, 135.2, 132.7, 128.4, 127.7, 127.2, 124.9, 121.6, 118.9, 111.2, 103.0, 16.2.

MS (70 eV, EI) *m/z* (%): 240 (15), 239 (M^+, 100), 224 (54), 57 (12).

IR (ATR) υ (cm^{-1}): 3402, 3022, 2920, 1738, 1594, 1578, 1464, 1412, 1342, 1230, 1210, 1096, 1066, 1008, 970, 954, 886, 800, 722.

HRMS (EI): *m/z* calc. for **$C_{15}H_{13}NS$** (239.0769):239.0764 (M^+).

Synthesis of 6-hydroxy-5-methoxy-4'-(methylsulfanyl)biphenyl-3-carbaldehyde (86l):



According to **TP9**, 4-bromothioanisole (**79g**, 406 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 1 h) leading to a THF solution of the diarylborate **84g**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 5-bromovanillin (**85d**, 1.6 mmol, 370 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.30 g, 4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 6 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 3:1) affording **86l** as a white solid (382 mg, 87%).

m.p.: 124.9-125.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.88 (s, 1H), 7.57 (d, *J*=8.2Hz, 2H), 7.52 (d, *J*=1.9Hz, 1H), 7.42 (d, *J*=1.9Hz, 1H), 7.35 (d, *J*=8.5Hz, 2H), 6.46 (br s, 1H), 4.03 (s, 3H), 2.54 (s, 3H).

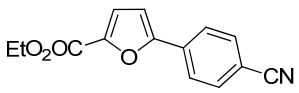
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 190.9, 148.6, 147.5, 138.3, 132.9, 129.4, 128.3, 127.1, 126.4, 108.7, 107.4, 56.5, 15.7.

MS (70 eV, EI) *m/z* (%): 276 (5), 275 (14), 274 (M^+, 100), 212 (5), 184 (6).

IR (ATR) υ (cm^{-1}): 3198, 2978, 2922, 2848, 2362, 1732, 1666, 1588, 1498, 1454, 1428, 1388, 1366, 1304, 1246, 1150, 1124, 1090, 1044, 1014, 854, 822, 732, 706, 680.

HRMS (EI): *m/z* calc. for **$C_{15}H_{14}O_3S$** (274.0664): 274.0655 (M^+).

Synthesis of ethyl 5-(4-cyanophenyl)furan-2-carboxylate (86m):



According to **TP9**, ethyl 5-bromofuran-2-carboxylate (**79h**, 438 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 1 h) leading to a THF solution of the diarylborate **84h**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 4-bromobenzonitrile (**85k**, 1.6 mmol, 291 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.3 g, 4 mmol) in

EtOH/DMF (5 mL, 4:1) followed by stirring at 65 °C for 12 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 9:1) affording **86m** as a pale yellow solid (329 mg, 80%).

m.p.: 112.6-114.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.89 (d, *J*=8.4Hz, 2H), 7.72 (d, *J*=8.4Hz, 2H), 7.27 (d, *J*=3.7Hz, 1H), 6.90 (d, *J*=3.7Hz, 1H), 4.42 (q, *J*=7.2Hz, 2H); 1.43 (t, *J*=7.2Hz, 3H).

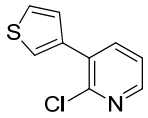
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 158.7, 155.2, 145.5, 133.6, 132.9, 125.3, 119.8, 118.8, 112.2, 109.7, 61.5, 14.6.

MS (70 eV, EI) *m/z* (%): 242 (16), 241 (M^+, 100), 213 (93), 197 (20), 196 (55), 169 (48), 141 (11), 140 (76), 113 (13).

IR (ATR) υ (cm^{-1}): 2984, 2926, 2856, 2224, 1714, 1608, 1482, 1450, 1416, 1396, 1300, 1274, 1146, 1112, 1018, 842, 804, 760.

HRMS (EI): *m/z* calc. for **$C_{14}H_{11}NO_3$** (241.0739): 241.0731 (M^+).

Synthesis of 2-chloro-3-thiophen-3-ylpyridine (86n):



According to **TP9**, 3-bromothiophene (**79i**, 326 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 30 min) leading to a THF solution of the diarylborate **84i**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 2-chloro-3-iodopyridine (**85l**, 1.6 mmol, 383 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.3 g, 4 mmol) in EtOH/DMF (5 mL, 4:1) followed by stirring at 65 °C for 1 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 9:1 with 0.5% NEt_3) affording **86n** as a pale yellow solid (290 mg, 93%).

m.p.: 53.4-54.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.37 (dd, *J*=4.9Hz, 1.9Hz, 1H), 7.76 (dd, *J*=7.6Hz, 2.0Hz, 1H), 7.54 (dd, *J*=3.0Hz, 1.3Hz, 1H), 7.38-7.46 (m, 1H), 7.26-7.37 (m, 2H).

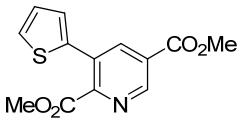
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 149.4, 148.0, 139.3, 137.3, 132.0, 128.4, 125.6, 125.1, 122.5.

MS (70 eV, EI) *m/z* (%): 197 (41), 196 (17), 195 (M^+, 100), 194 (17), 175 (19), 160 (67), 159 (59), 150 (15), 133 (15), 116 (16), 114 (16), 89 (16), 63 (14), 57 (27).

IR (ATR) υ (cm^{-1}): 3074, 3046, 2922, 2852, 1974, 1936, 1896, 1674, 1558, 1526, 1448, 1410, 1388, 1362, 1354, 1332, 1202, 1192, 1186, 1120, 1096, 1058, 864, 792, 774, 730, 642.

HRMS (EI): *m/z* calc. for **C_9H_6ClNS** (194.9909): 194.9899 (M^+).

Synthesis of dimethyl 3-thiophen-2-ylpyridine-2,5-dicarboxylate (86o):



According to **TP9**, 2-chlorothiophene (**79k**, 237 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 30 min) leading to a THF solution of the diarylborate **84k**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with dimethyl 3-chloropyridine-2,5-dicarboxylate (**85m**, 1.6 mmol, 367 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.3 g, 4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 6 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 9:1 with 0.5% NEt_3) affording **86o** as a pale yellow solid (381 mg, 86%).

m.p.: 110.9-111.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.17 (d, *J*=1.9Hz, 1H), 8.46 (d, *J*=1.9Hz, 1H), 7.48 (dd, *J*=5.1Hz, 1.2Hz, 1H), 7.21 (dd, *J*=3.6Hz, 1.2Hz, 1H), 7.13 (dd, *J*=5.0Hz, 3.6Hz, 1H), 4.01 (s, 3H), 3.90 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.7, 164.7, 152.0, 148.8, 139.3, 137.3, 129.3, 128.0, 127.8, 127.7, 127.1, 53.0, 52.8.

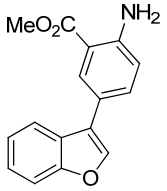
MS (70 eV, EI) *m/z* (%): 277 (M+, 57), 246 (11), 219 (56), 218 (25), 171 (21), 161 (65), 70 (15), 61 (21), 45 (15), 43 (100).

IR (ATR) υ (cm^{-1}):

3074, 2956, 1736, 1724, 1594, 1556, 1450, 1424, 1300, 1256, 1198, 1130, 1106, 1012, 766, 734.

HRMS (EI): *m/z* calc. for **$C_{13}H_{11}NO_4S$** (277.0409): 277.0405 (M^+).

Synthesis of methyl 2-amino-5-(1-benzofuran-3-yl)benzoate (86p):



According to **TP9**, 3-bromo-1-benzofuran (**79i**, 394 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 30 min) leading to a THF solution of the diarylborate **84i**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with methyl 2-amino-5-bromobenzoate (**85n**, 1.6 mmol, 368 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.3 g, 4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 6 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 4:1 with 0.5% NEt_3) affording **86p** as a white solid (359 mg, 84%).

m.p.: 86.3-87.4 °C.

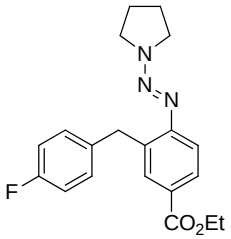
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.17 (d, *J*=2.2Hz, 1H), 7.81 (dd, *J*=4.7Hz, 2.2Hz, 1H), 7.74 (s, 1H), 7.51-7.59 (m, 2H), 7.28-7.40 (m, 2H), 6.81 (d, *J*=8.4Hz, 1H), 3.93 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 168.4, 155.7, 149.5, 140.5, 133.4, 130.0, 126.6, 124.4, 122.8, 121.5, 120.2, 120.2, 117.4, 111.7, 111.2, 51.7.

IR (ATR) υ (cm^{-1}): 3492, 3378, 2954, 1684, 1628, 1578, 1556, 1450, 1438, 1360, 1306, 1292, 1230, 1102, 1084, 826, 790, 746, 710.

HRMS (ESI): *m/z* calc. for **$C_{16}H_{14}NO_3$** (268.0974): 268.0967 ($[M+H]^+$).

Synthesis of ethyl 3-(4-fluorobenzyl)-4-(pyrrolidin-1-yldiazenyl)benzoate (86q):



According to **TP9**, 4-fluorobenzyl chloride (**79l**, 289 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 1 h) leading to a THF solution of the diarylborate **84l**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with ethyl 3-iodo-4-(pyrrolidin-1-yldiazenyl)benzoate (**85o**, 1.6 mmol, 597 mg), $Pd(PPh_3)_4$ (4 mol%, 93 mg), and K_3PO_4 (849 mg, 4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 2 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 9:1) affording **86q** as a red solid (500 mg, 88%).

m.p.: 89.5-91.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.89 (s, 1H), 7.49 (d, *J*=8.8Hz, 1H), 7.43 (d, *J*=8.3Hz, 1H), 7.19 (dd, *J*=8.7Hz, 5.4Hz, 2H), 6.93 (t, *J*=8.7Hz, 2H), 4.36 (q, *J*=7.2Hz, 2H), 4.21 (s, 2H), 3.9-4.1 (m, 2H), 3.5-3.8 (m, 2H), 2.05 (t, *J*=6.8Hz, 4H), 1.40 (t, *J*=7.2Hz, 3H).

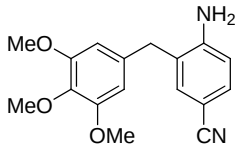
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.8, 164.7 (d, *J*=302.1Hz), 152.3, 137.3, 132.0, 130.1 (d, *J*=7.9Hz), 129.5, 128.6, 126.6, 116.2, 114.8 (d, *J*=21.0Hz), 60.7, 49.8 (br s), 36.4, 28.1 (br s), 14.4.

MS (70 eV, EI) *m/z* (%): 356 (13), 355 (M^+, 53), 310 (19), 303 (24), 285 (39), 274 (36), 247 (19), 229 (14), 211 (13), 186 (12), 185 (87), 184 (50), 183 (100), 165 (33), 70 (15).

IR (ATR) υ (cm^{-1}): 2978, 2874, 1706, 1600, 1506, 1398, 1362, 1310, 1284, 1242, 1176, 1106, 1026, 844, 766.

HRMS (ES): *m/z* calc. for **$C_{20}H_{22}FN_3O_2$** (355.1696): 355.1695 (M^+).

Synthesis of 4-amino-3-(3,4,5-trimethoxybenzyl)benzonitrile (86r):



According to **TP9**, 3,4,5-trimethoxybenzyl chloride (**79m**, 432 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 1 h) leading to a THF solution of the diarylborate **84m**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 4-amino-3-iodobenzonitrile (**85b**, 1.6 mmol, 391 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.3 g,

4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 6 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 3:2) affording **86r** as a pale yellow solid (425 mg, 89%).

m.p.: 148.3-149.8 °C.

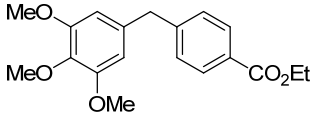
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37 (dd, *J*=8.2Hz, 1.7Hz, 1H), 7.30 (d, *J*=1.5Hz, 1H), 6.66 (d, *J*=8.2Hz, 1H), 6.36 (s, 2H), 3.86 (s, 2H), 3.84 (s, 3H), 3.80 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 153.6, 148.9, 136.9, 134.4, 133.2, 132.2, 124.6, 115.2, 105.4, 103.8, 60.8, 56.1, 56.0, 37.9.

IR (ATR) υ (cm^{-1}): 3460, 3374, 2922, 2838, 2360, 2332, 2214, 1622, 1586, 1504, 1456, 1420, 1328, 1306, 1240, 1180, 1118, 1004, 826.

HRMS (ESI): *m/z* calc. for **$C_{17}H_{19}N_2O_3$** (299.1396): 299.1389 ($[M+H]^+$).

Synthesis of ethyl 4-(3,4,5-trimethoxybenzyl)benzoate (86s):



According to **TP9**, 3,4,5-trimethoxybenzyl chloride (**79m**, 432 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 1 h) leading to a THF solution of the diarylborate **84m**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with ethyl 4-bromobenzoate (**85g**, 1.6 mmol, 367 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.3 g, 4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 6 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 4:1) affording **86s** as a yellow oil (444 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.00 (d, *J*=8.6Hz, 2H), 7.30 (d, *J*=8.6Hz, 2H), 6.40 (s, 2H), 4.39 (q, *J*=7.1Hz, 2H), 3.99 (s, 2H), 3.85 (s, 3H), 3.83 (s, 6H), 1.41 (t, *J*=7.1Hz, 3H).

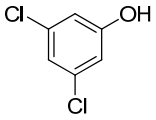
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.5, 153.3, 146.1, 136.6, 135.7, 129.8, 128.8, 128.6, 106.0, 60.8, 60.8, 56.1, 42.1, 14.3.

MS (70 eV, EI) *m/z* (%): 331 (20), 330 (M^+, 100), 315 (35), 285 (11), 71 (12), 57 (17), 43 (21).

IR (ATR) υ (cm^{-1}): 2938, 2838, 2362, 1712, 1590, 1506, 1456, 1416, 1334, 1274, 1236, 1122, 1100, 1008, 972, 782, 756, 712.

HRMS (EI): *m/z* calc. for **$C_{19}H_{22}O_5$** (330.1467): 330.1457 (M^+).

Synthesis of 3,5-dichlorophenol (87):



According to **TP9**, 1,3,5-trichlorobenzene (**79n**, 362 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 1 h) leading to a THF solution of the diarylborate **84n**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new Schlenk flask charged with aq. 2M NaOH (6 mmol, 3 mL) and H_2O_2 (30w%, 1 mL) followed by stirring for 2 h at 25 °C. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with aq. 2M HCl(10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 9:1) affording **87** as a white solid (255 mg, 78%).

m.p.: 68.6-70.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.96 (s, 1H), 6.76 (s, 2H), 5.18 (br s, 1H).

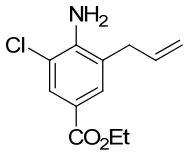
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 156.5, 135.5, 121.4, 114.5.

MS (70 eV, EI) *m/z* (%):

IR (ATR) υ (cm^{-1}): 3208, 3168, 3052, 2922, 2362, 2350, 1576, 1482, 1416, 1366, 1244, 1212, 1090, 920, 840, 802, 666.

HRMS (ESI): *m/z* calc. for **$C_6H_3Cl_2O$** (160.9561): 160.9568 ($[M-H]^-$).

Synthesis of ethyl 4-amino-3-chloro-5-prop-2-en-1-ylbenzoate (88a):



According to **TP9**, allyl bromide (**79o**, 242 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 30 min) leading to a THF solution of the diallylborate **84o**. In order to separate the organoborate from residual

magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with ethyl 4-amino-5-chloro-3-iodobenzoate (**85e**, 1.6 mmol, 521 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.3 g, 4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 6 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 9:1) affording **88a** as a yellow oil (310 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.86 , (s, 1H), 7.80 (s, 1H), 6.01-6.35 (m, 1H), 4.99-5.33 (m, 2H), 4.54 (br s, 2H), 4.34 (q, *J*=7.2Hz, 2H), 1.93 (d, *J*=6.5Hz, 2H), 1.38 (t, *J*=7.1Hz, 3H).

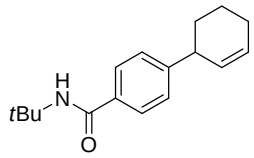
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.9, 143.9, 134.5, 130.7, 130.2, 127.7, 125.4, 118.7, 113.5, 60.7, 36.8, 14.4.

MS (70 eV, EI) *m/z* (%): 240 (12), 239 (M^+, 82), 211 (19), 196 (31), 195 (14), 194 (100), 131 (29), 130 (29), 113 (14), 85 (46), 71 (65), 70 (13), 69 (20), 57 (88), 55 (24), 43 (45).

IR (ATR) υ (cm^{-1}): cm-1, 3480, 3376, 2980, 2930, 1708, 1614, 1474, 1366, 1306, 1252, 1180, 1110, 1026, 966, 912, 766, 752, 726.

HRMS (EI): *m/z* calc. for **$C_{12}H_{14}ClNO_2$** (239.0713): 239.0711 (M^+).

Synthesis of *N-tert*-butyl-4-cyclohex-2-en-1-ylbenzamide (88b):



According to **TP9**, 3-bromocyclohexene (**79p**, 322 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 30 min) leading to a THF solution of the diallylborate **84p**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 4-bromo-*N*-*tert*-butylbenzamide (**85f**, 1.6 mmol, 410 mg), $PdCl_2$ (4 mol%, 14 mg), dppf (4 mol%, 44 mg) and Cs_2CO_3 (1.3 g, 4 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 6 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by

flash column chromatography (SiO_2, pentane/EtOAc = 9:1) affording **88b** as a yellow oil (358 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.66 (d, *J*=8.2Hz, 2H), 7.26 (d, *J*=8.3Hz, 2H), 5.82-6.02 (m, 1H), 5.59-5.74 (m, 1H), 3.35-3.52 (m, 1H), 2.03-2.18 (m, 2H), 1.52-1.84 (m, 4H), 1.47 (s, 9H).

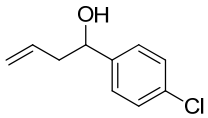
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.9, 150.1, 133.7, 129.4, 128.9, 127.8, 126.7, 51.5, 41.7, 32.4, 28.9, 24.9, 21.0.

MS (70 eV, EI) *m/z* (%): 257 (M+, 19), 202 (13), 201 (38), 199 (36), 187 (49), 186 (17), 185 (100), 184 (27), 182 (27), 131 (13), 129 (17), 128 (19), 115 (23), 91 (16), 77 (15), 57 (15), 43 (65).

IR (ATR) υ (cm^{-1}): 3288, 2928, 2360, 2342, 1738, 1636, 1540, 1448, 1364, 1314, 1228, 1218, 876, 846, 768.

HRMS (EI): *m/z* calc. for **$C_{17}H_{23}NO$** (257.1780): 257.1777 (M^+).

Synthesis of ethyl 1-(4-chlorophenyl)but-3-en-1-ol (89a):

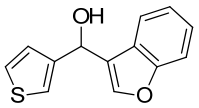


According to **TP9**, allyl bromide (**79o**, 242 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 30 min) leading to a THF solution of the diallylborate **84o**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 4-chlorobenzaldehyde (**85p**, 1.6 mmol, 225 mg) in THF (1 mL) followed by stirring for 1 h at 25 °C. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 9:1) affording **89a** as a yellow oil (262 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.26 (d, *J*=8.2Hz, 2H), 7.19 (d, *J*=8.2Hz, 2H), 5.66-5.75 (m, 1H), 5.09 (br s, 1H), 5.06-5.07 (m, 1H), 4.58 (t, J=6.6Hz, 1H), 3.05-3.15 (m, 1H), 2.40 (dd, *J*=6.58, 12.75 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 142.37, 134.01, 133.01, 128.43, 127.30, 118.41, 72.69, 43.61.

Synthesis of 1-benzofuran-3-yl(thiophen-3-yl)methanol (89b):

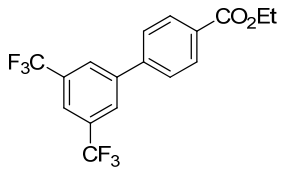


According to **TP9**, 3-bromothiophene (**79i**, 326 mg, 2 mmol) reacted with Mg (78 mg, 3.2 mmol), LiCl (93 mg, 2.2 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 25 °C, 30 min) leading to a THF solution of the heteroarylborate **84i**. In order to separate the organoborate from residual magnesium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 1-benzofuran-3-carbaldehyde (**85q**, 1.6 mmol, 234 mg) in THF (1 mL) followed by stirring for 1 h at 25 °C. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc = 9:1) affording **89b** as a yellow oil (217 mg, 59%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.86-7.89 (m, 1H), 7.75-7.79 (m, 1H), 7.50 (d, *J*=0.9Hz, 1H), 7.43 (d, *J*=1.2Hz, 1H), 7.34-7.37 (m, 2H), 6.35 (dd, *J* = 1.8Hz, 3.3Hz, 1H), 6.23 (t, *J*=3.3Hz, 1H), 6.20 (d, *J*=4.8Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 154.9, 142.8, 141.1, 137.3, 136.0, 124.7, 124.4, 124.3, 123.1, 122.7, 110.6, 108.0, 66.2.

Synthesis of ethyl 3',5'-bis(trifluoromethyl)biphenyl-4-carboxylate (86t):



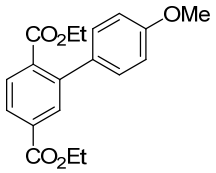
According to **TP10**, 3,5-di(trifluoromethyl)bromobenzene (**79b**, 586 mg, 2 mmol) reacted with Al (162 mg, 6 mmol), LiCl (127 mg, 3 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 65 °C, 1 h) leading to a THF solution of the diarylborate **84b**. In order to separate the organoborate from residual aluminium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with ethyl 4-iodobenzoate (**85a**, 1.6 mmol, 442 mg), $Pd(PPh_3)_4$ (4 mol%, 93 mg), and Cs_2CO_3 (652 mg, 2 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 2 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the

solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/ EtOAc = 98:2) affording **86a** as white solid (400 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.19 (d, *J*=8.6Hz, 2H), 8.05 (s, 1H), 7.91 (s, 2H), 7.69 (d, *J*=8.6Hz, 2H), 4.44 (t, *J*=7.1Hz, 2H), 1.44 (q, *J*=7.1Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.0, 142.2, 132.36 (q, *J*=33.4Hz), 130.9, 130.5, 127.35 (m), 127.2, 125.0, 121.67 (m), 121.4, 61.3, 14.3.

Synthesis of diethyl 4'-methoxybiphenyl-2,5-dicarboxylate (86u):



According to **TP10**, diethyl 2-bromobenzene-1,4-dicarboxylate (**79p**, 602 mg, 2 mmol) reacted with Al (162 mg, 6 mmol), LiCl (127 mg, 3 mmol) in the presence of $B(OBu)_3$ (230 mg, 1 mmol, 65 °C, 7 h) leading to a THF solution of the diarylborate **84b**. In order to separate the organoborate from residual aluminium, the supernatant solution was cannulated dropwise into a new argon-flushed Schlenk flask charged with 4-bromoanisole (**85h**, 1.6 mmol, 300 mg), $Pd(PPh_3)_4$ (4 mol%, 93 mg), and Cs_2CO_3 (652 mg, 2 mmol) in EtOH (4 mL) followed by stirring at 65 °C for 12 h. Subsequently, the reaction mixture was diluted with 5 mL EtOAc and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane/ EtOAc = 9:1) affording **86u** as colorless oil (378 mg, 72%).

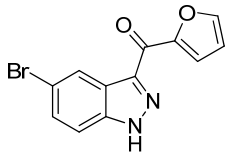
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.01-8.03 (m, 2H), 7.79-7.81 (m, 1H), 7.25-7.28 (m, 2H), 6.92-6.96 (m, 2H), 4.40 (q, *J*=7.1Hz, 2H), 4.14 (q, *J*=7.1Hz, 2H), 3.8 (s, 3H), 1.40 (t, *J*=7.1Hz, 3H), 1.07 (t, *J*=7.1Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 168.7, 166.0, 159.5, 142.1, 135.5, 133.0, 132.8, 131.8, 129.8, 129.4, 127.9, 113.9, 61.6, 61.5, 55.6, 14.5, 14.0.

5. Functionalization of Pyridines and Related Heterocycles Using Frustrated Lewis Pairs

5.1 *In situ* Metalation with TMPMgCl·LiCl in the Presence of $ZnCl_2$

Synthesis of (5-bromo-1*H*-indazol-3-yl)(2-furyl)methanone (98b):



According to **TP 11**, the zincation of *tert*-butyl 5-bromo-1*H*-indazole-1-carboxylate (**95b**; 891 mg, 3 mmol) was completed within 5 min at 25 °C using TMPMgCl (**91**; 2.75 mL, 3.3 mmol, 1.2M in THF) and $ZnCl_2$ (1.5 mL, 1.5 mmol, 1M in THF). At –40 °C, CuCN·2LiCl (3 mL, 3 mmol, 1M in THF) was added. After stirring for 10 min at –40 °C, 2-furoyl chloride (**97b**; 469 mg, 3.6 mmol) was added. The mixture was allowed to warm to 25 °C and continuously stirred for 4 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3× 20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The crude product was purified by column chromatography (pentane/EtOAc = 9:1) to give **98b** as a white solid (642 mg, 74%).

m.p.: 171.1–172.3°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.61 (br s, 1H), 8.50 (d, J=9.6 Hz, 1H), 7.74–7.70 (m, 2H), 7.60–7.56 (m, 1H), 7.33–7.28 (m, 1H), 6.61–6.57 (m, 1H).

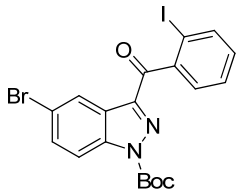
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 155.8, 145.4, 139.3, 137.4, 134.4, 132.6, 123.6, 122.2, 116.9, 116.2, 114.8, 113.0.

MS (70 eV, EI) *m/z* (%): 292 (M^+, 18), 290 (M^+, 18), 96 (5), 95 (100), 67 (3), 57 (3).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3397, 3126, 3075, 2218, 1691, 1602, 1578, 1518, 1458, 1396, 1304, 1273, 1158, 1122, 1010, 933, 884, 853, 833, 754.

HRMS (EI): *m/z* calc. for $\mathbf{C_{12}H_7{}^{79}BrN_2O_2}$ (289.9691): 289.9680 (M^+).

Synthesis of *tert*-butyl 5-bromo-3-(2-iodobenzoyl)-1*H*-indazole-1-carboxylate (98c):



According to **TP 11**, the zincation of *tert*-butyl 5-bromo-1*H*-indazole-1-carboxylate (**95b**; 891 mg, 3 mmol) was completed within 5 min at 25 °C using TMPMgCl (**91**; 2.75 mL, 3.3 mmol, 1.2M in THF) and $ZnCl_2$ (1.5 mL, 1.5 mmol, 1M in THF). At –40 °C, CuCN·2LiCl (3 mL, 3 mmol, 1M in THF) was added. After stirring for 10 min at –40 °C, and 2-iodobenzoyl chloride (**97c**; 960 mg, 3.6 mmol) was added. The mixture was allowed to warm to 25 °C and continuously stirred for 4 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3× 20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The crude product was purified by column chromatography (pentane/EtOAc = 9:1) to give **98c** as a pale yellow solid (1.25 g, 79%).

m.p.: 50.2 – 51.9°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.88 (d, *J*=2.1 Hz, 1H), 7.84 – 7.79 (m, 2H), 7.50 (m, 2H), 7.43 (t, *J*=7.21 Hz, 1H), 7.13 (dt, *J*=7.60, 1.7 Hz, 1H), 1.20 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 170.46, 149.86, 142.70, 139.61, 138.77, 136.85, 135.47, 131.22, 130.76, 127.96, 127.24, 122.30, 114.88, 114.46, 91.35, 85.53, 27.19.

MS (70 eV, EI) *m/z* (%): 526 (<1) [M^+], 427 (7), 247 (6), 232 (6), 231 (100), 203 (13), 76 (11), 57 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2234, 1742, 1685, 1584, 1564, 1486, 1351, 1239, 1145, 1058, 1014, 890, 840, 819, 766, 742, 728, 682, 655, 636.

HRMS (EI): *m/z* calc. for **$C_{19}H_{16}{}^{79}BrIN_2O_3$** (525.9389): 525.9373 (M^+).

5.2 Highly Selective Metalations of Pyridines and Related Heterocycles Using New Frustrated Lewis Pairs or TMP-Zn and TMP-Mg Bases with or without BF_3·OEt_2

XYZ-coordinates of calculated structures (**91A**, **99A**, **99B**, **TS-1**, **TS-2**, **101A**, and **101B**) are given in supplementary material of the following report:

M. Jaric, B. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem, Int. Ed.* **2010**, *49*, 5451–5455.

(http://onlinelibrary.wiley.com/store/10.1002/anie.201002031/asset/supinfo/anie_201002031_sm_miscellaneous_information.pdf?v=1&s=f4966c1dbf0e91766f842c3beda291a1afb0bc99)

Computational details: Density functional theory (DFT) calculations were carried out with the Gaussian03 Rev.B.04 package[306] running on Debian GNU/Linux 4.0 64-Bit workstations using the nonlocal hybrid B3LYP exchange-correlation functional[307] and the Møller-Plesset second-order correlation energy correction (MP2)[308]. The basis set denoted as 631SVP consists of the Ahlrich def2-SVP all electron basis set[309] for Mg atoms and the 6-31G(d,p) basis set[310] for other atoms. Geometry optimizations were performed without any symmetry constraints followed by harmonic vibrational analysis at the same level of theory. Frequency calculations were used to identify all the energy-minimized stationary points as local minima (absence of imaginary frequencies) or transition states (one imaginary frequency). Transition states were located using the Berny algorithm. Subsequent single-point electronic energies were calculated on the second-order Møller-Plesset perturbation level of theory combined with the 631SVP basis set for the optimized structures in order to obtain the relative zero-point corrected electronic energies (ZPEs) and the relative Gibbs energies (ΔG) including thermal corrections and entropic contributions derived from the vibrational analysis. In order to calculate the relative solvation free energies, we used the Integral Equation Formalism Polarizable Continuum Model (IEF-PCM) method at B3LYP/6-311++G(2df,2p) level (solvent=DMSO, TSNUM=60, TSARE = 0.4, radii = bondi, alpha =1.2). The gas-phase geometry was used for all the solution-phase calculations, as it has been shown that the

[306] Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.

[307] a) R. G. Parr, W. Yang, *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, **1989**; b) T. Ziegler, *Chem. Rev.* **1991**, *91*, 651; c) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; d) A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098.

[308] a) C. Moller, M. S. Plesset, *Phys. Rev.* **1934**, *46*, 618; b) M. Head-Gordon, J. A. Pople, M. J. Frisch, *Chem. Phys. Lett*. **1988**, *153*, 503; c) M. J. Frisch, M. Head-Gordon, J. A. Pople, *Chem. Phys. Lett.* **1990**, *166*, 275; d) M. J. Frisch, M. Head-Gordon, J. A. Pople, *Chem. Phys. Lett*. **1990**, *166*, 281; e) M. Head-Gordon, T. Head-Gordon, *Chem. Phys. Lett*. **1994**, *220*, 122; f) S. Saebo, J. Almlof, *Chem. Phys. Lett.* **1989**, *154*, 83.

[309] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.

[310] a) P. C. Hariharan, J. A. Pople, *Theoret. Chimica Acta* **1973**, *28*, 213; b) M. M. Francl, W. J. Petro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. DeFrees, J. A. Pople, *J. Chem. Phys.* **1982**, *77*, 3654; c) V. A. Rassolov, J. A. Pople, M. A. Ratner, T. L. Windus, *J. Chem. Phys.* **1998**, *109*, 1223.

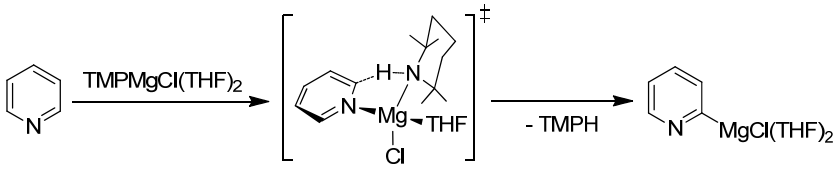
change of geometry by the solvation effect is usually not significant[311]. All of the solution-phase free energies reported in the paper correspond to the reference state 1 mol/L and 298.15 K with a DMSO as solvent.

Calculated energies using DFT-methods

Table 20. Electronic, zero-point-corrected electronic and Gibbs free energies of cyclohexylzinc and palladium complexes based on DFT calculations (MP2/631SVP//B3LYP/631SVP) and solvation energies (B3LYP/6-311++G(2df,2p)/IEFPCM).

Entry	Compound	E_e (a.u.)	E_0 (a.u.)	G_{298} (a.u.)	ΔG_{solv} (kcal·mol^{-1})
1	**91A**	-1530.04177837	-1529.543432	-1529.602552	-13.20
2	**BF_3·THF**	-555.52918580	-555.396827	-555.432376	-9.88
3	**99A**	-1622.12499095	-1621.729738	-1621.786196	-11.78
4	**99B**	-1622.12890380	-1621.731999	-1621.785266	-12.40
5	**pyridine**	-247.51168300	-247.422796	-247.449543	-5.41
6	**100A**	-571.32485329	-571.220391	-571.254612	-13.03
7	**TS-1**	-1869.63368721	-1869.151549	-1869.211278	-13.91
8	**TS-2**	-1869.61464620	-1869.132786	-1869.188873	-16.84
9	**101A**	-1461.80912493	-1461.594821	-1461.643756	-15.23
10	**101B**	-1461.83059512	-1461.616364	-1461.664903	-15.96
11	**TMPH**	-407.83608154	-407.565612	-407.600283	-3.81
12	**$MgCl(THF)_3$**	-1354.39712130	-1354.038041	-1354.092096	-50.22
13	**THF**	-231.72603395	-231.609122	-231.637757	-3.89

5.2.1 DFT calculations on the deprotonation of pyridine with $TMPMgCl(THF)_2$



TS-3
$\Delta E_0^{\ddagger}$ = 14.6 kcal/mol

101C
ΔE_0 = 0.2 kcal/mol

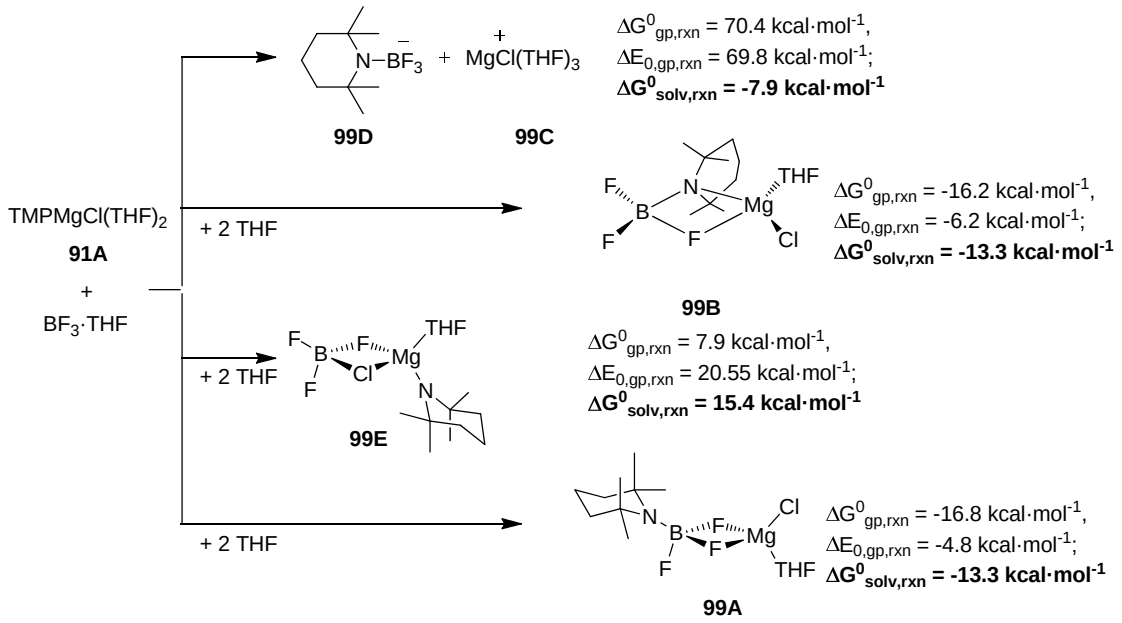
Scheme 91. Magnesiation of pyridine using $TMPMgCl(THF)_2$.

[311] a) V. Barone, M. Cossi, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3210; b) R. Cammi, B. Mennucci, J. Tomasi, *J. Phys. Chem. A* **1998**, *102*, 870 ; c) R. Cammi, B. Mennucci, J. Tomasi, *J. Phys. Chem. A* **2000**, *104*, 4690 ; d) G. Schurmann, M. Cossi, V. Barone, J. Tomasi, *J. Phys. Chem. A* **1998**, *102*, 6706; e) C. da Silva, E. da Silva, M. Nascimento, *J. Phys. Chem. A* **1999**, *103*, 11194; f) C. da Silva, E. da Silva, M. Nascimento, *J. Phys. Chem. A* **2000**, *104*, 2402; g) M. Liptak, G. Shields, *J. Am. Chem. Soc.* **2001**, *123*, 7314; h) A. Toth, M. Liptak, D. Phillips, G. Shields, *J. Chem. Phys.* **2001**, *114*, 4595; i) M. Liptak, G. Shields, *Int. J. Quantum Chem.***2001**, *85*, 727; j) M. Liptak, K. Gross, P. Seybold, S. Feldgus, G. Shields, *J. Am. Chem. Soc.* **2002**, *124*, 6421; k) M. Namazian, H. Heidary, *TheoChem.* **2003**, *620*, 257; l) G. Saracino, R. Improta, V. Barone, *Chem. Phys. Lett.* **2003**, *373*, 411; m) J. Pliego, Jr., J. Riveros, *J. Phys. Chem. A* **2002**, 106, 7434; n) J. Pliego, Jr., J. Riveros, *J. Phys. Chem. A* **2001**, *105*, 7241; o) M. Cancès, B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032; p) B. Mennucci and J.Tomasi, *J. Chem. Phys.* **1997**, *106*, 5151 ; q) B. Mennucci, E. Cancès, J. Tomasi, *J. Phys. Chem. B* **1997**, *101*, 10506; r) J. Tomasi, B. Mennucci, E. Cancès, *J. Mol. Struct. (Theochem)* **1999**, *464*, 211.

The deprotonation of pyridine with $TMPMgCl(THF)_2$ in absence of $BF_3{\cdot}OEt_2$ has been investigated by DFT and post-HF, *ab initio*, methods[307] (MP2/631SVP//B3LYP/631SVP) (Scheme 91). In contrast to the deprotonation mechanism described in Scheme 56, the metalation without the complexing Lewis acid $BF_3{\cdot}OEt_2$ via transition state **TS-3** is energetically more demanding, as illustrated by a higher activation barrier ($\Delta E_0^{\ddagger}$ = 14.6 kcal·mol-1). Since the stabilization of the magnesiated product (**101C**) producing a borate compound is missing, the reaction was calculated to be slightly endothermic (ΔE_0 = 0.2 kcal·mol^{-1}). This insight into the reaction pathway provided by the theoretical calculations corroborates the experimental observations of a hampered metalation with unsubstituted pyridine.

5.2.2 Theoretical Investigation of the Nature of "$TMPBF_3{\cdot}MgCl$" (99)

The isomeric structures (**99A**–**E**; Scheme 92) have thermodynamically been analyzed using DFT and post-HF, *ab initio*, methods[307,308] in gas-phase (MP2/631SVP//B3LYP/631SVP) as well as in solution-phase (IEF-PCM/B3LYP/6-311++G(2df,2p)). Dinuclear boron-magnesium complexes with varying positions of the TMP moiety (TMP = 2,2,6,6-tetramethylpiperidyl) and the isolated ionic structures were considered. The calculations revealed that the structure **99E** bearing the TMP moiety terminal on the Mg center in gas-phase ($\Delta G_{298,gp}$ = 7.9 kcal·mol^{-1}) and in solution phase ($\Delta G_{298,sol}$ = 15.4 kcal·mol^{-1}) is disfavoured. In contrast, the formation of the ionic structures **99D** and **99C** is, as expected, in gas-phase very high in energy ($\Delta G_{298,gp}$ = 70.4 kcal·mol^{-1}). However, in solution-phase the formation of the anionic (**99D**) and cationic (**99C**) species seems thermodynamically possible ($\Delta G_{298,sol}$ = –7.9 kcal·mol^{-1}). Dinuclear complexes **99A** and **99B** are from an energetical point of view the most favoured geometries bearing the TMP moiety either in terminal position on the boron center ($\Delta G(\mathbf{99A})_{298,gp}$ = –16.8 kcal·mol^{-1}, $\Delta G(\mathbf{99A})_{298,sol}$ = –13.3 kcal·mol^{-1}) or as a bridging ligand between the Mg- and the B-atom ($\Delta G(\mathbf{99B})_{298,gp}$ = –16.2 kcal·mol^{-1}, $\Delta G(\mathbf{99B})_{298,sol}$ = –13.3 kcal·mol^{-1}).

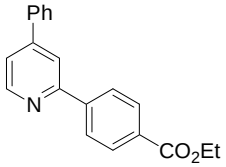


Scheme 92. Thermodynamical analysis of the frustrated Lewis pair **99** in gas-phase and in solution phase.

In conclusion, the complexes **99A** and **99B** are the most likely to be formed by premixing $TMPMgCl(THF)_2$ and $BF_3 \cdot THF$ acting as reactive intermediates.

5.2.3 Experimental procedures

Synthesis of ethyl 4-(4-phenylpyridin-2-yl)benzoate (98d):



A) Preparation of **98d** via metalation of BF_3-precomplexed 4-phenylpyridine:

A mixture of 4-phenylpyridine (**95c**; 310 mg, 2.0 mmol) and $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**91**; 2.5 mL, 3 mmol, 1.2M in THF) according to **TP13** (–40 °C, 20 min). $ZnCl_2$ (2.2 mL, 2.2 mmol, 1M in THF) was added at –40 °C and was stirred for 30 min. $Pd(dba)_2$ (56 mg, 5 mol%) and P(*o*-furyl)$_3$ (46 mg, 10 mol%) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (**97d**; 441 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. Subsequently, sat. aq. NH_4Cl (9 mL) and conc. aq. NH_3 (1 mL) were added to the reaction mixture. The aqueous layer was extracted with diethyl ether (3x30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/diethyl ether, 4:1) furnished **98d** as a pale yellow solid (407 mg, 84%).

B) Preparation of **98d** via metalation using "TMPBF$_3$·MgCl·LiCl":

According to **TP14**, $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) was added dropwise to TMPMgCl·LiCl (**91**; 1.85 mL, 2.2 mmol, 1.2M in THF) at –40 °C and the resulting mixture was stirred at –40 °C for 10 min followed by dropwise addition of a solution of 4-phenylpyrdine (**95c**; 310 mg, 2 mmol) in dry THF (10 mL). After stirring for 10 min at –40 °C, $ZnCl_2$ (2.2 mL, 2.2 mmol, 1M in THF) and stirred for 30 min at –40 °C. $Pd(dba)_2$ (56 mg, 5 mol%) and P(2-furyl)$_3$ (46 mg, 10 mol%) in dry THF (2 mL) were added to the reaction mixture, followed by addition of ethyl 4-iodobenzoate (**97d**; 441 mg, 1.6 mmol) in dry THF (2 mL). Subsequently, the reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 12 h at 25 °C. Then, sat. aq. NH_4Cl (9 mL) and conc. aq. NH_3 (1 mL) were added. The aqueous layer was extracted with diethyl ether (3x 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/diethyl ether, 4:1) furnished **98d** as a pale yellow solid (339 mg, 70%).

m.p.: 72.5-78.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.76 (d, *J* = 5.1 Hz, 1H), 8.10-8.19 (m, 4H), 7.96-7.98 (m, 1H), 7.66-7.71 (m, 2H), 7.43-7.54 (m, 4H), 4.41 (q, *J* = 7.3 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

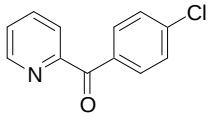
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.3, 156.7, 150.0, 149.8, 143.1, 138.1, 130.9, 130.0, 129.3, 129.2, 127.1, 126.9, 121.0, 119.2, 61.1, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2988, 1708, 1608, 1594, 1570, 1546, 1500, 1466, 1446, 1410, 1386, 1368, 1310, 1270, 1194, 1176, 1158, 1124, 1104, 1076, 1044, 1024, 1016, 1002, 988, 978, 918, 886, 872, 862, 836, 808, 780, 758, 740, 732, 694, 672, 638, 626, 614.

MS (70 eV, EI) *m/z* (%): 303 (72) [M$^+$], 275 (29), 258 (100), 227 (10), 202 (13), 129 (12), 115 (10).

HRMS (EI): *m/z* calc. for **$C_{20}H_{17}O_2N$** (303.1259): 303.1250 (M$^+$).

Synthesis of (4-chlorophenyl)(pyridin-2-yl)methanone (98e):



According to **TP14**, $BF_3{\cdot}OEt_2$ (156 mg, 1.1 mmol) was added dropwise to TMPMgCl·LiCl (**91**; 0.92 mL, 1.1 mmol, 1.2 M in THF) at –40 °C and the resulting mixture was stirred at –40 °C for 10 min before pyridine (**95d**; 79 mg, 1 mmol) in dry THF (5 mL) was added dropwise. After stirring for 15 min, CuCN·2LiCl (1.1 mL, 1.1 mmol, 1M in THF) was added

and the reaction mixture was stirred for 30 min at the same temperature. Then, 4-chlorobenzoyl chloride (**97e**; 149 mg, 0.8 mmol) was added at -40 °C. The reaction mixture was slowly warmed to 25 °C and stirred for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl (4.5 mL) and conc. aq. NH_3 (0.5 mL) and the aqueous layer was extracted with Et_2O (3x 20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 4:1) furnished the compound **98e** as a white solid (146 mg, 84%).

m.p.: 81.5-82.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.69-8.74 (m, 1H), 8.01-8.09 (m, 3H), 7.88-7.96 (m, 1H), 7.48-7.55 (m, 1H), 7.42-7.48 (m, 2H).

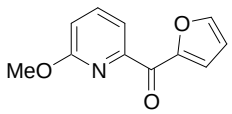
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 192.0, 154.3, 148.2, 139.5, 137.5, 134.4, 132.4, 128.5, 126.5, 124.7.

IR (ATR) υ (cm^{-1}): 3086, 3060, 1658, 1582, 1568, 1488, 1468, 1434, 1402, 1312, 1304, 1290, 1282, 1240, 1182, 1158, 1088, 1048, 1016, 996, 974, 964, 934, 896, 852, 800, 752, 742, 724, 692, 670, 632, 618.

MS (70 eV, EI) *m/z* (%): 218 (100) [M^+-H], 203 (39), 189 (73), 154 (18), 139 (66), 111 (39), 73 (72), 45 (62).

HRMS (EI): *m/z* calc. for **$C_{12}H_9ON$** (217.0294): 218.0365 (M^+).

Synthesis of 2-furyl(6-methoxypyridin-2-yl)methanone (98f):



According to **TP14**, $BF_3{\cdot}OEt_2$ (156 mg, 1.1 mmol) was added dropwise to TMPMgCl·LiCl (**91**; 0.92 mL, 1.1 mmol, 1.2M in THF) at –40 °C and the resulting mixture was stirred at this temperature for 10 min before 2-methoxypyridine (**95e**; 109 mg, 1 mmol) in dry THF (5 mL) was added dropwise. After stirring for 15 min, CuCN·2LiCl (1.1 mL, 1.1 mmol, 1M in THF) was added and the reaction mixture was stirred for 30 at –40 °C. Then, 2-furoyl chloride (**97f**; 104 mg, 0.8 mmol) was added at –40 °C. The reaction mixture was warmed slowly to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq. NH_4Cl (4.5 mL) and con. aq. NH_3 (0.5 mL) and the aqueous layer was extracted with Et_2O (3x 20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 5:1) furnished compound **98f** as a yellow solid (124 mg, 76%).

m.p.: 60.1-62.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.06-8.09 (m, 1H), 7.69-7.82 (m, 3H), 6.93-6.97 (m, 1H), 6.58-6.61 (m, 1H), 4.02 (s, 3H).

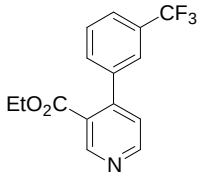
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 178.5, 163.1, 151.2, 151.1, 147.5, 139.2, 123.1, 117.5, 115.1, 112.2, 53.8.

IR (ATR) υ (cm^{-1}): 3126, 3106, 3006, 2950, 2850, 1632, 1612, 1586, 1554, 1470, 1458, 1436, 1422, 1388, 1364, 1336, 1284, 1272, 1222, 1202, 1184, 1146, 1084, 1076, 1038, 1020, 992, 968, 920, 906, 880, 872, 838, 814, 792, 758, 722, 714, 664, 636, 618.

MS (70 eV, EI) *m/z* (%): 203 (86) [M^+], 174 (100), 146 (24), 117 (17), 95 (59).

HRMS (EI): *m/z* calc. for **$C_{11}H_9O_3N$** (203.0582): 203.0583 (M^+).

Synthesis of ethyl 4-[3-(trifluoromethyl)phenyl]nicotinate (98g):



According to **TP14**, $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) was added dropwise to TMPMgCl·LiCl (**91**; 1.85 mL, 2.2 mmol, 1.2M in THF) at –40 °C and the resulting mixture was stirred at –40 °C for 10 min, followed by addition of ethyl nicotinate (**95f**; 302 mg, 2 mmol) in dry THF (10 mL). After stirring for 15 min, $ZnCl_2$ (2.2 mL, 2.2 mmol, 1M in THF) was added at –40 °C and stirred for 30 min. $Pd(dba)_2$ (56 mg, 5 mol%) and P(2-furyl)$_3$ (46 mg, 10 mol%) in THF (4 mL) were transferred via cannula to the reaction mixture, followed by addition of 1-iodo-3-(trifluoromethyl)benzene (**97g**; 435 mg, 1.6 mmol) in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at 25 °C. Then, sat. aq. NH_4Cl (9 mL) and conc. aq. NH_3 (1 mL) were added, the aqueous layer was extracted with Et_2O (3x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 1:1) furnished **98g** as a yellow oil (335 mg, 71% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.12 (s, 1H), 8.78 (d, *J*=4.9Hz, 1H), 7.35 (d, *J*=5.1 Hz, 1H), 7.66-7.73 (m, 1H), 7.48-7.61 (m, 3H), 4.17 (q, *J*=7.1 Hz, 2H), 1.07 (t, *J*=7.1Hz, 3H).

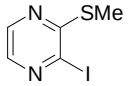
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.7, 151.2, 150.5, 149.6, 139.2, 131.4 (q, *J*=1.4 Hz), 130.9 (q, *J*=32.6Hz), 128.9, 125.3 (q, *J*=3.7Hz), 125.0 (q, *J*=3.8Hz), 123.8 (q, *J*=272.5Hz), 61.7, 13.6.

IR (ATR) υ (cm^{-1}): 3058, 2984, 2940, 2916, 2876, 1720, 1588, 1548, 1478, 1436, 1406, 1368, 1336, 1306, 1272, 1256, 1216, 1166, 1124, 1098, 1076, 1052, 1042, 1016, 906, 846, 826, 808, 788, 704, 660, 624.

MS (70 eV, EI) *m/z* (%): 295 (38) [M^+], 267 (41), 250 (100), 228 (35), 149 (31), 85 (24), 71 (33), 69 (19), 59 (42), 43 (23).

HRMS (EI): *m/z* calc. for **$C_{15}H_{12}O_2NF_3$** (295.0820): 295.0824 (M^+).

Synthesis of 2-iodo-3-(methylthio)pyrazine (98h):



According to **TP14**, $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) was added dropwise to TMPMgCl·LiCl (**91**; 1.85 mL, 2.2 mmol, 1.2M in THF) at –40 °C and the resulting mixture was stirred for 10 min at –40 °C. Then, 2-(thiomethyl)pyrazine (**95g**; 252 mg, 2 mmol) in dry THF (10 mL) was added dropwise. After stirring for 10 min, a solution of iodine (762 mg, 3 mmol) in dry THF (3 mL) was added and the reaction mixture was slowly warmed to 25 °C. The reaction solution was quenched with sat. aq. NH_4Cl (5 mL), aq. NH_3 (5 mL, 2M) and sat. aq. $Na_2S_2O_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **98h** as an off-white solid (408 mg, 81%).

m.p.: 90.8 – 92.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.30 (d, *J*=2.4Hz, 1H), 7.95 (d, *J*=1.0Hz, 1H), 2.50 (s, 3H).

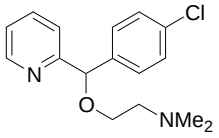
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 162.7, 142.1, 138.9, 118.6, 15.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2918, 2018, 1534, 1486, 1418, 1402, 1318, 1188, 1132, 1056, 1022, 970, 838, 772, 672.

MS (70 eV, EI) *m/z* (%): 253 (10), 252 (100) [M^+], 125 (72), 109 (10), 81 (19).

HRMS (EI): *m/z* calc. for **$C_5H_5IN_2S$** (251.9218): 251.9212 (M^+).

Synthesis of *carbinoxamine* (102; 2-[(4-chlorophenyl)(pyridin-2-yl)methoxy]-N,N-dimethylethanamine) :



According to **TP14**, $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) was added dropwise to TMPMgCl·LiCl (**91**; 1.85 mL, 2.2 mmol, 1.2M in THF) at –40 °C and the resulting mixture was stirred at –40 °C for 10 min pyridine (**95d**; 158 mg, 2 mmol) in dry THF (1 mL) was added dropwise. After stirring for 10 min at –40 °C, 4-chlorobenzaldehyde (**97h**; 281 mg, 2.2 mmol) in dry THF (2 mL) was added dropwise. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Thereafter, 1-chloro-*N,N*-dimethylaminoethane hydrochloride (**97i**; 346 mg 2.4 mmol) was added neat at 25 °C, followed by addition of sodium hydride (96 mg, 2.4 mmol, 60 wt% in mineral oil) and catalytic amounts of sodium iodide. The reaction mixture was refluxed for 2 h. After cooling down the reaction mixture to 25 °C, the mixture was diluted with Et_2O (5 mL) and quenched with aq. NaOH (10 mL, 2M). The aqueous layer was extracted with EtOAc (4x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on neutral aluminium oxide (pentane/EtOAc/MeOH, 8:2:1) furnished **102** as a yellow oil (419 mg, 72%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.47 (dd, *J*=4.9Hz, 0.8Hz, 1H), 7.62 (dt, *J*=7.7Hz, 1.8Hz, 1H), 7.47 (d, *J*=7.9Hz, 1H), 7.34 (d, *J*=8.4Hz, 2H), 7.23 (d, *J*=8.6Hz, 2H), 7.10 (dt, *J*=4.8Hz, 1.1Hz, 1H), 5.43 (s, 1H), 3.57 (t, *J*=6.0Hz, 2H), 2.57 (t, *J*=5.9Hz, 2H), 2.23 (s, 6H).

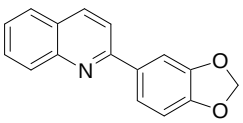
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 161.2, 148.9, 139.6, 136.8, 133.3, 128.4, 128.2, 122.4, 120.5, 84.3, 67.6, 58.8, 45.9.

IR (ATR) υ (cm^{-1}): 3396, 2942, 2864, 2820, 2770, 2362, 2334, 1588, 1572, 1490, 1468, 1434, 1406, 1370, 1328, 1294, 1274, 1190, 1116, 1088, 1040, 1014, 994, 958, 852, 806, 766, 748, 718, 700.

MS (70 eV, EI) *m/z* (%): 291 (5) [M^+], 218 (9), 201 (12), 167 (27), 139 (13), 71 (68), 58 (100).

HRMS (EI): *m/z* calc. for **$C_{16}H_{20}ClN_2O$** (291.1264): 291.1249 (M^+).

Synthesis of *dubamine* (103; 2-(1,3-benzodioxol-5-yl)quinoline) :



According to **TP14**, $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) was added dropwise to TMPMgCl·LiCl (**91**; 0.92 mL, 1.1 mmol, 1.2M in THF) at –40 °C and the resulting mixture was stirred at –40 °C for 10 min. Then, quinoline (**95h**; 129 mg, 1 mmol) in dry THF (5 mL) was added dropwise. After stirring for 20 min, $ZnCl_2$ (1.1 mL, 1.1 mmol, 1M in THF) was added

at –40 °C and stirred for 30 min. $Pd(dba)_2$ (28 mg, 5 mol%) and $P(2\text{-furyl})_3$ (23 mg, 10 mol%) in THF (2 mL) were added, followed by addition of 5-iodo-1,3-benzodioxole (**97j**; 198 mg, 0.8 mmol) in THF (1 mL). The reaction mixture was allowed to warm to 25 °C and stirred for 12 h at 25 °C. Sat. aq. NH_4Cl (4.5 mL) and conc. aq. NH_3 (0.5 mL) were added. The aqueous layer was extracted with Et_2O (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 20:1) furnished **103** as a pale yellow solid (158 mg, 79%).

m.p.: 94-95 °C.

^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm): 8.11-8.18 (m, 2H), 7.63-7.81 (m, 5H), 7.46-7.52 (m, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.03 (s, 2H).

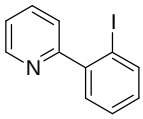
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 156.6, 148.8, 148.4, 148.0, 136.7, 134.0, 129.7, 129.4, 127.4, 127.0, 126.1, 121.8, 118.6, 108.4, 107.9, 101.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3050, 3008, 2896, 2780, 1596, 1558, 1496, 1486, 1454, 1444, 1426, 1354, 1292, 1254, 1234, 1222, 1206, 1162, 1138, 1110, 1098, 1048, 1036, 932, 908, 892, 860, 838, 828, 814, 800, 784, 742, 720, 682, 624, 604.

MS (70 eV, EI) *m/z* (%): 249 (100) [M^+], 220 (3), 191 (17), 163 (3), 128 (3), 96 (6).

HRMS (EI): *m/z* calc. for **$C_{16}H_{11}O_2N$** (249.0790): 249.0787 (M^+).

Synthesis of 2-(2-iodophenyl)pyridine (106a):



According to **TP1**, 2-phenylpyridine (**95i**; 2 mmol, 310 mg) reacted with TMPMgCl·LiCl (**91**; 3.3 mL, 4 mmol, 1.2M in THF) (55 °C, 30 h). At –30 °C, a solution of iodine (4 mmol, 1 g) in dry THF (4 mL) was added and the reaction mixture was allowed to slowly warm to 25 °C. Then, sat. aq. NH_4Cl (4.5 mL), conc. aq. NH_3 (0.5 mL) and sat. aq. $Na_2S_2O_3$ (2 mL) was added. The aqueous layer was extracted with Et_2O (3x 30 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 4:1) furnished compound **106a** as a yellow oil (478 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.70 (ddd, *J*=4.9Hz, 1.8Hz, 1.0Hz, 1H), 7.93-7.97 (m, 1H), 7.72-7.81 (m, 1H), 7.38-7.52 (m, 3H), 7.27-7.33 (m, 1H), 7.03-7.11 (m, 1H).

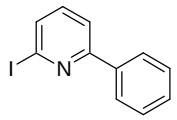
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.6, 149.0, 144.8, 139.7, 136.1, 130.3, 129.7, 128.2, 124.5, 122.5, 96.6 ppm.

IR (ATR) υ (cm^{-1}): 3048, 3006, 1606, 1588, 1580, 1566, 1478, 1456, 1424, 1416, 1288, 1232, 1148, 1094, 1074, 1046, 1022, 1010, 988, 946, 890, 866, 790, 744, 720, 654, 630, 614.

MS (70 eV, EI) *m/z* (%): 281 (100) [M^+], 155 (11), 154 (87), 153 (12), 128 (16), 127 (50), 126 (12).

HRMS (EI): *m/z* calc. for **$C_{11}H_8IN$** (280.9701): 280.9682 (M^+).

Synthesis of 2-iodo-6-phenylpyridine (107a):



According to **TP13**, a mixture of 2-phenylpyridine (**95i**; 310 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**91**; 2.5 mL, 3 mmol, 1.2M in THF) at 0 °C for 30 h. At –30 °C, a solution of iodine (4 mmol, 1 g) in dry THF (4 mL) was added and the reaction mixture was allowed to slowly warm to 25 °C. Then, sat. aq. NH_4Cl (9 mL), conc. aq. NH_3 (1 mL) and sat. aq. $Na_2S_2O_3$ (2 mL) was added. The aqueous layer was extracted with Et_2O(3x 30 mL). The combined organic phases were dried over Na_2SO_4. The solvents were removed *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 40:1) furnished **107a** as a pale yellow solid (467 mg, 83%).

m.p.: 81.7-82.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.93-7.99 (m, 2H), 7.67 (dd, *J* = 7.8Hz, 0.8Hz, 1H), 7.63 (dd, *J*=7.8Hz, 0.8Hz, 1H), 7.38-7.49 (m, 3H), 7.37 (t, *J*=7.8Hz, 1H).

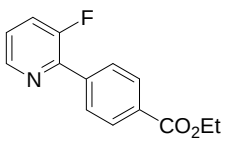
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.0, 138.0, 137.7, 133.1, 129.5, 128.8, 126.9, 119.3, 118.2.

IR (ATR) υ (cm^{-1}): 3050, 3032, 1568, 1542, 1422, 1384, 1166, 1114, 1048, 980, 972, 800, 774, 756, 728, 696, 662, 622, 612.

MS (70 eV, EI) *m/z* (%): 281 (55) [M^+], 154 (100), 127 (26), 77 (8).

HRMS (EI): *m/z* calc. for **$C_{11}H_8NI$** (280.9701): (280.9693) (M^+).

Synthesis of ethyl 4-(3-fluoropyridin-2-yl)benzoate (106b):



According to **TP12**, 3-fluoropyridine (**95j**; 196 mg, 2 mmol) reacted with TMPMgCl·LiCl (**91**; 1.8 mL, 2.2 mmol, 1.2M in THF) at –78 °C for 30 min. Then, $ZnCl_2$ (2.2 mL, 2.2 mmol, 1M in THF) was added and the mixture was continuously stirred for 30 min at –78 °C.

$Pd(dba)_2$ (56 mg, 5 mol%) and $P(2\text{-furyl})_3$ (46 mg, 10 mol%) in THF (4 mL) was added to the reaction mixture, followed by addition of ethyl 4-iodobenzoate (**97d**; 442 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was allowed to warm to 25 °C and stirred for 12 h at 25 °C. Subsequently, a mixture of sat. aq. NH_4Cl (9 mL) and conc. aq. NH_3 (1 mL) was added. The aqueous layer was extracted with Et_2O (3x 30 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 4:1) furnished **106b** as a yellow oil (282 mg, 72%).

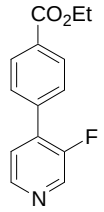
^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm): 8.52-8.56 (m, 1H), 8.15-8.17 (m, 1H), 8.12-8.14 (m, 1H), 8.05-8.08 (m, 1H), 8.02-8.05 (m, 1H), 7.48-7.56 (m, 1H), 7.28-7.35 (m, 1H), 4.39 (q, *J*=7.1Hz, 2H), 1.40 ppm (t, *J*=7.2Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.3, 157.7 (d, *J*=261.6Hz), 145.3 (d, *J*=5.4Hz), 144.9 (d, *J*=10.8Hz), 139.1 (d, *J*=5.4Hz), 131.0, 129.6, 128.7 (d, *J*=6.2Hz), 124.6 (d, *J*=20.6Hz), 124.3 (d, *J*=4.1Hz), 61.1, 14.3.

IR (ATR) υ (cm^{-1}): 3066, 2982, 2362, 2338, 1940, 1712, 1610, 1596, 1578, 1512, 1442, 1402, 1368, 1312, 1268, 1248, 1186, 1096, 1060, 1034, 1016, 864, 838, 800, 786, 742, 730, 698, 640, 630.

HRMS (ESI): *m/z* calc. for **$C_{14}H_{13}FNO_2$** (246.0930): 246.0923 ($[M+H]^+$).

Synthesis of ethyl 4-(3-fluoropyridin-4-yl)benzoate (107b):



According to **TP13**, a mixture of 3-fluoropyridine (**95j**; 97 mg, 1 mmol) and $BF_3{\cdot}OEt_2$ (156 mg, 1.1 mmol) reacted with TMPMgCl·LiCl (**91**; 0.92 mL, 1.1 mmol, 1.2M in THF) at −78 °C for 30 min. Them, $ZnCl_2$ (1.1 mmol, 1.1 mL, 1M in THF) was added dropwise at −78 °C and the mixture was continuously stirred for 30 min. $Pd(dba)_2$ (28 mg, 5 mol%) and $P(2\text{-fur})_3$ (23 mg, 10 mol%) in THF (2 mL) were added to the reaction mixture, followed by addition of ethyl 4-iodobenzoate (**97d**; 221 mg, 0.8 mmol) in THF (1 mL). The reaction mixture was allowed to warm to 25 °C and stirred for 12 h. Subsequently, sat. aq. NH_4Cl (4.5 mL) and conc. aq. NH_3 (0.5 mL) were added. The aqueous layer was extracted with Et_2O (3× 20 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed

in vacuo. Flash column chromatographical purification (pentane/Et_2O, 3:1) furnished **107b** as a yellow solid (145 mg, 74%).

m.p.: 60.4-62.9 °C.

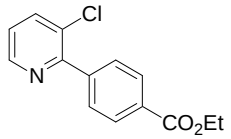
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.56 (d, *J*=2.2Hz, 1H), 8.49 (d, *J*=4.9Hz, 1H), 8.10-8.18 (m, 2H), 7.63-7.70 (m, 2H), 7.37-7.45 (m, 1H), 4.40 (q, *J*=7.1Hz, 2H), 1.40 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.0, 156.5 (d, *J*=258.2Hz), 145.0 (d, *J* =5.4Hz), 139.0 (d, *J*=25.8Hz), 137.1 (d, *J*=1.3Hz), 135.2 (d, *J*=10.6Hz), 131.2, 130.0, 128.8 (d, *J*=3.4Hz), 124.1, 61.3, 14.3.

IR (ATR) υ (cm^{-1}): 2986, 2908, 1710, 1668, 1604, 1576, 1546, 1482, 1464, 1450, 1418, 1400, 1362, 1312, 1280, 1268, 1234, 1210, 1186, 1156, 1130, 1110, 1062, 1034, 1020, 1012, 972, 912, 882, 868, 858, 842, 828, 776, 736, 712, 698, 672, 644, 618.

HRMS (ESI): *m/z* calc. for **$C_{14}H_{13}FNO_2$** (246.0930): 246.0923 ($[M+H]^+$).

Synthesis of ethyl 4-(3-fluoropyridin-2-yl)benzoate (106c):



According to **TP12**, 3-chloropyridine (**95k**, 113 mg, 1.0 mmol) reacted with TMPMgCl·LiCl (**91**; 0.92 mL, 1.1 mmol, 1.2M in THF) at −78 °C for 45 min). Then, $ZnCl_2$ (1.1 mL, 1.1 mmol, 1M in THF) was added dropwise at −78 °C and stirred for 30 min. Subsequently, $Pd(dba)_2$ (28 mg, 5 mol%) and $P(2\text{-fur})_3$ (23 mg, 10 mol%) in THF (2 mL) was added to the reaction mixture, followed by addition of ethyl 4-iodobenzoate (**97d**; 221 mg, 0.8 mmol) in THF (1 mL). The reaction mixture was allowed to warm to 25 °C and stirred for 12 h. Sat. aq. NH_4Cl (4.5 mL) and conc. aq. NH_3 (0.5 mL) were added. The aqueous layer was extracted with Et_2O (3× 20 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 3:1) furnished **106c** as a yellow solid (157 mg, 75%).

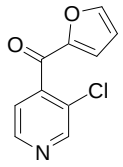
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.59-8.64 (m, 1H), 8.11-8.18 (m, 2H), 7.76-7.86 (m, 3H), 7.26-7.31 (m, 1H), 4.41 (q, *J*=7.1Hz, 2H), 1.40 (t, *J*=7.2Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.2, 155.4, 147.5, 142.1, 138.4, 130.7, 130.3, 129.4, 129.2, 123.6, 61.1, 14.3.

IR (ATR) υ (cm^{-1}): 3050, 2982, 2938, 2904, 1712, 1612, 1572, 1554, 1426, 1398, 1366, 1310, 1268, 1178, 1100, 1088, 1038, 1028, 1014, 862, 794, 786, 748, 702, 636, 628.

HRMS (ESI): *m/z* calc. for **$C_{14}H_{13}ClNO_2$** (262.0635): 262.0627 ($[M+H]^+$).

Synthesis of (3-chloropyridin-4-yl)(2-furyl)methanone (107c):



According to **TP13**, a mixture of 3-chloropyridine (**95k**; 228 mg, 2.0 mmol) and $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**91**; 1.8 mL, 2.2 mmol, 1.2M in THF) at −78 °C for 45 min. Then, CuCN·2LiCl (2.2 mL, 2.2 mmol, 1M in THF) was added at −78 °C and continuously stirred for 30 min, followed by addition of 2-furoyl chloride (**97f**; 209 mg, 1.6 mmol) at −78 °C. Subsequently, the reaction mixture was allowed to slowly warm to 25 °C and was stirred for 12 h. Thereafter, sat. aq. NH_4Cl (9 mL) and conc. aq. NH_3 (1 mL) were added. The aqueous layer was extracted with Et_2O (3x 30 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 1:1) furnished **107c** as a brown oil (259 mg, 78%).

m.p.: 64.3-65.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.71 (s, 1H), 8.61 (d, *J*=4.9Hz, 1H), 7.71 (dd, *J*=1.8Hz, 0.8Hz, 1H), 7.37 (dd, *J*=4.9Hz, 0.7Hz, 1H), 7.14 (dd, *J*=3.7Hz, 0.8Hz, 1H), 6.61 (dd, *J*=3.7Hz, 0.8Hz, 1H).

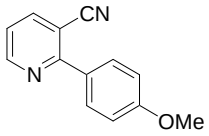
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 179.3, 151.1, 150.0, 148.8, 147.4, 144.6, 128.8, 122.6, 122.1, 113.1.

IR (ATR) υ (cm^{-1}): 3142, 3118, 3074, 2362, 1634, 1584, 1562, 1460, 1400, 1394, 1324, 1272, 1246, 1202, 1170, 1148, 1100, 1080, 1036, 970, 958, 918, 892, 876, 838, 794, 772, 754, 720, 666, 616.

MS (70 eV, EI) *m/z* (%): 207 (43) [M^+], 141 (15), 127 (14), 111 (10), 99 (32), 95 (95), 85 (65).

HRMS (EI): *m/z* calc. for **$C_{10}H_6ClNO_2$** (207.0087): 207.0075 (M^+).

Synthesis of 2-(4-methoxyphenyl)nicotinonitrile (106d):



According to **TP12**, nicotinonitrile (**95l**, 208 mg, 2.0 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93b**; 2.75 mL, 1.1 mmol, 0.4M in THF) at 25 °C for 12 h. Then, $Pd(dba)_2$ (56 mg, 5 mol%) and $P(2\text{-fur})_3$ (46 mg, 10 mol%) in THF (4 mL) were added at 25 °C, followed by addition of ethyl 4-iodoanisole (221 mg, 1.6 mmol) in THF (2 mL) and continuous stirring for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl (9 mL) and conc. aq. NH_3 (1 mL). The aqueous layer was extracted with Et_2O (3× 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 3:1) furnished the compound **106d** as a yellow solid (286 mg, 85%).

m.p.: 138.1-139.3 °C.

^{1}H-NMR (300 MHz, $CDCL_3$) δ (ppm): 8.82 (dd, *J*=4.9Hz, 1.8Hz, 1H), 8.02 (dd, *J*=7.9Hz, 1.7Hz, 1H), 7.93 (ddd, *J*=9.4Hz, 3.0Hz, 2.6Hz, 2H), 7.29 (dd, *J*=7.9Hz, 4.9Hz, 1H), 7.03 (ddd, *J*=9.4Hz, 3.0Hz, 2.6Hz, 2H), 3.87 (s, 3H).

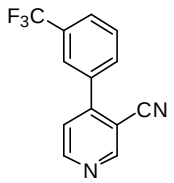
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 161.3, 160.4, 152.5, 141.9, 130.4, 129.5, 120.9, 117.9, 114.1, 106.7, 55.4.

IR (ATR) υ (cm^{-1}): 3064, 2846, 2224, 1606, 1582, 1572, 1554, 1516, 1458, 1432, 1312, 1252, 1192, 1182, 1114, 1038, 1018, 836, 826, 812, 788, 776, 722, 632, 616.

MS (70 eV, EI) *m/z* (%): 210 (100) [M^+], 195 (8), 167 (22), 139 (9).

HRMS (EI): *m/z* calc. for **$C_{13}H_{10}N_2O$** (210.0793): 210.0790 (M^+).

Synthesis of 4-[3-(trifluoromethyl)phenyl]nicotinonitrile (107d):



According to **TP13**, a mixture of nicotinonitrile (**95l**; 208 mg, 2 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93b**; 3.1 mL, 2.2 mmol, 0.71M in THF) at −30 °C for 30 min. Subsequently, $Pd(dba)_2$ (56 mg, 5 mol%) and $P(2\text{-fur})_3$ (46 mg, 10 mol%) in THF (4 mL) was added to the reaction mixture, followed by addition of 1-iodo-3-(trifluoromethyl)benzene (**97g**; 435 mg, 1.6 mmol) in THF (2 mL). The reaction mixture was allowed to warm to 25 °C and stirred for 12 h. Sat. aq. NH_4Cl (9 mL) and conc. aq. NH_3 (1 mL) were added. The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 1:2) furnished **107d** as a white solid (313 mg, 78%).

m.p.: 125.6-128.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.98 (s, 1H), 8.86 (d, *J*=5.2Hz, 1H), 7.75-7.87 (m, 3H), 7.64-7.73 (m, 1H), 7.49 (d, *J*=5.2Hz, 1H).

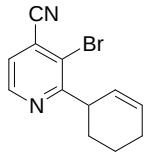
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 154.0, 153.1, 150.7, 136.2, 131.8 (q, *J*=33.0Hz), 131.7 (q, *J*=1.3 Hz), 129.8, 127.0 (q, *J*=3.7Hz), 125.3 (q, *J*=3.8Hz), 123.7, 123.6 (q, *J*=272.6Hz), 116.1, 108.7.

IR (ATR) υ (cm^{-1}): 3070, 2226, 1614, 1584, 1544, 1482, 1430, 1406, 1334, 1308, 1266, 1230, 1188, 1166, 1110, 1100, 1078, 1042, 1000, 934, 924, 852, 838, 806, 776, 756, 724, 700, 658, 624.

MS (70 eV, EI) *m/z* (%): 248 (100) [M^+], 228 (11), 221 (7), 201 (12), 152 (3).

HRMS (EI): *m/z* calc. for **$C_{13}H_7F_3N_2$** (248.0561): 248.0550 (M^+).

Synthesis of 3-bromo-2-cyclohexylisonicotinonitrile (106e):



According to **TP12**, 3-bromoisonicotinonitrile (**95m**; 366 mg, 2.0 mmol) reacted with TMPMgCl·LiCl (**91**; 1.85 mL, 2.2 mmol, 1.2M in THF) at −78 °C for 1 h. Then, CuCN·2LiCl (1.1 mL, 1.1 mmol, 1M in THF) was added and stirred for 30 min at −78 °C. Subsequently, 3-bromocyclohexene (258 mg, 1.6 mmol) was added at −78 °C. The reaction mixture was allowed to slowly warm to 25 °C and stirred for 12 h. Sat. aq. NH_4Cl (9 mL) and conc. aq. NH_3 (1 mL) were added. The aqueous layer was extracted with Et_2O (3x 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 5:1) furnished **106e** as a yellow oil (274 mg, 65%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.63 (d, *J*=4.9Hz, 1H), 7.84 (d, *J*=4.9Hz, 1H), 5.90-5.98 (m, 1H), 5.61-5.68 (m, 1H), 4.08-4.15 (m, 1H), 2.00-2.17 (m, 3H), 1.78-1.89 (m, 1H), 1.53-1.72 (m, 2H).

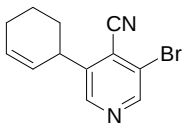
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.2, 148.3, 129.0, 127.1, 124.6, 124.3, 122.2, 115.5, 42.6, 28.4, 24.5, 21.3.

IR (ATR) υ (cm^{-1}): 3026, 2932, 2860, 2836, 2238, 2192, 1680, 1650, 1568, 1536, 1446, 1432, 1394, 1382, 1344, 1326, 1298, 1266, 1238, 1192, 1156, 1136, 1114, 1082, 1060, 1048, 1022, 944, 916, 892, 838, 810, 784, 760, 744, 720, 702, 634, 618.

MS (70 eV, EI) *m/z* (%): 262 (33) [M^+], 235 (100), 223 (16), 198 (21), 183 (20), 155 (11), 142 (10), 79 (5), 67 (19).

HRMS (EI): *m/z* calc. for **$C_{12}H_{11}BrN_2$** (262.0106): 262.0115 (M^+).

Synthesis of 3-bromo-5-cyclohex-2-en-1-ylisonicotinonitrile (107e):



According to **TP13**, a mixture of 3-bromo-isonicotinonitrile (**95m**; 366 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93b**; 3.1 mL, 2.2 mmol, 0.71M in THF) at −78 °C for 1 h. Then, CuCN·2LiCl (1.1 mL, 1.1 mmol, 1M in THF) was added and stirred for 30 min. Subsequently, 3-bromocyclohexene (258 mg, 1.6 mmol) was added. The reaction mixture was allowed to slowly warm to 25 °C and stirred for 12 h. Sat. aq. NH_4Cl (9 mL) and conc. aq. NH_3 (1 mL) were added. The aqueous layer was extracted with Et_2O (3x30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 5:1) furnished **107e** as a yellow oil (266 mg, 63%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.72 (s, 1H), 8.56 (s, 1H), 5.97-6.13 (m, 1H), 5.55-5.70 (m, 1H), 3.72-3.90 (m, 1H), 2.02-2.26 (m, 3H), 1.47-1.80 (m, 3H).

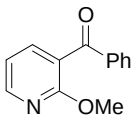
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 150.4, 149.7, 148.3, 145.6, 131.3, 125.8, 122.7, 113.9, 38.8, 31.0, 24.6, 20.5.

IR (ATR) υ (cm^{-1}): 3024, 2932, 2860, 2836, 2236, 1650, 1528, 1448, 1432, 1404,1344,1302, 1272, 1248, 1222, 1198, 1160, 1130, 1058, 1044, 996, 932, 906, 894, 882 ,856, 842, 802, 780, 754, 744, 724, 714, 626.

MS (70 eV, EI) *m/z* (%): 263 (100) [M^+-H], 247 (49), 235 (40), 211 (8), 183 (10), 166 (28), 155 (12), 142 (14), 54 (18).

HRMS (EI): *m/z* calc. for **$C_{12}H_{11}BrN_2$** (262.0106): 262.0114 (M^+).

Synthesis of (2-methoxypyridin-3-yl)(phenyl)methanone (106f):



According to **TP12**, 2-methoxypyrdine (**95n**; 218 mg, 2.0 mmol) reacted with $[(t\text{Bu})NCH(i\text{Pr})(t\text{Bu})]_3Al{\cdot}3LiCl$ (**94b**; 6.67 mL, 2.0 mmol, 0.3M in THF) at 25 °C for 2 h. At −40 °C, $ZnCl_2$ (2.2 mL, 2.2 mmol, 1M in THF) was added, followed by the addition of

CuCN·2LiCl (2.2 mL, 2.2 mmol, 1M in THF). After stirring for 20 min at –40 °C, benzoyl chloride (308 mg, 1.6 mmol) was added and the reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 12 h. Sat. aq. NH_4Cl (9 mL) and conc. aq. NH_3 (1 mL) were added. The aqueous layer was extracted with Et_2O (3x 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 5:1) furnished **106f** as a white solid (272 mg, 80%).

m.p.: 80.2-81.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.31 (dd, *J*=5.0Hz, 2.0Hz, 1H), 7.81–7.76 (m, 2H), 7.71 (dd, *J*=7.3Hz, 2.1Hz, 1H), 7.60–7.54 (m, 1H), 7.47–7.40 (m, 2H), 7.00 (dd, *J*=7.3Hz, 5.1Hz, 1H), 3.87 (s, 3H).

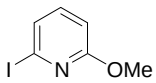
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 194.7, 161.1, 149.2, 138.9, 137.2, 133.3, 129.7, 128.4, 122.7, 116.5, 53.7.

IR (ATR) υ (cm^{-1}): 2984, 1654, 1596, 1576, 1468, 1448, 1406, 1322, 1312, 1302, 1284, 1256, 1232, 1180, 1152, 1104, 1014, 952, 944, 930, 858, 830, 816, 784, 770, 706, 686, 646.

MS (70 eV, EI) *m/z* (%): 213 (92) [M^+], 184 (13), 136 (94), 122 (95), 105 (100), 77 (64), 60 (10), 57 (10), 51 (15), 45 (10), 43 (52).

HRMS (EI): *m/z* calc. for **$C_{13}H_{11}NO_2$** (213.0790): 213.0784 (M^+).

Synthesis of 2-iodo-6-methoxypyridine (107f):



According to **TP13**, a mixture of 2-methoxypyridine (**95n**; 218 mg, 2 mmol) and BF_3·OEt_2 (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**91**; 1.8 mL, 2.2 mmol, 1.2M in THF) at 0 °C for 60 h. At –30 °C, a solution of iodine (4 mmol, 1 g) in THF (4 mL) was added. The reaction mixture was allowed to slowly warm to 25 °C. Sat. aq. NH_4Cl (9 mL), conc. aq. NH_3 (1 mL) and sat. aq. $Na_2S_2O_3$ (2 mL) were added. The aqueous layer was extracted with Et_2O (3x 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 150:1) furnished **107f** as a yellow solid (353 mg, 75%).

m.p.: 49.1-50.3 °C.

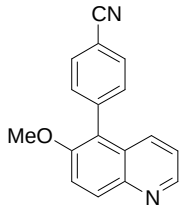
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.29 (dd, *J*=7.5Hz, 0.7Hz, 1H), 7.13-7.19 (m, 1H), 6.67 (dd, *J*=8.2Hz, 0.9Hz, 1H), 3.90 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 163.4, 139.6, 127.5, 113.7, 109.9, 54.1.

IR (ATR) υ (cm^{-1}): 3010, 2980, 1590, 1576, 1548, 1458, 1436, 1406, 1390, 1306, 1286, 1252, 1220, 1190, 1154, 1114, 1072, 1022, 980, 878, 780, 720, 652, 606.

HRMS (ESI): *m/z* calc. for **C_6H_7INO** (235,9572): 235.9566 ($[M+H]^+$).

Synthesis of 4-(6-methoxyquinolin-5-yl)benzonitrile (106g):



According to **TP12**, 6-methoxyquinoline (**95o**; 318 mg, 2.0 mmol) reacted with [(*t*Bu)NCH(*i*Pr)(*t*Bu)]$_3$Al·3LiCl (**94b**; 2.0 mmol, 6.67 mL, 0.3M in THF) at −78 °C for 1 h. Then, $ZnCl_2$ (2.2 mmol, 2.2 mL, 1M in THF) was added dropwise at −78 °C and stirred for 30 min, followed by addition of $Pd(dba)_2$ (56 mg, 5 mol%) and P(2-fur)$_3$ (46 mg, 10 mol%) in THF (4 mL) and 4-iodobenzonitrile (503 mg, 1.6 mmol) in THF (2 mL). The reaction mixture was allowed to warm to 25 °C and continuously stirred for 12 h. Then, sat. aq. NH_4Cl (9 mL) and conc. aq. NH_3 (1 mL) were added. The aqueous layer was extracted with Et_2O (3× 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 4:1) furnished **106g** as a white solid (283 mg, 68% yield).

m.p.: 183.4-185.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.77 (dd, *J*=4.3Hz, 1.7Hz, 1H), 8.11 (dd, *J*=8.3Hz, 1.8Hz, 1H), 7.82–7.73 (m, 4H), 7.41–7.37 (m, 2H), 7.14 (d, *J*=2.8Hz, 1H), 3.97 (s, 3H).

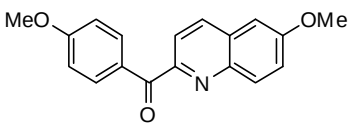
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 157.2, 148.0, 143.8, 141.7, 140.2, 135.3, 131.8, 131.3, 130.1, 123.1, 121.7, 119.1, 111.2, 106.0, 55.7.

IR (ATR) υ (cm^{-1}): 2224, 1606, 1596, 1472, 1444, 1426, 1400, 1380, 1372, 1340, 1312, 1234, 1212, 1202, 1188, 1176, 1150, 1122, 1114, 1046, 1026, 988, 964, 918, 882, 850, 836, 798, 784, 770, 744, 660, 642, 604.

MS (70 eV, EI) *m/z* (%): 260 (M^+, 65), 259 (100), 244 (9), 229 (10), 216 (24).

HRMS (EI): *m/z* calc. for **$C_{17}H_{12}N_2O$** (260.0950): 260.0943 (M^+).

Synthesis of (4-methoxyphenyl)(6-methoxyquinolin-2-yl)methanone (107g):



According to **TP13**, a mixture of 6-methoxyquinoline (**95o**; 318 mg, 2 mmol) and $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**91**; 1.83 mL, 2.2 mmol, 1.2M in THF) at 0 °C for 1 h. At –40 °C, CuCN·2LiCl (2.2 mL, 2.2 mmol, 1M in THF) was added and continuously stirred for 30 min. Subsequently, 4-methoxybenzoyl chloride (273 mg, 1.6 mmol) was added at –40 °C. The reaction mixture was allowed to slowly warm to 25 °C and stirred for 12 h. Then, sat. aq. NH_4Cl (9 mL) and conc. aq. NH_3 (1 mL) were added. The aqueous layer was extracted with Et_2O (3x 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 2:1) furnished **107g** as a white solid (441 mg, 94% yield).

m.p.: 138.1-139.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.27 (ddd, *J*=9.4Hz, 2.8Hz, 2.4Hz, 2H), 8.21 (d, *J*=8.6Hz, 1H), 8.12 (d, *J*=9.4Hz, 1H), 8.05 (d, *J*=8.4Hz, 1H), 7.42 (dd, *J*=9.2Hz, 2.8Hz, 1H), 7.13 (d, *J*=2.8Hz, 1H), 6.98 (ddd, *J*=9.4Hz, 2.8Hz, 2.4Hz, 2H), 3.97 (s, 3H), 3.89 (s, 3H).

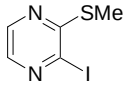
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 191.8, 163.6, 159.3, 152.8, 142.4, 135.7, 133.9, 131.7, 130.2, 129.2, 123.2, 121.4, 113.5, 104.9, 55.7, 55.5.

IR (ATR) υ (cm^{-1}): 3006, 2932, 2842, 1646, 1620, 1596, 1512, 1498, 1480, 1434, 1406, 1384, 1344, 1330, 1308, 1292, 1256, 1232, 1186, 1162, 1134, 1120, 1108, 1022, 972, 944, 904, 850, 830, 812, 792, 782, 754, 732, 710, 654, 634, 612.

MS (70 eV, EI) *m/z* (%): 293 (84) [M^+], 278 (13), 265 (87), 250 (23), 234 (15), 135 (100), 107 (13), 92 (11), 77 (15).

HRMS (EI): *m/z* calc. for **$C_{18}H_{15}NO_3$** (293.1052): 293.1046 (M^+).

Synthesis of 2-iodo-3-(methylthio)pyrazine (106h):

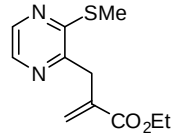


$BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) was added dropwise to $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**93b**; 2.75 mL, 1.1 mmol, 0.4M in THF) at –40 °C and the resulting mixture was stirred for 10 min at –40 °C. Then, 2-(thiomethyl)pyrazine (**95g**; 252 mg, 2 mmol) in dry THF (2 mL) was added dropwise. After stirring for 2 h, a solution of iodine (762 mg, 3 mmol) in dry THF (3 mL) was added and the reaction mixture was slowly warmed to 25 °C. The reaction solution was quenched with brine (5 mL), aq. NH_3 (5 mL, 2M) and sat. aq. $Na_2S_2O_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **106h** as an off-white solid (388 mg, 77%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.30 (d, *J*=2.4Hz, 1H), 7.95 (d, *J*=1.0Hz, 1H), 2.50 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 162.7, 142.1, 138.9, 118.6, 15.6.

Synthesis of ethyl 2-{[3-(methylsulfanyl)pyrazin-2-yl]methyl}prop-2-enoate (106i):



$BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) was added dropwise to $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**93b**; 2.75 mL, 1.1 mmol, 0.4M in THF) at –40 °C and the resulting mixture was stirred for 10 min at –40 °C. Then, 2-(thiomethyl)pyrazine (**95g**; 252 mg, 2 mmol) in dry THF (2 mL) was added dropwise. After stirring for 2 h, CuCN·2LiCl (0.2 mL, 0.2 mmol, 1M in THF) were added at –40 °C, followed by addition of 2-(bromomethyl)acrylate (**97k**; 1.6 mmol, 309 mg). The reaction mixture was allowed to warm to 25 °C and continuously stirred for 4 h. The reaction solution was quenched with brine (10 mL) and aq. NH_3 (5 mL, 2M). The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **106i** as a yellow oil (324 mg, 77%).

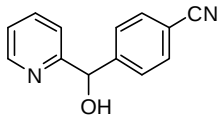
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.30 (d, *J*=2.6Hz, 1H), 8.15 (d, *J*=2.6Hz, 1H), 6.36 (s, 1H), 5.56 (d, *J*=1.1Hz, 1H), 4.20 (q, *J*=7.2Hz, 2H), 3.85 (s, 2H), 2.58 (s, 3H), 1.25 (t, *J*=7.1Hz, 3H).

MS (70 eV, EI) *m/z* (%): 239 (13), 238 (M^+, 89), 223 (38), 209 (49), 195 (15), 193 (39), 192 (46), 191 (15), 169 (24), 167 (89), 166 (19), 165 (18), 152 (26), 151 (48), 150 (100), 131 (18).

IR (ATR) υ (cm^{-1}): 2982, 2930, 2362, 2340, 2252, 1712, 1636, 1516, 1368, 1292, 1204, 1144, 1088, 1024, 952, 912, 858, 814, 728, 646.

HRMS (EI): *m/z* calc. for **$C_{11}H_{14}N_2O_2S$** (238.0776): 238.0770 (M^+).

Synthesis of 4-[hydroxy(pyridin-2-yl)methyl]benzonitrile (106k):



According to **TP14**, pyridine (**95d**; 158 mg, 2 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**91**; 1.83 mL, 2.2 mmol, 1.2M in THF) at –40 °C for 10 min. Subsequently, addition of 4-cyanobenzaldehyde (**97l**; 2.2 mmol, 288 mg) produced, after

usual work-up, the crude alcohol. Flash column chromatographical purification (SiO_2, pentane/EtOAc, 3:2) furnished **106k** as a pale brown oil (307 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.58 (d, *J*=4.3Hz, 1H), 7.69 (dd, *J*=7.5Hz, 1.7Hz, 1H), 7.63 (d, *J*=8.4Hz, 2H), 7.54 (d, *J*=8.4Hz, 2H), 7.24 (dd, *J*=7.5Hz, 0.7Hz, 1H), 7.18 (d, *J*=7.9Hz, 1H), 5.81 (s, 1H).

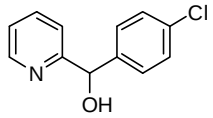
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.4, 148.3, 148.0, 137.0, 132.2, 127.4, 122.8, 121.0, 118.5, 111.4, 74.2.

MS (70 eV, EI) *m/z* (%): 211 (15), 210 (M^+, 100), 209 (43), 193 (14), 192 (15), 180 (12), 130 (17), 108 (42), 104 (11), 102 (18), 80 (18), 79 (91), 78 (29), 77 (12), 52 (16), 51 (20).

IR (ATR) υ (cm^{-1}): 3192, 3062, 2872, 2228, 1738, 1724, 1668, 1608, 1592, 1572, 1502, 1472, 1436, 1406, 1312, 1196, 1114, 1056, 870, 810, 780, 750, 616.

HRMS (EI): *m/z* calc. for **$C_{13}H_{10}N_2O$** (210.0793): 210.0791 (M^+).

Synthesis of (4-chlorophenyl)(pyridin-2-yl)methanol (106l):



According to **TP14**, pyridine (**95d**; 158 mg, 2 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**91**; 1.83 mL, 2.2 mmol, 1.2M in THF) at –40 °C for 10 min. Subsequently, addition of 4-chlorobenzaldehyde (**97h**; 2.2 mmol, 309 mg) produced, after usual work-up, the crude alcohol. Flash column chromatographical purification (SiO_2, pentane/EtOAc, 2:1) furnished **106l** as a pale yellow solid (298 mg, 68%).

m.p.: 96.3-97.5 °C.

^{1}H NMR (300 MHz, D6-acetone) δ (ppm): 8.52 (d, *J*=4.1Hz, 1H), 7.78 (dt, *J*=7.6Hz, 1.8Hz, 1H), 7.56 (d, *J*=8.0Hz, 1H), 7.53 (d, *J*=8.2Hz, 2H), 7.37 (d, *J*=8.8Hz, 2H), 7.25 (ddd, *J*=7.5Hz, 4.8Hz, 1.2Hz, 1H), 5.90 (s, 1H), 5.64 (br s, 1H).

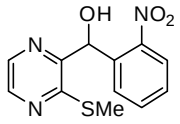
^{13}C NMR (75 MHz, D6-acetone) δ (ppm): 163.4, 149.0, 143.9, 137.6, 133.1, 129.0, 128.8, 123.0, 121.1, 75.6.

MS (70 eV, EI) *m/z* (%): 221 (31), 220 (24), 219 (M^+, 100), 217 (41), 216 (16), 215 (22), 203 (17), 202 (18), 201 (47), 200 (12), 190 (17), 188 (46), 16 (33), 141 (18), 139 (40), 111 (25), 108 (40), 80 (22), 79 (94), 78 (24), 77 (21).

IR (ATR) υ (cm^{-1}): 3142, 2848, 1592, 1572, 1492, 1468, 1438, 1410, 1334, 1192, 1114, 1090, 1056, 1018, 1002, 856, 812, 770, 748, 624.

HRMS (EI): *m/z* calc. for **$C_{12}H_{10}ClNO$** (219.0451): 219.0444 (M^+).

Synthesis of [3-(methylsulfanyl)pyrazin-2-yl](2-nitrophenyl)methanol (106m):



According to **TP14**, 2-(thiomethyl)pyrazine (**95q**; 252 mg, 2 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**91**; 1.83 mL, 2.2 mmol, 1.2M in THF) at –40 °C for 10 min. Subsequently, addition of 2-nitrobenzaldehyde (**97m**; 2.2 mmol, 333 mg) produced, after usual work-up, the crude alcohol. Flash column chromatographical purification (SiO_2, pentane/EtOAc, 2:1) furnished **106m** as a brown oil (310 mg, 56%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.53 (d, *J*=1.5Hz, 1H), 8.34 (d, *J*=1.7Hz, 1H), 7.96 (dd, *J*=8.0Hz, 1.3Hz, 1H), 7.80 (dd, *J*=8.0Hz, 1.5Hz, 1H), 7.64 (dt, *J*=7.6Hz, 1.3Hz, 1H), 7.45 (ddd, *J*=8.3Hz, 7.2Hz, 1.5Hz, 1H), 6.51 (s, 1H), 2.55 (s, 3H).

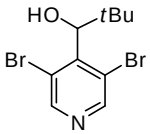
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 156.3, 150.3, 143.5, 142.6, 141.6, 137.7, 133.5, 129.6, 128.6, 124.5, 68.9, 12.7.

MS (70 eV, EI) *m/z* (%): 277 (M^+, 3), 245 (13), 243 (14), 229 (16), 226 (25), 215 (17), 197 (12), 196 (20), 183 (17), 182 (100), 19 (17), 155 (26), 126 (36), 125 (37), 105 (39), 98 (46), 58 (20), 51 (16).

IR (ATR) υ (cm^{-1}): 2954, 2926, 2868, 2360, 2342, 1528, 1458, 1348, 1238, 1182, 1118, 1022, 936, 824, 786, 750, 726.

HRMS (EI): *m/z* calc. for **$C_{12}H_{11}N_3O_3S$** (277.0521): 277.0496 (M^+).

Synthesis of [1-(3,5-dibromopyridin-4-yl)-2,2-dimethylpropan-1-ol (106n):



According to **TP14**, 3,5-dibromopyridine (**95q**; 474 mg, 2 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**91**; 1.83 mL, 2.2 mmol, 1.2M in THF) at –40 °C for 30 min. Subsequently, addition of pivaldehyde (**97n**; 2.2 mmol, 190 mg) produced, after usual work-up, the crude alcohol. Flash column chromatographical purification (SiO_2, pentane/EtOAc, 4:1) furnished **106n** as a yellow oil (511 mg, 79%).

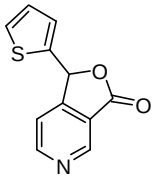
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.82 (s, 2H), 4.97 (s, 1H), 1.01 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 150.6, 146.7, 120.8, 77.5, 38.1, 25.9.

IR (ATR) υ (cm^{-1}): 2956, 2928, 2868, 2360, 2342, 1716, 1554, 1514, 1464, 1396, 1364, 1198, 1064, 1014, 908, 886, 764, 730, 642.

HRMS (ESI): *m/z* calc. for **$C_{10}H_{14}Br_2NO$** (321,9442): 321.9430 ($[M+H]^+$).

Synthesis of 1-thiophen-2-ylfuro[3,4-*c*]pyridin-3(1*H*)-one (106o):



According to **TP14**, ethyl nicotinate (**95f**; 302 mg, 2 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**91**; 1.83 mL, 2.2 mmol, 1.2M in THF) at −40 °C for 30 min. Subsequently, addition of thiopehen-2-carbaldehyde (**97o**; 2.2 mmol, 247 mg) produced, after usual work-up, the crude lactone. Flash column chromatographical purification (SiO_2, pentane/EtOAc, 1:1) furnished **106m** as a yellow solid (304 mg, 70%).

m.p.: 85.6-87.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.38 (s, 1H), 8.98 (d, *J*=7.6Hz, 1H), 7.41 (d, *J*=5.0Hz, 1H), 7.30-7.37 (m, 1H), 7.14-7.20 (m, 2H), 6.85 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.3, 156.4, 154.3, 152.5, 149.9, 148.1, 134.8, 128.2, 127.5, 127.1, 88.5.

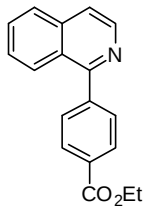
MS (70 eV, EI) *m/z* (%): 218 (14), 217 (M^+, 61), 216 (80), 189 (31), 156 (23), 142 (90), 123 (40), 110 (100), 106 (60), 105 (16), 78 (30).

IR (ATR) υ (cm^{-1}): 3102, 2972, 2930, 2362, 2342, 1788, 1722, 1652, 1600, 1588, 1410, 1380, 1282, 1258, 1228, 1102, 1076, 1026, 994, 906, 846, 718.

HRMS (EI): *m/z* calc. for **$C_{11}H_7NO_2S$** (217.0197): 217.0185 (M^+).

5.3 Direct Preparation of Functionalized Organoborates via Accelerated C-H Activation Using Amidoborates

Synthesis of ethyl 4-isoquinolin-1-ylbenzoate (116b):



According to **TP16**, isoquinoline (**113a**; 258 mg, 2 mmol) reacted with $TMPBEt_3 \cdot MgCl \cdot LiCl$ (**110b**; 2.2 mL, 2.2 mmol, 1.0M in THF) at 25 °C for 15 min. Then, $ZnCl_2$ (0.2 mL, 0.2 mmol, 1M in THF), $Pd(dba)_2$ (23 mg, 2 mol%) and P(2-furyl)$_3$ (19 mg, 4 mol%) were added to the reaction mixture, followed by addition of ethyl 4-iodobenzoate (**115a**; 442 mg, 1.6 mmol). The reaction mixture was continuously stirred at 25 °C for 12 h. Subsequently, a mixture of

sat. aq. brine (10 mL) and conc. aq. NH_3 (0.5 mL) were added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 9:1) furnished **116b** as an off-white solid (342 mg, 77%).

m.p.: 68.0-70.0 °C.

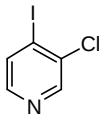
^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm): 8.63 (d, *J*=5.7Hz, 1H), 8.22 (d, *J*=8.6Hz, 2H), 8.03 (d, *J*=8.5Hz, 1H), 7.90 (d, *J*=8.2Hz, 1H), 7.78 (d, *J*=8.5Hz, 2H), 7.72–7.67 (m, 2H), 7.55 (dt, *J*=8.3Hz, 1.3Hz, 1H), 4.44 (q, *J*=7.2Hz, 2H), 1.44 (t, *J*=7.2Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.4, 159.6, 143.9, 142.3, 136.8, 130.5, 130.2, 130.0, 129.6, 127.5, 127.1, 127.1, 126.6, 120.4, 61.1, 14.4.

IR (ATR) υ (cm^{-1}): 2981, 1715, 1273, 1102, 827, 772, 707.

HRMS (EI): *m/z* calc. for **$C_{18}H_{15}NO_2$** (277.1103): 277.1098 (M^+).

Synthesis of 3-chloro-4-iodopyridine (116c):



According to **TP16**, pyridine (**113a**; 156 mg, 2 mmol) reacted with $TMPBEt_3$·MgCl·LiCl (**110b**; 2.2 mL, 2.2 mmol, 1.0M in THF) at 25 °C for 3 min. Then, a solution of iodine (3 mmol, 762 mg) in THF (3 mL) was added at 25 °C and continuously stirred for 30 min. Subsequently, a mixture of sat. aq. brine (10 mL), conc. aq. NH_3 (0.5 mL), sat. aq. $Na_2S_2O_3$ (5 mL) were added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 9:1) furnished **116c** as a pale yellow solid (388 mg, 81%).

m.p.: 100.8-102.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm): 8.56 (s, 1H), 8.08 (d, *J*=5.1Hz, 1H), 7.80 (d, *J*=5.1Hz, 1H).

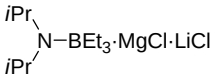
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 148.4, 147.3, 137.1, 134.8, 109.1.

MS (70 eV, EI) *m/z* (%): 241 (45), 239 (M^+, 100), 165 (26), 112 (53), 111 (22), 97 (28), 85 (61), 83 (41), 81 (41), 71 (69), 69 (37), 57 (96), 55 (36), 43 (37).

IR (ATR) υ (cm^{-1}): 2960, 2918, 2850, 2428, 2362, 1932, 1738, 1548, 1452, 1382, 1264, 1176, 1124, 1058, 1022, 910, 822, 738, 708, 656.

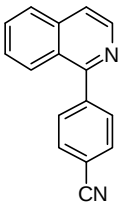
HRMS (EI): *m/z* calc. for **C_5H_3ClIN** (238.8999): 238.8993 (M^+).

Preparation of the reagent *i*Pr$_2$NBEt$_3$·MgCl·LiCl (110k)



A dried, argon flushed 250 mL *Schlenk*-flask equipped with magnetic stirring bar and rubber septum was charged with *i*Pr$_2$NMgCl·LiCl[312] (**111e**; 54.5 mL, 1.1 M in THF, 60 mmol). At –20 °C, BEt$_3$ (60 mmol, 5.86 g) was added dropwise via syringe to the vigorously stirred solution. Subsequently, the solution was allowed to slowly warm to 25 °C and continuously stirred for 30 min. The freshly prepared reagent *i*Pr$_2$NBEt$_3$·MgCl·LiCl (**110k**) was titrated prior to use at 0 °C versus benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.7 M in THF was obtained.

Synthesis of 4-isoquinolin-1-ylbenzonitrile (116d):



According to **TP16**, isoquinoline (**113a**; 258 mg, 2 mmol) reacted with *i*Pr$_2$NBEt$_3$·MgCl·LiCl (**110k**; 3.1 mL, 2.2 mmol, 0.7M in THF) at 25 °C for 15 min. Then, ZnCl$_2$ (0.2 mL, 0.2 mmol, 1M in THF), Pd(OAc)$_2$ (14 mg, 3 mol%) and S-Phos (50 mg, 6 mol%) were added to the reaction mixture, followed by addition of 4-bromobenzonitrile (**115b**; 292 mg, 1.6 mmol). The reaction mixture was continuously stirred at 50 °C for 12 h. Subsequently, a mixture of sat. aq. brine (10 mL) and conc. aq. NH$_3$ (0.5 mL) were added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 9:1) furnished **116d** as a pale yellow solid (291 mg, 79%).

m.p.: 179.0-180.0 °C.

^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm): 8.63 (d, *J*=5.7Hz, 1H), 7.96 (d, *J*=8.2Hz, 2H), 7.71-7.84 (m, 6H), 7.52-7.62 (m, 1H).

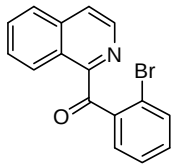
Preparation of the reagent TMPB(N*i*Pr$_2$)$_3$·MgCl·LiCl (110r):

A dried, argon flushed 100 mL *Schlenk*-flask equipped with magnetic stirring bar and rubber septum was charged with TMPMgCl·LiCl[312] (**91**; 16.6 mL, 1.2 M in THF, 20 mmol). At –20

[312] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed*. **2004**, *43*, 3333; b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed*. **2005**, *44*, 159; c) A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497.

°C, B(N*i*Pr$_2$)$_3$ (20 mmol, 6.21 g) was added dropwise via syringe to the vigorously stirred solution. Subsequently, the solution was allowed to slowly warm to 25 °C and continuously stirred for 30 min. The freshly prepared reagent TMPB(N*i*Pr$_2$)$_3$·MgCl·LiCl (**110r**) was titrated prior to use at 0 °C versus benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.9 M in THF was obtained.

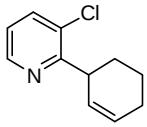
Synthesis of (2-bromophenyl)(isoquinolin-1-yl)methanone (116e):



According to **TP16**, isoquinoline (**113a**; 258 mg, 2 mmol) reacted with TMPB(N*i*Pr$_2$)$_3$·MgCl·LiCl (**110r**; 2.4 mL, 2.2 mmol, 0.9M in THF) at 25 °C for 15 min. At –40 °C, $ZnCl_2$ (2 mL, 2 mmol, 1M in THF) and CuCN·2LiCl (10 mol%, 0.2 mL, 1M in THF) were added, followed by addition of 2-bromobenzoyl chloride (**115c**; 1.6 mmol, 351 mg). Then, the reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 4 h. Subsequently, sat. aq. brine (10 mL) and conc. aq. NH_3 (0.5 mL) were added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 9:1) furnished **116e** as a pale yellow solid (393 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.74-8.84 (m, 1H), 8.53 (d, *J*=5.7Hz, 1H), 7.87-7.98 (m, 1H), 7.11-7.84 (m, 7H).

Synthesis of 3-chloro-2-cyclohex-2-en-1-ylpyridine (116f):



According to **TP16**, 3-chloropyridine (**113b**; 227 mg, 2 mmol) reacted with TMPB(N*i*Pr$_2$)$_3$·MgCl·LiCl (**110r**; 2.4 mL, 2.2 mmol, 0.9M in THF) at 25 °C for 15 min. At –40 °C, CuCN·2LiCl (10 mol%, 0.2 mL, 1M in THF) was added, followed by addition of 3-bromobyclohexene (**115d**; 1.6 mmol, 258 mg). Thereafter, reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 4 h. Subsequently, sat. aq. brine (10 mL) and conc. aq. NH_3 (0.5 mL) were added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*.

Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **116f** as a yellow oil (343 mg, 78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.49 (dd, *J*=4.7Hz, 1.3Hz, 1H), 7.62 (dd, *J*=7.9 Hz, 1.5Hz, 1H), 7.07 (dd, *J*=8.0Hz, 4.7Hz, 1H), 5.86-6.06 (m, 1H), 5.88-5.88 (m, 1H), 5.65-5.85 (m, 1H), 4.00-4.14 (m, 3H), 1.98-2.25 (m, 1H), 1.78-1.95 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.7, 147.5, 136.9, 130.8, 128.5, 128.0, 122.1, 40.1, 28.5, 24.7, 21.7.

MS (70 eV, EI) *m/z* (%): 194 (8), 193 (M^+, 44), 192 (28), 166 (28), 165 (24), 164 (100), 158 (11), 127 (16), 67 (14), 57 (19), 55 (15), 44 (21), 43 (25), 41 (25).

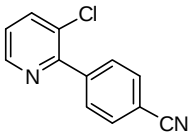
IR (ATR) υ (cm^{-1}): 3026, 2932, 2860, 2836, 1680, 1572, 1444, 1422, 1310, 1266, 1186, 1128, 1026, 886, 794, 760, 720, 648, 608.

HRMS (EI): *m/z* calc. for **$C_{11}H_{12}ClN$** (193.0658): 193.0660 (M^+).

Preparation of the reagent TMPB(F)$(HMDS)_2$·MgCl·LiCl (110q):

A dried, argon flushed 100 mL *Schlenk*-flask equipped with magnetic stirring bar and rubber septum was charged with TMPMgCl·LiCl[312] (**91**; 41.6 mL, 1.2 M in THF, 50 mmol). At –20 °C, B(F)$(HMDS)_2$ (50 mmol, 17.5 g) was added dropwise via syringe to the vigorously stirred solution. Subsequently, the solution was allowed to slowly warm to 25 °C and continuously stirred for 30 min. The freshly prepared reagent TMPB(F)$(HMDS)_2$·MgCl·LiCl (**110q**) was titrated prior to use at 0 °C versus benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.7 M in THF was obtained.

Synthesis of 4-(3-chloropyridin-2-yl)benzonitrile (116g):



According to **TP16**, 3-chloropyridine (**113b**; 227 mg, 2 mmol) reacted with TMPB(F)$(HMDS)_2$·MgCl·LiCl (**110q**; 3.1 mL, 2.2 mmol, 0.7M in THF) at 25 °C for 15 min followed by addition of $ZnCl_2$ (0.2 mL, 0.2 mmol, 1M in THF), $Pd(OAc)_2$ (14 mg, 3 mol%) and S-Phos (50 mg, 6 mol%) and 4-iodobenzonitrile (550 mg, 2.4 mmol). Subsequently, the reaction mixture was continuously stirred at 50 °C for 12 h. Then, sat. aq. brine (10 mL) and conc. aq. NH_3 (0.5 mL) were added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*.

Flash column chromatographical purification (pentane/EtOAc, 9:1) furnished **116g** as a pale yellow solid (351 mg, 82%).

m.p.: 163.6-164.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.61 (dd, *J*=4.5Hz, 1.1Hz, 1H), 7.79-7.89 (m, 3H), 7.74 (d, *J*=8.4Hz, 2H), 7.29 (dd, *J*=8.0Hz, 4.7Hz, 1H).

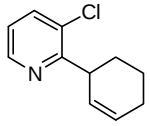
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 184.0, 153.2, 146.6, 141.9, 138.5, 136.3, 136.0, 130.1, 128.2, 125.8.

MS (70 eV, EI) *m/z* (%): 216 (13), 214 (M+, 41), 180 (12), 179 (100), 152 (13), 51 (22), 50 (14).

IR (ATR) υ (cm^{-1}): 3320, 2980, 2362, 2342, 1672, 1580, 1458, 1382, 1276, 1172, 1128, 1116, 966, 904, 790, 748, 708, 684.

HRMS (EI): *m/z* calc. for **$C_{12}H_7ClN_2$** (214.0298): 214.0287 (M^+).

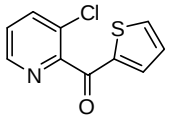
Synthesis of 3-chloro-2-cyclohex-2-en-1-ylpyridine (116h):



According to **TP16**, 3-chloropyridine (**113b**; 227 mg, 2 mmol) reacted with TMPB(F)$(HMDS)_2$·MgCl·LiCl (**110q**; 3.1 mL, 2.2 mmol, 0.7M in THF) at 25 °C for 15 min. At –40 °C, CuCN·2LiCl (10 mol%, 0.2 mL, 1M in THF) was added, followed by addition of 3-bromobyclohexene (2.4 mmol, 387 mg). Thereafter, reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 4 h. Subsequently, sat. aq. brine (10 mL) and conc. aq. NH_3 (0.5 mL) were added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **116h** as a yellow oil (282 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.49 (dd, *J*=4.7Hz, 1.3Hz, 1H), 7.62 (dd, *J*=7.9 Hz, 1.5Hz, 1H), 7.07 (dd, *J*=8.0Hz, 4.7Hz, 1H), 5.86-6.06 (m, 1H), 5.88-5.88 (m, 1H), 5.65-5.85 (m, 1H), 4.00-4.14 (m, 3H), 1.98-2.25 (m, 1H), 1.78-1.95 (m, 2H).

Synthesis of (3-chloropyridin-2-yl)(thiophen-2-yl)methanone (116i):



According to **TP16**, 3-chloropyridine (**113b**; 227 mg, 2 mmol) reacted with TMPB(F)(HMDS)$_2$·MgCl·LiCl (**110q**; 3.1 mL, 2.2 mmol, 0.7M in THF) at 25 °C for 15 min. At –40 °C, CuCN·2LiCl (10 mol%, 0.2 mL, 1M in THF) was added, followed by addition of 2-thiophenecarbonyl chloride (2.4 mmol, 352 mg). Thereafter, reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 4 h. Subsequently, sat. aq. brine (10 mL) and conc. aq. NH_3 (0.5 mL) were added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 9:1) furnished **116i** as a yellow oil (344 mg, 77%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.58 (dd, *J*=4.6Hz, 1.0Hz, 1H), 7.84 (dd, *J*=8.2Hz, 1.1Hz, 1H), 7.76 (d, *J*=4.9Hz, 1H), 7.65 (d, *J*=3.0Hz, 1H), 7.40 (dd, *J*=8.2Hz, 4.7Hz, 1H), 7.13 (t, *J*=4.5Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 184.0, 153.2, 146.6, 141.9, 138.5, 136.3, 136.0, 130.1, 128.2, 125.8.

IR (ATR) υ (cm^{-1}): 3086, 2926, 2854, 2362, 2342, 1720, 1650, 1514, 1406, 1354, 1298, 1230, 1208, 1168, 1134, 1066, 1038, 890, 850, 798, 724, 634.

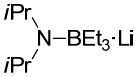
Synthesis of 2-iodopyridine (116j):

A dry and argon-flushed Schlenk-flask equipped with magnetic stirring bar and rubber septum was charged with TMPMgCl·LiCl[312] (**91**; 0.82 mL, 1.2M in THF, 1.1 mmol). At –40 °C, $B(C_6F_5)_3$ (1.1 mmol, 512 mg) in THF (1 mL) was added dropwise via syringe. After stirring for 10 min at –40 °C, pyridine (**113c**; 1 mmol, 79 mg) in THF (1 mL) was added dropwise and stirred for additional 2 min, followed by addition of iodine (1.5 mmol, 381 mg) in THF (1 mL). Then, the solution was allowed to slowly warm to 25 °C and continuously stirred for 30 min. Subsequently, a mixture of sat. aq. brine (10 mL), conc. aq. NH_3 (0.5 mL), sat. aq. $Na_2S_2O_3$ (5 mL) were added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **116j** as a yellow oil (154 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm): 8.39 (d, *J*=4.4Hz, 1H), 7.75 (d, *J*=7.7Hz, 1H), 7.91 (t, *J*=7.6Hz, 1H), 7.27-7.37 (m, 1H).

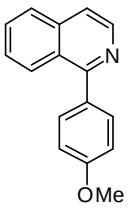
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 150.8, 137.6, 135.0, 122.9, 118.2.

Preparation of the reagent *i*Pr$_2$NBEt$_3$·Li (110j):



A dried, argon flushed 250 mL Schlenk-flask equipped with magnetic stirring bar and rubber septum was charged with diisopropylamine (14.8 mL, 105 mmol) in THF (20 mL) followed by dropwise addition of BuLi (55 mL, 100 mmol, 1.8M in hexane) at –40 °C and continuous stirring for 30 min. At –20 °C, BEt_3 (100 mmol, 9.78 g) was added dropwise via syringe to the vigorously stirred solution. Subsequently, the solution was allowed to slowly warm to 25 °C and continuously stirred for 30 min. The freshly prepared reagent *i*Pr$_2$NBEt$_3$·Li (**110j**) was titrated prior to use at 0 °C versus benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 1.1 M in THF was obtained.

Synthesis of 1-(4-methoxyphenyl)isoquinoline (116k):



According to **TP16**, isoquinoline (**113a**; 258 mg, 2 mmol) reacted with *i*Pr$_2$NBEt$_3$·Li (**110j**; 2.0 mL, 2.2 mmol, 1.1M in THF) at 25 °C for 15 min. Then, $ZnCl_2$ (0.2 mL, 0.2 mmol, 1M in THF), $Pd(OAc)_2$ (14 mg, 3 mol%) and S-Phos (50 mg, 6 mol%) were added to the reaction mixture, followed by addition of 4-bromoanisole (**115e**; 300 mg, 1.6 mmol). The reaction mixture was continuously stirred at 50 °C for 12 h. Subsequently, a mixture of sat. aq. brine (10 mL) and conc. aq. NH_3 (0.5 mL) were added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 4:1) furnished **116k** as a yellow oil (282 mg, 75%).

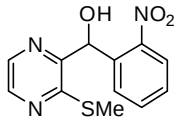
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.58 (d, *J*=5.8Hz, 1H), 8.15 (d, *J*=8.6Hz, 1H), 7.86 (d, *J*=8.6Hz, 1H), 7.58-7.73 (m, 4H), 7.53 (t, *J*=5.8Hz, 1H), 7.06 (d, *J*=6.6Hz, 2H), 3.89 (s, 3H).

Preparation of the reagent *i*Pr$_2$NBEt$_3$·MgCl·LiCl (110k):

A dried, argon flushed Schlenk-flask equipped with magnetic stirring bar and rubber septum was charged with *i*PrMgCl (30 mL, 50 mmol, 1.65M in THF) followed by slow and dropwise addition of diisopropylamine (7.3 mL , 52.5 mmol) at 25 °C. The reaction mixture was

vigorously stirred at 25 °C for 1 h. At –20 °C, BEt_3 (50 mmol, 4.89 g) was added dropwise via syringe to the vigorously stirred solution. Subsequently, the solution was allowed to slowly warm to 25 °C and continuously stirred for 30 min. The freshly prepared reagent *i*Pr_2NBEt_3·MgCl·LiCl (**110k**) was titrated prior to use at 0 °C versus benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.7 M in THF was obtained.

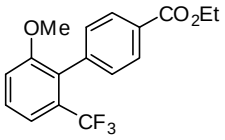
Synthesis of [3-(methylsulfanyl)pyrazin-2-yl](2-nitrophenyl)methanol (118):



According to **TP16**, 2-(thiomethyl)pyrazine (**113d**; 252 mg, 2 mmol) reacted with *i*Pr_2NBEt_3·MgCl·LiCl (**110k**; 3.1 mL, 2.2 mmol, 0.7M in THF) at 25 °C for 15 min. Subsequently, 2-nitrobenzaldehyde (**115f**; 2.2 mmol, 333 mg) in THF (1 mL) was added dropwise at 25 °C to the reaction mixture and continuously stirred for 1 h, followed by addition of EtOAc (10 mL) and aq. 2M NaOH (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (SiO_2, pentane/EtOAc, 3:1) furnished **118** as a brown oil (404 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.53 (d, *J*=1.5Hz, 1H), 8.34 (d, *J*=1.7Hz, 1H), 7.96 (dd, *J*=8.0Hz, 1.3Hz, 1H), 7.80 (dd, *J*=8.0Hz, 1.5Hz, 1H), 7.64 (dt, *J*=7.6Hz, 1.3Hz, 1H), 7.45 (ddd, *J*=8.3Hz, 7.2Hz, 1.5Hz, 1H), 6.51 (s, 1H), 2.55 (s, 13H).

Synthesis of ethyl 2'-methoxy-6'-(trifluoromethyl)biphenyl-4-carboxylate (116l):



According to **TP16**, 1-methoxy-3-(trifluoromethyl)benzene (**113e**; 352 mg, 2 mmol) reacted with TMPBEt_3·MgCl·LiCl (**110b**; 2.2 mL, 2.2 mmol, 1.0M in THF) at 25 °C for 1 h. To a solution of $ZnCl_2$ (0.2 mL, 0.2 mmol, 1M in THF), $Pd(OAc)_2$ (14 mg, 3 mol%), S-Phos (50 mg, 6 mol%) and ethyl 4-iodobenzoate (**115g**; 441 mg, 1.6 mmol) in THF (2 mL), the reaction mixture was added dropwise at 25 °C and continuously stirred for 2 h at 65 °C. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **116l** as a pale yellow solid (493 mg, 95%).

m.p.: 62.8-63.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.11 (d, *J*=8.4Hz, 2H), 7.47 (dt, *J*=8.1Hz, 0.9Hz, 1H), 7.38 (dd, *J*=7.1Hz, 0.7Hz, 1H), 7.33 (d, *J*=8.1Hz, 2H), 7.16 (d, *J*=8.2Hz, 1H), 4.41 (q, *J*=7.1Hz, 2H), 3.73 (s, 3H), 1.42 (t, *J*=7.1Hz, 3H).

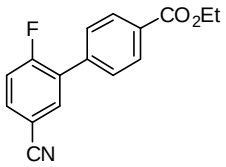
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.5, 157.4, 139.7, 130.1 (q, *J*=1.4Hz), 129.6, 129.1, 128.8, 128.8, 126.5, 124.3 (q, *J*=274.1Hz), 117.8 (q, *J*=5.4Hz), 114.2, 60.9, 56.0, 14.3.

MS (70 eV, EI) *m/z* (%): 325 (11), 324 (M^+, 44), 296 (24), 279 (17), 278 (100), 235 (52), 231 (12), 217 (11), 188 (12), 139 (11), 57 (14), 43 (26), 42 (30).

IR (ATR) υ (cm^{-1}): 2980, 2942, 2906, 2844, 2360, 2342, 1708, 1612, 1468, 1368, 1320, 1290, 1262, 1180, 1170, 1114, 1090, 1034, 852, 798, 774, 742, 710.

HRMS (EI): *m/z* calc. for **$C_{17}H_{15}F_3O_3$** (324.0973): 324.0962 (M^+).

Synthesis of ethyl 5'-cyano-2'-fluorobiphenyl-4-carboxylate (116m):



According to **TP16**, 4-fluorobenzonitrile (**113f**; 242 mg, 2 mmol) reacted with $TMPBEt_3 \cdot MgCl \cdot LiCl$ (**110b**; 2.2 mL, 2.2 mmol, 1.0M in THF) at 25 °C for 30 min. To a solution of $ZnCl_2$ (0.2 mL, 0.2 mmol, 1M in THF), $Pd(OAc)_2$ (14 mg, 3 mol%), S-Phos (50 mg, 6 mol%) and ethyl 4-iodobenzoate (**115g**; 441 mg, 1.6 mmol) in THF (2 mL), the reaction mixture was added dropwise at 25 °C and continuously stirred for 2 h at 65 °C. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **116m** as an off-white solid (345 mg, 80%).

m.p.: 111.2-113.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.16 (d, *J*=8.6Hz, 2H), 7.80 (dd, *J*=6.9Hz, 2.2Hz, 1H), 7.69 (ddd, *J*=8.5Hz, 4.5Hz, 2.2Hz, 1H), 7.60 (d, *J*=8.6Hz, 2H), 7.31 (dd, *J*=9.9Hz, 8.6Hz, 1H), 4.42 (q, *J*=7.1Hz, 2H), 1.43 (t, *J*=7.1Hz, 3H).

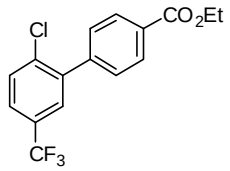
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.0, 162.0 (d, *J*=258.7Hz), 137.6, 135.0 (d, *J*=4.6Hz), 133.7 (d, *J*=9.6Hz), 130.7, 130.0, 128.9, 127.2, 117.8 (d, *J*=24.2Hz), 117.7, 109.1 (d, *J*=4.2Hz), 61.2, 14.3.

MS (70 eV, EI) *m/z* (%): 270 (5), 269 (M^+, 25), 241 (35), 225 (18), 224 (100), 196 (18).

IR (ATR) υ (cm^{-1}): 3066, 2982, 2230, 1706, 1608, 1486, 1390, 1380, 1274, 1252, 1222, 1174, 1102, 1016, 930, 858, 824, 776, 752, 728, 706, 610.

HRMS (EI): *m/z* calc. for **$C_{16}H_{12}FNO_2$** (269.0852): 269.0855 (M^+).

Synthesis of ethyl 2'-chloro-5'-(trifluoromethyl)biphenyl-4-carboxylate (116n):



According to **TP16**, 1-chloro-4-(trifluoromethyl)benzene (**113g**; 361 mg, 2 mmol) reacted with $TMPBEt_3{\cdot}MgCl{\cdot}LiCl$ (**110b**; 2.2 mL, 2.2 mmol, 1.0M in THF) at 25 °C for 12 h. To a solution of $ZnCl_2$ (0.2 mL, 0.2 mmol, 1M in THF), $Pd(OAc)_2$ (14 mg, 3 mol%), S-Phos (50 mg, 6 mol%) and ethyl 4-iodobenzoate (**115g**; 441 mg, 1.6 mmol) in THF (2 mL), the reaction mixture was added dropwise at 25 °C and continuously stirred for 2 h at 65 °C. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 98:2) furnished **116n** as an off-white solid (426 mg, 81%).

m.p.: 58.6-59.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.14 (d, *J*=8.8Hz, 2H), 7.55-7.64 (m, 3H), 7.51 (d, *J*=8.8Hz, 2H), 4.42 (q, *J*=7.1Hz, 2H), 1.41 (t, *J*=7.1Hz, 3H).

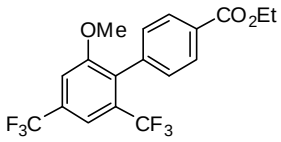
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.2, 142.3, 140.3, 130.7, 130.3, 129.5, 129.4, 127.54-128.32 (m), 126.0, 125.8, 122.2, 121.5 (q, *J*=248.0Hz), 61.2, 14.3.

MS (70 eV, EI) *m/z* (%): 328 (M^+, 30), 302 (16), 300 (49), 285 (39), 284 (21), 283 (100), 234 (18), 220 (57), 219 (16), 133 (23), 105 (22), 77 (16), 57 (12), 43 (25).

IR (ATR) υ (cm^{-1}): 2984, 2934, 1714, 1612, 1472, 1414, 1334, 1272, 1168, 1102, 1096, 1090, 1018, 934, 860, 816, 772, 704.

HRMS (EI): *m/z* calc. for **$C_{16}H_{12}ClF_3O_2$** (328.0478): 328.0478 (M^+).

Synthesis of ethyl 2'-methoxy-4',6'-bis(trifluoromethyl)biphenyl-4-carboxylate (116o):



According to **TP16**, 1-methoxy-3,5-bis(trifluoromethyl)benzene (**113h**; 488 mg, 2 mmol) reacted with $TMPBEt_3 \cdot MgCl \cdot LiCl$ (**110b**; 2.2 mL, 2.2 mmol, 1.0M in THF) at 25 °C for 30 min. To a solution of $ZnCl_2$ (0.2 mL, 0.2 mmol, 1M in THF), $Pd(OAc)_2$ (14 mg, 3 mol%), S-Phos (50 mg, 6 mol%) and ethyl 4-iodobenzoate (**115g**; 441 mg, 1.6 mmol) in THF (2 mL), the reaction mixture was added dropwise at 25 °C and continuously stirred for 2 h at 65 °C. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **116o** as an off-white solid (602 mg, 96%).

m.p.: 93.5-94.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.11 (d, *J*=8.6Hz, 2H), 7.63 (s, 1H), 7.36 (s, 1H), 7.29 (d, *J*=8.1Hz, 2H), 4.41 (q, *J*=7.1Hz, 2H), 3.78 (s, 3H), 1.41 (t, *J*=7.1Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.3, 158.1, 138.1, 131.6 (q, *J*=33.4Hz), 131.0 (q, *J*=30.7Hz), 130.2, 129.7, 129.0, 127.0-127.3 (m), 123.3 (q, *J*=272.6Hz), 122.5 (q, *J*=274.5Hz), 114.5-115.0 (m), 110.5-110.9 (m), 61.0, 56.3, 14.3.

MS (70 eV, EI) *m/z* (%): 392 (M^+, 30), 364 (31), 348 (100), 304 (64), 285 (15), 253 (18), 225 (18), 152 (16), 84 (15), 57 (20), 49 (25), 44 (18), 43 (64).

IR (ATR) υ (cm^{-1}): 2984, 1726, 1710, 1466, 1366, 1274, 1250, 1130, 1100, 1036, 902, 884, 870, 848, 770, 710, 676.

HRMS (EI): *m/z* calc. for $\mathbf{C_{18}H_{14}F_6O_3}$ (392,0847): 392.0840 (M^+).

5.4 Calculation of C-H Acidities in Polysubstituted Aromatics and Heteroaromatics

Computational details: Theoretical calculations were conducted with the Gaussian03 Rev.B.04 package[306]. HF, B3LYP,[307] and MP2(FC) methods applying various basis sets, such as 6-31+G(2d,2p), G3MP2large, 6-311++G(2df,2p), or aug-CC-pVDZ, and different solvation models, like IEFPCM, CPCM or IPCM, in combination with varying cavity models, i.e. UA0 or bondi, and electrostatic scaling factors (0.9-1.30) were systematically utilized and compared. In conclusion, the gas-phase energy calculations were most accurately conducted using the B3LYP/6-311++G(2df,2p)//B3LYP/6-311++G(2df,2p) method. The PCM solvation model was used in its integral equation formalism (IEFPCM) calculating solvation free energies in DMSO. Based on the linear correlation between THF and DMSO, all pKa values have been converted to THF-solvent. All IEFPCM calculations were performed at RHF/aug-CC-pVDZ level (TSNUM=60; TSARE = 0.4; alpha = 1.20).

Calculated energies

Table 20. Electronic, zero-point-corrected electronic and Gibbs free energies for gas-phase acidities (B3LYP/6-311++G(2df,2p)//B3LYP/6-311++G(2df,2p)) and solvation Gibbs free energies (RHF/aug-CC-pVDZ/IEFPCM) for substituted aromatics and heteroaromatics.

Entry	Compound	E_e (a.u.)	E_0 (a.u.)	G_{298} (a.u.)	ΔG_{solv} (kcal·mol^{-1})
1	**furan**	-230.10347109	-230.03357400	-230.05917600	-3.21
2	**furan-2H**	-229.46764771	-229.41270200	-229.43894100	-66.82
3	**furan-3H**	-229.46031212	-229.40498000	-229.43120400	-66.70
4	**121a**	-248.36755595	-248.27893300	-248.30566800	-4.54
5	**121a-2H**	-247.71429511	-247.64130500	-247.66878500	-68.11
6	**121a-3H**	-247.72743037	-247.65358000	-247.68098500	-63.81
7	**121a-4H**	-247.73074033	-247.65688200	-247.68361100	-62.6
8	**121b**	-515.65795812	-515.49818600	-515.53468200	-4.14
9	**121b-2H**	-515.01560489	-514.87174100	-514.90908600	-63.71
10	**121b-4H**	-515.02834852	-514.88377500	-514.92083800	-59.85
11	**121b-5H**	-515.02825138	-514.88334800	-514.92038300	-59.49
12	**121b-6H**	-515.01920398	-514.87494700	-514.91170100	-61.22
13	**121c**	-975.2778614	-975.128032	-975.166904	-4.46
14	**121c-2H**	-974.6661395	-974.531202	-974.570854	-54.38
15	**121c-4H**	-974.6596487	-974.524559	-974.563574	-55.31
16	**121c-5H**	-974.6517504	-974.517341	-974.556489	-56.87
17	**121d**	-1468.609107	-1468.36385	-1468.411547	-1.44
18	**121d-3H**	-1467.998493	-1467.767931	-1467.815039	-49.26
19	**121d-4H**	-1468.002157	-1467.771482	-1467.818445	-50.32
20	**121d-6H**	-1467.987556	-1467.757397	-1467.804058	-51.88
21	**121e**	-707.99702358	-707.91800500	-707.94770900	-5.23
22	**121e-3H**	-707.37545747	-707.31123500	-707.34113900	-60.22
23	**121e-4H**	-707.37628539	-707.31191400	-707.34177900	-56.7
24	**121e-5H**	-707.37050982	-707.30615300	-707.33597900	-58.23
25	**121e-6H**	-707.36064754	-707.29712000	-707.32705900	-61.63
26	**121f**	-1167.62485181	-1167.55556100	-1167.58748500	-5.33
27	**121f-3H**	-1167.01441512	-1166.95970600	-1166.99185900	-55.29
28	**121f-4H**	-1167.01811178	-1166.96330100	-1166.99551000	-51.73
29	**121g**	-515.65672126	-515.49696900	-515.53349600	-3.86
30	**121g-2H**	-515.01394793	-514.86985500	-514.90693000	-63.42
31	**121g-3H**	-515.02755615	-514.88269400	-514.91981900	-59.01
32	**121h**	-340.6356648	-340.548484	-340.578042	-6.67
33	**121h-2H**	-340.0080022	-339.936066	-339.966526	-59.78
34	**121h-3H**	-340.0245191	-339.951667	-339.981912	-56.7
35	**121i**	-838.57751070	-838.57751070	-838.51179700	-6.41
36	**121i-2H**	-837.97198590	-837.88742200	-837.92090100	-57.01
37	**121i-3H**	-837.97163422	-837.88693900	-837.92025800	-56.95
38	**121j**	-264.41091772	-264.33402500	-264.36137300	-6.19
39	**121j-2H**	-263.76242261	-263.70164500	-263.72921500	-71.06
40	**121j-4H**	-263.77439322	-263.71245200	-263.73989200	-65.58
41	**121j-5H**	-263.78442180	-263.72167700	-263.74903800	-60.39
42	**121k**	-673.16236648	-672.98479000	-673.02305700	1.06
43	**121k-2H**	-672.51594873	-672.35458300	-672.39317800	-60.39
44	**121k-5H**	-672.53793676	-672.37508800	-672.41365900	-49.75
45	**121k-6H**	-672.52660374	-672.36407500	-672.40259300	-56.13
46	**121k-SiH**	-672.53872216	-672.37668800	-672.41501300	-50.91
47	**121l**	-1081.91333825	-1081.63536800	-1081.68516600	8.86
48	**121l-2H**	-1081.26874192	-1081.00693400	-1081.05651400	-49.29

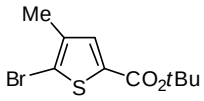
49	**121l-5H**	-1081.29044786	-1081.02774100	-1081.07548200	-34.23
50	**121l-SiH**	-1081.28994294	-1081.28994294	-1081.07740100	-41.96
51	**121m**	-792.5579497	-792.340111	-792.381465	3.19
52	**121m-3H**	-791.9334217	-791.730787	-791.77265	-48.53
53	**121m-4H**	-791.9171739	-791.714384	-791.755843	-52.84
54	**121m-5H**	-791.909306	-791.706764	-791.748299	-55.73
55	**121m-6H**	-791.9126102	-791.710027	-791.751599	-54.52
56	**121m-7H**	-791.9231204	-791.720357	-791.761858	-55.12
57	**122a**	-959.24438580	-959.08241400	-959.12118600	-2.47
58	**122a-2H**	-958.62515982	-958.47844800	-958.51786800	-55.79
59	**122a-4H**	-958.62707668	-958.48012400	-958.51907900	-53.86
60	**122a-5H**	-958.61695955	-958.47015300	-958.50937400	-54.88
61	**122a-6H**	-958.61075279	-958.46423600	-958.50371400	-56.56
62	**122b**	-591.88860841	-591.71847000	-591.75771800	-5.34
63	**122b-2H**	-591.27415803	-591.11900700	-591.15875100	-55.4
64	**122b-4H**	-591.27658045	-591.12118700	-591.16038100	-53.23
65	**122b-5H**	-591.27016253	-591.11504800	-591.15476900	-53.83
66	**122b-6H**	-591.26797387	-591.11307700	-591.15328300	-54.52
67	**122c**	-598.8918046	-598.728654	-598.766514	-2.8
68	**122c-2H**	-598.2711481	-598.123057	-598.161356	-58.1
69	**122c-4H**	-598.2732914	-598.124978	-598.162987	-56.67
70	**122c-5H**	-598.2597698	-598.11183	-598.150126	-56.82
71	**122c-6H**	-598.2539242	-598.106406	-598.145641	-58.98
72	**122d**	-1250.84455092	-1250.77108300	-1250.80354100	-3.09
73	**122d-4H**	-1250.23308602	-1250.17441300	-1250.20787400	-52.67
74	**122d-5H**	-1250.22614393	-1250.16753100	-1250.20094500	-51.89
75	**122e**	-1082.556785	-1082.370306	-1082.414021	-7.51
76	**122e-2H**	-1081.964908	-1081.792552	-1081.83464	-47.35
77	**122e-4H**	-1081.950241	-1081.778771	-1081.822156	-54
78	**122e-5H**	-1081.940879	-1081.769316	-1081.810533	-55.16
79	**122e-6H**	-1081.941631	-1081.769893	-1081.813288	-57.05
80	**122f**	-1257.577825	-1257.319072	-1257.369163	-4.52
81	**122f-2H**	-1256.968156	-1256.724311	-1256.773221	-47.28
82	**122f-4H**	-1256.960295	-1256.716832	-1256.766632	-55.92
83	**122f-5H**	-1256.948257	-1256.704725	-1256.754976	-57.95
84	**122f-6H**	-1256.946702	-1256.703212	-1256.753033	-57.8
85	**122g**	-688.2468444	-688.060947	-688.102223	-4.68
86	**122g-2H**	-687.6168744	-687.446542	-687.488876	-59.06
87	**122g-4H**	-687.6155936	-687.445178	-687.487274	-62.86
88	**122g-5H**	-687.6147532	-687.444362	-687.486553	-59.34
89	**122h**	-1092.209591	-1091.951261	-1091.998667	0.2
90	**122h-2H**	-1091.601416	-1091.357818	-1091.403649	-46.72
91	**122h-4H**	-1091.583892	-1091.340527	-1091.387421	-54.78
92	**122h-5H**	-1091.575896	-1091.332556	-1091.378866	-52.66
93	**122h-6H**	-1091.588204	-1091.344694	-1091.389964	-46.06
94	**123a**	-959.24591142	-959.08402500	-959.12272800	-2.81
95	**123a-2H**	-958.61950071	-958.47291400	-958.51225600	-54.26
96	**123a-3H**	-958.62661353	-958.47978400	-958.51898800	-55.48
97	**123b**	-598.89303370	-598.72976700	-598.76750500	-2.58
98	**123b-2H**	-598.26230288	-598.11433500	-598.15254600	-56.03
99	**123b-3H**	-598.27277416	-598.12433800	-598.16239900	-57.67
100	**123c**	-591.88920330	-591.71921800	-591.75845700	-5.4
101	**123c-2H**	-591.27168342	-591.11680800	-591.15678100	-53.44
102	**123c-3H**	-591.27455691	-591.11941700	-591.15907300	-54.82
103	**123d**	-692.8408828	-692.581965	-692.624641	-0.1
104	**123d-2H**	-692.1986097	-691.955446	-691.999465	-55.71

105	**123d-3H**	-692.2044375	-691.96082	-692.003948	-59.05
106	**123e**	-1082.557561	-1082.371004	-1082.414754	-7.71
107	**123e-2H**	-1081.945384	-1081.773652	-1081.817084	-56.43
108	**123e-3H**	-1081.962492	-1081.790182	-1081.832473	-46.24
109	**123f**	-1257.578417	-1257.31963	-1257.369754	-4.78
110	**123f-2H**	-1256.946233	-1256.703042	-1256.754457	-59.48
111	**123f-3H**	-1256.970084	-1256.725990	-1256.775830	-48.58
112	**123g**	-446.1631393	-446.038617	-446.071053	-3.24
113	**123g-2H**	-445.5350059	-445.425747	-445.458532	-55.97
114	**123g-3H**	-445.5325582	-445.422944	-445.455706	-62.06

6 Regioselective Preparation of Heteroarylmagnesium Reagents and its Applications in Functionalization and Regioregular Polymerization Reactions

6.1 Functionalization of Regioselectively Generated Heteroarylmagnesium Derivatives

Synthesis of *tert*-butyl 5-bromo-4-methylthiophene-2-carboxylate (130a):



According to **TP17**, 2,5-dibromo-3-methylthiophene (**128a**; 2 mmol, 512 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the 2-bromo-3-methylthiophenylmagnesium bromide (**126a**; –20 °C, 16 h). Subsequently, $ZnCl_2$ (2 mmol, 2 mL, 1M in THF) was added at –20 °C and stirred for 10 min. At –40 °C, CuCN·2LiCl (0.2 mmol, 0.2 mL, 1M in THF) was added followed by addition of di-*tert*-butyl dicarbonate (**129a**; 2.4 mmol, 480 mg). The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 4 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 99:1) furnished **130a** as a yellow oil (460 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.39 (s, 1H), 2.19 (s, 3H), 1.56 (s, 9H).

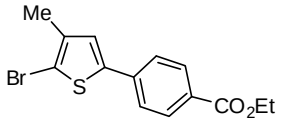
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.6, 138.2, 134.5, 134.1, 116.7, 82.1, 28.2, 15.2.

MS (70 eV, EI) *m/z* (%): 278 (M^+, 14), 276 (M^+, 15), 223 (10), 222 (100), 221 (12), 220 (100), 205 (43), 203 (44), 186 (26), 141 (60), 96 (24), 69 (10), 57 (60), 55 (21).

IR (ATR) υ (cm^{-1}): 2978, 2932, 1702, 1426, 1368, 1296, 1254, 1156, 1074, 848, 818, 798, 748, 718.

HRMS (EI): *m/z* calc. for **$C_{10}H_{13}BrO_2S$** (275.9820): 275.9817 (M^+).

Synthesis of ethyl 4-(5-bromo-4-methylthiophen-2-yl)benzoate (130b):



According to **TP17**, 2,5-dibromo-3-methylthiophene (**128a**; 2 mmol, 512 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the 2-bromo-3-methylthiophenylmagnesium bromide (**126a**; –20 °C, 16 h). Subsequently, $ZnCl_2$ (2 mmol, 2 mL, 1M in THF) was added at –20 °C and stirred for 10 min. To a solution of $Pd(PPh_3)_4$ (4 mol%, 93 mg) and ethyl 4-iodobenzoate (**129b**; 663 mg, 2.4 mmol) in THF (6 mL), the heteroarylzinc reagent was added dropwise at 0 °C. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 95:5) furnished **130b** as a pale yellow solid (556 mg, 83%).

m.p.: 89.2-90.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.03 (d, *J*=8.8Hz, 2H), 7.54 (d, *J*=8.6Hz, 2H), 7.09 (s, 1H), 4.39 (q, *J*=7.1Hz, 2H), 2.22 (s, 3H), 1.41 (t, *J*=7.1Hz, 3H).

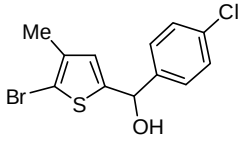
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.1, 142.1, 138.6, 137.8, 130.3, 129.4, 126.2, 124.9, 110.4, 61.0, 15.3, 14.4.

MS (70 eV, EI) *m/z* (%):327 (14), 326 (M^+, 100), 325 (14), 324 (M^+, 93), 298 (33), 296 (30), 281 (57), 279 (56), 217 (11), 172 (32), 171 (31).

IR (ATR) υ (cm^{-1}): 3076, 2984, 2906, 1704, 1604, 1510, 1472, 1438, 1364, 1272, 1232, 1186, 1128, 1110, 1020, 850, 764, 690.

HRMS (EI): *m/z* calc. for **$C_{14}H_{13}BrO_2S$** (323.9820): 323.9807 (M^+).

Synthesis of (5-bromo-4-methylthiophen-2-yl)(4-chlorophenyl)methanol (130c):



According to **TP17**, 2,5-dibromo-3-methylthiophene (**128a**; 2 mmol, 512 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the 2-bromo-3-methylthiophenylmagnesium bromide (**126a**; –20 °C, 16 h). To a solution of 4-chlorobenzaldehyde (**129c**; 337 mg, 2.4 mmol), the heteroarylmagnesium bromide (**126a**) was added dropwise at 0 °C and continuously stirred for 1 h. Subsequently, aq. HCl (2M, 10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 17:3) furnished **130c** as an off-white solid (597 mg, 94%).

m.p.: 63.2-64.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.3-7.4 (m, 4H), 6.46 (s, 1H), 5.47 (s, 1H), 2.11 (s, 3H).

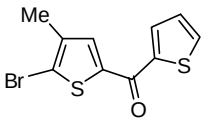
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 144.2, 138.4, 136.8, 134.4, 128.9, 128.3, 127.6, 110.3, 71.8, 15.2.

MS (70 eV, EI) *m/z* (%):319 (8), 318 (M^+, 54), 317 (10), 315 (M^+, 43), 301 (19), 299 (13), 239 (33), 238 (13), 237 (100), 205 (15), 176 (17), 139 (17).

IR (ATR) υ (cm^{-1}): 3204, 2844, 1670, 1548, 1460, 1418, 1278, 1156, 1062, 1004, 820, 752.

HRMS (EI): *m/z* calc. for **$C_{12}H_{10}BrClOS$** (315.9324): 315.9326 (M^+).

Synthesis of (5-bromo-4-methylthiophen-2-yl)(thiophen-2-yl)methanone (130d):



According to **TP17**, 2,5-dibromo-3-methylthiophene (**128a**; 2 mmol, 512 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the 2-bromo-3-methylthiophenylmagnesium bromide (**126a**; –20 °C, 16 h). Subsequently, $ZnCl_2$ (2 mmol, 2 mL, 1M in THF) was added at –20 °C and stirred for 10 min. At –40 °C, CuCN·2LiCl (0.2 mmol, 0.2 mL, 1M in THF) was added followed by addition of thiophene-2-carbonyl chloride (**129d**; 2.4 mmol, 352 mg). The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 4 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 95:5) furnished **130d** as an off-white solid (488 mg, 85%).

m.p.: 100.2-101.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.85 (dd, *J*=3.8Hz, 1.1Hz, 1H), 7.69 (dd, *J*=4.9Hz, 1.1Hz, 1H), 7.57 (s, 1H), 7.17 (dd, *J*=5.0Hz, 3.8Hz, 1H), 2.25 (s, 3H).

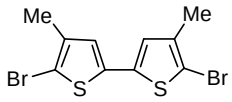
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.6, 142.2, 141.8, 138.7, 134.6, 133.6, 133.0, 128.0, 120.0, 15.4.

MS (70 eV, EI) *m/z* (%):289 (11), 288 (M^+, 100), 287 (11), 286 (M^+, 93), 207 (13), 205 (37), 203 (36), 111 (77), 96 (11).

IR (ATR) υ (cm^{-1}): cm-1, 3004, 2362, 2340, 1740, 1658, 1582, 1522, 1432, 1366, 1228, 1222, 1204, 1098, 1056, 780, 706.

HRMS (EI): *m/z* calc. for **$C_{10}H_7BrOS_2$** (285.9122): 285.9117 (M^+).

Synthesis of 5,5'-dibromo-4,4'-dimethyl-2,2'-bithiophene (130e):



According to **TP17**, 2,5-dibromo-3-methylthiophene (**128a**; 4 mmol, 1.02 g) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 6.2 mL, 4.4 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 704 mg, 4.4 mmol) producing regioselectively the 2-bromo-3-methylthiophenylmagnesium bromide (**126a**; –20 °C, 16 h). At –40 °C, $ZnCl_2$ (2 mmol, 2 mL, 1M in THF) and CuCN·2LiCl (2 mmol, 2 mL, 1M in THF) were successively added and continuously stirred for 10 min. The reaction mixture was added dropwise to a solution of chloranil (1.47 g, 6 mmol) in THF (15 mL) at 0 °C. Then, the solution was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (5x 10 mL). The combined organic phases were washed with aq. NH_3 (2M, 2x 30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **130e** as a pale yellow solid (612 mg, 87%).

m.p.: 106.2-107.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.77 (s, 2H), 2.17 (s, 6H).

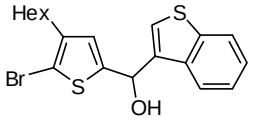
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 138.1, 135.9, 125.5, 108.4, 15.2.

MS (70 eV, EI) *m/z* (%): 354 (M^+, 51), 353 (10), 352 (M^+, 100), 350 (M^+, 43), 229 (10), 192 (19), 191 (11).

IR (ATR) υ (cm^{-1}): 3054, 2916, 1740, 1634, 1544, 1410, 1374, 1318, 1186, 1022, 994, 942, 834, 812, 734.

HRMS (EI): *m/z* calc. for $\mathbf{C_{10}H_8{}^{79}Br_2S_2}$ (349.8434): 349.8422 (M^+).

Synthesis of 1-benzothiophen-3-yl(5-bromo-4-hexylthiophen-2-yl)methanol (130f):



According to **TP17**, 2,5-dibromo-3-hexylthiophene (**128b**; 2 mmol, 652 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the 2-bromo-3-hexylthiophenylmagnesium bromide (**126b**; –20 °C, 16 h). To a solution of 1-benzothiophene-3-carbaldehyde (**129e**; 389 mg, 2.4 mmol), the heteroarylmagnesium bromide (**126b**) was added dropwise at 0 °C and continuously stirred for 1 h followed by quenching with aq. HCl (2M, 10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **130f** as a yellow oil (679 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.41 (d, *J*=9.3Hz, 1H), 8.16 (s, 1H), 7.91 (d, *J*=9.3Hz, 1H), 7.4-7.6 (m, 4H), 6.73 (s, 1H), 2.60 (t, *J*=7.3Hz, 2H), 1.5-1.7 (m, 2H), 1.0-1.5 (m, 6H), 0.89 (t, *J*=6.4Hz, 3H).

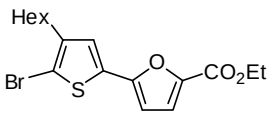
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 147.1, 139.9, 136.8, 136.3, 133.1, 132.0, 131.0, 130.3, 126.6, 125.7, 122.4, 108.2, 62.2, 31.6, 30.1, 29.6, 28.9, 23.2, 14.1.

MS (70 eV, EI) *m/z* (%): 408 (M^+, 20), 337 (15), 335 (13), 327 (10), 258 (17), 257 (54), 162 (10), 161 (100), 133 (14), 90 (13).

IR (ATR) υ (cm^{-1}): 2954, 2926, 2856, 1712, 1622, 1494, 1458, 1422, 1376, 1214, 1194, 1068, 908, 864, 750, 730, 702.

HRMS (EI): *m/z* calc. for $\mathbf{C_{19}H_{21}BrOS_2}$ (408.0217): 408.0057 (M^+).

Synthesis of ethyl 5-(5-bromo-4-hexylthiophen-2-yl)furan-2-carboxylate (130g):



According to **TP17**, 2,5-dibromo-3-hexylthiophene (**128b**; 2 mmol, 652 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the 2-bromo-3-hexylthiophenylmagnesium bromide (**126b**; –20 °C, 16 h). Subsequently, $ZnCl_2$

(2 mmol, 2 mL, 1M in THF) was added at –20 °C and stirred for 10 min. To a solution of $Pd(PPh_3)_4$ (4 mol%, 93 mg) and ethyl 5-bromofuroate (**129f**; 526 mg, 2.4 mmol) in THF (6 mL), the heteroarylzinc reagent was added dropwise at 0 °C. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 98:2) furnished **130g** as a yellow oil (609 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.17 (d, *J*=3.7Hz, 1H), 7.13 (s, 1H), 6.48 (d, *J*=3.7Hz, 1H), 4.35 (q, *J*=7.1Hz, 2H), 2.53 (t, *J*=7.3Hz, 2H), 1.5-1.7 (m, 2H), 1.1-1.4 (m, 9H), 0.89 (t, *J*=6.4Hz, 3H).

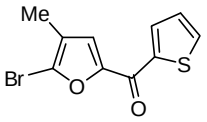
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 158.6, 152.0, 143.2, 131.6, 125.7, 119.8, 113.9, 110.3, 106.7, 61.2, 61.0, 31.6, 29.5, 28.8, 22.6, 14.3, 14.0.

MS (70 eV, EI) *m/z* (%):387 (6), 386 (M^+, 33), 385 (6), 384 (M^+, 32), 305 (10), 275 (11), 273 (11), 236 (26), 235 (100), 207 (15).

IR (ATR) υ (cm^{-1}): 2928, 2858, 2362, 2340, 1716, 1664, 1508, 1466, 1416, 1370, 1296, 1138, 1014, 860, 796, 754, 668.

HRMS (EI): *m/z* calc. for **$C_{17}H_{21}BrO_3S$** (384.0395): 384.0391 (M^+).

Synthesis of (5-bromo-4-methylfuran-2-yl)(thiophen-2-yl)methanone (130h):



According to **TP17**, 2,5-dibromo-3-methylfuran (**128c**; 2 mmol, 480 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the 2-bromo-3-methylfurylmagnesium bromide (**126a**; –10 °C, 16 h). Subsequently, $ZnCl_2$ (2 mmol, 2 mL, 1M in THF) was added at –10 °C and stirred for 10 min. At –40 °C, CuCN·2LiCl (0.2 mmol, 0.2 mL, 1M in THF) was added followed by addition of thiophene-2-carbonyl chloride (**129d**; 2.4 mmol, 352 mg). The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 4 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 95:5) furnished **130h** as a pale yellow solid (428 mg, 79%).

m.p.: 80.6-81.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.14 (dd, *J*=3.8Hz, 1.1Hz, 1H), 7.70 (dd, *J*=5.0Hz, 1.2Hz, 1H), 7.24 (s, 1H), 7.19 (t, *J*=4.4Hz, 1H), 2.07 (s, 3H).

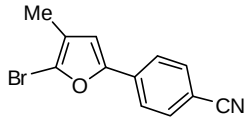
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.1, 152.9, 141.9, 134.1, 133.8, 128.3, 126.6, 123.0, 122.0, 10.5.

MS (70 eV, EI) *m/z* (%):272 (M^+, 31), 270 (M^+, 31), 190 (11), 135 (26), 111 (100).

IR (ATR) υ (cm^{-1}): 3118, 3112, 2962, 2926, 2360, 2342, 1714, 1608, 1596, 1490, 1410, 1356, 1306, 1294, 1240, 1208, 1168, 1074, 1060, 964, 812, 744, 734, 616.

HRMS (EI): *m/z* calc. for **$C_{10}H_7BrO_2S$** (269.9350): 269.9347 (M^+).

Synthesis of 4-(5-bromo-4-methylfuran-2-yl)benzonitrile (130i):



According to **TP17**, 2,5-dibromo-3-methylfuran (**128c**; 2 mmol, 480 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the 2-bromo-3-methylfurylmagnesium bromide (**126a**; −10 °C, 16 h). Subsequently, $ZnCl_2$ (2 mmol, 2 mL, 1M in THF) was added at −10 °C and stirred for 10 min. To a solution of $Pd(PPh_3)_4$ (4 mol%, 93 mg) and 4-iodobenzonitrile (**129g**; 550 mg, 2.4 mmol) in THF (6 mL), the heteroarylzinc reagent was added dropwise at 0 °C. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 95:5) furnished **130i** as a yellow solid (409 mg, 78%).

m.p.: 99.5-101.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.6-7.7 (m, 4H), 6.68 (s, 1H), 2.03 (s, 3H).

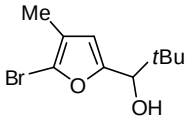
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 152.7, 133.7, 132.6, 124.9, 123.5, 122.3, 118.8, 112.0, 110.5, 10.6.

MS (70 eV, EI) *m/z* (%): 264 (9), 263 (M^+, 72), 262 (10), 261 (M^+, 73), 182 (22), 155 (13), 154 (100), 153 (24), 130 (19), 127 (45), 126 (11), 102 (13), 77 (11), 63 (13).

IR (ATR) υ (cm^{-1}): 3108, 2962, 2926, 2870, 2222, 1918, 1766, 1606, 1532, 1516, 1484, 1446, 1386, 1348, 1266, 1178, 1078, 924, 834, 814, 684, 660.

HRMS (EI): *m/z* calc. for **$C_{12}H_8BrNO$** (260.9789): 260.9780 (M^+).

Synthesis of 1-(5-bromo-4-methylfuran-2-yl)-2,2-dimethylpropan-1-ol (130j):



According to **TP17**, 2,5-dibromo-3-methylfuran (**128c**; 2 mmol, 480 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the 2-bromo-3-methylfurylmagnesium bromide (**126a**; –10 °C, 16 h). To a solution of pivaldehyde (**129h**; 206 mg, 2.4 mmol), the heteroarylmagnesium bromide (**126b**) was added dropwise at 0 °C and continuously stirred for 1 h followed by quenching with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **130j** as a yellow oil (361 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.11 (s, 1H), 4.21 (s, 1H), 1.96 (s, 3H), 0.96 (s, 9H).

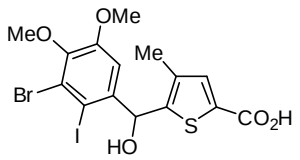
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 156.7, 119.6, 118.6, 111.5, 76.4, 35.6, 25.7, 10.5.

MS (70 eV, EI) *m/z* (%): 248 (M^+, 6), 246 (M^+, 8), 231 (19), 229 (19), 192 (8), 191 (94), 190 (11), 189 (100), 57 (32), 55 (17), 53 (18).

IR (ATR) υ (cm^{-1}): 3426, 2956, 2870, 1542, 1396, 1366, 1206, 1158, 1074, 1048, 1008, 934, 902, 814, 794, 734, 612.

HRMS (EI): *m/z* calc. for **$C_{10}H_{15}BrO_2$** (246.0255): 246.0242 (M^+).

Synthesis of 5-[(3-bromo-2-iodo-4,5-dimethoxyphenyl)(hydroxy)methyl]-4-methyl-thiophene-2-carboxylic acid (133):



According to **TP17**, 2,5-dibromo-3-methylthiophene (**128a**; 5 mmol, 1.28 g) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 7.75 mL, 5.5 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 880 mg, 5.5 mmol) producing regioselectively the 2-bromo-3-methylthiophenylmagnesium bromide (**126a**; –20 °C, 16 h). At 0 °C, dry gaseous CO_2 was bubbled through the reaction mixture for 30 min. After addition of THF (20 mL), *i*PrMgCl·LiCl (4.4 mL, 5.5 mmol, 1.2M in THF) was added –20 °C and continuously stirred for 30 min. To a solution of 3-bromo-2-iodo-4,5-dimethoxybenzaldehyde (**132**; 1.85 g, 5 mmol), the heteroarylmagnesium bromide (**126a**) was added dropwise at 0 °C, slowly

warmed to 25 °C and continuously stirred for 30 min followed by quenching with aq. HCl (2M, 30 mL). The aqueous phase was extracted with CH_2Cl_2 (30 mL). Then, the combined organic phases were extracted with a mixture of brine (20 mL) and conc. aq. NH_3 (20 mL). Subsequently, this mixture was acidified with conc. aq. HCl (pH=1). The precipitate was dissolved and successively extracted with CH_2Cl_2 (3x 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* providing **133** as an off-white solid (1.84 g, 72%).

m.p.: 182.3-184.2 °C.

^{1}H NMR (300 MHz, D6-DMSO) δ (ppm): 7.47 (s, 1H), 7.44 (s, 1H), 6.51 (br s, 1H), 5.98 (s, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 2.28 (s, 3H).

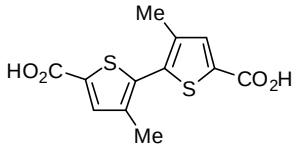
^{13}C NMR (75 MHz, D6-DMSO) δ (ppm): 163.3, 153.5, 148.8, 146.3, 144.7, 138.6, 136.5, 132.0, 126.2, 111.8, 95.4, 74.3, 60.4, 56.6, 14.5.

MS (70 eV, EI) *m/z* (%): 514 (M^+, 87), 512 (M^+, 94), 498 (18), 497 (36), 495 (28), 387 (35), 385 (38), 372 (34), 371 (41), 370 (30), 369 (37), 268 (77), 174 (55), 169 (56), 143 (61), 142 (85), 141 (60), 128 (42), 125 (71), 97 (100), 45 (51), 44 (98).

IR (ATR) υ (cm^{-1}): 3218, 2958, 2930, 2842, 2574, 2362, 2342, 1666, 1548, 1460, 1418, 1362, 1274, 1154, 1062, 998, 858, 752.

HRMS (EI): *m/z* calc. for **$C_{15}H_{14}BrIO_5S$** (511.8790): 511.8775 (M^+).

Synthesis of 3,3'-dimethyl-2,2'-bithiophene-5,5'-dicarboxylic acid (134):



According to **TP17**, 2,5-dibromo-3-methylthiophene (**128a**; 5 mmol, 1.28 g) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 7.75 mL, 5.5 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 880 mg, 5.5 mmol) producing regioselectively the 2-bromo-3-methylthiophenylmagnesium bromide (**126a**; –20 °C, 16 h). At 0 °C, dry gaseous CO_2 was bubbled through the reaction mixture for 30 min. After addition of THF (20 mL), *i*PrMgCl·LiCl (4.4 mL, 5.5 mmol, 1.2M in THF) was added –20 °C and continuously stirred for 30 min followed by addition of CuCN·2LiCl (2.5 mmol, 2.5 mL, 1M in THF). After 10 min stirring, a solution of chloranil (2.2 g, 7.5 mmol) in THF (20 mL) was added dropwise at –20 °C. Then, the solution was allowed to slowly warm to 25 °C and continuously stirred for 4 h followed by quenching with brine (20 mL) and conc. aq. NH_3 (20 mL). The aqueous layer was washed with Et_2O (20 mL). Subsequently, the aqueous phase was acidified with

conc. aq. HCl (pH=1) affording precipitation. The precipitate was filtered, redissolved in MeOH (50 mL). The solution was dried over Na_2SO_4 and concentrated *in vacuo* providing **134** as an off-white solid (1.13 g, 76%).

m.p.: >275 °C.

^{1}H NMR (300 MHz, D6-DMSO) δ (ppm): 13.24 (br s, 2H), 7.65 (s, 2H), 2.19 (s, 6H).

^{13}C NMR (75 MHz, D6-DMSO) δ (ppm): 162.3, 137.7, 135.8, 134.0, 133.7, 14.5.

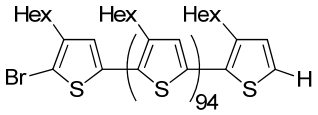
MS (70 eV, EI) *m/z* (%): 282 (M^+, 54), 239 (19), 238 (89), 237 (42), 223 (22), 194 (15), 193 (31), 149 (25), 135 (15), 134 (16), 115 (11), 91 (12), 45 (11), 44 (100).

IR (ATR) υ (cm^{-1}): 3456, 3014, 2592, 2362, 1738, 1662, 1532, 1438, 1372, 1322, 1280, 1218, 1204, 1078, 914, 876, 754, 714.

HRMS (EI): *m/z* calc. for **$C_{12}H_{10}O_4S_2$** (282.0021): 282.0006 (M^+).

6.2 Preparation of 3-Substituted Polythiophenes

Synthesis of regioregular poly(3-hexylthiophene) (rrHT-P3HT, 136a):



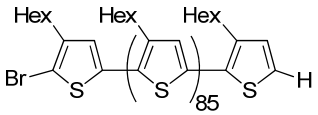
According to **TP17**, 2,5-dibromo-3-hexylthiophene (**128b**; 2 mmol, 652 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the 2-bromo-3-hexylthiophenylmagnesium bromide (**126b**; –20 °C, 16 h). Subsequently, $ZnCl_2$ (2 mmol, 2 mL, 1M in THF) was added dropwise at –20 °C and stirred for 10 min, followed by addition of Ni-catalyst (Ni(dppe)Cl_2 (0.1 mol%), 1 mL, 0.002M in THF) and THF (10 mL). The reaction mixture was allowed to warm slowly to 25 °C and continuously stirred for 24 h followed by quenching with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with $CHCl_3$ (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane:EtOAc (1:1) →$CHCl_3$) furnished **136a** as a black solid (150 mg, ~45%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.0 (s, 1H), 2.8 (t, *J*=7.5Hz, 2H), 1.1-1.9 (m, 8H), 0.7-1.0 (m, 3H).

M_w=24263; **PDI**=1.54.

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 139.9, 133.7, 130.5, 128.6, 31.7, 30.5, 29.5, 29.3, 22.6, 14.1.

Synthesis of regioregular poly(3-hexylthiophene) (rrHT-P3HT, 136b):



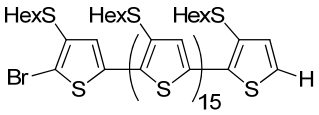
According to **TP17**, 2,5-dibromo-3-hexylthiophene (**128b**; 2 mmol, 652 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the 2-bromo-3-hexylthiophenylmagnesium bromide (**126b**; –20 °C, 16 h). Subsequently, Ni-catalyst (Ni(dppe)Cl_2 (0.1 mol%), 1 mL, 0.002M in THF) and THF (10 mL) were added at –20 °C. The reaction mixture was allowed to warm slowly to 25 °C and continuously stirred for 24 h followed by quenching with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with $CHCl_3$ (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane:EtOAc (1:1) →$CHCl_3$) furnished **136b** as a black solid (191 mg, ~56%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.0 (s, 1H), 2.8 (t, *J*=7.5Hz, 2H), 1.1-1.9 (m, 8H), 0.7-1.0 (m, 3H).

M_w=20637; **PDI**=1.48.

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 139.9, 133.7, 130.5, 128.6, 31.7, 30.5, 29.5, 29.3, 22.6, 14.1.

Synthesis of regioregular poly(3-thiohexylthiophene) (136c):

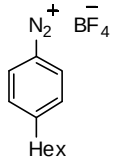


According to **TP17**, 2,5-dibromo-3-thiohexylthiophene (**128e**; 2 mmol, 716 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the corresponding heteroarylmagnesium derivative (**126e**; –20 °C, 16 h). Subsequently, Ni-catalyst (Ni(dppp)Cl_2 (0.1 mol%), 1 mL, 0.002M in THF) and THF (10 mL) were added at –20 °C. The reaction mixture was slowly warmed to 50 °C and continuously stirred for 24 h followed by quenching with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with $CHCl_3$ (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane:EtOAc=1:1) furnished **136c** as a dark red solid (210 mg, ~53%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.90 (s, 1H), 2.82 (t, 2H), 1.58 (m, 2H), 1.37 (m, 2H), 1.26 (m, 6H), 0.88 (t, 3H).

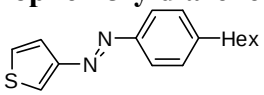
M_w=3381; **PDI**=1.33.

Synthesis of 4-hexylbenzenediazonium tetrafluoroborate:



According to **TP2**, 4-hexylaniline (90w%, 45.0 g, 254 mmol) was converted to the diazonium salt. The diazonium salt did not precipitate cleanly. Thus, the reaction mixture was extracted with CH_2Cl_2 (3x 200 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting dark solid, 4-hexylbenzenediazonium tetrafluoroborate,[313] was stored at −30 °C and used for synthesis without further purifications (58.9 g, 84% yield).

Synthesis of 1-(4-hexylphenyl)-2-thiophen-3-yldiazene:



According to **TP3**, 3-bromothiophene (16.3 g, 100 mmol) was converted to the dithiophenylzinc reagent and reacted with 4-hexylbenzenediazonium tetrafluoroborate (27.6 g, 100 mmol). After usual work-up and purification by flash column chromatography (silica gel, pentane) afforded 1-(4-hexylphenyl)-2-thiophen-3-yldiazene as a red oil (17.1 g, 63%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.01 (dd, *J*=3.2Hz, 1.3Hz, 1H), 7.80 (d, *J*=8.2Hz, 2H), 7.61 (dd, *J*=5.2Hz, 1.3Hz, 1H), 7.35 (dd, *J*=5.4Hz, 3.2Hz, 1H), 7.31 (d, *J*=8.2Hz, 2H), 2.69 (t, *J*=7.5Hz, 2H), 1.6-1.7 (m, 2H), 1.2-1.4 (m, 6H), 0.91 (t, *J*=6.7Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 157.0, 151.0, 146.3, 129.1, 126.2, 126.0, 122.6, 119.0, 35.9, 31.7, 31.3, 29.0, 22.6, 14.1.

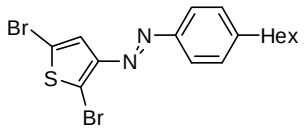
MS (70 eV, EI) *m/z* (%): 273 (17), 272 (M^+, 100), 162 (11), 161 (85).

IR (ATR) υ (cm^{-1}): 3028, 2970, 2956, 2922, 2864, 1738, 1600, 1430, 1366, 1228, 1152, 1114, 1024, 962, 958, 940, 846, 830.

HRMS (EI): *m/z* calc. for **$C_{16}H_{20}N_2S$** (272.1347): 272.1341 (M^+).

[313] D. Ghosh, S. Chen, *Chem. Phys. Lett.* **2008**, *465*, 115.

Synthesis of 1-(2,5-dibromothiophen-3-yl)-2-(4-hexylphenyl)diazene (128f):



To a solution of 1-(4-hexylphenyl)-2-thiophen-3-yldiazene (5.44 g, 20 mmol) in THF (50 mL), *N*-bromosuccinimide (7.15 g, 40 mmol) was added portionwise at –20 °C. The reaction mixture was slowly warmed to 50 °C and continuously stirred for 1 h. After cooling to 25 °C, $Na_2S_2O_3$ (2 g) and Na_2CO_3 (2 g) were added. The suspension was then poured into pentane (100 mL), filtered through a pad of neutral Al_2O_3 and concentrated *in vacuo*. Flash column chromatographical purification (silica gel, pentane) furnished **128f** as a red solid (7.65 g, 89%).

m.p.: 54.5-55.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.84 (d, *J*=8.4Hz, 2H), 7.43 (s, 1H), 7.31 (d, *J*=8.2Hz, 2H), 2.69 (t, *J*=7.51Hz, 2H), 1.5-1.8 (m, 2H), 1.2-1.5 (m, 6H), 0.91 (t, *J*=6.4Hz, 3H).

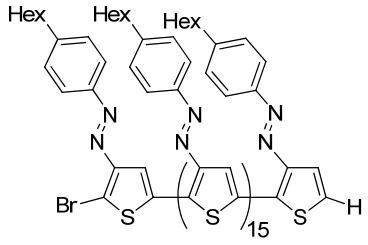
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 152.5, 150.8, 147.3, 129.2, 123.2, 121.2, 118.0, 113.1, 36.0, 31.7, 31.2, 29.0, 22.6, 14.1.

MS (70 eV, EI) *m/z* (%):432 (M^+, 24), 430 (M^+, 50) 428 (M^+, 24), 162 (11), 161 (100), 91 (40).

IR (ATR) υ (cm^{-1}): 3026, 2964, 2922, 2846, 1738, 1430, 1366, 1228, 1206, 1152, 1124, 1014, 940, 846, 830.

HRMS (EI): *m/z* calc. for **$C_{16}H_{18}{}^{79}Br_2N_2S$** (427.9557): 427.9546 (M^+).

Synthesis of regioregular poly(3-[1-(4-hexylphenyl)diazen-2-yl)]thiophene) (136d):



According to **TP17**, **128f** (2 mmol, 860 mg) reacted with 2,4,6-triisopropylmagnesium bromide (**124d**; 3.1 mL, 2.2 mmol, 0.7M in THF) and bis(dimethylaminoethyl)ether (**125b**; 352 mg, 2.2 mmol) producing regioselectively the corresponding heteroarylmagnesium derivative (**126e**; –20 °C, 16 h). Subsequently, Ni-catalyst (Ni(dppp)Cl_2 (0.1 mol%), 1 mL, 0.002M in THF) and THF (10 mL) were added at –20 °C. The reaction mixture was slowly warmed to 50 °C and continuously stirred for 24 h followed by quenching with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with $CHCl_3$ (3x 20 mL). The combined organic

phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane:EtOAc (1:1)) furnished **136d** as a dark red solid (313 mg, ~58%).

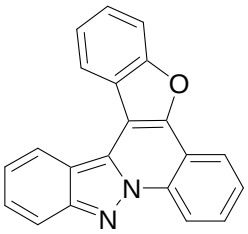
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.84 (d, *J*=8.4Hz, 2H), 7.43 (s, 1H), 7.31 (d, *J*=8.2Hz, 2H), 2.62-2.75 (m, 2H), 1.5-1.8 (m, 2H), 1.2-1.5 (m, 6H), 0.80-0.94 (m, 3H).

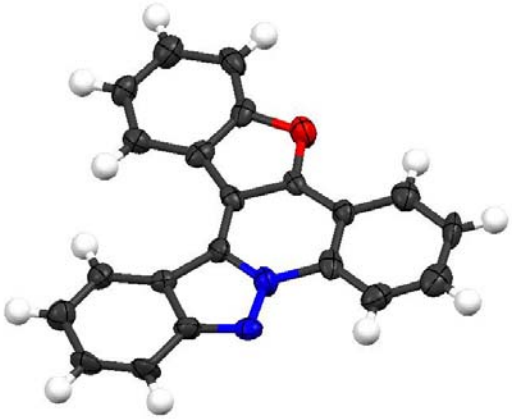
M_w=2464; **PDI**=1.03.

D. Appendix

1 X-Ray Structures

1.1 Molecular structure of 32b





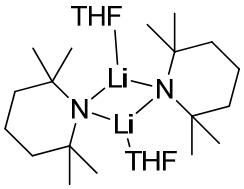
Empirical formula	$C_{21}H_{12}N_2O$
Formula weight	308.33
Temperature	200(2) K
Radiation wavelength/type	0.71073/MoKα
Crystal system	orthorhombic
Space group	P2/c
Unit cell dimensions	a= 15.8840(9); α=90°
	b= 4.6260(2); β=90°
	c= 19.4181(10); γ=90°
Volume	1426.83(13) Å^2
Z	4
Density (calc.)	1.435 Mg/m^3
Absorption coefficient	0.090
F(000)	640
Reflections average R equiv	0.0663
Reflections average sigma I/netI	0.0463
Theta range for data collection	3.31 to 24.11°
Index ranges	-18≤h≤18; -5≤k≤5; -22≤l≤22;
Reflections number	7787
Independent reflections	1170 [R(Int)= 0.0415]
Completeness to theta=24.11°	99.7%
Absorption correction	None
Refinement method	Full-matrix least-square on F^2
Goodness-of-fit on F^2	1.020

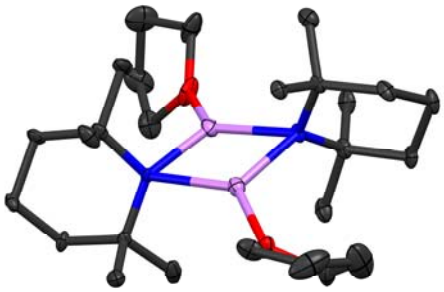
Final R indices [I>2sigma(I)]	R1=0.0415, wR2=0.0895
R indices (all data)	R1=0.0641, wR2=0.1008
Largest diff. peak and hole	0.287 and -0.176 e·Å^{-3}

This data has been deposited in the supplementary material of *Org. Lett.* **2009**, *11* (19), pp 4270–4273 and can be obtained free of charge via internet:

http://pubs.acs.org/doi/suppl/10.1021/ol901585k

1.2 Molecular structure of [TMPLi(THF)]$_2$





Empirical formula	$C_{26}H_{52}Li_2N_2O_2$
Formula weight	438.58
Temperature	200(2) K
Radiation wavelength/type	0.71073/MoKα
Crystal system	orthorhombic
Space group	Pbca
Unit cell dimensions	a= 15.189(3); α=90°
	b= 15.624(3); β=90°
	c= 23.008(5); γ=90°
Volume	5460.1 Å^2

2 Curriculum vitae

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PERSONAL

Born on August 16th, 1981 in Heidelberg, Germany.

EDUCATION

03/2007 – 12/2010	Ph.D., Department of Chemistry and Biochemistry, Ludwig-Maximilians-University Munich Topic: ”Synthesis, Functionalization and Polymerization of Heterocycles Using Frustrated Lewis Pairs, Boron, Magnesium and Zinc Reagents.“ Research Advisor : Prof. Dr. Paul Knochel
06/2006 – 12/2006	Diploma thesis, Ruprecht-Karls-University Heidelberg Topic: “Iron-Bispidin-Complex Catalyzed Oxidative CH-Activation of Cyclic Alkanes“ Research Advisor : Prof. Dr. Peter Comba
05/2006	Diploma examinations in Inorganic Chemistry, Organic Chemistry, Physical Chemistry at the Ruprecht-Karls University Heidelberg
10/2005	Diploma examinations in Pharmacology and Toxicology at the Ruprecht-Karls University Heidelberg
08/2004 – 01/2005	Graduate studies at the University of Bergen (Norway) Topic: „DFT Investigations of Pd-catalyzed Suzuki Cross-coupling“ Research Advisor: Prof. Dr. Vidar R. Jensen
10/2003	“Vordiplom“ in Chemistry at the Ruprecht-Karls University Heidelberg

AWARDS AND FELLOWSHIPS

- DAAD Postdoctoral Reseach Program (2010)
- KLAUS-RÖMER Prize, Doctoral Prize, Munich (2009)
- ERASMUS Scholarship, Heidelberg (2004)
- PRIZE of the chemistry contest "Chemistry in Everyday Life", Stuttgart (1997)
- PRIZE of the chemistry contest "Chemistry in Everyday Life", Stuttgart(1996)

POSTER-PRESENTATIONS

- "5th Asian-European Symposium on Metal Mediated Efficient Organic Synthesis", May 2008, Obernai (France).
- 116th International Summer Course of BASF SE, August 2008, Ludwigshafen (Germany).
- "Synthesefest", March 2009, Ludwig-Maximilians-University, Munich (Germany).
- "Heidelberger Forum of Molecular Catalysis", November 2009, Ruprecht-Karls-University, Heidelberg (Germany).

PUBLICATIONS

1. Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. "Preparation of Polyfunctional Arylmagnesium, Arylzinc, and Benzylic Zinc Reagents by Using Magnesium in the Presence of LiCl" *Chem. Eur. J*. **2009**, *15*, 7192-7202.
2. Haag, B.; Peng, Z.; Knochel, P. "Preparation of Polyfunctional Indazoles and Heteroarylazo Compounds Using Highly Functionalized Zinc Reagents" *Org. Lett.* **2009**, *11*, 4270-4273.
3. Thaler, T.; Haag, B.; Gavryushin, A.; Schober, K.; Hartmann, E.; Gschwind, R.; Zipse, H.; Knochel, P. "Highly Diastereoselective Csp^3-Csp^2-Negishi Cross-Coupling with Cycloalkylzinc Compounds" *Nature Chem*. **2010**, *2*, 125.
4. Jaric, M.; Haag, B.; Unsinn, A.; Karaghiosoff, K.; Knochel, P. "Highly Selective Metalations of Pyridines and Related Heterocycles Using New Frustrated Lewis Pairs or tmp-Zinc and tmp-Magnesium Bases with $BF_3 \cdot OEt_2$" *Angew. Chem, Int. Ed.* **2010**, *49*, 5451-5455.
5. Peng, Z.; Haag, B.; Knochel, P.* "Preparation of 2-Magnesiated 1,3,5-Triazines via an Iodine-Magnesium Exchange" *Org. Lett.* **2010**, *12*, 5398–5401.

6. *Designated "Hot Paper"*: Haag, B.; Zhang, Z.-G.; Li, J.-S.; Knochel, P. "Fischer Indole Synthesis with Organozinc Reagents" *Angew. Chem.* **2010**, *122*, 9703-9706; *Angew. Chem. Int. Ed.* **2010**, *49*, 9513–9516.
7. Zhang, Z.-G.; Haag, B.; Li, J.-S.; Knochel, P. "Efficient Preparation of Polyfunctional Indoles via a Zinc Organometallic Variation of the Fischer Indole Synthesis" *Synthesis* **2011**, 23-29.
8. Jaric, M.; Haag, B.; Manolikakes, S.; Knochel, P. "Selective and Multiple Functionalization of Complex Pyridines and Alkaloids via Mg- and Zn-Organometallic Intermediates" **2011**, *submitted*.

REVIEWS AND PATENTS

1. Haag, B.; Mosrin, M.; Hiriyakkana, I.; Malakhov, V.; Knochel, P.; "Regio- and Chemoselective Metalations of Arenes and Heteroarenes Using Hindered Metal Amides" *Angew. Chem. Int. Ed.* **2011**, *submitted*.
2. Knochel, P.; Haag, B. "Process for preparation of highly regioregular heterocyclic polymers" **2010**, *patent pending*.
3. Knochel, P.; Haag, B. "Metallic Amidoborates for Functionalizing Organic Compounds" **2010**, *patent pending*.
4. Knochel, P.; Haag, B. "Process for the direct preparation of organoboron and organoaluminium reagents" **2010**, *patent pending.*

SKILLS

Language : German (native), English (fluent), French (fluent), Norwegian (intermediate).

Computational Chemistry : Gaussian program package, Spartan'08, Pov-Ray, MOE, Momec´97, Macromodel, MS Office, Origin 7.0, Hyperchem45, Molden, J-Mol.

Teaching and Guidance : Chemistry, biology and medicine students and foreign Ph.D.s, in internships as well as in practical courses and theoretical seminars during my studies and my Ph.D.