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The Preparations of Functionalized Lithium, Magnesium, Aluminum, Zinc, and Indium Organometallics and Their Applications in Organic Synthesis

von

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Erklärung

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Ehrenwörtliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, _____

Dissertation eingereicht am _____

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

1. Preparation of Functionalized Organoindium Reagents via Magnesium Insertion to Organic Halides in the Presence of $InCl_3$ at Room Temperature
Sebastian Bernhardt,[†] Zhi-Liang Shen,[†] and Paul Knochel*
Chemistry-A European Journal **2013**, *19*, 828-833.
([†] Equal contribution; VIP paper; highlighted as frontispiece; also highlighted in ChemViews Magazine).

2. Highly Diastereoselective Preparation of Aldol Products Using New Functionalized Allylic Aluminum Reagents
Zhi-Liang Shen, Zhihua Peng, Chun-Ming Yang, Julian Helberg, Peter Mayer, Ilan Marek, and Paul Knochel*
Organic Letters **2014**, *16*, 956–959.

3. C_{60}-Catalyzed Preparation of Aryl and Heteroaryl Magnesium and Zinc Reagents using Mg/LiCl
Zhi-Liang Shen and Paul Knochel*
ACS Catalysis **2015**, *5*, 2324−2328.

4. Stereoselective Preparation of Polyfunctional Alkenylindium(III) Halides and Their Cross-Coupling with Unsaturated Halides
Zhi-Liang Shen and Paul Knochel*
Chemistry-A European Journal **2015**, *21*, 7061-7065.

5. Expedient Preparation of Aryl-Lithium and Zinc Reagents from Aryl Chlorides Using Lithium 4,4'-Di-*tert*-Butylbiphenylide and $ZnCl_2$
Zhi-Liang Shen, Korbinian Sommer, and Paul Knochel*
Synthesis **2015**, in press (DOI: 10.1055/s-0034-1380697).

6. Polyfunctional Alkenyl Li, Mg, or Zn-Organometallics as Versatile Building Blocks for the Synthesis of Complex Heterocycles
Zhi-Liang Shen, Shuo Li, Korbinian Sommer, Peter Mayer, and Paul Knochel*
Manuscript under preparation.

To

Li, Jingzhe & my parents and sister

如果冬天已经来了，春天还会远吗？

------英国诗人 雪莱

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Chapter 1. Introduction

1.1 Overview

Organometallic chemistry, which studies chemical compounds containing at least one bond between a carbon atom of an organic compound and a metal, plays a central role in the fast development of organic chemistry over the last century.[1] The importance of organometallic chemistry can be easily seen from the tremendous publications where most of the organic reactions required the participation of either metal or organometallic reagent/catalyst. Since V. Grignard was awarded the Nobel Prize in 1912 for the landmark development of Grignard reagent, many organic chemists in the field of organometallic chemistry have been awarded Nobel Prize because of their outstanding achievements in the development of organic chemistry with the use of metal or organometallic compound.[2] Especially from 2001-2010, Nobel Prize has been awarded three times to the field of organometallic chemistry, including metal-catalyzed asymmetric hydrogenation (W. S. Knowles, R. Noyori, and K. B. Sharpless in 2001), metal-catalyzed alkene metathesis (Y. Chauvin, R. Grubbs, and R. Schrock in 2005), and palladium catalyzed cross-coupling reactions (R. F. Heck, E. Negishi, and A. Suzuki in 2010).

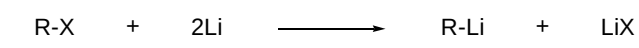
Organometallic reagent,[3] as an important part of organometallic chemistry, has considerably contributed to the advancement of synthetic organic chemistry. With more than one century of development, organometallic reagents such as organolithium, organomagnesium, organozinc, and organoindium compounds with different reactivities, have been developed and found wide applications in both academia and industry. Below, a brief introduction of these fundamental organometallic reagents which is relevant to the research topics developed in this thesis, is described.

[1] *Comprehensive Organometallic Chemistry III*; R. H. Crabtree, D. M. P. Mingos, Eds.; Elsevier: Oxford, **2007**.
[2] *All Nobel Prizes in Chemistry*. http://www.nobelprize.org/nobel_prizes/chemistry/laureates
[3] (a) *Handbook of Functionalized Organometallics*; P. Knochel, Ed.; Wiley-VCH: Weinheim, **2005**. (b) *Organometallics in Organic Synthesis*; E. Negishi, Ed.; Wiley: New York, **1980**.

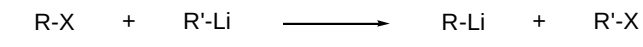
1.2 Organolithium reagents

The preparation and application of organolithium reagents in organic synthesis have been widely studied because of their strong nucleophilic reactivity.[4] Normally organolithium reagents can be synthesized by the following three methods (Scheme 1): (i) reduction of carbon-halogen bond with lithium(0); (ii) halogen-lithium exchange of organolithium reagent (such as *n*-BuLi) with organic halides; (iii) deprotonation of relatively acidic carbon-hydrogen bond by lithium base such as LDA or TMPLi. The thus-formed organolithium reagents are very reactive and can be trapped with various electrophiles.

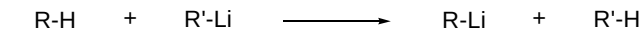
(i) Reduction of carbon-halogen bond with lithium(0)



(ii) Halo-lithium exchange of organolithium reagent with organic halide



(iii) Deprotonation of acidic carbon-hydrogen bond by lithium base

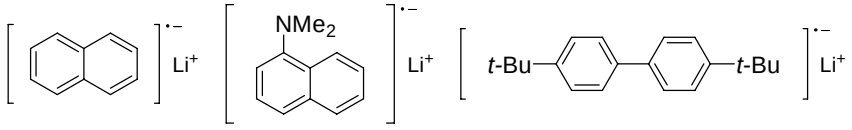


Scheme 1. Selected typical methods for the preparation of organolithium reagents

Among the methods for the preparation of organolithium reagent through the lithium(0)-mediated reduction of carbon-halogen bond of organic halides, activated lithium(0) in a form of dark-colored lithium-arene complex (also called lithium arenide) by reacting lithium(0) with arene, has been proven to be an attractive method. Generally, lithium arenides such as lithium naphthalenide (LiNp), lithium 1-(dimethylamino)naphthalenide (LiDMAN), or lithium 4,4'-di-*tert*-butylbiphenylide

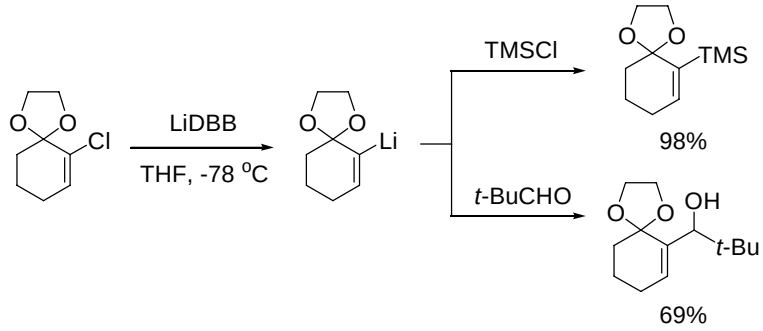
[4] For selected reviews on organolithium reagents, see: (a) *Organolithiums: Selectivity for Synthesis*; J. Clayden, Ed.; Pergamon: Oxford, **2002**. (b) *The Chemistry of Organolithium Compounds*; Z. Rappoport, I. Marek, Eds.; John Wiley and Sons: New York, **2004**. (c**)** *Lithium Compounds in Organic Synthesis: From Fundamentals to Applications*; R. Luisi, V. Capriati, Eds.; Wiley-VCH: Weinheim, **2014.** (d) M. Gray, M. Tinkel, V. Snieckus, In *Comprehensive Organolithium Chemistry II*; E. W. Abel, F. G. A. Stone, G. Wilkinson, A. McKillop, Eds.; Pergamon: Oxford, **1995**; vol. 11, pp. 1–92. (e) C. Nájera, J. M. Sansano, M. Yus, *Tetrahedron* **2003**, *59*, 9255. (f) R. Chinchilla, C. Nájera, M. Yus, *Tetrahedron* **2005**, *61*, 3139. (g) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667.

(LiDBB) was employed for the purpose (Scheme 2).[5] In comparison, 4,4'-di-*tert*-butylbiphenyl was found to be generally more efficient as a lithium activator because 4,4'-di-*tert*-butylbiphenyl is sterically more hindered and thus less prone to side reactions arising from attack of the *in situ* formed organolithium reagent on the arene ring.



Scheme 2. Commonly used lithium arenide radical species as lithiation agents

Yus and co-workers reported that when an unsaturated chlorinated ketal of *β*-chloro unsaturated ketal was treated with a catalytic amount of DBB (5%) and lithium metal, the lithiation occurred in THF at −78 °C, generating the corresponding alkenyllithium reagent (Scheme 3).[6] After trapping the thus-formed organolithium reagent with different electrophiles at the same temperature, the desired products was produced in moderate to good yields**.** A special case for the lithiation of 2-chloro-1,3-dienes using LiDBB as lithiation reagent was also reported.[7]



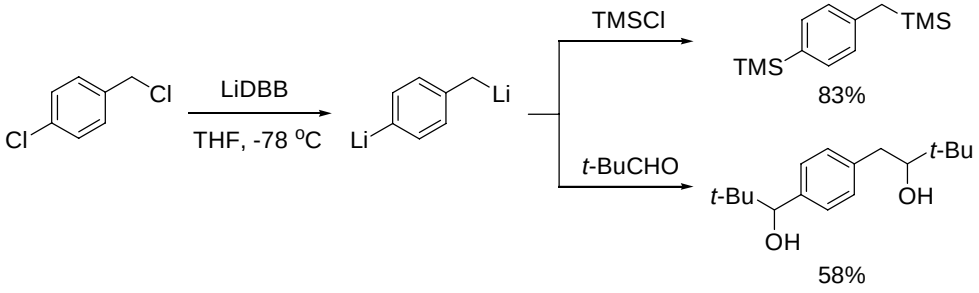
Scheme 3. Lithiation of *β*-chloro unsaturated ketal and trapping with electrophiles.

[5] For reviews on the application of lithium naphthalenide and lithium 4,4'-di-*tert*-butylbiphenylide (LiDBB) in organic synthesis, see: (a) F. Foubelo, M. Yus, *Chem. Soc. Rev.* **2008**, *37*, 2620. (b) T. Cohen, M. Bupathy, *Acc. Chem. Res.* **1989**, *22*, 152. (c) M. D. Ferguson, In *Encyclopedia of Reagents for Organic Synthesis*; L. A. Paquette, D. Crich, P. L. Fuchs, G. A. Molander, Eds.; John Wiley and Sons: Chichester, **2009**; vol. 8, pp. 6249-6251. (d) K. M. Short, In *Encyclopedia of Reagents for Organic Synthesis*; L. A. Paquette, D. Crich, P. L. Fuchs, G. A. Molander, Eds.; John Wiley and Sons: Chichester, **2009**; vol. 8, pp. 6136-6139. (e) M. Yus, *Chem. Soc. Rev.* **1996**, *25*, 155. (f) D. J. Ramón, M. Yus, *Eur. J. Org. Chem.* **2000**, 225. (g) M. Yus, *Synlett* **2001**, 1197. (h) M. Yus, In *The Chemistry of Organolithium Compounds*; Z. Rappoport, I. Marek, Eds.; Wiley and Sons: Chichester, **2004**; Chap. 11, pp. 647-748.

[6] A. Bachki, F. Foubelo, M. Yus, *Tetrahedron* **1997**, *53*, 4921.

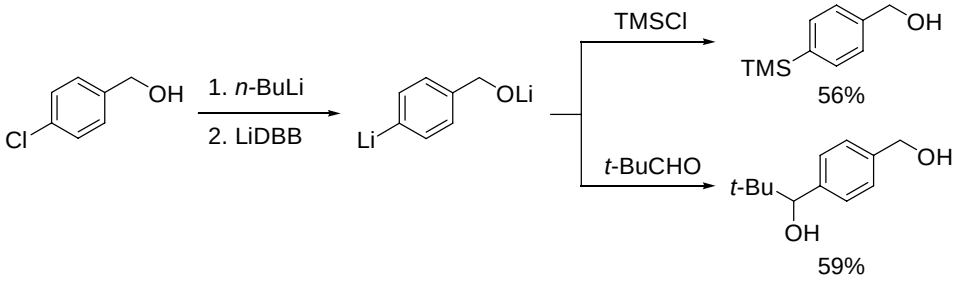
[7] R. Bloch, N. Chaptal-Gradoz, *Tetrahedron Lett.* **1992**, *33*, 6147.

LiDBB also can be applied to the preparation of aryllithium reagents by using even less reactive aryl chloride as starting material. However, till now, only very special aryl chlorides were used for the purpose. For instance, when 4-chlorobenzyl chloride was subjected to LiDBB-mediated double-lithiation followed by treatment with electrophiles, difunctionalized products were obtained (Scheme 4). [8] Other dichlorinated materials such as dibenzylic dichlorides were also proven to be suitable candidates.[9]



Scheme 4. LiDBB-mediated double-lithiation of 4-chlorobenzyl chloride followed by quenching with electrophiles.

In cases where aryl chlorides containing a hydroxyl group (e.g., 4-chlorobenzyl alcohol) were used as substrates, the acidic hydroxyl group can be pre-deprotonated by *n*-BuLi prior to the lithiation by LiDBB (Scheme 5). After treatment of the resulting dianion intermediate with electrophiles followed by acidic hydrolysis, the expected mono-adduct can be obtained.[8a]



Scheme 5. LiDBB-mediated double-lithiation of 4-chlorobenzyl alcohol followed by reactions with electrophiles.

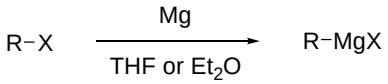
[8] (a) C. Gomez, F. F. Huerta, M. Yus, *Tetrahedron* **1998**, *54*, 1853. (b) C. Gomez, F. F. Huerta, M. Yus, *Tetrahedron Lett*. **1997**, *38*, 687.
[9] (a) C. Gomez, F. F. Huerta, M. Yus, *Tetrahedron* **1997**, *53*, 13897. (b) M. Yus, D. J. Ramon, I. Gomez, *J. Organomet. Chem.* **2002**, *663*, 21.

1.3 Organomagnesium reagents

Organomagnesium reagent, also known as Grignard reagent,[10] was named after Victor Grignard (Nobel Laureate in 1912) and is probably one of the most important and widely used organometallic reagents in organic synthesis in the last century. The Grignard reaction is an important tool for forming carbon-carbon bonds because organomagnesium reagent shows excellent reactivity and is able to react with a variety of electrophiles such as a carbonyl compound, an electron-deficient alkene, or an epoxide.[11] In addition, the reactivity of organomagnesium reagent can be fine-tuned by transmetalation to other less reactive but more chemoselective organometallic reagents (e.g., zinc, copper, or titanium).

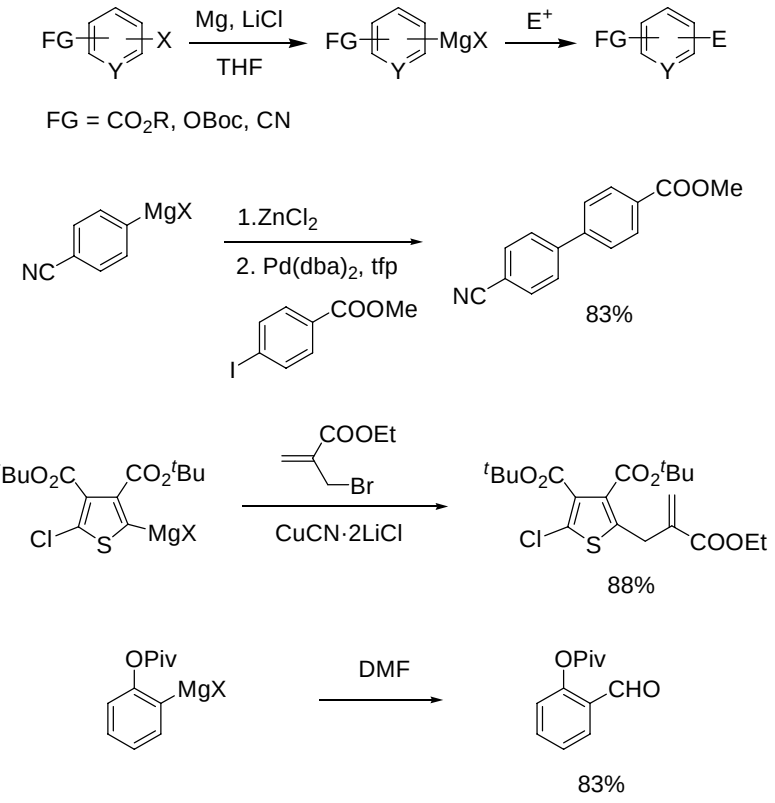
Normally, organomagnesium reagents can be prepared by the direct insertion of magnesium metal into organic halides in ethereal solvents (such as THF or Et_2O which also serve as a ligand to stabilize the formed organomagnesium reagents through coordination; Scheme 6). The insertion reaction was proposed to proceed through a radical-type mechanism.[12] Activation of the magnesium metal by removing the "oxide layer"[13] formed on the metal surface is very important, otherwise the insertion reaction is difficult to take place. Several activators, including alkyl halides (e.g., 1,2-dibromoethane[14]), iodine,[15] transition metal catalysis of $FeCl_2$,[16] and DIBAL-H,[17] were found to be effective in the activation of the magnesium surface.

[10] V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1990**, *130*, 1322.
[11] (a) *Handbook of Grignard Reagents*; G. S. Silverman, P. E. Rakita, Eds.; Marcel Dekker: New York, **1996**. (b) *The Chemistry of Organomagnesium Compounds*; Z. Rappoport, I. Marek, Eds.; Wiley-VCH: Weinheim, **2008**. (c) 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. (d) C. Nájera, J. M. Sansano, M. Yus, *Tetrahedron* **2003**, *59*, 9255. (e) R. Chinchilla, C. Najera, M. Yus, *Tetrahedron* **2005**, *61*, 3139. (f) F. Foubelo, M. Yus, *Chem. Soc. Rev.* **2008**, *37*, 2620. (g) Z. Xi, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1021. (i) Z. Xi, *Acc. Chem. Res.* **2010**, *43*, 1342.
[12] (a) H. M. Walborsky, *Acc. Chem. Res.* **1990**, *23*, 286. (b) J. F. Garst, *Acc. Chem. Res.* **1991**, *24*, 95. (c) C. Walling, *Acc. Chem. Res.* **1991**, *24*, 255. (d) H. R. Rogers, C. L. Hill, Y. Fujiwara, R. J. Rogers, H. L. Mitchell, G. M. Whitesides, *J. Am. Chem. Soc.* **1980**, *102*, 217.
[13] J. F. Garst, M. P. Seriaga, *Coord. Chem. Rev.* **2004**, *248*, 623.
[14] W. E. Lindsell, In *Comprehensive Organometallic Chemistry I*; G. Wilkinson, F. G. S. Stone, G. E. Ebel, Eds.; Pergamon Press: Oxford, **1982**; Vol. 1, Chap. 3, pp. 155–252 and references therein
[15] H. Gold, M. Larhed, P. Nilsson, *Synlett* **2005**, 1596.
[16] B. Bogdanovic, M. Schwickardi, *Angew. Chem.*, *Int. Ed.* **2000**, *39*, 4610.
[17] U. Tilstam, H. Weinmann, *Org. Process Res. Dev.* **2002**, *6*, 906.



Scheme 6. Preparation of organomagnesium reagent by direct magnesium insertion

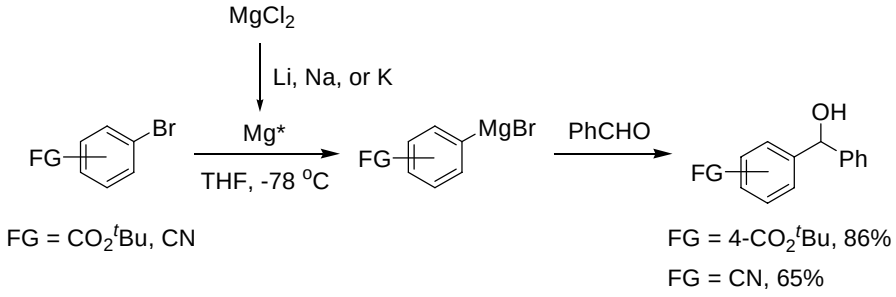
In 2008, Knochel and co-workers reported that LiCl considerably facilitated the magnesium insertion into aryl halides under mild conditions.[18] The insertion reaction proceeded efficiently in the presence of LiCl to give the expected arylmagnesium reagents in moderate to good yields with tolerance to nitrile and ester groups (Scheme 7). LiCl is proposed to solubilise and remove the formed organometallic species from the metal surface, thus allowing a further insertion to occur on the clean metal surface.



Scheme 7. Preparation of functionalized organomagnesium reagent by LiCl-facilitated magnesium insertion into aryl halides

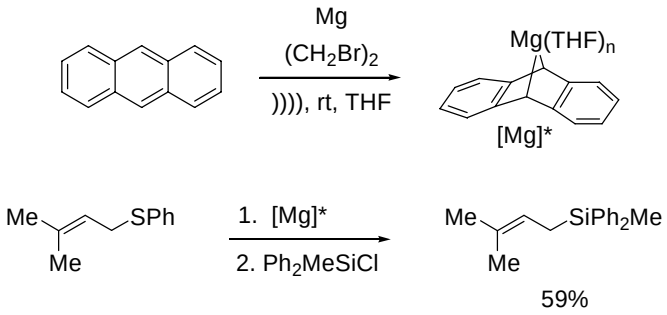
[18] (a) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem.-Eur. J.* **2009**, *15*, 7192. (b) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem., Int. Ed.* **2008**, *47*, 6802.

Rieke *et al.* found that a highly reactive magnesium [also called Rieke magnesium (Mg*)] can be facilely generated by reduction of magnesium halides with sodium, potassium, or lithium.[19] The thus-formed magnesium species readily inserts into aryl halides in THF even at very low temperature (-78 °C) to afford the corresponding organomagnesium reagents with high functional group tolerance (Scheme 8).[20]



Scheme 8. Preparation of functionalized organomagnesium reagents by using Rieke magnesium

Polycyclic arene such as anthracene was found to be a source for generating highly reactive magnesium in the form of a soluble Mg-anthracene species (Scheme 9). This activated magnesium species can be used for the reductive metalation of allylic phenyl sulfides.[21,22]

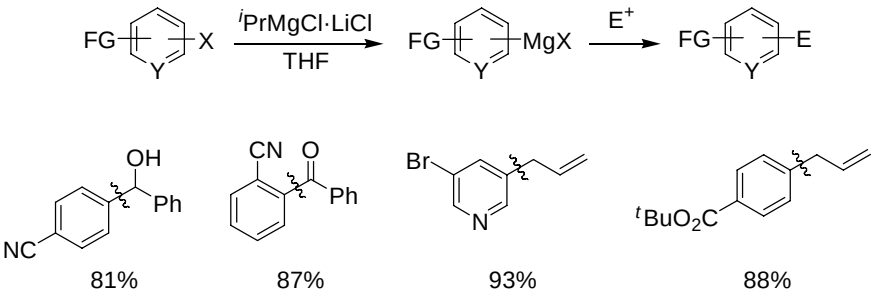


Scheme 9. Preparation of Mg-anthracene species and application in the reductive metalation of allylic phenyl sulfides

[19] (a) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925. (b) R. D. Rieke, M. S. Sell, W. R. Klein, T.-A. Chen, J. D. Brown, M. U. Hansen, In *Active Metals. Preparation, Characterization, Application*; A. Furstner, Ed.; Wiley-VCH: Weinheim, **1996**, p. 1.
[20] J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428.
[21] B. Bogdanovic, *Acc. Chem. Res.* **1988**, *21*, 261.
[22] D. Cheng, S. Zhu, Z. Yu, T. Cohen, *J. Am. Chem. Soc.* **2001**, *123*, 30.

However, the preparation of functionalized organomagnesium reagents via a direct magnesium insertion into organic halides still suffers from limitations due to the intrinsic high reducing power of magnesium. Thus, the scope for the preparation of functionalized Grignard reagents can be considerably expanded by halogen–magnesium exchange which is pioneered by Prevost in 1931.[23]

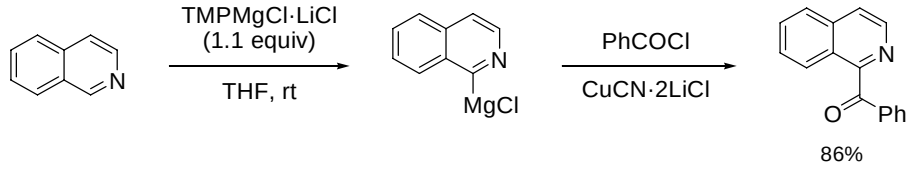
Recently, Knochel and co-workers demonstrated a very practical and useful method for the synthesis of arylmagnesium reagents by a halogen-magnesium exchange of aryl halides with commercially available ^{i}PrMgCl·LiCl (Turbo-Grignard reagent).[24,25] Most importantly, the feasibility of performing the reaction at low temperature allows the use of aryl halides containing functional groups such as ester or nitrile (Scheme 10).



Scheme 10. Preparation of arylmagnesium reagent by a halogen-magnesium exchange of aryl halides with ^{i}PrMgCl·LiCl.

Finally, it should be noted that organomagnesium reagent also can be accessed via a metallation of aromatic ring by using magnesium amide base.[26] For example, isoquinoline can be conveniently metalated by TMPMgCl·LiCl leading to the corresponding heteroarylmagnesium reagent. After a copper(I)-catalyzed acylation, a biaryl ketone was obtained (Schem 11).[27]

[23] C. Prevost, *Bull. Soc. Chim. Fr.* **1931**, 1372.
[24] For a review, see: 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.
[25] A. Krasovskiy, P. Knochel, *Angew. Chem.*, *Int. Ed.* **2004**, *43*, 3333.
[26] For a review, see: B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem.*, *Int. Ed.* **2011**, *50*, 9794.
[27] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem.*, *Int. Ed.* **2006**, *45*, 2958.



Scheme 11. Preparation of arylmagnesium reagent by using a TMPMgCl·LiCl-mediated metallation

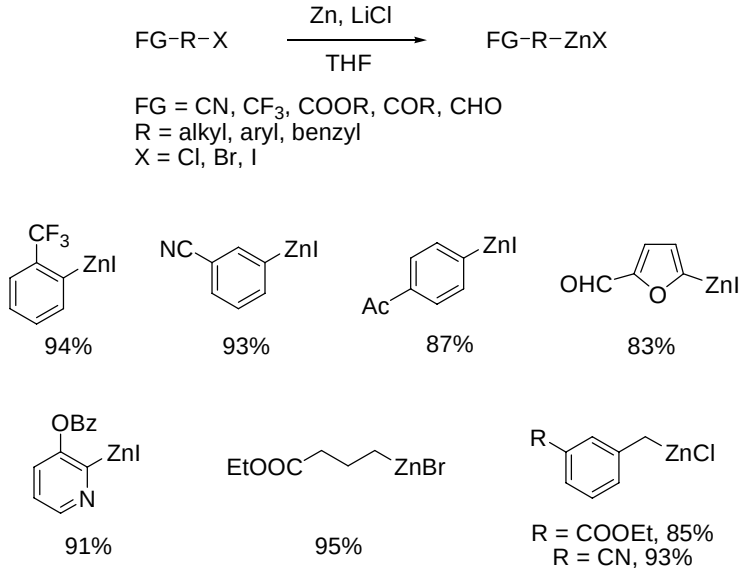
1.4 Organozinc reagents

In 1849, Frankland described the first preparation of organozinc reagents (dialkylzinc species) by the oxidative addition of zinc metal to alkyl iodide.[28] However, this work has not received too much attention because the relatively low reactivity of organozinc reagent as compared to organolithium and Grignard reagent rendered them less attractive at that time. With more than 150 years of development, organozinc reagents have been demonstrated to be synthetically versatile organometallic intermediates which can be seen from several named reactions including Negishi cross-coupling,[29] Reformatsky reaction,[30] and Simmons-Smith cyclopanation.[31] The intrinsically moderate reactivity of organozinc reagent allowed its tolerance to many functional groups, such as nitrile, ester, ketone, nitro and even formyl group.

Similar to the preparation of organomagnesium reagents, organozinc reagents can be conveniently prepared by direct oxidative insertion of zinc metal into organic halides. Knochel *et al.* developed an efficient method for the synthesis of aryl, alkyl, and benzyl zinc reagents by a LiCl-mediated zinc insertion into aryl, alkyl, and benzyl

[28] (a) E. Frankland, *Ann. Chem.* **1849**, *71*, 171; (b) E. Frankland, *Ann. Chem.* **1849**, *71*, 213.
[29] For selected reviews, see: (a) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340. (b) E. I. Negishi, Q. Hu, Z. Huang, M. Qian, G. Wang, *Aldrichimica Acta* **2005**, *38*, 71. (c) *Metal-Catalyzed Cross-Coupling Reactions*; F. Diederich, P. J. Stang, Eds.; Wiley-VCH: Weinheim, **1998**. (d) J. De Houwer, B. U. W. Maes, *Synthesis* **2014**, *46*, 2533.
[30] (a) S. Reformatsky, *Ber. Dtsch. Chem.* **1887**, *20*, 1210. For selected reviews, see: (b) R. Ocampo, W. R. Dolbier, *Tetrahedron* **2004**, *60*, 9325. (c) F. Orsini, G. Sello, *Curr. Org. Synth.* **2004**, *1*, 111. (d) C. M. R. Ribeiro, F. M. C. de Farias, *Mini-Rev. Org. Chem.* **2006**, *3*, 1. (e) P. G. Cozzi, A. Mignogna, L. Zoli, *Pure App. Chem.* **2008**, *80*, 891. (f) A. Fürstner, *Synthesis* **1989**, 571. (g) M. Gaudemar, *Organomet. Chem. Rev. A* **1972**, *8*, 183.
[31] (a) R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323. (b) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 4256. (c) J. M. Denis, J. M. Girard, J. M. Conia, *Synthesis* **1972**, 549.

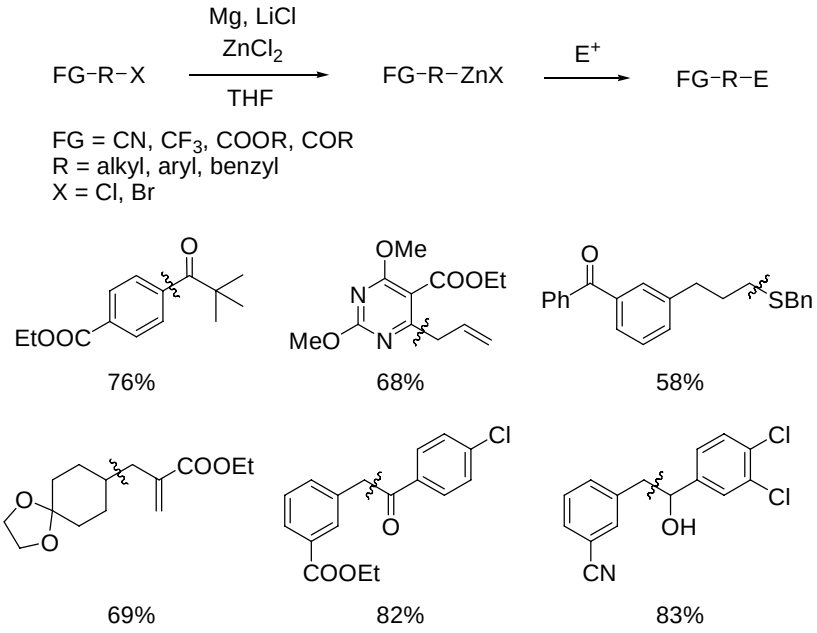
halides under mild conditions (Scheme 12).[32-34] By using this approach, the corresponding organozinc reagents were produced in good to excellent yields with wide functional group tolerance. Very recently, Yoshikai and co-workers also reported a cobalt/Xantphos-catalyzed preparation of arylzinc reagents starting from aryl halides in the presence of LiCl.[35]



Scheme 12. Preparation of organozinc reagents by a direct zinc insertion in the presence of LiCl

In cases where less reactive aryl bromides were used as substrates, the preparation of organozinc reagents can be achieved by using a more reactive Mg/LiCl insertion in the presence of $ZnCl_2$.[18b, 36] The *in situ* formed arylmagnesium species were transmetallated with $ZnCl_2$ to form the expected arylzinc reagents (Scheme 13). Mono-zinc or bis-zinc organometallics were obtained depending on the equivalents of $ZnCl_2$ used. Important functional groups including nitrile, ketal, ester, and ketone can be kept intact in the reaction.

[32] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem.*, *Int. Ed.* **2006**, *45*, 6040.
[33] N. Boudet , S. Sase , P. Sinha , C.-Y. Liu , A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358.
[34] A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.
[35] M.-Y. Jin, N. Yoshikai, *J. Org. Chem.* **2011**, *76*, 1972.
[36] (a) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824; (b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192; (c) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082; (d) A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem.*, *Int. Ed.* **2010**, *49*, 4665; (e) M. A. Schade, G. Manolikakes, P. Knochel, *Org. Lett.* **2010**, *12*, 3648.



Scheme 13. Preparation of organozinc reagent by using Mg/LiCl insertion followed by *in situ* transmetallation with $ZnCl_2$.

Alternatively, organozinc reagents can be synthesized by treating either aryl iodide with dialkylzinc reagent (such as $^{i}Pr_2Zn$; in the presence of lithium halide) through iodo-zinc exchange[37] or arene with zinc amide base (such as TMPZnCl·LiCl) through deprotonation.[38]

1.5 Organoindium reagents

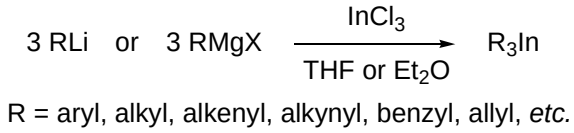
In comparison with organolithium, organomagnesium, and organozinc reagents, organoindium reagents show relatively poor reactivity and thus better functional group tolerance.[39]

[37] (a) S. Achyutha Rao, C. E. Tucker, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 7575. (b) F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem.*, *Int. Ed.* **2004**, *43*, 1017. (c) L.-Z. Gong, P. Knochel, *Synlett* **2005**, 267.

[38] (a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837. (b) T. Bresser, M. Mosrin, G. Monzón, P. Knochel, *J. Org. Chem.* **2010**, *75*, 4686. (c) T. Bresser, M. Mosrin, G. Monzón, P. Knochel, *J. Org. Chem.* **2010**, *75*, 4686.

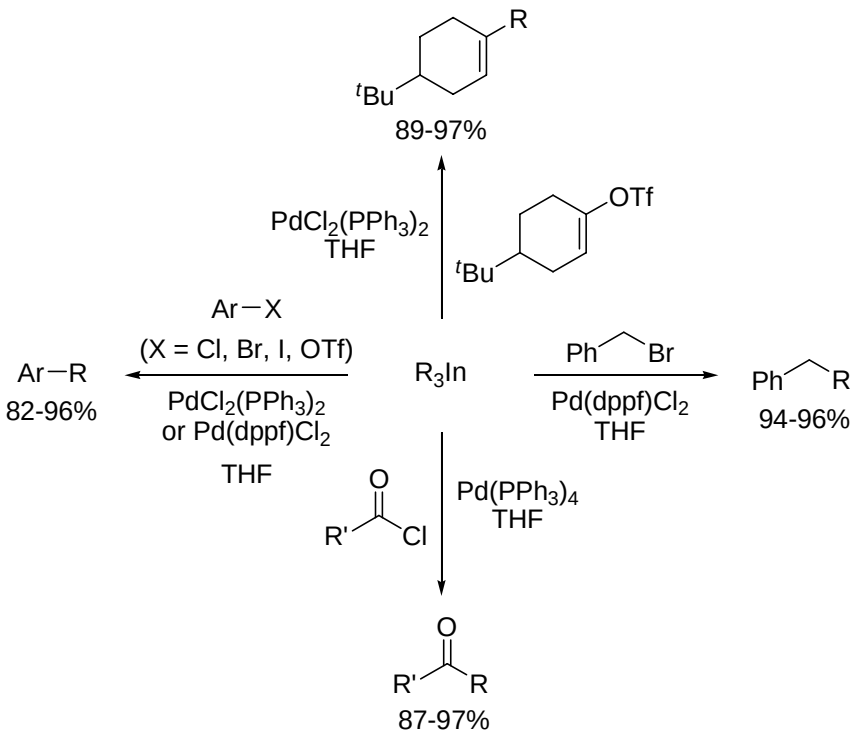
[39] For selected typical reviews on organoindium reagents, see: (a) S. Araki, T. Hirashita, in *Comprehensive Organometallic Chemistry III*; R. H. Crabtree, D. M. P. Mingos, Eds.; Elsevier: Oxford, **2007**; vol. 9, chap. 9.14, pp. 649–722; (b) Z. L. Shen, S. Y. Wang, Y. K. Chok, Y. H. Xu, T. P. Loh, *Chem. Rev.* **2013**, *113*, 271.

In 1934, Dennis and co-workers[40] reported the first preparation of organoindium compound of trimethylindium (Me_3In) via the transmetallation of dimethylmercury with indium.[41] Thereafter, it was found that organoindium reagents also can be prepared by the transmetallation of indium(III) halides with other reactive organometallics such as organoaluminum,[42] organomagnesium,[43,44] and organolithium reagents.[45] In 1999, Sarandeses and co-workers pioneered the applications of triorganoindium reagents (R_3In; prepared via the direct transmetallation of the corresponding Grignard reagent with $InCl_3$; Scheme 14) in the transition metal-catalyzed cross-coupling with various electrophiles (Scheme 15).[46] Later, Oshima and co-workers discovered that the cross-coupling involving triorganoindium reagents even can be performed in aqueous media.[47]



Scheme 14. Preparation of triorganoindium reagents via the transmetallation of organolithium or Grignard reagent with $InCl_3$

[40] L. M. Dennis, R. W. Work, E. G. Rochow, *J. Am. Chem. Soc.* **1934**, *56*, 1047.
[41] W. S. Schumb, H. I. Crane, *J. Am. Chem. Soc.* **1938**, *60*, 306. (b) H. Gilman, R. G. Jones, *J. Am. Chem. Soc.* **1940**, *62*, 2353. (c) E. L. Amma, R. E. Rundle, *J. Am. Chem. Soc.* **1958**, *80*, 4141.
[42] J. J. Eisch, *J. Am. Chem. Soc.* **1962**, *84*, 3605.
[43] F. Runge, W. Zimmermann, H. Pfeiffer, I. Pfeiffer, *Z. Anorg. Allgem. Chem.* **1951**, *267*, 39.
[44] J. L.W. Pohlmann, F. E. Brinckmann, *Z. Naturforsch.* **1965**, *20b*, 5.
[45] . H. C. Clark, A. L. Pickard, *J. Organomet. Chem.* **1967**, *8*, 427.
[46] For the use of triorganoindium reagent (R_3In) in organic synthesis by Sarandeses *et al.*, see: (a) I. Perez, J. Perez Sestelo, L. A. Sarandeses, *J. Am. Chem. Soc.* **2001**, *123*, 4155; (b) I. Perez, J. Perez Sestelo, L. A. Sarandeses, *Org. Lett.* **1999**, *1*, 1267; (c) J. Caeiro, J. Perez Sestelo, L. A. Sarandeses, *Chem. Eur. J.* **2008**, *14*, 741; (d) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997; (e) S. Bernhardt, Z. L. Shen, P. Knochel, *Chem. Eur. J.* **2013**, *19*, 828; (f) L. Jin, Y. Zhao, L. Zhu, H. Zhang, A. Lei, *Adv. Synth. Catal.* **2009**, *351*, 630; (g) Y. Zhao, L. Jin, P. Li, A. Lei, *J. Am. Chem. Soc.* **2008**, *130*, 9429.
[47] K. Takami, H. Yorimitsu, H. Shinokubo, S. Matsubara, K. Oshima, *Org. Lett.* **2001**, *3*, 1997.



Scheme 15. Selected synthetic utility of triorganoindium reagent (R_3In) in transition metal-catalyzed cross-coupling

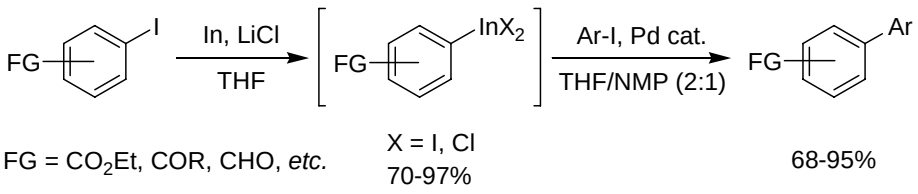
However, it should be noted that the method for the preparation of triorganoindium reagent using more reactive Grignard reagent suffered from poor functional group tolerance because important functional groups such as ester and nitrile cannot be tolerated.

In addition to the above methods for the preparation of organoindium reagents through transmetallation, organoindium reagents also can be prepared by the direct insertion of indium metal to organic halides. In addition to the extensive studies on the preparation and application of allylindium and propargylindium reagents in organic synthesis,[48] the preparation of arylindium, benzylindium and alkylindium reagents have received considerable attention from synthetic community only very recently.

In 2008, Knochel and co-workers descried an efficient method for the synthesis of arylindium reagents by a LiCl-mediated direct insertion of commercial indium(0)

[48] (a) U. K. Roy, S. Roy, *Chem. Rev.* **2010**, *110*, 2472. (b) For a review article, see: L. A. Paquette, *Synthesis* **2003**, 765. (c) C. J. Li, T. H. Chan, *Tetrahedron Lett.* **1991**, *32*, 7017.

metal into aryl iodide (Scheme 16).[49] Various arylindium reagents containing functional groups such as nitrile, ester, and aldehyde can be conveniently prepared by this protocol. The resulting arylindium reagents smoothly underwent palladium-catalyzed cross-coupling with aryl halides in NMP/THF (1:2) in the presence of $Pd(dppf)Cl_2$. Aryl halide bearing acidic proton (such as indole, alcohol, and phenol) can be used as coupling partner as well, provided that appropriate palladium catalyst such as $Pd(dppf)Cl_2$ or $Pd(OAc)_2$/S-Phos is used. Almost simultaneously, Minehan *et al.* reported a similar strategy for performing the direct insertion of indium into aryl iodides in the presence of LiCl.[50] A further contribution from Yoshikai and co-workers by adding catalytic amounts of $CoBr_2$ (5 mol%) as catalyst and bathophen (5 mol%) as ligand also allowed the use of less reactive aryl bromide as substrate for the synthesis of the corresponding arylindium species.[51]

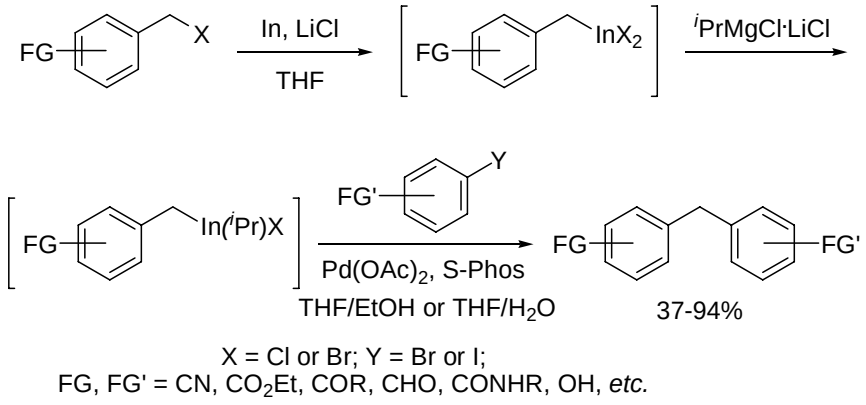


Scheme 16. Preparation of arylindium reagents by a LiCl-mediated direct insertion of indium(0) into aryl iodide

Later, another similar method for the synthesis of benzylindium reagent via a LiCl-mediated direct insertion of indium(0) into benzyl halide was independently reported by the groups of Knochel[52] and Chupak[53] (Scheme 17). A broad range of sensitive functional groups such as CO_2Et, COR, CHO, CN, and CH_2OH embedded in the benzyl bromides were tolerated in the insertion step. These formed benzylindium species, after transmetallation with $^{i}PrMgCl{\cdot}LiCl$ to generate a more robust mixed benzylindium reagent, was capable of undergoing palladium-catalyzed cross-coupling with various aryl iodides and aryl bromides, giving rise to diarylmethane derivatives in moderate to good yields. Coupling partners bearing important functional groups

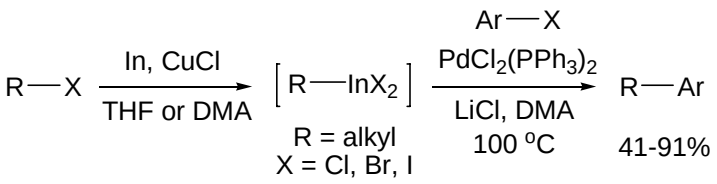
[49] Y. H. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648.
[50] V. Papoian, T. Minehan, *J. Org. Chem.* **2008**, *73*, 7376.
[51] L. Adak, N. Yoshikai, *J. Org. Chem.* **2011**, *76*, 7563.
[52] Y. H. Chen, M. Sun, P. Knochel, *Angew. Chem.*, *Int. Ed.* **2009**, *48*, 2236.
[53] L. S. Chupak, J. P. Wolkowski, Y. A. Chantigny, *J. Org. Chem.* **2009**, *74*, 1388.

(e.g., CN, CO_2Et, COR, CHO, CH_2OH, NHTs, and CONHR) was found to be compatible with the benzylindium reagents as well.



Scheme 17. Synthesis of benzylindium reagent via a LiCl-mediated direct insertion of indium(0) into benzyl halide

Recently, Loh and co-workers reported that alkylindium reagent can be readily accessed by a direct insertion of indium metal into alkyl iodide in the presence of CuCl (Scheme 18).[54] Alkyl bromide can be used as substrate as well provided that a harsher reaction conditions were employed (100 ^oC, DMA). The thus-formed alkylindium reagent was capable of undergoing palladium-catalyzed coupling with aryl halides in DMA, affording the corresponding products in moderate to good yields. Similarly, the alkylindium reagents were found to be compatible with various functional groups or substituents including COR, COOR, CHO, CN, OH, OTBS, NO_2, C=C, Br, and Cl.

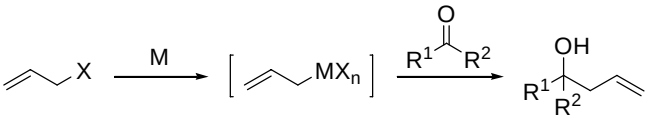


Scheme 18. Preparation of alkylindium reagent by a direct insertion of indium metal into alkyl iodide in the presence of CuCl

[54] Z. L. Shen, K. K. K. Goh, Y. S. Yang, Y. C. Lai, C. H. A. Wong, H. L. Cheong, T. P. Loh, *Angew. Chem. Int. Ed.* **2011**, *50*, 511.

1.6 Allylmetallic reagents

Allylmetallic reagent, which can be prepared by the insertion of metal into allyl halide, is an important intermediate in organic synthesis; it reacts with carbonyl compounds to provide synthetically useful homoallylic alcohols (Scheme 19).[55]

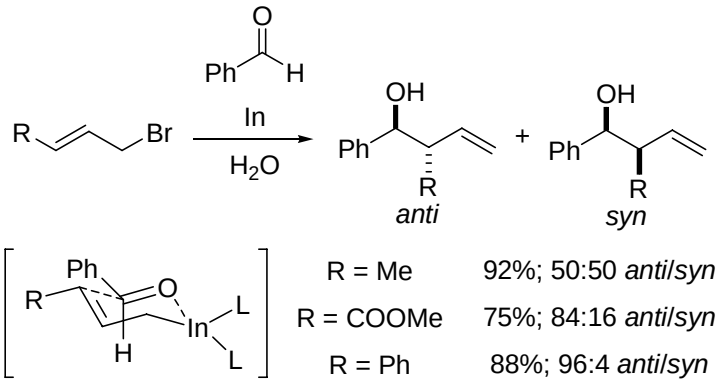


X = Cl, Br, I
M = Mg, Zn, In, Al, *etc.*

Scheme 19. Preparation of allylmetallic reagents by direct metal insertion and their reactions with carbonyl compounds for the synthesis of homoallylic alcohols

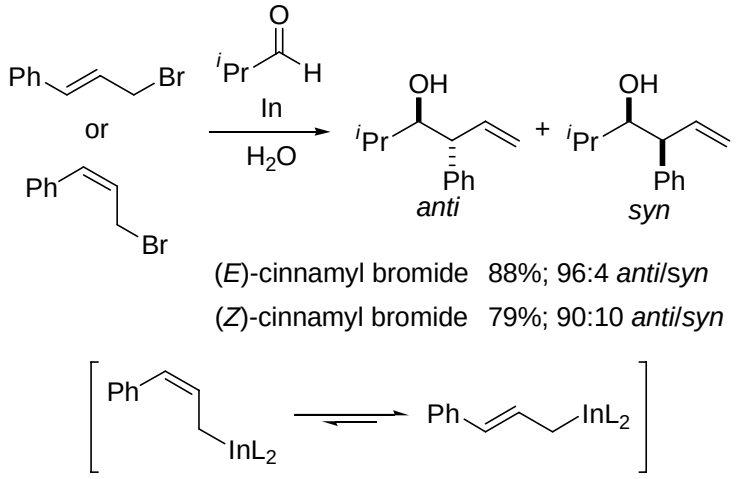
In cases where *γ*-substituted allylmetallic reagent was used, its addition to a carbonyl compound lead to a mixture of two diastereomers. For examples, when allylindium reagent bearing a small *γ*-substituent (R = Me) was used, it reacted with a benzaldehyde to give the corresponding product in a non-selective manner (50:50 *anti*/*syn*).[56] In comparison, the use of an allylindium reagent derived from a bulkier *γ*-substituted allyl bromide (R = Ph or COOR) gave rise to the desired products with good to excellent *anti*-selectivities (Scheme 20). An acyclic or Zimmerman–Traxler[57]-[58] transition state has been proposed to explain the varying diastereoselectivities observed.

[55] For selected reviews of allylmetallic reagents, see: (a) M. Yus, J. C. Gonzalez-Gomez, F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774. (b) I. Marek, G. Sklute, *Chem. Commun.* **2007**, 1683. (c) P. Merino, T. Tejero, J. I. Delso, V. Mannucci, *Curr. Org. Synth.* **2005**, *2*, 479. (d) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763.
[56] 56. M. B. Issac, T.-H. Chan, *Tetrahedron Lett.* **1995**, *36*, 8957.
[57] (a) H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920. (b) C. H. Heathcock, *Science* **1981**, *214*, 395.
[58] J. H. Dam, P. Fristrup, R. Madsen, *J. Org. Chem.* **2008**, *73*, 3228.



Scheme 20. Addition of γ-substituted allylindium reagents to aldehyde with varying diastereoselectivities

Interestingly, the use of allylindium reagent derived from either (*Z*)- or (*E*)-cinnamyl bromides to react with an aliphatic aldehyde both resulted in the predominant formation of *anti*-products (Scheme 21). A facile *E*/*Z* equilibration of the resulting allylindium organometallic was postulated by Paquette and Chan to account for this behavior. [56, 59]

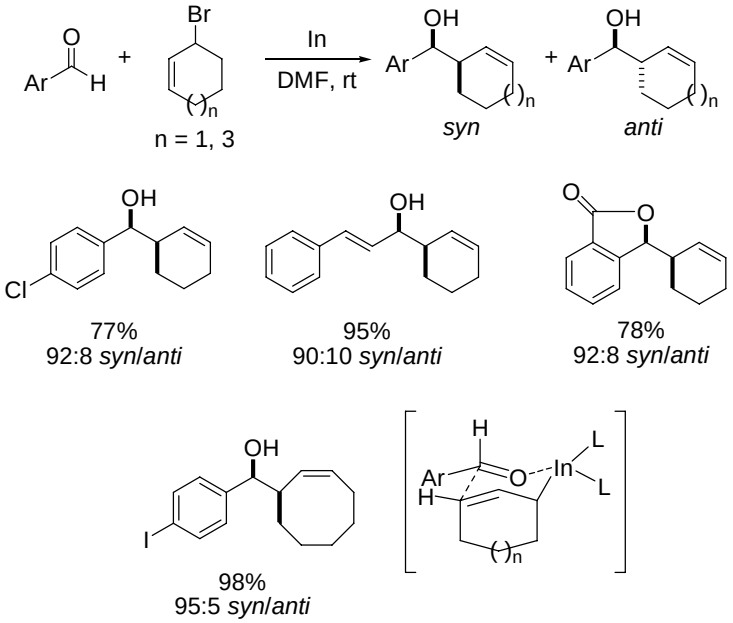


Scheme 21. Addition of (*Z*)- or (*E*)-cinnamylindium reagent to an aliphatic aldehyde with the same *anti*-diastereoselectivity

Thus, when an allylmetallic reagent which is unsusceptible to *E* to *Z* isomerization of the C-C double bond was used as substrate, the stereochemical outcome of its reaction with a carbonyl compounds can be tuned. One typical example is the use of

[59] L. A. Paquette, T. M. Mitzel, *J. Org. Chem.* **1996**, *61*, 8799.

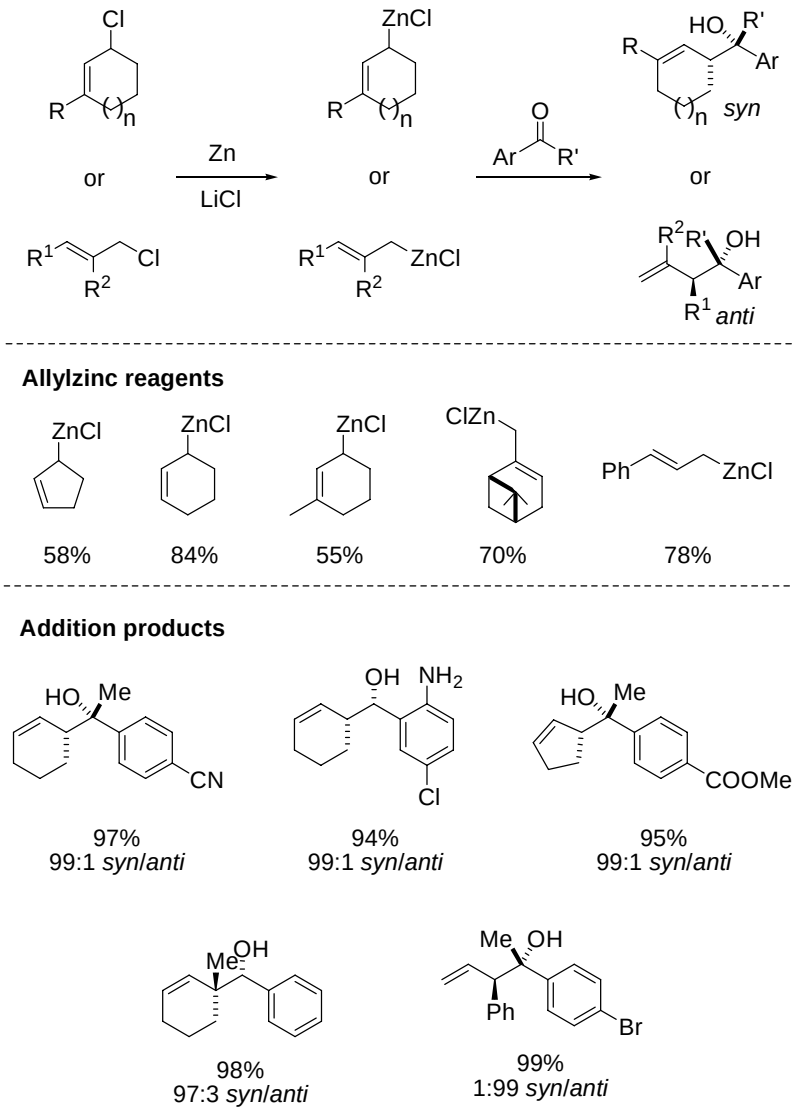
allylindium reagent derived from 3-bromocyclohexene in which the C-C double bond always possesses an *E* configuration. As shown in Scheme 22, the indium-mediated reactions of 3-bromocyclohexene with aromatic aldehydes proceeded smoothly to give substituted cyclohexenyl homoallylic alcohols with good *syn*/*anti* diastereoselectivities (up to >99:1 dr). [60] The use of 3-bromocyclooctene also delivered reasonable to good *syn*/*anti* diastereoselectivity. The observed *syn* diastereoselectivity can be explained by a Felkin-Anh six-membered cyclic transition state.[57]



Scheme 22. Diastereoselective addition of cyclic allylindium reagent to carbonyl compounds.

In 2007, Knochel and co-workers reported an efficient method for the preparation of various allylic zinc reagents in the presence of LiCl (Scheme 23).[61] The allylic zinc reagents readily underwent addition to carbonyl compounds producing homoallylic alcohols bearing up to two adjacent quaternary centers with highly diastereoselectivity.

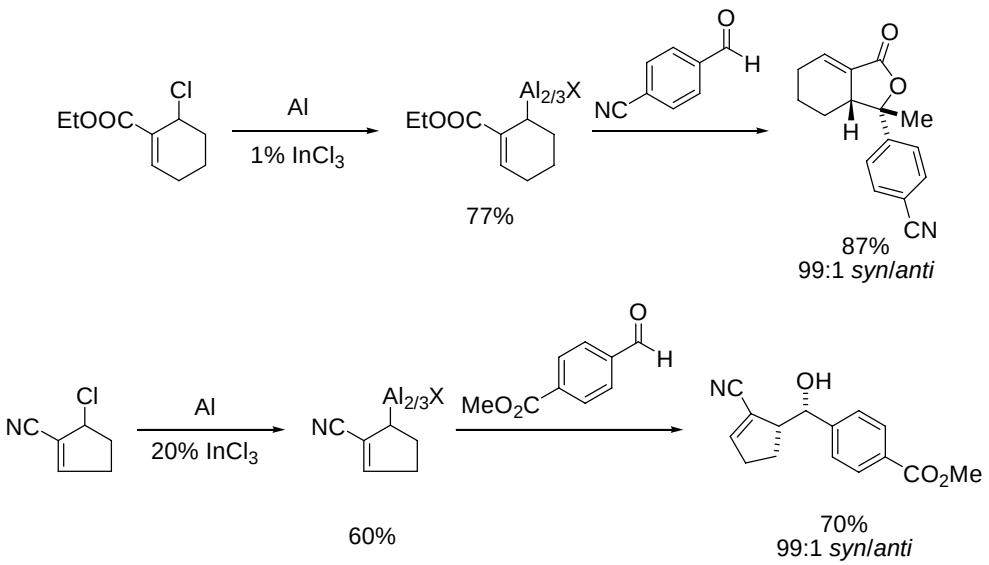
[60] F. A. Khan, B. Prabhudas, *Tetrahedron* **2000**, *56*, 7595.
[61] H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 5376.



Scheme 23. Preparation of allylic zinc reagent and diastereoselective addition to carbonyl compounds

In 2010, Knochel *et al.* further extended the method to the preparation of allylic aluminum regents as well as their diastereoselective addition to carbonyl compounds. In this case, the insertion of aluminum metal to allyl halide was achieved by using a catalytic amount of $InCl_3$ as catalyst. The subsequent addition to a variety of functionalized carbonyl compounds proceeded with high diastereoselectivity leading to the corresponding homoallylic alcohols in most cases as single diastereomer (Scheme 24).[62] Most importantly, the mildness of the allylic aluminum reagent entailed the presence of sensitive functional groups such as ester and cyano group.

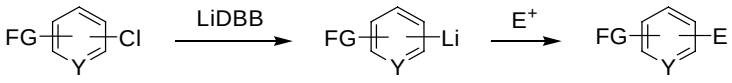
[62] Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem.*, *Int. Ed.* **2010**, *49*, 8516.



Scheme 24. Preparation of functionalized allylic aluminum reagents and their diastereoselective addition to carbonyl compounds

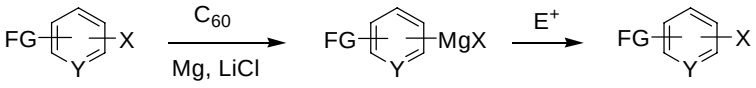
1.7 Objectives

Although several very special examples regarding the LiDBB-mediated lithiation of aryl halides have been investigated, the substrates scope is extremely limited. Thus, the purpose of the first project is to develop a general method for preparation of arylithium reagent through a LiDBB-mediated lithiation of commonly used aryl chlorides bearing functional groups (Scheme 25).



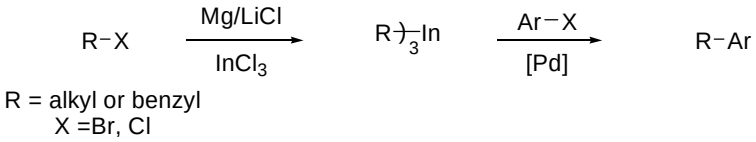
Scheme 25. LiDBB-mediated lithiation of commonly used aryl chlorides

Similar to polycyclic arenes such as naphthalene, 4,4'-di-*tert*-butylbiphenyl, and anthracene which can be used for the activation of either lithium or magnesium metal insertion, we envisaged that the highly conjugated C_{60} fullerene might also serve as a magnesium activator through a single electron transfer process. Therefore we attempted to investigate C_{60} fullerene-catalyzed magnesium insertion into aryl halides for the synthesis of organomagnesium reagents (Scheme 26).



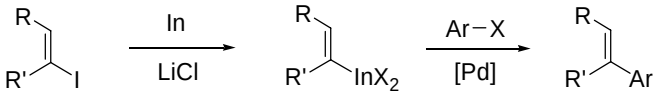
Scheme 26. C_{60} fullerene-catalyzed magnesium insertion into aryl halides

Normally, triorganoindium reagents are prepared by the transmetallation of pre-prepared organomagnesium reagent with one third equivalent of $InCl_3$. In the third project, we wanted to develop a convenient and fast one-pot method for the synthesis of tribenzylindium and trialkylindium regents via a magnesium insertion into benzyl halides and alkyl halides in the presence of LiCl and $InCl_3$ (Scheme 27). The obtained triorganoindium reagents should be applied in palladium-catalyzed cross-coupling with aryl halides with wide functional group tolerance.



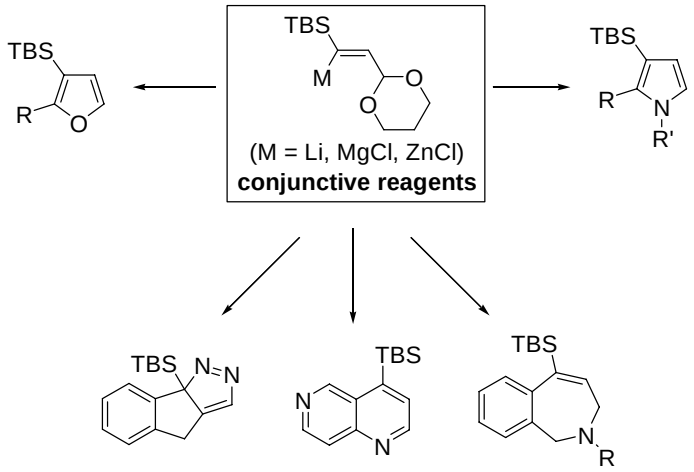
Scheme 27. A practical one-pot protocol for the preparation of triorganoindium reagents by Mg/LiCl insertion in the presence of $InCl_3$

Though the preparation of aryl-, benzyl-, alkyl-indium reagent through the direct insertion of indium metal into organic halides have been reported, till now there is no documented method for the direct preparation of alkenylindium(III) reagent through indium(0) insertion into alkenyl halides. Our next goal is to study the LiCl-mediated direct insertion of indium into cycloalkenyl iodides for the preparation of cycloalkenylindium(III) derivatives (Scheme 28). In addition, we planned to investigate the direct insertion of In/LiCl to stereodefined (*Z*)- and (*E*)-styryl iodides to see whether the stereochemistry of the alkene can be retained or not during insertion step and the subsequent palladium-catalyzed cross-coupling reaction.



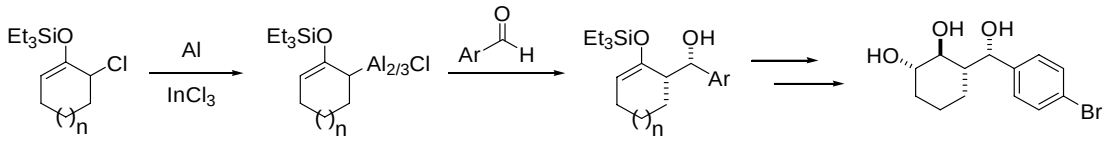
Scheme 28. Preparation of alkenylindium(III) reagent by a direct insertion of indium into alkenyl halide

Next, we planned to study the preparation and reaction of conjunctive alkenylmetallic reagents with various electrophiles, including aldehydes, aldimines, 1-halo-2-nitroarenes and 1-formyl-2-haloarenes (via palladium-catalyzed Negishi cross-coupling). After further manipulations, a variety of interesting functionalized 5-, 6-, 7-membered heterocycles (including furans, pyrroles, quinolines, benzo[*b*]thieno[2,3-*b*]pyridine, naphthyridines, fused pyrazoles, and 2,3-dihydro-benzo[*c*]azepine) should be obtained (Scheme 29).



Scheme 29. Preparations and reactions of conjunctive alkenylmetallic reagents with various electrophiles for the synthesis of a variety of functionalized 5-, 6-, 7-membered heterocycles

Finally, we wanted to extend our previous work on diastereoselective addition of allylic aluminum reagent to carbonyl compounds to the use of allylic aluminum reagent containing silyl enol ether functionality. After a diastereoselective addition of the silyl enol ether-containing allylic aluminum reagents to carbonyl compounds, The present silyl enol ether functionality could be further manipulated for the preparation of diastereomerically enriched triol (Scheme 30).



Scheme 30. Preparation of silyl enol ether-containing allylic aluminum reagents and their diastereoselective addition to carbonyl compounds followed by a further manipulation to triol derivatives.

Chapter 2. Expedient Preparation of Aryllithium and Arylzinc Reagents from Aryl Chlorides Using Lithium 4,4'-Di-*tert*-Butylbiphenylide and $ZnCl_2$

2.1 Introduction

The preparation of organolithiums is an important synthetic transformation since these highly reactive organometallics react with a broad range of electrophiles.[1] The direct insertion of lithium(0) to organic halides constitutes a very atom-economical method for the preparation of aryllithiums.[2] Although lithium naphthalenide[3] constitutes a soluble form of lithium(0) and inserts readily, a more convenient source of reactive lithium(0) is the sterically hindered lithium 4,4'-di-*tert*-butylbiphenylide (LiDBB)[4] which has found numerous applications pioneered by Freeman, Yus, and

[1] For selected reviews on organolithium reagents, see: (a) *Handbook of Functionalized Organometallics*; P. Knochel, Ed.; Wiley-VCH: Weinheim, **2005**. (b) *Organolithiums: Selectivity for Synthesis*; J. Clayden, Ed.; Pergamon: Oxford, **2002**. (c) *The Chemistry of Organolithium Compounds*; Z. Rappoport, I. Marek, Ed.; John Wiley and Sons: New York, **2004**. (d) *Lithium Compounds in Organic Synthesis: From Fundamentals to Applications*; R. Luisi, V. Capriati, Eds.; Wiley-VCH: Weinheim, **2014.** (e) M. Gray, M. Tinkel, V. Snieckus, In *Comprehensive Organolithium Chemistry II*; E. W. Abel, F. G. A. Stone, G. Wilkinson, A. McKillop, Eds.; Pergamon: Oxford, **1995**; vol. 11, pp. 1–92. (f) Z. Xi, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1021. (g) Z. Xi, *Acc. Chem. Res.* **2010**, *43*, 1342. (h) C. Nájera, J. M. Sansano, M. Yus, *Tetrahedron* **2003**, *59*, 9255. (i) R. Chinchilla, C. Nájera, M. Yus, *Tetrahedron* **2005**, *61*, 3139. (j) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667. (k) G. Dagousset, C. François, T. León, R. Blanc, E. Sansiaume-Dagousset, P. Knochel, *Synthesis* **2014**, *46*, 3133.

[2] B. M. Trost, *Science* **1991**, *254*, 1471.

[3] For selected examples on the application of lithium naphthalenide in organic synthesis, see: (a) C. G. Screttas, M. Micha-Screttas, *J. Org. Chem.* **1978**, *43*, 1064. (b) P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1980**, *45*, 3191. (c) A. Guijarro, D. J. Ramón, M. Yus, *Tetrahedron* **1993**, *49*, 469. (d) F. F. Huerta, C. Gómez, M. Yus, *Tetrahedron* **1999**, *55*, 4043. (e) I. Gómez, E. Alonso, D. J. Ramón, M. Yus, *Tetrahedron* **2000**, *56*, 4043. (f) C. G. Screttas, B. R. Steele, M. Micha-Screttas, G. A. Heropoulos, *Org. Lett.* **2012**, *14*, 5680. (g) F. Alonso, P. Candela, C. Gómez, M. Yus, *Adv. Synth. Catal.* **2003**, *345*, 275. (h) M. Yus, R. P. Herrera, A. Guijarro, *Tetrahedron Lett.* **2001**, *42*, 3455. (i) M. Yus, R. P. Herrera, A. Guijarro, *Chem.–Eur. J.* **2002**, *8*, 2574. (j) F. Alonso, E. Lorenzo, M. Yus, *J. Org. Chem.* **1996**, *61*, 6058. (k) J. Almena, F. Foubelo, M. Yus, *J. Org. Chem.* **1994**, *59*, 3210. (l) D. J. Ramon, M. Yus, *J. Org. Chem.* **1991**, *56*, 3825. (m) M. Yus, D. J. Ramon, *J. Org. Chem.* **1992**, *57*, 750. (n) J.-P. Tsao, T.-Y. Tsai, I-C. Chen, H.-J. Liu, J.-L. Zhu, S.-W. Tsao, *Synthesis* **2010**, 4242. (o) C. Behloul, A. Chouti, D. Guijarro, C. Nájera, M. Yus, *Synthesis* **2015**, *47*, 507. (p) C. Behloul, K. Bouchelouche, D. Guijarro, C. Nájera, M. Yus, *Synthesis* **2014**, *46*, 2065.

[4] For selected examples on the application of LiDBB in organic synthesis, see: (a) P. K. Freeman, L. L. Hutchinson, *Tetrahedron Lett.* **1976**, *17*, 1849. (b) P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1980**, *45*, 1924. (c) P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1983**, *48*, 4705. (d) P. Knochel, D. Seebach, *Tetrahedron Lett.* **1981**, *22*, 3223. (e) T. J. Donohoe, A. Jahanshahi, M. J. Tucker, F. L.

others.[5] Only some aryl and alkenyl chlorides have so far been used as substrates.[6] Herein we wish to report the scope of the insertion of LiDBB to various functionalized aryl chlorides of type **1** leading to the corresponding aryllithium derivatives **2**. We demonstrated that these aryllithiums react either directly with electrophiles **3** providing products of type **4** or undergo a transmetallation with $ZnCl_2$ leading to an arylzinc reagent of type **5** and after a subsequent Pd-catalyzed Negishi[7] cross-coupling with aryl halides[8] or acid chlorides[9] produces various coupling products of type **4** (Scheme 1).

Bhatti, I. A. Roslan, M. Kabeshov, G. Wrigley, *Chem. Commun.* **2011**, *47*, 5849. (f) P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1983**, *48*, 4705. (g) T. J. Donohoe, D. House, *J. Org. Chem.* **2002**, *67*, 5015. (h) D. P. Curran, A. Boussonnière, S. J. Geib, E. Lacôte, *Angew. Chem. Int. Ed.* **2012**, *51*, 1602. (i) E. A. Tiong, J. L. Gleason, *Org. Lett.* **2009**, *11*, 1725. (j) T. J. Donohoe, C. L. Rigby, R. E. Thomas, W. F. Nieuwenhuys, F. L. Bhatti, A. R. Cowley, G. Bhalay, I. D. Linney, *J. Org. Chem.* **2006**, *71*, 6298. (k) A. Yang, H. Butela, K. Deng, M. D. Doubleday, T. Cohen, *Tetrahedron* **2006**, *62*, 6526. (l) M. D. Morin, S. D. Rychnovsky, *Org. Lett.* **2005**, *7*, 2051. (m) K. Deng, A. Bensari, T. Cohen, *J. Am. Chem. Soc.* **2002**, *124*, 12106. (n) S. D. Rychnovsky, L. R. Takaoka, *Angew. Chem. Int. Ed.* **2003**, *42*, 818. (o) J. Shin, O. Gerasimov, D. H. Thompson, *J. Org. Chem.* **2002**, *67*, 6503. (p) S. D. Rychnovsky, T. Hata, A. I. Kim, A. J. Buckmelter, *Org. Lett.* **2001**, *3*, 807. (q) T. Cohen, M. D. Doubleday, *J. Org. Chem.* **1990**, *55*, 4784. (r) J. P. Cherkauskas, T. Cohen, *J. Org. Chem.* **1992**, *57*, 6. (s) P. K. Freeman, N. Ramnath, *J. Org. Chem.* **1991**, *56*, 3646. (t) J. M. Manthorpe, J. L. Gleason, *J. Am. Chem. Soc.* **2001**, *123*, 2091. (u) D. Cheng, S. Zhu, X. Liu, S. H. Norton, T. Cohen, *J. Am. Chem. Soc.* **1999**, *121*, 10241. (v) B. Mudryk, T. Cohen, *J. Org. Chem.* **1989**, *54*, 5657. (w) M. Yus, D. J. Ramón, *J. Chem. Soc.*, *Chem. Commun.* **1991**, 398. (x) J. Almena, F. Foubelo, M. Yus, *J. Org. Chem.* **1996**, *61*, 1859. (y) M. Yus, T. Soler, F. Foubelo, *J. Org. Chem.* **2001**, *66*, 6207. (z) F. Foubelo, S. A. Saleh, M. Yus, *J. Org. Chem.* **2000**, *65*, 3478.

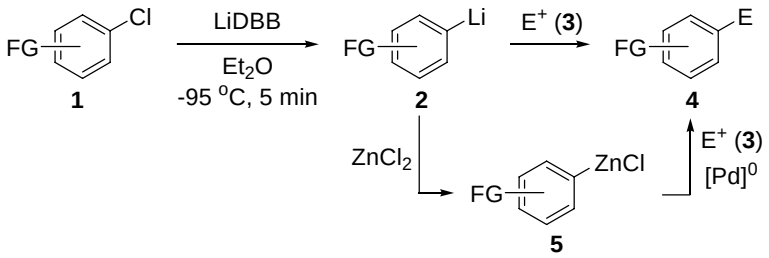
[5] For reviews on the application of lithium naphthalenide and lithium 4,4'-di-*tert*-butylbiphenylide (LiDBB) in organic synthesis, see: (a) F. Foubelo, M. Yus, *Chem. Soc. Rev.* **2008**, ***37***, 2620. (b) T. Cohen, M. Bupathy, *Acc. Chem. Res.* **1989**, *22*, 152. (c) M. D. Ferguson, In *Encyclopedia of Reagents for Organic Synthesis*; L. A. Paquette, D. Crich, P. L. Fuchs, G. A. Molander, Eds.; John Wiley and Sons: Chichester, **2009**; vol. 8, pp. 6249-6251. (d) K. M. Short, In *Encyclopedia of Reagents for Organic Synthesis*; L. A. Paquette, D. Crich, P. L. Fuchs, G. A. Molander, Eds.; John Wiley and Sons: Chichester, **2009**; vol. 8, pp. 6136-6139. (e) M. Yus, *Chem. Soc. Rev.* **1996**, *25*, 155. (f) D. J. Ramón, M. Yus, *Eur. J. Org. Chem.* **2000**, 225. (g) M. Yus, *Synlett* **2001**, 1197. (h) M. Yus, In *The Chemistry of Organolithium Compounds*; Z. Rappoport, I. Marek, Eds.; Wiley and Sons: Chichester, **2004**; Chap. 11, pp. 647-748.

[6] (a) C. Gómez, F. F. Huerta, M. Yus, *Tetrahedron* **1998**, *54*, 1853. (b) A. Bachki, F. Foubelo, M. Yus, *Tetrahedron* **1997**, *53*, 4921. (c) R. Bloch, N. Chaptal-Gradoz, *Tetrahedron Lett.* **1992**, *33*, 6147.

[7] For selected reviews, see: (a) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340. (b) E. I. Negishi, Q. Hu, Z. Huang, M. Qian, G. Wang, *Aldrichimica Acta* **2005**, *38*, 71. (c) F*Metal-Catalyzed Cross-Coupling Reactions*; . Diederich, P. J. Stang, Eds.; Wiley-VCH: Weinheim, **1998**. (d) J. De Houwer, B. U. W. Maes, *Synthesis* **2014**, *46*, 2533.

[8] For examples, see: (a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821. (b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298. (c) G. Wang, N. Yin, E. Negishi, *Chem. Eur. J.* **2011**, *17*, 4118. (d) X. Zeng, M. Qian, Q. Hu, E. Negishi, *Angew. Chem. Int. Ed.* **2004**, *43*, 2259. (e) R. Matsubara, M. Koide, Y.-S. Shin, T. Shimada, M. Hayashi, *Synthesis* **2015**, *47*, 187. (f) N. M. Barl, V. Malakhov, C. Mathes, P. Lustenberger, P. Knochel, *Synthesis* **2015**, *47*, 692. (g) E. P. Coutant, Y. L. Janin, *Synthesis* **2015**, *47*, 511. (h) J. Dubovik, A. Bredihhi, *Synthesis* **2015**, *47*, 538. (i) R. Blanc, K. Groll, S. Bernhardt, P. N. Stockmann, P. Knochel, *Synthesis* **2014**, *46*, 1052. (j) F. Crestey, S. Zimdars, P. Knochel, *Synthesis* **2013**, *45*, 3029.

[9] For examples, see: (a) P. A. Evans, J. D. Nelson, A. L. Stanley, *J. Org. Chem.* **1995**, *60*, 2298. (b) Y. Zhang, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 15964. (c) H. Xu, K. Ekoue-Kovi, C. Wolf, *J. Org. Chem.* **2008**, *73*, 7638.



Scheme 1. Preparation of aryllithium and zinc reagents of type **2** and **5** from the corresponding aryl chloride of type **1** using LiDBB and subsequent reaction with an electrophile (E^+) leading to products of type **4**

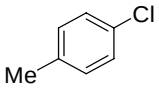
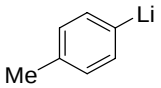
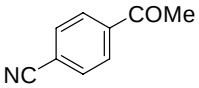
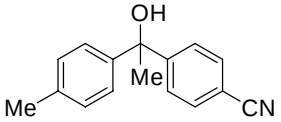
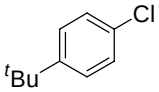
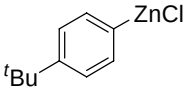
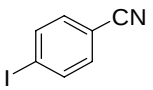
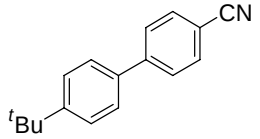
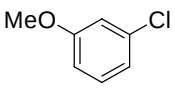
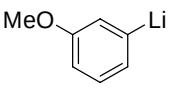
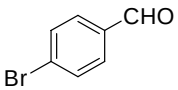
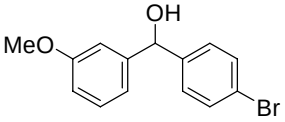
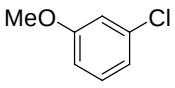
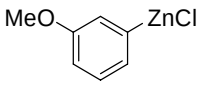
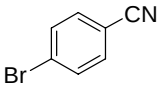
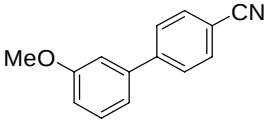
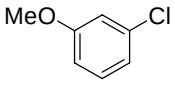
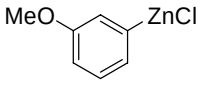
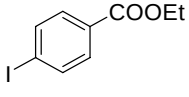
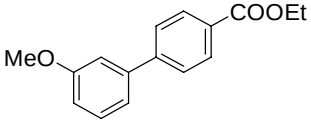
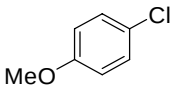
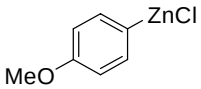
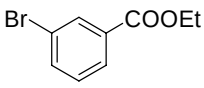
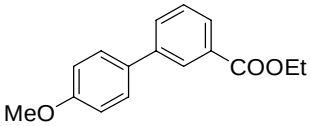
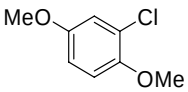
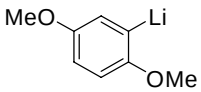
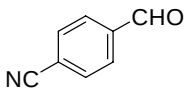
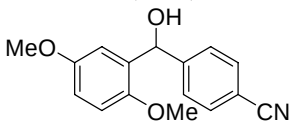
2.2 Results and Discussion

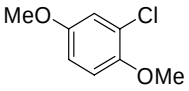
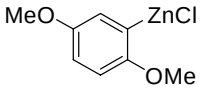
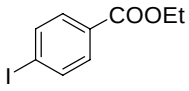
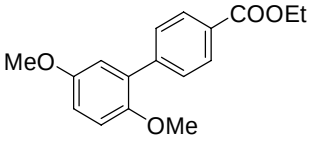
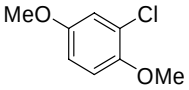
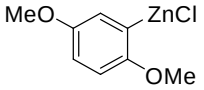
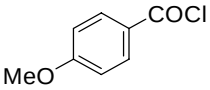
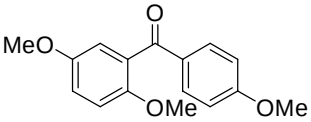
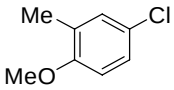
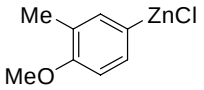
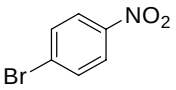
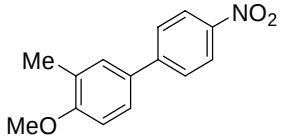
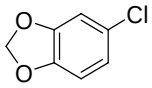
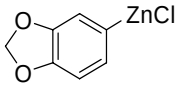
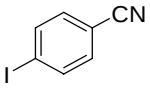
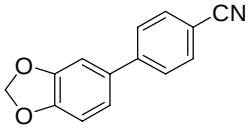
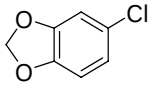
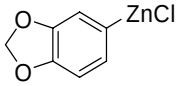
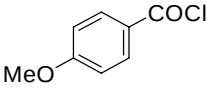
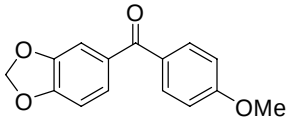
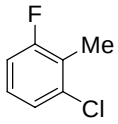
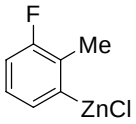
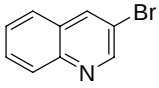
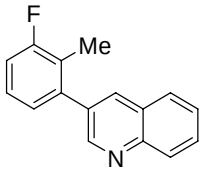
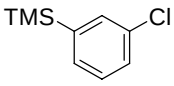
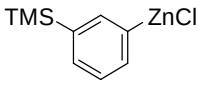
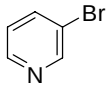
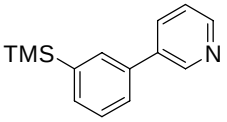
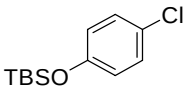
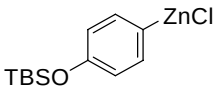
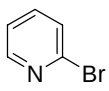
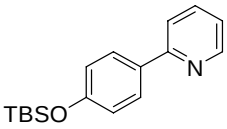
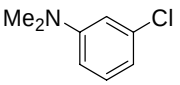
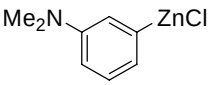
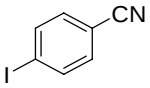
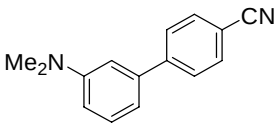
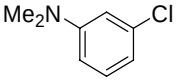
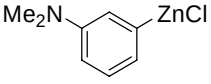
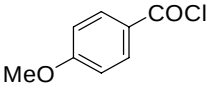
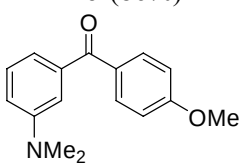
Thus, a solution of LiDBB (*ca.* 0.25 M in THF) was prepared by stirring lithium ribbon (36 mmol, 3 equiv) with 4,4'-di-*tert*-butylbiphenyl (12 mmol, 1 equiv) in THF (40 mL, 0 °C, 4-5 h). Titration was performed with a calibrated menthol solution in THF. The resulting LiDBB solution (2 mmol, 8 mL, *ca.* 0.25 M in THF, 2 equiv) was added to 4-tolyl chloride (**1a**, 1 mmol, 1 equiv) in diethyl ether at –95 °C (liquid nitrogen/methanol bath) within 5 min resulting in the formation of the corresponding lithium reagent **2a** in 71% yield as determined by iodolysis (after transmetallation with $ZnCl_2$). Quenching of **2a** with 4-cyanoacetophenone (**3a**) produced the expected tertiary alcohol **4a** in 72% yield (Table 1, entry 1). Using 4-*tert*-butylphenyl chloride (**1b**) delivered under the same conditions 4-*tert*-butylphenyllithium (**2b**) which was transmetallated with $ZnCl_2$ (1 equiv) leading to the arylzinc reagent **5b**. Palladium-catalyzed cross-coupling of **5b** with 4-iodobenzonitrile (**3b**, 0.7 equiv) using PEPPSI-IPr (4 mol%)[10] as catalyst produced under mild conditions (60 °C, 12 h) the expected biphenyl **4b** in 85% yield (entry 2). Various methoxy-substituted aryllithium and arylzinc reagents (**2c**, **2e**, and **5c-f**) were prepared in the same way in 57-77% yields and quenched with various electrophiles such as aryl bromides and iodides (**3d-f** and **3i**; using Pd-catalysis, entries 4-6, 8, and 10), an aldehyde (**3c** and **3g**; entries 3 and 7), or an acid chloride (**3h**; using Pd-catalysis, entry 9).[9] Similarly, the method was also

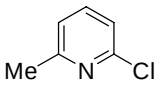
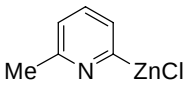
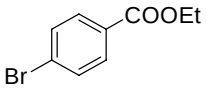
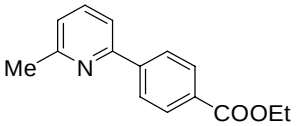
[10] J. Nasielski, N. Hadei, G. Achonduh, E. A. B. Kantchev, C. J. O'Brien, A. Lough, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 10844.

applied to aryl chlorides bearing substituents such as 3,4-methylenedioxy (**1g**, entries 11-12), fluoride (**1h**, entry 13), TMS (**1i**, entry 14), OTBS (**1j**, entry 15), and a dimethylamino group (**1k**, entries 16-17), leading to the corresponding aryllithium and arylzinc reagents in 59-83% yields. The subsequent palladium-catalyzed reactions with various electrophiles afforded the expected cross-coupling products in 72-95% yields (entries 11-17). In addition, the reaction using 2-chloro-6-methylpyridine (**1l**) as a substrate proceeded equally well under the same conditions, leading to the arylzinc reagent **5l** (after transmetallation with $ZnCl_2$) in 69% yield. Pd-catalyzed cross-coupling of **5l** with ethyl 4-bromobenzoate (**3m**) produced the 2-arylated pyridine **4l** in 63% yield (entry 18).

Table 1. Preparation of aryllithium and arylzinc reagents and subsequent reactions with electrophiles

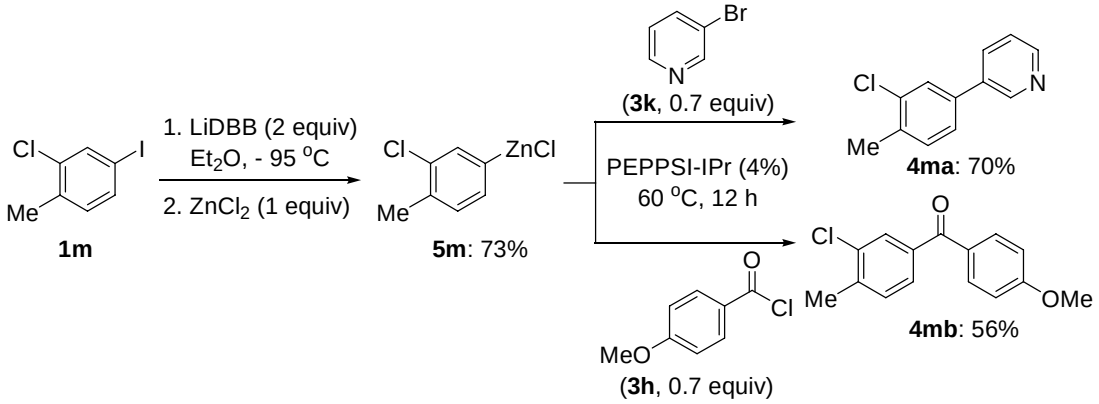
Entry	Aryl chloride	Organometallic reagent (Yield)[a]	Electrophile	Product (Yield)[b]
				
1	**1a**	**2a** (71%)	**3a**	**4a** (72%)
				
2	**1b**	**5b** (66%)	**3b**	**4b** (85%)[c]
				
3	**1c**	**2c** (77%)	**3c**	**4ca** (82%)
				
4	**1c**	**5c** (77%)	**3d**	**4cb** (70%)[c]
				
5	**1c**	**5c** (77%)	**3e**	**4cc** (77%)[c]
				
6	**1d**	**5d** (57%)	**3f**	**4d** (81%)[c]
				

7	**1e**	**2e** (74%)	**3g**	**4ea** (71%)
				
8	**1e**	**5e** (74%)	**3e**	**4eb** (86%)[c]
				
9	**1e**	**5e** (74%)	**3h**	**4ec** (69%)[c]
				
10	**1f**	**5f** (63%)	**3i**	**4f** (73%)[c]
				
11	**1g**	**5g** (61%)	**3b**	**4ga** (95%)[c]
				
12	**1g**	**5g** (61%)	**3h**	**4gb** (70%)[c]
				
13	**1h**	**5h** (59%)	**3j**	**4h** (89%)[c]
				
14	**1i**	**5i** (62%)	**3k**	**4i** (74%)[c]
				
15	**1j**	**5j** (63%)	**3l**	**4j** (72%)[c]
				
16	**1k**	**5k** (83%)	**3b**	**4ka** (86%)[c]
				
17	**1k**	**5k** (83%)	**3h**	**4kb** (80%)[c]

				
18	**1l**	**5l** (69%)	**3m**	**4l** (63%)[c]

[a] Determined by titration with I_2. [b] Yield of isolated, analytically pure product. [c] 4 mol% PEPPSI-IPr was used as reaction catalyst.

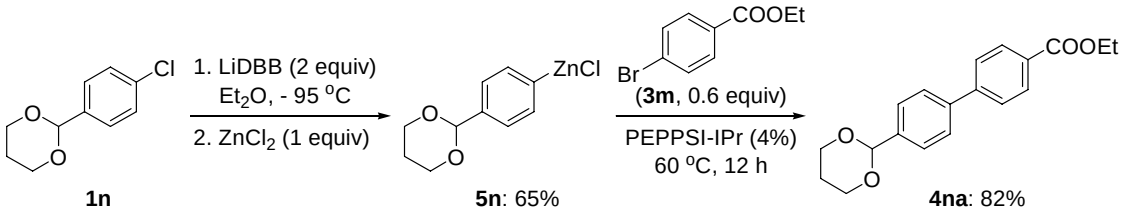
Interestingly, the lithiation of 2-chloro-4-iodo-1-methylbenzene (**1m**) with LiDBB (2 equiv) selectively occurred at the C-I bond (without touching the C-Cl bond), giving rise to the arylzinc reagent **5m** in 73% yield (Scheme 2). This arylzinc reagent **5m** readily underwent Pd-catalyzed cross-coupling with 3-bromopyridine (**3k**) and 4-methoxylbenzoyl chloride (**3h**), producing the desired products **4ma** and **4mb** in 56-70% yields.



Scheme 2. Selective lithiation of the carbon-iodide bond of 2-chloro-4-iodo-1-methylbenzene (**1m**) and subsequent reactions with electrophiles **3k** and **3h** leading to the coupling products **4ma** and **4mb**

Although we have described in Table 1 the preparation of relatively unfunctionalized aryllithium and zinc reagents, we have now extended this reductive lithiation to several aryl chlorides bearing an acetal or ketal groups using the standard conditions. As shown in Scheme 3, when 2-(4-chlorophenyl)-1,3-dioxane (**1n**) containing an acetal group was treated with LiDBB (2 equiv) followed by a transmetallation with $ZnCl_2$, the corresponding arylzinc reagent **5n** was obtained in 65% yield. After a PEPPSI-IPr-catalyzed[10] cross-coupling with ethyl 4-bromobenzoate (**3m**), a biphenyl derivative **4na** was produced in 82% yield. Similarly, several aryl chlorides bearing acetal/ketal groups were successfully converted into the desired aryllithium and zinc reagents (**2n-p**, **5n**, and **5o**) in 57-65% yields (Table 2). After treating the newly prepared organometallic reagents with electrophiles, such as an acid chloride (**3n**, using palladium-catalysis, entry 1), an alkenyl iodide (**3o**, using

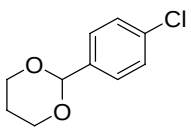
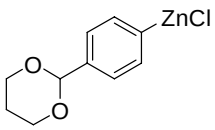
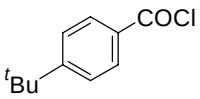
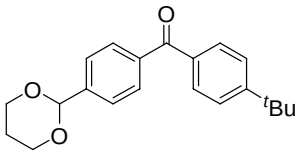
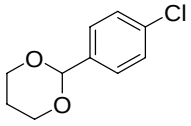
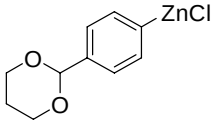
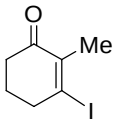
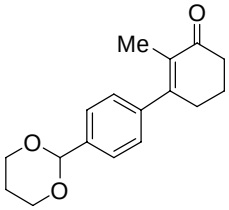
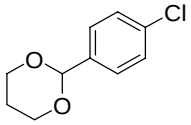
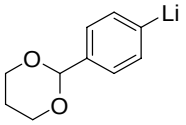
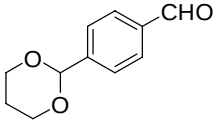
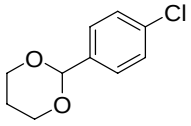
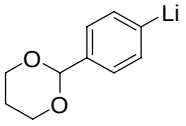
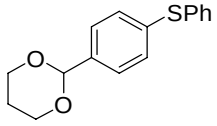
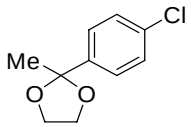
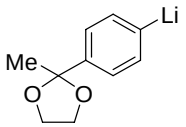
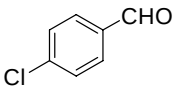
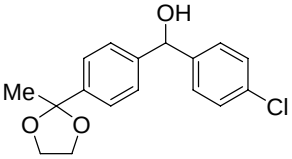
palladium-catalysis, entries 2 and 6), DMF (**3p**, entry 3), $PhSSO_2Ph$ (**3q**, entry 4), an aldehyde (**3r**, entry 5), and TsCN (**3s**, entry 7), the desired products were produced in 59-87% yields.

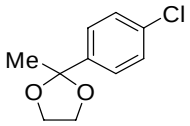
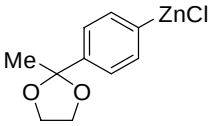
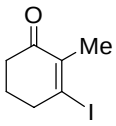
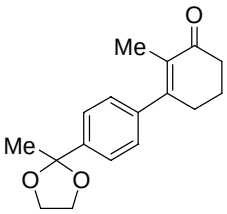
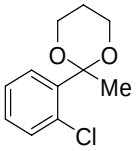
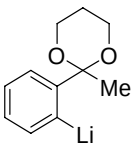
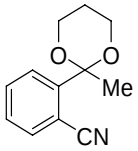


1n **5n**: 65% **4na**: 82%

Scheme 3. Lithiation of aryl chloride **1n** bearing cyclic acetal group and subsequent cross-coupling with electrophile **3m** leading to the biphenyl **4na**

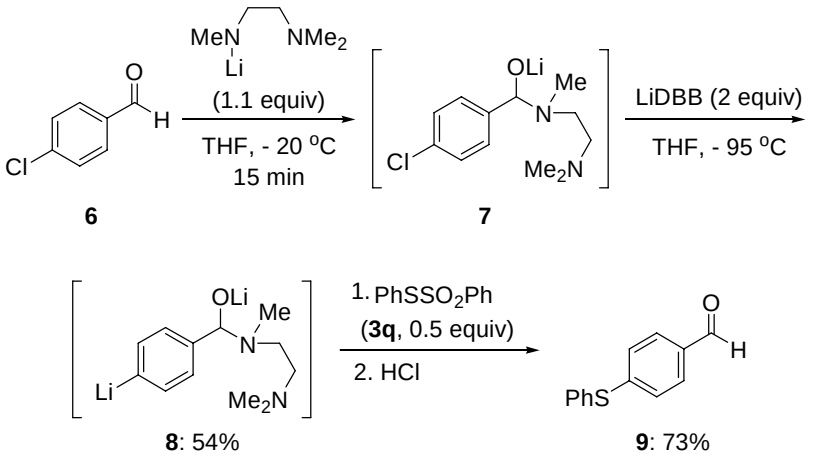
Table 2. Preparation of organolithium and organozinc reagents of type **5** bearing acetal/ketal groups and subsequent reactions with electrophiles

Entry	Aryl chloride	Organometallic reagent (Yield)[a]	Electrophile	Product (Yield)[b]
				
1	**1n**	**5n** (65%)	**3n**	**4nb** (62%)[c]
				
2	**1n**	**5n** (65%)	**3o**	**4nc** (74%)[c]
			DMF	
3	**1n**	**2n** (65%)	**3p**	**4nd** (87%)
			$PhSSO_2Ph$	
4	**1n**	**2n** (65%)	**3q**	**4ne** (64%)
				
5	**1o**	**2o** (58%)	**3r**	**4oa** (70%)

6	 **1o**	 **5o** (58%)	 **3o**	 **4ob** (71%)[c]
7	 **1p**	 **2p** (57%)	TsCN **3s**	 **4p** (59%)

[a] Determined by titration with I_2. [b] Yield of isolated, analytically pure product. [c] 4 mol% PEPPSI-IPr was used as reaction catalyst.

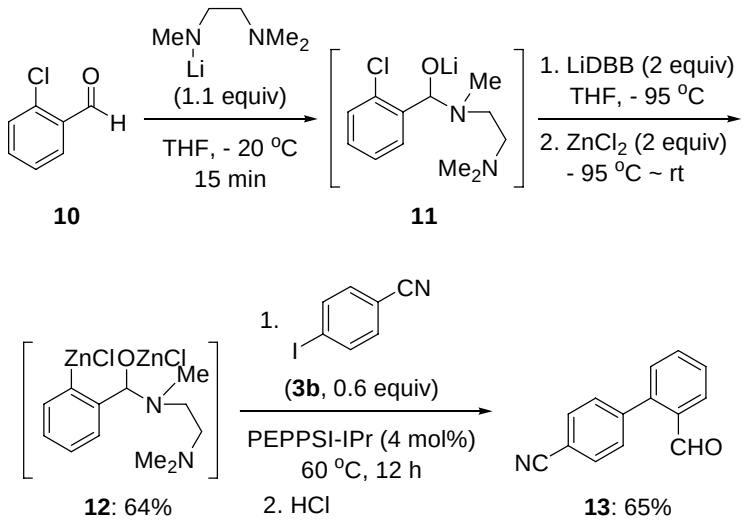
Aryl chloride bearing a formyl group was *in situ* protected as an α-amino alkoxide and could then be directly lithiated by LiDBB as well. As shown in Scheme 4, after subjection of 4-chlorobenzaldehyde (**6**) with lithium amide of *N*,*N*,*N*'-trimethylethylenediamine (LiTMDA, 1.1 equiv, THF, -20 °C, 15 min),[11] an α-amino alkoxide (**7**; as masked aldehyde) was formed *in situ*. Subsequent treatment of the intermediate **7** with LiDBB (2 equiv) led to the corresponding aryllithium reagent **8** in 54% yield. After quenching **8** with $PhSSO_2Ph$ (**3q**; 0.5 equiv) followed by hydrolysis, the desired product 4-(phenylthio)benzaldehyde (**9**) was generated in 73% yield.



Scheme 4. *In situ* protection of 4-chlorobenzaldehyde (**6**) as an α-amino alkoxide **7** followed by LiDBB-mediated lithiation and subsequent reaction with electrophile **3q**

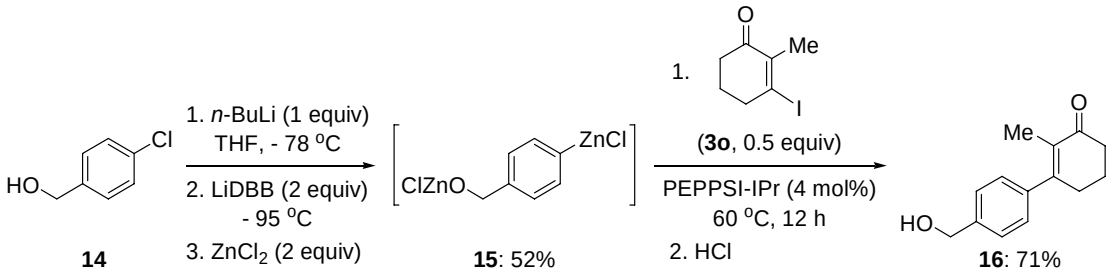
[11] For a review, see: (a) D. L. Comins, *Synlett* **1992**, 615. For additional examples, see: (b) D. L. Comins, J. D. Brown, *J. Org. Chem.* **1984**, *49*, 1078. (c) D. L. Comins, J. D. Brown, *Tetrahedron Lett.* **1981**, *22*, 4213.

The same method was also applied to the functionalization of 2-chlorobenzaldehyde (**10**) and the *α*-amino alkoxide **11** was produced as a capped-aldehyde intermediate (Scheme 5). After lithiation by LiDBB (2 equiv) followed by a transmetallation with $ZnCl_2$, the expected arylzinc reagent **12** was produced in 64% yield. A palladium-catalyzed cross-coupling of **12** with 4-iodobenzonitrile (**3b**) followed by an acidic hydrolysis afforded a biphenyl compound **13** containing both cyano and formyl groups in 65% yield.



Scheme 5. *In situ* protection of 2-chlorobenzaldehyde (**10**) as an *α*-amino alkoxide **11** followed by LiDBB-mediated lithiation and transmetallation with $ZnCl_2$ and subsequent cross-coupling with electrophile **3b** leading to the biphenyl **13**

Finally, 4-chlorobenzyl alcohol (**14**) was proven to be an appropriate substrate for LiDBB-mediated lithiation provided that the hydroxyl group was initially deprotonated. As shown in Scheme 6, after deprotonation of benzyl alcohol **14** with *n*-BuLi (1 equiv, THF, -78 °C), it could be readily converted into the corresponding arylzinc reagent **15** in 52% yield after lithiation by LiDBB (2 equiv) followed by a transmetallation with $ZnCl_2$. A subsequent Pd-catalyzed cross-coupling of **15** with alkenyl iodide **3o** produced the desired product **16** in 71% yield.



Scheme 6. *In situ* deprotonation of 4-chlorobenzyl alcohol (**14**) by *n*-BuLi followed by LiDBB-mediated lithiation and transmetallation with $ZnCl_2$ and subsequent cross-coupling with electrophile **3o** leading to the enone **16**

2.3 Conclusion

In summary, we have developed an efficient method for the preparation of aryllithium and zinc reagents from cheap and readily available aryl chlorides by using LiDBB as a lithiation reagent. The resulting organometallic reagents efficiently underwent subsequent reactions with a variety of electrophiles, such as an aldehyde, DMF, $PhSSO_2Ph$, TsCN, an aryl halide (via Pd-catalyzed Negishi cross-coupling), and an acid chloride (via Pd-catalyzed cross-coupling). Aryl chlorides bearing substituents, including methoxy, 3,4-methylenedioxy, fluoride, TMS, OTMS, NMe_2, acetal, and ketal, were proven to be appropriate substrates. Interestingly, aryl chlorides containing a formyl group can be used as well, provided that the formyl group was temporarily converted into an α-amino alkoxide by using lithium amide of *N*,*N*,*N*'-trimethylethylenediamine (LiTMDA). A hydroxyl group is also tolerated if it is deprotonated with *n*-BuLi, prior to the addition of LiDBB.

2.4 Experimental

All reactions were carried out under argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^1H

NMR (25 °C) and capillary GC. Column chromatographic purification was performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck. All the aryl chlorides containing acetal/ketal group were prepared by reported method.[12] All other reagents were obtained from commercial sources.

Preparation of lithium 4,4'-di-*tert*-butylbiphenylide (LiDBB) solution[13]

Lithium ribbon (0.252 g, 36 mmol, 3 equiv), cut into small pieces, was introduced into a pre-dried *Schlenk*-flask flushed with dry argon. Dry THF (40 mL) and 4,4'-di-*tert*-butylbiphenyl (DBB, 3.2 g, 12 mmol, 1 equiv) were sequentially added into the flask and the reaction mixture was vigorously stirred at 0 ^oC. After 4-5 h, a deep-blue LiDBB solution in THF was obtained (~0.25 M; determined by titration with a calibrated menthol solution in THF at 0 ^oC until the blue colour of LiDBB solution persists).

Preparation of $ZnCl_2$ (1 M solution in THF)

A dry and nitrogen flushed 250 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with $ZnCl_2$ (13.6 g, 100 mmol). The salt was heated to 140 °C under high vacuum for 6 h. After cooling to room temperature, anhydrous THF (100 mL) was added and stirring was continued overnight until the salt was dissolved.

Typical procedure for the LiDBB-mediated preparation of aryllithium and zinc reagent from aryl chloride (TP1)

Aryl chloride (1 mmol, 1 equiv), $C_{10}H_{22}$ (internal standard, 0.2 mL), and anhydrous Et_2O (5 mL) were sequentially added to a pre-dried *Schlenk*-flask equipped with a magnetic stirrer and a rubber septum under argon. The flask was cooled to -95 ^oC (methanol/liquid nitrogen bath) followed by the dropwise addition of a pre-prepared LiDBB solution (2 mmol, 8 mL, ~0.25 M in THF, 2 equiv). After addition and 5 min of stirring at this temperature, the aryllithium reagent **2** was obtained. The corresponding arylzinc reagent **5** was prepared by the addition of $ZnCl_2$ solution (1 mmol, 1 mL, 1.0 M in THF) followed by warming to room temperature. The yield of

[12] (a) T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley and Sons: New York, **1991**; (b) P. J. Kocienski, *Protecting Groups*, Thieme: New York, **1994**.
[13] B. Mudryk, T. Cohen, *Org. Synth.* **1995**, *72*, 173.

the aryllithium or arylzinc reagent was determined by the GC-analysis of reaction aliquot of the resulting arylzinc reagent quenched with a solution of iodine in anhydrous THF in the presence of an internal standard ($C_{10}H_{22}$).

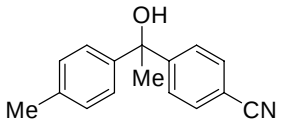
Typical procedure for the reaction of aryllithium reagent with various electrophiles (aldehyde, DMF, $PhSSO_2Ph$, and TsCN) (TP2)

The electrophile (0.6-0.7 equiv) was added to the freshly prepared aryllithium reagent at -95 ^oC with stirring under argon. Then, the cooling bath was removed and the reaction mixture was slowly warmed to room temperature over 2 h. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) followed by extraction with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude residue was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the analytically pure product.

Typical procedure for palladium-catalyzed cross-coupling reactions using arylzinc reagent (TP3)

PEPPSI-IPr[10] (27 mg, 4 mol%) and aryl halide or acid chloride (0.6-0.7 equiv) were sequentially added to the prepared arylzinc reagent and the reaction mixture was stirred at 60 ^oC under nitrogen. After 12 h, the reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the analytically pure product.

4-(1-Hydroxy-1-*p*-tolylethyl)benzonitrile (4a)



The aryllithium reagent **2a** was prepared according to **TP1** from 4-tolyl chloride (**1a**, 0.127 g, 1 mmol) at -95 ^oC for 5 min in 71% yield. Reaction with 4-cyano acetophenone (**3a**, 0.102 g, 0.7 mmol, 0.7 equiv) was performed according to **TP2**

from -95 °C to rt over 2 h, leading to the corresponding alcohol **4a** in 72% yield (120 mg) as a colorless oil.

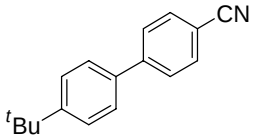
^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.58-7.51 (m, 4H), 7.28-7.25 (m, 2H), 7.14 (dd, *J* = 8.0, 0.6 Hz, 2H), 2.33 (s, 3H), 2.28 (brs, 1H), 1.93 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm = 153.5, 143.7, 137.3, 131.9, 129.1, 126.4, 125.7, 118.8, 110.4, 75.8, 30.5, 20.9.

MS (EI, 70 eV): *m/z* (%) = 237 (M^+, 8), 223 (18), 222 (100), 130 (56), 102 (16), 91 (13), 43 (27).

HRMS ($C_{16}H_{15}NO$, EI): calc.: 237.1154; found: 237.1188 (M^+).

4-(4-*tert*-Butylphenyl)benzonitrile (4b)



The arylzinc reagent **5b** was prepared according to **TP1** from 4-*tert*-butylphenyl chloride (**1b**, 0.169 g, 1 mmol) at -95 °C for 5 min in 66% yield. Palladium-catalyzed cross-coupling with 4-iodobenzonitrile (**3b**, 0.16 g, 0.7 mmol, 0.7 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding biphenyl **4b** in 85% yield (140 mg) as a colorless oil. Spectroscopic data are in accordance with the reported data.[14]

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 7.74-7.67 (m, 4H), 7.58-7.51 (m, 4H), 1.39 (s, 9H).

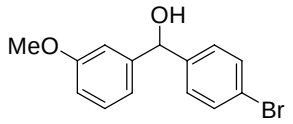
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 151.9, 145.4, 136.2, 132.5, 127.4, 126.8, 126.0, 119.0, 110.5, 34.6, 31.2.

MS (EI, 70 eV): *m/z* (%) = 235 (M^+, 19), 221 (18), 220 (100), 203 (11), 192 (59), 190 (18), 180 (24), 178 (10), 177 (16), 165 (17), 152 (19), 151 (20), 140 (10).

HRMS ($C_{17}H_{17}N$, EI): calc.: 235.1361; found: 235.1339 (M^+).

[14] H. Wang, L. Li, X.-F. Bai, W.-H. Deng, Z.-J. Zheng, K.-F. Yang, L.-W. Xu, *Green Chem.* **2013**, *15*, 2349.

(4-Bromophenyl)(3-methoxyphenyl)methanol (4ca)



The aryllithium reagent **2c** was prepared according to **TP1** from 1-chloro-3-methoxybenzene (**1c**, 0.143 g, 1 mmol) at -95 °C for 5 min in 77% yield. Reaction with 4-bromobenzaldehyde (**3c**, 0.130 g, 0.7 mmol, 0.7 equiv) was performed according to **TP2** from -95 °C to rt over 2 h, leading to the corresponding alcohol **4ca** in 82% yield (168 mg) as a colorless oil.

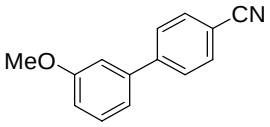
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 7.46-7.42 (m, 2H), 7.25-7.22 (m, 3H), 6.91-6.88 (m, 2H), 6.83-6.79 (m, 1H), 5.71 (s, 1H), 3.77 (s, 3H), 2.52 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 159.7, 144.9, 142.5, 131.5, 129.6, 128.1, 121.4, 118.8, 113.1, 112.1, 75.5, 55.2.

MS (EI, 70 eV): *m/z* (%) = 294 (38), 293 (10), 292 (M^+, 44), 185 (33), 183 (27), 181 (10), 157 (11), 153 (11), 152 (20), 136 (15), 135 (91), 109 (100), 108 (18), 105 (23), 78 (17), 77 (32).

HRMS ($C_{14}H_{13}BrO_2$, EI): calc.: 292.0099; found: 292.0102 (M^+).

4-(3-Methoxyphenyl)benzonitrile (4cb)



The arylzinc reagent **5c** was prepared according to **TP1** from 1-chloro-3-methoxybenzene (**1c**, 0.143 g, 1 mmol) at -95 °C for 5 min in 77% yield. Palladium-catalyzed cross-coupling with 4-bromobenzonitrile (**3d**, 0.127 g, 0.7 mmol, 0.7 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding biphenyl **4cb** in 70% yield (102 mg) as a colorless oil. Spectroscopic data are in accordance with the reported data.[15]

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 7.74-7.66 (m, 4H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.18 (ddd, *J* = 7.7, 1.7, 0.8 Hz, 1H), 7.12-7.11 (m, 1H), 6.98 (dt, *J* = 8.3, 1.2 Hz, 1H), 3.88 (s, 3H).

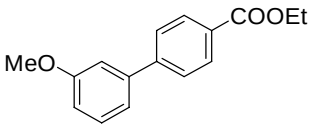
[15] C.-W. Zhao, J.-P. Ma, Q.-K. Liu, Y. Yu, P. Wang, Y.-A. Li, K. Wang, Y.-B. Dong, *Green Chem.* **2013**, *15*, 3150.

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 160.1, 145.5, 140.6, 132.5, 130.1, 127.7, 119.6, 118.8, 113.8, 113.0, 111.0, 55.3.

MS (EI, 70 eV): m/z (%) = 210 (17), 209 (M^+, 100), 180 (10), 179 (23), 178 (11), 166 (22), 140 (17).

HRMS ($C_{14}H_{11}NO$, EI): calc.: 209.0841; found: 209.0822 (M^+).

Ethyl 4-(3-methoxyphenyl)benzoate (4cc)



The arylzinc reagent **5c** was prepared according to **TP1** from 1-chloro-3-methoxybenzene (**1c**, 0.143 g, 1 mmol) at -95 °C for 5 min in 77% yield. Palladium-catalyzed cross-coupling with ethyl 4-iodobenzoate (**3e**, 0.193 g, 0.7 mmol, 0.7 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding biphenyl **4cc** in 77% yield (138 mg) as a colorless oil. Spectroscopic data are in accordance with the reported data.[16]

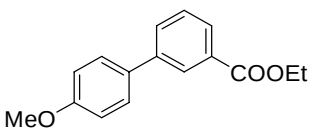
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 8.14-8.10 (m, 2H), 7.68-7.64 (m, 2H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.24-7.20 (m, 1H), 7.17-7.15 (m, 1H), 6.97-6.93 (m, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 160.0, 145.4, 141.5, 130.0, 129.9, 129.4, 127.0, 119.7, 113.4, 113.0, 60.9, 55.3, 14.3.

MS (EI, 70 eV): *m/z* (%) = 257 (14), 256 (M^+, 84), 228 (24), 212 (16), 211 (100), 168 (15), 152 (11), 140 (15), 139 (21).

HRMS ($C_{16}H_{16}O_3$, EI): calc.: 256.1099; found: 256.1127 (M^+).

Ethyl 3-(4-methoxyphenyl)benzoate (4d)



The arylzinc reagent **5d** was prepared according to **TP1** from 1-chloro-4-methoxybenzene (**1d**, 0.143 g, 1 mmol) at -95 °C for 5 min in 57% yield. Palladium-

[16] M. Amatore, C. Gosmini, *Angew. Chem. Int. Ed.* **2008**, *47*, 2089.

catalyzed cross-coupling with ethyl 3-bromobenzoate (**3f**, 0.137 g, 0.6 mmol, 0.6 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding biphenyl **4d** in 81% yield (124 mg) as a colorless oil. Spectroscopic data are in accordance with the reported data.[16]

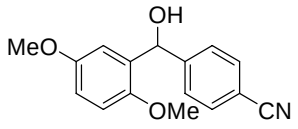
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 8.26-8.25 (m, 1H), 7.99 (ddd, *J* = 7.7, 1.1, 0.8 Hz, 1H), 7.75 (ddd, *J* = 7.7, 1.9, 1.1 Hz, 1H), 7.60-7.55 (m, 2H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.03-6.98 (m, 2H), 4.42 (q, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 1.45-1.37 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 166.6, 159.5, 141.0, 132.7, 131.0, 130.9, 128.7, 128.2, 127.7, 127.7, 114.3, 61.0, 55.3, 14.3.

MS (EI, 70 eV): *m/z* (%) = 257 (17), 256 (M^+, 100), 228 (30), 213 (17), 211 (44), 185 (15), 183 (22), 168 (18), 152 (12), 140 (20), 139 (30).

HRMS ($C_{16}H_{16}O_3$, EI): calc.: 256.1099; found: 256.1125 (M^+).

4-((2,5-Dimethoxyphenyl)(hydroxy)methyl)benzonitrile (4ea)



The aryllithium reagent **2e** was prepared according to **TP1** from 2-chloro-1,4-dimethoxybenzene (**1e**, 0.173 g, 1 mmol) at -95 °C for 5 min in 74% yield. Reaction with 4-cyanobenzaldehyde (**3g**, 0.092 g, 0.7 mmol, 0.7 equiv) was performed according to **TP2** from -95 °C to rt over 2 h, leading to the corresponding alcohol **4ea** in 71% yield (133 mg) as a colorless oil.

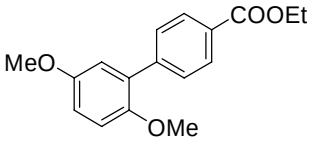
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 7.61-7.49 (m, 4H), 6.85-6.78 (m, 3H), 6.02 (d, *J* = 5.0 Hz, 1H), 3.75 (s, 6H), 3.22 (d, *J* = 4.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 153.8, 150.6, 148.7, 131.9, 131.8, 127.0, 118.9, 114.0, 113.2, 111.9, 110.8, 71.5, 55.8, 55.7.

MS (EI, 70 eV): *m/z* (%) = 270 (20), 269 (M^+, 100), 251 (18), 236 (14), 167 (16), 166 (10), 165 (10), 140 (10), 139 (34), 130 (26), 102 (10).

HRMS ($C_{16}H_{15}NO_3$, EI): calc.: 269.1052; found: 269.1030 (M^+).

Ethyl 4-(2,5-dimethoxyphenyl)benzoate (4eb)



The arylzinc reagent **5e** was prepared according to **TP1** from 2-chloro-1,4-dimethoxybenzene (**1e**, 0.173 g, 1 mmol) at -95 °C for 5 min in 74% yield. Palladium-catalyzed cross-coupling with ethyl 4-iodobenzoate (**3e**, 0.193 g, 0.7 mmol, 0.7 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding biphenyl **4eb** in 86% yield (172 mg) as a colorless oil.

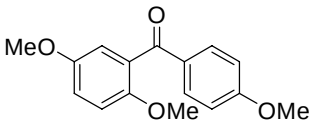
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 8.12-8.08 (m, 2H), 7.64-7.61 (m, 2H), 6.96-6.88 (m, 3H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 166.5, 153.8, 150.7, 143.0, 130.5, 129.3, 129.2, 128.9, 116.6, 113.7, 112.8, 60.8, 56.2, 55.7, 14.3.

MS (EI, 70 eV): *m/z* (%) = 287 (16), 286 (M^+, 100), 241 (11), 199 (28), 198 (21), 184 (11), 183 (9), 155 (9).

HRMS ($C_{17}H_{18}O_4$, EI): calc.: 286.1205; found: 286.1215 (M^+).

(2,5-Dimethoxyphenyl)(4-methoxyphenyl)methanone (4ec)



The arylzinc reagent **5e** was prepared according to **TP1** from 2-chloro-1,4-dimethoxybenzene (**1e**, 0.173 g, 1 mmol) at -95 °C for 5 min in 74% yield. Palladium-catalyzed cross-coupling with 4-methoxybenzoyl chloride (**3h**, 0.119 g, 0.7 mmol, 0.7 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding benzophenone **4ec** in 69% yield (131 mg) as a colorless oil.

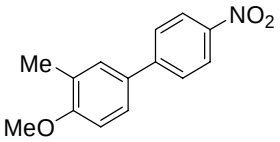
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 7.84-7.79 (m, 2H), 7.00-6.88 (m, 5H), 3.86 (s, 3H), 3.78 (s, 3H), 3.69 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 194.6, 163.6, 153.4, 151.1, 132.2, 130.4, 129.9, 116.7, 114.2, 113.5, 113.0, 56.4, 55.8, 55.4.

MS (EI, 70 eV): *m/z* (%) = 273 (16), 272 (M^+, 100), 255 (22), 241 (11), 227 (12), 214 (12), 165 (14), 151 (50), 135 (40), 92 (11), 77 (10).

HRMS ($C_{16}H_{16}O_4$, EI): calc.: 272.1049; found: 272.0916 (M^+).

3-Methyl-4-methoxy-4'-nitrobiphenyl (4f)



The arylzinc reagent **5f** was prepared according to **TP1** from 4-chloro-1-methoxy-2-methylbenzene (**1f**, 0.157 g, 1 mmol) at -95 °C for 5 min in 63% yield. Palladium-catalyzed cross-coupling with 1-bromo-4-nitrobenzene (**3i**, 0.121 g, 0.6 mmol, 0.6 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding biphenyl **4f** in 73% yield (107 mg) as a colorless oil.

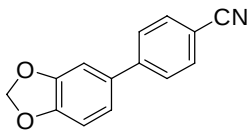
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 8.28-8.23 (m, 2H), 7.71-7.68 (m, 2H), 7.48-7.43 (m, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 3.91 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 158.6, 147.4, 146.4, 130.5, 129.5, 127.5, 126.9, 125.9, 124.0, 110.3, 55.4, 16.3.

MS (EI, 70 eV): *m/z* (%) = 244 (15), 243 (M^+, 100), 228 (20), 213 (17), 182 (17), 153 (13), 152 (13).

HRMS ($C_{14}H_{13}NO_3$, EI): calc.: 243.0895; found: 243.0873 (M^+).

4-(1,3-Benzodioxol-5-yl)benzonitrile (4ga)



The arylzinc reagent **5g** was prepared according to **TP1** from 5-chlorobenzo[*d*][1,3]dioxole (**1g**, 0.157 g, 1 mmol) at -95 °C for 5 min in 61% yield. Palladium-catalyzed cross-coupling with 4-iodobenzonitrile (**3b**, 0.137 g, 0.6 mmol, 0.6 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60

°C for 12 h, leading to the corresponding biphenyl **4ga** in 95% yield (127 mg) as a colorless oil. Spectroscopic data are in accordance with the reported data.[17]

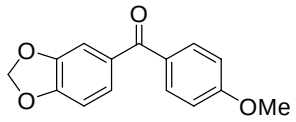
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 7.70-7.66 (m, 2H), 7.61-7.58 (m, 2H), 7.09-7.05 (m, 2H), 6.92-6.89 (m, 1H), 6.03 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 148.4, 148.2, 145.2, 133.3, 132.5, 127.2, 121.1, 118.9, 110.4, 108.8, 107.4, 101.4.

MS (EI, 70 eV): *m/z* (%) = 224 (14), 223 (M^+, 100), 222 (53), 165 (7), 164 (24), 138 (7).

HRMS ($C_{14}H_9NO_2$, EI): calc.: 223.0633; found: 223.0641 (M^+).

Benzo[*d*][1,3]dioxol-5-yl(4-methoxyphenyl)methanone (4gb)



The arylzinc reagent **5g** was prepared according to **TP1** from 5-chlorobenzo[*d*][1,3]dioxole (**1g**, 0.157 g, 1 mmol) at -95 °C for 5 min in 61% yield. Palladium-catalyzed cross-coupling with 4-methoxybenzoyl chloride (**3h**, 0.102 g, 0.6 mmol, 0.6 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding benzophenone **4gb** in 70% yield (107 mg) as a colorless oil. Spectroscopic data are in accordance with the reported data.[18]

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 7.80-7.75 (m, 2H), 7.35-7.31 (m, 2H), 6.98-6.93 (m, 2H), 6.85 (dd, *J* = 8.0, 0.6 Hz, 1H), 6.05 (s, 2H), 3.88 (s, 3H).

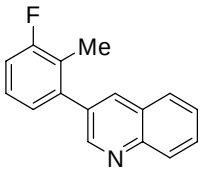
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 193.9, 162.9, 151.0, 147.7, 132.4, 132.1, 130.5, 126.1, 113.4, 109.8, 107.6, 101.7, 55.4.

MS (EI, 70 eV): *m/z* (%) = 257 (10), 256 (M^+, 45), 225 (11), 149 (53), 136 (10), 135 (100), 121 (19), 107 (21), 92 (42), 91 (17), 77 (50), 65 (46), 64 (30), 63 (60), 62 (19), 51 (14), 50 (15), 43 (12).

HRMS ($C_{15}H_{12}O_4$, EI): calc.: 256.0736; found: 256.0717 (M^+).

[17] V. Colombel, M. Presset, D. Oehlrich, F. Rombouts, G. A. Molander, *Org. Lett.* **2012**, *14*, 1680.
[18] H. Li, Y. Xu, E. Shi, W. Wei, X. Suo, X. Wan, *Chem. Commun.* **2011**, *47*, 7880.

3-(3-Fluoro-2-methylphenyl)quinoline (4h)



The arylzinc reagent **5h** was prepared according to **TP1** from 1-chloro-3-fluoro-2-methylbenzene (**1h**, 0.145 g, 1 mmol) at -95 °C for 5 min in 59% yield. Palladium-catalyzed cross-coupling with 3-bromoquinoline (**3j**, 0.125 g, 0.6 mmol, 0.6 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding 3-arylated quinoline **4h** in 89% yield (126 mg) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 8.90 (d, *J* = 2.2 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 2.2 Hz, 1H), 7.85 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.75 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.62-7.56 (m, 1H), 7.30-7.23 (m, 1H), 7.13-7.07 (m, 2H), 2.23 (d, *J* = 2.4 Hz, 3H)

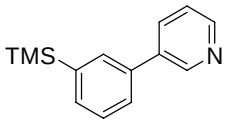
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 161.6 (d, *J* = 245.0 Hz), 151.1, 147.1, 140.4 (d, *J* = 4.8 Hz), 135.4, 133.5 (d, *J* = 3.1 Hz), 129.6, 129.3, 127.8, 127.6, 127.0, 126.9 (d, *J* = 9.3 Hz), 125.7 (d, *J* = 3.4 Hz), 123.3 (d, *J* = 16.8 Hz), 114.7 (d, *J* = 23.0 Hz), 12.2 (d, *J* = 5.3 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ / ppm = -114.88 ~ -114.93 (m, 1F).

MS (EI, 70 eV): *m/z* (%) = 238 (17), 237 (M^+, 97), 236 (100), 235 (41), 234 (11), 207 (12), 183 (10), 133 (12), 118 (22), 109 (12), 103 (9), 95 (9).

HRMS ($C_{16}H_{12}FN$, EI): calc.: 237.0954; found: 237.0945 (M^+).

3-(3-(Trimethylsilyl)phenyl)pyridine (4i)



The arylzinc reagent **5i** was prepared according to **TP1** from (3-chlorophenyl)trimethylsilane (**1i**, 0.185 g, 1 mmol) at -95 °C for 5 min in 62% yield. Palladium-catalyzed cross-coupling with 3-bromopyridine (**3k**, 0.095 g, 0.6 mmol, 0.6 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C

for 12 h, leading to the corresponding 3-arylated pyridine **4i** in 74% yield (101 mg) as a colorless oil.

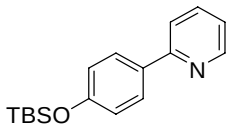
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 8.87 (s, 1H), 8.61 (d, *J* = 3.9 Hz, 1H), 7.91 (ddd, *J* = 7.9, 2.1, 1.9 Hz, 1H), 7.72-7.71 (m, 1H), 7.60-7.55 (m, 2H), 7.51-7.46 (m, 1H), 7.40 (dd, *J* = 7.9, 4.8 Hz, 1H), 0.33 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 148.1, 148.0, 141.7, 137.2, 137.0, 134.7, 133.1, 132.0, 128.4, 127.6, 123.6, -1.2.

MS (EI, 70 eV): *m/z* (%) = 228 (10), 227 (M^+, 51), 214 (12), 213 (47), 212 (100), 182 (17).

HRMS ($C_{14}H_{17}NSi$, EI): calc.: 227.1130; found: 227.1062 (M^+).

2-(4-(*tert*-Butyldimethylsilyloxy)phenyl)pyridine (4j)



The arylzinc reagent **5j** was prepared according to **TP1** from *tert*-butyl(4-chlorophenoxy)dimethylsilane (**1j**, 0.243 g, 1 mmol) at -95 °C for 5 min in 63% yield. Palladium-catalyzed cross-coupling with 2-bromopyridine (**3l**, 0.095 g, 0.6 mmol, 0.6 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding 2-arylated pyridine **4j** in 72% yield (124 mg) as a colorless oil.

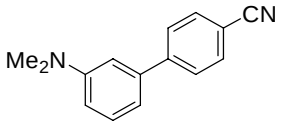
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 8.67-8.65 (m, 1H), 7.92-7.87 (m, 2H), 7.73-7.64 (m, 2H), 7.16 (ddd, *J* = 6.8, 4.9, 1.8 Hz, 1H), 6.97-6.92 (m, 2H), 1.02 (s, 9H), 0.24 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 157.2, 156.7, 149.5, 136.5, 132.6, 128.1, 121.3, 120.3, 119.8, 25.7, 18.2, -4.4.

MS (EI, 70 eV): *m/z* (%) = 285 (M^+, 10), 229 (29), 228 (100), 200 (9), 198 (9), 154 (14), 127 (9), 73 (10), 59 (9), 57 (12), 41 (19).

HRMS ($C_{17}H_{23}NOSi$, EI): calc.: 285.1549; found: 285.1401 (M^+).

4-(3-Dimethylaminophenyl)benzonitrile (4ka)



The arylzinc reagent **5k** was prepared according to **TP1** from 3-chloro-*N*,*N*-dimethylbenzenamine (**1k**, 0.156 g, 1 mmol) at -95 °C for 5 min in 83% yield. Palladium-catalyzed cross-coupling with 4-iodobenzonitrile (**3b**, 0.160 g, 0.7 mmol, 0.7 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding biphenyl **4ka** in 86% yield (133 mg) as a colorless oil.

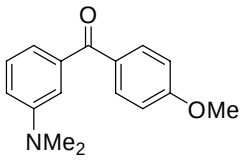
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 7.74-7.68 (m, 4H), 7.38-7.33 (m, 1H), 6.93 (ddd, *J* = 7.5, 1.7, 0.8 Hz, 1H), 6.90-6.88 (m, 1H), 6.82 (ddd, *J* = 8.3, 2.8, 0.8 Hz, 1H), 3.04 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 151.0, 146.7, 140.1, 132.4, 129.7, 127.8, 119.0, 115.5, 112.7, 111.0, 110.6, 40.5.

MS (EI, 70 eV): *m/z* (%) = 223 (13), 222 (M^+, 96), 221 (100), 178 (11), 177 (10), 151 (10), 110 (8).

HRMS ($C_{15}H_{14}N_2$, EI): calc.: 222.1157; found: 222.1150 (M^+).

(3-(Dimethylamino)phenyl)(4-methoxyphenyl)methanone (4kb)



The arylzinc reagent **5k** was prepared according to **TP1** from 3-chloro-*N*,*N*-dimethylbenzenamine (**1k**, 0.156 g, 1 mmol) at -95 °C for 5 min in 83% yield. Palladium-catalyzed cross-coupling with 4-methoxybenzoyl chloride (**3h**, 0.119 g, 0.7 mmol, 0.7 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding benzophenone **4kb** in 80% yield (142 mg) as a colorless oil.

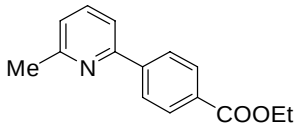
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 7.89-7.84 (m, 2H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.14-7.12 (m, 1H), 7.03 (dd, *J* = 7.5, 0.8 Hz, 1H), 6.98-6.91 (m, 3H), 3.89 (s, 3H), 3.00 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 196.2, 163.0, 150.4, 139.0, 132.5, 130.5, 128.5, 118.2, 115.8, 113.3, 113.1, 55.4, 40.5.

MS (EI, 70 eV): *m/z* (%) = 256 (17), 255 (M^+, 100), 254 (42), 135 (42), 77 (9).

HRMS ($C_{16}H_{17}NO_2$, EI): calc.: 255.1259; found: 255.1245 (M^+).

6-Methyl-2-[4-(ethoxycarbonyl)phenyl]pyridine (4l)



The arylzinc reagent **5l** was prepared according to **TP1** from 2-chloro-6-methylpyridine (**1l**, 0.128 g, 1 mmol) at -95 °C for 5 min in 69% yield. Palladium-catalyzed cross-coupling with ethyl 4-bromobenzoate (**3m**, 0.160 g, 0.7 mmol, 0.7 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding 2-arylated pyridine **4l** in 63% yield (106 mg) as a colorless oil.

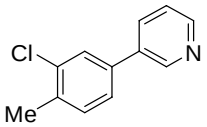
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 8.54 (dd, *J* = 1.5, 0.7 Hz, 1H), 8.15-8.11 (m, 2H), 8.06-8.02 (m, 2H), 7.68-7.66 (m, 1H), 7.59-7.55 (m, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 153.5, 150.3, 143.4, 137.3, 132.5, 130.3, 129.9, 126.4, 120.4, 60.9, 18.2, 14.3.

MS (EI, 70 eV): *m/z* (%) = 241 (M^+, 33), 213 (21), 197 (16), 196 (100), 169 (17), 168 (58), 167 (34), 166 (13), 153 (14), 140 (15), 139 (23), 115 (41), 98 (19), 89 (16), 84 (43), 75 (19), 65 (24), 63 (21), 50 (21).

HRMS ($C_{15}H_{15}NO_2$, EI): calc.: 241.1103; found: 241.1072 (M^+).

3-(3-Chloro-4-methylphenyl)pyridine (4ma)



The arylzinc reagent **5m** was prepared according to **TP1** from 2-chloro-4-iodo-1-methylbenzene (**1m**, 0.252 g, 1 mmol) at -95 °C for 5 min in 73% yield. Palladium-catalyzed cross-coupling with 3-bromopyridine (**3k**, 0.111 g, 0.7 mmol, 0.7 equiv)

was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding 3-arylated pyridine **4ma** in 70% yield (99 mg) as a colorless oil.

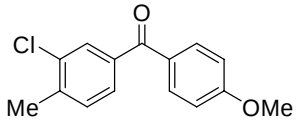
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 8.82 (d, *J* = 2.5 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.84 (ddd, *J* = 7.9, 2.4, 1.7 Hz, 1H), 7.57 (d, *J* = 1.4 Hz, 1H), 7.40-7.32 (m, 3H), 2.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 148.7, 148.1, 137.0, 135.9, 135.2, 135.1, 134.1, 131.5, 127.5, 125.2, 123.5, 19.7.

MS (EI, 70 eV): *m/z* (%) = 205 (31), 204 (17), 203 (M^+, 100), 202 (12), 169 (12), 168 (78), 167 (31), 166 (10), 139 (13).

HRMS ($C_{12}H_{10}ClN$, EI): calc.: 203.0502; found: 203.0482 (M^+).

(3-Chloro-4-methylphenyl)(4-methoxyphenyl)methanone (4mb)



The arylzinc reagent **5m** was prepared according to **TP1** from 2-chloro-4-iodo-1-methylbenzene (**1m**, 0.252 g, 1 mmol) at -95 °C for 5 min in 73% yield. Palladium-catalyzed cross-coupling with 4-methoxybenzoyl chloride (**3h**, 0.119 g, 0.7 mmol, 0.7 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding benzophenone **4mb** in 56% yield (103 mg) as a colorless oil.

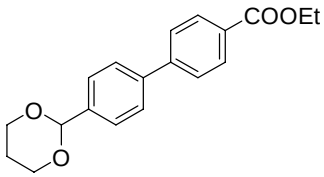
^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 7.83-7.78 (m, 2H), 7.76 (d, *J* = 1.7 Hz, 1H), 7.56 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.00-6.95 (m, 2H), 3.90 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 193.8, 163.3, 140.4, 137.4, 134.4, 132.4, 130.7, 130.3, 129.8, 128.0, 113.6, 55.5, 20.2.

MS (EI, 70 eV): *m/z* (%) = 262 (13), 261 (7), 260 (M^+, 43), 153 (8), 135 (100), 92 (8), 77 (8).

HRMS ($C_{15}H_{13}ClO_2$, EI): calc.: 260.0604; found: 260.0526 (M^+).

Ethyl 4-(4-(1,3-dioxan-2-yl)phenyl)benzoate (4na)



The arylzinc reagent **5n** was prepared according to **TP1** from 2-(4-chlorophenyl)-1,3-dioxane (**1n**, 0.199 g, 1 mmol) at -95 °C for 5 min in 65% yield. Palladium-catalyzed cross-coupling with ethyl 4-bromobenzoate (**3m**, 0.138 g, 0.6 mmol, 0.6 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding biphenyl **4na** in 82% yield (154 mg) as a colorless oil.

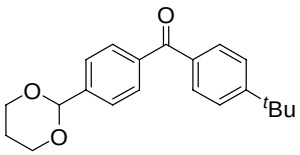
^{1}H NMR (400 MHz, CD_3COCD_3): δ / ppm = 8.11-8.08 (m, 2H), 7.81-7.78 (m, 2H), 7.72-7.69 (m, 2H), 7.59-7.56 (m, 2H), 5.58 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.21 (ddt, *J* = 10.4, 5.1, 1.4 Hz, 2H), 4.05-3.98 (m, 2H), 2.16-2.07 (m, 1H), 1.47 (dtt, *J* = 13.4, 2.6, 1.3 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CD_3COCD_3): δ / ppm = 166.6, 145.9, 140.7, 140.6, 130.8, 130.4, 127.9, 127.8, 127.6, 101.8, 67.9, 61.5, 26.7, 14.7.

MS (EI, 70 eV): *m/z* (%) = 312 (M^+, 79), 311 (100), 267 (36), 254 (32), 253 (50), 239 (17), 226 (33), 225 (37), 210 (17), 209 (55), 198 (17), 181 (55), 163 (31), 153 (38), 152 (97), 151 (33), 144 (40), 129 (31), 104 (19), 87 (34), 76 (21), 57 (17), 44 (18), 42 (20).

HRMS ($C_{19}H_{20}O_4$, EI): calc.: 312.1362; found: 312.1305 (M^+).

(4-(1,3-Dioxan-2-yl)phenyl)(4-*tert*-butylphenyl)methanone (4nb)



The arylzinc reagent **5n** was prepared according to **TP1** from 2-(4-chlorophenyl)-1,3-dioxane (**1n**, 0.199 g, 1 mmol) at -95 °C for 5 min in 65% yield. Palladium-catalyzed cross-coupling with 4-*tert*-butylbenzoyl chloride (**3n**, 0.118 g, 0.6 mmol, 0.6 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding benzophenone **4nb** in 62% yield (128 mg) as a colorless oil.

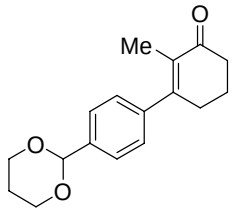
^{1}H NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.77-7.73 (m, 4H), 7.63-7.58 (m, 4H), 5.63 (s, 1H), 4.22 (ddt, *J* = 10.6, 5.1, 1.4 Hz, 2H), 4.07-4.00 (m, 2H), 2.17-2.08 (m, 1H), 1.49 (dtt, *J* = 13.5, 2.6, 1.3 Hz, 1H), 1.37 (s, 9H).

^{13}C NMR (100 MHz, CD_3COCD_3): δ / ppm = 195.9, 156.9, 144.3, 138.9, 135.9, 130.8, 130.3, 127.1, 126.3, 101.5, 68.0, 35.7, 31.5, 26.7.

MS (EI, 70 eV): *m/z* (%) = 325 (18), 324 (M^+, 61), 323 (86), 309 (46), 267 (21), 266 (21), 265 (76), 252 (20), 251 (69), 223 (33), 222 (100), 207 (27), 195 (12), 167 (12), 161 (35), 133 (35), 118 (14), 111 (16), 105 (57), 104 (13), 91 (14), 87 (52), 77 (27), 57 (20), 41 (20).

HRMS ($C_{21}H_{24}O_3$, EI): calc.: 324.1725; found: 324.1711 (M^+).

3-(4-(1,3-Dioxan-2-yl)phenyl)-2-methylcyclohex-2-enone (4nc)



The arylzinc reagent **5n** was prepared according to **TP1** from 2-(4-chlorophenyl)-1,3-dioxane (**1n**, 0.199 g, 1 mmol) at -95 °C for 5 min in 65% yield. Palladium-catalyzed cross-coupling with 3-iodo-2-methylcyclohex-2-enone (**3o**, 0.142 g, 0.6 mmol, 0.6 equiv) was performed according to **TP3** using PEPPSI-IPr (27 mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding 3-arylated enone **4nc** in 74% yield (121 mg) as a colorless oil.

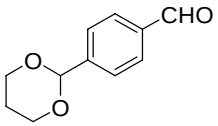
^{1}H NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.52-7.48 (m, 2H), 7.28-7.25 (m, 2H), 5.55 (s, 1H), 4.19 (ddt, *J* = 10.5, 5.1, 1.4 Hz, 2H), 4.03-3.97 (m, 2H), 2.64 (tq, *J* = 6.0, 1.9 Hz, 2H), 2.45-2.42 (m, 2H), 2.14-2.02 (m, 3H), 1.63 (t, *J* = 2.0 Hz, 3H), 1.47 (dtt, *J* = 13.5, 2.6, 1.4 Hz, 1H).

^{13}C NMR (100 MHz, CD_3COCD_3): δ / ppm = 199.1, 156.7, 142.6, 140.1, 132.0, 127.7, 127.1, 101.8, 67.9, 38.3, 33.5, 26.7, 23.6, 13.1.

MS (EI, 70 eV): *m/z* (%) = 272 (M^+, 49), 271 (85), 216 (24), 214 (20), 213 (44), 186 (12), 185 (56), 163 (17), 158 (12), 157 (10), 142 (12), 130 (12), 129 (26), 128 (26), 127 (11), 115 (27), 87 (100), 59 (12), 42 (12), 41 (14).

HRMS ($C_{17}H_{20}O_3$, EI): calc.: 272.1412; found: 272.1463 (M^+).

4-(1,3-Dioxan-2-yl)benzaldehyde (4nd)



The aryllithium reagent **2n** was prepared according to **TP1** from 2-(4-chlorophenyl)-1,3-dioxane (**1n**, 0.199 g, 1 mmol) at -95 °C for 5 min in 65% yield. Reaction with DMF (0.044 g, 0.6 mmol, 0.6 equiv) was performed according to **TP2** from -95 °C to rt over 2 h, leading to the corresponding aldehyde **4nd** in 87% yield (100 mg) as a colorless oil.

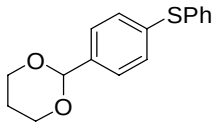
^{1}H NMR (400 MHz, CD_3COCD_3): δ / ppm = 10.05 (s, 1H), 7.93-7.90 (m, 2H), 7.68-7.65 (m, 2H), 5.61 (s, 1H), 4.23-4.19 (m, 2H), 4.05-3.99 (m, 2H), 2.16-2.06 (m, 1H), 1.51-1.45 (m, 1H).

^{13}C NMR (100 MHz, CD_3COCD_3): δ / ppm = 192.8, 146.3, 137.7, 130.1, 127.8, 101.3, 68.0, 26.6.

MS (EI, 70 eV): *m/z* (%) = 192 (M^+, 21), 191 (30), 149 (15), 134 (20), 133 (100), 105 (32), 87 (19), 77 (25), 51 (14), 42 (13).

HRMS ($C_{11}H_{12}O_3$, EI): calc.: 192.0786; found: 192.0787 (M^+).

2-(4-(Phenylthio)phenyl)-1,3-dioxane (4ne)



The aryllithium reagent **2n** was prepared according to **TP1** from 2-(4-chlorophenyl)-1,3-dioxane (**1n**, 0.199 g, 1 mmol) at -95 °C for 5 min in 65% yield. Reaction with $PhSSO_2Ph$ (**3q**, 0.15 g, 0.6 mmol, 0.6 equiv) was performed according to **TP2** from -95 °C to rt over 2 h, leading to the corresponding acetal **4ne** in 64% yield (105 mg) as a colorless oil.

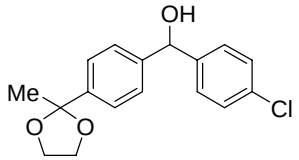
^{1}H NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.45-7.42 (m, 2H), 7.39-7.28 (m, 7H), 5.51 (s, 1H), 4.19-4.15 (m, 2H), 4.01-3.94 (m, 2H), 2.13-2.01 (m, 1H), 1.47-1.42 (m, 1H).

^{13}C NMR (100 MHz, CD_3COCD_3): δ / ppm = 139.8, 136.7, 136.4, 131.9, 131.3, 130.3, 128.2, 128.2, 101.6, 67.9, 26.7.

MS (EI, 70 eV): *m/z* (%) = 273 (20), 272 (M^+, 100), 271 (53), 215 (17), 214 (69), 213 (60), 186 (55), 185 (27), 184 (43), 109 (19), 77 (10), 51 (10).

HRMS ($C_{16}H_{16}O_2S$, EI): calc.: 272.0871; found: 272.0868 (M^+).

(4-Chlorophenyl)(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)methanol (4oa)



The aryllithium reagent **2o** was prepared according to **TP1** from 2-(4-chlorophenyl)-2-methyl-1,3-dioxolane (**1o**, 0.199 g, 1 mmol) at -95 °C for 5 min in 58% yield. Reaction with 4-chlorobenzaldehyde (**3r**, 0.084 g, 0.6 mmol, 0.6 equiv) was performed according to **TP2** from -95 °C to rt over 2 h, leading to the corresponding alcohol **4oa** in 70% yield (127 mg) as a colorless oil.

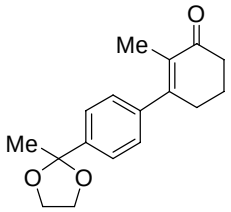
^{1}H NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.46-7.32 (m, 8H), 5.84 (d, *J* = 3.7 Hz, 1H), 4.96 (d, *J* = 3.9 Hz, 1H), 4.02-3.93 (m, 2H), 3.74-3.66 (m, 2H), 1.53 (s, 3H).

^{13}C NMR (100 MHz, CD_3COCD_3): δ / ppm = 145.5, 145.4, 143.7, 133.0, 129.1, 129.0, 127.1, 126.1, 109.3, 75.3, 65.2, 28.1.

MS (EI, 70 eV): *m/z* (%) = 291 (31), 190 (16), 289 (100), 139 (12), 87 (14), 77 (10), 43 (11).

HRMS ($C_{17}H_{16}ClO_3$, EI): calc.: 303.0770; found: 303.0788 (M^+-H).

2-Methyl-3-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)cyclohex-2-enone (4ob)



The arylzinc reagent **5o** was prepared according to **TP1** from 2-(4-chlorophenyl)-2-methyl-1,3-dioxolane (**1o**, 0.199 g, 1 mmol) at -95 °C for 5 min in 58% yield. Palladium-catalyzed cross-coupling with 3-iodo-2-methylcyclohex-2-enone (**3o**, 0.142 g, 0.6 mmol, 0.6 equiv) was performed according to **TP3** using PEPPSI-IPr (27

mg, 4 mol%) at 60 °C for 12 h, leading to the corresponding 3-arylated enone **4ob** in 71% yield (115 mg) as a colorless oil.

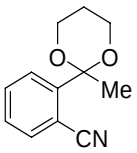
^{1}H NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.53-7.50 (m, 2H), 7.29-7.26 (m, 2H), 4.04-4.00 (m, 2H), 3.78-3.75 (m, 2H), 2.65 (tq, *J* = 6.0, 1.9 Hz, 2H), 2.45-2.42 (m, 2H), 2.10-2.04 (m, 2H), 1.64 (t, *J* = 1.9 Hz, 3H), 1.58 (s, 3H).

^{13}C NMR (100 MHz, CD_3COCD_3): δ / ppm = 199.1, 156.7, 144.4, 141.9, 132.0, 127.9, 126.2, 109.2, 65.3, 38.3, 33.5, 28.0, 23.6, 13.2.

MS (EI, 70 eV): *m/z* (%) = 272 (M^+, 1), 258 (14), 257 (100), 213 (12), 87 (11), 43 (9).

HRMS ($C_{17}H_{20}O_3$, EI): calc.: 272.1412; found: 272.1402 (M^+).

2-(2-Methyl-1,3-dioxan-2-yl)benzonitrile (4p)



The aryllithium reagent **2p** was prepared according to **TP1** from 2-(2-chlorophenyl)-2-methyl-1,3-dioxane (**1p**, 0.212 g, 1 mmol) at -95 °C for 5 min in 57% yield. Reaction with TsCN (**3s**, 0.109 g, 0.6 mmol, 0.6 equiv) was performed according to **TP2** from -95 °C to rt over 2 h, leading to the benzonitrile **4p** in 59% yield (72 mg) as a colorless oil.

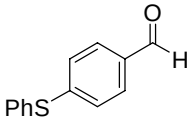
^{1}H NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.83 (ddd, *J* = 7.6, 1.4, 0.6 Hz, 1H), 7.74 (ddd, *J* = 8.0, 7.5, 1.4 Hz, 1H), 7.68-7.65 (m, 1H), 7.54 (td, *J*=7.5, 1.4 Hz, 1H), 3.95-3.90 (m, 2H), 3.73-3.66 (m, 2H), 2.08-1.96 (m, 1H), 1.52 (s, 3H), 1.41-1.35 (m, 1H).

^{13}C NMR (100 MHz, CD_3COCD_3): δ / ppm = 146.0, 136.3, 133.9, 129.7, 129.5, 118.9, 111.7, 100.3, 62.1, 31.1, 25.9.

MS (EI, 70 eV): *m/z* (%) = 203 (M^+, 2), 189 (8), 188 (57), 131 (10), 130 (100), 128 (9), 102 (22), 101 (50), 73 (9), 57 (9), 43 (45).

HRMS ($C_{12}H_{13}NO_2$, EI): calc.: 203.0946; found: 203.0929 (M^+).

Synthesis of 4-(phenylthio)benzaldehyde (9)



n-BuLi (1.1 mmol, 0.52 mL, 2.13 M in *n*-hexane) was dropwise added to *N*,*N*,*N*'-trimethylethylenediamine (0.112 g, 1.1 mmol) in THF (2 mL) at -20 °C. After stirring at the same temperature for 15 min, 4-chlorobenzaldehyde (**6**, 0.141 g, 1 mmol) was added and continuously stirred at -20 °C for another 15 min. Then the reaction mixture was cooled to -95 °C and the pre-prepared LiDBB solution (2 mmol, 8 mL, ~0.25 M in THF, 2 equiv) was dropwise added into the reaction mixture. After addition and 5 min of stirring at the same temperature, $PhSSO_2Ph$ (**3q**, 0.125 g, 0.5 mmol) was added and the reaction mixture was stirred from -95 °C to room temperature over 2 h. Then aq. HCl (2 mL, 2 M) and water (10 mL) was added into the flask followed by extraction with ethyl acetate (20 mL x 3). The combined organic layers were sequentially washed with sat. $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under vacuum. The crude residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the analytically pure product **9** in 73% yield (78 mg) as a white solid. Spectroscopic data are in accordance with the reported data.[19]

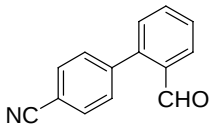
^{1}H NMR (600 MHz, $CDCl_3$): δ / ppm = 9.92 (s, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.54 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.44-7.43 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ / ppm = 191.1, 147.2, 134.3, 133.7, 131.3, 130.1, 129.8, 129.1, 127.2, 77.2, 77.0, 76.8.

MS (EI, 70 eV): *m/z* (%) = 215 (17), 214 (M^+, 100), 213 (55), 186 (10), 185 (46), 152 (14), 109 (10), 77 (10), 51 (13).

HRMS ($C_{13}H_{10}OS$, EI): calc.: 214.0452; found: 214.0461 (M^+).

Synthesis of 4-(2-formylphenyl)benzonitrile (13)



n-BuLi (1.1 mmol, 0.52 mL, 2.13 M in *n*-hexane) was dropwise added to *N*,*N*,*N*'-trimethylethylenediamine (0.112 g, 1.1 mmol) in THF (2 mL) at -20 °C. After stirring at the same temperature for 15 min, 2-chlorobenzaldehyde (**10**, 0.141 g, 1 mmol) was added and continuously stirred at -20 °C for another 15 min. Then the reaction was

[19] N. Taniguchi, *J. Org. Chem.* **2007**, *72*, 1241.

cooled to -95 °C and the pre-prepared LiDBB solution (2 mmol, 8 mL, ~0.25 M in THF, 2 equiv) was dropwise added into the reaction mixture. After addition and 5 min of stirring at the same temperature, a $ZnCl_2$ solution (2 mmol, 2 mL, 1.0 M in THF) was added and the reaction mixture was allowed to warm to room temperature over 30 min. 4-Iodobenzonitrile (**3b**, 0.137 g, 0.6 mmol, 0.6 equiv) and PEPPSI-IPr (27 mg, 4 mol%) were added into the flask and stirred at 60 °C for 12 h. Then aq. HCl (2 mL, 2 M) and water (10 mL) was added into the flask followed by extraction with ethyl acetate (20 mL x 3). The combined organic layers were sequentially washed with sat. $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under vacuum. The crude residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the analytically pure product **13** in 65% yield (81 mg) as a white solid. Spectroscopic data are in accordance with the reported data.[20]

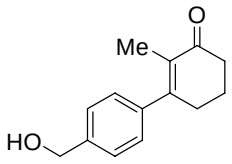
^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 9.93 (s, 1H), 8.02 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.77-7.75 (m, 2H), 7.68 (td, *J* = 7.5, 1.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.51-7.49 (m, 2H), 7.41 (dd, *J* = 7.6, 0.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm = 191.0, 143.3, 142.6, 133.7, 133.4, 132.0, 130.5, 130.4, 128.8, 128.5, 118.3, 111.9.

MS (EI, 70 eV): *m/z* (%) = 208 (10), 207 (M^+, 72), 206 (100), 179 (18), 178 (34), 177 (35), 152 (16), 151 (43), 150 (24), 104 (14), 76 (12).

HRMS ($C_{14}H_9NO$, EI): calc.: 207.0684; found: 207.0682 (M^+).

Synthesis of 3-(4-(hydroxymethyl)phenyl)-2-methylcyclohex-2-enone (16)



n-BuLi (1.0 mmol, 0.47 mL, 2.13 M in *n*-hexane) was dropwise added to (4-chlorophenyl)methanol (**14**, 0.143 g, 1.0 mmol) in THF (2 mL) at -78 °C. After stirring at the same temperature for 5 min, the reaction mixture was cooled to -95 °C and the pre-prepared LiDBB solution (2 mmol, 8 mL, ~0.25 M in THF, 2 equiv) was

[20] M. L. Hossain, F. Ye, Z. Liu, Y. Xia, Y. Shi, L. Zhou, Y. Zhang, J. Wang, *J. Org. Chem.* **2014**, *79*, 8689.

dropwise added into the reaction mixture. After addition and 5 min of stirring at the same temperature, a $ZnCl_2$ solution (2 mmol, 2 mL, 1.0 M in THF) was added and the reaction mixture was allowed to warm to room temperature over 30 min. 3-Iodo-2-methylcyclohex-2-enone (**3o**, 0.118 g, 0.5 mmol, 0.5 equiv) and PEPPSI-IPr (27 mg, 4 mol%) were added into the flask and stirred at 60 ^oC for 12 h. Then aq. HCl (2 mL, 2 M) and water (10 mL) was added into the flask followed by extraction with ethyl acetate (20 mL x 3). The combined organic layers were sequentially washed with sat. $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under vacuum. The crude residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the analytically pure product **16** in 71% yield (92 mg) as a colorless oil.

^{1}H NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.43-7.40 (m, 2H), 7.26-7.23 (m, 2H), 4.66 (s, 1H), 4.24 (brs, 1H), 2.65 (tq, *J* = 6.0, 1.9 Hz, 2H), 2.45-2.42 (m, 2H), 2.10-2.06 (m, 2H), 1.65 (t, *J* = 1.9 Hz, 3H).

^{13}C NMR (100 MHz, CD_3COCD_3): δ / ppm = 199.1, 157.0, 143.2, 141.1, 131.9, 128.0, 127.4, 64.5, 38.4, 33.6, 23.7, 13.2.

MS (EI, 70 eV): *m/z* (%) = 216 (M^+, 11), 186 (15), 185 (100), 158 (25), 141 (10), 130 (9), 129 (18), 128 (15), 115 (20), 91 (9), 77 (8).

HRMS ($C_{14}H_{16}O_2$, EI): calc.: 216.1150; found: 216.1144 (M^+).

Chapter 3. C_{60}-Catalyzed Preparation of Aryl and Heteroaryl Magnesium and Zinc Reagents using Mg/LiCl

3.1 Introduction

The preparation of organometallics by the direct insertion of a main-group metal, such as magnesium, into unsaturated organic halides is a very atom-economical method.[1] Due to the insolubility of metallic powders, such insertion reactions are heterogeneous and proceed readily only after the activation of the metal. The preparation of organomagnesium reagents largely depends on the activation of the magnesium surface.[2] Numerous methods for the activation of magnesium have been reported.[3] Several additives (such as catalytic amounts of $FeCl_2$,[4] DIBAL-H,[5] or transition metal-phosphine complexes[6]) were found to facilitate the magnesium insertion to organic halides. The pioneering work of Rieke led to the discovery of much activated magnesium by the *in situ* reduction of $MgCl_2$ with Li-naphthalenide.[7] We have reported that the treatment of magnesium powder or turnings with lithium chloride lead to a similar activation.[8,9] LiCl plays the role of a Lewis acid and "surface

[1] B. M. Trost, *Science* **1991**, *254*, 1471.
[2] For reviews, see: (a) *Handbook of Functionalized Organometallics*; P. Knochel, Ed.; Wiley-VCH: Weinheim, **2005**. (b) *Handbook of Grignard Reagents*; G. S. Silverman, P. E. Rakita, Eds.; Marcel Dekker: New York, **1996**. (c) *The Chemistry of Organomagnesium Compounds*; Z. Rappoport, I. Marek, Eds.; Wiley-VCH: Weinheim, **2008**. (d) 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. (e) C. Nájera, J. M. Sansano, M. Yus, *Tetrahedron* **2003**, *59*, 9255. (f) R. Chinchilla, C. Najera, M. Yus, *Tetrahedron* **2005**, *61*, 3139. (g) F. Foubelo, M. Yus, *Chem. Soc. Rev.* **2008**, *37*, 2620. (h) Z. Xi, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1021. (i) Z. Xi, *Acc. Chem. Res.* **2010**, *43*, 1342.
[3] For examples, see: (a) K. J. Klabunde, H. F. Efner, L. Satek, W. Donley, *J. Organomet. Chem.* **1974**, *71*, 309. (b) W. Oppolzer, P. Schneider, *Tetrahedron Lett.* **1984**, *25*, 3305.
[4] B. Bogdanović, M. Schwickardi, *Angew. Chem., Int. Ed.* **2000**, *39*, 4610.
[5] U. Tilstam, H. Weinmann, *Org. Process Res. Dev.* **2002**, *6*, 906.
[6] (a) M. Y. Jin, N. Yoshikai, *J. Org. Chem.* **2011**, *76*, 1972. (b) L. Adak, N. Yoshikai, *J. Org. Chem.* **2011**, *76*, 7563.
[7] (a) R. D. Rieke, *Acc. Chem. Res.* **1977**, *10*, 301. (b) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925. (c) R. D. Rieke, *Science* **1989**, 246, 1260. (d) R. D. Rieke, P. M. Hudnall, *J. Am. Chem. Soc.* **1972**, *94*, 7178. (e) R. D. Rieke, S. E. Bales, *J. Am. Chem. Soc.* **1974**, *96*, 1775.
[8] For representative LiCl-mediated metal insertions into organic halides, see: (a) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem.-Eur. J.* **2009**, *15*, 7192. (b) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem., Int. Ed.* **2008**, *47*, 6802. (c) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem., Int. Ed.* **2006**, *45*, 6040. (d) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358. (e) Y.-H. Chen, P. Knochel, *Angew. Chem., Int. Ed.* **2008**, *47*, 7648. (f) Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem., Int. Ed.* **2009**, *48*, 2236.

cleaner". Its promoter activity can be enhanced by the presence of activated Lewis acids such as $InCl_3$,[9-11] $PbCl_2$,[9,11,12] $TiCl_4$,[9] or $B(OR)_3$.[13] Aryl chlorides are usually cheaper and more readily available than the corresponding bromides or iodides, thus there is still a lot of interest to convert aryl chlorides to Grignard reagents using mild conditions. Since the mechanism of the insertion involves electron transfer reaction steps,[14] we have envisioned that molecules that facilitate electron transfer reactions may be good catalysts for the magnesium insertion. After several unsuccessful attempts, we turned our attention to C_{60} fullerene, since it is known that this highly unsaturated molecule readily accepts and transfers electrons.[15-17] Herein, we report that the addition of catalytic amounts of C_{60} catalyzes the magnesium insertion in the additional presence of LiCl, allowing the synthesis of aryl and heteroaryl magnesium or zinc reagents under mild conditions.

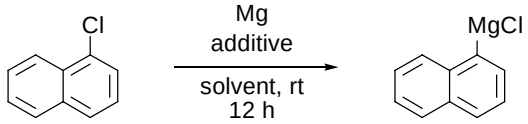
3.2 Results and Discussion

First, we tested the magnesium insertion to 1-chloronaphthalene (**1a**) using various ethereal solvents. Initially, the reaction of **1a** (1 equiv) with Mg turnings (3 equiv) in DME at 25 °C for 12 h was examined. The magnesium turnings were activated by the addition of 1,2-dibromoethane (5 mol%) and TMSCl (5 mol%). No reaction was

[9] T. D. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313.
[10] (a) K. Takai, Y. Ikawa, *Org. Lett.* **2002**, *4*, 1727. (b) Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem., Int. Ed.* **2010**, *49*, 8516. (c) T. D. Blümke, T. Klatt, K. Koszinowski, P. Knochel, *Angew. Chem., Int. Ed.* **2012**, *51*, 9926. (d) K. Groll, T. D. Blümke, A. Unsinn, D. Haas, P. Knochel, *Angew. Chem., Int. Ed.* **2012**, *51*, 11157. (e) T. D. Blümke, K. Groll, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2011**, *13*, 6440. (f) Z.-L. Shen, Z. Peng, C.-M. Yang, J. Helberg, P. Mayer, I. Marek, P. Knochel, *Org. Lett.* **2014**, *16*, 956.
[11] Z. Peng, P. Knochel, *Org. Lett.* **2011**, *13*, 3198.
[12] (a) K. Takai, T. Ueda, T. Hayashi, T. Moriwake, *Tetrahedron Lett.* **1996**, *37*, 7049. (b) K. Takai, T. Ueda, N. Ikeda, T. Ishiyama, H. Matsushita, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 347.
[13] B. A. Haag, C. Sämann, A. Jana, P. Knochel, *Angew. Chem., Int. Ed.* **2011**, *50*, 7290.
[14] For review regarding the use of electron as catalyst, see: A. Studer, D. P. Curran, *Nat. Chem.* **2014**, *6*, 765.
[15] *Fullerenes: Chemistry and Reactions*; A. Hirsch, M. Brettreich, Eds.; Wiley-VCH: Weinheim, **2005**.
[16] For the only two applications of fullerene as reaction catalyst in organic synthesis, see: (a) B. Li, Z. Xu, *J. Am. Chem. Soc.* **2009**, *131*, 16380. (b) Y. Shi, L. Gan, X. Wei, S. Jin, S. Zhang, F. Meng, Z. Wang, C. Yan, *Org. Lett.* **2000,** *2*, 667.
[17] Based on the high reduction potential of magnesium (E^o = -2.37 V), the transfer of an electron from the magnesium surface to the absorbed C_{60} fullerene should readily take place. For the reduction potential of magnesium and C_{60} fullerene, see: (a) C. A. Reed, R. D. Bolskar, *Chem. Rev.* **2000**, *100*, 1075. (b) *CRC Handbook of Chemistry and Physics*, 87th ed.; D. R. Lide, Ed.; CRC Press: Boca Raton, **2006**.

observed with Mg turnings alone or in the presence of either LiCl (2 equiv) or C_{60} (3 mol%) (Table 1, entries 1-2). The addition of C_{60} (3 mol%) led to a complete conversion in the presence of LiCl and the formation of the corresponding Grignard reagent (**2a**) was achieved in 84% yield as determined by iodolysis (Table 1, entry 3). It was important to use 99.9% pure C_{60}, since we noticed that 98% pure C_{60} did not catalyze the magnesium insertion to an appreciable extent.[18] Under the same conditions, the insertion performed in other ethereal solvents led to either poor yields of Grignard reagent **2a** (THF, 29%, Table 1, entry 4) or no insertion reaction occurs (Table 1, entries 5-7). Quenching with various electrophiles (Fig. 1) such as a benzaldehyde (**3a**), an acid chloride (**3e**), an allylic bromide (**3g**),[19] or an aryl iodide (**3h**, after transmetallation with $ZnCl_2$; Negishi cross-coupling[20] using $Pd(OAc)_2$ and S-Phos[21]) produced the expected products (**4a-d**) in 77-91% yields (Table 2, entries 1-4).

Table 1. Screening of different additives and solvents for magnesium insertion into 1-chloronaphthalene (**1a**)



1a **2a**

Entry	Additive	Solvent	Yield (%)[a]
1	LiCl	DME	0
2	C_{60}	DME	0
3	LiCl, C_{60}	DME	84
4	LiCl, C_{60}	THF	29
5	LiCl, C_{60}	Et_2O	0
6	LiCl, C_{60}	^{t}BuOMe	0
7	LiCl, C_{60}	tetrahydropyran	0

[a] Determined by iodolysis.

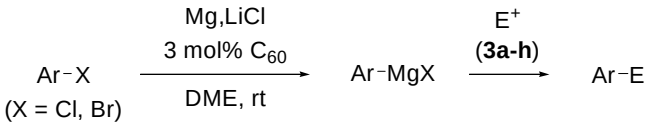
[18] Both 99.9% and 98% pure C_{60} powders were purchased from Aldrich company (product No**.** 572500 and 483036). It should be noted that the use of only 1 mol% of C_{60} (99.9%) did not lead to a metal activation; the minimum amount of C_{60} was *ca.* 3 mol%. We suggest that C_{60} facilitates the electron transfer from the magnesium surface to the organic halide. In addition, attempts to extend this activation to zinc dust failed.

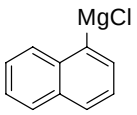
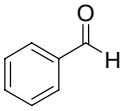
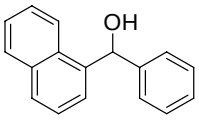
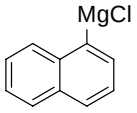
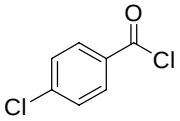
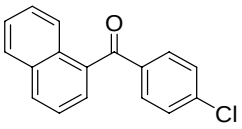
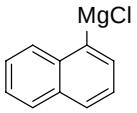
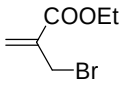
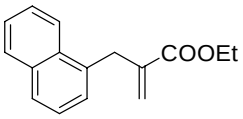
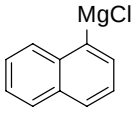
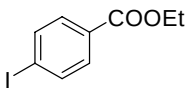
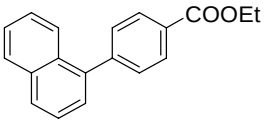
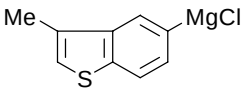
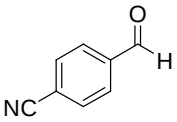
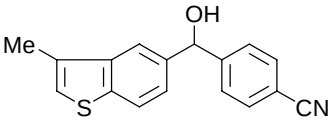
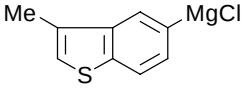
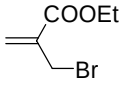
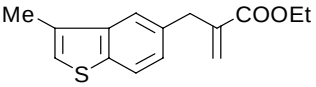
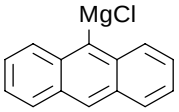
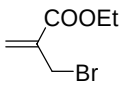
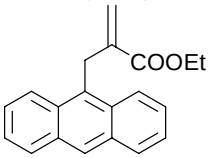
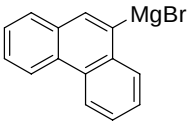
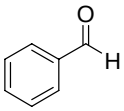
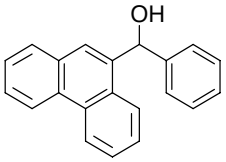
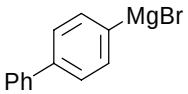
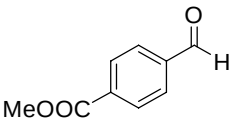
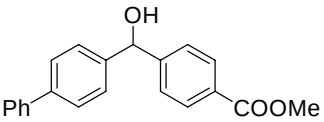
[19] For the preparation of ethyl 2-(bromomethyl)acrylate, see: J. Villieras, M. Rambaud, *Org. Synth.* **1988**, *66*, 220.

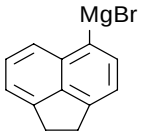
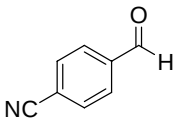
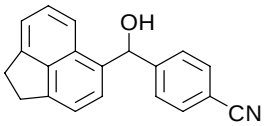
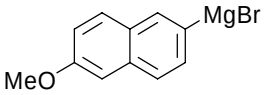
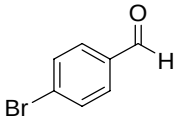
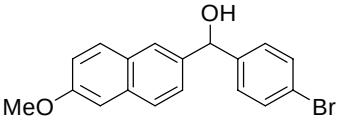
[20] E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.

[21] (a) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (b) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685. (c) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461. (d) D. S. Surry, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (e) S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27.

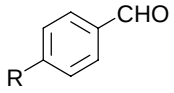
Table 2. Preparation of organomagnesium reagents and further reactions with electrophiles



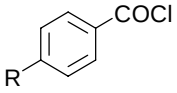
Entry	ArMgX (Yield,[a] Time)	E^+	Product (Yield)[b]
1	 **2a** (84%,12 h)	 **3a**	 **4a** (82%)
2	 **2a**	 **3e**	 **4b** (77%)[c]
3	 **2a**	 **3g**	 **4c** (78%)[c]
4	 **2a**	 **3h**	 **4d** (91%)[d]
5	 **2b** (67%, 22 h)	 **3b**	 **4e** (68%)
6	 **2b**	 **3g**	 **4f** (70%)[c]
7	 **2c** (61%, 1 h)	 **3g**	 **4g** (65%)[c]
8	 **2d** (79%, 10 min)	 **3a**	 **4h** (85%)
9	 **2e** (70%, 2 h)	 **3c**	 **4i** (75%)

10	 **2f** (74%, 4 h)	 **3b**	 **4j** (82%)
11	 **2g** (86%, 1 h)	 **3d**	 **4k** (80%)

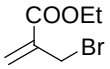
[a] Determined by iodolysis. [b] Yield of isolated, analytically pure product. [c] 20 mol% CuCN·2LiCl was used. [d] 4 mol% $Pd(OAc)_2$ and 8 mol% S-Phos were used and the reactions were performed at 60 °C for 12 h.



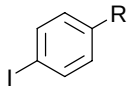
3a (R = H)
3b (R = CN)
3c (R = COOMe)
3d (R = Br)



3e (R = Cl)
3f (R = OMe)



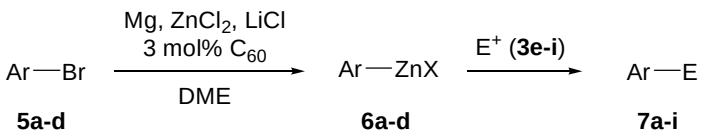
3g



3h (R = COOEt)
3i (R = CN)

Figure 1. Electrophiles used for reactions with the formed organometallic reagents.

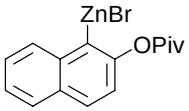
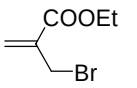
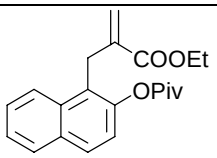
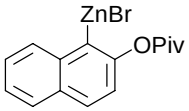
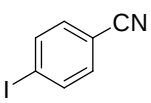
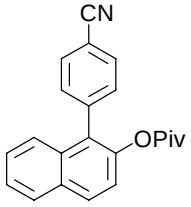
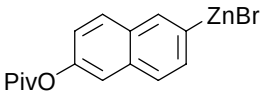
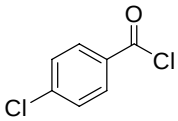
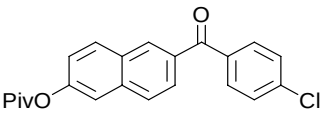
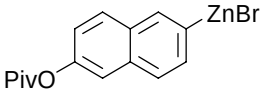
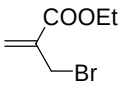
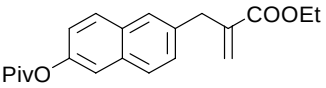
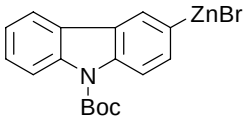
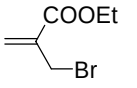
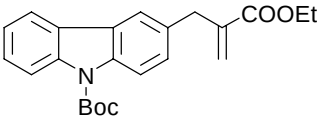
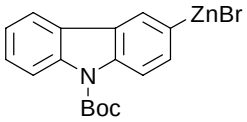
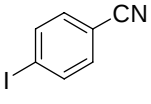
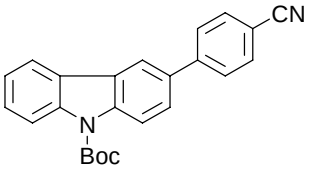
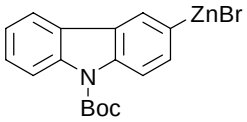
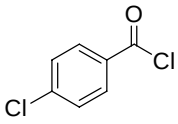
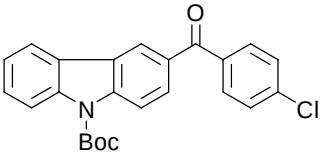
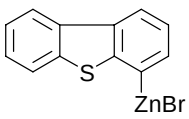
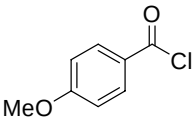
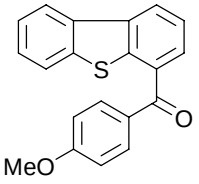
With 99.9% pure C_{60}, it was possible to convert aryl chlorides (**1b-c**) into the corresponding Grignard reagents (**2b-c**; Table 2, entries 5-7). Similarly, these two organomagnesium reagents were capable of undergoing either direct reactions with an aldehyde (**3b**) or CuCN·2LiCl-catalyzed allylation with ethyl 2-(bromomethyl)acrylate (**3g**),[22] affording the corresponding products (**4e-g**) in 65-68% yields. Interestingly, it was found that several aryl bromides (**1d-g**) smoothly underwent the magnesium insertion reactions to generate the corresponding Grignard reagents (**2d-g**) in 10 min to 4 h (Table 2, entries 8-11). In a same manner, reactions of the resulting organomagnesium reagents with aromatic aldehydes (with functional groups such as ester and nitrile) proceeded efficiently to produce the benzylic alcohols (**4h-k**) in 75-85% yields. It should be noted that polyaromatic halides are by far the best substrates and attempts to activate simple aryl chlorides failed.

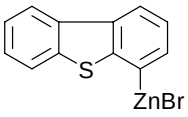
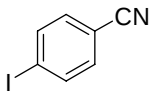
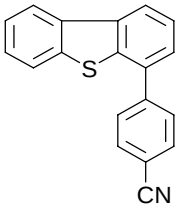


Scheme 1. One-pot preparation of organozinc reagents with improved functional group tolerance and their subsequent reactions with electrophiles

[22] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

Table 3. Preparation of organozinc reagents and subsequent reactions with electrophiles

Entry	ArZnX (Yield,[a] Temp., Time)	E^+	Product (Yield)[b]
1	 **6a** (83%, -10 °C, 4 h)	 **3g**	 **7a** (80%)[c]
2	 **6a**	 **3i**	 **7b** (62%)[d]
3	 **6b** (75%, -10 °C, 20 h)	 **3e**	 **7c** (63%)[c]
4	 **6b**	 **3g**	 **7d** (88%)[c]
5	 **6c** (79%, rt, 1 h)	 **3g**	 **7e** (78%)[c]
6	 **6c**	 **3i**	 **7f** (69%)[d]
7	 **6c**	 **3e**	 **7g** (71%)[c]
8	 **6d** (84%, rt, 1 h)	 **3f**	 **7h** (85%)[c]

9	**6d** 	**3i** 	**7i** (80%)[d] 

[a] Determined by iodolysis. [b] Yield of isolated, analytically pure product. [c] 20 mol% CuCN·2LiCl was used. [d] 4 mol% $Pd(OAc)_2$ and 8 mol% S-Phos were used and the reactions were performed at 60 °C for 12 h.

By using simultaneously Mg (3 equiv), $ZnCl_2$ (1 equiv), LiCl (2 equiv) and 3 mol% C_{60}, it was possible to convert functionalized organic bromides such as 1-bromonaphthalen-2-yl pivalate (**5a**) to the corresponding organozinc reagent **6a** in 83% yield at -10 °C within 4 h reaction time (Scheme 1 and Table 3, entry 1). It should be noted that, under the same conditions, in the absence of C_{60}, only a poor conversion was obtained (less than 5%). The generated organozinc reagent **6a** efficiently underwent either copper-catalyzed allylation with allylic bromide **3g** or palladium-catalyzed cross-coupling with aryl iodide **3i** leading to the respective products **7a-b** in 62-80% yields (entries 1-2). The same one-pot protocol was also successfully applied to aromatic bromides (**5b-d**) affording the desired organozinc reagents (**6b-d**) in 75-84% yields. Trapping of these organozinc species with electrophiles such as an allyl bromide, an acid chloride, or an aryl iodide led to the desired products (**7c-i**) in 63-88% yields (entries 3-9).

3.3 Conclusion

In summary, we have shown that the addition of a catalytic amount of C_{60} fullerene catalyzes the insertion of magnesium turnings to polycyclic aromatic halides (X = Cl or Br) allowing the preparation of the corresponding Grignard reagent in good yields. The use of a cocktail of metallic salts (Mg, $ZnCl_2$, LiCl) in the presence of 3 mol% of C_{60} fullerene (99.9% purity) allows furthermore to prepare some functionalized polyaromatic zinc reagents. Extension to other metal insertions is currently underway in our laboratories.

3.4 Experimental

General Information

All reactions were carried out under nitrogen atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC. Column chromatography was performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck. Substrates of 1-bromonaphthalen-2-yl pivalate (**5a**),[23] 6-bromonaphthalen-2-yl pivalate (**5b**),[23] *tert*-butyl 3-bromo-9*H*-carbazole-9-carboxylate (**5c**),[24] 4-bromodibenzothiophene (**5d**)[25] were prepared based on reported methods. All other reagents were obtained from commercial sources.

Preparation of CuCN·2LiCl solution:

CuCN·2LiCl solution (1.0 M in THF) was prepared by drying CuCN (7.17 g, 80 mmol) and LiCl (6.78 g, 160 mmol) in a Schlenk-tube under vacuum at 140 °C for 5 h. After cooling, anhydrous THF (80 mL) was added and stirring was continued until all salts were dissolved (24 h).

Typical procedure for the magnesium insertion (TP1):

LiCl (0.17 g, 4 mmol, 2 equiv) was added to 20 mL Schlenk-flask, equipped with a magnetic stirrer and a rubber septum, and dried at 380 °C by heat gun for 5 min under high vacuum. After cooling, the flask was flushed with nitrogen gas, and magnesium turnings (0.144 g, 6 mmol, 3 equiv) and anhydrous dimethoxyethane (DME, 6 mL) were introduced into the flask. The magnesium was sequentially activated by using 1,2-dibromoethane (5 mol%) and TMSCl (5 mol%). Then aryl halide (2 mmol, 1 equiv), internal standard ($C_{10}H_{22}$, 0.2 mL), and C_{60} (0.044 g, 0.06 mmol, 3 mol%, 99.9% purity) were added to the flask, and the reaction mixture was stirred at room

[23] A. R. Ehle, Q. Zhou, M. P. Watson, *Org. Lett.* **2012**, *14*, 1202.
[24] (a) A. Midya, Z. Xie, J.-X. Yang, Z.-K. Chen, D. J. Blackwood, J. Wang, S. Adams, K. P. Loh, *Chem. Commun.* **2010**, *46*, 2091; (b) V. Diep, J. J. Dannenberg, R. W. Franck, *J. Org. Chem.* **2003**, *68*, 7907.
[25] A. Tronnier, A. Risler, N. Langer, G. Wagenblast, I. Münster, T. Strassner, *Organometallics* **2012**, *31*, 7447.

temperature for the time indicated in Table 2. The reaction progress was monitored by GC-analysis of the reaction aliquots quenched by sat. NH_4Cl solution until it showed >95% conversion of the starting material. The yield of the insertion reaction was determined by GC-analysis of reaction aliquots quenched with a solution of iodine in anhydrous THF. The supernatant solution was carefully transferred to another predried and nitrogen-flushed Schlenk-flask by a syringe and used in subsequent reactions with electrophiles.

Typical procedure for the magnesium insertion in the presence of $ZnCl_2$ (TP2):
LiCl (0.17 g, 4 mmol, 2 equiv) was added to 20 mL Schlenk-flask, equipped with a magnetic stirrer and a rubber septum, and dried at 380 °C by heat gun for 5 min under high vacuum. After cooling, the flask was flushed with nitrogen gas, and magnesium turnings (0.144 g, 6 mmol, 3 equiv) and anhydrous dimethoxyethane (DME, 6 mL) were introduced into the flask. The magnesium was sequentially activated by using 1,2-dibromoethane (5 mol%) and TMSCl (5 mol%), then aryl halide (2 mmol, 1 equiv), internal standard ($C_{10}H_{22}$, 0.2 mL), C_{60} (0.044 g, 0.06 mmol, 3 mol%), and $ZnCl_2$ (2 mmol, 2 mL, 1 M solution in THF) were sequentially added to the flask, and the reaction mixture was stirred at room temperature or -10 ^oC for the time indicated in Table 3. The reaction progress was monitored by GC-analysis of reaction aliquots quenched by sat. NH_4Cl solution until it showed >95% conversion of the starting material. The yield of the insertion reaction was determined by GC-analysis of reaction aliquots quenched with a solution of iodine in anhydrous THF using an internal standard. The supernatant solution was carefully transferred to another predried and nitrogen-flushed Schlenk-flask by a syringe and used in subsequent reactions with electrophiles.

Typical procedure for the reaction of Grignard reagents with aldehyde (TP3):
The freshly prepared organomagnesium reagent was cooled to -20 ^oC with stirring and aldehyde (0.6-0.7 equiv) was added. The reaction mixture was stirred at -20 ^oC for 30 min before quenching with sat. NH_4Cl solution (20 mL) followed by extraction with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the analytically pure product.

Typical procedure for the allylation and acylation of organomagnesium or organozinc reagents (TP4):

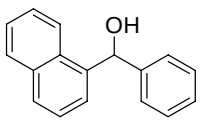
CuCN·2LiCl (0.4 mmol, 0.4 mL, 1 M in THF) was added to the freshly prepared organomagnesium or organozinc reagent at room temperature and stirred for 15 min. Then allyl bromide (0.6–0.7 equiv) was added and the reaction was stirred for 3 h at the same temperature. The reaction mixture was quenched with sat. NH_4Cl solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the analytically pure product.

Typical procedure for palladium-catalyzed cross-coupling reactions (TP5):

$ZnCl_2$ (2.0 mL, 1.0 M in THF, 2.0 mmol) was added to the freshly prepared organomagnesium reagent and the reaction mixture was stirred for 15 min (organozinc reagents were used directly). $Pd(OAc)_2$ (18 mg, 4 mol%) and S-Phos (66 mg, 8 mol %) were added, followed by the addition of the corresponding aryl halide (1.4 mmol, 0.7 equiv), and it was stirred at 60 °C for 12 h. The reaction mixture was quenched with sat. NH_4Cl solution (20 mL) and extracted with ethyl acetate (3x 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the analytically pure product.

Characterization data of products

Naphthalen-1-yl(phenyl)methanol (4a)



The organomagnesium reagent **2a** was prepared according to **TP1** from 1-chloronaphthalene (**1a**, 0.325 g, 2 mmol) at room temperature for 12 h in 84% yield. Reaction with benzaldehyde (**3a**, 0.148 g, 1.4 mmol, 0.7 equiv) was performed according to **TP3** at -20 ^{o}C for 30 min, leading to the corresponding alcohol **4a** in 82%

yield (270 mg) as a white solid. Spectroscopic data are in accordance with the reported data.[26]

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.06 (d, *J* = 8.0 Hz, 1H), 7.89 (dd, *J* = 16.9, 7.7 Hz, 2H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.54-7.29 (m, 8H), 6.50 (s, 1H), 2.73 (brs, 1H).

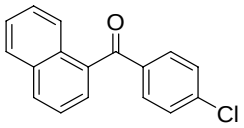
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 143.0, 138.7, 133.8, 130.6, 128.7, 128.4, 128.3, 127.5, 127.0, 126.0, 125.5, 125.2, 124.5, 123.9, 73.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3224, 1058, 989, 799, 781, 765, 755, 733, 696, 661.

MS (EI, 70 eV): m/z (%) = 235 (19), 234 (M^+, 90), 233 (12), 217 (13), 215 (33), 202 (14), 157 (12), 155 (23), 130 (11), 129 (100), 128 (86), 127 (32), 105 (84), 77 (23).

HRMS ($C_{17}H_{14}O$, EI): calc.: 234.1045; found: 234.1055 (M^+).

(4-Chlorophenyl)(naphthalen-1-yl)methanone (4b)



The organomagnesium reagent **2a** was prepared according to **TP1** from 1-chloronaphthalene (**1a**, 0.325 g, 2 mmol) at room temperature for 12 h in 84% yield. Acylation with 4-chlorobenzoyl chloride (**3e**, 0.245 g, 1.4 mmol, 0.7 equiv) was performed according to **TP4** using CuCN·2LiCl (0.4 mmol, 0.4 mL, 1 M in THF) at room temperature for 3 h, leading to the corresponding ketone **4b** in 77% yield (288 mg) as a pale yellow solid. Spectroscopic data are in accordance with the reported data.[27]

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.11-8.07 (m, 1H), 8.04-8.01 (m, 1H), 7.95-7.91 (m, 1H), 7.84-7.80 (m, 2H), 7.59-7.50 (m, 4H), 7.46-7.42 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 196.6, 139.6, 136.6, 135.8, 133.7, 131.6, 131.4, 130.8, 128.7, 128.4, 127.7, 127.3, 126.5, 125.5, 124.3.

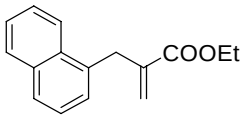
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1673, 1584, 1279, 1252, 1248, 1205, 1174, 1089, 1014, 909, 854, 798, 775, 754.

MS (EI, 70 eV): m/z (%) = 268 (31), 267 (28), 266 (M^+, 100), 265 (36), 231 (51), 202 (11), 155 (84), 138 (31), 127 (60), 126 (11), 111 (20), 101 (19), 75 (11).

[26] K. Li, N. Hu, R. Luo, W. Yuan, W. Tang, *J. Org. Chem.* **2013**, *78*, 6350.
[27] M. Cai**,** G. Zheng, G. Ding, *Green Chem.* **2009**, *11*, 1687.

HRMS ($C_{17}H_{11}ClO$, EI): calc.: 266.0498; found: 266.0510 (M^+).

Ethyl 2-(naphthalen-1-ylmethyl)acrylate (4c)



The organomagnesium reagent **2a** was prepared according to **TP1** from 1-chloronaphthalene (**1a**, 0.325 g, 2 mmol) at room temperature for 12 h in 84% yield. Allylation with ethyl 2-(bromomethyl)acrylate (**3g**, 0.27 g, 1.4 mmol, 0.7 equiv) was performed according to **TP4** using CuCN·2LiCl (0.4 mmol, 0.4 mL, 1 M in THF) at room temperature for 3 h, leading to the corresponding ester **4c** in 78% yield (262 mg) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.96-7.85 (m, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.54-7.42 (m, 3H), 7.38-7.35 (m, 1H), 6.26 (q, *J* = 1.3 Hz, 1H), 5.19 (q, *J* = 1.8 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.12 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

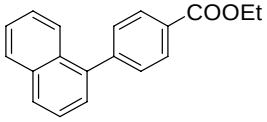
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.1, 139.6, 134.7, 133.9, 132.0, 128.6, 127.5, 127.3, 126.3, 125.9, 125.5, 125.5, 124.2, 60.8, 34.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1711, 1281, 1251, 1159, 1131, 1025, 947, 799, 791, 777.

MS (EI, 70 eV): m/z (%) = 240 (M^+, 41), 211 (13), 195 (13), 194 (12), 168 (13), 167 (97), 166 (49), 165 (100), 152 (18), 141 (11).

HRMS ($C_{16}H_{16}O_2$, EI): calc.: 240.1150; found: 240.1138 (M^+).

Ethyl 4-(naphthalen-1-yl)benzoate (4d)



The organomagnesium reagent **2a** was prepared according to **TP1** from 1-chloronaphthalene (**1a**, 0.325 g, 2 mmol) at room temperature for 12 h in 84% yield. Palladium-catalyzed cross-coupling with ethyl 4-iodobenzoate (**3h**, 0.386 g, 1.4 mmol, 0.7 equiv) was performed according to **TP5** using $ZnCl_2$ (2 mmol, 2 mL, 1 M in THF), $Pd(OAc)_2$ (18 mg, 4 mol%) and S-Phos (66 mg, 8 mol %) at 60 °C for 12 h, leading to

the corresponding ester **4d** in 91% yield (351 mg) as a pale yellow solid. Spectroscopic data are in accordance with the reported data.[28]

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.25 (d, *J* = 7.5 Hz, 2H), 7.97-7.90 (m, 3H), 7.63-7.45 (m, 6H), 4.50 (q, *J* = 7.2 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H).

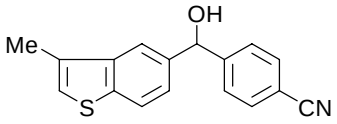
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 145.3, 139.0, 133.7, 131.1, 130.0, 129.4, 129.3, 128.3, 128.1, 126.8, 126.2, 125.8, 125.5, 125.2, 60.9, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1716, 1290, 1274, 1128, 1100, 1024, 801, 779, 770, 703.

MS (EI, 70 eV): m/z (%) = 277 (20), 276 (M^+, 100), 248 (12), 232 (10), 231 (49), 203 (42), 202 (53), 101 (17).

HRMS ($C_{19}H_{16}O_2$, EI): calc.: 276.1150; found: 276.1145 (M^+).

4-(Hydroxy(3-methylbenzo[b]thiophen-5-yl)methyl)benzonitrile (4e)



The organomagnesium reagent **2b** was prepared according to **TP1** from 5-chloro-3-methylbenzo[*b*]thiophene (**1b**, 0.365 g, 2 mmol) at room temperature for 22 h in 67% yield. Reaction with 4-formylbenzonitrile (**3b**, 0.157 g, 1.2 mmol, 0.6 equiv) was performed according to **TP3** at -20 °C for 30 min, leading to the corresponding alcohol **4e** in 68% yield (230 mg) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.78 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 1.7 Hz, 1H), 7.53-7.46 (m, 4H), 7.23 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.09 (d, *J* = 0.8 Hz, 1H), 5.91 (s, 1H), 3.31 (brs, 1H), 2.41 (d, *J* = 1.4 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.0, 139.8, 139.7, 138.7, 131.9, 126.8, 123.0, 122.7, 122.5, 119.6, 118.7, 110.5, 75.5, 13.7.

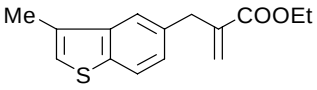
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3430, 2227, 1607, 1441, 1249, 1089, 1046, 1017, 833, 812, 765, 757, 735.

MS (EI, 70 eV): m/z (%) = 280 (17), 279 (M^+, 90), 263 (20), 262 (16), 246 (16), 177 (21), 176 (11), 175 (25), 150 (10), 149 (100), 147 (34), 134 (19), 130 (39), 115 (12), 104 (15), 103 (16), 102 (23), 77 (19).

HRMS ($C_{17}H_{13}NOS$, EI): calc.: 279.0718; found: 279.0729 (M^+).

[28] F.-Y. Mo, D. Qiu, Y.-B. Jiang, Y. Zhang, J.-B. Wang, *Tetrahedron Lett.* **2011**, *52*, 518.

Ethyl 2-((3-methylbenzo[*b*]thiophen-5-yl)methyl)acrylate (4f)



The organomagnesium reagent **2b** was prepared according to **TP1** from 5-chloro-3-methylbenzo[*b*]thiophene (**1b**, 0.365 g, 2 mmol) at room temperature for 22 h in 67% yield. Allylation with ethyl 2-(bromomethyl)acrylate (**3g**, 0.232 g, 1.2 mmol, 0.6 equiv) was performed according to **TP4** using CuCN·2LiCl (0.4 mmol, 0.4 mL, 1 M in THF) at room temperature for 3 h, leading to the corresponding ester **4f** in 70% yield (219 mg) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.77 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 0.8 Hz, 1H), 7.21 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.07 (d, *J* = 1.1 Hz, 1H), 6.26 (d, *J* = 1.1 Hz, 1H), 5.49 (q, *J* = 1.5 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 2.43 (d, *J* = 1.1 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

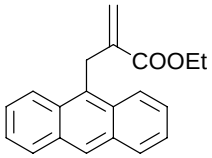
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.0, 140.7, 140.0, 138.4, 134.6, 131.9, 126.0, 125.6, 122.6, 122.0, 121.8, 60.7, 38.1, 14.2, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1712, 1630, 1443, 1367, 1299, 1276, 1249, 1198, 1189, 1129, 1090, 1026, 944, 834, 809, 771, 747, 730.

MS (EI, 70 eV): m/z (%) = 261 (15), 260 (M^+, 100), 231 (11), 215 (18), 187 (34), 186 (98), 185 (37), 172 (16), 171 (21), 161 (15).

HRMS ($C_{15}H_{16}O_2S$, EI): calc.: 260.0871; found: 260.0880 (M^+).

Ethyl 2-(anthracen-9-ylmethyl)acrylate (4g)



The organomagnesium reagent **2c** was prepared according to **TP1** from 9-chloroanthracene (**1c**, 0.426 g, 2 mmol) at room temperature for 1 h in 61% yield. Allylation with ethyl 2-(bromomethyl)acrylate (**3g**, 0.232 g, 1.2 mmol, 0.6 equiv) was performed according to **TP4** using CuCN·2LiCl (0.4 mmol, 0.4 mL, 1 M in THF) at room temperature for 3 h, leading to the corresponding ester **4g** in 65% yield (227 mg) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.44 (s, 1 H), 8.16 (d, *J* = 8.2 Hz, 2 H), 8.07-8.04 (m, 2 H), 7.56-7.48 (m, 4 H), 6.23 (s, 1 H), 4.85 (s, 1 H), 4.70 (s, 2 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 1.47 (t, *J* = 7.2 Hz, 3 H).

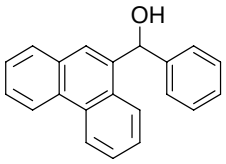
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.2, 138.9, 131.5, 130.3, 130.1, 129.0, 126.6, 126.2, 125.8, 124.8, 124.4, 60.9, 29.5, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1714, 1673, 1316, 1304, 1284, 1261, 1184, 1170, 1159, 1094, 1079, 1020, 967, 932, 763, 717, 693.

MS (EI, 70 eV): m/z (%) = 291 (20), 290 (M^+, 92), 245 (14), 244 (11), 218 (17), 217 (95), 216 (40), 215 (100), 213 (14), 202 (32), 191 (23), 189 (21).

HRMS ($C_{20}H_{18}O_2$, EI): calc.: 290.1307; found: 290.1321 (M^+).

Phenanthren-9-yl(phenyl)methanol (4h)



The organomagnesium reagent **2d** was prepared according to **TP1** from 9-bromophenanthrene (**1d**, 0.514 g, 2 mmol) at room temperature for 10 min in 79% yield. Reaction with benzaldehyde (**3a**, 0.148 g, 1.4 mmol, 0.7 equiv) was performed according to **TP3** at -20 °C for 30 min, leading to the corresponding alcohol **4h** in 85% yield (338 mg) as pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.76-8.67 (m, 2H), 8.03 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.97 (s, 1H), 7.91 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.71-7.60 (m, 3H), 7.55-7.44 (m, 3H), 7.38-7.30 (m, 3H), 6.51 (s, 1H), 2.51 (brs, 1H).

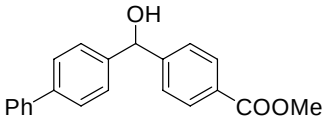
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 142.8, 136.7, 131.3, 130.8, 130.3, 129.7, 129.0, 128.6, 127.8, 127.2, 126.8, 126.7, 126.5, 126.2, 125.5, 124.9, 123.1, 122.4, 74.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3295, 1450, 1248, 1077, 1062, 985, 826, 810, 763, 743, 723, 696.

MS (EI, 70 eV): m/z (%) = 285 (15), 284 (M^+, 66), 265 (18), 180 (15), 179 (100), 177 (16), 176 (15), 77 (11).

HRMS ($C_{21}H_{16}O$, EI): calc.: 284.1201; found: 284.1193 (M^+).

Methyl 4-((1,1'-biphenyl)-4-yl-hydroxymethyl)benzoate (4i)



The organomagnesium reagent **2e** was prepared according to **TP1** from 4-bromobiphenyl (**1e**, 0.466 g, 2 mmol) at room temperature for 2 h in 70% yield. Reaction with methyl 4-formylbenzoate (**3c**, 0.23 g, 1.4 mmol, 0.7 equiv) was performed according to **TP3** at -20 °C for 30 min, leading to the corresponding alcohol **4i** in 75% yield (333 mg) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.03 (dd, *J* = 8.3, 1.7 Hz, 2H), 7.60-7.34 (m, 11H), 5.93 (s, 1H), 3.92 (s, 3H), 2.57 (brs, 1H).

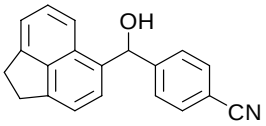
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.9, 148.6, 142.2, 140.8, 140.6, 129.8, 129.3, 128.8, 127.4, 127.1, 127.0, 126.3, 75.6, 52.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3466, 1689, 1438, 1293, 1286, 1120, 1109, 1031, 1016, 851, 804, 777, 757, 739, 711, 686.

MS (EI, 70 eV): m/z (%) = 319 (18), 318 (M^+, 100), 317 (14), 287 (10), 238 (10), 165 (13), 164 (23), 163 (67), 154 (42), 153 (26), 152 (35), 143 (10), 137 (46), 136 (14), 135 (13), 77 (30).

HRMS ($C_{21}H_{18}O_3$, EI): calc.: 318.1256; found: 318.1267 (M^+).

4-((1,2-Dihydroacenaphthylen-5-yl)(hydroxy)methyl)benzonitrile (4j)



The organomagnesium reagent **2f** was prepared according to **TP1** from 5-bromo-1,2-dihydroacenaphthylene (**1f**, 0.466 g, 2 mmol) at room temperature for 4 h in 74% yield. Reaction with 4-formylbenzonitrile (**3b**, 0.183 g, 1.4 mmol, 0.7 equiv) was performed according to **TP3** at -20 °C for 30 min, leading to the corresponding alcohol **4j** in 82% yield (330 mg) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.67 (d, *J* = 8.3 Hz, 1H), 7.59-7.53 (m, 4H), 7.46-7.40 (m, 2H), 7.32-7.25 (m, 2H), 6.40 (s, 1H), 3.40 (s, 4H), 2.67 (brs, 1H).

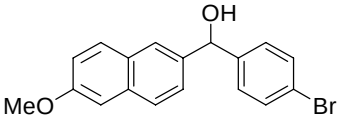
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 148.7, 147.1, 146.7, 139.8, 134.0, 132.1, 128.9, 128.3, 127.1, 127.0, 119.6, 119.2, 118.8, 118.8, 110.8, 73.1, 30.5, 29.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3172, 2230, 1607, 1500, 1368, 1302, 1266, 1140, 1047, 1029, 1016, 837, 783, 731, 708, 701.

MS (EI, 70 eV): m/z (%) = 286 (28), 285 (M^+, 100), 266 (13), 264 (11), 154 (19), 153 (39), 152 (37), 151 (13), 130 (19).

HRMS ($C_{20}H_{15}NO$, EI): calc.: 285.1154; found: 285.1155 (M^+).

(4-Bromophenyl)(6-methoxynaphthalen-2-yl)methanol (4k)



The organomagnesium reagent **2g** was prepared according to **TP1** from 2-bromo-6-methoxynaphthalene (**1g**, 0.474 g, 2 mmol) at room temperature for 1 h in 86% yield. Reaction with 4-bromobenzaldehyde (**3d**, 0.259 g, 1.4 mmol, 0.7 equiv) was performed according to **TP3** at -20 °C for 30 min, leading to the corresponding alcohol **4k** in 85% yield (410 mg) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.75-7.69 (m, 3H), 7.48-7.45 (m, 2H), 7.37-7.28 (m, 3H), 7.19-7.12 (m, 2H), 5.90 (s, 1H), 3.92 (s, 3H), 2.50 (brs, 1H).

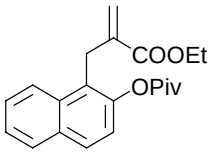
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.9, 142.7, 138.4, 134.1, 131.5, 129.5, 128.6, 128.3, 127.4, 125.1, 125.1, 121.3, 119.1, 105.7, 75.7, 55.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3287, 1647, 1606, 1482, 1390, 1263, 1229, 1217, 1196, 1167, 1029, 1008, 895, 857, 844, 814, 794, 774, 744.

MS (EI, 70 eV): m/z (%) = 344 (58), 343 (13), 342 (M^+, 52), 202 (13), 187 (15), 185 (21), 183 (20), 160 (12), 159 (100), 158 (13), 115 (14).

HRMS ($C_{18}H_{15}BrO_2$, EI): calc.: 342.0255; found: 342.0271 (M^+).

Ethyl 2-((2- pivaloyloxy)naphthalen-1-ylmethyl)acrylate (7a)



The organozinc reagent **6a** was prepared according to **TP2** from 1-bromonaphthalen-2-yl pivalate (**5a**, 0.61 g, 2 mmol) at –10 °C for 4 h in 83% yield. Allylation with ethyl 2-(bromomethyl)acrylate (**3g**, 0.27 g, 1.4 mmol, 0.7 equiv) was performed according

to **TP4** using CuCN·2LiCl (0.4 mmol, 0.4 mL, 1 M in THF) at room temperature for 3 h, leading to the corresponding ester **7a** in 80% yield (383 mg) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.89-7.80 (m, 3H), 7.54-7.45 (m, 2H), 7.23 (d, *J* = 8.8 Hz, 1H), 6.18-6.17 (m, 1H), 5.00 (td, *J* = 2.0, 0.9 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.03 (t, *J* = 2.0 Hz, 2H), 1.39 (s, 9H), 1.37 (q, *J* = 7.1 Hz, 3H).

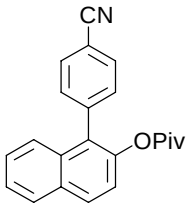
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 177.0, 167.0, 147.3, 137.8, 132.8, 131.8, 128.5, 128.3, 126.6, 126.0, 125.3, 124.7, 124.1, 121.6, 60.8, 39.2, 27.2, 27.0, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1749, 1711, 1277, 1251, 1210, 1106, 1026, 798, 742.

MS (EI, 70 eV): m/z (%) = 340 (M^+, 26), 256 (40), 210 (100), 183 (11), 182 (25), 181 (36), 165 (12), 152 (13), 57 (23).

HRMS ($C_{21}H_{24}O_4$, EI): calc.: 340.1675; found: 340.1671 (M^+).

1-(4-Cyanophenyl)naphthalen-2-yl pivalate (7b)



The organozinc reagent **6a** was prepared according to **TP2** from 1-bromonaphthalen-2-yl pivalate (**5a**, 0.61 g, 2 mmol) at –10 °C for 4 h in 83% yield. Palladium-catalyzed cross-coupling with 4-iodobenzonitrile (**3i**, 0.321 g, 1.4 mmol, 0.7 equiv) was performed according to **TP5** using $Pd(OAc)_2$ (18 mg, 4 mol%) and S-Phos (66 mg, 8 mol %) at 60 °C for 12 h, leading to the corresponding pivalate **7b** in 62% yield (288 mg) as a pale yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94 (t, *J* = 8.6 Hz, 2H), 7.81-7.77 (m, 2H), 7.54-7.40 (m, 5H), 7.27 (dd, *J* = 8.8, 1.6 Hz, 1H), 1.07 (s, 9H).

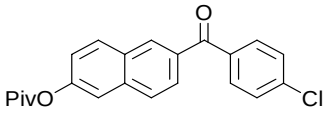
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 176.8, 145.6, 140.6, 132.5, 131.9, 131.6, 131.4, 129.9, 128.9, 128.2, 126.9, 125.7, 125.2, 121.4, 118.7, 111.6, 38.8, 26.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2227, 1754, 1462, 1393, 1272, 1230, 1204, 1116, 1101, 1031, 1024, 890, 843, 832, 805, 744, 678, 656.

MS (EI, 70 eV): m/z (%) = 329 (M^+, 15), 246 (20), 245 (90), 244 (19), 85 (18), 57 (100), 41 (15).

HRMS ($C_{22}H_{19}NO_2$, EI): calc.: 329.1416; found: 329.1409 (M^+).

6-(4-Chlorobenzoyl)naphthalen-2-yl pivalate (7c)



The organozinc reagent **6b** was prepared according to **TP2** from 6-bromonaphthalen-2-yl pivalate (**5b**, 0.61 g, 2 mmol) at –10 °C for 20 h in 75% yield. Acylation with 4-chlorobenzoyl chloride (**3e**, 0.245 g, 1.4 mmol, 0.7 equiv) was performed according to **TP4** using CuCN·2LiCl (0.4 mmol, 0.4 mL, 1 M in THF) at room temperature for 3 h, leading to the corresponding ketone **7c** in 63% yield (322 mg) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.24 (d, *J* = 0.8 Hz, 1H), 7.95-7.88 (m, 3H), 7.83-7.79 (m, 2H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.53-7.48 (m, 2H), 7.30 (dd, *J* = 9.0, 2.2 Hz, 1H), 1.43 (s, 9H).

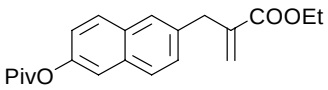
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 195.2, 177.0, 150.8, 138.8, 136.1, 135.9, 134.2, 131.5, 131.4, 130.8, 130.1, 128.7, 128.1, 126.3, 122.4, 118.5, 39.2, 27.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1754, 1650, 1623, 1586, 1469, 1274, 1202, 1146, 1135, 1120, 1103, 1090, 1028, 1014, 987, 923, 910, 892, 843, 822, 793, 744, 698.

MS (EI, 70 eV): m/z (%) = 366 (M^+, 25), 284 (23), 281 (13), 282 (76), 171 (54), 143 (15), 139 (16), 114 (11), 111 (13), 85 (24), 57 (100), 41 (10).

HRMS ($C_{22}H_{19}ClO_3$, EI): calc.: 366.1023; found: 366.1023 (M^+).

Ethyl 2-((6-pivaloyloxy)naphthalen-2-ylmethyl)acrylate (7d)



The organozinc reagent **6b** was prepared according to **TP2** from 6-bromonaphthalen-2-yl pivalate (**5b**, 0.61 g, 2 mmol) at –10 °C for 20 h in 75% yield. Allylation with ethyl 2-(bromomethyl)acrylate (**3g**, 0.27 g, 1.4 mmol, 0.7 equiv) was performed according to **TP4** using CuCN·2LiCl (0.4 mmol, 0.4 mL, 1 M in THF) at room temperature for 3 h, leading to the corresponding ester **7d** in 88% yield (420 mg) as a pale yellow solid.

MS (EI, 70 eV): m/z (%) = 341 (10), 340 (M^+, 39), 257 (16), 256 (100), 183 (15), 182 (47), 181 (22), 153 (16), 57 (40).

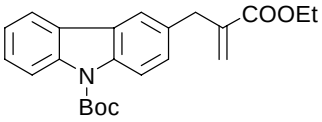
HRMS ($C_{21}H_{24}O_4$, EI): calc.: 340.1675; found: 340.1666 (M^+).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1742, 1711, 1325, 1214, 1203, 1159, 1139, 1122, 1107, 1028, 970, 934, 910, 822, 813, 652.

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 7.80 (d, *J* = 8.8 Hz, 1 H), 7.75 (d, *J* = 8.4 Hz, 1 H), 7.67 (s, 1 H), 7.53 (d, *J* = 2.1 Hz, 1 H), 7.36 (dd, *J* = 8.4, 1.5 Hz, 1 H), 7.20 (dd, *J* = 9.0, 2.2 Hz, 1 H), 6.30 (s, 1 H), 5.52 (d, *J* = 1.1 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.81 (s, 2 H), 1.43 (s, 9 H), 1.28 (t, *J* = 7.2 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 177.1, 166.7, 148.4, 140.1, 136.0, 132.4, 131.4, 128.8, 128.1, 127.5, 127.2, 126.1, 121.1, 118.1, 60.7, 39.0, 38.0, 27.1, 14.0.

tert-Butyl 3-(2-(ethoxycarbonyl)allyl)-9*H*-carbazole-9-carboxylate (7e)



The organozinc reagent **6c** was prepared according to **TP2** from *tert*-butyl 3-bromo-9*H*-carbazole-9-carboxylate (**5c**, 0.692 g, 2 mmol) at room temperature for 1 h in 79% yield. Allylation with ethyl 2-(bromomethyl)acrylate (**3g**, 0.27 g, 1.4 mmol, 0.7 equiv) was performed according to **TP4** using CuCN·2LiCl (0.4 mmol, 0.4 mL, 1 M in THF) at room temperature for 3 h, leading to the corresponding ester **7e** in 78% yield (414 mg) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.32 (d, *J* = 8.3 Hz, 1H), 8.24 (d, *J* = 8.6 Hz, 1H), 7.97 (dt, *J* = 7.7, 0.7 Hz, 1H), 7.83 (d, *J* = 1.9 Hz, 1H), 7.47 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H), 7.38-7.32 (m, 2H), 6.29 (d, *J* = 1.1 Hz, 1H), 5.53 (q, *J* = 1.3 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 2H), 1.78 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H).

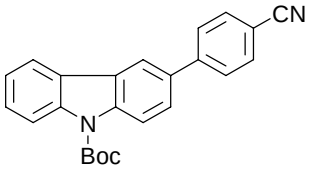
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.9, 151.0, 140.7, 138.7, 137.2, 133.5, 128.1, 127.0, 125.9, 125.9, 125.6, 122.9, 119.9, 119.5, 116.2, 116.1, 83.7, 60.7, 37.9, 28.3, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1715, 1449, 1357, 1322, 1303, 1253, 1221, 1193, 1151, 1116, 1027, 943, 810, 766, 746.

MS (EI, 70 eV): m/z (%) = 379 (M^+, 19), 324 (17), 323 (100), 279 (52), 278 (11), 250 (14), 249 (28), 233 (19), 206 (22), 205 (54), 204 (48), 180 (14), 57 (82), 41 (14).

HRMS ($C_{23}H_{25}NO_4$, EI): calc.: 379.1784; found: 379.1770 (M^+).

***tert*-Butyl 3-(4-cyanophenyl)-9*H*-carbazole-9-carboxylate (7f)**



The organozinc reagent **6c** was prepared according to **TP2** from *tert*-butyl 3-bromo-9*H*-carbazole-9-carboxylate (**5c**, 0.692 g, 2 mmol) at room temperature for 1 h in 79% yield. Palladium-catalyzed cross-coupling with 4-iodobenzonitrile (**3i**, 0.321 g, 1.4 mmol, 0.7 equiv) was performed according to **TP5** using $Pd(OAc)_2$ (18 mg, 4 mol%) and S-Phos (66 mg, 8 mol %) at 60 °C for 12 h, leading to the corresponding benzonitrile **7f** in 69% yield (355 mg) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.41 (d, *J* = 8.9 Hz, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 8.17 (d, *J* = 1.9 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.81-7.74 (m, 4H), 7.69 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.52 (td, *J* = 7.8, 1.2 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 1.80 (s, 9H).

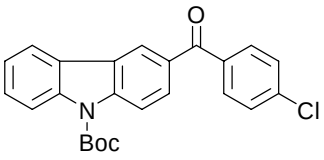
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.9, 145.6, 138.9, 138.7, 134.0, 132.6, 127.7, 127.6, 126.4, 126.1, 125.3, 123.2, 119.6, 119.0, 118.1, 116.8, 116.4, 110.5, 84.3, 28.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2216, 1712, 1600, 1476, 1451, 1363, 1326, 1253, 1216, 1159, 1120, 809, 767, 744, 727.

MS (EI, 70 eV): m/z (%) = 368 (M^+, 2), 312 (9), 269 (22), 268 (100), 267 (13), 266 (13), 134 (9), 57 (9).

HRMS ($C_{24}H_{20}N_2O_2$, EI): calc.: 368.1525; found: 368.1507 (M^+).

***tert*-Butyl 3-(4-chlorobenzoyl)-9*H*-carbazole-9-carboxylate (7g)**



The organozinc reagent **6c** was prepared according to **TP2** from *tert*-butyl 3-bromo-9*H*-carbazole-9-carboxylate (**5c**, 0.692 g, 2 mmol) at room temperature for 1 h in 79% yield. Acylation with 4-chlorobenzoyl chloride (**3e**, 0.245 g, 1.4 mmol, 0.7 equiv) was

performed according to **TP4** using CuCN·2LiCl (0.4 mmol, 0.4 mL, 1 M in THF) at room temperature for 3 h, leading to the corresponding ketone **7g** in 71% yield (402 mg) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.44 (s, 1H), 8.41 (d, *J* = 8.6 Hz, 1H), 8.32 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.91 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.81-7.78 (m, 2H), 7.55-7.47 (m, 3H), 7.38 (t, *J* = 7.5 Hz, 1H), 1.80 (s, 9H).

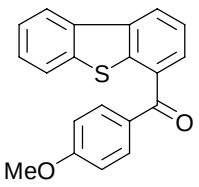
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 194.9, 150.6, 141.1, 139.0, 138.5, 136.4, 131.8, 131.3, 129.2, 128.5, 127.8, 125.7, 125.1, 123.4, 121.9, 119.9, 116.3, 115.8, 84.6, 28.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1726, 1660, 1598, 1450, 1351, 1320, 1262, 1220, 1150, 1118, 1084, 956, 836, 772, 755, 725.

MS (EI, 70 eV): m/z (%) = 405 (M^+, 5), 349 (21), 332 (26), 307 (27), 306 (18), 305 (77), 195 (15), 194 (100), 166 (36), 139 (16), 111 (10), 57 (34), 44 (15), 43 (30), 41 (16).

HRMS ($C_{24}H_{20}ClNO_3$, EI): calc.: 405.1132; found: 405.1128 (M^+).

(4-Dibenzothienyl)(4-methoxyphenyl)methanone (7h)



The organozinc reagent **6d** was prepared according to **TP2** from 4-bromodibenzothiophene (**5d**, 0.526 g, 2 mmol) at room temperature for 1 h in 84% yield. Acylation with 4-methoxybenzoyl chloride (**3f**, 0.239 g, 1.4 mmol, 0.7 equiv) was performed according to **TP4** using CuCN·2LiCl (0.4 mmol, 0.4 mL, 1 M in THF) at room temperature for 3 h, leading to the corresponding ketone **7h** in 85% yield (381 mg) as a pale yellow solid.

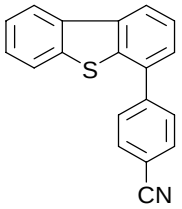
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.38 (dd, *J* = 7.7, 1.1 Hz, 1H), 8.23-8.20 (m, 1H), 7.97-7.83 (m, 4H), 7.58-7.47 (m, 3H), 7.04-6.99 (m, 2H), 3.90 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 194.5, 162.9, 141.6, 140.7, 137.3, 134.1, 132.2, 130.8, 130.8, 130.5, 127.1, 125.2, 124.4, 123.6, 122.7, 121.4, 113.6, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1639, 1597, 1507, 1391, 1308, 1276, 1252, 1174, 1161, 1094, 1026, 958, 840, 746, 724, 696

MS (EI, 70 eV): m/z (%) = 319 (20), 318 (M^+, 100), 211 (12), 139 (10), 135 (97).
HRMS ($C_{20}H_{14}O_2S$, EI): calc.: 318.0715; found: 318.0699 (M^+).

4-(4-Dibenzothienyl)benzonitrile (7i)



The organozinc reagent **6d** was prepared according to **TP2** from 4-bromodibenzothiophene (**5d**, 0.526 g, 2 mmol) at room temperature for 1 h in 84% yield. Palladium-catalyzed cross-coupling with 4-iodobenzonitrile (**3i**, 0.321 g, 1.4 mmol, 0.7 equiv) was performed according to **TP5** using $Pd(OAc)_2$ (18 mg, 4 mol%) and S-Phos (66 mg, 8 mol %) at 60 ^oC for 12 h, leading to the corresponding benzonitrile **7i** in 80% yield (319 mg) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.22-8.17 (m, 2H), 7.87-7.76 (m, 5H), 7.60-7.44 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 145.0, 139.1, 138.1, 136.5, 135.4, 134.8, 132.5, 128.8, 127.1, 126.8, 125.2, 124.6, 122.5, 121.8, 121.5, 118.7, 111.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2223, 1604, 1440, 1377, 1098, 1017, 842, 832, 800, 744, 722.

MS (EI, 70 eV): m/z (%) =286 (18), 285 (M^+, 100), 283 (15), 143 (6).

HRMS ($C_{19}H_{11}NS$, EI): calc.: 285.0612; found: 285.0625 (M^+).

Chapter 4. One-pot Preparation of Functionalized Tribenzylindium and Trialkylindium Reagents via Magnesium Insertion into Benzyl Halides and Alkyl Halides in the Presence of Indium Trichloride and Lithium Chloride

4.1 Introduction

The conversion of organic halides to organometallics by direct metal insertion (the Grignard reaction) is a very general method. Especially, the LiCl-mediated insertion of Mg,[1] Zn,[2] Al,[3] Mn,[4] and In[5] has proven to be very effective and provides an access to a range of functionalized organometallic reagents which can be readily used for cross-couplings [6] and other reactions with electrophiles. [7] Nevertheless, some functionalized halides like for example 4-bromobenzonitrile (**1a**) do not insert magnesium under standard conditions requiring a specific optimization due to radical side-reactions. Takai has first reported the beneficial effect of indium(III) halides for facilitating the insertion of aluminium metal to allylic halides.[8] This observation proved to solve the erratic direct insertion of magnesium to the bromonitrile **1a** and led us to develop a new general one-pot procedure for the preparation of triorganoindium compounds starting from various organic halides (chlorides and

[1] (a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; (b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192; (c) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824; (d) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082.

[2] (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.

[3] (a) T. D. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313; (b) L.-N. Guo, H. Gao, P. Mayer, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 9829; (c) Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 8516; (d) T. D. Blümke, K. Groll, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2011**, *13*, 6440.

[4] Z. Peng, P. Knochel, *Org. Lett.* **2011**, *13*, 3198.

[5] (a) Y.-H. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648; (b) V. Papoian, T. Minehan, *J. Org. Chem.* **2008**, *73*, 7376; (c) Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236.

[6] (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed; A. de Meijere, F. Diederich, Eds.; Wiley-VCH: Weinheim, **2004**; (b) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062; (c) V. F. Slagt, A. H. M. de Vries, J. G. de Vries, R. M. Kellog, *Org. Process Res. Dev.* **2010**, *14*, 30.

[7] *Handbook of Functionalized Organometallics*; P. Knochel, Ed.; Wiley-VCH: Weinheim, **2005**.

[8] (a) K. Takai, Y. Ikawa, *Org. Lett.* **2002**, *4*, 1727; for the $InCl_3$-mediated preparation of 1,2-dimetallics, see also: (b) T. D. Blümke, T. Klatt, K. Koszinowki, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9926.

bromides). Organoindiums are versatile organometallic intermediates for organic synthesis as they display a high functional group tolerance and are mainly prepared by transmetalation reactions.[9]

4.2 Results and Discussion

A direct insertion of indium powder is only possible with activated organic halides and requires a large excess of this expensive metal.[5,10] However, the treatment of **1a** (1.00 equiv) with magnesium turnings (2.50 equiv) in the presence LiCl (2.50 equiv) and $InCl_3$ (0.33 equiv) at room temperature in THF for 4 h leads to the corresponding triorganoindium reagent **2a** in good yield (77 %; Scheme 1).[11] No excess of indium(III) is necessary under these conditions. Iodolysis followed by gas-chromatographic analysis showed complete conversion and more importantly the absence of significant amounts of side-products. Sarandeses and co-workers pioneered and further established Pd-catalyzed cross-couplings of organoindium reagents.[12] Interestingly, a Pd-catalyzed cross-coupling of tri(4-cyanophenyl)indium **2a** using Buchwald's ligand (S-Phos)[13] led to a smooth cross-coupling with ethyl 4-

[9] (a) S. Araki, T. Hirashita, In *Comprehensive Organometallic Chemistry III, Vol. 9;* P. Knochel, Ed.; Pergamon: Oxford, **2007**; p. 649; (b) P. Cintas, *Synlett* **1995**, 1087; (c) C.-J. Li, T.-H. Chan, *Tetrahedron* **1999**, *55*, 11149, (d) B. C. Ranu, *Eur. J. Org. Chem.* **2000**, 2347; (e) T. P. Loh, G. L. Chua, *Chem. Commun.* **2006**, 2739; (f) J. Augé, N. Luben-Germain, J. Uziel, *Synthesis* **2007**, 1739.

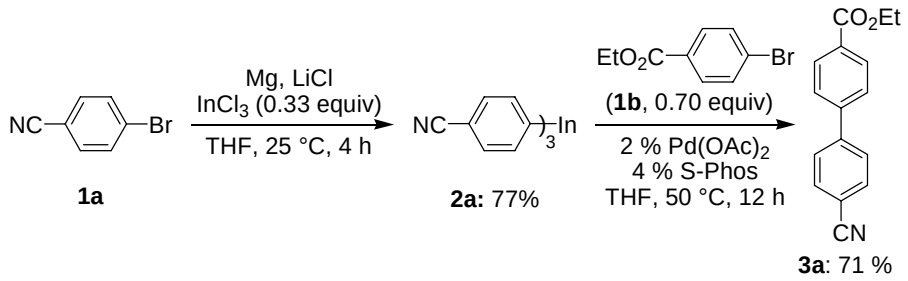
[10] (a) N. Fujiwara, Y. Yamamoto, *J. Org. Chem.* **1999**, *64*, 4095; (b) N. W. E. Tyrra, *J. Fluorine Chem.* **2001**, *112*, 149; (c) L. S. Chupak, J. P. Wolkowski, Y. A. Chantigny, *J. Org. Chem.* **2009**, *74*, 1388; (d) K. Koszinowski, *J. Am. Chem. Soc.* **2010**, *132*, 6032; (e) Z. L. Shen, K. K. K. Goh, Y. S. Yang, Y. C. Lai, C. H. A. Wong, H. L. Cheong, T. P. Loh, *Angew. Chem. Int. Ed.* **2011**, *50*, 511; (f) Z. L. Shen, K. K. K. Goh, C. H. A. Wong, Y. S. Yang, Y. C. Lai, H. L. Cheong, T. P. Loh, *Chem. Commun.* **2011**, *47*, 4778; (g) L. Adak, N. Yoshikai, *J. Org. Chem.* **2011**, *76*, 7563.

[11] This part of work involving the preparation of triarylindium reagents starting from aryl halides was performed by my collaborator, Dr. Sebastian Bernhardt. See: Sebastian Bernhardt, Dissertation, LMU-Muenchen, 2012. To make the completeness of this project, two typical examples using substrates **1a** and **4b** (Schemes 1 and 2) is described here.

[12] (a) M. A. Pena, J. Pérez Sestelo, L. A. Sarandeses, *Synthesis* **2005**, 485; (b) I. Pérez, J. Pérez Sestelo, L. A. Sarandeses, *Org. Lett.* **1999**, *1*, 1267; (c) I. Pérez, J. Pérez Sestelo, L. A. Sarandeses, *J. Am. Chem. Soc.* **2001**, *123*, 4155; (d) I. Pérez, J. Pérez Sestelo, L. A. Sarandeses, *Chem. Commun.* **2002**, 2246; (e) D. Rodríguez, J. Pérez Sestelo, L. A. Sarandeses, *J. Org. Chem.* **2004**, *69*, 8136; (f) R. Riveiros, D. Rodríguez, J. Pérez Sestelo, L. A. Sarandeses, *Org. Lett.* **2006**, *8*, 1403; (g) M. A. Pena, J. Pérez Sestelo, L. A. Sarandeses, *J. Org. Chem.* **2007**, *72*, 1271; (h) R. Riveiros, L. Saya, J. Pérez Sestelo, L. A. Sarandeses, *Eur. J. Org. Chem.* **2008**, 1959; (i) Á. Mosquera, R. Riveiros, J. Pérez Sestelo, L. A. Sarandeses, *Org. Lett.* **2008**, *10*, 3745; (j) L. Bouissane, J. Pérez Sestelo, L. A. Sarandeses, *Org. Lett.* **2009**, *11*, 1285; (k) M. Montserrat Martínez, M. Peña-López, J. Pérez Sestelo, L. A. Sarandeses, *Org. Biomol. Chem.* **2012**, *10*, 3892.

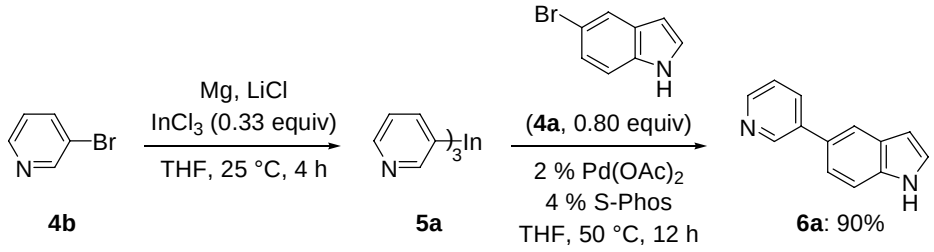
[13] (a) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871; (b) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*,

bromobenzoate (**1b**; THF, 50 °C, 12 h) providing the desired biphenyl **3a** in 71 % yield.



Scheme 1. Preparation of tri(4-cyanophenyl)indium **2a** from 4-bromobenzonitrile (**1a**) *via* Mg insertion in the presence of LiCl and $InCl_3$ and subsequent Pd-catalyzed cross-coupling

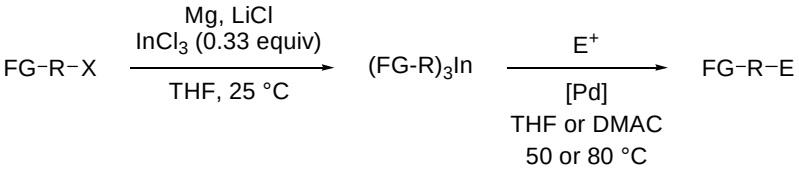
The method could also be applied to the preparation of heteroaromatic indium reagents. Thus, 3-bromopyridine (**4b**) was reacted with Mg turnings, LiCl, and $InCl_3$ (1.50, 1.50, and 0.33 equiv, respectively) at 25 ^{o}C in THF and after 4 h full conversion to the corresponding organometallic reagent **5a** was detected by GC-MS analysis of a reaction aliquot. The tri(3-pyridyl)indium reagent **5a** could be coupled with the unprotected 5-bromoindole (**4a**) by using $Pd(OAc)_2$ (2%) and S-Phos (4%), leading to the heteroarylated indole **6a** in 90% yield (Scheme 2).



Scheme 2. Preparation of tri(3-pyridyl)indium **5a** from 3-bromopyridine (**4b**) by means of Mg insertion in the presence of LiCl and $InCl_3$ and subsequent Pd-catalyzed cross-coupling.

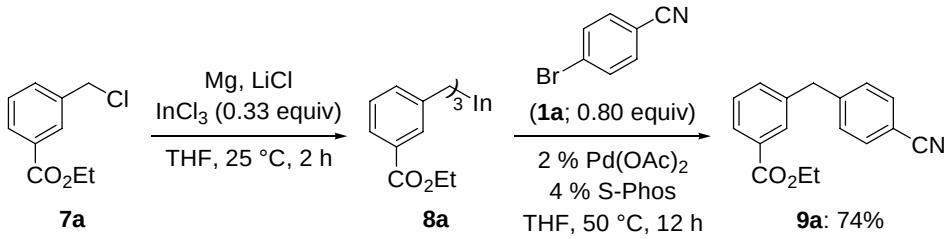
In addition, we observed that this preparation is general and applicable to alkyl bromides and benzyl chlorides. In all cases the resulting indium reagents react well with aryl halides in the presence of a palladium catalyst (Scheme 3).

4685; (c) R. A. Altman, S. L. Buchwald, *Nat. Protoc.* **2007**, *2*, 3115; (d) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.



Scheme 3. Preparation of triorganoindium reagents *via* Mg insertion in the presence of LiCl and $InCl_3$. X = Br, Cl; Y = Br, I; R = benzyl, alkyl; E = aryl, heteroaryl; [Pd] = $PdCl_2(PPh_3)_2$ (4 %)

The one-pot *in situ* transmetalation procedure using Mg/LiCl/$InCl_3$ was also efficiently used for the preparation of tribenzylindiums of type **8** starting from benzyl chlorides and bromides of type **7**. Thus, the reaction of Mg-turnings (1.50 equiv) with ethyl 3-(chloromethyl)benzoate (**7a**) in the presence of LiCl (1.50 equiv) and $InCl_3$ (0.33 equiv) in THF led to the tri(3-(ethoxycarbonyl)benzyl)indium reagent **8a** after 2 h at 25 °C. Direct cross-coupling in THF with 4-bromobenzonitrile (**1a**) using $Pd(OAc)_2$ (2 %) and S-Phos (4 %) as the catalytic system produced the diarylmethane **9a** in 74 % yield after 12 h of reaction time (Scheme 4).

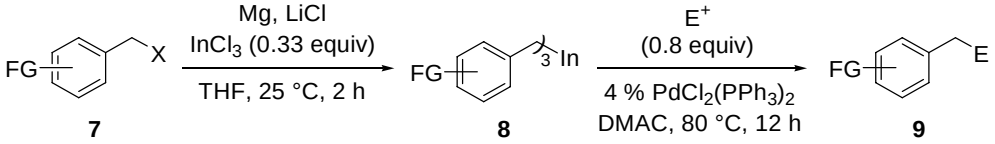


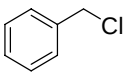
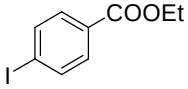
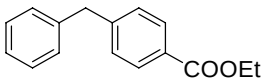
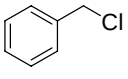
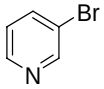
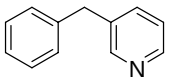
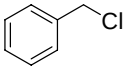
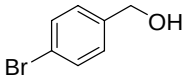
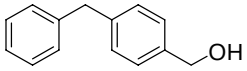
Scheme 4. Preparation of tri(3-(ethoxycarbonyl)benzyl)indium **8a** from ethyl 3-(chloromethyl)benzoate (**7a**) *via* Mg insertion in the presence of LiCl and $InCl_3$ and subsequent Pd-catalyzed cross-coupling

Tribenzylindium **8b** prepared from benzyl chloride (**7b**) reacted efficiently with ethyl 4-iodobenzoate (**1c**) and 3-bromopyridine (**4b**) and the coupling products were obtained in 75-88 % yield (entries 1-2, Table 1) after 12 h of reaction time. For these insertions, the use of lower amounts of magnesium turnings (1.2 equiv) proved to be sufficient. Here, *N*,*N*-dimethylacetamide (DMAC) was used as solvent, the reaction temperature was raised to 80 °C and $PdCl_2(PPh_3)_2$ (4 %) was used as the catalytic system. These reaction conditions proved to be superior to the use of the combination $Pd(OAc)_2$/S-Phos/THF/50 °C and were also used for the subsequent described

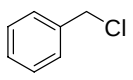
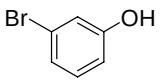
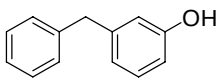
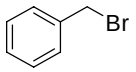
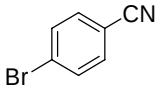
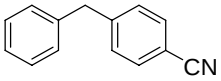
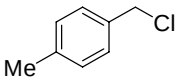
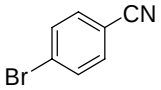
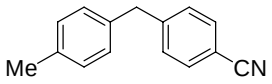
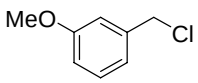
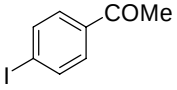
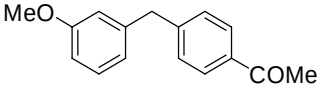
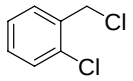
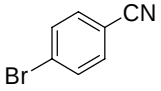
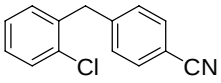
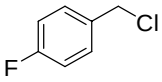
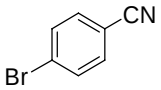
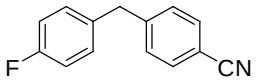
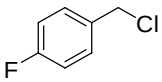
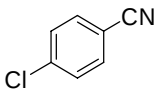
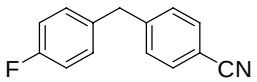
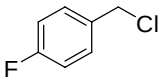
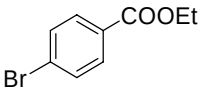
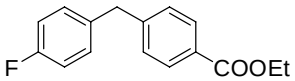
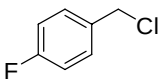
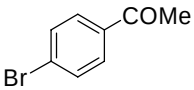
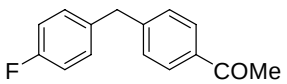
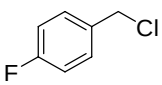
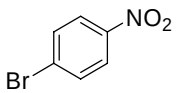
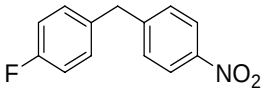
coupling reactions in Table 3.[14] Remarkably, tribenzylindium **8b** could also be coupled with (4-bromophenyl)methanol (**1n**; 0.80 equiv in respect to 1.00 equiv of benzyl chloride (**7b**) used for the preparation of **8b**) and 3-bromophenol (**1o**; 0.60 equiv in respect to 1.00 equiv of benzyl chloride (**7b**) used for the preparation of **8b**) in 77-82 % yield under the optimized reaction conditions (entries 3-4). The acidic proton of the alcohol function does not disturb the cross-coupling. Moreover, tribenzylindium **8b** was also efficiently generated from benzyl bromide (**7c**) and yielded after cross-coupling the benzonitrile **9f** in 78 % yield (entry 5). In the same manner, tri(4-methylbenzyl)indium **8c** was arylated with 4-bromobenzonitrile (**1a**) in 84 % yield (entry 6). The 3-methoxybenzyl- and 2-chlorobenzylindium reagents **8d** and **8e** could also be prepared and coupled in good yields (76-91 %, entries 7-8). Tri(4-fluorobenzyl)indium **8f** proved also to be accessible under the standard conditions and reacted with a variety of aryl bromides and 4-chlorobenzonitrile (**1q**) in 81-95 % yield (entries 9-13).

Table 1. Cross-coupling of tribenzylindium reagents of type **8** obtained from benzyl halides **7** by Mg insertion in the presence of LiCl and $InCl_3$ with different organic halides as electrophiles[a]



Entry	Benzyl halide (**7**)	E^+	Product (Yield)[b]
1	 **7b**	 **1c**	 **9b** (88%)
2	 **7b**	 **4b**	 **9c** (75%)
3	 **7b**	 **1n**	 **9d** (77%)

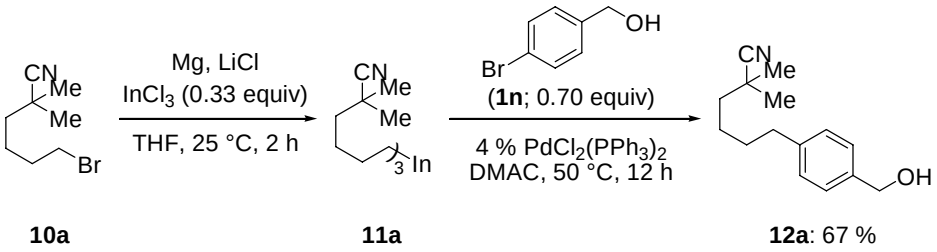
[14] Because of the relatively low reactivity of benzylindium[5c] and alkylindium reagents[10e] as compared to the arylindium counterparts,[5a] a poor yield was obtained when the cross-coupling was carried out using $Pd(OAc)_2$/S-Phos catalytic system in THF. Thus, the comparatively more robust catalytic system [$PdCl_2(PPh_3)_2$/DMAC][10e] was employed for the subsequent cross-coupling reactions using tribenzylindium and trialkylindium reagents.

			
4	**7b**	**1o**[c]	**9e** (82%)
			
5	**7c**	**1a**	**9f** (78%)
			
6	**7d**	**1a**	**9g** (84%)
			
7	**7e**	**1p**	**9h** (91%)
			
8	**7f**	**1a**	**9i** (76%)
			
9	**7g**	**1a**	**9j** (87%)
			
10	**7g**	**1q**	**9j** (82%)
			
11	**7g**	**1b**	**9k** (95%)
			
12	**7g**	**1r**	**9l** (92%)
			
13	**7g**	**1s**	**9m** (81%)

[a] Mg-turnings (1.20 equiv), LiCl (1.20 equiv), $InCl_3$ (0.33 equiv) were used for the preparation of the tribenzylindium reagent. [b] Isolated yield of analytically pure product. [c] 0.60 equiv of electrophile was used.

The treatment of alkyl bromides with magnesium-turnings in the presence of $InCl_3$ and LiCl gives also access to trialkylindium reagents of type **11**. Thus, tri(5-cyano-5-methylhexyl)indium **11a** was prepared from 6-bromo-2,2-dimethylhexanenitrile (**10a**) in 2 h at 25 °C in THF using 1.20 equiv of Mg/LiCl. Cross-coupling with (4-

bromophenyl)methanol (**1n**) in DMAC using 4 % of $PdCl_2(PPh_3)_2$ as catalyst afforded the alkylated benzyl alcohol derivative **12a** in 67 % yield (Scheme 5).



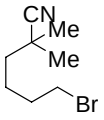
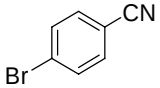
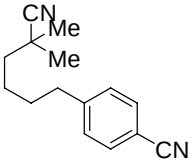
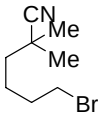
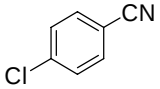
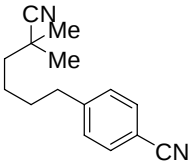
10a **11a** **12a**: 67 %

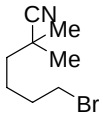
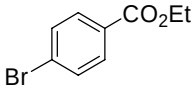
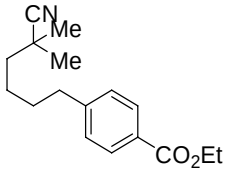
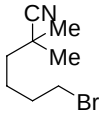
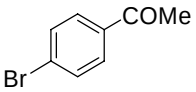
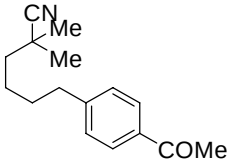
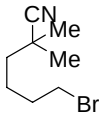
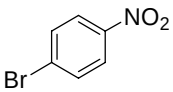
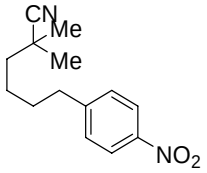
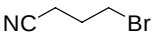
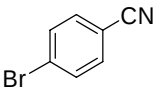
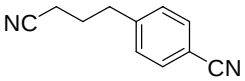
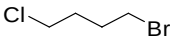
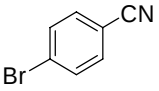
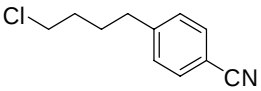
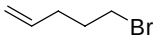
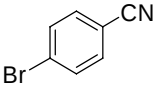
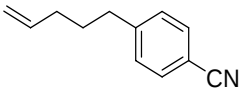
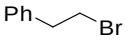
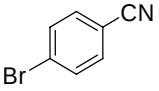
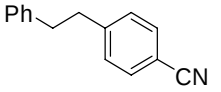
Scheme 5. Preparation of tri(5-cyano-5-methylhexyl)indium **11a** from 6-bromo-2,2-dimethylhexanenitrile (**10a**) *via* Mg insertion in the presence of LiCl and $InCl_3$ and subsequent Pd-catalyzed cross-coupling

Moreover, tri(5-cyano-5-methylhexyl)indium **11a** was coupled with a range of different aryl bromides as well as 4-chlorobenzonitrile (**1q**) in 75-93 % yield (Table 2, entries 1-5). Tri(3-cyanopropyl)indium **11b** and tri(4-chlorobutyl)indium **11c** could also be efficiently generated from the corresponding alkyl bromides **10b** and **10c** and reacted well in a cross-coupling reaction with 4-bromobenzonitrile (**1a**; 61-85 % yield; entries 6-7). Furthermore, tri(pent-4-en-1-yl)indium **11d** and tri(phenethyl)indium (**11e**) were arylated with 4-bromobenzonitrile (**1a**) in 87-94 % yield (entries 8-9).

Table 2. Cross-coupling of trialkylindium reagents of type **11** obtained from alkyl bromides **10** by Mg insertion in the presence of LiCl and $InCl_3$ with different organic halides as electrophiles[a]

10 **11** **12**

Entry	Alkyl-Br	E^+	Product (Yield)[b]
1	 **10a**	 **1a**	 **12b** (93%)
			

2	**10a** 	**1q** 	**12b** (75%) 
3	**10a** 	**1b** 	**12c** (85%) 
4	**10a** 	**1r** 	**12d** (83%) 
5	**10a** 	**1s** 	**12e** (77%) 
6	**10b** 	**1a** 	**12f** (85%) 
7	**10c** 	**1a** 	**12g** (61%) 
8	**10d** 	**1a** 	**12h** (87%) 
9	**10e**	**1a**	**12i** (94%)

[a] Mg-turnings (1.20 equiv), LiCl (1.20 equiv), $InCl_3$ (0.33 equiv) were used for the preparation of the trialkylindium reagent. [b] Isolated yield of analytically pure product.

4.3 Conclusion

In conclusion we have developed a new efficient one-pot procedure that enables a direct preparation of triorganoindium reagents from organic halides *via* a magnesium insertion in the presence of $InCl_3$ and LiCl. Starting from functionalized alkyl

bromides and benzyl chlorides the corresponding organoindium reagents are accessible at 25 °C within 4 h in good yields. Moreover, the obtained organoindium reagents could undergo efficiently Pd-catalyzed cross-coupling reactions.

4.4 Experimental

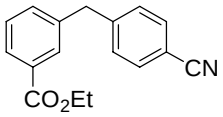
General Information

All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC. Column chromatography was performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck. All reagents were obtained from commercial sources. Magnesium turnings (> 99.5 %) were obtained from Fluka. $InCl_3$ was obtained from Rockwood Lithium Holdings, Inc.

Preparation of Tribenzylindium and Trialkylindium Reagents and Subsequent Cross-Coupling (TP1):

LiCl (102 mg, 2.4 mmol, 1.2 equiv) and $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv) were placed in a *Schlenk*-flask, equipped with a magnetic stirrer and a septum, dried for 5 min at 400 °C (heat gun) in high vacuum and then dissolved in dry THF. The organic halide (2.00 mmol, 1.00 equiv) was added and the mixture was stirred for 2 min at 25 °C. Magnesium turnings (58.4 mg, 2.4 mmol, 1.2 equiv) were added and the reaction mixture was stirred for the given time at 25 °C until GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was carefully transferred to a new dry and argon-flushed *Schlenk*-flask and THF was removed *in vacuo*. Subsequently, DMAC (4 mL), the organic halide (0.6~0.8 equiv) and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the desired product.

Ethyl 3-(4-cyanobenzyl)benzoate (9a)



The organoindium reagent was prepared according to **TP1** from ethyl 3-(chloromethyl)benzoate (**7a**; 397 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (127 mg, 3.0 mmol, 1.50 equiv) and magnesium turnings (73 mg, 3.00 mmol, 1.50 equiv) in dry THF (4 mL). The supernatant solution was added to a solution of $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), S-Phos (32.0 mg, 0.08 mmol) and 4-bromobenzonitrile (**1a**; 291 mg, 1.60 mmol, 0.8 equiv) in dry THF (2 mL). The mixture was stirred for 12 h at 50 °C. Then, sat. aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with AcOEt (3 × 20 mL). Purification by flash chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the diphenylmethane **9a** (316 mg, 74 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.93-7.90 (m, 1H), 7.87-7.85 (m, 1H), 7.59-7.55 (m, 2H), 7.40-7.30 (m, 2H), 7.28-7.25 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.87 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

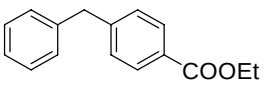
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 146.0, 139.6, 133.4, 132.4, 131.0, 130.0, 129.6, 128.8, 127.9, 118.9, 110.3, 61.1, 41.7, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981 (w), 2227 (m), 1712 (vs), 1605 (m), 1587 (w), 1503 (w), 1443 (m), 1366 (m), 1278 (vs), 1185 (s), 1104 (s), 1080 (m), 1020 (m), 934 (w), 853 (m), 812 (m), 758 (m), 736 (s), 697 (m), 670 (w).

MS (EI, 70 eV): m/z (%) = 265 (M^+, 45), 237 (38), 220 (100), 190 (48), 177 (27), 165 (27), 151 (15), 130 (13).

HRMS ($C_{17}H_{15}NO_2$): calc.: 265.1103; found: 265.1095 (M^+).

Ethyl 4-benzylbenzoate (9b)



The organoindium reagent was prepared according to **TP1** from benzyl chloride (**7b**; 251 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to

another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), ethyl 4-iodobenzoate (**1c**; 442 mg, 1.6 mmol, 0.8 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the diphenylmethane **9b** (337 mg, 88 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.05-8.01 (m, 2H), 7.37-7.21 (m, 7H), 4.41 (q, *J* = 7.11 Hz, 2H), 4.07 (s, 2H), 1.42 (t, *J* = 7.11 Hz, 3H).

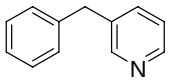
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.5, 146.3, 140.1, 129.7, 128.9, 128.8, 128.5, 128.4, 126.3, 60.7, 41.8, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1712 (s), 1610 (m), 1495 (m), 1453 (w), 1414 (m), 1366 (m), 1270 (vs), 1176 (m), 1098 (s), 1020 (s), 753 (s), 740 (s), 702 (s), 695 (s).

MS (EI, 70 eV): m/z (%) = 241 (10), 240 (M^+, 59), 212 (11), 196 (15), 195 (100), 168 (15), 167 (99), 166 (18), 165 (55), 152 (29), 105 (19), 91 (15), 77 (11), 43 (13).

HRMS ($C_{16}H_{16}O_2$): calc.: 240.1150; found: 240.1146 (M^+).

3-Benzylpyridine (9c)



The organoindium reagent was prepared according to **TP1** from benzyl chloride (**7b**; 251 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 3-bromopyridine (**4b**; 253 mg, 1.6 mmol, 0.8 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the diphenylmethane **9c** (202 mg, 75 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.52-8.46 (m, 2H), 7.46 (d, *J* = 7.85 Hz, 1H), 7.34-7.16 (m, 6H), 3.97 (s, 2H).

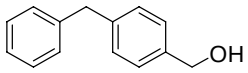
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.0, 147.5, 139.7, 136.4, 136.2, 128.7, 128.6, 126.4, 123.3, 38.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1571 (w), 1493 (m), 1478 (m), 1453 (m), 1421 (s), 1074 (m), 1027 (m), 777 (m), 743 (s), 712 (s), 697 (vs).

MS (EI, 70 eV): m/z (%) = 169 (M^+, 49), 168 (50), 167 (13), 70 (11), 61 (14), 45 (14), 43 (100).

HRMS ($C_{12}H_{11}N$): calc.: 169.0891; found: 169.0905 (M^+).

(4-Benzylphenyl)methanol (9d)



The organoindium reagent was prepared according to **TP1** from benzyl chloride (**7b**; 251 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), (4-bromophenyl)methanol (**1n**; 299 mg, 1.6 mmol, 0.8 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the diphenylmethane **9d** (245 mg, 77 %) as a white solid.

M.p. (°C): 45-47.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.37-7.22 (m, 9H), 4.66 (s, 2H), 4.03 (s, 2H), 2.06 (brs, 1H).

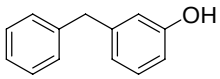
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 141.0, 140.5, 138.6, 129.0, 128.8, 128.4, 127.2, 126.0, 65.0, 41.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3240 (m), 1601 (w), 1511 (w), 1494 (m), 1433 (m), 1293 (m), 1211 (m), 1029 (m), 1017 (s), 913 (w), 856 (m), 770 (m), 740 (s), 717 (s), 698 (vs).

MS (EI, 70 eV): m/z (%) = 199 (12), 198 (M^+, 75), 168 (17), 167 (100), 166 (15), 165 (42), 152 (23), 107 (38), 92 (13), 91 (45), 79 (24), 77 (14), 65 (11), 43 (40).

HRMS ($C_{14}H_{14}O$): calc.: 198.1045; found: 198.1032 (M^+).

3-Benzylphenol (9e)



The organoindium reagent was prepared according to **TP1** from benzyl chloride (**7b**; 251 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 3-bromophenol (**1o**; 208 mg, 1.2 mmol, 0.6 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the diphenylmethane **9e** (182 mg, 82 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.34-7.15 (m, 6H), 6.82-6.79 (m, 1H), 6.71-6.65 (m, 2H), 4.82 (brs, 1H), 3.95 (s, 2H).

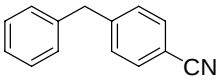
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 155.5, 143.0, 140.7, 129.6, 128.9, 128.5, 126.1, 121.5, 115.8, 113.0, 41.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3328 (w), 1588 (m), 1493 (m), 1450 (s), 1248 (m), 1150 (m), 1074 (w), 953 (m), 863 (m), 780 (m), 766 (m), 724 (vs), 690 (vs).

MS (EI, 70 eV): m/z (%) = 185 (15), 184 (M^+, 100), 183 (42), 167 (15), 165 (37), 153 (11), 152 (12), 115 (10), 107 (12), 106 (19), 91 (20), 77 (11), 43 (30).

HRMS ($C_{13}H_{12}O$): calc.: 184.0888; found: 184.0884 (M^+).

4-Benzylbenzonitrile (9f)



The organoindium reagent was prepared according to **TP1** from benzyl bromide (**7c**, 342 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 4-bromobenzonitrile (**1a**; 291 mg, 1.6 mmol, 0.8 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv,

56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the diphenylmethane **9f** (242 mg, 78 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.61-7.57 (m, 2H), 7.40-7.20 (m, 7H), 4.07 (s, 2H).

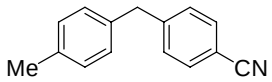
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 146.5, 139.2, 132.0, 129.4, 128.8, 128.6, 126.5, 118.8, 109.8, 41.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2226 (m), 1662 (w), 1602 (m), 1495 (m), 1453 (m), 1413 (w), 1274 (m), 1177 (w), 1020 (w), 854 (m), 796 (m), 761 (m), 725 (s), 697 (vs).

MS (EI, 70 eV): m/z (%) = 207 (11), 194 (12), 193 (M^+, 100), 192 (31), 190 (14), 165 (16), 105 (29), 91 (10), 77 (13).

HRMS ($C_{14}H_{11}N$): calc.: 193.0891; found: 193.0890 (M^+).

4-(4-Methylbenzyl)benzonitrile (9g)



The organoindium reagent was prepared according to **TP1** from 1-(chloromethyl)-4-methylbenzene (**7d**; 281 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 4-bromobenzonitrile (**1a**; 291 mg, 1.6 mmol, 0.8 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the diphenylmethane **9g** (280 mg, 84 %) as a white solid.

M.p. (°C): 64-66.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.60-7.56 (m, 2H), 7.32-7.28 (m, 2H), 7.17-7.07 (m, 4H), 4.02 (s, 2H), 2.36 (s, 3H).

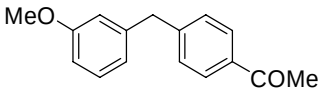
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 147.0, 136.2, 136.1, 132.2, 129.5, 129.4, 128.7, 118.9, 109.8, 41.5, 20.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921 (w), 2224 (s), 1603 (m), 1510 (m), 1502 (m), 1433 (m), 1413 (m), 1175 (m), 1118 (m), 1107 (w), 1019 (m), 912 (w), 859 (m), 813 (vs), 806 (s), 755 (vs), 681 (m).

MS (EI, 70 eV): m/z (%) = 208 (15), 207 (M^+, 100), 206 (18), 193 (12), 192 (94), 191 (15), 190 (28), 165 (16), 105 (11), 91 (14), 43 (20).

HRMS ($C_{15}H_{13}N$): calc.: 207.1048; found: 207.1036 (M^+).

1-(4-(3-Methoxybenzyl)phenyl)ethanone (9h)



The organoindium reagent was prepared according to **TP1** from 1-(chloromethyl)-3-methoxybenzene (**7e**; 313 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 1-(4-iodophenyl)ethanone (**1p**; 394 mg, 1.6 mmol, 0.8 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the diphenylmethane **9h** (349 mg, 91 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.92-7.88 (m, 2H), 7.32-7.21 (m, 3H), 6.80-6.74 (m, 3H), 4.01 (s, 2H), 3.78 (s, 3H), 2.58 (s, 3H).

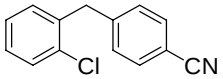
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.6, 159.7, 146.5, 141.5, 135.2, 129.5, 129.0, 128.5, 121.2, 114.8, 111.5, 55.0, 41.8, 26.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1677 (vs), 1597 (s), 1583 (s), 1487 (s), 1435 (m), 1411 (m), 1356 (m), 1255 (vs), 1180 (m), 1147 (s), 1047 (s), 1016 (m), 957 (m), 779 (s), 750 (s), 697 (s).

MS (EI, 70 eV): m/z (%) = 241 (13), 240 (M^+, 66), 226 (18), 225 (100), 182 (10), 165 (24), 153 (15), 152 (13), 113 (10), 43 (36).

HRMS ($C_{16}H_{16}O_2$): calc.: 240.1150; found: 240.1143 (M^+).

4-(2-Chlorobenzyl)benzonitrile (9i)



The organoindium reagent was prepared according to **TP1** from 1-chloro-2-(chloromethyl)benzene (**7f**; 322 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 4-bromobenzonitrile (**1a**; 291 mg, 1.6 mmol, 0.8 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the diphenylmethane **9i** (279 mg, 76 %) as a white solid.

M.p. (°C): 56-58.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.60-7.56 (m, 2H), 7.43-7.40 (m, 1H), 7.33-7.29 (m, 2H), 7.26-7.19 (m, 3H), 4.18 (s, 2H).

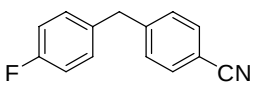
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 145.0, 136.8, 134.1, 132.1, 131.0, 129.7, 129.4, 128.2, 127.0, 118.8, 110.0, 39.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2224 (m), 1606 (w), 1507 (w), 1471 (m), 1443 (m), 1433 (m), 1413 (m), 1049 (m), 1032 (m), 915 (w), 843 (m), 806 (m), 759 (s), 741 (vs), 674 (m).

MS (EI, 70 eV): m/z (%) = 229 (16), 227 (M^+, 44), 193 (18), 192 (100), 191 (21), 190 (45), 165 (24), 89 (10), 43 (28).

HRMS ($C_{14}H_{10}ClN$): calc.: 227.0502; found: 227.0502 (M^+).

4-(4-Fluorobenzyl)benzonitrile (9j)



The organoindium reagent was prepared according to **TP1** from 1-(chloromethyl)-4-fluorobenzene (**7g**; 289 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution

was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 4-bromobenzonitrile (**1a**; 0.8 equiv, 291 mg, 1.6 mmol) or 4-chlorobenzonitrile (**1q**; 220 mg, 1.6 mmol, 0.8 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford diphenylmethane **9j** (for 4-bromobenzonitrile: 293 mg, 87 %; for 4-chlorobenzonitrile: 278 mg, 82%) as a white solid.

M.p. (°C): 61-63.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.60-7.56 (m, 2H), 7.30-7.28 (m, 2H), 7.18-7.11 (m, 2H), 7.05-6.97 (m, 2H), 4.03 (s, 2H).

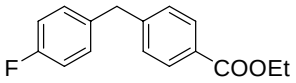
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.5 (d, *J* = 245 Hz), 146.4, 134.9 (d, *J* = 3 Hz), 132.2, 130.3 (d, *J* = 8 Hz), 129.4, 118.8, 115.4 (d, *J* = 21 Hz), 110.0, 40.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2222 (m), 1606 (m), 1507 (s), 1500 (s), 1446 (m), 1413 (w), 1213 (s), 1177 (m), 1154 (m), 1116 (m), 869 (m), 814 (vs), 765 (vs), 734 (m).

MS (EI, 70 eV): m/z (%) = 212 (14), 211 (M^+, 100), 210 (25), 208 (12), 190 (11), 183 (14), 109 (16).

HRMS ($C_{14}H_{10}FN$): calc.: 211.0797; found: 211.0792 (M^+).

Ethyl 4-(4-fluorobenzyl)benzoate (9k)



The organoindium reagent was prepared according to **TP1** from 1-(chloromethyl)-4-fluorobenzene (**7g**; 289 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), ethyl 4-bromobenzoate (**1b**; 367 mg, 1.6 mmol, 0.8 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the diphenylmethane **9k** (391 mg, 95 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.03-7.99 (m, 2H), 7.28-7.24 (m, 2H), 7.17-7.12 (m, 2H), 7.04-6.97 (m, 2H), 4.40 (q, *J* = 7.11 Hz, 2H), 4.02 (s, 2H), 1.41 (t, *J* = 7.11 Hz, 3H).

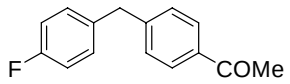
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 161.5 (d, *J* = 244 Hz), 146.1, 135.8 (d, *J* = 4 Hz), 130.2 (d, *J* = 8 Hz), 129.8, 128.7, 128.5, 115.3 (d, *J* = 21 Hz), 60.8, 41.0, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1711 (s), 1610 (m), 1507 (s), 1271 (vs), 1220 (s), 1176 (s), 1157 (m), 1099 (s), 1020 (s), 834 (m), 779 (m), 742 (s), 696 (m).

MS (EI, 70 eV): m/z (%) = 258 (M^+, 51), 230 (10), 214 (14), 213 (100), 186 (11), 185 (68), 184 (11), 183 (36), 165 (28), 109 (16).

HRMS ($C_{16}H_{15}FO_2$): calc.: 258.1056; found: 258.1048 (M^+).

1-(4-(4-Fluorobenzyl)phenyl)ethanone (9l)



The organoindium reagent was prepared according to **TP1** from 1-(chloromethyl)-4-fluorobenzene (**7g**; 289 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 1-(4-bromophenyl)ethanone (**1r**; 319 mg, 1.6 mmol, 0.8 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the diphenylmethane **9l** (337 mg, 92 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.93-7.89 (m, 2H), 7.30-7.26 (m, 2H), 7.18-7.12 (m, 2H), 7.04-6.97 (m, 2H), 4.02 (s, 2H), 2.59 (s, 3H).

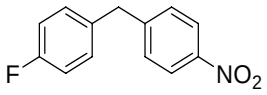
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.6, 161.5 (d, *J* = 245 Hz), 146.5, 135.6 (d, *J* = 3 Hz), 135.3, 130.3 (d, *J* = 8 Hz), 128.9, 128.6, 115.3 (d, *J* = 21 Hz), 40.9, 26.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1678 (vs), 1605 (s), 1507 (vs), 1411 (m), 1357 (s), 1264 (vs), 1219 (vs), 1181 (m), 1157 (s), 1015 (m), 957 (m), 812 (vs), 767 (s), 676 (m).

MS (EI, 70 eV): m/z (%) = 228 (M^+, 31), 227 (11), 214 (12), 213 (100), 183 (23), 165 (20), 43 (18).

HRMS ($C_{15}H_{13}FO$): calc.: 228.0950; found: 228.0940 (M^+).

1-(4-Fluorobenzyl)-4-nitrobenzene (9m)



The organoindium reagent was prepared according to **TP1** from 1-(chloromethyl)-4-fluorobenzene (**7g**; 289 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 1-bromo-4-nitrobenzene (**1s**; 323 mg, 1.6 mmol, 0.8 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the diphenylmethane **9m** (299 mg, 81 %) as a white solid.

M.p. (°C): 58-60.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.17-8.12 (m, 2H), 7.35-7.31 (m, 2H), 7.18-7.12 (m, 2H), 7.05-6.97 (m, 2H), 4.07 (s, 2H).

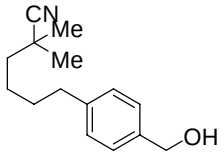
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.5 (d, J = 245 Hz), 148.6, 146.5, 134.9 (d, J = 3 Hz), 130.4 (d, J = 8 Hz), 129.5, 123.7, 115.6 (d, J = 21 Hz), 40.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1604 (m), 1505 (vs), 1343 (vs), 1319 (m), 1214 (s), 1156 (m), 1109 (m), 1016 (w), 874 (m), 859 (m), 830 (m), 794 (s), 774 (s), 730 (s), 709 (m), 690 (s), 679 (m).

MS (EI, 70 eV): m/z (%) = 232 (16), 231 (M^+, 100), 214 (15), 185 (40), 184 (40), 183 (69), 170 (18), 165 (39), 133 (11), 109 (40), 107 (23), 83 (12), 77 (15), 43 (49).

HRMS ($C_{13}H_{10}FNO_2$): calc.: 231.0696; found: 231.0686 (M^+).

6-(4-(Hydroxymethyl)phenyl)-2,2-dimethylhexanenitrile (12a)



The organoindium reagent was prepared according to **TP1** from 6-bromo-2,2-dimethylhexanenitrile (**10a**; 408 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), (4-bromophenyl)methanol (**1n**; 262 mg, 1.4 mmol, 0.7 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the desired product **12a** (218 mg, 67 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.29-7.26 (m, 2H), 7.18-7.15 (m, 2H), 4.61 (s, 2H), 2.67-2.62 (m, 2H), 2.28 (s, 1H), 1.70-1.63 (m, 2H), 1.59-1.50 (m, 4H), 1.33 (s, 6H).

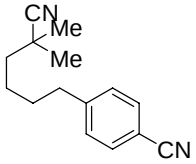
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 141.4, 138.4, 128.3, 127.0, 125.0, 64.8, 40.7, 35.2, 32.2, 31.3, 26.5, 24.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3419 (m), 2975 (m), 2933 (s), 2859 (m), 2232 (w), 1513 (m), 1470 (s), 1458 (m), 1420 (m), 1391 (m), 1368 (m), 1203 (m), 1034 (s), 1016 (vs), 806 (s), 758 (m).

MS (EI, 70 eV): m/z (%) = 231 (M^+, 6), 213 (16), 145 (16), 131 (27), 121 (40), 117 (31), 110 (11), 107 (100), 105 (16), 104 (38), 93 (23), 91 (53), 79 (16), 77 (30), 42 (16), 40 (14).

HRMS ($C_{15}H_{21}NO$): calc.: 231.1623; found: 231.1617 (M^+).

4-(5-Cyano-5-methylhexyl)benzonitrile (12b)



The organoindium reagent was prepared according to **TP1** from 6-bromo-2,2-dimethylhexanenitrile (**10a**; 408 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 4-bromobenzonitrile (**1a**; 0.7 equiv, 255 mg, 1.4 mmol) or 4-chlorobenzonitrile (**1q**; 193 mg, 1.4 mmol, 0.7 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the product **12b** (for 4-bromobenzonitrile: 294 mg, 93 %; for 4-chlorobenzonitrile: 239 mg, 75%) as a white solid.

M.p. (°C): 47-49.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.60-7.56 (m, 2H), 7.30-7.28 (m, 2H), 2.74-2.69 (m, 2H), 1.73-1.64 (m, 2H), 1.56-1.53 (m, 4H), 1.34 (s, 6H).

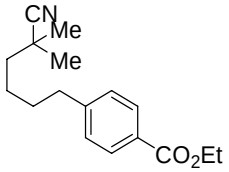
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 147.7, 132.1, 129.1, 124.9, 119.0, 109.7, 40.7, 35.8, 32.3, 30.8, 26.6, 24.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2944 (m), 2229 (m), 2218 (m), 1605 (m), 1473 (m), 1461 (m), 1432 (m), 1173 (w), 873 (w), 844 (s), 825 (vs), 765 (m), 733 (m).

MS (EI, 70 eV): m/z (%) = 226 (M^+, 42), 225 (35), 211 (34), 198 (12), 183 (10), 170 (10), 155 (12), 144 (15), 143 (11), 142 (11), 130 (70), 129 (50), 117 (33), 116 (100), 90 (11), 89 (33), 83 (12), 77 (10), 71 (39), 69 (14), 69 (14), 55 (18), 42 (32), 41 (29).

HRMS ($C_{15}H_{18}N_2$): calc.: 226.1470; found: 226.1467 (M^+).

Ethyl 4-(5-cyano-5-methylhexyl)benzoate (12c)



The organoindium reagent was prepared according to **TP1** from 6-bromo-2,2-dimethylhexanenitrile (**10a**; 408 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The

supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), ethyl 4-bromobenzoate (**1b**; 321 mg, 1.4 mmol, 0.7 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the product **12c** (325 mg, 85 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.98-7.94 (m, 2H), 7.25-7.21 (m, 2H), 4.36 (q, *J* = 7.11 Hz, 2H), 2.69 (t, *J* = 7.64 Hz, 2H), 1.71-1.62 (m, 2H), 1.56-1.50 (m, 4H), 1.38 (t, *J* = 7.11 Hz, 3H), 1.32 (s, 6H).

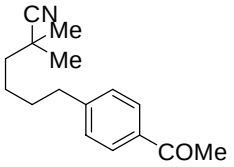
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.5, 147.4, 129.6, 128.2, 128.1, 125.0, 60.7, 40.8, 35.6, 32.2, 31.0, 26.6, 24.8, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 2936 (w), 2861 (w), 2232 (vw), 1711 (s), 1610 (m), 1366 (m), 1271 (vs), 1177 (m), 1105 (s), 1021 (m), 852 (w), 762 (m), 705 (m).

MS (EI, 70 eV): m/z (%) = 273 (M^+, 8), 229 (10), 228 (62), 227 (100), 226 (23), 177 (10), 163 (20), 149 (10), 135 (18), 131 (59), 116 (10), 107 (14), 91 (18), 90 (13).

HRMS ($C_{17}H_{23}NO_2$): calc.: 273.1729; found: 273.1726 (M^+).

6-(4-Acetylphenyl)-2,2-dimethylhexanenitrile (12d)



The organoindium reagent was prepared according to **TP1** from 6-bromo-2,2-dimethylhexanenitrile (**10a**; 408 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 1-(4-bromophenyl)ethanone (**1r**; 279 mg, 1.4 mmol, 0.7 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the product **12d** (284 mg, 83 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.89-7.85 (m, 2H), 7.27-7.23 (m, 2H), 2.71-2.66 (m, 2H), 2.56 (s, 3H), 1.71-1.62 (m, 2H), 1.56-1.50 (m, 4H), 1.31 (s, 6H).

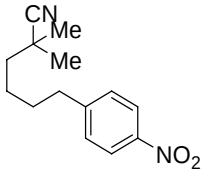
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.6, 147.8, 135.0, 128.4, 124.9, 40.7, 35.6, 32.2, 30.9, 26.5, 26.4, 24.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2974 (w), 2936 (w), 2861 (w), 2231 (w), 1678 (vs), 1605 (s), 1412 (m), 1357 (m), 1266 (vs), 1181 (m), 1016 (w), 956 (m), 845 (m), 818 (m), 690 (w).

MS (EI, 70 eV): m/z (%) = 243 (M^+, 29), 229 (16), 228 (100), 149 (10), 147 (43), 147 (27), 116 (12), 105 (12), 91 (11), 90 (11), 43 (31).

HRMS ($C_{16}H_{21}NO$): calc.: 243.1623; found: 243.1618 (M^+).

2,2-Dimethyl-6-(4-nitrophenyl)hexanenitrile (12e)



The organoindium reagent was prepared according to **TP1** from 6-bromo-2,2-dimethylhexanenitrile (**10a**; 408 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 1-bromo-4-nitrobenzene (**1s**; 279 mg, 1.4 mmol, 0.7 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the product **12e** (267 mg, 77 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.15-8.11 (m, 2H), 7.35-7.30 (m, 2H), 2.78-2.72 (m, 2H), 1.74-1.66 (m, 2H), 1.56-1.53 (m, 4H), 1.33 (s, 6H).

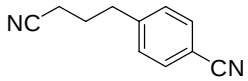
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.9, 146.3, 129.0, 124.9, 123.6, 40.7, 35.5, 32.3, 30.8, 26.6, 24.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2977 (w), 2937 (w), 2862 (w), 2232 (vw), 1598 (m), 1514 (s), 1341 (vs), 1109 (w), 912 (w), 851 (m), 732 (m), 698 (m).

MS (EI, 70 eV): m/z (%) = 246 (M^+, 16), 230 (12), 229 (60), 228 (100), 199 (11), 160 (22), 150 (18), 142 (16), 137 (96), 136 (14), 130 (12), 120 (16), 117 (18), 116 (34), 115 (19), 107 (31), 106 (10), 106 (15), 104 (11), 103 (15), 91 (32), 90 (37), 89 (29), 78 (39), 77 (21), 69 (19), 65 (10), 55 (19), 43 (24), 41 (31).

HRMS ($C_{14}H_{18}N_2O_2$): calc.: 246.1368; found: 246.1365 (M^+).

4-(3-Cyanopropyl)benzonitrile (12f)



The organoindium reagent was prepared according to **TP1** from 4-bromobutanenitrile (**10b**; 296 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 4-bromobenzonitrile (**1a**; 255 mg, 1.4 mmol, 0.7 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the product **12f** (202 mg, 85 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.61-7.57 (m, 2H), 7.32-7.28 (m, 2H), 2.84 (t, *J* = 7.68 Hz, 2H), 2.35 (t, *J* = 7.01 Hz, 2H), 2.03-1.93 (m, 2H).

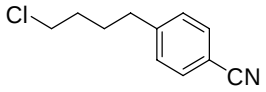
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 145.3, 132.3, 129.1, 118.9, 118.6, 110.3, 34.3, 26.2, 16.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926 (m), 2858 (w), 2245 (w), 2226 (vs), 1676 (w), 1607 (s), 1505 (m), 1458 (m), 1416 (m), 1178 (m), 1111 (w), 1020 (m), 840 (vs), 813 (vs).

MS (EI, 70 eV): m/z (%) = 172 (10), 170 (M^+, 27), 130 (66), 129 (11), 117 (15), 116 (100), 89 (22), 43 (50), 41 (15).

HRMS ($C_{11}H_{10}N_2$): calc.: 170.0844; found: 170.0830 (M^+).

4-(4-Chlorobutyl)benzonitrile (12g)



The organoindium reagent was prepared according to **TP1** from 1-bromo-4-chlorobutane (**10c**; 343 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 4-bromobenzonitrile (**1a**; 255 mg, 1.4 mmol, 0.7 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the product **12g** (202 mg, 61 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.56-7.52 (m, 2H), 7.29-7.25 (m, 2H), 3.56-3.50 (m, 2H), 2.72-2.66 (m, 2H), 1.81-1.74 (m, 4H).

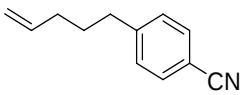
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 147.3, 132.0, 129.0, 118.8, 109.6, 44.4, 35.0, 31.7, 27.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2944 (m), 2864 (w), 2226 (vs), 1607 (s), 1504 (s), 1414 (m), 1309 (m), 1177 (m), 1020 (m), 843 (s), 819 (vs), 724 (s).

MS (EI, 70 eV): m/z (%) = 193 (M^+, 15), 129 (23), 117 (32), 116 (100), 89 (15), 43 (25).

HRMS ($C_{11}H_{12}ClN$): calc.: 193.0658; found: 193.0654 (M^+).

4-(Pent-4-enyl)benzonitrile (12h)



The organoindium reagent was prepared according to **TP1** from 5-bromopent-1-ene (**10d**; 298 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 4-bromobenzonitrile (**1a**; 255 mg, 1.4 mmol, 0.7 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv,

56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the product **12h** (209 mg, 87 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.55-7.52 (m, 2H), 7.28-7.24 (m, 2H), 5.79 (ddt, *J* = 16.99, 10.31, 6.64 Hz, 1H), 5.05-4.96 (m, 2H), 2.66 (t, *J* = 7.77 Hz, 2H), 2.11-2.03 (m, 2H), 1.76-1.66 (m, 2H).

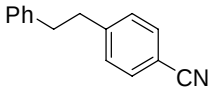
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 147.9, 137.7, 131.9, 129.0, 118.9, 115.0, 109.4, 35.1, 32.8, 29.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3076 (w), 2927 (m), 2860 (w), 2226 (s), 1640 (m), 1607 (s), 1504 (m), 1414 (m), 1177 (m), 992 (m), 912 (vs), 842 (vs).

MS (EI, 70 eV): m/z (%) = 171 (M^+, 3), 130 (23), 129 (100), 117 (27), 116 (39), 103 (10), 89 (16), 61 (11), 55 (16), 45 (11), 43 (74).

HRMS ($C_{12}H_{13}N$): calc.: 171.1048; found: 171.1035 (M^+).

4-Phenethylbenzonitrile (12i)



The organoindium reagent was prepared according to **TP1** from 1-(2-bromoethyl)benzene (**10e**; 370 mg, 2.00 mmol, 1.00 equiv) in 2 h using LiCl (102 mg, 2.4 mmol, 1.20 equiv), $InCl_3$ (146 mg, 0.66 mmol, 0.33 equiv), and magnesium turnings (58 mg, 2.4 mmol, 1.20 equiv) in dry THF (4 mL). The supernatant solution was transferred to another pre-dried flask and THF was removed *in vacuo*. Then DMAC (4 mL), 4-bromobenzonitrile (**1a**; 255 mg, 1.4 mmol, 0.7 equiv), and $PdCl_2(PPh_3)_2$ (0.04 equiv, 56 mg, 0.08 mmol) were sequentially introduced to the flask followed by stirring of the reaction mixture at 80 °C for 12 h. After reaction it was directly purified by flash chromatography (silica gel, *i*hexane / EtOAc) to afford the product **12i** (274 mg, 94 %) as a white solid.

M.p. (°C): 40-42.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.59-7.56 (m, 2H), 7.35-7.14 (m, 7H), 3.06-2.93 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 147.1, 140.5, 132.0, 129.2, 128.4, 128.3, 126.2, 119.0, 109.8, 37.8, 37.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2225 (m), 1692 (m), 1601 (m), 1503 (m), 1451 (m), 1322 (m), 1287 (s), 1177 (m), 1021 (m), 865 (s), 821 (s), 750 (s), 702 (s), 692 (vs).

MS (EI, 70 eV): m/z (%) = 207 (M^+, 15), 92 (11), 91 (100), 65 (10), 43 (32).

HRMS ($C_{15}H_{13}N$): calc.: 207.1048; found: 207.1045 (M^+).

Chapter 5. Stereoselective Preparation of Polyfunctional Alkenylindium(III) Halides and Their Cross-Coupling with Unsaturated Halides

5.1 Introduction

Organometallics which are compatible with many functionalities are important nucleophilic intermediates in organic synthesis.[1-3] The tolerance of functional groups is essential to shorten long natural product syntheses since such reagents avoid protecting and deprotecting steps.[4] Recently, we and others reported that the insertion of indium into aryl and heteroaryl iodides[5] or benzylic chlorides[6] is dramatically accelerated by the presence of lithium chloride,[7-10] allowing the preparation of functionalized organoindium species. The high functional group tolerance of

[1] *Handbook of Functionalized Organometallics*; P. Knochel, Ed.; Wiley-VCH: Weinheim, **2005**.
[2] For selected reviews regarding the preparation of functionalized organolithium reagents, see: (a) C. Nájera, J. M. Sansano, M. Yus, *Tetrahedron* **2003**, *59*, 9255; (b) R. Chinchilla, C. Najera, M. Yus, *Tetrahedron* **2005**, *61*, 3139; (c) F. Foubelo, M. Yus, *Chem. Soc. Rev.* **2008**, *37*, 2620.
[3] For selected reviews involving polyfunctionalized organoboron reagents, see: (a) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*; D. G. Hall, Ed.; Wiley-VCH: Weinheim, **2011**; (b) A. Suzuki, *Acc. Chem. Res*. **1982**, *15*, 178; (c) A. Pelter, *Chem. Soc. Rev.* **1982**, *11*, 191; (d) E. I. Negishi, M. J. Idacavage, *Org. React.* **1985**, *33*, 1; (e) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633; (f) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; (g) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.
[4] For recent reviews on the protecting group-free synthesis, see: (a) E. Roulland, *Angew. Chem. Int. Ed.* **2011**, *50*, 1226; (b) I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, *1*, 193; (c) R. W. Hoffmann, *Synthesis* **2006**, 3531.
[5] (a) Y. H. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648; (b) V. Papoian, T. Minehan, *J. Org. Chem.* **2008**, *73*, 7376; (c) L. Adak, N. Yoshikai, *J. Org. Chem.* **2011**, *76*, 7563; (d) L. Adak, N. Yoshikai, *Tetrahedron* **2012**, *68*, 5167.
[6] (a) Y. H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236; (b) L. S. Chupak, J. P. Wolkowski, Y. A. Chantigny, *J. Org. Chem.* **2009**, *74*, 1388; (c) N. Fujiwara, Y. Yamamoto, *J. Org. Chem.* **1999**, *64*, 4095.
[7] (a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; (b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192; (c) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824; (d) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082.
[8] (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.
[9] (a) T. D. Blümke, Y. H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313; (b) L. N. Guo, H. Gao, P. Mayer, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 9829; (c) Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 8516; (d) T. D. Blümke, K. Groll, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2011**, *13*, 6440.
[10] Z. Peng, P. Knochel, *Org. Lett.* **2011**, *13*, 3198.

indium(III) organometallics[11,12] led us to examine the preparation of polyfunctional alkenylindium(III) reagents for organic synthesis. In fact, organoindium(III) derivatives have been shown to be compatible with various functional groups.[13] The insertion rate of a metal into a carbon-halide bond highly depends on the activation of its surface and lithium chloride has been found to be an excellent activator for many metals, such as magnesium,[7] zinc,[8] aluminum,[9] and manganese.[10] Although such activation leads to a fast insertion, the stereoselectivity of the metal insertion into *E*- and *Z*-alkenyl halides usually cannot be controlled.[14] Metal insertions are dominated by electron-transfer reaction steps[15] which implies the formation of free radical intermediates and therefore lead to a loss of stereoselectivity. The use of zinc activated by lithium chloride has allowed a stereoselective insertion to some electron-poor alkenyl bromides.[16] Herein, we report a mild preparation of highly functionalized alkenylindium(III) reagents[17] and the stereoselective insertion of indium powder into functionalized *E*- and *Z*-styryl iodides as well as their subsequent Pd-catalyzed stereoselective cross-coupling with unsaturated iodides.

5.2 Results and Discussion

[11] For the use of triorganoindium reagent (R_3In) in organic synthesis by Sarandeses *et al.*, see: (a) I. Perez, J. Perez Sestelo, L. A. Sarandeses, *J. Am. Chem. Soc.* **2001**, *123*, 4155; (b) I. Perez, J. Perez Sestelo, L. A. Sarandeses, *Org. Lett.* **1999**, *1*, 1267; (c) J. Caeiro, J. Perez Sestelo, L. A. Sarandeses, *Chem. Eur. J.* **2008**, *14*, 741; (d) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997; (e) S. Bernhardt, Z. L. Shen, P. Knochel, *Chem. Eur. J.* **2013**, *19*, 828; (f) L. Jin, Y. Zhao, L. Zhu, H. Zhang, A. Lei, *Adv. Synth. Catal.* **2009**, *351*, 630; (g) Y. Zhao, L. Jin, P. Li, A. Lei, *J. Am. Chem. Soc.* **2008**, *130*, 9429.

[12] For recent examples concerning the preparation of other organoindium reagents, see: (a) D. Lee, T. Ryu, Y. Park, P. H. Lee, *Org. Lett.* **2014**, *16*, 1144; (b) Y. Nishimoto, H. Ueda, Y. Inamoto, M. Yasuda, A. Baba, *Org. Lett.* **2010**, *12*, 3390; (c) Z. L. Shen, K. K. K. Goh, Y. S. Yang, Y. C. Lai, C. H. A. Wong, H. L. Cheong, T. P. Loh, *Angew. Chem. Int. Ed.* **2011**, *50*, 511; (d) Z. L. Shen, K. K. K. Goh, H. L. Cheong, C. H. A. Wong, Y. C. Lai, Y. S. Yang, T. P. Loh, *J. Am. Chem. Soc.* **2010**, *132*, 15852.

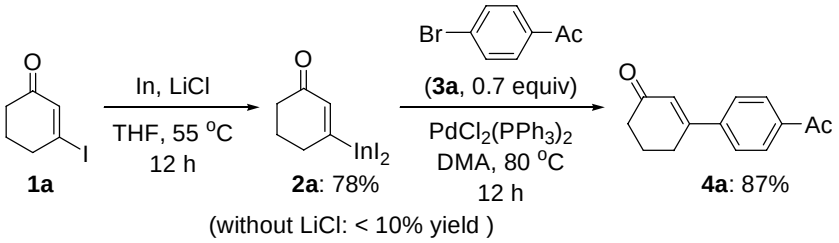
[13] For selected typical reviews on organoindium reagents, see: (a) S. Araki, T. Hirashita, *in Comprehensive Organometallic Chemistry III* (R. H. Crabtree, D. M. P. Mingos, Eds.); Elsevier: Oxford, **2007**; Vol. 9, Chap. 9.14, pp. 649–722; (b) Z. L. Shen, S. Y. Wang, Y. K. Chok, Y. H. Xu, T. P. Loh, *Chem. Rev.* **2013**, *113*, 271.

[14] P. Knochel, J. F. Normant, *Tetrahedron Lett.* **1986**, *37*, 4431.

[15] A. Studer, D. P. Curran, *Nat. Chem.* **2014**, *6*, 765.

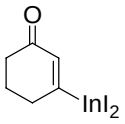
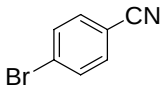
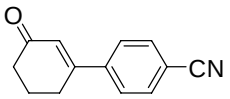
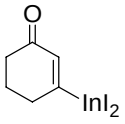
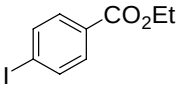
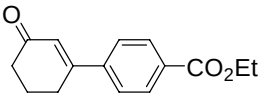
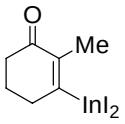
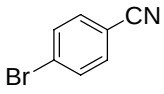
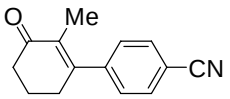
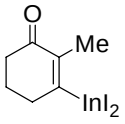
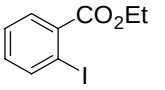
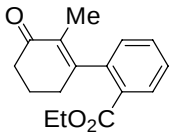
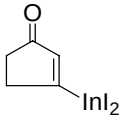
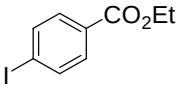
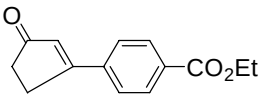
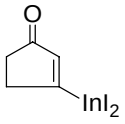
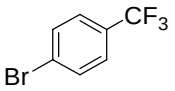
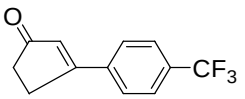
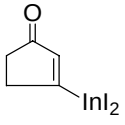
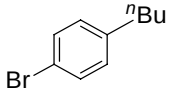
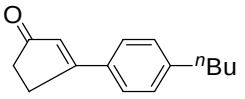
[16] (a) T. Hatakeyama, N. Nakagawa, M. Nakamura, *Org. Lett.* **2009**, *11*, 4496; (b) C. Sämann, M. A. Schade, S. Yamada, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 9495.

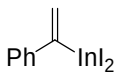
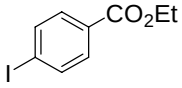
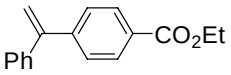
[17] For other indirect methods for the preparation of alkenylindium(III) reagents by the addition of indium(III) species to alkyne or the transmetallation of alkenyllithium reagent with indium(III) halide, see: (a) K. Takami, H. Yorimitsu, K. Oshima, *Org. Lett.* **2004**, *6*, 4555; (b) Y. Nishimoto, R. Moritoh, M. Yasuda, A. Baba, *Angew. Chem. Int. Ed.* **2009**, *48*, 4577; (c) K. Takami, H. Yorimitsu, K. Oshima, *Org. Lett.* **2002**, *4*, 2993; (d) K. Takami, S. Mikami, H. Yorimitsu, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2003**, *68*, 6627.



Scheme 1. Preparation of organoindium reagent **2a** by In/LiCl insertion and its subsequent palladium-catalyzed cross-coupling with aryl bromide **3a**

Table 1. Preparation of alkenylindium(III) reagents **2a-d** and subsequent palladium-catalyzed cross-coupling with aryl halides **3b-f**[a]

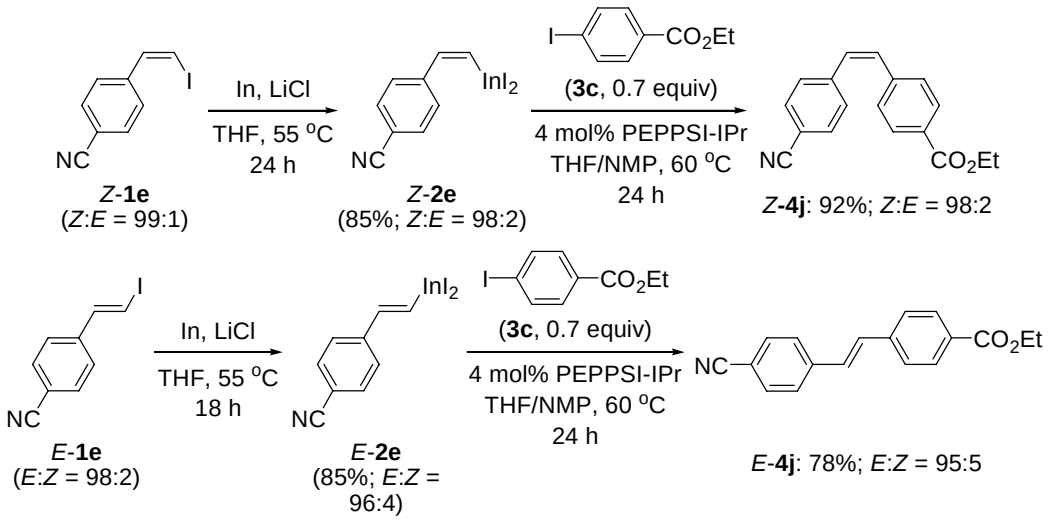
Entry	Indium reagent	Electrophile[b]	Product (Yield)[c]
			
1	**2a** (12 h, 78%)	**3b**	**4b** (98%)
			
2	**2a**	**3c**	**4c** (96%)
			
3	**2b** (16 h, 90%)	**3b**	**4d** (91%) (<10%)[d]
			
4	**2b**	**3d**	**4e** (88%)
			
5	**2c** (20 h, 66%)	**3c**	**4f** (79%)
			
6	**2c**	**3e**	**4g** (94%)
			

7	**2c** 	**3f** 	**4h** (53%) 
8	**2d** (12 h, 68%)	**3c**	**4i** (91%)

[a] The cross-coupling reactions were performed in DMAC at 80 °C for 12 h using 5 mol% $PdCl_2(PPh_3)_2$. [b] 0.7 equivalent of electrophile was used. [c] Yield of isolated, analytically pure product. [d] The same reaction using 4-chlorobenzonitrile as an electrophile led to <10% yield of the product **4d**.

Thus, we have treated 3-iodocyclohex-2-enone (**1a**) with indium powder (2 equiv), lithium chloride (2 equiv) in THF at 55 °C for 12 h leading to a full conversion and affording the indium(III) species **2a** in 78% yield as determined by GC-analysis of reaction aliquots quenched with a THF solution of iodine (Scheme 1). In the absence of lithium chloride, less than 10% of insertion was observed. The organoindium reagent **2a** readily underwent a palladium-catalyzed cross-coupling with 4-bromoacetophenone (**3a**) in *N*, *N*-dimethylacetamide (DMAC)[11e] at 80 °C for 12 h leading to the expected 3-arylated cyclohexenone **4a** in 87% yield. This reaction sequence has some generality and the organoindium reagent **2a** underwent couplings with aryl bromide **3b** and iodide **3c** affording the corresponding cyclohexenones **4b-c** in high yields (Table 1, entries 1-2). Similarly, we have prepared the 2-methyl 3-indium cyclohexenone derivative **2b** (55 °C, 16 h, 90% yield) and the 3-indium cyclopentenone reagent **2c** (55 °C, 20 h, 66% yield) under similar reaction conditions. These indium-species underwent smooth cross-couplings with electron-poor and electron-rich aryl halides leading to the 3-arylated enones **4d-h** in 53-94% yields (entries 3-7). In addition, we noticed that the indium insertion to α-iodostyrene (**1d**) proceeded also smoothly to generate the corresponding organoindium **2d** in 68% yield (55 °C, 12 h), which cross-coupled with aryl iodide **3c** to produce the expected product **4i** in 91% yield (entry 8). This led us to examine the stereochemistry of indium insertion into the carbon-iodine bond of stereodefined styryl iodides.[18]

[18] Stereodefined styryl iodides **1e-k** were prepared according to reported methods: (a) J. J. Mousseau, J. A. Bull, C. L. Ladd, A. Fortier, D. Sustac Roman, A. B. Charette, *J. Org. Chem.* **2011**, *76*, 8243; (b) J. A. Bull, J. J. Mousseau, A. B. Charette, *Org. Lett.* **2008**, *10*, 5485.



Scheme 2. Preparation of stereodefined cyano-containing *Z*- and *E*-styrylindium reagents **2e** and their palladium-catalyzed cross-coupling with ethyl 4-iodobenzoate (**3c**)

Thus, we treated *Z*- and *E*-(2-iodovinyl)benzonitrile (**1e**)[19] with indium powder and lithium chloride (55 °C, 18-24 h) leading to the styrylindium reagents *Z*-**2e** and *E*-**2e** in 85% yield (Scheme 2). Remarkably, the *Z*-styrylindium *Z*-**2e** retained its stereochemistry almost completely and an iodolysis showed a *Z*:*E* ratio of 98:2.[20] It should be noted that THF is the solvent of choice for the insertion reaction since the performance of the same reaction in other ethereal solvents led to either low yield or relatively low stereochemistry (DME: 82% yield, *Z*:*E* = 90:10; ^{t}BuOMe: 22% yield, *Z*:*E* = 99:1; tetrahydropyran: 80% yield, *Z*:*E* = 81:19; 1,4-dioxane: 68% yield, *Z*:*E* = 98:2). Subsequently, Pd-catalyzed cross-coupling of *Z*-**2e** with ethyl 4-iodobenzoate (**3c**) using 4 mol% PEPPSI-IPr[21,22] led to the unsymmetrical *Z*-stilbene *Z*-**4j** in 92% yield and *Z*:*E* ratio of 98:2. Also, the styrylindium reagent *E*-**2e** showed by iodolysis a *E*:*Z* purity of 96:4. Pd-catalyzed cross-coupling of *E*-**2e** with the aryl iodide **3c** produced the *E*-stilbene *E*-**4j** in 78% yield and *E*:*Z* ratio of 95:5.

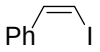
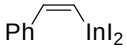
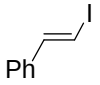
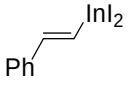
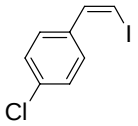
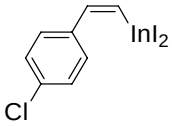
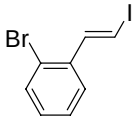
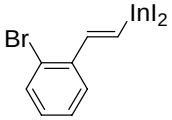
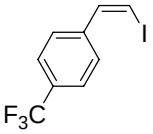
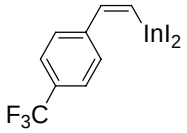
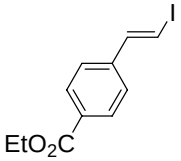
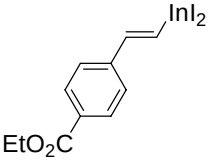
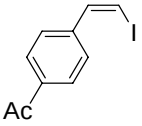
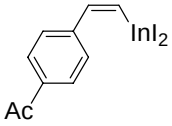
[19] The insertion of indium to *E*-(2-bromovinyl)benzonitrile proceeded sluggishly under the same conditions. The insertion reaction proceeded only efficiently with electron-poor styryl iodides. Alkyl-substituted alkenyl iodides are not appropriate substrates for indium insertion.

[20] See Supporting Information for the GC method for the determination of the yield and *Z*:*E* ratio of the formed alkenylindium(III) reagent by using the insertion of indium into (*Z*)-4-(2-iodovinyl)benzonitrile (*Z*-**1e**) as an example.

[21] J. Nasielski, N. Hadei, G. Achonduh, E. A. B. Kantchev, C. J. O'Brien, A. Lough, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 10844.

[22] The same reaction performed by using other catalyst (4 mol%) and ligand (8 mol%) led to relatively low yield but with the same stereochemistry [$Pd(PPh_3)_4$: 88% yield; $PdCl_2(PPh_3)_2$: 75% yield; $Pd(OAc)_2$/S-Phos: 66% yield; $NiCl_2(PPh_3)_2$: 0% yield].

Table 2. Stereoselective preparation of styrylindium(III) reagents **2f-k**

Entry	Styryl iodide (*E*:*Z*)	Time	Styrylindium reagent [Yield[a] (*E*:*Z*)[b]]
			
1	*Z*-**1f** (3:97)	48 h	*Z*-**2f** [51% (5:95)]
			
2	*E*-**1f** (99:1)	5 d	*E*-**2f** [72% (98:2)]
			
3	*Z*-**1g** (1:99)	12 h	*Z*-**2g** [83% (2:98)]
			
4	*E*-**1h** (99:1)	6 d	*E*-**2h** [70% (99:1)]
			
5	*Z*-**1i** (3:97)	70 h	*Z*-**2i** [72% (5:95)]
			
6	*E*-**1j** (98:2)	20 h	*E*-**2j** [73% (98:2)]
			
7	*Z*-**1k** (1:99)	18 h	*Z*-**2k** [86% (2:98)]

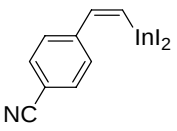
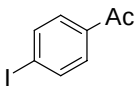
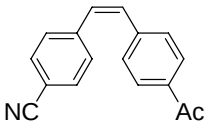
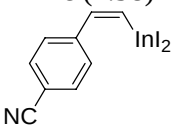
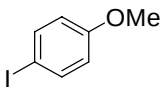
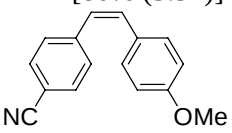
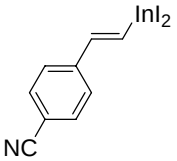
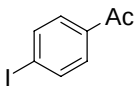
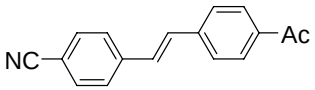
[a] The yield was determined by GC-analysis of reaction aliquots quenched with a THF solution of iodine against internal standard. [b] The *E*:*Z* ratio was determined by GC analysis.

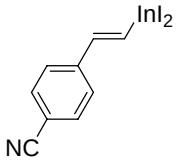
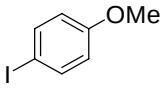
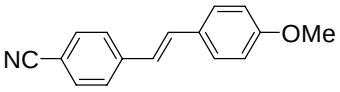
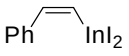
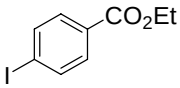
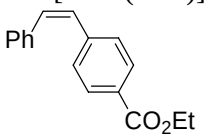
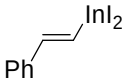
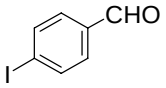
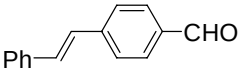
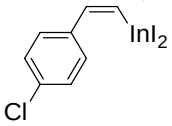
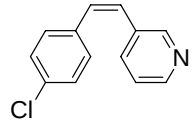
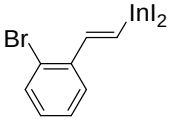
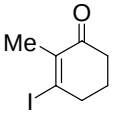
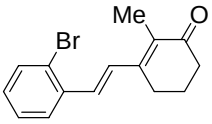
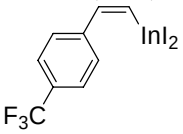
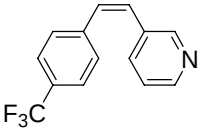
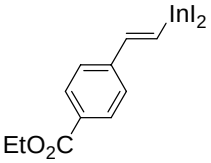
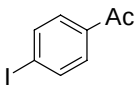
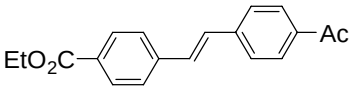
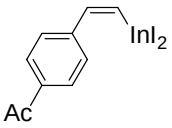
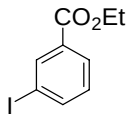
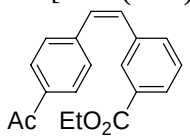
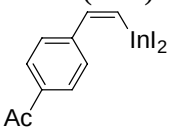
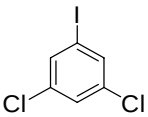
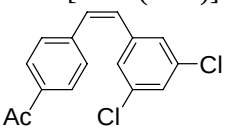
Subsequently, the method was extended to the preparation of a variety of styrylindium(III) reagents using various styryl iodides. As shown in Table 2, unsubstituted *Z*- and *E*-**1f** were converted to the corresponding indium reagents *Z*- and *E*-**2f** in 51-72% yields with high stereoselectivities (entries 1-2). Styryl iodides **1g-i** bearing a halogen-substituent either in the *ortho* or *para* position readily underwent the insertion reactions without touching the halogen substituent, leading to the desired styrylindium(III) reagents **2g-i** in 70-83% yields and excellent stereoretention (> 95:5

dr, entries 2-5). The presence of an ester or acetyl substituent in the starting styryl iodides **1j**-**k** was well tolerated and the resulting indium reagents *E*-**2j** and *Z*-**2k** were obtained under the standard conditions in 73-86% yields and 98:2 dr (entries 6-7).

In the same manner, the palladium-catalyzed cross-coupling of *Z*- and *E*-**2e** with aryl iodides **3g**-**h** proceeded well, leading to the corresponding stilbenes **4k**-**l** in 69-80% yields and high stereoselectivities (Table 3, entries 1-4). Unsubstituted styrylindium(III) reagents *Z*- and *E*-**2f** also underwent efficient cross-coupling with iodoarenes **3c** and **3i** with good yields and high level of stereoselectivities (entries 5-6). The palladium-catalyzed cross-coupling reactions of indium reagents *Z*-**2g**, *E*-**2h**, and *Z*-**2i** with electrophiles **3j**-**k** proceeded smoothly to furnish the corresponding products **4o**-**q** in 65-94% yields and high stereoretention (entries 7-9). This behavior of cross-coupling was further extended to the use of organoindium reagents *E*-**2j** and *Z*-**2k** (bearing an ester or acetyl substituent) with aryl iodides **3g**-**m**, providing the expected stilbenes *E*-**4r**, *Z*-**4s** and *Z*-**4t** in 72-84% yields (up to 98:2 dr, entries 10-12). In addition, it is noteworthy that important functional groups embedded in the coupling partners, including nitrile, ester, ketone, and even aldehyde, were compatible with the styrylindium(III) reagents.

Table 3. Pd-catalyzed cross-coupling of styrylindium(III) reagents **2e-k** with electrophiles **3c-m** using 4 mol% PEPPSI-IPr as catalyst

Entry	Styrylindium (*E*:*Z*)	Electrophile[a]	Product[b] [Yield[c] (*E*:*Z*)[d]]
1	 *Z*-**2e** (2:98)	 **3g**	 *Z*-**4k** [80% (3:97)]
2	 *Z*-**2e** (2:98)	 **3h**	 *Z*-**4l** [74% (6:94)]
3	 *E*-**2e** (96:4)	 **3g**	 *E*-**4k** [71% (96:4)]

			
4	*E*-**2e** (96:4)	**3h**	*E*-**4l** [69% (96:4)]
			
5	*Z*-**2f** (5:95)	**3c**[e]	*Z*-**4m** [82% (6:94)]
			
6	*E*-**2f** (98:2)	**3i**	*E*-**4n** [89% (97:3)]
			
7	*Z*-**2g** (2:98)	**3j**	*Z*-**4o** [65% (2:98)]
			
8	*E*-**2h** (99:1)	**3k**	*E*-**4p** [94% (98:2)]
			
9	*Z*-**2i** (5:95)	**3j**	*Z*-**4q** [77% (6:94)]
			
10	*E*-**2j** (98:2)	**3g**	*E*-**4r** [74% (98:2)]
			
11	*Z*-**2k** (2:98)	**3l**	*Z*-**4s** [72% (5:95)]
			
12	*Z*-**2k** (2:98)	**3m**	*Z*-**4t** [84% (4:96)]

[a] Unless otherwise indicated, 0.7 equivalent of electrophile was used for the cross-coupling reaction. [b] The cross-coupling reactions were performed in THF/NMP (2:1) at 60 °C for 24 h using 4 mol% PEPPSI-IPr. [c] Yield of isolated, analytically pure product. [d] The *E*:*Z* ratio was determined by GC analysis. [e] 0.5 equivalent of electrophile **3c** was used.

5.3 Conclusion

In summary, we have reported that the direct insertion of indium powder into cycloalkenyl iodides in the presence of LiCl in THF allows the preparation of new highly functionalized cycloalkenylindium(III) derivatives, such as 1-oxo-cyclohexen-3-yl indium. In addition, we discovered that, in contrast to many metal insertions to alkenyl iodides which proceed with a loss of stereochemistry,[23] the insertion of In/LiCl to stereodefined (*Z*)- and (*E*)-styryl iodides in THF led to the corresponding indium reagents with high retention of stereochemistry. After a palladium-catalyzed cross-coupling, various polyfunctionalized diastereomerically enriched (*Z*)- and (*E*)-stilbenes were obtained.

5.4 Experimental

General Information

All reactions were carried out under nitrogen atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC. Column chromatographic purification was performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck. Substrates of 3-iodocyclohex-2-enone (**1a**),[24] 3-iodo-2-methylcyclohex-2-enone (**1b**),[25] 3-iodocyclopent-2-enone (**1c**),[26] 1-(1-iodovinyl)benzene (**1d**),[27] and styryl iodides (**1e-k**)[18] were prepared based on reported methods. All other reagents were obtained from commercial sources.

[23] Indium is up to now the only metal that undergoes insertion to alkenyl iodides with retention of the configuration. The use of zinc dust is not general and limited to some isolated examples (see ref. 16a).
[24] E. Piers, I. Nagakura, *Synth. Commun.* **1975**, *5*, 193.
[25] L. F. Tietze, C. A. Vock, I. K. Krimmelbein, J. M. Wiegand, L. Nacke, T. Ramachandar, K. M. D. Islam, C. Gatz, *Chem. Eur. J.* **2008**, *14*, 3670.
[26] (a) G. Lemière, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A.-L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2009**, *131*, 2993; (b) R. Lauchli, W. Boland, *Tetrahedron* **2003**, *59*, 149.
[27] G. Bartoli, R. Cipolletti, G. Di Antonio, R. Giovannini, S. Lanari, M. Marcolini, E. Marcantoni, *Org. Biomol. Chem.* **2010**, *8*, 3509.

Typical procedure for the indium insertion (TP1):

To a 20 mL *Schlenk*-flask equipped with a magnetic stirrer and a rubber septum was added LiCl (0.17 g, 4 mmol, 2 equiv) and dried at 380 °C by heat gun for 5 min under high vacuum. After cooling, the flask was flushed with nitrogen gas, anhydrous THF (6 mL), indium powder (0.46 g, 4 mmol, 2 equiv), internal standard ($C_{10}H_{22}$, 0.2 mL), and alkenyl iodides (2 mmol) were sequentially added. The reaction mixture was stirred vigorously at 55 ^{o}C for the time indicated in Tables 1 and 2. The reaction progress was monitored by GC-analysis of reaction aliquots quenched by sat. NH_4Cl solution until it showed >95% conversion of the starting material. The insertion yield was determined by GC-analysis of reaction aliquots quenched with a THF solution of iodine.

Typical procedure for palladium-catalyzed cross-coupling reactions (TP2):

The supernatant solution of the prepared alkenylindium(III) reagents **2a-d** in THF was carefully transferred into another pre-dried and nitrogen-flushed flask (without the remaining indium powder; otherwise relatively low yield of the cross-coupling product was obtained) with a syringe. Then, THF was carefully removed under vacuum and the flask was flushed with nitrogen gas. DMAC (6 mL), aryl halide (0.7 equiv), and $PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol, 5 mol%) were sequentially added and the reaction mixture was stirred at 80 ^{o}C for 12 h. Then, the reaction mixture was quenched with sat. NH_4Cl solution (20 mL) followed by extraction with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the analytically pure product.

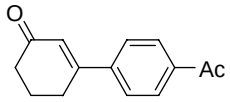
Typical procedure for palladium-catalyzed cross-coupling reactions (TP3):

The supernatant solution of the prepared alkenylindium(III) reagents **2e-k** in THF was carefully transferred into another pre-dried and nitrogen-flushed flask (without the remaining indium powder; otherwise relatively low yield of the cross-coupling product was obtained) with a syringe. *N*-Methyl-2-pyrrolidon (NMP, 3 mL), aryl iodide (0.5~0.7 equiv), and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) were sequentially added and the reaction mixture was stirred at 60 ^{o}C for 24 h. After reaction, the reaction mixture was quenched with sat. NH_4Cl solution (20 mL)

followed by extraction with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the analytically pure product.

Characterization data of products

3-(4-Acetylphenyl)cyclohex-2-enone (4a)



The alkenylindium(III) reagent **2a** was prepared according to **TP1** from 3-iodocyclohex-2-enone (**1a**, 0.444 g, 2 mmol) at 55 °C for 12 h in 78% yield. Its palladium-catalyzed cross-coupling reaction was performed according to **TP2** using 4-bromoacetophenone (**3a**, 0.28 g, 1.4 mmol, 0.7 equiv) and $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol, 5 mol%) in DMAC (6 mL) at 80 °C for 12 h, leading to the corresponding ketone **4a** in 87% yield (261 mg) as a white solid. Spectroscopic data are in accordance with the reported data.[28]

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.98 (d, *J* = 8.6 Hz, 2 H), 7.60 (d, *J* = 8.3 Hz, 2 H), 6.43 (s, 1 H), 2.78 (td, *J* = 6.1, 1.4 Hz, 2 H), 2.61 (s, 3 H), 2.49 (t, *J* = 6.6 Hz, 2 H), 2.21-2.13 (m, 2 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 199.4, 197.2, 158.2, 143.2, 137.7, 128.6, 126.7, 126.2, 37.1, 28.0, 26.6, 22.6.

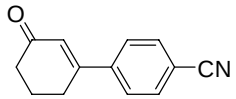
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1680, 1658, 1602, 1406, 1260, 1185, 1119, 960, 884, 829, 816, 723, 693, 599, 588.

MS (EI, 70 eV): m/z (%) = 215 (15), 214 (M^+, 100), 199 (29), 186 (26), 170 (35), 128 (10), 115 (31), 43 (25).

HRMS ($C_{14}H_{14}O_2$, EI): calc.: 214.0994; found: 214.0994 (M^+).

[28] C.-Y. Liu, H. Ren, P. Knochel, *Org. Lett.* **2006**, *8*, 617.

4-(3-Oxocyclohex-1-enyl)benzonitrile (4b)



The alkenylindium(III) reagent **2a** was prepared according to **TP1** from 3-iodocyclohex-2-enone (**1a**, 0.444 g, 2 mmol) at 55 °C for 12 h in 78% yield. Its palladium-catalyzed cross-coupling reaction was performed according to **TP2** using 4-bromobenzonitrile (**3b**, 0.255 g, 1.4 mmol, 0.7 equiv) and $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol, 5 mol%) in DMAC (6 mL) at 80 °C for 12 h, leading to the corresponding substituted benzonitrile **4b** in 98% yield (269 mg) as a white solid. Spectroscopic data are in accordance with the reported data.[16b]

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.74-7.50 (m, 4 H), 6.36 (s, 1 H), 2.73 (td, *J* = 6.0, 1.5 Hz, 2 H), 2.46 (t, *J* = 6.8 Hz, 2 H), 2.18-2.10 (m, 2 H).

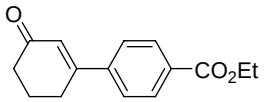
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 199.0, 157.1, 143.1, 132.3, 127.1, 126.5, 118.1, 113.0, 36.9, 27.7, 22.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2222, 1660, 1602, 1453, 1405, 1341, 1314, 1258, 1175, 1130, 953, 888, 830, 814, 575.

MS (EI, 70 eV): m/z (%) = 198 (7), 197 (M^+, 48), 168 (8), 169 (100), 140 (37), 127 (9).

HRMS ($C_{13}H_{11}NO$, EI): calc.: 197.0841; found: 197.0829 (M^+).

Ethyl 4-(3-oxocyclohex-1-enyl)benzoate (4c)



The alkenylindium(III) reagent **2a** was prepared according to **TP1** from 3-iodocyclohex-2-enone (**1a**, 0.444 g, 2 mmol) at 55 °C for 12 h in 78% yield. Its palladium-catalyzed cross-coupling reaction was performed according to **TP2** using ethyl 4-iodobenzoate (**3c**, 0.386 g, 1.4 mmol, 0.7 equiv) and $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol, 5 mol%) in DMAC (6 mL) at 80 °C for 12 h, leading to the corresponding ester **4c** in 96% yield (330 mg) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.04 (d, *J* = 8.6 Hz, 2 H), 7.55 (d, *J* = 8.3 Hz, 2 H), 6.40 (s, 1 H), 4.36 (q, *J* = 7.0 Hz, 2 H), 2.75 (t, *J* = 6.5 Hz, 2 H), 2.47 (t, *J* = 6.6 Hz, 2 H), 2.19-2.10 (m, 2 H), 1.37 (t, *J* = 7.2 Hz, 3 H).

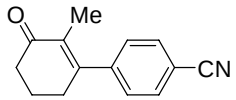
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 199.4, 165.8, 158.3, 142.9, 131.4, 129.8, 126.5, 125.9, 61.1, 37.1, 27.9, 22.6, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1707, 1663, 1605, 1410, 1288, 1269, 1230, 1189, 1129, 1118, 1111, 1019, 909, 872, 770, 751, 722, 698.

MS (EI, 70 eV): m/z (%) = 244 (M^+, 52), 216 (21), 171 (100), 128 (11), 116 (10), 115 (41).

HRMS ($C_{15}H_{16}O_3$, EI): calc.: 244.1099; found: 244.1103 (M^+).

4-(2-Methyl-3-oxocyclohex-1-enyl)benzonitrile (4d)



The alkenylindium(III) reagent **2b** was prepared according to **TP1** from 3-iodo-2-methylcyclohex-2-enone (**1b**, 0.468 g, 2 mmol) at 55 °C for 16 h in 90% yield. Its palladium-catalyzed cross-coupling reaction was performed according to **TP2** using 4-bromobenzonitrile (**3b**, 0.255 g, 1.4 mmol, 0.7 equiv) and $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol, 5 mol%) in DMAC (6 mL) at 80 °C for 12 h, leading to the corresponding substituted benzonitrile **4d** in 91% yield (271 mg) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.68 (d, *J* = 8.3 Hz, 2 H), 7.31 (d, *J* = 8.6 Hz, 2 H), 2.59 (td, *J* = 5.9, 1.9 Hz, 2 H), 2.52 (t, *J* = 6.8 Hz, 2 H), 2.14-2.06 (m, 2 H), 1.66 (t, *J* = 1.8 Hz, 3 H).

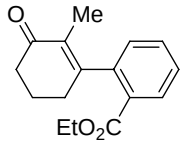
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 199.1, 153.8, 145.8, 132.7, 132.2, 127.9, 118.4, 111.6, 37.5, 32.3, 22.6, 12.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2230, 1657, 1620, 1604, 1403, 1379, 1351, 1329, 1306, 1193, 1106, 1038, 908, 853, 835, 815, 734, 698, 582, 571.

MS (EI, 70 eV): m/z (%) = 212 (12), 211 (M^+, 90), 210 (100), 183 (54), 168 (9), 155 (43), 154 (30), 141 (21), 140 (37), 127 (13), 115 (10).

HRMS ($C_{14}H_{13}NO$, EI): calc.: 211.0997; found: 211.0982 (M^+).

Ethyl 2-(2-methyl-3-oxocyclohex-1-enyl)benzoate (4e)



The alkenylindium(III) reagent **2b** was prepared according to **TP1** from 3-iodo-2-methylcyclohex-2-enone (**1b**, 0.468 g, 2 mmol) at 55 °C for 16 h in 90% yield. Its palladium-catalyzed cross-coupling reaction was performed according to **TP2** using ethyl 2-iodobenzoate (**3d**, 0.386 g, 1.4 mmol, 0.7 equiv) and $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol, 5 mol%) in DMAC (6 mL) at 80 °C for 12 h, leading to the corresponding ester **4e** in 88% yield (318 mg) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.01 (dd, *J* = 7.7, 0.8 Hz, 1 H), 7.54 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.39 (td, *J* = 7.6, 1.1 Hz, 1 H), 7.08 (dd, *J* = 7.6, 0.7 Hz, 1 H), 4.29 (qd, *J* = 7.1, 3.0 Hz, 2 H), 2.67-2.44 (m, 4 H), 2.25-2.04 (m, 2 H), 1.47 (s, 3 H), 1.32 (t, *J* = 7.1 Hz, 3 H).

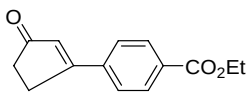
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 199.4, 166.2, 158.2, 142.8, 132.4, 130.7, 130.7, 127.8, 127.6, 127.5, 61.0, 37.8, 33.2, 23.0, 14.2, 12.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1713, 1658, 1626, 1273, 1259, 1224, 1137, 1103, 1087, 1038, 754, 707.

MS (EI, 70 eV): m/z (%) = 259 (19), 258 (M^+, 72), 231 (14), 230 (100), 229 (49), 213 (27), 212 (33), 211 (32), 202 (44), 201 (20), 197 (27), 195 (13), 194 (12), 185 (15), 184 (40), 183 (19), 174 (13), 173 (63), 169 (10), 128 (16), 43 (36).

HRMS ($C_{16}H_{18}O_3$, EI): calc.: 258.1256; found: 258.1244 (M^+).

Ethyl 4-(3-oxocyclopent-1-enyl)benzoate (4f)



The alkenylindium(III) reagent **2c** was prepared according to **TP1** from 3-iodocyclopent-2-enone (**1c**, 0.412 g, 2 mmol) at 55 °C for 20 h in 66% yield. Its palladium-catalyzed cross-coupling reaction was performed according to **TP2** using ethyl 4-iodobenzoate (**3c**, 0.386 g, 1.4 mmol, 0.7 equiv) and $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol, 5 mol%) in DMAC (6 mL) at 80 °C for 12 h, leading to the corresponding ester **4f** in 79% yield (254 mg) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.09 (d, *J* = 8.4 Hz, 2 H), 7.69 (d, *J* = 8.2 Hz, 2 H), 6.62 (s, 1 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 3.05 (dd, *J* = 4.8, 2.9 Hz, 2 H), 2.59 (dt, *J* = 4.8, 2.5 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

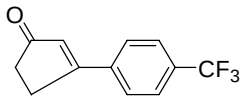
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 208.8, 172.2, 165.7, 137.9, 132.5, 129.9, 129.1, 126.6, 61.2, 35.2, 28.6, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1718, 1675, 1592, 1564, 1438, 1412, 1318, 1273, 1185, 1127, 1105, 1020, 851, 831, 765, 692.

MS (EI, 70 eV): m/z (%) = 230 (M^+, 43), 202 (14), 201 (19), 186 (10), 185 (76), 158 (23), 157 (100), 129 (58), 128 (67), 127 (29), 115 (44), 78 (13), 77 (33), 76 (16), 65 (12), 65 (12), 64 (22), 63 (32), 62 (11), 55 (12), 53 (23), 52 (17), 50 (44), 45 (19), 43 (17).

HRMS ($C_{14}H_{14}O_3$, EI): calc.: 230.0943; found: 230.0944 (M^+).

3-(4-(Trifluoromethyl)phenyl)cyclopent-2-enone (4g)



The alkenylindium(III) reagent **2c** was prepared according to **TP1** from 3-iodocyclopent-2-enone (**1c**, 0.412 g, 2 mmol) at 55 °C for 20 h in 66% yield. Its palladium-catalyzed cross-coupling reaction was performed according to **TP2** using 1-bromo-4-(trifluoromethyl)benzene (**3e**, 0.315 g, 1.4 mmol, 0.7 equiv) and $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol, 5 mol%) in DMAC (6 mL) at 80 °C for 12 h, leading to the corresponding ketone **4g** in 94% yield (298 mg) as a white solid. Spectroscopic data are in accordance with the reported data.[16b]

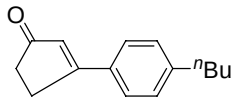
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.73 (q, *J* = 8.6 Hz, 4 H), 6.63 (s, 1 H), 3.07 (td, *J* = 4.8, 1.7 Hz, 2 H), 2.64-2.60 (m, 2 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 208.7, 171.7, 137.4 (q, *J* = 1.4 Hz), 132.5 (q, *J* = 32.7 Hz), 129.3, 127.0, 125.8 (q, *J* = 3.7 Hz), 123.7 (q, *J* = 272.2 Hz), 35.3, 28.6.

MS (EI, 70 eV): m/z (%) = 227 (10), 226 (M^+, 100), 225 (26), 177 (15), 158 (10), 151 (13), 129 (38), 128 (24).

HRMS ($C_{12}H_9F_3O$**, EI):** calc.: 226.0605; found: 226.0589 (M^+).

3-(4-Butylphenyl)cyclopent-2-enone (4h)



The alkenylindium(III) reagent **2c** was prepared according to **TP1** from 3-iodocyclopent-2-enone (**1c**, 0.412 g, 2 mmol) at 55 °C for 20 h in 66% yield. Its palladium-catalyzed cross-coupling reaction was performed according to **TP2** using 1-bromo-4-butylbenzene (**3f**, 0.298 g, 1.4 mmol, 0.7 equiv) and $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol, 5 mol%) in DMAC (6 mL) at 80 °C for 12 h, leading to the corresponding ketone **4h** in 53% yield (160 mg) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.55 (d, *J* = 8.0 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 6.50 (s, 1 H), 2.99 (dd, *J* = 4.8, 2.9 Hz, 2 H), 2.63 (t, *J* = 7.6 Hz, 2 H), 2.55-2.52 (m, 2 H), 1.60 (qd, *J* = 7.7, 7.5 Hz, 2 H), 1.40-1.28 (m, 2 H), 0.91 (t, *J* = 7.3 Hz, 3 H).

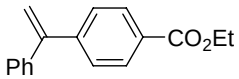
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 209.2, 173.9, 146.7, 131.4, 128.8, 126.7, 126.5, 35.5, 35.1, 33.2, 28.5, 22.2, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} =1675, 1595, 1562, 1508, 1438, 1332, 1271, 1189, 990, 882, 838, 822, 798, 776, 618, 566.

MS (EI, 70 eV): m/z (%) = 215 (10), 214 (M^+, 75), 172 (13), 171 (100), 158 (13), 157 (83), 115 (21).

HRMS ($C_{15}H_{18}O$, EI): calc.: 214.1358; found: 214.1335 (M^+).

Ethyl 4-(1-phenylvinyl)benzoate (4i)



The alkenylindium(III) reagent **2d** was prepared according to **TP1** from 1-(1-iodovinyl)benzene (**1d**, 0.46 g, 2 mmol) at 55 °C for 12 h in 68% yield. Its palladium-catalyzed cross-coupling reaction was performed according to **TP2** using ethyl 4-iodobenzoate (**3c**, 0.386 g, 1.4 mmol, 0.7 equiv) and $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol, 5 mol%) in DMAC (6 mL) at 80 °C for 12 h, leading to the corresponding ester **4i** in 91% yield (319 mg) as a white solid. Spectroscopic data are in accordance with the reported data.[16b]

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.03 (d, *J* = 8.3 Hz, 2 H), 7.42 (d, *J* = 8.6 Hz, 2 H), 7.37-7.31 (m, 5 H), 5.56 (d, *J* = 3.6 Hz, 2 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 1.42 (t, *J* = 7.1 Hz, 3 H).

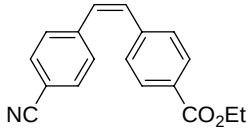
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 149.3, 145.9, 140.8, 129.7, 129.4, 128.3, 128.2, 127.9, 115.7, 60.9, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1714, 1661, 1610, 1448, 1406, 1367, 1269, 1175, 1101, 1078, 1018, 1002, 938, 926, 852, 770, 758, 714, 696, 656, 574.

MS (EI, 70 eV): m/z (%) = 253 (15), 252 (M^+, 76), 224 (20), 208 (20), 207 (100), 179 (60), 178 (87), 177 (15), 176 (16), 152 (17), 89 (14).

HRMS ($C_{17}H_{16}O_2$, EI): calc.: 252.1150; found: 252.1145 (M^+).

(*Z*)-Ethyl 4-(4-cyanostyryl)benzoate (*Z*-4j)



The alkenylindium(III) reagent *Z*-**2e** was prepared according to **TP1** from (*Z*)-4-(2-iodovinyl)benzonitrile (*Z*-**1e**, 0.51 g, 2 mmol, *Z*:*E* = 99:1) at 55 °C for 24 h in 85% yield (*Z*:*E* = 98:2). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using ethyl 4-iodobenzoate (**3c**, 0.386 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding ester *Z*-**4j** in 92% yield (358 mg, *Z*:*E* = 98:2) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.91 (d, *J* = 8.3 Hz, 2 H), 7.49 (d, *J* = 8.3 Hz, 2 H), 7.27 (d, *J* = 8.6 Hz, 2 H), 7.23 (d, *J* = 8.3 Hz, 2 H), 6.77 (d, *J* = 12.2 Hz, 1 H), 6.66 (d, *J* = 12.4 Hz, 1 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 1.37 (t, *J* = 7.2 Hz, 3 H).

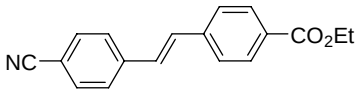
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.0, 141.4, 140.7, 132.1, 132.0, 130.0, 129.6, 129.6, 129.4, 128.6, 118.6, 110.8, 60.9, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2223, 1705, 1604, 1366, 1277, 1238, 1182, 1150, 1127, 1107, 1021, 889, 880, 855, 828, 783, 755, 750, 711, 687, 583, 567.

MS (EI, 70 eV): m/z (%) = 278 (19), 277 (M^+, 87), 249 (22), 233 (22), 232 (100), 205 (14), 204 (16), 203 (55), 202 (10), 177 (23), 176 (19), 88 (11).

HRMS ($C_{18}H_{15}NO_2$, EI): calc.: 277.1103; found: 277.1099 (M^+).

(*E*)-Ethyl 4-(4-cyanostyryl)benzoate (*E*-4j)



The alkenylindium(III) reagent *E*-**2e** was prepared according to **TP1** from (*E*)-4-(2-iodovinyl)benzonitrile (*E*-**1e**, 0.51 g, 2 mmol, *Z*:*E* = 2:98) at 55 °C for 18 h in 85% yield (*Z*:*E* = 4:96). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using ethyl 4-iodobenzoate (**3c**, 0.386 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding ester *E*-**4j** in 78% yield (304 mg, *Z*:*E* = 5:95) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.02 (d, *J* = 7.9 Hz, 2 H), 7.62-7.53 (m, 6 H), 7.20 (d, *J* = 16.8 Hz, 1 H), 7.13 (d, *J* = 16.8 Hz, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 1.38 (t, *J* = 7.1 Hz, 3 H).

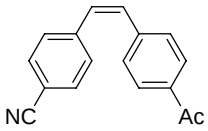
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 165.9, 141.0, 140.4, 132.3, 131.0, 130.0, 129.9, 128.8, 127.0, 126.5, 118.7, 110.9, 60.9, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2222, 1703, 1604, 1464, 1416, 1364, 1276, 1173, 1102, 1019, 976, 968, 959, 858, 850, 823, 764, 721, 697, 690, 553.

MS (EI, 70 eV): m/z (%) = 278 (14), 277 (M^+, 79), 249 (13), 233 (18), 232 (100), 204 (41), 203 (35), 177 (13), 176 (11).

HRMS ($C_{18}H_{15}NO_2$, EI): calc.: 277.1103; found: 277.1098 (M^+).

(*Z*)-4-(4-Acetylstyryl)benzonitrile (*Z*-4k)



The alkenylindium(III) reagent *Z*-**2e** was prepared according to **TP1** from (*Z*)-4-(2-iodovinyl)benzonitrile (*Z*-**1e**, 0.51 g, 2 mmol, *Z*:*E* = 99:1) at 55 °C for 24 h in 85% yield (*Z*:*E* = 98:2). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using 4-iodoacetophenone (**3g**, 0.344 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding ketone *Z*-**4k** in 80% yield (278 mg, *Z*:*E* = 97:3) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.83 (d, *J* = 8.3 Hz, 2 H), 7.50 (d, *J* = 8.3 Hz, 2 H), 7.27 (t, *J* = 8.0 Hz, 4 H), 6.77 (d, *J* = 12.4 Hz, 1 H), 6.68 (d, *J* = 12.2 Hz, 1 H), 2.57 (s, 3 H).

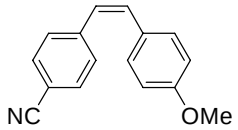
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.3, 141.4, 141.0, 136.1, 132.1, 132.0, 130.3, 129.5, 128.9, 128.5, 118.6, 110.9, 26.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2225, 1671, 1599, 1356, 1265, 1186, 1013, 956, 885, 862, 829, 761, 658, 637, 620, 594, 561.

MS (EI, 70 eV): m/z (%) = 247 (M^+, 47), 233 (17), 232 (100), 204 (12), 203 (28), 177 (12), 176 (11), 43 (13).

HRMS ($C_{17}H_{13}NO$, EI): calc.: 247.0997; found: 247.0986 (M^+).

(*Z*)-4-(4-Methoxystyryl)benzonitrile (*Z*-4l)



The alkenylindium(III) reagent *Z*-**2e** was prepared according to **TP1** from (*Z*)-4-(2-iodovinyl)benzonitrile (*Z*-**1e**, 0.51 g, 2 mmol, *Z*:*E* = 99:1) at 55 °C for 24 h in 85% yield (*Z*:*E* = 98:2). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using 1-iodo-4-methoxybenzene (**3h**, 0.328 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding substituted benzonitrile *Z*-**4l** in 74% yield (242 mg, *Z*:*E* = 94:6) as a pale yellow solid. Spectroscopic data are in accordance with the reported data.[29]

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.51 (d, *J* = 8.3 Hz, 2 H), 7.35 (d, *J* = 8.3 Hz, 2 H), 7.14 (d, *J* = 8.9 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 6.69 (d, *J* = 12.2 Hz, 1 H), 6.48 (d, *J* = 12.2 Hz, 1 H), 3.81 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.2, 142.5, 132.8, 132.0, 130.1, 129.4, 128.5, 126.8, 118.9, 113.8, 110.2, 55.2.

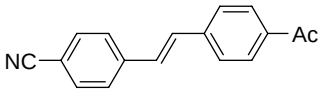
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2227, 1599, 1570, 1507, 1426, 1252, 1180, 1172, 1110, 1022, 879, 831, 813, 765, 702, 569.

MS (EI, 70 eV): m/z (%) = 236 (17), 235 (M^+, 100), 220 (11), 190 (19), 165 (16).

[29] D.-J. Dong, H.-H. Li, S.-K. Tian, *J. Am. Chem. Soc.* **2010**, *132*, 5018.

HRMS ($C_{16}H_{13}NO$, EI): calc.: 235.0997; found: 235.0996 (M^+).

(*E*)-4-(4-Acetylstyryl)benzonitrile (*E*-4k)



The alkenylindium(III) reagent *E*-**2e** was prepared according to **TP1** from (*E*)-4-(2-iodovinyl)benzonitrile (*E*-**1e**, 0.51 g, 2 mmol, *Z*:*E* = 2:98) at 55 °C for 18 h in 85% yield (*Z*:*E* = 4:96). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using 4-iodoacetophenone (**3g**, 0.344 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding ketone *E*-**4k** in 71% yield (246 mg, *Z*:*E* = 4:96) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.97 (d, *J* = 8.6 Hz, 2 H), 7.67-7.59 (m, 6 H), 7.24 (d, *J* = 16.6 Hz, 1 H), 7.18 (d, *J* = 16.6 Hz, 1 H), 2.61 (s, 3 H).

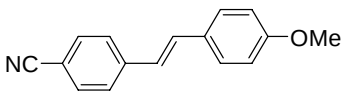
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.2, 141.1, 140.7, 136.6, 132.5, 131.0, 129.2, 128.9, 127.1, 126.9, 118.7, 111.2, 26.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2220, 1671, 1601, 1500, 1410, 1354, 1268, 1174, 983, 958, 853, 836, 827, 798, 696, 589.

MS (EI, 70 eV): m/z (%) = 247 (M^+, 43), 233 (18), 232 (100), 204 (12), 203 (32), 177 (13), 176 (14), 88 (10).

HRMS ($C_{16}H_{10}NO$, EI): calc.: 232.0762; found: 232.0748 (M^+-CH_3).

(*E*)-4-(4-Methoxystyryl)benzonitrile (*E*-4l)



The alkenylindium(III) reagent *E*-**2e** was prepared according to **TP1** from (*E*)-4-(2-iodovinyl)benzonitrile (*E*-**1e**, 0.51 g, 2 mmol, *Z*:*E* = 2:98) at 55 °C for 18 h in 85% yield (*Z*:*E* = 4:96). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using 1-iodo-4-methoxybenzene (**3h**, 0.328 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding substituted benzonitrile *E*-**4l** in 69% yield (226 mg, *Z*:*E*

= 4:96) as a pale yellow solid. Spectroscopic data are in accordance with the reported data.[29,30]

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.61 (d, *J* = 8.6 Hz, 2 H), 7.54 (d, *J* = 8.6 Hz, 2 H), 7.48 (d, *J* = 8.9 Hz, 2 H), 7.16 (d, *J* = 16.3 Hz, 1 H), 6.97-6.91 (m, 3 H), 3.85 (s, 3 H).

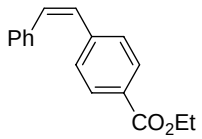
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.0, 142.2, 132.4, 131.9, 129.0, 128.2, 126.5, 124.5, 119.1, 114.2, 110.0, 55.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2220, 1596, 1571, 1512, 1422, 1294, 1252, 1224, 1174, 1111, 1029, 974, 954, 941, 833, 770, 648, 555.

MS (EI, 70 eV): m/z (%) = 236 (19), 235 (M^+, 100), 220 (18), 192 (12), 191 (14), 190 (30), 177 (10), 165 (26).

HRMS ($C_{16}H_{13}NO$, EI): calc.: 235.0997; found: 235.0998 (M^+).

(*Z*)-Ethyl 4-styrylbenzoate (*Z*-4m)



The alkenylindium(III) reagent *Z*-**2f** was prepared according to **TP1** from (*Z*)-1-(2-iodovinyl)benzene (*Z*-**1f**, 0.46 g, 2 mmol, *Z*:*E* = 97:3) at 55 °C for 48 h in 51% yield (*Z*:*E* = 95:5). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using ethyl 4-iodobenzoate (**3c**, 0.276 g, 1.0 mmol, 0.5 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding ester *Z*-**4m** in 82% yield (208 mg, *Z*:*E* = 94:6) as a white solid. Spectroscopic data are in accordance with the reported data.[31]

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.92 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 7.24 (s, 5H), 6.73 (d, *J* = 12.3 Hz, 1 H), 6.62 (d, *J* = 12.2 Hz, 1 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 141.9, 136.7, 132.1, 129.4, 129.2, 128.9, 128.8, 128.8, 128.3, 127.4, 60.8, 14.3.

[30] (a) T. Nishizawa, H. K. Lim, K. Tajima, K. Hashimoto, *J. Am. Chem. Soc.* **2009**, *131*, 2464; (b) P. Colbon, J. H. Barnard, M. Purdie, K. Mulholland, I. Kozhevnikov, J. Xiao, *Adv. Synth. Catal.* **2012**, *354*, 1395.

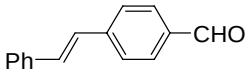
[31] (a) A. Moncomble, P. L. Floch, A. Lledos, C. Gosmini, *J. Org. Chem.* **2012**, *77*, 5056; (b) Y. Nakao, H. Imanaka, J. Chen, A. Yada, T. Hiyama, *J. Organomet. Chem.* **2007**, *692*, 585.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1704, 1605, 1474, 1448, 1414, 1367, 1324, 1273, 1178, 1125, 1103, 1068, 1019, 973, 962, 877, 836, 775, 713, 697, 554.

MS (EI, 70 eV): m/z (%) = 253 (19), 252 (M^+, 100), 208 (12), 207 (65), 180 (13), 179 (84), 178 (78), 177 (12), 176 (13), 152 (13), 89 (11).

HRMS ($C_{17}H_{16}O_2$, EI): calc.: 252.1150; found: 252.1143 (M^+).

(*E*)-4-Styrylbenzaldehyde (*E*-4n)



The alkenylindium(III) reagent *E*-**2f** was prepared according to **TP1** from (*E*)-1-(2-iodovinyl)benzene (*E*-**1f**, 0.46 g, 2 mmol, *Z*:*E* = 1:99) at 55 °C for 5 d in 72% yield (*Z*:*E* = 2:98). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using 4-iodobenzaldehyde (**3i**, 0.324 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding aldehyde *E*-**4n** in 89% yield (261 g, *Z*:*E* = 3:97) as a pale yellow solid. Spectroscopic data are in accordance with the reported data.[32]

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 10.00 (s, 1 H), 7.88 (d, *J* = 8.3 Hz, 2 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 7.56 (d, *J* = 7.2 Hz, 2 H), 7.40 (t, *J* = 7.3 Hz, 2 H), 7.33 (t, *J* = 7.2 Hz, 1 H), 7.27 (d, *J* = 16.6 Hz, 1 H), 7.15 (d, *J* = 16.3 Hz, 1 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 191.6, 143.3, 136.5, 135.2, 132.1, 130.2, 128.8, 128.5, 127.3, 126.8.

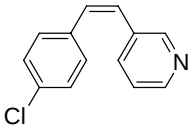
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} =1694, 1591, 1563, 1491, 1448, 1419, 1301, 1210, 1167, 1106, 1073, 969, 956, 844, 817, 792, 760, 712, 689, 653.

MS (EI, 70 eV): m/z (%) = 209 (16), 208 (M^+, 93), 207 (25), 180 (17), 179 (100), 178 (82), 177 (13), 176 (15), 165 (15), 152 (18), 89 (19), 77 (11), 76 (13), 51 (10).

HRMS ($C_{15}H_{12}O$, EI): calc.: 208.0888; found: 208.0890 (M^+).

[32] (a) G.-Q. Kong, S. Ou, C. Zou, C.-D. Wu, *J. Am. Chem. Soc.* **2012**, *134*, 19851; (b) L. Zhang, X. Bi, X. Guan, X. Li, Q. Liu, B.-D. Barry, P. Liao, *Angew. Chem.*, *Int. Ed.* **2013**, *52*, 11303.

(*Z*)-3-(4-Chlorostyryl)pyridine (*Z*-4o)



The alkenylindium(III) reagent *Z*-**2g** was prepared according to **TP1** from (*Z*)-1-chloro-4-(2-iodovinyl)benzene (*Z*-**1g**, 0.528 g, 2 mmol, *Z*:*E* = 98:2) at 55 °C for 12 h in 83% yield (*Z*:*E* = 98:2). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using 3-iodopyridine (**3j**, 0.288 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding pyridine derivative *Z*-**4o** in 65% yield (194 mg, *Z*:*E* = 98:2) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.47 (d, *J* = 1.4 Hz, 1 H), 8.44 (dd, *J* = 4.7, 1.4 Hz, 1 H), 7.49 (d, *J* = 7.7 Hz, 1 H), 7.23-7.12 (m, 5 H), 6.69 (d, *J* = 12.2 Hz, 1 H), 6.57 (d, *J* = 12.2 Hz, 1 H).

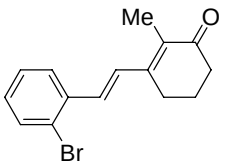
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.0, 148.3, 135.7, 134.9, 133.3, 132.6, 131.3, 130.0, 128.7, 127.1, 123.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1585, 1566, 1489, 1473, 1418, 1401, 1182, 1089, 1024, 1014, 954, 877, 823, 807, 776, 736, 709, 625, 603, 560

MS (EI, 70 eV): m/z (%) = 217 (31), 216 (41), 215 (M^+, 83), 214 (100), 180 (53), 179 (27), 178 (26), 153 (10), 152 (35), 151 (16), 149 (12), 127 (11), 76 (14), 75 (12), 63 (10), 51 (10), 43 (13).

HRMS ($C_{13}H_{10}ClN$, EI): calc.: 215.0502; found: 215.0487 (M^+).

(*E*)-3-(2-Bromostyryl)-2-methylcyclohex-2-enone (*E*-4p)



The alkenylindium(III) reagent *E*-**2h** was prepared according to **TP1** from (*E*)-1-bromo-2-(2-iodovinyl)benzene (*E*-**1h**, 0.618 g, 2 mmol, *Z*:*E* = 1:99) at 55 °C for 6 d in 70% yield (*Z*:*E* = 1:99). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using 3-iodo-2-methylcyclohex-2-enone (**3k**, 0.33 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at

60 °C for 24 h, leading to the corresponding ketone *E*-**4p** in 94% yield (382 mg, *Z*:*E* = 2:98) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.65 (dd, *J* = 7.9, 1.2 Hz, 1 H), 7.60 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.35-7.30 (m, 2 H), 7.23 (d, *J* = 16.0 Hz, 1H), 7.21-7.14 (m, 1H), 2.68 (t, *J* = 5.4 Hz, 2 H), 2.50 (t, *J* = 6.8 Hz, 2 H), 2.10-2.02 (m, 2 H), 2.01 (s, 3 H).

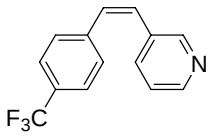
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 199.7, 149.1, 136.5, 133.2, 133.2, 133.0, 129.7, 129.3, 127.7, 127.1, 124.6, 37.9, 26.1, 22.0, 10.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1648, 1606, 1573, 1461, 1431, 1377, 1354, 1330, 1300, 1280, 1259, 1218, 1192, 1137, 1078, 1044, 1018, 951, 928, 756, 746, 704, 690, 655, 558.

MS (EI, 70 eV): m/z (%) = 292 (59), 291 (16), 290 (M^+, 52), 275 (13), 236 (11), 234 (12), 211 (39), 183 (37), 168 (20), 167 (19), 165 (12), 165 (13), 156 (15), 155 (100), 154 (29), 153 (39), 152 (33), 142 (18), 141 (25), 139 (21), 135 (40), 129 (16), 128 (35), 127 (16), 115 (45), 91 (13), 89 (11), 77 (29), 76 (29), 70 (13), 63 (20), 57 (15), 55 (16), 51 (18), 44 (12), 43 (13), 43 (57), 41 (21).

HRMS ($C_{15}H_{15}BrO$, EI): calc.: 290.0306; found: 290.0305 (M^+).

(*Z*)-3-(4-(Trifluoromethyl)styryl)pyridine (*Z*-4q)



The alkenylindium(III) reagent *Z*-**2i** was prepared according to **TP1** from (*Z*)-1-(2-iodovinyl)-4-(trifluoromethyl)benzene (*Z*-**1i**, 0.596 g, 2 mmol, *Z*:*E* = 97:3) at 55 °C for 70 h in 72% yield (*Z*:*E* = 95:5). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using 3-iodopyridine (**3j**, 0.288 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding pyridine derivative *Z*-**4q** in 77% yield (270 mg, *Z*:*E* = 94:6) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.47 (s, 2 H), 7.52-7.48 (m, 3 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.17 (dd, *J* = 7.3, 4.8 Hz, 1 H), 6.77 (d, *J* = 12.2 Hz, 1 H), 6.67 (d, *J* = 12.4 Hz, 1 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.0, 148.5, 140.2, 135.8, 132.3, 131.1, 129.5 (q, *J* = 32.5 Hz), 129.0, 128.4, 125.5 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 272.2 Hz), 123.1.

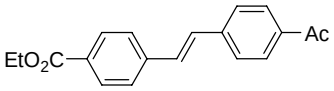
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -62.7 (s, 3F).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1407, 1320, 1163, 1118, 1108, 1064, 1024, 1017, 880, 836, 811, 788, 751, 727, 711, 625, 601, 571.

MS (EI, 70 eV): m/z (%) = 249 (M^+, 51), 248 (100), 180 (17), 152 (13), 57 (19), 42 (13).

HRMS ($C_{14}H_{10}F_3N$, EI): calc.: 249.0765; found: 249.0783 (M^+).

(*E*)-Ethyl 4-(4-acetylstyryl)benzoate (*E*-4r)



The alkenylindium(III) reagent *E*-**2j** was prepared according to **TP1** from (*E*)-ethyl 4-(2-iodovinyl)benzoate (*E*-**1j**, 0.604 g, 2 mmol, *Z*:*E* = 2:98) at 55 °C for 24 h in 73% yield (*Z*:*E* = 2:98). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using 4-iodoacetophenone (**3g**, 0.344 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding ketone *E*-**4r** in 74% yield (338 mg, *Z*:*E* = 2:98) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.04 (d, *J* = 8.2 Hz, 2 H), 7.96 (d, *J* = 8.4 Hz, 2 H), 7.60 (d, *J* = 5.6 Hz, 2 H), 7.57 (d, *J* = 5.8 Hz, 2 H), 7.22 (s, 2 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 2.60 (s, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

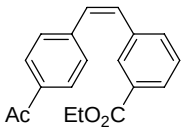
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.3, 166.2, 141.3, 140.9, 136.3, 130.2, 130.0, 129.8, 129.7, 128.8, 126.7, 126.5, 60.9, 26.5, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1712, 1685, 1603, 1411, 1358, 1263, 1220, 1178, 1111, 1100, 1015, 962, 956, 849, 816, 765, 726, 715, 693, 652, 592, 581.

MS (EI, 70 eV): m/z (%) = 295 (19), 294 (M^+, 96), 280 (19), 279 (100), 251 (15), 249 (20), 178 (28), 176 (11).

HRMS ($C_{19}H_{18}O_3$, EI): calc.: 294.1256; found: 294.1264 (M^+).

(*Z*)-Ethyl 3-(4-acetylstyryl)benzoate (*Z*-4s)



The alkenylindium(III) reagent *Z*-**2k** was prepared according to **TP1** from (*Z*)-1-(4-(2-iodovinyl)phenyl)ethanone (*Z*-**1k**, 0.544 g, 2 mmol, *Z*:*E* = 99:1) at 55 °C for 18 h in 86% yield (*Z*:*E* = 98:2). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using ethyl 3-iodobenzoate (**3l**, 0.386 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding ester *Z*-**4s** in 72% yield (298 mg, *Z*:*E* = 95:5) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.94-7.91 (m, 2 H), 7.84 (d, *J* = 8.3 Hz, 2 H), 7.39 (d, *J* = 7.7 Hz, 1 H), 7.33-7.30 (m, 3 H), 6.76 (d, *J* = 12.4 Hz, 1 H), 6.70 (d, *J* = 12.2 Hz, 1 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 2.58 (s, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

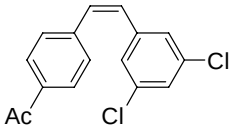
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.4, 166.2, 141.7, 136.8, 135.7, 133.0, 131.2, 130.7, 130.1, 130.0, 128.9, 128.5, 128.3, 128.3, 60.9, 26.5, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1712, 1675, 1601, 1434, 1356, 1287, 1261, 1221, 1185, 1104, 1014, 988, 956, 926, 822, 748, 728, 682, 670, 618, 590.

MS (EI, 70 eV): m/z (%) = 295 (19), 294 (M^+, 85), 280 (20), 279 (100), 251 (13), 249 (12), 205 (11), 178 (28), 177 (14), 176 (15).

HRMS ($C_{19}H_{18}O_3$, EI): calc.: 294.1256; found: 294.1252 (M^+).

(*Z*)-1-(4-(3,5-Dichlorostyryl)phenyl)ethanone (*Z*-4t)



The alkenylindium(III) reagent *Z*-**2k** was prepared according to **TP1** from (*Z*)-1-(4-(2-iodovinyl)phenyl)ethanone (*Z*-**1k**, 0.544 g, 2 mmol, *Z*:*E* = 99:1) at 55 °C for 18 h in 86% yield (*Z*:*E* = 98:2). Its palladium-catalyzed cross-coupling reaction was performed according to **TP3** using 1,3-dichloro-5-iodobenzene (**3m**, 0.382 g, 1.4 mmol, 0.7 equiv) and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) in THF/NMP (2:1) at 60 °C for 24 h, leading to the corresponding ketone *Z*-**4t** in 84% yield (342 mg, *Z*:*E* = 96:4) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.84 (d, *J* = 8.0 Hz, 2 H), 7.28 (d, *J* = 8.3 Hz, 2 H), 7.20 (s, 1 H), 7.07 (s, 2 H), 6.69 (d, *J* = 12.4 Hz, 1 H), 6.56 (d, *J* = 12.4 Hz, 1 H), 2.57 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.4, 140.8, 139.6, 136.1, 134.9, 131.5, 129.3, 128.9, 128.5, 127.4, 127.1, 26.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1677, 1602, 1583, 1557, 1421, 1406, 1357, 1263, 1202, 1182, 1115, 1099, 1014, 957, 936, 853, 845, 827, 800, 771, 672, 650, 631, 596, 564.

MS (EI, 70 eV): m/z (%) = 292 (35), 291 (10), 290 (M^+, 54), 279 (11), 278 (11), 277 (68), 276 (18), 275 (100), 214 (15), 212 (46), 177 (12), 176 (32).

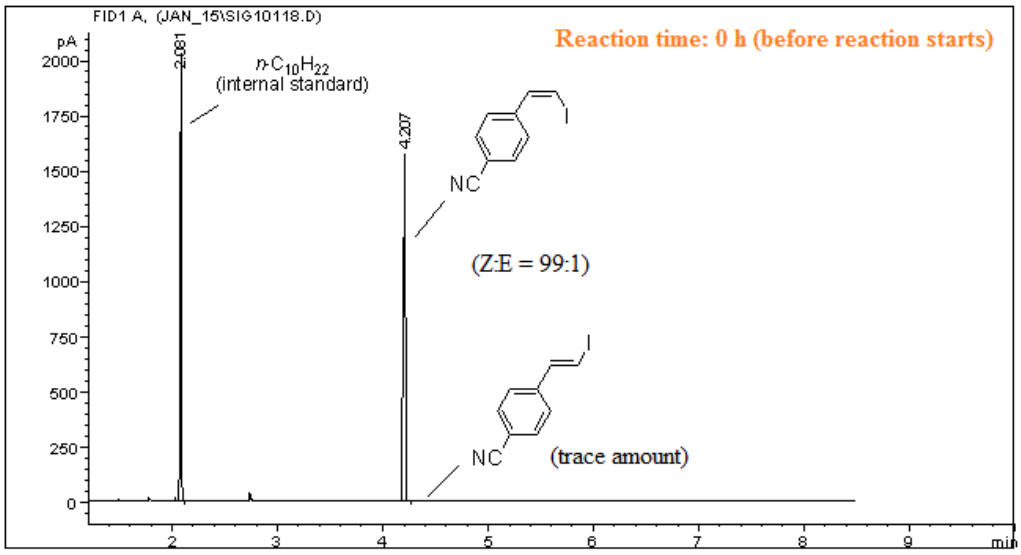
HRMS ($C_{16}H_{12}Cl_2O$, EI): calc.: 290.0265; found: 290.0258 (M^+).

Determination of the Yield and *Z*:*E* Ratio of the Alkenylindium(III) Reagent: Using the Insertion of Indium into (*Z*)-4-(2-Iodovinyl)benzonitrile as An Example

Data File C:\HPCHEM\2\DATA\JAN_15\SIG10118.D Sample Name: z10

```
==========================================================================
Injection Date  : 1/18/2015 6:37:00 PM          Seq. Line :   1
Sample Name     : z10                            Location : Vial 26
Acq. Operator   : AK Knochel                        Inj :   1
                                                Inj Volume : 1 µl
Acq. Method     : C:\HPCHEM\2\METHODS\50.M
Last changed    : 10/24/2014 9:47:42 AM by AK Knochel
Analysis Method : C:\HPCHEM\2\METHODS\70.M
Last changed    : 1/30/2015 9:51:27 AM by AK Knochel
                  (modified after loading)
Kolja
```

GC 1



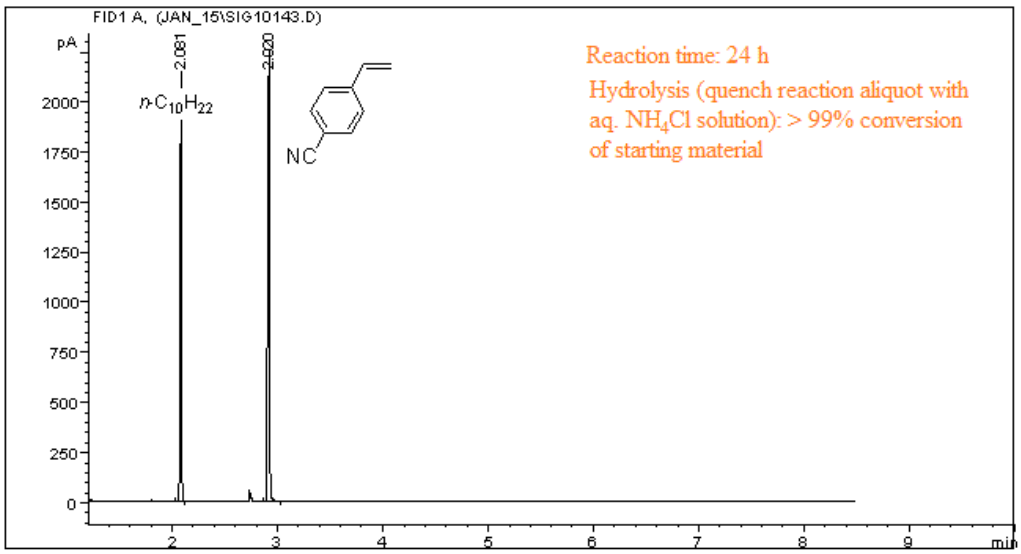

```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   2.081 BB S  0.0110 1486.02222 2019.49243 42.83949
   2   4.207 PB    0.0180 1982.79187 1568.08093 57.16051

Totals :                  3468.81409 3587.57336

 Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***
```

GC9 1/30/2015 9:55:26 AM AK Knochel Page 1 of 1

Data File C:\HPCHEM\2\DATA\JAN_15\SIG10143.D Sample Name: zll

```
==================================================================
Injection Date  : 1/19/2015 8:01:44 PM          Seq. Line :   2
Sample Name     : zll                            Location : Vial 27
Acq. Operator   : AK Knochel                        Inj :   1
                                                Inj Volume : 1 µl
Acq. Method     : C:\HPCHEM\2\METHODS\50.M
Last changed    : 10/24/2014 9:47:42 AM by AK Knochel
Analysis Method : C:\HPCHEM\2\METHODS\70.M
Last changed    : 1/30/2015 9:55:27 AM by AK Knochel
                  (modified after loading)
Kolja
```

GC 2



Reaction time: 24 h
Hydrolysis (quench reaction aliquot with aq. NH_4Cl solution): > 99% conversion of starting material

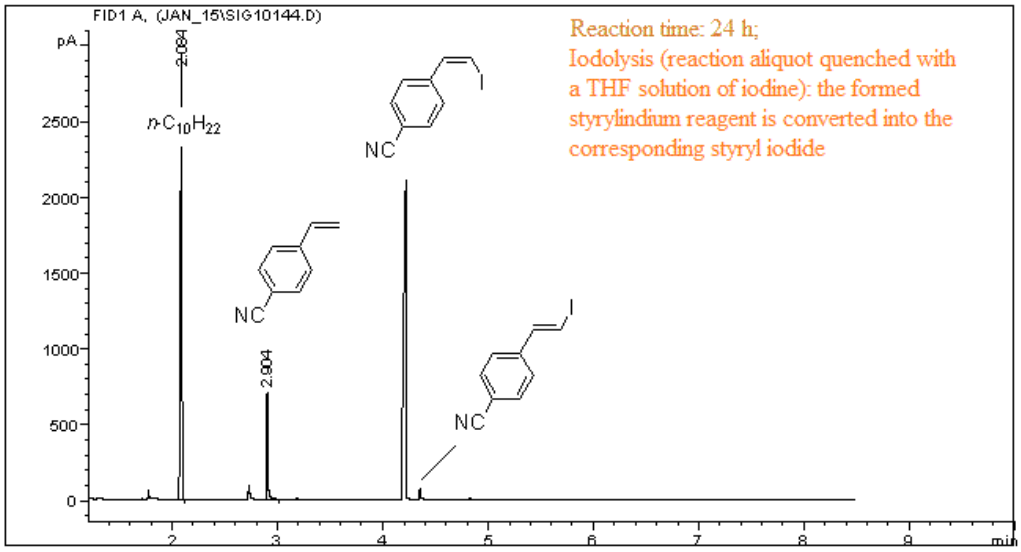
```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   2.081 PB S  0.0128 1698.52234 2142.86768 41.06506
   2   2.920 PB    0.0159 2437.65186 2203.59204 58.93494

Totals :                  4136.17419 4346.45972

 Results obtained with enhanced integrator!
==================================================================
                        *** End of Report ***
```

GC9 1/30/2015 9:56:05 AM AK Knochel Page 1 of 1

Data File C:\HPCHEM\2\DATA\JAN_15\SIG10144.D Sample Name: z12

```
==================================================================
Injection Date  : 1/19/2015 8:16:56 PM          Seq. Line :   3
Sample Name     : z12                            Location : Vial 26
Acq. Operator   : AK Knochel                        Inj :   1
                                                Inj Volume : 1 µl
Acq. Method     : C:\HPCHEM\2\METHODS\50.M
Last changed    : 1/19/2015 8:12:57 PM by AK Knochel
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\70.M
Last changed    : 1/30/2015 10:00:05 AM by AK Knochel
                  (modified after loading)
Kolja
```

GC 3



Reaction time: 24 h;
Iodolysis (reaction aliquot quenched with a THF solution of iodine): the formed styrylindium reagent is converted into the corresponding styryl iodide

```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------
   1   2.084 BB S  0.0127 2597.92798 2944.68823 82.7223
   2   2.904 VB    0.0121  542.61078  709.14545 17.2776

Totals :                  3140.53876 3653.83368

 Results obtained with enhanced integrator!
==================================================================
                      *** End of Report ***
```

percent of styrene remained after iodolysis:

$$\frac{8.577}{58.935} = 15\%$$

convert → 41.065 / 8.577

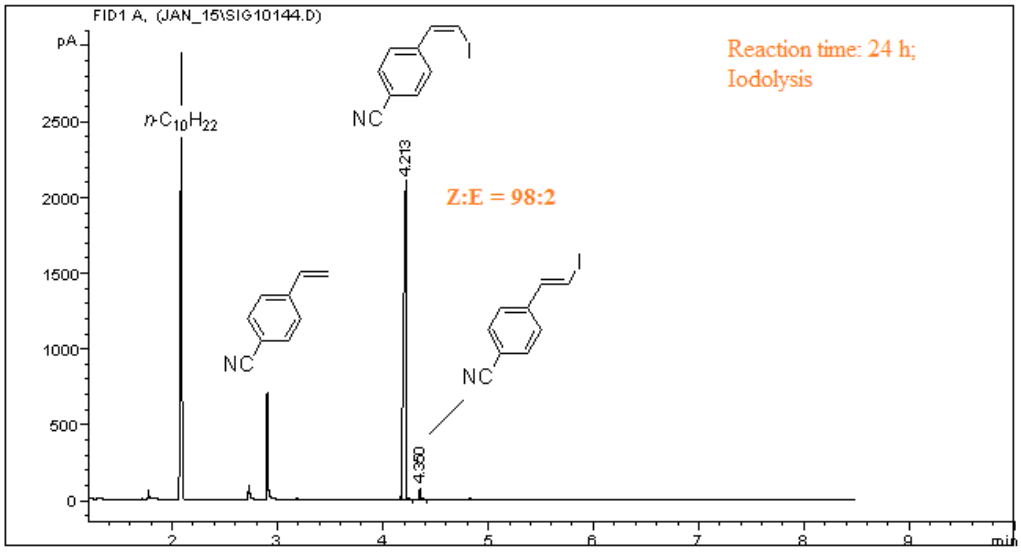
85% yield of styrylindium reagent

GC9 1/30/2015 10:00:08 AM AK Knochel Page 1 of 1

Data File C:\HPCHEM\2\DATA\JAN_15\SIG10144.D Sample Name: z12

```
==================================================================
Injection Date  : 1/19/2015 8:16:56 PM          Seq. Line :   3
Sample Name     : z12                            Location : Vial 26
Acq. Operator   : AK Knochel                         Inj :   1
                                                Inj Volume : 1 µl
Acq. Method     : C:\HPCHEM\2\METHODS\50.M
Last changed    : 1/19/2015 8:12:57 PM by AK Knochel
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\70.M
Last changed    : 1/30/2015 9:59:13 AM by AK Knochel
                  (modified after loading)
Kolja
```

GC 4

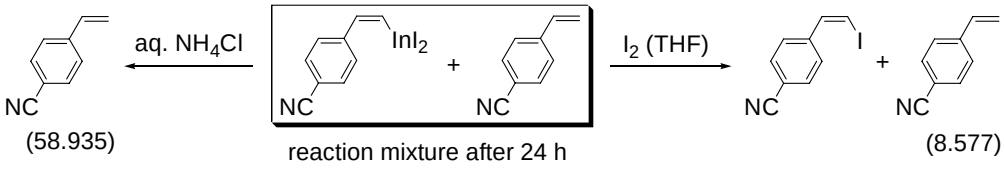



```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   4.213 PB    0.0197 2995.44702 2093.33008 97.80461
   2   4.350 PB    0.0131   67.23801   74.58783  2.19539

Totals :                  3062.68504 2167.91791

 Results obtained with enhanced integrator!
==================================================================
                      *** End of Report ***
```

Z:E = 98:2

GC9 1/30/2015 9:59:16 AM AK Knochel Page 1 of 1

Based on spectrum GC 1 and GC 2 after hydrolysis (quenching with sat. NH_4Cl solution), the insertion reaction proceeded with > 99% conversion of the starting material of (*Z*)-4-(2-iodovinyl)benzonitrile.



After 24 h, the reaction mixture mainly contains two types of products (see above Scheme): one is the desired styrylindium reagent (mainly *Z* isomer), another is styrene (presumably generated from partial hydrolysis of the formed styrylindium reagent by moisture or proton source from THF during insertion step involving a radical-type mechanism). After hydrolysis with sat. NH_4Cl solution, all are converted into styrene; after iodolysis with THF solution of iodine, styryl iodide is re-generated from the formed styrylindium reagent (the styrene remains there). Thus, based on the overall amount of the styrene generated (after hydrolysis) and the remained amount of the styrene (after iodolysis), both against the same amount of internal standard, the yield of the formed styrylindium reagent can be determined.

Thus, based on spectrum GC 2 with the internal standard (which always remains the same), the overall amount (or area percent) of the styrene is 58.935 and the amount of internal standard is 41.065; Then, after iodolysis (seen spectrum GC 3), still 8.577 amount of styrene (after conversion based on the same amount of internal standard of 41.065) remains there.

Then, the percent of styrene in the reaction mixture is calculated to be “8.577/58.935 = 15%”. Thus, the yield of the formed styrylindium reagent is calculated to be “100% - 15% = 85%”.

In cases where no full conversion of the starting material was observed (for example, 90% yield of conversion) by GC analysis against internal standard, the yield of the formed organometallic reagent can also be calculated based on above method but multiply further by conversion yield (for example, 90%) to give the final yield.

In cases where the formed organometallic reagent also undergoes considerable other side reactions, such as homo-coupling reaction, this method is not adaptable; under such circumstance, titration by iodine to know the actual concentration of the formed organometallic reagent is suggested (then the yield can be calculated based on the determined concentration and the volume of the reaction mixture).

Based on the spectrum GC 4 (the spectrum is the same as GC 3), the *Z*:*E* ratio of the formed styrylindium reagent is determined to be 98:2.

It should be noted that the authenticity of compounds (peaks in the GC spectrum) are determined by GC-MS analysis.

Chapter 6. Polyfunctional Alkenyl Li, Mg, or Zn-Organometallics as Versatile Building Blocks for the Synthesis of Complex Heterocycles

6.1 Introduction

The preparation of polyfunctional organometallic reagents has found many synthetic applications.[1-5] The presence of electrophilic functional groups in close proximity to a reactive carbon-metal bond opens numerous synthetic opportunities to perform cyclizations and therefore to construct new heterocyclic scaffolds of high interest for the pharmaceutical and agrochemical industry. Such conjunctive organometallic reagents[6] may allow the expeditive preparation of heterocycles not readily available by standard methods. Herein, we wish to report the synthesis of the conjunctive organometallic reagents **1a-c** (Met = Li, MgCl, ZnCl) which provides an entry to important functionalized 5-, 6-, 7-membered heterocycles (e.g., furan, pyrrole,

[1] (a) *Handbook of Functionalized Organometallics*; P. Knochel, Ed.; Wiley-VCH: Weinheim, **2005**; (b) T. Klatt, J. T. Markiewicz, C. Sämann, P. Knochel, *J. Org. Chem.* **2014**, *79*, 4253; (c) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794; (d) 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.

[2] For selected reviews regarding the preparation of functionalized organolithium reagents, see: (a) C. Nájera, J. M. Sansano, M. Yus, *Tetrahedron* **2003**, *59*, 9255; (b) R. Chinchilla, C. Najera, M. Yus, *Tetrahedron* **2005**, *61*, 3139; (c) F. Foubelo, M. Yus, *Chem. Soc. Rev.* **2008**, **37**, 2620; (d) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667; (e) Z. Xi, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1021; (f) Z. Xi, *Acc. Chem. Res.* **2010**, *43*, 1342; (g) *The Chemistry of Organolithium Compounds*; Z. Rappoport, I. Marek, Eds.; John Wiley and Sons: New York, **2004**.

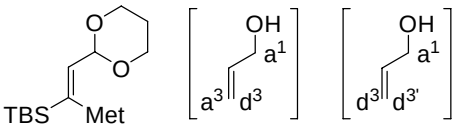
[3] For recent reviews on the protecting group-free synthesis, see: (a) E. Roulland, *Angew. Chem. Int. Ed.* **2011**, *50*, 1226; (b) I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, *1*, 193; (c) R. W. Hoffmann, *Synthesis* **2006**, 3531.

[4] (a) *The Chemistry of Organomagnesium Compounds*; Z. Rappoport, I. Marek, Eds.; Wiley-VCH: Weinheim, **2008**; (b) *Titanium and Zirconium in Organic Synthesis*; I. Marek, Ed.; Wiley-VCH: Weinheim, **2002**.

[5] (a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; (b) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.

[6] (a) B. M. Trost, *Acc. Chem. Res.* **1978**, *11*, 453; (b) D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239; (c) B. M. Trost, J. E. Vincent, *J. Am. Chem. Soc.* **1980**, *102*, 5680; (d) D. Seebach, P. Knochel, *Helv. Chim. Acta* **1984**, *67*, 261; (e) B. M. Trost, H. C. Arndt, P. E. Strege, T. R. Verhoeven, *Tetrahedron Lett.* **1976**, *4*, 3477; (f) B. M. Trost, D. M. T. Chan, *J. Am. Chem. Soc.* **1979**, *101*, 6429; (g) B. M. Trost, D. P. Curran, *J. Am. Chem. Soc.* **1981**, *103*, 7380; (h) B. M. Trost, N. R. Schmuff, *J. Am. Chem. Soc.* **1985**, *107*, 396; (i) P. Breulles, D. Uguen, *Tetrahedron Lett.* **1987**, *28*, 6053; (j) X. Jia, D. A. Petrone, M. Lautens, *Angew. Chem. Int. Ed.* **2012**, *51*, 9870; (k) B. D. Chandler, J. T. Roland, Y. Li, E. J. Sorensen, *Org. Lett.* **2010**, *12*, 2746, and references cited therein.

quinoline, naphthyridine, and fused pyrazole) and are synthetic equivalent of the two allylic conjunctive synthons[6b] **2** and **3** (Figure 1).



1a: Met = Li
1b: Met = MgCl
1c: Met = ZnCl

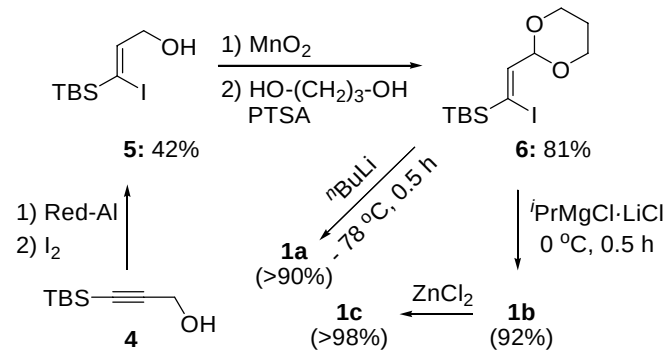
2 **3**

Figure 1. The *β*-metalated unsaturated acetal (**1a-c**; Met = Li, MgCl, and ZnCl) are excellent conjunctive reagents for the preparation of various classes of important heterocycles, such as pyrrole, quinoline, naphthyridine, fused pyrazole, and 2,3-dihydro-benzo[*c*]azepine

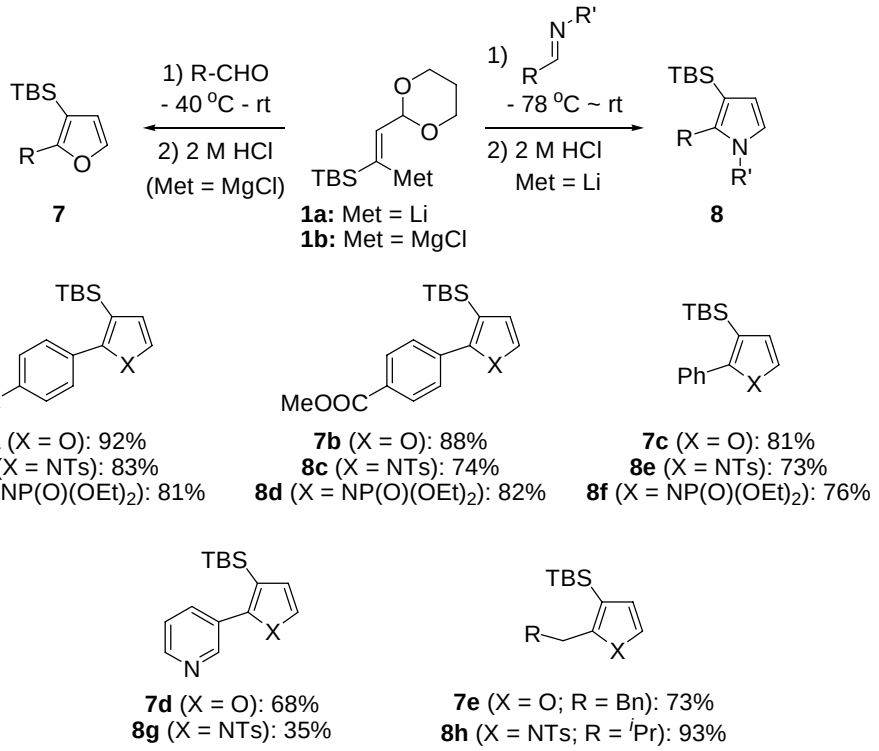
6.2 Results and Discussion

Thus, the TBS-substituted[7] propargyl alcohol (**4**) was hydroaluminated with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al)[8] followed by iodolysis providing the *Z*-allylic alcohol **5** in 42% overall yield (Scheme 1). After MnO_2-oxidation[9] and standard acetal formation[10] the *Z*-alkenyl iodide **6** was obtained in 81% yield. Treatment of **6** with BuLi[2] (1.1 equiv, THF, -78 ^oC, 0.5 h) furnished the expected lithium reagent **1a** in > 90% yield. The reaction of **6** with ^{i}PrMgCl·LiCl[11] (1.2 equiv, THF, 0 ^oC, 0.5 h) gave the corresponding magnesium reagent **1b** in 92% yield. Further transmetalation of **1b** with $ZnCl_2$ led to the corresponding alkenylzinc reagent **1c** in >98% yield.[12] With the three alkenylmetallic reagents **1a-c** in hand, we have prepared important classes of heterocycles.

[7] Silyl group (e.g. TBS group in this case) serves as both a protecting group and a latent halide which can be kept for further manipulation. For an example, see: M. Sidera, A. M. Costa, J. Vilarrasa, *Org. Lett.* **2011**, *13*, 4934.
[8] (a) K. D. Kim, P. A. Magriotis, *Tetrahedron Lett.* **1990**, *31*, 6137; (b) S. Ma, F. Liu, E.-i. Negishi, *Tetrahedron Lett.* **1997**, *38*, 3829; (c) D. Beruben, I. Marek, J. F. Normant, N. Platzert, *J. Org. Chem.* **1995**, *60*, 2488; (d) S. E. Denmark, T. K. Jones, *J. Org. Chem.* **1982**, *47*, 4595; (e) J. R. Hwu, P. S. Furth, *J. Am. Chem. Soc.* **1989**, *111*, 8834.
[9] (a) *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice*; G. Tojo, M. I. Fernández, Eds.; Springer: New York; **2006**, pp 290-314; (b) M. Shimizu, H. Okimura, N. Manabe, I. Hachiya, *Chem. Lett.* **2008**, *37*, 28.
[10] (a) *Protective Groups in Organic Synthesis*; T. W. Greene, P. G. M. Wuts, Eds.; John Wiley and Sons: New York, **1991**; (b) *Protecting Groups*; P. J. Kocienski, Ed.; Thieme: New York, **1994**.
[11] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[12] The yield of the organometallic reagent was determined by iodolysis; see the Supporting Information for details.



Scheme 1. Preparation of acetal-containing organometallic reagents **1a-c** from TBS-substituted propargylic alcohol **4**



Scheme 2. Preparation of furans **7** and pyrroles **8** by using alkenylmetallics **1a** and **1b**

Thus, after treating the alkenylmagnesium reagent **1b** with various aldehydes (-40 °C - rt, 6 h) followed by an acid-mediated deacetalization, we observed a spontaneous cyclization, leading to a variety of 1,2-disubstituted furans[13,14] **7a-e** in 68-92% overall

[13] For reviews on furan and pyrrole syntheses, see: (a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; (b) C. Winter, N. Krause, *Chem. Rev.* **2011**, *111*, 1994; (c) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* **2013**, *113*, 3084; (d) S. F. Kirsch, *Org. Biomol. Chem.* **2006**, *4*, 2076; (e) N. T. Patil, Y. Yamamoto, *ARKIVOC* **2007**, 121; (f) B. A. Beay, *Chem. Soc. Rev.* **1999**, *28*, 209; (g) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong, H. N. C. Wong, *Tetrahedron* **1998**, *54*, 1955; (h) X. L. Hou, Z. Yang, H. N. C. Wong, In *Progress in Heterocyclic Chemistry*, Vol. 15; G. W. Gribble, T. L. Gilchrist, Eds.; Pergamon: Oxford, **2003**; p. 167; (i) *Comprehensive Heterocyclic Chemistry II*; A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Eds.; Pergamon, Oxford, **1996**; Vol. 2; (j) V. Estévez, M. Villacampa, J. C. Menéndez, *Chem. Soc. Rev.* **2010**, *39*, 4402; (k) T. S. A. Heugebaert,

yields (Scheme 2). Both aryl (including heteroaryl) and alkyl aldehydes are appropriate substrates and important functional groups embedded in the aryl aldehyde, such as a nitrile and an ester, are tolerated.

We have extended the method to the synthesis of pyrroles[13,15] by replacing the aldehyde to an aldimine and using more reactive alkenyllithium reagent **1a**. As shown in Scheme 2, alkenyllithium reagent **1a** added to various *N*-sulfonylaldimines or *N*-(diethoxyphosphoryl)aldimines at -78 ^{o}C for 6 h, providing after an acidic

B. I. Roman, C. V. Stevens, *Chem. Soc. Rev.* **2012**, *41*, 5626; (l) C. Schmuck, D. Rupprecht, *Synthesis* **2007**, 3095.

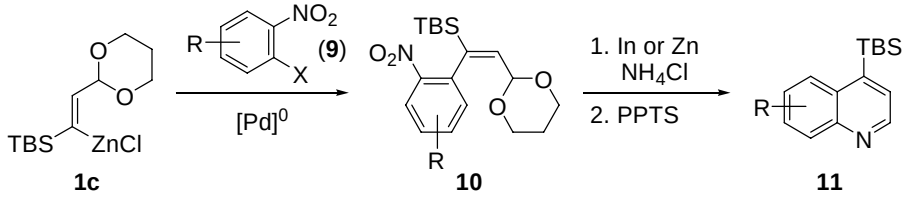
[14] For selected recent examples on furan synthesis, see: (a) L. Peng, X. Zhang, M. Ma, J. Wang, *Angew. Chem. Int. Ed.* **2007**, *46*, 1905; (b) Y. Xia, Y. Xia, R. Ge, Z. Liu, Q. Xiao, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 3917; (c) V. Rauniyar, Z. J. Wang, H. E. Burks, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 8486; (d) C. He, S. Guo, J. Ke, J. Hao, H. Xu, H. Chen, A. Lei, *J. Am. Chem. Soc.* **2012**, *134*, 5766; (e) N. Kuhl, M. N. Hopkinson, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 8230; (f) T. Wang, S. Shi, M. M. Hansmann, E. Rettenmeier, M. Rudolph, A. S. K. Hashmi, *Angew. Chem.* **2014**, *126*, 3789; *Angew. Chem. Int. Ed.* **2014**, *53*, 3715; (g) A. R. Kelly, M. H. Kerrigan, P. J. Walsh, *J. Am. Chem. Soc.* **2008**, *130*, 4097; (h) X. Cui, X. Xu, L. Wojtas, M. M. Kim, X. P. Zhang, *J. Am. Chem. Soc.* **2012**, *134*, 19981; (i) L. Zhou, M. Zhang, W. Li, J. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 6542; (j) T. J. Donohoe, J. F. Bower, *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 3373; (k) P. Lenden, D. A. Entwistle, M. C. Willis, *Angew. Chem. Int. Ed.* **2011**, *50*, 10657; (l) M. Zhang, H. F. Jiang, H. Neumann, M. Beller, P. H. Dixneuf, *Angew. Chem. Int. Ed.* **2009**, *48*, 1681; (m) J. Zhang, H.-G. Schmalz, *Angew. Chem.* **2006**, *118*, 6856; *Angew. Chem. Int. Ed.* **2006**, *45*, 6704; (n) J. González, J. González, C. Pérez-Calleja, L. A. López, R. Vicente, *Angew. Chem. Int. Ed.* **2013**, *52*, 5853; (o) X. Huang, B. Peng, M. Luparia, L. F. R. Gomes, L. F. Veiros, N. Maulide, *Angew. Chem. Int. Ed.* **2012**, *51*, 8886; (p) Y. Ma, S. Zhang, S. Yang, F. Song, J. You, *Angew. Chem. Int. Ed.* **2014**, *53*, 7870; (q) K. Yamashita, Y. Yamamoto, H. Nishiyama, *J. Am. Chem. Soc.* **2012**, *134*, 7660; (r) E. L. Fisher, S. M. Wilkerson-Hill, R. Sarpong, *J. Am. Chem. Soc.* **2012**, *134*, 9946; (s) S. Kramer, T. Skrydstrup, *Angew. Chem. Int. Ed.* **2012**, *51*, 4681; (t) Y. Li, J. P. Brand, J. Waser, *Angew. Chem. Int. Ed.* **2013**, *52*, 6743; (u) Y. Lian, T. Huber, K. D. Hesp, R. G. Bergman, J. A. Ellman, *Angew. Chem. Int. Ed.* **2013**, *52*, 629; (v) E. L. McInturff, K. D. Nguyen, M. J. Krische, *Angew. Chem. Int. Ed.* **2014**, *53*, 3232; (w) B. Lu, J. Wu, N. Yoshikai, *J. Am. Chem. Soc.* **2014**, *136*, 11598; (x) J. J. Hirner, D. J. Faizi, S. A. Blum, *J. Am. Chem. Soc.* **2014**, *136*, 4740.

[15] For selected recent examples on pyrrole synthesis, see: (a) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585; (b) Z. Shi, M. Suri, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 4892; (c) E. E. Schultz, R. Sarpong, *J. Am. Chem. Soc.* **2013**, *135*, 4696; (d) G.-Q. Chen, X.-N. Zhang, Y. Wei, X.-Y. Tang, M. Shi, *Angew. Chem. Int. Ed.* **2014**, *53*, 8492; (e) Y. Jiang, W. C. Chan, C.-M. Park, *J. Am. Chem. Soc.* **2012**, *134*, 4104; (f) E. Lourdusamy, L. Yao, C. M. Park, *Angew. Chem. Int. Ed.* **2010**, *49*, 7963; (g) M. Gao, C. He, H. Chen, R. Bai, B. Cheng, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 6958; (h) M. Zhang, X. Fang, H. Neumann, M. Beller, *J. Am. Chem. Soc.* **2013**, *135*, 11384; (i) X. Xin, D. Wang, X. Li, B. Wang, *Angew. Chem. Int. Ed.* 2012, *51*, 1693; (j) D. J. Gorin, N. R. Davis, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 11260; (k) W. Geng, W.-X. Zhang, W. Hao, Z. Xi, *J. Am. Chem. Soc.* **2012**, *134*, 20230; (l) J. Xuan, X.-D. Xia, T.-T. Zeng, Z.-J. Feng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2014**, *53*, 5653; (m) J. S. Alford, J. E. Spangler, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, *135*, 11712; (n) J.-Y. Liao, P.-L. Shao, Y. Zhao, *J. Am. Chem. Soc.* **2015**, *137*, 628; (o) B. M. Trost, J.-P. Lumb, J. M. Azzarelli, *J. Am. Chem. Soc.* **2011**, *133*, 740; (p) S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140; (q) T. J. Donohoe, N. J. Race, J. F. Bower, C. K. A. Callens, *Org. Lett.* **2010**, *12*, 4094; (r) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* 2010, *132*, 18326; (s) W. J. Humenny, P. Kyriacou, K. Sapeta, A. Karadeolian, M. A. Kerr, *Angew. Chem. Int. Ed.* 2012, *51*, 11088; (t) M. Zhang, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 597; (u) M. P. Huestis, L. Chan, D. R. Stuart, K. Fagnou, *Angew. Chem. Int. Ed.* **2011**, *50*, 1338; (v) S. Yu, M. Xiong, X. Xie, Y. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 11596; (w) J. Liu, Z. Fang, Q. Zhang, Q. Liu, X. Bi, *Angew. Chem. Int. Ed.* **2013**, *52*, 6953.

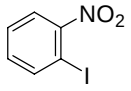
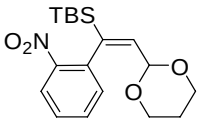
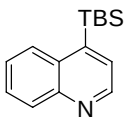
deacetalization and spontaneous cyclization various 1,2-disubstituted pyrroles **8a-h** in 35-93% yields. Both aryl and alkyl aldimines can be used and functional groups, such as a nitrile or an ester, were compatible with the organolithium reagent **1a**.

Annelated pyridines such as quinolines or naphthyridines [16] are relevant heterocycles for pharmaceutical applications.[17] The alkenylzinc reagent **1c** underwent the Pd-catalyzed Negishi[18,19] cross-coupling with various 1-halo-2-nitroarenes **9a-g** providing alkenylated nitroarenes of type **10** which after indium- or zinc-mediated reduction[20] and acidic acetal cleavage[10] gave the annelated pyridines of type **11** (Table 1). Not only quinolines **11a-d** are obtained by this method (entries 1-4), but also the benzo[*b*]thieno[2,3-*b*]pyridine **11e** (54% yield, entry 5) and the 1,5- and 1,6-naphthyridine **11f-g** (62-65% yields; entries 6-7). X-ray diffraction analysis of both **11e** and **11f** confirmed the structure (Figure 2; also see the Appendix for details).

Table 1. Pd-catalyzed cross-coupling of alkenylzinc reagent **1c** with 1-halo-2-nitroarene **9** followed by an indium- or zinc-mediated reduction and acidic hydrolysis and *in situ* cyclization leading to annelated pyridine **11**



1c **10** **11**

Entry	Substrate **9**	Product **10** (Yield)	Product **11** (Yield)
1	 **9a**	 **10a** (85%)	 **11a** (70%)

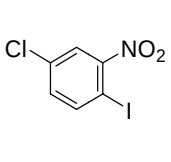
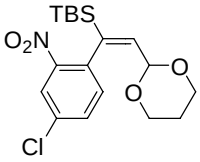
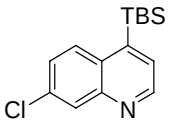
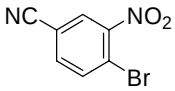
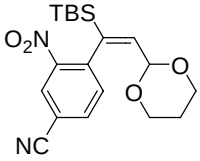
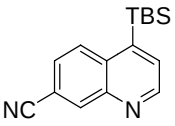
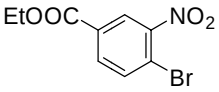
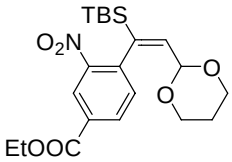
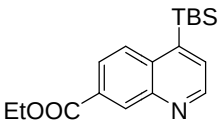
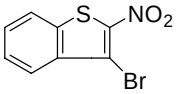
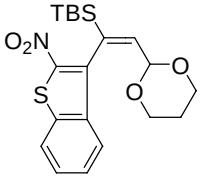
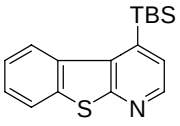
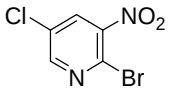
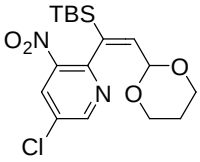
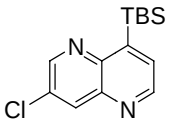
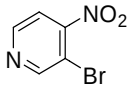
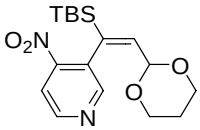
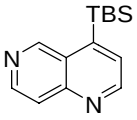
[16] For reviews on quinoline and naphthyridine synthesis, see: (a) S. Madapa, A. Tusi, S. Batra, *Curr. Org. Chem.* **2008**, *12*, 1116. (b) J. Marco-Contelles, E. Perez-Mayoral, A. Samadi, M. C. Carreiras, E. Soriano, *Chem. Rev.* **2009**, *109*, 2652. (c) R. H. Manske, *Chem. Rev.* **1942**, *30*, 113. (d) C. F. H. Allen, *Chem. Rev.* **1950**, *47*, 275.

[17] For reviews, see: (a) *Modern Heterocyclic Chemistry*; J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, Eds.; Wiley-VCH: Weinheim, **2011**. (b) *Natural Products in the Chemical Industry*; B. Schaefer, Ed.; Springer-Verlag: Heidelberg, **2014**.

[18] For selected reviews, see: (a) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340. (b) E. I. Negishi, Q. Hu, Z. Huang, M. Qian, G. Wang, *Aldrichimica Acta* **2005**, *38*, 71. (c) *Metal-Catalyzed Cross-Coupling Reactions*; F. Diederich, P. J. Stang, Eds.; Wiley-VCH: Weinheim, **1998**.

[19] See the Supporting Information for the palladium catalysts and ligands used for the cross-coupling of alkenylzinc reagent **1c** with various electrophiles of 1-halo-2-nitroarene and 1-formyl-2-haloarene.

[20] For a typical example on indium-mediated reduction of nitro group to amine, see: M. R. Pitts, J. R. Harrison, C. J. Moody, *J. Chem. Soc., Perkin Trans. 1* **2001**, 955.

2	 **9b**	 **10b** (68%)	 **11b** (41%)
3	 **9c**	 **10c** (61%)	 **11c** (55%)
4	 **9d**	 **10d** (64%)	 **11d** (60%)
5	 **9e**	 **10e** (74%)	 **11e** (54%)
6	 **9f**	 **10f** (69%)	 **11f** (62%)
7	 **9g**	 **10g** (56%)	 **11g** (65%)

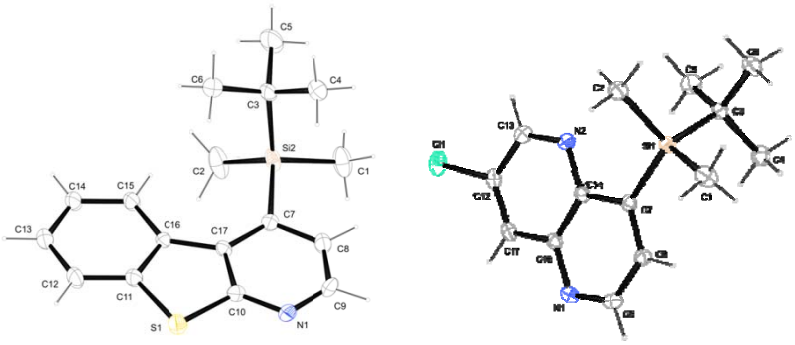
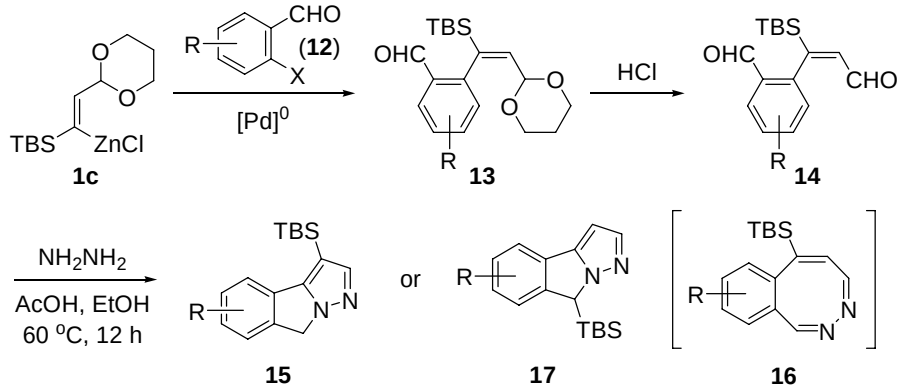


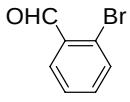
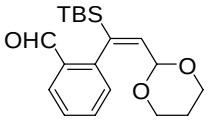
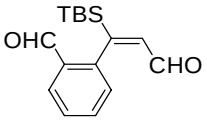
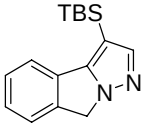
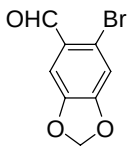
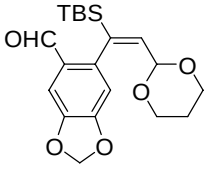
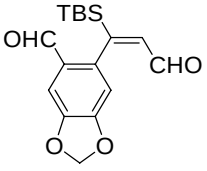
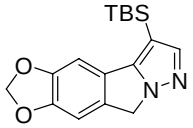
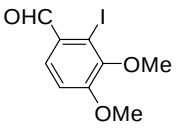
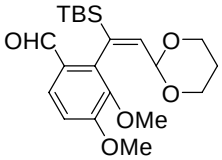
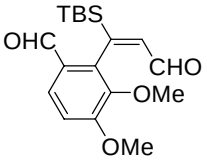
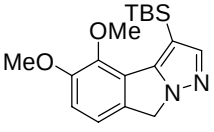
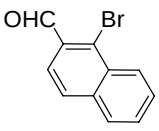
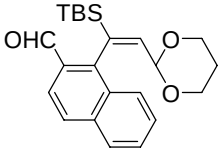
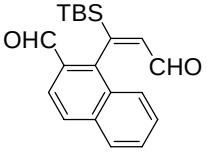
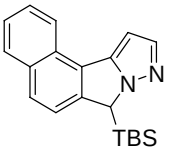
Figure 2. X-ray crystal structures of **11e** and **11f**

Palladium-catalyzed cross-coupling[18,19] proceeded well between alkenylzinc reagent and aryl bromides containing a formyl group. Thus, the cross-coupling of **1c**

with various 1-formyl-2-haloarene **12a-d** occurred readily, leading to after acidic hydrolysis 1,6-dialdehydes **14a-d** in 44-84% yields (Table 2). Interestingly, the 1,6-dialdehydes **14a-c** readily underwent a novel cyclization after treatment with hydrazine monohydrate (4 equiv) in a mixture of acetic acid and ethanol, leading to the tricyclic fused pyrazoles **15a-c** in 62-77% yields (entries 1-3), instead of expected eight-membered ring compound of type **16** (Table 2). Interestingly, performing this reaction using 1,6-dialdehyde **14d** proceeded equally well under the same conditions, giving rise to a similar fused pyrazole **17d** in 65% yield, but in which the TBS group

Table 2. Pd-catalyzed cross-coupling of alkenylzinc reagent **1c** with 1-formyl-2-haloarene **12** followed by an acidic deacetalization and further reaction with hydrazine monohydrate leading to tricyclic fused pyrazoles **15** and **17**



Entry	Substrate **12**	Product **13** (Yield)	Product **14** (Yield)	Product **15/17** (Yield)
				
1	**12a**	**13a** (77%)	**14a** (84%)	**15a** (68%)
				
2	**12b**	**13b** (65%)	**14b** (81%)	**15b** (77%)
				
3	**12c**	**13c** (51%)	**14c** (44%)	**15c** (62%)
				
4	**12d**	**13d** (57%)	**14d** (68%)	**17d** (65%)

has migrated formerly from the pyrazole ring to a benzylic position. The structures of these two types of products were ambiguously determined by X-ray diffraction analysis of the product **15c** and **17d** (Figure 3; also see the Appendix for details). A plausible mechanism involving the initial formation of an eight-membered ring of type **16** followed by an acidic rearrangement leading to the condensed tricyclic heterocycles **18** may explain the formation of the final products of type **15** and **17** (Figure 4). Thus, the cyclic iminium **18** may undergo a proton migration leading to **19** which undergoes a 1,2-silyl migration,[21] affording the intermediate **20** which after aromatization furnish product of type **15**. On another hand, if an annelated ring is present as in the intermediate **21** (obtained from substrate **14d**; Table 2, entry 4), the high steric hinderance leads to a 1,3-silyl migration, affording intermediate **22**. After proton loss, the observed silyl derivative **17d** is obtained.

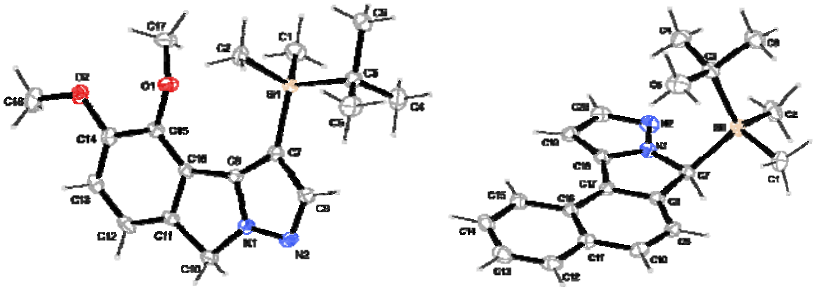


Figure 3. X-ray crystal structures of **15c** and **17d**

In addition, the 1,6-dialdehydes of type **14** also can be converted into benzo[*c*]azepine derivative of type **23** via a double reductive amination using $NaBH(OAc)_3$ and an aniline (Scheme 3). These double reductive aminations[22] proceeded well under mild conditions (AcOH, DCE, rt, 12 h) and produced the corresponding 2,3-dihydro-benzo[*c*]azepines[23] **23a-d** in 63-89% yields.

[21] M. Kira, T. Iwamoto, In *The Chemistry of Organic Silicon Compounds*; Z. Rappoport, Y. Apeloig, Eds.; John Wiley and Sons: Chichester, **2001**; Vol. 3, Chap. 16, pp 853–948.
[22] A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849.
[23] For selected examples on the synthesis of similar 7-membered nitrogen-containing heterocycles, see: (a) Z. Dong, C.-H. Liu, Y. Wang, M. Lin, Z.-X. Yu, *Angew. Chem.* **2013**, *125*, 14407; *Angew. Chem. Int. Ed.* **2013**, *52*, 14157, and references therein; (b) J.-M. Yang, C.-Z. Zhu, X.-Y. Tang, M. Shi, *Angew. Chem.* **2014**, *126*, 5242; *Angew. Chem. Int. Ed.* **2014**, *53*, 5142.

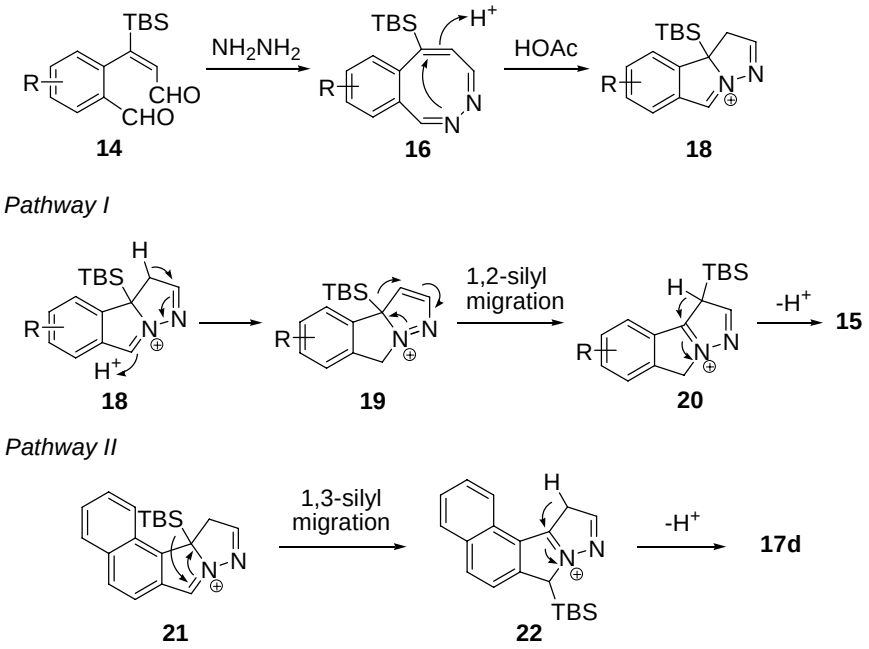
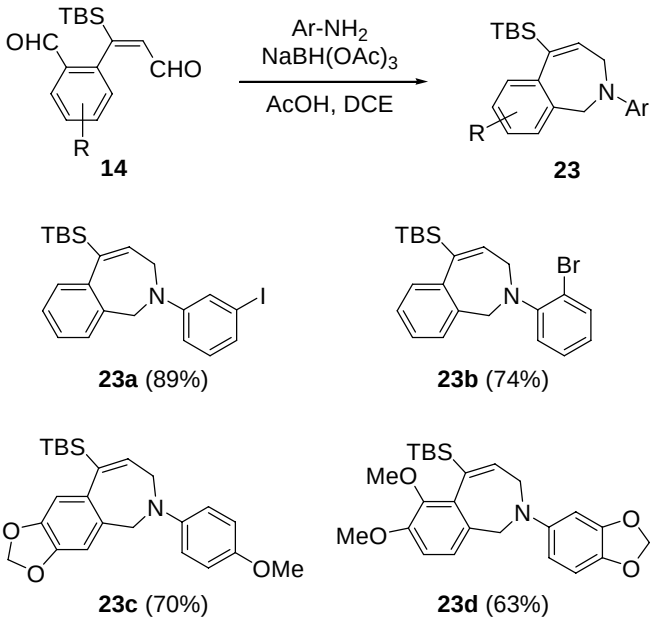


Figure 4. Proposed mechanism for the formation of products **15** and **17d**



Scheme 3. $NaBH(OAc)_3$-mediated double reductive amination of 1,6-dialdehyde **14** with aryl amine leading to 7-membered nitrogen-containing heterocycles **23**.

6.3 Conclusion

In conclusion, we have described the preparation of the new conjunctive Li, Mg, and Zn alkenyl organometallic reagents bearing latent aldehyde function which serve

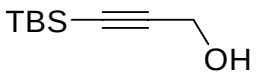
as versatile building blocks for the synthesis of various classes of important heterocycles (including furans, pyrroles, quinolines, benzo[*b*]thieno[2,3-*b*]pyridine, 1,5-naphthyridine and 1,6-naphthyridine) as well as 2,3-dihydro-benzo[*c*]azepine and fused pyrazole via acidic arrangement. Further extensions to the preparation of other complex heterocycles are currently underway in our laboratories.

6.4 Experimental

General Information

All reactions were carried out under nitrogen atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC. Column chromatography was performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck. Substrates of *N*-sulfonylaldimines, [24] or *N*-(diethoxyphosphoryl)aldimines, [25] 3-bromo-2-nitrobenzo[*b*]thiophene (**9e**),[26] 2-bromo-5-chloro-3-nitropyridine (**9f**),[27] 3-bromo-4-nitropyridine (**9g**), [28] 6-bromobenzo[*d*][1,3]dioxole-5-carbaldehyde (**12b**),[29] 1-bromo-2-naphthaldehyde (**12d**).[30] All other reagents were obtained from commercial sources.

3-(*tert*-Butyldimethylsilyl)prop-2-yn-1-ol (4)



[24] F. Chemla, V. Hebbe, J.-F. Normant, *Synthesis* **2000**, 75.
[25] A. Zwierzak, A. Napieraj, *Tetrahedron* **1996**, *52*, 8789.
[26] L. Zeng, B. Ma, Z. Elshenawy, C. Xia, C. Lin, U.S. Pat. Appl. Publ. 20140027733, 30 Jan 2014.
[27] Z.-C. Ding, X. Ma, W. Zhou, *Synth. Commun.* **2012**, *42*, 2791.
[28] (a) R. W. Daisley, J. R. Hanbali, *Org. Prep. Proced. Int.* **1983**, *15*, 280. (b) J. Yao, P. R. Blake, J. Yang, *Heterocycles* **2005**, *65*, 2071.
[29] G. Poli, G. Giambastiani, *J. Org. Chem.* **2002**, *67*, 9456.
[30] G. J. Domski, J. B. Edson, I. Keresztes, E. B. Lobkovsky, G. W. Coates, *Chem. Commun.* **2008**, 6137.

This starting material is prepared by reported method.[31]

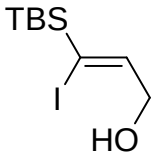
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 4.26 (s, 2 H), 2.20 (brs, 1H), 0.93 (s, 9H), 0.10 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 104.5, 88.7, 51.5, 26.0, 16.4, -4.7.

MS (EI, 70 eV): m/z (%) = 170 (M^+, 7), 114 (11), 113 (100), 87 (14), 85 (96), 75 (36), 61 (21), 45 (28), 43 (10), 41 (14).

HRMS ($C_9H_{18}OSi$, EI): calc.: 170.1127; found: 170.1132 (M^+).

(*Z*)-3-(*tert*-Butyldimethylsilyl)-3-iodoprop-2-en-1-ol (5)[8]



Red-Al (340 mmol, 97 mL, 70% in toluene, ~3.5 M) and anhydrous diethyl ether (130 mL) were added into a pre-dried three-necked flask (1L) under nitrogen. After cooling to 0 ^oC, propargylic alcohol **4** (36.1 g, 212 mmol) dissolved in anhydrous diethyl ether (130 mL) was dropwise added into the flask. After completion of addition and stirring at 0 ^oC for 1 h and room temperature for 10 min, the reaction mixture was cooled to -78 ^oC followed by dropwise addition of iodine (86.4 g, 340 mmol) in anhydrous THF (100 mL). The reaction mixture was slowly warmed to room temperature over 1 h before quenching with aq. sodium potassium L-tartrate and sat. aq. $Na_2S_2O_3$ and stirred overnight. The reaction mixture was extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. The solvent was removed under vacuum and the residue was distilled (0.18 mbar, bp: ~ 85 ^oC) to give the desired product **5** (26.8 g, 89.9 mmol, 42% yield) as a light yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = (t, *J* = 4.7 Hz, 1 H), 4.28 (d, *J* = 4.2 Hz, 2 H), 2.07 (brs, 1 H), 0.96 (s, 9 H), 0.20 (s, 6 H).

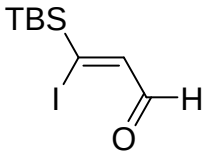
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.1, 107.7, 69.9, 27.1, 17.4, -4.8.

MS (EI, 70 eV): m/z (%) = 298 (M^+, 7), 241 (45), 187 (22), 185 (78), 115 (21), 113 (38), 97 (9), 83 (43), 75 (100), 73 (19), 57 (29).

HRMS ($C_9H_{19}IOSi$, EI): calc.: 298.0250; found: 298.0239 (M^+).

[31] (a) R. L. Danheiser, E. J. Stoner, H. Koyama, D. S. Yamashita, C. A. Klade, *J. Am. Chem. Soc.* **1989**, *111*, 4407. (b) M. Mohamed, M. A. Brook, *Helv. Chim. Acta* **2002**, *85*, 4165.

(*Z*)-3-(*tert*-Butyldimethylsilyl)-3-iodoacrylaldehyde[9]



(*Z*)-3-(*Tert*-butyldimethylsilyl)-3-iodoprop-2-en-1-ol (**5**; 55.2 g, 185.1 mmol) was stirred at room temperature with activated MnO_2 (161.9 g, 1.8 mol) in CH_2Cl_2 (1.0 L) for 24 h. After the completion of the reaction as indicated by GC monitoring, the reaction mixture was filtered through a Buchner funnel and washed with CH_2Cl_2 (0.2 L), then the solvent was removed under vacuum and the product (53.3 g, 180 mmol, 97% yield) was dried under high vacuum. The product was analytically pure enough to be directly used in further reactions.

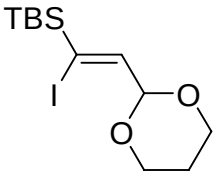
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.63 (d, *J* = 5.8 Hz, 1 H), 6.73 (d, *J* = 5.8 Hz, 2 H), 0.97 (s, 9 H), 0.26 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.0, 143.1, 132.2, 27.0, 17.5, -5.0.

MS (EI, 70 eV): m/z (%) = 296 (M^+, 5), 240 (11), 239 (22), 211 (17), 185 (44), 113 (11), 83 (100), 73 (12), 57 (54), 43 (12), 41 (15).

HRMS ($C_9H_{17}IOSi$, EI): calc.: 296.0093; found: 296.0106 (M^+).

(*Z*)-(2-(1,3-Dioxan-2-yl)-1-iodovinyl)(*tert*-butyl)dimethylsilane (6)[10]



To a round-bottomed flask (1 L) equipped with a reflux condenser and a Dean-Stark was sequentially added (*Z*)-3-(*tert*-butyldimethylsilyl)-3-iodoacrylaldehyde (53.3 g, 180 mmol), propane-1,3-diol (42.2 g, 555 mmol), $TsOH \cdot H_2O$ (1.7 g, 5 mol%) and benzene. The reaction mixture was vigorously stirred under reflux for 12 h. Then the reaction solvent was removed under vacuum in fumehood. The residue was dissolved in ethyl acetate (400 mL), washed with sat. $NaHCO_3$ solution (50 mL) and brine (2 x 50 mL), dried over sodium sulfate. The organic layer was concentrated under vacuum to yield the analytically pure product (**6**; 54.9 g, 155 mmol, 83% yield) as a light yellow liquid.

^{1}H-NMR (400 MHz, d-acetone): δ / ppm = 6.29 (d, *J* = 5.3 Hz, 1 H), 5.18 (d, *J* = 5.3 Hz, 1 H), 4.07 (dd, *J* = 10.7, 5.1 Hz, 2 H), 3.87 (td, *J* = 12.2, 2.5 Hz, 2 H), 2.06-1.96 (m, 1 H), 1.39 (dt, *J* = 13.4, 1.2 Hz, 1 H), 0.97 (s, 9 H), 0.22 (s, 6 H).
^{13}C-NMR (100 MHz, d-acetone): δ / ppm = 206.0, 147.5, 110.5, 106.4, 67.2, 27.5, 26.5, 18.0, -4.6.
MS (EI, 70 eV): m/z (%) = 354 (M^+, 28), 297 (31), 239 (46), 229 (12), 185 (51), 169 (13), 155 (10), 113 (19), 101 (12), 88 (25), 87 (100), 84 (53), 77 (27), 59 (44), 57 (26).
HRMS ($C_{12}H_{23}IO_2Si$, EI): calc.: 354.0512; found: 354.0508 (M^+).

Preparation of alkenyllithium reagent 1a[2]

To a pre-dried 20 mL flask was added (*Z*)-(2-(1,3-dioxan-2-yl)-1-iodovinyl)(*tert*-butyl)dimethylsilane (**6**; 0.354 g, 1 mmol), anhydrous THF (3 mL) and the flask was cooled to -78 °C prior to the dropwise addition of *n*-BuLi solution (0.52 mL, 1.1 mmol, 2.13 M in *n*-hexane). The reaction mixture was stirred at -78 °C for 30 minutes to give the corresponding alkenyllithium reagent **1a** in > 90% yield.

Preparation of alkenylmagnesium reagent 1b[10]

To a pre-dried 20 mL flask was added (*Z*)-(2-(1,3-dioxan-2-yl)-1-iodovinyl)(*tert*-butyl)dimethylsilane (**6**; 0.354 g, 1 mmol), anhydrous THF (3 mL) and the flask was cooled to 0 °C prior to the dropwise addition of *i*PrMgCl·LiCl solution (1.0 mL, 1.2 mmol, 1.19 M in THF). The reaction mixture was stirred at 0 °C for 30 min to give the corresponding alkenylmagnesium reagent **1b** in 92% yield.

Preparation of alkenylzinc reagent 1c

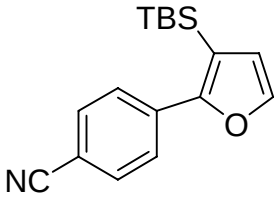
The alkenylzinc reagent **1c** (1 mmol) was prepared by treating the afore-mentioned alkenylmagnesium reagent **1b** (1 mmol) with $ZnCl_2$ solution (1.0 mL, 1 mmol, 1 M in THF) at 0 °C followed by continuous stirring for additional 10 min.

Preparation of furan 7 by the reaction of alkenylmagnesium reagent 1b with aldehyde

The pre-prepared alkenylmagnesium reagent **1b** (1 mmol) was cooled to – 40 °C

followed by the addition of aldehyde (0.9 mmol). Then the reaction mixture was allowed to slowly warm to room temperature and stir for 6 h. 2M HCl (2 mL) was added into the flask and it was stirred at room temperature for 12 h to effect deacetalization and spontaneous cyclization. The reaction mixture was quenched with sat. $NaHCO_3$ solution (20 mL), extracted with ethyl acetate (3 x 30 mL), washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography with a mixture of ethyl acetate and isohexane as eluant to give the product **7**.

4-(3-(*tert*-Butyldimethylsilyl)furan-2-yl)benzonitrile (7a)



The reaction was performed according to the above procedure using alkenylmagnesium reagent **1b** (1 mmol) and 4-cyanobenzaldehyde (0.118 g, 0.9 mmol), leading to the corresponding furan **7a** in 92% yield (0.234 g) as a white solid.

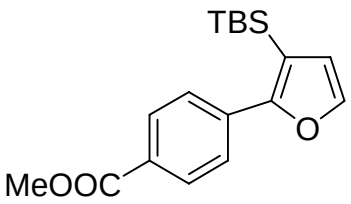
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.72 (d, *J* = 8.6 Hz, 2 H), 7.66 (d, *J* = 8.6 Hz, 2 H), 7.58 (d, *J* = 1.7 Hz, 1 H), 6.53 (d, *J* = 1.7 Hz, 1 H), 0.92 (s, 9 H), 0.20 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 156.7, 142.5, 136.9, 131.8, 128.2, 118.7, 118.2, 114.9, 111.2, 26.7, 17.9, -3.9.

MS (EI, 70 eV): m/z (%) = 283 (M^+, 6), 258 (21), 242 (12), 230 (22), 227 (23), 226 (100), 214 (15), 210 (22), 204 (24), 130 (29), 102 (16), 87 (20), 75 (36), 73 (44), 59 (10), 57 (14), 41 (10).

HRMS ($C_{17}H_{21}NOSi$, EI): calc.: 283.1392; found: 283.1388 (M^+).

Methyl 4-(3-(*tert*-butyldimethylsilyl)furan-2-yl)benzoate (7b)



The reaction was performed according to the above procedure using alkenylmagnesium reagent **1b** (1 mmol) and ethyl 4-formylbenzoate (0.148 g, 0.9 mmol), leading to the corresponding furan **7b** in 88% yield (0.25 g) as a white solid.

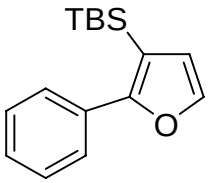
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (d, *J* = 8.4 Hz, 2 H), 7.68 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 1.8 Hz, 1 H), 6.51 (d, *J* = 1.6 Hz, 1 H), 3.93 (s, 3 H), 0.92 (s, 9 H), 0.19 (s, 6 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.7, 157.9, 142.0, 137.0, 129.3, 129.3, 127.8, 117.9, 113.8, 52.1, 26.8, 17.9, -4.0.

MS (EI, 70 eV): m/z (%) = 316 (M^+, 12), 260 (25), 259 (100), 243 (33), 213 (29), 200 (14), 199 (13), 185 (68), 141 (9), 89 (12), 59 (14).

HRMS ($C_{18}H_{24}O_3Si$, EI): calc.: 316.1495; found: 316.1488 (M^+).

***tert*-Butyldimethyl(2-phenylfuran-3-yl)silane (7c)**



The reaction was performed according to the above procedure using alkenylmagnesium reagent **1b** (1 mmol) and benzaldehyde (0.095 g, 0.9 mmol), leading to the corresponding furan **7c** in 81% yield (0.188 g) as a colorless oil.

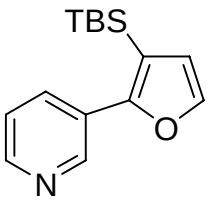
^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.57 (d, *J* = 7.4 Hz, 2 H), 7.54 (s, 1 H), 7.40-7.34 (m, 3 H), 6.49 (s, 1 H), 0.92 (s, 9 H), 0.15 (s, 6 H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 159.4, 141.3, 132.9, 128.5, 128.1, 127.9, 117.2, 111.8, 26.8, 17.8, -4.1.

MS (EI, 70 eV): m/z (%) = 258 (M^+, 10), 202 (19), 201 (100), 185 (39), 145 (13).

HRMS ($C_{16}H_{22}OSi$, EI): calc.: 258.1440; found: 258.1445 (M^+).

3-(3-(*tert*-Butyldimethylsilyl)furan-2-yl)pyridine (7d)



The reaction was performed according to the above procedure using alkenylmagnesium reagent **1b** (1 mmol) and nicotinaldehyde (0.096 g, 0.9 mmol), leading to the corresponding furan **7d** in 68% yield (0.159 g) as a colorless oil.

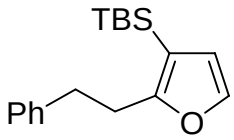
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.79 (s, 1 H), 8.54 (d, *J* = 4.4 Hz, 1 H), 7.83 (d, *J* = 7.7 Hz, 1 H), 7.54 (d, *J* = 1.1 Hz, 1 H), 7.28 (dd, *J* = 8.0, 5.0 Hz, 1 H), 6.48 (s, 1 H), 0.88 (s, 9 H), 0.12 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 155.8, 149.1, 148.9, 142.3, 135.4, 128.9, 122.8, 117.5, 113.9, 26.7, 17.7, -4.2.

MS (EI, 70 eV): m/z (%) = 259 (M^+, 5), 234 (11), 219 (10), 218 (29), 206 (29), 203 (22), 202 (100), 190 (31), 180 (32), 136 (11), 123 (19), 106 (29), 105 (10), 78 (28), 75 (36), 73 (38), 59 (10), 57 (20), 51 (15), 43 (12), 41 (11).

HRMS ($C_{15}H_{21}NOSi$, EI): calc.: 259.1392; found: 259.1382 (M^+).

***tert*-Butyldimethyl(2-phenethylfuran-3-yl)silane (7e)**



The reaction was performed according to the above procedure using alkenylmagnesium reagent **1b** (1 mmol) and 3-phenylpropanal (0.121 g, 0.9 mmol), leading to the corresponding furan **7e** in 73% yield (0.188 g) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.42 (d, *J* = 1.7 Hz, 1 H), 7.33-7.28 (m, 2 H), 7.24-7.17 (m, 3 H), 6.29 (d, *J* = 1.7 Hz, 1 H), 2.97 (s, 4 H), 0.88 (s, 9 H), 0.19 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.3, 141.4, 140.4, 128.4, 128.4, 126.0, 115.4, 110.0, 35.6, 31.5, 26.4, 17.3, -5.0.

MS (EI, 70 eV): m/z (%) = 231 (12), 230 (44), 229 (100), 211 (11), 155 (41), 153 (20), 139 (16), 123 (16), 91 (15), 75 (28).

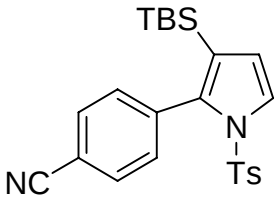
HRMS ($C_{17}H_{23}OSi$, EI): calc.: 271.1518; found: 271.1527 (M^+-CH_3).

Preparation of pyrrole 8 by the reaction of alkenyllithium reagent 1a with aldimine

The pre-prepared alkenyllithium reagent **1a** (1 mmol) was cooled to – 78 ^{o}C followed by the addition of aldimine (0.9 mmol). Then the reaction mixture was allowed to

slowly warm to room temperature and stir for 6 h. 2M HCl (2 mL) was added into the flask and it was stirred at room temperature for 12 h to effect deacetalization and spontaneous cyclization. The reaction mixture was quenched with sat. $NaHCO_3$ solution (20 mL), extracted with ethyl acetate (3 x 30 mL), washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography with a mixture of ethyl acetate and isohexane as eluant to give the desired product **8**.

4-(3-(*tert*-Butyldimethylsilyl)-1-tosyl-1*H*-pyrrol-2-yl)benzonitrile (8a)



The reaction was performed according to the above procedure using alkenyllithium reagent **1a** (1 mmol) and (*E*)-*N*-(4-cyanobenzylidene)-4-methylbenzenesulfonamide (0.256 g, 0.9 mmol), leading to the corresponding pyrrole **8a** in 83% yield (0.327 g) as a white solid.

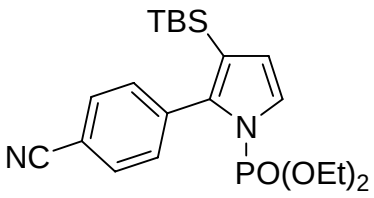
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.55-7.50 (m, 3 H), 7.25-7.11 (m, 6 H), 6.38 (d, *J* = 3.2 Hz, 1 H), 2.41 (s, 3 H), 0.75 (s, 9 H), -0.23 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 145.1, 137.4, 136.8, 135.8, 133.3, 130.3, 129.6, 127.1, 123.2, 122.2, 118.6, 117.1, 112.3, 26.6, 21.6, 17.2, -5.0.

MS (EI, 70 eV): m/z (%) = 436 (M^+, 3), 381 (12), 380 (29), 379 (100), 225 (14), 224 (58), 209 (27), 194 (9), 91 (13).

HRMS ($C_{24}H_{28}N_2O_2SSi$, EI): calc.: 436.1641; found: 436.1635 (M^+).

Diethyl 3-(*tert*-butyldimethylsilyl)-2-(4-cyanophenyl)-1*H*-pyrrol-1-ylphosphonate (8b)



The reaction was performed according to the above procedure using alkenyllithium reagent **1a** (1 mmol) and (*E*)-diethyl 4-cyanobenzylidenephosphoramidate (0.24 g, 0.9 mmol), leading to the corresponding pyrrole **8b** in 81% yield (0.306 g) as a white solid.

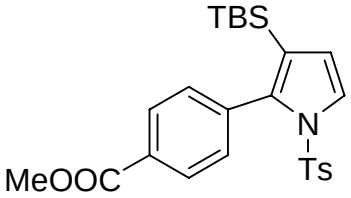
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.63-7.59 (m, 2 H), 7.46-7.43 (m, 2 H), 7.25-7.23 (m, 1 H), 6.35 (dd, *J* = 4.2, 3.0 Hz, 1 H), 4.05-3.84 (m, 4 H), 1.17 (td, *J* = 7.1, 0.8 Hz, 6 H), 0.79 (s, 9 H), -0.18 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 140.0, 138.8 (d, *J* = 3.9 Hz), 132.8, 130.6, 125.1 (d, *J* = 7.3 Hz), 121.1 (d, *J* = 7.0 Hz), 118.7, 117.6 (d, *J* = 12.6 Hz), 112.1, 64.0 (d, *J* = 5.3 Hz), 26.7, 17.3, 15.8 (d, *J* = 6.7 Hz), -4.7.

MS (EI, 70 eV): m/z (%) = 418 (M^+, 6), 362 (24), 361 (100), 306 (12), 305 (59), 289 (12), 287 (21), 209 (20).

HRMS ($C_{21}H_{31}N_2O_3PSi$, EI): calc.: 418.1842; found: 418.1854 (M^+).

Methyl 4-(3-(*tert*-butyldimethylsilyl)-1-tosyl-1*H*-pyrrol-2-yl)benzoate (8c)



The reaction was performed according to the above procedure using alkenyllithium reagent **1a** (1 mmol) and (*E*)-methyl 4-((4-methylphenylsulfonamido)methyl)benzoate (0.285 g, 0.9 mmol), leading to the corresponding pyrrole **8c** in 74% yield (0.311 g) as a white solid.

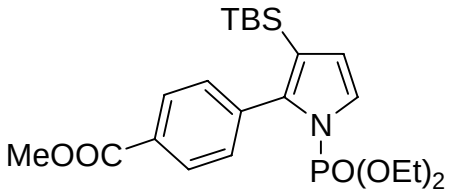
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.89 (d, *J* = 8.2 Hz, 2 H), 7.54 (d, *J* = 3.2 Hz, 1 H), 7.23 (d, *J* = 8.3 Hz, 2 H), 7.14 (d, *J* = 8.2 Hz, 2 H), 7.08 (d, *J* = 8.2 Hz, 2 H), 6.37 (d, *J* = 3.2 Hz, 1 H), 3.96 (s, 3 H), 2.40 (s, 3 H), 0.75 (s, 9 H), -0.24 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.8, 144.8, 138.0, 137.2, 135.9, 132.7, 130.0, 129.5, 127.8, 127.3, 122.9, 121.6, 117.0, 52.2, 26.6, 21.6, 17.2, -5.0.

MS (EI, 70 eV): m/z (%) = 469 (M^+, 3), 414 (13), 413 (28), 412 (95), 258 (22), 257 (100), 242 (11), 198 (23), 183 (11), 91 (10).

HRMS ($C_{25}H_{31}NO_4SSi$, EI): calc.: 469.1743; found: 469.1750 (M^+).

Methyl 4-(3-(*tert*-butyldimethylsilyl)-1-(diethoxyphosphoryl)-1*H*-pyrrol-2-yl)benzoate (8d)



The reaction was performed according to the above procedure using alkenyllithium reagent **1a** (1 mmol) and *N*-(diethoxyphosphoryl)aldimines (0.27 g, 0.9 mmol), leading to the corresponding pyrrole **8d** in 82% yield (0.332 g) as a white solid.

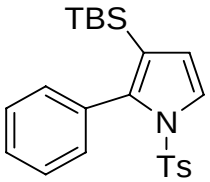
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.98 (d, *J* = 8.3 Hz, 2 H), 7.40 (d, *J* = 8.3 Hz, 2 H), 7.25 (t, *J* = 2.5 Hz, 1 H), 6.33 (t, *J* = 3.5 Hz, 1 H), 4.02-3.81 (m, 7 H), 1.14 (t, *J* = 7.2 Hz, 6 H), 0.79 (s, 9 H), -0.20 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.9, 139.8 (d, *J* = 3.9 Hz), 139.5, 132.1, 129.8, 128.0, 124.9 (d, *J* = 7.6 Hz), 120.6 (d, *J* = 7.0 Hz), 117.3 (d, *J* = 12.3 Hz), 63.8 (d, *J* = 5.3 Hz), 52.1, 26.8, 17.3, 15.8 (d, *J* = 7.3 Hz), -4.8.

MS (EI, 70 eV): m/z (%) = 451 (M^+, 6), 395 (26), 394 (100), 338 (14), 336 (13), 322 (11), 320 (13), 307 (20), 306 (96), 264 (6), 242 (7), 184 (8).

HRMS ($C_{22}H_{34}NO_5PSi$, EI): calc.: 451.1944; found: 451.1940 (M^+).

3-(*tert*-Butyldimethylsilyl)-2-phenyl-1-tosyl-1*H*-pyrrole (8e)



The reaction was performed according to the above procedure using alkenyllithium reagent **1a** (1 mmol) and (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (0.233 g, 0.9 mmol), leading to the corresponding pyrrole **8e** in 73% yield (0.269 g) as a white solid.

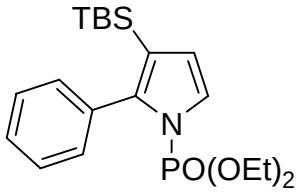
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.54 (d, *J* = 3.0 Hz, 1 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.25-7.12 (m, 6 H), 6.99 (d, *J* = 7.2 Hz, 2 H), 6.36 (d, *J* = 3.3 Hz, 1 H), 2.39 (s, 3 H), 0.78 (s, 9 H), -0.22 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 144.5, 139.4, 136.1, 132.7, 132.2, 129.3, 128.4, 127.4, 126.6, 122.4, 121.0, 116.6, 26.7, 21.6, 17.2, -5.1.

MS (EI, 70 eV): m/z (%) = 411 (M^+, 4), 355 (20), 354 (71), 200 (24), 199 (100), 184 (34), 169 (11), 91 (9).

HRMS ($C_{23}H_{29}NO_2SSi$, EI): calc.: 411.1688; found: 411.1698 (M^+).

Diethyl 3-(*tert*-butyldimethylsilyl)-2-phenyl-1*H*-pyrrol-1-ylphosphonate (8f)



The reaction was performed according to the above procedure using alkenyllithium reagent **1a** (1 mmol) and (*E*)-diethyl benzylidenephosphoramidate (0.217 g, 0.9 mmol), leading to the corresponding pyrrole **8f** in 76% yield (0.268 g) as a white solid.

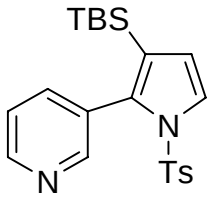
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.36-7.23 (m, 6 H), 6.33 (td, *J* = 3.5, 1.0 Hz, 1 H), 4.01-3.79 (m, 4 H), 1.16-1.11 (m, 6 H), 0.80 (s, 9 H), -0.19 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 141.2 (d, *J* = 3.7 Hz), 134.4, 132.1, 128.2, 126.7, 124.5 (d, *J* = 7.6 Hz), 120.0 (d, *J* = 7.3 Hz), 117.1 (d, *J* = 12.6 Hz), 63.6 (d, *J* = 5.3 Hz), 26.8, 17.3, 15.7 (d, *J* = 7.0 Hz), -4.9.

MS (EI, 70 eV): m/z (%) = 393 (M^+, 11), 337 (26), 336 (97), 290 (11), 281 (22), 280 (100), 264 (24), 263 (12), 262 (58), 184 (37), 169 (11).

HRMS ($C_{20}H_{32}NO_3PSi$, EI): calc.: 393.1889; found: 393.1887 (M^+).

3-(3-(*tert*-Butyldimethylsilyl)-1-tosyl-1*H*-pyrrol-2-yl)pyridine (8g)



The reaction was performed according to the above procedure using alkenyllithium reagent **1a** (1 mmol) and (*E*)-4-methyl-*N*-(pyridin-3-ylmethylene)benzenesulfonamide (0.234 g, 0.9 mmol), leading to the corresponding pyrrole **8g** in 35% yield (0.13 g) as a light yellow oil.

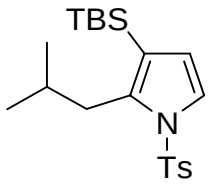
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.58 (dd, *J* = 4.8, 1.7 Hz, 1 H), 7.98 (d, *J* = 1.4 Hz, 1 H), 7.56-7.52 (m, 2 H), 7.27-7.15 (m, 5 H), 6.37 (d, *J* = 3.1 Hz, 1 H), 2.38 (s, 3 H), 0.74 (s, 9 H), -0.23 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 151.8, 149.3, 145.1, 140.3, 135.8, 135.2, 129.7, 128.6, 127.0, 123.2, 122.8, 121.8, 117.0, 26.5, 21.6, 17.1, -5.0.

MS (EI, 70 eV): m/z (%) = 412 (M^+, 4), 357 (13), 356 (31), 355 (100), 201 (16), 200 (65), 185 (21), 91 (9).

HRMS ($C_{22}H_{28}N_2O_2SSi$, EI): calc.: 412.1641; found: 412.1640 (M^+).

3-(*tert*-Butyldimethylsilyl)-2-isobutyl-1-tosyl-1*H*-pyrrole (8h)



The reaction was performed according to the above procedure using alkenyllithium reagent **1a** (1 mmol) and (*E*)-4-methyl-*N*-(3-methylbutylidene)benzenesulfonamide (0.22 g, 0.9 mmol), leading to the corresponding pyrrole **8h** in 93% yield (0.328 g) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.51 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 3.3 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 6.21 (d, *J* = 3.3 Hz, 1 H), 2.59 (d, *J* = 7.2 Hz, 2 H), 2.38 (s, 3 H), 2.06 (dt, *J* = 13.6, 6.9 Hz, 1 H), 0.85 (d, *J* = 6.9 Hz, 6 H), 0.68 (s, 9 H), 0.20 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 144.3, 142.0, 136.8, 129.6, 126.0, 124.0, 120.5, 118.7, 36.8, 30.5, 26.5, 22.1, 21.5, 17.6, -4.2.

MS (EI, 70 eV): m/z (%) = 391 (M^+, 13), 336 (21), 335 (46), 334 (100), 332 (39), 292 (10), 179 (19), 178 (13), 177 (36), 164 (10), 149 (23), 91 (24), 83 (11).

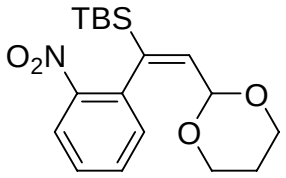
HRMS ($C_{21}H_{33}NO_2SSi$, EI): calc.: 391.2001; found: 391.2002 (M^+).

Palladium-catalyzed cross-coupling of alkenylzinc reagent 1c with 1-halo-2-nitroarene 9

To the pre-prepared alkenylzinc reagent **1c** (1 equiv) was added 1-halo-2-nitroarene **9** (0.8-0.9 equiv), palladium catalyst (4 mol%), and ligand (8 mol%). The reaction

mixture was stirred at 60 °C for 12 h before quenching with sat. NH_4Cl solution. The aqueous layer was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography with a mixture of ethyl acetate and isohexane as eluant to give the product **10**.

(*E*)-(2-(1,3-Dioxan-2-yl)-1-(2-nitrophenyl)vinyl)(*tert*-butyl)dimethylsilane (10a)



The cross-coupling reaction was performed according to the above procedure using the pre-prepared alkenylzinc reagent **1c** (4 mmol), 1-iodo-2-nitrobenzene **9a** (0.896 g, 3.6 mmol), $Pd(dba)_2$ (92 mg, 4 mol%), and tfp (74 mg, 8 mol%), leading to the product **10a** in 85% yield (1.07 g) as a white solid.

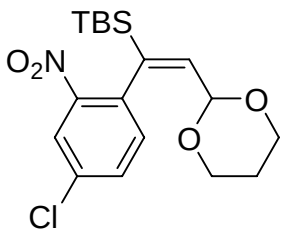
^{1}H-NMR (300 MHz, CD_3COCD_3): δ / ppm = 8.06 (dd, *J* = 8.2, 1.0 Hz, 1 H), 7.70 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.55-7.49 (m, 1 H), 7.26 (dd, *J* = 7.7, 1.1 Hz, 1 H), 5.97 (d, *J* = 6.1 Hz, 1 H), 4.55 (d, *J* = 6.1 Hz, 1 H), 3.95-3.81 (m, 2 H), 3.54-3.33 (m, 2 H), 1.95-1.79 (m, 1 H), 1.20 (ddd, *J* = 13.4, 1.2, 1.1 Hz, 1 H), 0.96 (s, 9 H), 0.26 (s, 3 H), -0.18 (s, 3 H).

^{13}C-NMR (75 MHz, CD_3COCD_3): δ / ppm = 148.5, 144.8, 139.4, 138.6, 133.8, 131.0, 128.2, 125.2, 99.4, 67.0, 66.9, 27.5, 26.3, 18.6, -4.4, -6.3.

MS (EI, 70 eV): m/z (%) = 349 (M^+, 2), 293 (27), 292 (100), 218 (10), 161 (13), 160 (12), 132 (49), 87 (18), 75 (12), 73 (13).

HRMS ($C_{17}H_{24}NO_4Si$, EI): calc.: 334.1475; found: 334.1466 (M^+-CH_3).

(*E*)-*tert*-Butyl(1-(4-chloro-2-nitrophenyl)-2-(1,3-dioxan-2-yl)vinyl)dimethylsilane (10b)



The cross-coupling reaction was performed according to the above procedure using the pre-prepared alkenylzinc reagent **1c** (10 mmol), 4-chloro-1-iodo-2-nitrobenzene **9b** (2.286 g, 8 mmol), $Pd(dba)_2$ (230 mg, 4 mol%), and tfp (186 mg, 8 mol%), leading to the product **10b** in 68% yield (1.542 g) as a white solid.

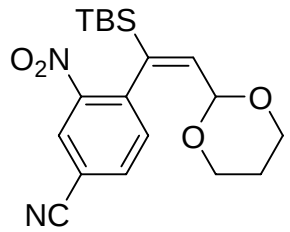
^{1}H-NMR (300 MHz, CD_3COCD_3): δ / ppm = 8.06 (d, *J* = 1.9 Hz, 1 H), 7.73 (dd, *J* = 8.3, 2.2 Hz, 1 H), 7.29 (d, *J* = 8.3 Hz, 1 H), 5.99 (d, *J* = 5.8 Hz, 1 H), 4.59 (d, *J* = 5.8 Hz, 1 H), 3.92 (dd, *J* = 11.3, 4.7 Hz, 1 H), 3.83 (dd, *J* = 11.3, 4.7 Hz, 1 H), 3.53 (td, *J* = 11.8, 2.5 Hz, 1 H), 3.42 (td, *J* = 11.9, 2.5 Hz, 1 H), 1.96-1.79 (m, 5 H), 1.21 (d, *J* = 13.3 Hz, 1 H), 0.96 (s, 9 H), 0.26 (s, 3 H), -0.16 (s, 3 H).

^{13}C-NMR (75 MHz, CD_3COCD_3): δ / ppm = 148.8, 143.9, 140.2, 137.4, 133.7, 132.9, 132.4, 125.0, 99.2, 67.0, 66.8, 27.5, 26.3, 18.6, -4.5, -6.3.

MS (EI, 70 eV): m/z (%) = 368 (M^+-CH_3, 2), 328 (40), 327 (18), 326 (100), 252 (12), 203 (16), 194 (10), 166 (44), 87 (19), 75 (10).

HRMS ($C_{17}H_{23}ClN_2O_4Si$, EI): calc.: 368.1085; found: 368.1094 (M^+-CH_3).

(*E*)-4-(1-(*tert*-Butyldimethylsilyl)-2-(1,3-dioxan-2-yl)vinyl)-3-nitrobenzonitrile (10c)



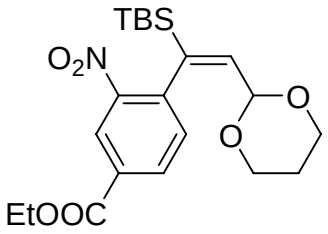
The cross-coupling reaction was performed according to the above procedure using the pre-prepared alkenylzinc reagent **1c** (10 mmol), 4-bromo-3-nitrobenzonitrile **9c** (2.26 g, 8 mmol), $Pd(OAc)_2$ (90 mg, 4 mol%) and S-Phos (328 mg, 8 mol%), leading to the product **10c** in 61% yield (1.731 g) as a white solid.

^{1}H-NMR (300 MHz, CD_3COCD_3): δ / ppm = 8.46 (d, *J* = 1.4 Hz, 1 H), 8.07 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 6.00 (d, *J* = 5.5 Hz, 1 H), 4.61 (d, *J* = 5.3 Hz, 1 H), 3.90 (dd, *J* = 11.3, 4.7 Hz, 1 H), 3.81 (dd, *J* = 11.3, 5.0 Hz, 1 H), 3.53 (td, *J* = 11.8, 2.4 Hz, 1 H), 3.40 (td, *J* = 11.9, 2.5 Hz, 1 H), 1.93-1.77 (m, 1 H), 1.21 (d, *J* = 13.6 Hz, 1 H), 0.98 (s, 9 H), 0.28 (s, 6 H), -0.15 (s, 6 H).

^{13}C-NMR (75 MHz, CD_3COCD_3): δ / ppm = 148.6, 143.9, 143.8, 140.0, 136.6, 132.2, 129.1, 117.6, 112.0, 99.2, 67.0, 66.8, 27.5, 26.2, 18.7, -4.4, -6.3.

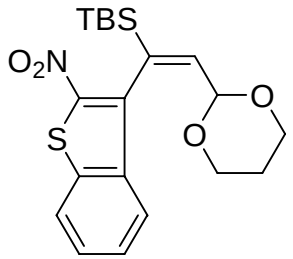
MS (EI, 70 eV): m/z (%) = 359 (M^+-Me, 1), 318 (20), 317 (84), 244 (11), 243 (26), 228 (10), 199 (15), 186 (23), 185 (13), 157 (100), 87 (22), 73 (19), 57 (25).
HRMS ($C_{19}H_{26}N_2O_4Si$, EI): calc.: 359.1440; found: 359.1427 (M^+-Me).

(*E*)-Ethyl 4-(1-(*tert*-butyldimethylsilyl)-2-(1,3-dioxan-2-yl)vinyl)-3-nitrobenzoate (10d)



The cross-coupling reaction was performed according to the above procedure using the pre-prepared alkenylzinc reagent **1c** (10 mmol), ethyl 4-bromo-3-nitrobenzoate **9d** (2.192 g, 8 mmol), $Pd(OAc)_2$ (90 mg, 4 mol%) and S-Phos (328 mg, 8 mol%), leading to the product **10d** in 64% yield (2.16 g) as a white solid.
^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 8.58 (d, *J* = 1.8 Hz, 1 H), 8.26 (dd, *J* = 8.1, 1.7 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 5.99 (d, *J* = 5.9 Hz, 1 H), 4.59 (d, *J* = 5.9 Hz, 1 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 3.91 (dd, *J* = 11.3, 4.9 Hz, 1 H), 3.81 (dd, *J* = 11.3, 4.9 Hz, 1 H), 3.52 (td, *J* = 11.9, 2.5 Hz, 1 H), 3.38 (td, *J* = 11.9, 2.4 Hz, 1 H), 1.92-1.80 (m, 1 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 1.20 (d, *J* = 13.5 Hz, 1 H), 0.97 (s, 9 H), 0.28 (s, 3 H), -0.17 (s, 3 H).
^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 165.0, 148.5, 144.4, 143.4, 139.7, 133.9, 131.5, 130.7, 125.9, 99.3, 67.0, 66.9, 62.4, 27.5, 26.3, 18.7, 14.6, -4.4, -6.3.
MS (EI, 70 eV): m/z (%) = 406 (M^+-Me, 2), 379 (36), 365 (22), 364 (100), 232 (11), 218 (15), 205 (18), 204 (74), 203 (17), 176 (32), 87 (24), 57 (16).
HRMS ($C_{21}H_{31}NO_6Si$, EI): calc.: 406.1678; found: 406.1686 (M^+).

(*E*)-(2-(1,3-Dioxan-2-yl)-1-(2-nitrobenzo[b]thiophen-3-yl)vinyl)(*tert*-butyl)dimethylsilane (10e)



The cross-coupling reaction was performed according to the above procedure using the pre-prepared alkenylzinc reagent **1c** (2.4 mmol), 3-bromo-2-nitrobenzo[*b*]thiophene **9e** (0.56 g, 2.16 mmol), $Pd(OAc)_2$ (29 mg, 4 mol%), and S-Phos (96 mg, 8 mol%), leading to the product **10e** in 74% yield (0.675 g) as a white solid.

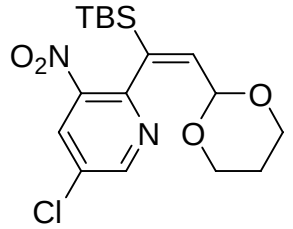
^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 8.06 (d, *J* = 8.2 Hz, 1 H), 7.86 (d, *J* = 8.2 Hz, 1 H), 7.72-7.68 (m, 1 H), 7.59-7.55 (m, 1 H), 6.28 (d, *J* = 6.3 Hz, 1 H), 4.64 (d, *J* =6.1 Hz, 1 H), 3.84 (dd, *J* = 10.9, 5.0 Hz, 2 H), 3.45-3.30 (m, 2 H), 1.92-1.80 (m, 1 H), 1.20-1.13 (m, 1 H), 0.93 (s, 9 H), 0.24 (s, 3 H), -0.07 (s, 3 H).

^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 142.7, 141.9, 139.4, 139.0, 137.2, 130.8, 128.3, 126.5, 123.9, 99.7, 67.1, 67.0, 27.4, 26.3, 18.5, -4.0, -5.8.

MS (EI, 70 eV): m/z (%) = 405 (M^+, 0.7), 350 (11), 349 (24), 348 (100), 262 (21), 260 (10), 259 (17), 232 (27), 230 (11), 217 (14), 188 (33), 186 (13), 172 (39), 160 (25), 145 (10), 115 (10), 100 (13), 87 (77), 75 (44), 73 (32), 59 (24), 57 (18).

HRMS ($C_{20}H_{27}NO_4SSi$, EI): calc.: 405.1430; found: 405.1429 (M^+).

(*E*)-2-(1-(*tert*-Butyldimethylsilyl)-2-(1,3-dioxan-2-yl)vinyl)-5-chloro-3-nitropyridine (10f)



The cross-coupling reaction was performed according to the above procedure using the pre-prepared alkenylzinc reagent **1c** (10 mmol), 2-bromo-5-chloro-3-nitropyridine **9f** (2.14 g, 9 mmol), $Pd(OAc)_2$ (90 mg, 4 mol%), and S-Phos (328 mg, 8 mol%), leading to the product **10f** in 69% yield (2.368 g) as a white solid.

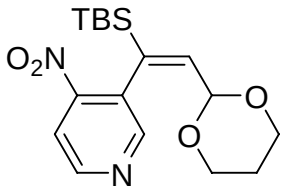
^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 8.84 (d, *J* = 2.2 Hz, 1 H), 8.43 (d, *J* = 2.2 Hz, 1 H), 5.96 (d, *J* = 4.9 Hz, 1 H), 4.58 (d, *J* = 5.1 Hz, 1 H), 3.88 (dd, *J* = 11.3, 4.9 Hz, 1 H), 3.77 (dd, *J* = 11.4, 4.8 Hz, 1 H), 3.54 (td, *J* = 11.9, 2.5 Hz, 1 H), 3.39 (td, *J* = 11.9, 2.3 Hz, 1 H), 1.89-1.77 (m, 1 H), 1.22-1.18 (m, 1 H), 1.00 (s, 9 H), 0.27 (s, 3 H), -0.14 (s, 3 H).

^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 155.3, 151.8, 146.2, 144.0, 140.5, 132.4, 129.8, 99.1, 67.1, 66.9, 27.4, 26.2, 18.4, -4.7, -6.3.

MS (EI, 70 eV): m/z (%) = 329 (26), 328 (28), 327 (M^+-^{t}Bu, 62), 311 (17), 265 (12), 255 (37), 254 (26), 253 (100), 241 (12), 240 (12), 225 (16), 211 (16), 210 (12), 198 (12), 197 (15), 169 (21), 167 (56), 127 (52), 87 (54), 75 (77), 73 (78), 59 (19), 57 (52).

HRMS ($C_{13}H_{16}ClN_2O_4Si$, EI): calc.: 327.0568; found: 327.0585 (M^+-^{t}Bu).

(*E*)-3-(1-(*tert*-Butyldimethylsilyl)-2-(1,3-dioxan-2-yl)vinyl)-4-nitropyridine (10g)



The cross-coupling reaction was performed according to the above procedure using the pre-prepared alkenylzinc reagent **1c** (10 mmol), 3-bromo-4-nitropyridine **9g** (1.82 g, 9 mmol), $Pd(OAc)_2$ (90 mg, 4 mol%), and S-Phos (328 mg, 8 mol%), leading to the product **10g** in 56% yield (1.76 g) as a colorless oil.

^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 8.78 (d, *J* = 5.3 Hz, 1 H), 8.55 (s, 1 H), 7.93 (d, *J* = 5.5 Hz, 1 H), 6.11 (d, *J* = 5.5 Hz, 1 H), 4.62 (d, *J* = 5.5 Hz, 1 H), 3.92 (dd, *J* = 11.4, 4.9 Hz, 1 H), 3.81 (dd, *J* = 11.4, 4.9 Hz, 1 H), 3.53 (td, *J* = 11.9, 2.5 Hz, 1 H), 3.40 (td, *J* = 11.8, 2.5 Hz, 1 H), 1.91-1.79 (m, 1 H), 1.21 (d, *J* = 13.3 Hz, 1 H), 0.98 (s, 9 H), 0.27 (s, 3 H), -0.14 (s, 3 H).

^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 153.5, 152.2, 150.4, 142.1, 141.2, 131.9, 117.4, 99.2, 67.1, 66.8, 27.4, 26.2, 18.6, -4.5, -6.2.

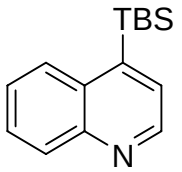
MS (EI, 70 eV): m/z (%) = 335 (M^+-CH_3, 1), 294 (26), 293 (100), 219 (18), 162 (23), 161 (13), 133 (77), 87 (32), 75 (28), 73 (27), 59 (15), 57 (22).

HRMS ($C_{16}H_{23}N_2O_4Si$, EI): calc.: 335.1427; found: 335.1430 (M^+-CH_3).

Preparation of annelated pyridine 11 by an indium- or zinc-mediated reduction of 10 followed by deacetalization and spontaneous cyclization

To a flask was added **10** (1 equiv), indium (2 equiv) or zinc (2.5 equiv), ammonium chloride (6 equiv), ethanol/water (2:1), and the reaction mixture was vigorously stirred at 60 °C for 4-12 h. Then the reaction mixture was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. To the resulting residue was added PPTS (0.5 equiv), THF and it was stirred at 60 °C for 24 h to effect deacetalization and spontaneous cyclization. Then it was quenched with sat. $NaHCO_3$ solution, extracted with ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography with a mixture of ethyl acetate and isohexane as eluant to give the product **11**.

4-(*tert*-Butyldimethylsilyl)quinoline (11a)



The reaction was performed according to above procedure using **10a** (0.584 g, 1.67 mmol), indium (0.384 g, 3.34 mmol), ammonium chloride (0.535 g, 10 mmol), ethanol (8 mL), water (4 mL) at 60 °C for 12 h followed by de-actalization using PPTS (0.21 g, 0.835 mmol) and spontaneous cyclization, leading to the desired product **11a** in 70% yield (0.283 g) as a colorless oil.

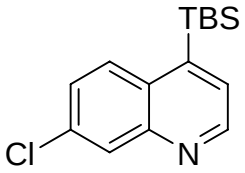
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.74 (d, *J* = 4.2 Hz, 1 H), 8.03 (d, *J* = 8.3 Hz, 1 H), 7.96 (d, *J* = 8.6 Hz, 1 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 7.43-7.39 (m, 2 H), 0.82 (s, 9 H), 0.40 (s, 6 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 148.6, 147.5, 147.1, 132.5, 130.2, 129.2, 129.0, 128.6, 125.8, 27.0, 17.6, -3.4.

MS (EI, 70 eV): m/z (%) = 243 (M^+, 8), 202 (9), 188 (12), 187 (24), 186 (100), 87 (8).

HRMS ($C_{15}H_{21}NSi$, EI): calc.: 243.1443; found: 243.1448 (M^+).

4-(*tert*-Butyldimethylsilyl)-7-chloroquinoline (11b)



The reaction was performed according to above procedure using **10b** (0.384 g, 1 mmol), zinc (0.163 g, 2.5 mmol), ammonium chloride (0.324 g, 6 mmol), ethanol (4 mL), water (2 mL) at 60 °C for 4 h followed by de-actalization using PPTS (0.126 g, 0.5 mmol) and spontaneous cyclization, leading to the desired product **11b** in 41% yield (0.113 g) as a white solid.

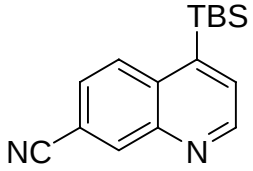
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.85 (d, *J* = 4.2 Hz, 1 H), 8.12 (d, *J* = 2.2 Hz, 1 H), 8.00 (d, *J* = 9.1 Hz, 1 H), 7.53 (d, *J* = 4.4 Hz, 1 H), 7.49 (dd, *J* = 9.1, 2.2 Hz, 1 H), 0.93 (s, 9 H), 0.52 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.7, 148.3, 147.2, 134.4, 130.9, 130.3, 129.4, 129.3, 126.9, 27.0, 17.6, -3.4.

MS (EI, 70 eV): m/z (%) = 277 (M^+, 10), 222 (38), 221 (26), 220 (100), 206 (6), 190 (4), 170 (3), 142 (3).

HRMS ($C_{15}H_{20}ClNSi$, EI): calc.: 277.1054; found: 277.1050 (M^+).

4-(*tert*-Butyldimethylsilyl)quinoline-7-carbonitrile (11c)



The reaction was performed according to above procedure using **10c** (0.375 g, 1 mmol), zinc (0.163 g, 2.5 mmol), ammonium chloride (0.324 g, 6 mmol), ethanol (4 mL), water (2 mL) at 60 °C for 4 h followed by de-actalization using PPTS (0.126 g, 0.5 mmol) and spontaneous cyclization, leading to the desired product **11c** in 55% yield (0.148 g) as a white solid.

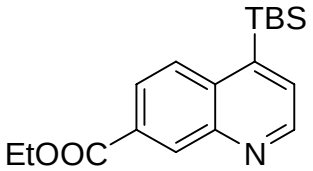
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.96 (d, *J* = 4.3 Hz, 1 H), 8.49 (d, *J* = 1.5 Hz, 1 H), 8.16 (d, *J* = 8.8 Hz, 1 H), 7.70-7.66 (m, 2 H), 0.94 (s, 9 H), 0.54 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.5, 147.7, 146.8, 136.4, 134.6, 131.6, 130.4, 126.5, 118.5, 112.2, 26.9, 17.6, -3.5.

MS (EI, 70 eV): m/z (%) = 268 (M^+, 7), 213 (8), 212 (26), 211 (100), 195 (5), 181 (4), 169 (2), 155 (2), 130 (1), 57 (2).

HRMS ($C_{16}H_{20}N_2Si$, EI): calc.: 268.1396; found: 268.1393 (M^+).

Ethyl 4-(*tert*-butyldimethylsilyl)quinoline-7-carboxylate (11d)



The reaction was performed according to above procedure using **10d** (0.421 g, 1 mmol), indium (0.23 g, 2 mmol), ammonium chloride (0.324 g, 6 mmol), ethanol (4 mL), water (2 mL) at 60 °C for 12 h followed by de-actalization using PPTS (0.126 g, 0.5 mmol) and spontaneous cyclization, leading to the desired product **11d** in 60% yield (0.19 g) as a white solid.

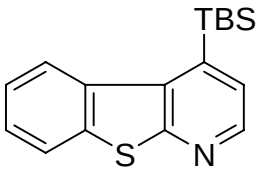
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.93 (d, *J* = 4.2 Hz, 1 H), 8.84 (s, 1 H), 8.13 (s, 2 H), 7.62 (d, *J* = 4.2 Hz, 1 H), 4.46 (q, *J* = 7.2 Hz, 1 H), 1.45 (t, *J* = 7.2 Hz, 3 H), 0.94 (s, 9 H), 0.54 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.3, 149.7, 147.2, 147.1, 135.0, 132.9, 130.9, 130.4, 129.3, 125.3, 61.3, 27.0, 17.7, 14.3, -3.4.

MS (EI, 70 eV): m/z (%) = 315 (M^+, 8), 259 (30), 258 (100), 230 (11), 186 (13), 184 (9), 170 (8).

HRMS ($C_{18}H_{25}NO_2Si$, EI): calc.: 315.1655; found: 315.1653 (M^+).

4-(*tert*-Butyldimethylsilyl)-[1]Benzothieno[2,3-b]pyridine (11e)



The reaction was performed according to above procedure using **10e** (0.677 g, 1.67 mmol), indium (0.384 g, 3.34 mmol), ammonium chloride (0.535 g, 10 mmol), ethanol (8 mL), water (4 mL) at 60 °C for 12 h followed by de-actalization using PPTS (0.21 g, 0.835 mmol) and spontaneous cyclization, leading to the desired product **11e** in 54% yield (0.27 g) as a white solid.

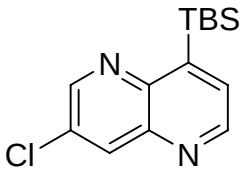
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.57 (d, *J* = 5.0 Hz, 1 H), 8.46-8.43 (m, 1 H), 7.89 (dd, *J* = 7.1, 1.8 Hz, 1 H), 7.58 (d, *J* = 4.7 Hz, 1 H), 7.52-7.42 (m, 2 H), 1.05 (s, 9 H), 0.60 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.9, 145.7, 143.3, 137.9, 134.1, 134.0, 127.5, 126.9, 125.7, 123.5, 123.0, 27.6, 18.8, -1.9.

MS (EI, 70 eV): m/z (%) = 299 (M^+, 13), 244 (11), 243 (31), 242 (100), 226 (18).

HRMS ($C_{17}H_{21}NSSi$, EI): calc.: 299.1164; found: 299.1163 (M^+).

8-(*tert*-Butyldimethylsilyl)-3-chloro-1,5-naphthyridine (11f)



The reaction was performed according to above procedure using **10f** (1.15 g, 3 mmol), indium (0.69 g, 6 mmol), ammonium chloride (0.963 g, 18 mmol), ethanol (12 mL), water (6 mL) at 60 °C for 12 h followed by de-actalization using PPTS (0.378 g, 1.5 mmol) and spontaneous cyclization, leading to the desired product **11f** in 62% yield (0.52 g) as a white solid.

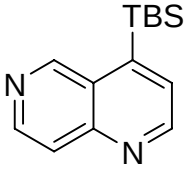
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.91 (d, *J* = 4.2 Hz, 1 H), 8.89 (d, *J* = 2.5 Hz, 1 H), 8.40 (d, *J* = 2.5 Hz, 1 H), 7.76 (d, *J* = 4.2 Hz, 1 H), 0.92 (s, 9 H), 0.49 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 151.6, 150.2, 148.9, 146.3, 142.5, 135.1, 131.5, 131.2, 27.3, 17.5, -4.1.

MS (EI, 70 eV): m/z (%) = 278 (M^+, 0.5), 263 (2), 223 (40), 222 (21), 221 (100), 191 (13).

HRMS ($C_{14}H_{19}ClN_2Si$, EI): calc.: 278.1006; found: 278.1012 (M^+).

4-(*tert*-Butyldimethylsilyl)-1,6-naphthyridine (11g)



The reaction was performed according to above procedure using **10g** (0.843 g, 2.41 mmol), indium (0.553 g, 4.82 mmol), ammonium chloride (0.774 g, 14.46 mmol),

ethanol (10 mL), water (5 mL) at 60 °C for 12 h followed by de-actalization using PPTS (0.3 g, 1.2 mmol) and spontaneous cyclization, leading to the desired product **11g** in 65% yield (0.384 g) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.42 (s, 1 H), 8.66 (d, *J* = 6.0 Hz, 1 H), 8.50 (d, *J* = 6.2 Hz, 1 H), 8.43 (d, *J* = 6.0 Hz, 1 H), 7.43 (d, *J* = 6.2 Hz, 1 H), 0.82 (s, 9 H), 0.43 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 153.5, 146.7, 143.7, 136.2, 130.3,129.7, 112.4, 26.5, 17.3, -3.8.

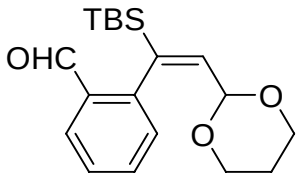
MS (EI, 70 eV): m/z (%) = 244 (M^+, 9), 189 (11), 188 (28), 187 (100), 171 (9), 157 (6).

HRMS ($C_{14}H_{20}N_2Si$, EI): calc.: 244.1396; found: 244.1391 (M^+).

Preparation of product 13 by palladium-catalyzed cross-coupling of alkenylzinc reagent 1c with 1-formyl-2-haloarene 12

To the pre-prepared alkenylzinc reagent **1c** (1 equiv) was added 1-formyl-2-haloarene **12** (0.8~0.9 equiv), and PEPPSI-IPr (4 mol%). The reaction mixture was stirred at 60 °C for 12 h before quenching the reaction with sat. NH_4Cl solution. The aqueous layer was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography with a mixture of ethyl acetate and isohexane as eluant to give the product **13**.

(*E*)-2-(1-(*tert*-Butyldimethylsilyl)-2-(1,3-dioxan-2-yl)vinyl)benzaldehyde (13a)



The cross-coupling reaction was performed according to the above procedure using the pre-prepared alkenylzinc reagent **1c** (8 mmol), 2-bromobenzaldehyde **12a** (1.332 g, 7.2 mmol), and PEPPSI-IPr (218 mg, 4 mol%) in THF/NMP (2:1), leading to the product **13a** in 77% yield (1.85 g) as a colorless oil.

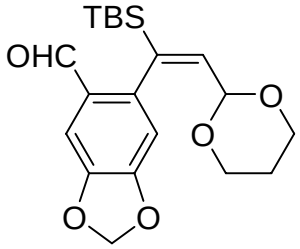
^{1}H-NMR (300 MHz, CD_3COCD_3): δ / ppm = 10.05 (s, 1 H), 7.89 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.62 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.16 (d, *J* = 7.7 Hz, 1 H), 6.17 (d, *J* = 6.6 Hz, 1 H), 4.56 (d, *J* = 6.6 Hz, 1 H), 3.93 (dd, *J* = 11.5, 4.8 Hz, 1 H), 3.83 (dd, *J* = 11.5, 4.8 Hz, 1 H), 3.49 (td, *J* = 11.9, 2.5 Hz, 1 H), 3.34 (td, *J* = 11.9, 2.5 Hz, 1 H), 1.98-.82 (m, 1 H), 1.21 (d, *J* = 13.6 Hz, 1 H), 0.90 (s, 9 H), 0.19 (s, 3 H), -0.04 (s, 3 H).

^{13}C-NMR (75 MHz, CD_3COCD_3): δ / ppm = 192.1, 146.3, 144.5, 142.1, 134.2, 133.8, 129.8, 128.0, 127.7, 99.1, 67.0, 67.0, 27.5, 26.4, 18.4, -4.8, -5.6.

MS (EI, 70 eV): m/z (%) = 332 (M^+, 2), 276 (23), 275 (100), 245 (10), 217 (18), 216 (13), 201 (11), 189 (45), 173 (11), 145 (18), 143 (14), 131 (13), 129 (12), 115 (38), 87 (47), 75 (27), 73 (19), 59 (8).

HRMS ($C_{19}H_{28}O_3Si$, EI): calc.: 332.1808; found: 332.1797 (M^+).

(*E*)-6-(1-(*tert*-Butyldimethylsilyl)-2-(1,3-dioxan-2-yl)vinyl)benzo[*d*][1,3]dioxole-5-carbaldehyde (13b)



The cross-coupling reaction was performed according to the above procedure using the pre-prepared alkenylzinc reagent **1c** (10 mmol), 6-bromobenzo[*d*][1,3]dioxole-5-carbaldehyde **12b** (1.84 g, 8 mmol), and PEPPSI-IPr (272 mg, 4 mol%) in THF at 60 ^oC for 12 h, leading to the product **13b** in 65% yield (1.943 g) as a colorless oil.

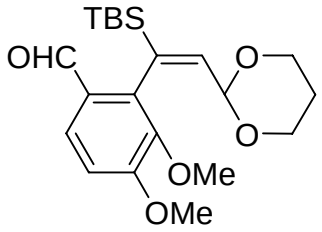
^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 9.84 (s, 1 H), 7.28 (s, 1 H), 6.58 (s, 1 H), 6.17 (d, *J* = 6.5 Hz, 1 H), 6.15 (s, 2 H), 4.66 (d, *J* = 6.5 Hz, 1 H), 3.95 (dd, *J* = 11.4, 4.9 Hz, 1 H), 3.86 (dd, *J* = 11.4, 4.9 Hz, 1 H), 3.57 (td, *J* = 11.9, 2.5 Hz, 1 H), 3.43 (td, *J* = 11.9, 2.5 Hz, 1 H), 1.98-1.86 (m, 1 H), 1.24 (d, *J* = 13.3 Hz, 1 H), 0.92 (s, 9 H), 0.18 (s, 3 H), 0.01 (s, 3 H).

^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 190.1, 153.1, 148.1, 143.9, 143.4, 142.9, 128.4, 109.0, 106.1, 103.3, 99.0, 67.0, 27.5, 26.4, 18.4, -4.8, -5.5.

MS (EI, 70 eV): m/z (%) = 376 (M^+, 2), 320 (19), 319 (78), 290 (12), 289 (53), 233 (53), 203 (13), 187 (11), 175 (10), 159 (29), 89 (11), 87 (100), 75 (63), 73 (87), 59 (19), 57 (10), 45 (11), 41 (32).

HRMS ($C_{20}H_{28}O_5Si$, EI): calc.: 376.1706; found: 376.1700 (M^+).

(*E*)-2-(1-(*tert*-Butyldimethylsilyl)-2-(1,3-dioxan-2-yl)vinyl)-3,4-dimethoxybenzaldehyde (13c)



The cross-coupling reaction was performed according to the above procedure using the pre-prepared alkenylzinc reagent **1c** (10 mmol), 2-iodo-3,4-dimethoxybenzaldehyde **12c** (2.63 g, 9 mmol), and PEPPSI-IPr (272 mg, 4 mol%) in THF at 60 °C for 12 h, leading to the product **13c** in 51% yield (1.8 g) as a white solid.

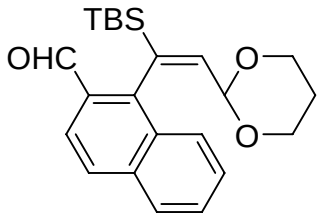
^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 9.90 (s, 1 H), 7.70 (d, *J* = 8.8 Hz, 1 H), 7.12 (d, *J* = 8.6 Hz, 1 H), 6.21 (d, *J* = 6.9 Hz, 1 H), 4.67 (d, *J* = 6.9 Hz, 1 H), 3.97 (s, 3 H), 3.97 (dd, *J* = 11.3, 4.9 Hz, 1 H), 3.88 (dd, *J* = 11.3, 4.9 Hz, 1 H), 3.68 (s, 3 H), 3.56 (td, *J* = 11.9, 2.5 Hz, 1 H), 3.42 (td, *J* = 11.9, 2.5 Hz, 1 H), 1.99-1.87 (m, 1 H), 1.24 (d, *J* = 13.2 Hz, 1 H), 0.94 (s, 9 H), 0.06 (s, 3 H), 0.00 (s, 3 H).

^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 190.6, 158.5, 145.3, 141.5, 141.0, 141.0, 127.3, 124.9, 111.7, 99.4, 67.0, 67.0, 60.1, 56.4, 27.6, 26.4, 18.5, -4.5, -5.0.

MS (EI, 70 eV): m/z (%) = 392 (M^+, 3), 336 (24), 335 (100), 250 (10), 249 (49), 247 (10), 246 (11), 233 (11), 219 (13), 203 (18), 191 (11), 175 (12), 145 (25), 131 (12), 115 (12), 87 (31), 75 (38), 73 (32), 59 (10), 41 (11).

HRMS ($C_{21}H_{32}O_5Si$, EI): calc.: 392.2019; found: 392.2021 (M^+).

(*E*)-1-(1-(*tert*-Butyldimethylsilyl)-2-(1,3-dioxan-2-yl)vinyl)-2-naphthaldehyde (13d)



The cross-coupling reaction was performed according to the above procedure using the pre-prepared alkenylzinc reagent **1c** (10 mmol), 1-bromo-2-naphthaldehyde **12d** (1.872 g, 8 mmol), and PEPPSI-IPr (272 mg, 4 mol%) in THF at 60 °C for 12 h, leading to the product **13d** in 57% yield (1.752 g) as a colorless oil.

^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 10.32 (s, 1 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 8.00 (d, *J* = 8.0 Hz, 1 H), 7.95 (d, *J* = 8.6Hz, 1 H), 7.91 (d, *J* = 8.8 Hz, 1 H), 7.72-7.68 (m, 1 H), 7.65-7.61 (m, 1 H), 6.55 (d, *J* = 6.5 Hz, 1 H), 4.52 (d, *J* = 6.7 Hz, 1 H), 3.89-3.81 (m, 2 H), 3.37-3.26 (m, 2 H), 1.95-1.83 (m, 1 H), 1.15 (d, *J* = 13.3 Hz, 1 H), 0.92 (s, 9 H), 0.05 (s, 3 H), -0.09 (s, 3 H).

^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 192.7, 146.9, 143.4, 142.2, 137.0, 131.4, 130.0, 130.0, 129.5, 128.5, 128.1, 127.4, 122.7, 99.4, 67.0, 67.0, 27.6, 26.4, 18.6, -4.2, -4.7.

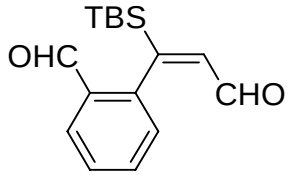
MS (EI, 70 eV): m/z (%) = 382 (M^+, 0.7), 326 (12), 325 (53), 267 (19), 266 (14), 251 (20), 239 (10), 223 (16), 193 (24), 181 (11), 179 (10), 166 (11), 165 (60), 152 (12), 131 (18), 87 (100), 75 (45), 73 (54), 59 (12), 59 (16), 41 (16).

HRMS ($C_{23}H_{30}O_3Si$, EI): calc.: 382.1964; found: 382.1965 (M^+).

Preparation of dialdehyde 14 by an acidic deacetalization of 13

To a flask was added the prepared acetal **13**, THF, and HCl (2 M), and the reaction mixture was stirred at room temperature for overnight or 60 °C for 5 h. Then the reaction mixture was diluted with ethyl acetate and it was sequentially washed with sat. $NaHCO_3$ solution and brine, dried over sodium sulfate. After concentration, the resulting residue was purified by silica gel column chromatography with a mixture of ethyl acetate and isohexane as eluant to give the dialdehyde **14**.

(*E*)-2-(1-(*tert*-Butyldimethylsilyl)-3-oxoprop-1-enyl)benzaldehyde (14a)



The deacetalization was performed according to above procedure using **13a** (0.665 g, 2 mmol), THF (18 mL), and 2 M HCl (6 mL) at room temperature for overnight, leading to dialdehyde **14a** in 84% yield (0.461 g) as a colorless oil.

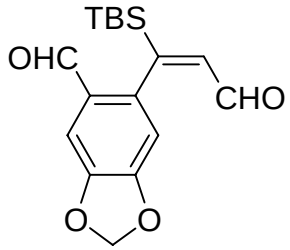
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 10.07 (s, 1 H), 9.27 (d, *J* = 8.0 Hz, 1 H), 7.93 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.60 (td, *J* = 7.5, 1.4 Hz, 1H), 7.49 (td, *J* = 7.5, 0.8 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1 H), 6.57 (d, *J* = 8.0 Hz, 1 H), 0.94 (s, 9 H), 0.31 (s, 3 H), -0.12 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 191.3, 190.9, 167.7, 142.5, 139.6, 133.7, 133.1, 131.5, 128.6, 127.6, 27.0, 18.2, -5.1, -6.7.

MS (EI, 70 eV): m/z (%) = 274 (M^+, 8), 233 (20), 218 (19), 217 (89), 216 (38), 203 (10), 189 (10), 145 (10), 143 (10), 141 (11), 115 (47), 104 (11), 77 (10), 76 (18), 75 (100), 73 (56), 59 (14), 57 (14), 43 (17), 41 (15).

HRMS ($C_{16}H_{22}O_2Si$, EI): calc.: 274.1389; found: 274.1391 (M^+).

(*E*)-6-(1-(*tert*-Butyldimethylsilyl)-3-oxoprop-1-enyl)benzo[*d*][1,3]dioxole-5-carbaldehyde (14b)



The deacetalization was performed according to above procedure using **13b** (1.73 g, 4.6 mmol), THF (20 mL), and 2 M HCl (3 mL) at 60 °C for 5 h, leading to dialdehyde **14b** in 81% yield (1.2 g) as a colorless oil.

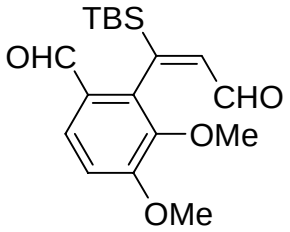
^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.83 (s, 1 H), 9.34 (d, *J* = 8.0 Hz, 1 H), 7.36 (s, 1 H), 6.57-6.56 (m, 2 H), 6.09 (d, *J* = 10.2 Hz, 2 H), 0.93 (s, 9 H), 0.24 (s, 3 H), -0.06 (s, 3 H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 190.7, 188.8, 166.0, 152.4, 147.5, 141.1, 140.2, 127.7, 108.0, 108.0, 102.4, 26.9, 18.0, -5.3, -6.5.

MS (EI, 70 eV): m/z (%) = 318 (M^+, 7), 289 (18), 262 (16), 261 (79), 205 (10), 204 (14), 203 (62), 187 (25), 160 (11), 159 (71), 103 (13), 75 (25), 73 (100), 59 (25), 57 (11), 45 (15), 43 (11), 41 (17).

HRMS ($C_{17}H_{22}O_4Si$, EI): calc.: 318.1287; found: 318.1276 (M^+).

(*E*)-2-(1-(*tert*-Butyldimethylsilyl)-3-oxoprop-1-enyl)-3,4-dimethoxybenzaldehyde (14c)



The deacetalization was performed according to above procedure using **13c** (1.62 g, 4.27 mmol), THF (8 mL), and 2 M HCl (2 mL) at 60 °C for 5 h, leading to dialdehyde **14c** in 44% yield (0.628 g) as a white solid.

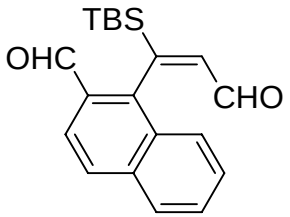
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.86 (s, 1 H), 9.37 (d, *J* = 8.0 Hz, 1 H), 7.70 (d, *J* = 8.6 Hz, 1 H), 6.98 (d, *J* = 8.6 Hz, 1 H), 6.63 (d, *J* = 8.0 Hz, 1 H), 3.95 (s, 3 H), 3.68 (s, 3 H), 0.93 (s, 9 H), 0.11 (s, 3 H), -0.02 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 190.6, 189.6, 164.5, 157.5, 144.2, 140.0, 137.1, 127.7, 126.7, 110.7, 60.2, 55.9, 26.9, 17.9, -5.3, -5.7.

MS (EI, 70 eV): m/z (%) = 335 (13), 334 (M^+, 7), 278 (20), 277 (100), 262 (21), 247 (35), 246 (91), 233 (13), 231 (34), 219 (14), 203 (26), 175 (16), 115 (13), 89 (16), 75 (19), 73 (60), 59 (19), 57 (10), 43 (27), 41 (17).

HRMS ($C_{18}H_{26}O_4Si$, EI): calc.: 334.1600; found: 334.1602 (M^+).

(*E*)-1-(1-(*tert*-Butyldimethylsilyl)-3-oxoprop-1-enyl)-2-naphthaldehyde (14d)



The deacetalization was performed according to above procedure using **13d** (1.84 g, 4.8 mmol), THF (20 mL), and 2 M HCl (3 mL) at 60 °C for 5 h, leading to dialdehyde **14d** in 68% yield (1.06 g) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 10.32 (s, 1 H), 9.17 (dd, *J* = 8.0, 1.1 Hz, 1 H), 8.01 (dd, *J* = 8.5, 1.1 Hz, 1 H), 7.91-7.85 (m, 3 H), 7.64 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.57-7.54 (m, 1 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 0.93 (s, 9 H), 0.05 (s, 3 H), -0.01 (s, 3 H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 191.0, 190.5, 164.5, 164.5, 143.7, 142.0, 135.9, 130.2, 129.3, 129.1, 128.7, 127.9, 127.3, 127.1, 123.0, 27.0, 18.0, -5.1, -5.2.

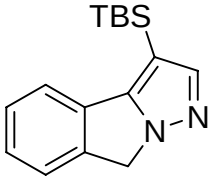
MS (EI, 70 eV): m/z (%) = 325 (27), 324 (M^+, 100), 268 (24), 267 (95), 266 (39), 239 (13), 207 (16), 193 (18), 191 (14), 181 (11), 166 (11), 165 (99), 164 (16), 163 (18), 153 (14), 152 (32), 151 (14), 75 (44), 73 (75), 59 (12).

HRMS ($C_{20}H_{24}O_2Si$, EI): calc.: 324.1546; found: 324.1541 (M^+).

Preparation of pyrazole 15 or 17 by the reaction of dialdehyde 14 with hydrazine

To a 10 mL flask was sequentially added dialdehyde **14** (0.5 mmol), EtOH (4 mL), acetic acid (2 mL) and hydrazine monohydrate (~0.2 mL, 2 mmol, ~65% aqueous solution). The reaction mixture was stirred at 60 °C for 12 h. Then, the reaction mixture was neutralized by sat. $NaHCO_3$ solution (30 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine, dried over sodium sulphate and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography with a mixture of ethyl acetate and isohexane as eluant to give the product **15** or **17**.

3-(*tert*-Butyldimethylsilyl)-8*H*-Pyrazolo[5,1-*a*]isoindole (15a)



The reaction was performed according to above procedure by using dialdehyde **14a** (0.137 g, 0.5 mmol), EtOH (4 mL), acetic acid (2 mL) and hydrazine monohydrate (~0.2 mL, 2 mmol, ~65% aqueous solution) and stirred at 60 ^{o}C for 12 h, leading to the product **15a** in 68% yield (0.092 g) as a white solid.

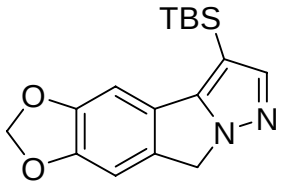
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.70 (d, *J* = 7.7 Hz, 1 H), 7.62 (s, 1 H), 7.46-7.25 (m, 3 H), 5.10 (s, 2 H), 0.93 (s, 9 H), 0.36 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 151.0, 149.9, 140.9, 131.8, 128.1, 127.0, 123.5, 121.2, 103.5, 51.6, 26.5, 17.6, -4.7.

MS (EI, 70 eV): m/z (%) = 270 (M^+, 3), 214 (17), 213 (100), 183 (4).

HRMS ($C_{16}H_{22}N_2Si$, EI): calc.: 270.1552; found: 270.1547 (M^+).

3-(*tert*-Butyldimethylsilyl)-5,6-(methylenedioxy)-8*H*-Pyrazolo[5,1-*a*]isoindole (15b)



The reaction was performed according to above procedure by using dialdehyde **14b** (0.159 g, 0.5 mmol), EtOH (4 mL), acetic acid (2 mL) and hydrazine monohydrate (~0.2 mL, 2 mmol, ~65% aqueous solution) and stirred at 60 ^{o}C for 12 h, leading to the product **15b** in 77% yield (0.121 g) as a white solid.

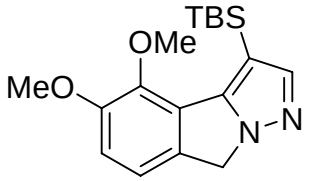
^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.58 (s, 1 H), 7.16 (s, 1 H), 6.94 (s, 1 H), 6.03 (s, 2 H), 5.00 (s, 2 H), 0.94 (s, 9 H), 0.35 (s, 6 H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 151.1, 149.7, 147.8, 147.2, 134.8, 125.5, 104.7, 102.4, 102.3, 101.5, 51.6, 26.5, 17.6, -4.6.

MS (EI, 70 eV): m/z (%) = 314 (M^+, 8), 258 (20), 259 (6), 257 (100), 128 (3).

HRMS ($C_{17}H_{22}N_2O_2Si$, EI): calc.: 314.1451; found: 314.1446 (M^+).

3-(*tert*-Butyldimethylsilyl)-4,5-dimethoxy-8*H*-Pyrazolo[5,1-*a*]isoindole (15c)



The reaction was performed according to above procedure by using dialdehyde **14c** (0.167 g, 0.5 mmol), EtOH (4 mL), acetic acid (2 mL) and hydrazine monohydrate (~0.2 mL, 2 mmol, ~65% aqueous solution) and stirred at 60 ^{o}C for 12 h, leading to the product **15c** in 62% yield (0.103 g) as a white solid.

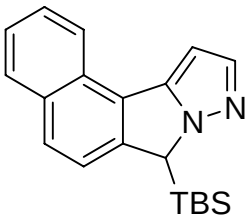
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.69 (s, 1 H), 7.06 (d, *J* = 8.2 Hz, 1 H), 6.88 (d, *J* = 8.2 Hz, 1 H), 5.02 (s, 2 H), 3.99 (s, 3 H), 3.89 (s, 3 H), 0.93 (s, 9 H), 0.37 (s, 6 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 152.0, 150.7, 148.7, 143.2, 133.9, 125.2, 117.7, 112.2, 105.1, 60.8, 56.3, 50.8, 26.9, 17.4, -3.8.

MS (EI, 70 eV): m/z (%) = 330 (M^+, 0.3), 274 (22), 273 (100), 259 (12), 258 (57), 244 (11), 243 (56).

HRMS ($C_{18}H_{26}N_2O_2Si$, EI): calc.: 330.1764; found: 330.1764 (M^+).

7-*(tert*-Butyldimethylsilyl)-*b*enzo[*g*]pyrazolo[5,1-*a*]isoindole (17d)



The reaction was performed according to above procedure by using dialdehyde **14d** (0.162 g, 0.5 mmol), EtOH (4 mL), acetic acid (2 mL) and hydrazine monohydrate (~0.2 mL, 2 mmol, ~65% aqueous solution) and stirred at 60 ^{o}C for 12 h, leading to the product **17d** in 65% yield (0.104 g) as a white solid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.26 (d, *J* = 8.2 Hz, 1 H), 7.95 (d, *J* = 8.2 Hz, 1 H), 7.82 (d, *J* = 8.5 Hz, 1 H), 7.77 (s, 1 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.59 (d, *J* = 8.2 Hz, 1 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 6.70 (s, 1 H), 5.22 (s, 1 H), 0.56 (s, 9 H), 0.48 (s, 3 H), 0.27 (s, 3 H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 145.0, 142.5, 142.3, 132.3, 128.5, 126.9, 126.8, 126.8, 125.8, 125.7, 124.1, 121.1, 96.8, 58.5, 26.5, 17.6, -5.4, -6.2.

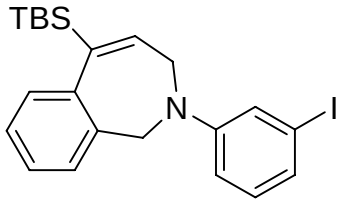
MS (EI, 70 eV): m/z (%) = 321 (18), 320 (M^+, 70), 265 (13), 264 (54), 263 (55), 206 (18), 205 (27), 151 (12), 73 (100), 59 (10).

HRMS ($C_{20}H_{24}N_2Si$, EI): calc.: 320.1709; found: 320.1700 (M^+).

$NaBH(OAc)_3$-mediated double reductive amination of 1,6-dialdehyde 14 with aryl amine leading to 7-membered nitrogen-containing heterocycles 23

To a 10 mL flask was sequentially added dialdehyde **14** (0.5 mmol), aryl amine (0.5 mmol), DCE (10 mL), AcOH (0.114 mL, 2 mmol), and $NaBH(OAc)_3$ (0.424 g, 2 mmol). The reaction mixture was stirred at room temperature for 12 h followed by dilution with CH_2Cl_2 (50 mL), washing with sat. $NaHCO_3$ solution, brine, and drying over sodium sulphate. After removal of solvent under vacuum, the resulting residue was purified by silica gel column chromatography with a mixture of ethyl acetate and isohexane as eluant to give the product **23**.

(*E*)-5-(*tert*-Butyldimethylsilyl)-2-(3-iodophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepine (23a)



The reductive amination was performed according to above procedure by using dialdehyde **14a** (0.137 g, 0.5 mmol), 3-iodobenzenamine (0.11 g, 0.5 mmol), DCE (10 mL), AcOH (0.114 mL, 2 mmol), and $NaBH(OAc)_3$ (0.424 g, 2 mmol) at room temperature for 12 h, leading to the desired product **23a** in 89% yield (0.206 g) as a yellow oil.

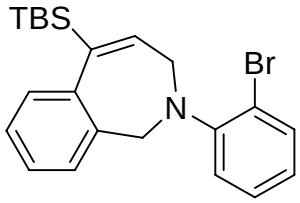
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.34-7.18 (m, 5 H), 7.08 (d, *J* = 7.5 Hz, 1 H), 6.95 (t, *J* = 8.0 Hz, 1 H), 6.84 (dd, *J* = 8.3, 1.6 Hz, 1 H), 6.48 (t, *J* = 7.0 Hz, 1 H), 4.09 (s, 2 H), 3.51 (d, *J* = 6.9 Hz, 2 H), 0.82 (s, 9 H), 0.26 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.5, 146.5, 142.4, 136.5, 134.6, 130.4, 129.9, 127.8, 127.3, 126.8, 126.4, 123.0, 113.5, 95.5, 52.7, 46.0, 27.0, 17.3, -4.4.

MS (EI, 70 eV): m/z (%) = 462 (23), 461 (M^+, 76), 404 (32), 347 (19), 346 (100), 219 (14), 218 (13), 217 (10), 145 (12), 73 (13).

HRMS ($C_{22}H_{28}INSi$, EI): calc.: 461.1036; found: 461.1033 (M^+).

(*E*)-2-(2-Bromophenyl)-5-(*tert*-butyldimethylsilyl)-2,3-dihydro-1*H*-benzo[*c*]azepine (23b)



The reductive amination was performed according to above procedure by using dialdehyde **14a** (0.137 g, 0.5 mmol), 2-bromobenzenamine (0.086 g, 0.5 mmol), DCE (10 mL), AcOH (0.114 mL, 2 mmol), and $NaBH(OAc)_3$ (0.424 g, 2 mmol) at room temperature for 12 h, leading to the desired product **23b** in 74% yield (0.152 g) as a yellow oil.

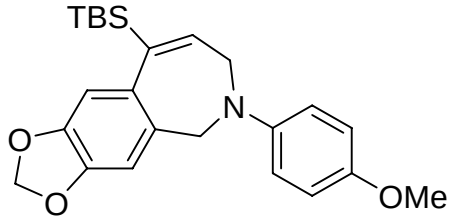
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.61 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.33-7.20 (m, 5 H), 7.09 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.90 (td, *J* = 7.5, 1.4 Hz, 1 H), 6.59 (t, *J* = 7.0 Hz, 1 H), 4.06 (s, 2 H), 3.41 (d, *J* = 6.9 Hz, 2 H), 0.86 (s, 9 H), 0.30 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.1, 146.5, 142.8, 137.5, 134.8, 134.0, 129.9, 127.8, 127.7, 127.1, 126.7, 123.8, 121.9, 118.8, 55.8, 49.0, 27.1, 17.4, -4.4.

MS (EI, 70 eV): m/z (%) = 416 (11), 415 (43), 414 (24), 413 (M^+, 40), 412 (13), 358 (16), 356 (17), 301 (16), 300 (89), 299 (20), 298 (100), 276 (21), 219 (11), 218 (20), 217 (13), 145 (12), 115 (10), 73 (13).

HRMS ($C_{22}H_{28}BrNSi$, EI): calc.: 413.1174; found: 413.1175 (M^+).

(*E*)-2-(4-Methoxyphenyl)-5-(*tert*-butyldimethylsilyl)-7,8-(methylenedioxy)-2,3-dihydro-1*H*-benzo[*c*]azepine (23c)



The reductive amination was performed according to above procedure by using dialdehyde **14b** (0.159 g, 0.5 mmol), 4-methoxybenzenamine (0.062 g, 0.5 mmol), DCE (10 mL), AcOH (0.114 mL, 2 mmol), and $NaBH(OAc)_3$ (0.424 g, 2 mmol) at room temperature for 12 h, leading to the desired product **23c** in 70% yield (0.143 g) as a yellow oil.

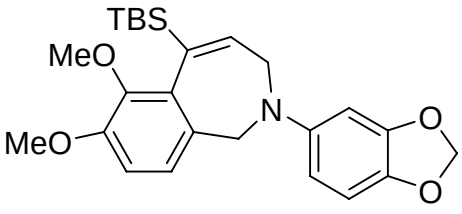
^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 6.91-6.88 (m, 2 H), 6.85 (s, 1 H), 6.83-6.80 (m, 2 H), 6.77 (s, 1 H), 6.56 (t, *J* = 6.9 Hz, 1 H), 5.98 (s, 2 H), 4.01 (s, 2 H), 3.71 (s, 3 H), 3.41 (d, *J* = 6.9 Hz, 2 H), 0.84 (s, 9 H), 0.27 (s, 6 H).

^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 153.6, 147.8, 147.2, 146.4, 145.4, 138.4, 137.3, 130.3, 117.6, 115.3, 110.7, 108.5, 102.2, 55.8, 54.3, 48.1, 27.5, 18.0, -4.0.

MS (EI, 70 eV): m/z (%) = 410 (25), 409 (M^+, 76), 408 (40), 295 (22), 294 (100), 218 (10), 217 (43), 134 (13), 73 (24).

HRMS ($C_{24}H_{31}NO_3Si$, EI): calc.: 409.2073; found: 409.2071 (M^+).

(*E*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-5-(*tert*-butyldimethylsilyl)-6,7-dimethoxy-2,3-dihydro-1*H*-benzo[*c*]azepine (23d)



The reductive amination was performed according to above procedure by using dialdehyde **14c** (0.167 g, 0.5 mmol), benzo[*d*][1,3]dioxol-5-amine (0.067 g, 0.5 mmol), DCE (10 mL), AcOH (0.114 mL, 2 mmol), and $NaBH(OAc)_3$ (0.424 g, 2

mmol) at room temperature for 12 h, leading to the desired product **23d** in 63% yield (0.139 g) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.96 (d, *J* = 8.2 Hz, 1 H), 6.79 (d, *J* = 8.2 Hz, 1 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 6.58 (t, *J* = 7.1 Hz, 1 H), 6.55 (d, *J* = 2.3 Hz, 1 H), 6.32 (dd, *J* = 8.6, 2.3 Hz, 1 H), 5.89 (d, *J* = 6.6 Hz, 2 H), 4.10 (d, *J* = 11.9 Hz, 1 H), 3.87 (s, 3 H), 3.86 (t, *J* = 11.3 Hz, 1 H), 3.74 (dd, *J* = 11.7, 7.0 Hz, 1 H), 3.65 (s, 3 H), 3.12 (dd, *J* = 11.7, 7.2 Hz, 1 H), 0.87 (s, 9 H), 0.20 (s, 3 H), 0.18 (s, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 152.0, 148.1, 146.0, 145.4, 144.9, 140.2, 136.8, 136.5, 128.2, 124.9, 110.7, 108.1, 107.7, 100.6, 98.7, 60.2, 55.7, 53.4, 47.8, 27.3, 17.7, -3.6, -4.2.

MS (EI, 70 eV): m/z (%) = 440 (19), 439 (M^+, 56), 383 (12), 382 (42), 368 (24), 367 (79), 366 (100), 352 (11), 324 (28), 73 (19).

HRMS ($C_{25}H_{33}NO_4Si$**, EI):** calc.: 439.2179; found: 439.2170 (M^+).

Chapter 7. Highly Diastereoselective Preparation of Aldol Products Using New Functionalized Allylic Aluminum Reagents

7.1 Introduction

The aldol functional unit has a central position in organic chemistry since this structural unit is found in numerous natural products.[1] Substituted aldol derivatives bearing quaternary centers are sensitive organic molecules due to retro-aldol decomposition pathways. Extensive research efforts have been made to prepare such molecules in a stereoselective manner.[2] Aluminum organometallic chemistry has received in recent years renewed attention.[3] Recently, we have shown that functionalized allylic aluminum reagents bearing electron-attracting groups in position 2 such as a cyano or an ester group undergo highly diastereoselective additions to aldehydes and aryl methyl ketones.[4-6] Herein, we report the preparation of

[1] *Modern Aldol Reactions*; R. Mahrwald, Ed.; Wiley-VCH: Weinheim, **2004**.

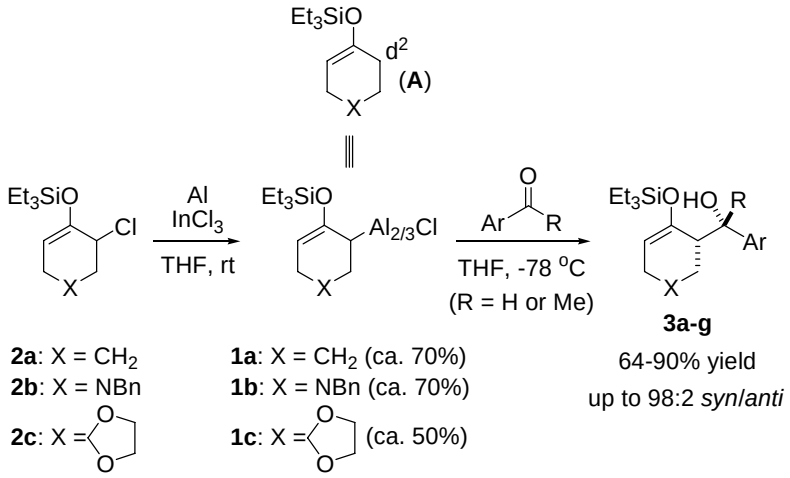
[2] For selected examples, see: (a) B. List, R. A. Lerner, C. F. Barbas, III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386. (c) N. Mase, F. Tanaka, C. F. Barbas, *Angew. Chem.*, *Int. Ed.* **2004**, *43*, 2420. (d) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.*, *Int. Ed.* **2006**, *45*, 958. (e) S. E. Denmark, T. W. Wilson, M. T. Burk, J. R. Heemstra, *J. Am. Chem. Soc.* **2007**, *129*, 14864. (f) R. R. Huddleston, D. F. Cauble, M. J. Krische, *J. Org. Chem.* **2003**, *68*, 11. (g) J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, *1*, 128. (h) Y. Minko, M. Pasco, L. Lercher, M. Botoshansky, I. Marek, *Nature* **2012**, *490*, 522. (i) S. Simaan, I. Marek, *J. Am. Chem. Soc.* **2010**, *132*, 4066. (j) G. Sklute, I. Marek, *J. Am. Chem. Soc.* **2006**, *128*, 4642. (k) C. Zheng, Y. Wu, X. Wang, G. Zhao, *Adv. Synth. Catal* **2008**, *350*, 2690, and references cited therein.

[3] For reviews, see: (a) *Modern Organoaluminum Reagents: Preparation, Structure, Reactivity and Use.* S. Woodward, S. Dagorne, Eds.; Springer-Verlag: Berlin, Heidelberg, **2013**. For recent examples, see: (b) O. Jackowski, T. Lecourt, L. Micouin, *Org. Lett.* **2011**, *13*, 5664. (c) Y. Zhou, T. Lecourt, L. Micouin, *Angew. Chem.*, *Int. Ed.* **2010**, *49*, 2607. (d) L. Palais, C. Bournaud, L. Micouin, A. Alexakis, *Chem.-Eur. J.* **2010**, *16*, 2567. (e) T. Ooi, K. Ohmatsu, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 2410. (f) T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 8834. (g) M. Welker, S. Woodward, A. Alexakis, *Org. Lett.* **2010**, *12*, 576. (h) C. Bleschke, M. Tissot, D. Müller, A. Alexakis, *Org. Lett.* **2013**, *15*, 2152. (i) C. Hawner, K. Li, V. Cirriez, A. Alexakis, *Angew. Chem.*, *Int. Ed.* **2008**, *47*, 8211. (j) L. Gremaud, A. Alexakis, *Angew. Chem.*, *Int. Ed.* **2012**, *51*, 794. (k) Y. Mata, M. Diéguez, O. Pàmies, S. Woodward, *J. Org. Chem.* **2006**, *71*, 8159. (l) C. Hawner, D. Müller, L. Gremaud, A. Felouat, S. Woodward, A. Alexakis, *Angew. Chem.*, *Int. Ed.* **2010**, *49*, 7769. (m) A. Kolb, S. Hirner, K. Harms, P. von Zezschwitz, *Org. Lett.* **2012**, *14*, 1978. (n) H. Shojaei, Z. Li-Böhmer, P. von Zezschwitz, *J. Org. Chem.* **2007**, *72*, 5091. (o) J. Siewert, R. Sandmann, P. von Zezschwitz, *Angew. Chem.*, *Int. Ed.* **2007**, *46*, 7122. (p) E. Raluy, M. Diéguez, O. Pàmies, *Tetrahedron Lett.* **2009**, *50*, 4495.

[4] Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem.*, *Int. Ed.* **2010**, *49*, 8516.

new functionalized allylic aluminum reagents of type **1** bearing a triethylsilyloxy substituent in position 2 and their diastereoselective additions to carbonyl derivatives (Scheme 1). These organometallic reagents were readily prepared from the corresponding allylic chloride of type **2** and represent a new type of d^2 enolate synthetic equivalents (**A**).[7] They underwent highly diastereoselective additions to aldehydes or ketones leading in the last case to aldol products of type **3** bearing a *β*-quaternary carbon center.[8]

7.2 Results and Discussion



Scheme 1. Preparation of allylic aluminum reagents **1a-c** and their additions to aldehydes and methyl ketones

The required chloro-triethylsilyl enol ethers **2a-c** were prepared in two steps from the corresponding ketones **4a-c** (Scheme 2). In the first step, the triethylsilyl enol

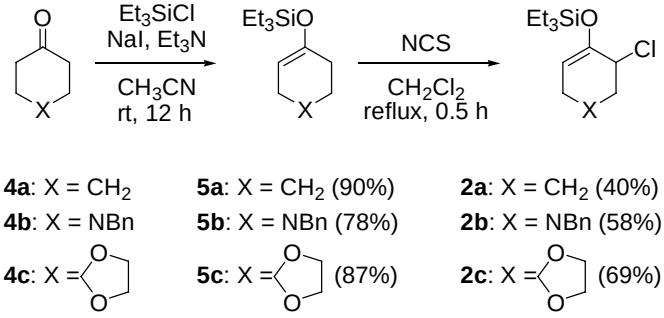
[5] For the preparation of analogous allylic zinc reagents, see: H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 5376.

[6] For the preparations of other organoaluminum reagents through aluminum insertion, see: (a) T. D. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313; (b) L.-N. Guo, H. Gao, P. Mayer, P. Knochel, *Chem.-Eur. J.* **2010**, *16*, 9829; (c) T. D. Blümke, K. Groll, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2011**, *13*, 6440; (d) T. D. Blümke, T. Klatt, K. Koszinowski, P. Knochel, *Angew. Chem.*, *Int. Ed.* **2012**, *51*, 9926.

[7] D. Seebach, *Angew. Chem.*, *Int. Ed.* **1979**, *18*, 239.

[8] For reviews on the construction of quaternary carbon centers, see: (a) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037. (b) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369. (c) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473. (d) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; J. Christoffers, A. Baro, Eds.; Wiley-VCH: Weinheim, **2005**. (e) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (f) E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943. (g) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593. (h) B. Wang, Y. Q. Tu, *Acc. Chem. Res.* **2011**, *44*, 1207.

ethers **5a-c** were obtained by the reaction of Et_3SiCl (1.2 equiv), NaI (1.2 equiv), and Et_3N (1.2 equiv) in CH_3CN (25 ^oC, 12 h) with the corresponding ketones **4a-c** in 78-90% yields.[9] The allylic chlorination of **5a-c** proceeds best using NCS (1.0 equiv) in CH_2Cl_2 (reflux, 0.5 h) leading to the allylic chlorides **2a-c** in 40-69% yields.[10] These allylic chlorides can be stored at -70 ^oC for several months without decomposition. Using aluminum powder (3 equiv) in the presence of 5 mol % $InCl_3$[11] in THF according to the method of Takai, the silyl enol ethers **2a-c** were converted into the corresponding allylic aluminum reagents **1** in ca. 70% yield for **1a-b** and ca. 50% yield for **1c** as determined by GC-analysis of hydrolyzed reaction aliquots (Scheme 1).



Scheme 2. Preparation of allylic chlorides 2a-c bearing silyl enol ether functional unit

The treatment of various aldehydes and methyl ketones (0.5 equiv) with these allylic aluminum reagents **1a-c** at -78 ^oC produced the expected aldol adducts of type **3** in 64-90% yields and high diastereoselectivities in favor of the *syn* diastereomer (Table 1).[12] The stereochemistry of the products **3** was established by treating the aldol product **3a** with HF·Py in THF (-20 ^oC ~ 0 ^oC, 2 h). This afforded the *β*-hydroxy ketone **7** in 72% yield as only one diastereoisomer (Scheme 3). Comparison of the ^1H and ^{13}C NMR data of the ketone **7** with the literature indicated that the diastereomer

[9] (a) F. C. E. Saraber, S. Dratch, G. Bosselaar, B. J. M. Jansen, A. de Groot, *Tetrahedron* **2006**, *62*, 1717. (b) A. Y. Hong, M. R. Krout, T. Jensen, N. B. Bennett, A. M. Harned, B. M. Stoltz, *Angew. Chem., Int. Ed.* **2011**, *50*, 2756. (c) L.-Q. Cui, K. Liu, C. Zhang, *Org. Biomol. Chem.* **2011**, *9*, 2258. (d) L. Huang, X. Zhang, Y. Zhang, *Org. Lett.* **2009**, *11*, 3730.

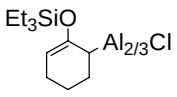
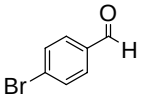
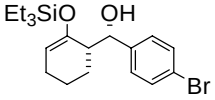
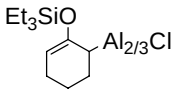
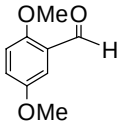
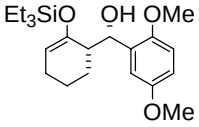
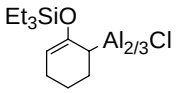
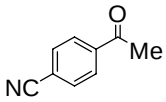
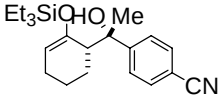
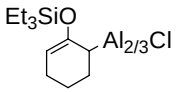
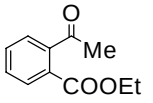
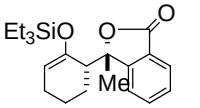
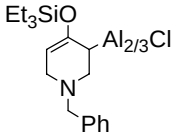
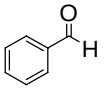
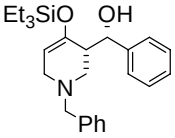
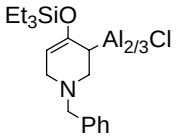
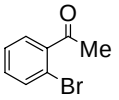
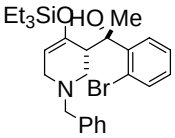
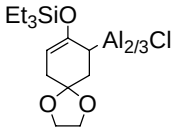
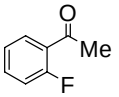
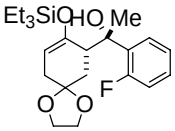
[10] G. F. Hambly, T. H. Chan, *Tetrahedron Lett.* **1986**, *27*, 2563. It should be noted that 20% and 5% regioisomers were obtained for allylic chlorides **2a** and **2c**, respectively (see the Supporting Information for detail). In addition, the TMS enol ethers were not suited for the chlorination step and the subsequent reactions due to relative instability. Also for the TBS enol ethers low yields of chlorinated products were obtained.

[11] K. Takai, Y. Ikawa, *Org. Lett.* **2002**, *4*, 1727.

[12] By using aliphatic aldehydes such as isobutylaldehyde, we have observed a *syn*/*anti* diastereoselectivity of 90:10. Although the yield was acceptable (ca. 72%), the product could not be obtained in a pure form.

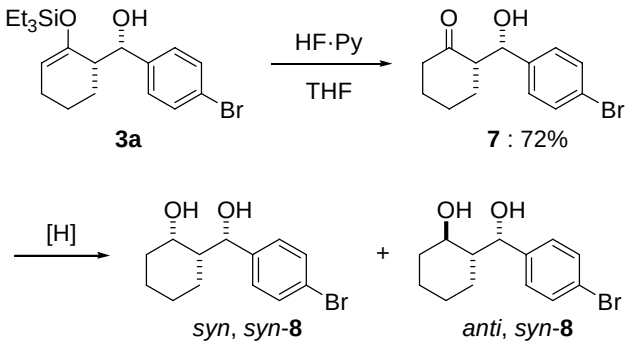
produced was the *syn*-isomer.[13] The *syn*-selectivity of the addition reaction can be well rationalized by the proposed transition state shown in Figure 1.[14]

Table 1. Diastereoselective Preparation of Homoallylic Alcohols **3** Using Allylic Aluminum Reagents **1a-c**

Entry	Aluminum reagent[a]	Carbonyl electrophile[b]	Product (Yield[c]; dr[d])
			
1	**1a**	**6a**	**3a** (85%; 95:5)
			
2	**1a**	**6b**	**3b** (90%; 92:8)
			
3	**1a**	**6c**	**3c** (76%; 95:5)
			
4	**1a**	**6d**	**3d** (79%; 98:2)
			
5	**1b**	**6e**	**3e** (69%; 95:5)
			
6	**1b**	**6f**	**3f** (72%; 96:4)
			
7	**1c**	**6g**	**3g** (64%; 95:5)

[a] All reactions were carried out on a 2 mmol scale. [b] 0.5 equiv of electrophiles were used. [c] Yield of isolated, analytically pure product. [d] The diastereoselectivities were determined by ^{1}H NMR spectroscopy.

[13] A. Yanagisawa, K. Asakawa, H. Yamamoto, *Chirality* **2000**, *12*, 421.
[14] (a) H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920. (b) C. H. Heathcock, *Science* **1981**, *214*, 395.



1) L-selectride, THF, -78 ^{o}C, 90% yield, 98:2 dr
2) DIBAL-H,CH_2Cl_2, -78 ^{o}C, 3 h, 89% yield, 95:5 dr
3) $Zn(BH_4)_2$, CH_2Cl_2, -78 ^{o}C, 2 h, 99% yield, 94:6 dr
4) $Me_4NBH(OAc)_3$, HOAc, -40 ^{o}C, 92%, 25:75 dr

Scheme 3. Conversion of alcohol 3a to *β*-hydroxy Ketone **7** by desilylation and diastereoselective preparation of 1,3-diol **8** bearing three contiguous stereogenic centers starting from *β*-hydroxy ketone **7**

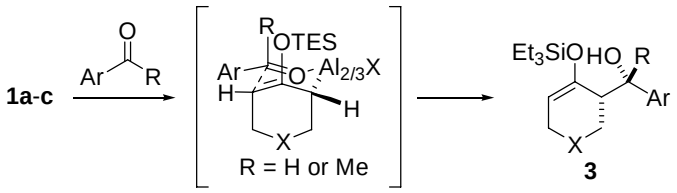
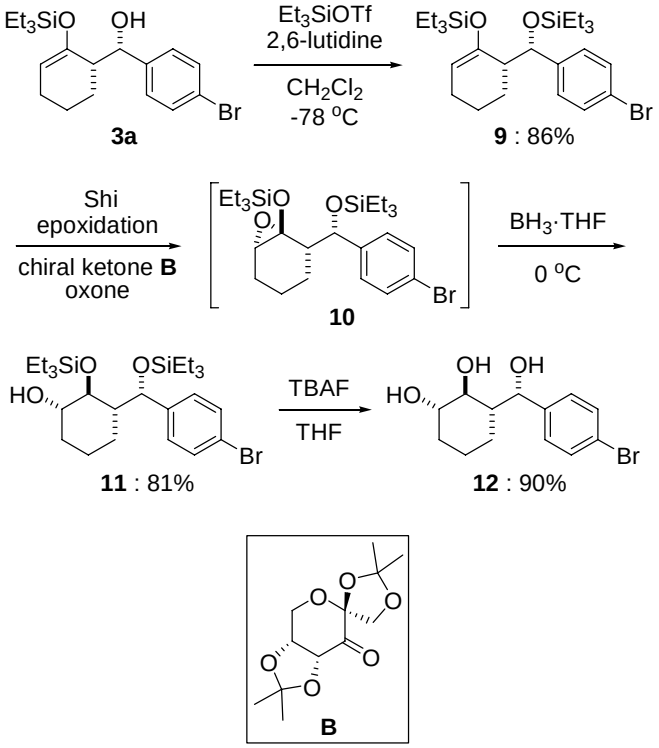


Figure 1. Proposed transition state for the diastereoselective additions of **1a-c** to aldehydes and methyl ketones

The diastereoselective reduction of the aldol product **7** was examined in some detail (Scheme 3) and the use of L-selectride[15] (THF, -78 ^{o}C) provided the *syn*,*syn*-1,3-diol **8** as major diastereomer (90% yield, dr = 98:2) with three contiguous chiral centers. Also, the use of DIBAL-H[16] and $Zn(BH_4)_2$[17] as reducing agents gave satisfactory diastereoselectivities via chelation-control. Interestingly, the opposite diastereomer *anti*,*syn*-1,3-diol **8** was predominantly obtained by using $Me_4NBH(OAc)_3$ [18] as

[15] (a) H. C. Brown, S. Krishnamurthy, *J. Am. Chem. Soc.* **1972**, *94*, 7159. (b) S. Krishnamurthy, H. C. Brown, *J. Am. Chem. Soc.* **1976**, *98*, 3383. (c) J. Chun, H.-S. Byun, G. Arthur, R. Bittman, *J. Org. Chem.* **2003**, *68*, 355.
[16] (a) S.-i. Kiyooka, H. Kuroda, Y. Shimasaki, *Tetrahedron Lett.* **1986**, *27*, 3009. (b) D. A. Evans, J. T. Starr, *J. Am. Chem. Soc.* **2003**, *125*, 13531.
[17] (a) S. Narasimhan, R. Balakumar, *Aldrichimica Acta* **1998**, *31*, 19. (b) A. H. Hoyveda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307. (c) D. A. Evans, A. S. Kim, R. Metternich, V. J. Novack, *J. Am. Chem. Soc.* **1998**, *120*, 5921. (d) L. A. Dakin, J. S. Panek, *Org. Lett.* **2003**, *5*, 3995.
[18] (a) D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560. (b) I. Paterson, O. Delgado, G. J. Florence, I. Lyothier, M. O'Brien, J. P. Scott, N. Sereinig, *J. Org. Chem.* **2005**, *70*, 150.

reductive reagent. The stereochemistry of the two diastereomers of the product **8** was determined by comparison with the already reported NMR data of similar 1,3-diol compounds.[19]



Scheme 4. Diastereoselective preparation of triol **12** with four contiguous chiral centers starting from aldol product **3a**

To functionalize the alcohols of type **3** further, we have used the method developed by Myers involving a Shi-epoxidation of the silyl enol ether followed by a reductive opening of the epoxide by $BH_3 \cdot THF$,[20] as shown in Scheme 4. Protection of the alcohol **3a** with Et_3SiOTf resulted in the formation of disilyl compound **9** (86% yield).[21] A subsequent Shi-epoxidation of **9** with oxone in the presence of chiral ketone **B**[22] produced the intermediate epoxide **10**, which was *in situ* opened with $BH_3 \cdot THF$ according to Myers' procedure, leading to the selectively protected triol **11**

[19] (a) D. Acetti, E. Brenna, C. Fuganti, F. G. Gatti, S. Serra, *Eur. J. Org. Chem.* **2010**, 142. (b) S. H. J. Thompson, M. F. Mahon, K. C. Molloy, M. S. Hadley, T. Gallagher, *J. Chem. Soc.*, *Perkin Trans. 1* **1995**, 379.

[20] S. M. Lim, N. Hill, A. G. Myers, *J. Am. Chem. Soc.* **2009**, *131*, 5763.

[21] (a) E. J. Corey, H. Cho, C. Rücker, D. H. Hua, *Tetrahedron Lett.* **1981**, *22*, 3455. (b) I. Paterson, R. D. Norcross, R. A. Ward, P. Romea, M. A. Lister, *J. Am. Chem. Soc.* **1994**, *116*, 11287. (c) T. Lister, M. V. Perkins, *Org. Lett.* **2006**, *8*, 1827.

[22] For a review on organocatalytic asymmetric epoxidation of olefins by chiral ketones, see: Y. Shi, *Acc. Chem. Res.* **2004**, *37*, 488.

in 81% yield. The use of cyclohexanone as a catalyst instead of Shi's chiral ketone **B** produced the same product **11** but in 66-70% yield. After desilylation of the product **11** with TBAF, a triol **12** with four contiguous chiral centers was formed in 90% yield. The stereochemistry of triol **12** was ambiguously determined by X-ray diffraction analysis. This further confirmed the stereochemistry of the previous aldol product **3a** as being the *syn*-diastereomer (Figure 2).

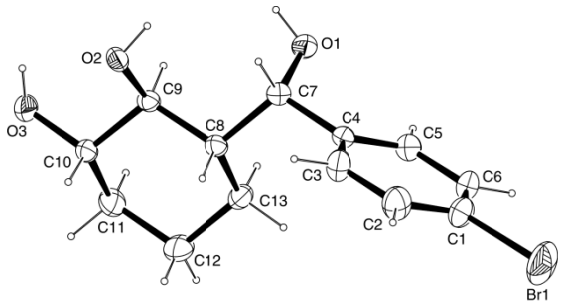
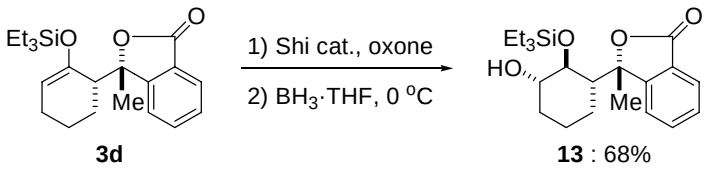


Figure 2. X-ray crystal structure of triol **12**

By applying the same sequence to the lactone **3d** obtained previously (Table 1, entry 4), we have prepared the selectively protected disilyloxy lactone **13** bearing four contiguous stereogenic centers in 68% yield as a single diastereomer (Scheme 5).



Scheme 5. Preparation of lactone **13** with four contiguous chiral centers starting from aldol product **3d**

7.3 Conclusion

In summary, we have reported a new approach to aldol products bearing a *β*-quaternary center with high diastereoselectivities using novel functionalized allylic aluminum reagents bearing a silyloxy-substituent in position 2. Extension of this reaction is currently underway in our laboratory.

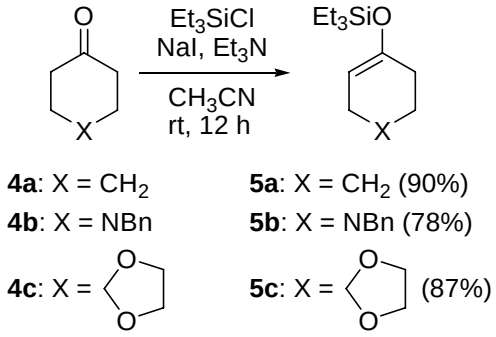
7.4 Experimental

General Information

All reactions were carried out under nitrogen atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves. Aluminum powder (99%, ~200 mesh) was purchased from Aldrich. Indium(III) chloride (anhydrous, 99.99%) was purchased from Chempur. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC. Column chromatography was performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck. All reagents were obtained from commercial sources.

Experimental Procedure

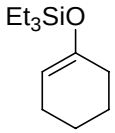
1. Preparation of silyl enol ethers **5a-c**.[9]



To a 250 mL round-bottomed flask was sequentially added ketone **4** (50 mmol), CH_3CN (80 mL), Et_3N (6.07 g, 8.4 mL, 60 mmol), TESCl (9.04 g, 60 mmol, 10 mL), and NaI (9 g, 60 mmol, pre-dried at 90 ^{o}C for 12 h under high vacuum). The reaction mixture was stirred at room temperature for 12 h. After the reaction conversion was completed as monitored by GC analysis, the resulting mixture was extracted by isohexane (100 mL x 3) through vigorous stirring of the reaction mixture with isohexane. The combined extracts were washed with saturated aqueous $NaHCO_3$ (50

mL), brine (50 mL), and dried over Na_2SO_4. After filtration and removal of the solvent under vacuum, the residue obtained was directly purified by silica gel column chromatography using isohexane and ethyl acetate as eluant to afford the corresponding silyl enol ether **5** as colorless oil.

Cyclohexenyloxytriethylsilane (5a)[9a]



The reaction was performed according to the above procedure using cyclohexanone **4a** (4.91 g, 50 mmol), leading to the corresponding silyl enol ether **5a** in 90% yield (9.6 g) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 4.88-4.85 (m, 1H), 2.04-1.96 (m, 4H), 1.69-1.61 (m, 2H), 1.54-1.47 (m, 2H), 1.00-0.95 (m, 9H), 0.69-0.61 (m, 6H).

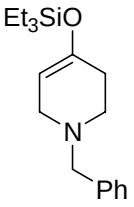
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.4, 103.9, 29.9, 23.8, 23.2, 22.4, 6.7, 5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2934, 2876, 1667, 1458, 1366, 1266, 1237, 1186, 1170, 1004, 986, 885, 827, 741, 726, 682.

MS (EI, 70 eV): m/z (%) = 212 (M^+, 17), 184 (15), 183 (100), 169 (22), 156 (15), 155 (13), 103 (12).

HRMS ($C_{12}H_{24}OSi$, EI): calc.: 212.1596; found: 212.1593 (M^+).

1-Benzyl-4-(triethylsilyloxy)-1,2,3,6-tetrahydropyridine (5b)



The reaction was performed according to the above procedure using 1-benzylpiperidin-4-one **4b** (9.47 g, 50 mmol), leading to the corresponding silyl enol ether **5b** in 78% yield (11.78 g).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.39-7.23 (m, 5H), 4.80 (tt, *J* = 3.5, 1.3 Hz, 1H), 3.61 (s, 2H), 3.01 (dt, *J* = 3.5, 2.5 Hz, 2H), 2.63 (t, *J* = 5.8 Hz, 2H), 2.18 (ttd, *J* = 5.8, 2.5, 1.3 Hz, 2H), 1.03-0.97 (m, 9H), 0.74-0.60 (m, 6H).

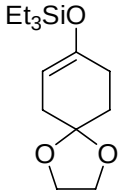
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.0, 138.5, 129.0, 128.1, 126.9, 101.0, 62.0, 51.4, 49.9, 30.3, 6.6, 5.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2910, 2874, 2798, 1677, 1454, 1371, 1360, 1238, 1215, 1185, 1125, 1004, 966, 873, 813, 771, 729, 697.

MS (EI, 70 eV): m/z (%) = 304 (17), 303 (M^+, 60), 302 (100), 274 (13), 266 (15), 211 (13), 187 (11), 172 (14), 161 (26), 149 (10), 91 (16).

HRMS ($C_{18}H_{28}NOSi$, EI): calc.: 302.1940; found: 302.1941 (M^+-H).

8-((Triethylsilyl)oxy)-1,4-dioxaspiro[4.5]dec-7-ene (5c)



The reaction was performed according to the above procedure using 1,4-dioxaspiro[4.5]decan-8-one **4c** (7.81 g, 50 mmol), leading to the corresponding silyl enol ether **5c** in 87% yield (11.8 g).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 4.73 (tt, *J* = 3.9, 1.1 Hz, 1H), 3.99-3.95 (m, 4H), 2.26-2.23 (m, 4H), 1.81 (t, *J* = 6.5 Hz, 2H), 1.01-0.95 (m, 9H), 0.70-0.62 (m, 6H).

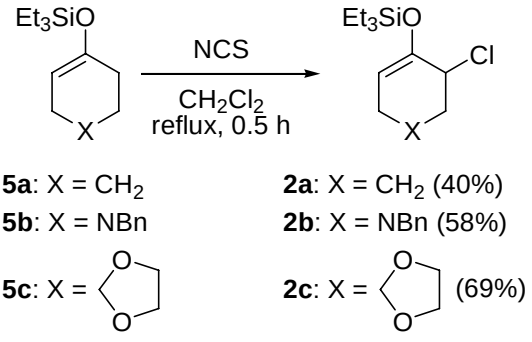
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.9, 107.7, 100.4, 64.4, 34.0, 31.2, 28.5, 6.7, 5.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2875, 1670, 1373, 1238, 1204, 1184, 1117, 1061, 1018, 986, 948, 857, 758, 742, 727, 669.

MS (EI, 70 eV): m/z (%) = 271 (19), 270 (M^+, 100), 240 (14), 227 (12), 197 (24), 171 (26), 157 (15), 143 (13), 141 (20), 138 (18), 127 (54), 115 (22), 103 (77), 101 (21), 99 (15), 92 (16), 87 (48), 75 (44), 67 (14), 59 (63), 57 (12), 55 (19), 47 (16), 42 (13), 41 (11).

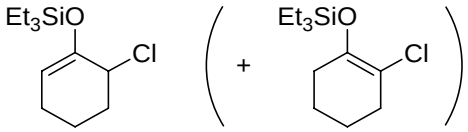
HRMS ($C_{14}H_{26}O_3Si$, EI): calc.: 270.1651; found: 270.1638 (M^+).

2. Chlorination of silyl enol ethers **5a-c** by NCS.[10]



To a solution of silyl enol ether **5** (20 mmol) in CH_2Cl_2 (100 mL) was added NCS (2.67 g, 20 mmol, pre-dissolved in CH_2Cl_2 (100 mL)) in one portion, and the mixture was stirred at 40 °C for 30 min. After reaction the solvent was removed under vacuum and the resulting residue was diluted by isohexane (300 mL). The white precipitate of succinimide was filtered off and the filtrate was evaporated under vacuum. Further purification by silica gel column chromatography using isohexane and ethyl acetate as eluant provided the product **2** as colorless oil.

(6-Chlorocyclohex-1-enyloxy)triethylsilane (2a)



A

The reaction was performed according to the above procedure using silyl enol ether **5a** (4.25 g, 20 mmol), leading to the corresponding allylic chloride **2a** in 40% yield (1.98 g, contaminated with 20% regioisomer **A**) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 4.99 (dd, *J* = 5.0, 2.8 Hz, 1H), 4.37 (t, *J* = 2.9 Hz, 1H), 2.35-1.56 (m, 6H), 1.04-0.98 (m, 9H), 0.75-0.67 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 148.7, 107.5, 58.3, 32.9, 23.8, 17.1, 6.7, 5.0.

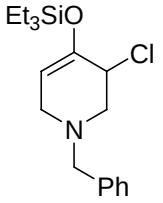
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2876, 1659, 1457, 1366, 1334, 1231, 1196, 1010, 982, 896, 877, 830, 766, 728, 705, 677.

MS (EI, 70 eV): m/z (%) = 219 (35), 218 (17), 217 (100), 210 (14), 181 (17), 179 (14), 151 (15), 149 (11), 123 (48), 121 (87), 111 (12), 108 (12), 103 (19), 97 (23), 95 (16), 95 (22), 87 (31), 85 (15), 83 (22), 82 (10), 81 (17), 79 (24), 77 (20), 75 (20), 71

(22), 70 (12), 69 (29), 68 (15), 67 (20), 65 (11), 59 (26), 57 (44), 56 (14), 55 (34), 44 (21), 43 (30), 43 (53), 41 (30).

HRMS ($C_{12}H_{23}ClOSi$, EI): calc.: 246.1207; found: 246.1202 (M^+).

1-Benzyl-3-chloro-4-(triethylsilyloxy)-1,2,3,6-tetrahydropyridine (2b)



The reaction was performed according to the above procedure using silyl enol ether **5b** (6.07 g, 20 mmol), leading to the corresponding allylic chloride **2b** in 58% yield (3.91 g) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.42-7.24 (m, 5H), 4.97 (dd, *J* = 4.2, 3.0 Hz, 1H), 4.33 (tt, *J* = 3.9, 1.3 Hz, 1H), 3.78 (d, *J* = 13.3 Hz, 1H), 3.59 (d, *J* = 13.3 Hz, 1H), 3.26 (ddt, *J* = 15.5, 4.2, 1.1 Hz, 1H), 3.02-2.92 (m, 2H), 2.82 (ddd, *J* = 12.4, 3.9, 1.1 Hz, 1H), 1.06-1.00 (m, 9H), 0.78-0.70 (m, 6H).

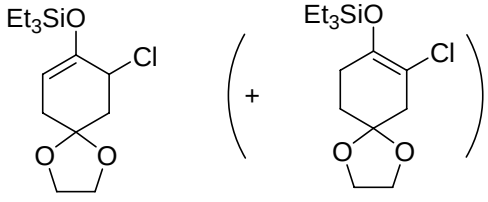
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 147.3, 137.6, 128.8, 128.2, 127.1, 105.0, 61.3, 57.6, 56.6, 51.3, 6.6, 4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2875, 2800, 1668, 1454, 1356, 1238, 1210, 1137, 1058, 1005, 976, 869, 802, 729, 696.

MS (EI, 70 eV): m/z (%) =338 (12), 337 (M^+, 14), 336 (27), 303 (20), 302 (84), 301 (21), 300 (22), 289 (22), 288 (100), 115 (5), 91 (42), 87 (6).

HRMS ($C_{18}H_{27}ClNOSi$, EI): calc.: 336.1550; found: 336.1544 (M^+-H).

9-Chloro-8-((triethylsilyl)oxy)-1,4-dioxaspiro[4.5]dec-7-ene (2c)



B

The reaction was performed according to the above procedure using silyl enol ether **5c** (5.41 g, 20 mmol), leading to the corresponding allylic chloride **2c** in 69% yield (4.22 g, contaminated with 5% regioisomer **B**) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 4.90-4.87 (m, 1H), 4.56-4.50 (m, 1H), 4.02-3.91 (m, 4H), 2.54-2.19 (m, 4H), 1.02-0.96 (m, 9H), 0.74-0.66 (m, 6H).

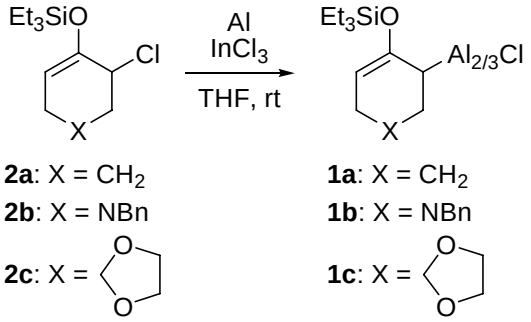
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 147.5, 106.7, 103.5, 64.5, 64.3, 56.3, 41.4, 34.3, 6.6, 4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2876, 1658, 1363, 1238, 1216, 1202, 1141, 1123, 1085, 1047, 1016, 1002, 946, 864, 828, 801, 727, 703, 676.

MS (EI, 70 eV): m/z (%) = 304 (M^+, 6), 277 (28), 276 (14), 275 (88), 270 (18), 269 (100), 262 (29), 216 (10), 190 (21), 188 (65), 123 (15), 121 (41), 115 (22), 87 (31), 86 (80), 73 (11), 59 (22).

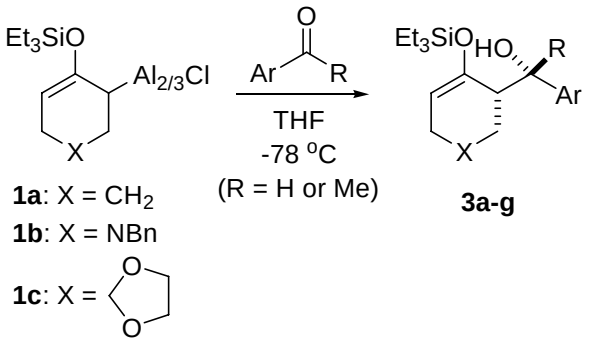
HRMS ($C_{14}H_{24}ClO_3Si$, EI): calc.: 304.1261; found: 304.1247 (M^+).

3. Preparation of allylic aluminium reagents **1a-c**.[4]



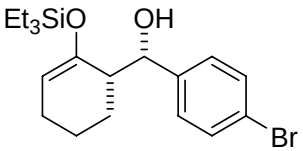
Aluminum powder (0.162 g, 6 mmol) and $InCl_3$ (22 mg, 0.1 mmol) were placed in a nitrogen-flushed flask and flame-dried for 5 min by heat gun (380 ^oC) under high vacuum. The flask was evacuated and backfilled with nitrogen 3 times and THF (2 mL) was added. A solution of allylic chloride **2** (2 mmol) in THF (2 mL) was added at room temperature, and the resulting solution was stirred at room temperature for 1-3 days (1 day for substrates **2a-b**, 3 days for substrate **2c**). The resulting allylic aluminum reagent **1** (ca. 70% yields for **1a-b**, ca. 50% yield for **1c**) was directly used in the following reactions with various aromatic aldehydes and methyl ketones.

4. General procedure for the reaction of allylic aluminum reagents **1a-c** with various carbonyl compounds.



The above preformed allylic aluminum reagents **1a-c** were slowly added to a solution of an aromatic aldehyde or methyl ketone (1 mmol) in THF (3 mL) at -78 °C and the mixture was stirred at this temperature for 2 h. After warming to room temperature, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Further purification by silica gel column chromatography using ethyl acetate and isohexane as eluant provided the homoallylic alcohols **3a-g** as colorless oil. The diastereoselectivities of the products were determined by ^{1}H NMR analysis of crude reaction mixture (after workup) by integration of the ratio of the two peaks arising from the alkene proton which mostly have typical doublet of doublet of doublets pattern (within 4.5-5.5 ppm area).

(4-Bromophenyl)(2-(triethylsilyloxy)cyclohex-2-enyl)methanol (3a)



The reaction was performed according to the above procedure using 4-bromobenzaldehyde (0.185 g, 1 mmol), leading to the corresponding homoallylic alcohol **3a** in 85% yield (0.337 g) with 95:5 dr as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.48-7.43 (m, 2H), 7.25-7.21 (m, 2H), 5.20 (d, *J* = 2.8 Hz, 1H), 5.09 (td, *J* = 4.1, 1.6 Hz, 1H), 2.52-2.46 (m, 1H), 2.39 (br, s, 1H),

2.01-1.95 (m, 2H), 1.65-1.41 (m, 2H), 1.37-1.22 (m, 2H), 1.06-1.01 (m, 9H), 0.78-0.70 (m, 6H).

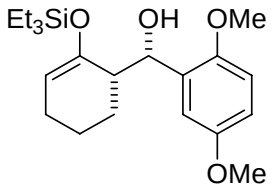
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.6, 141.6, 131.0, 127.8, 120.4, 107.5, 72.4, 46.3, 24.0, 22.7, 21.3, 6.8, 5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3461, 2952, 2874, 1700, 1662, 1486, 1457, 1237, 1212, 1172, 1070, 1009, 969, 911, 841, 815, 740, 724, 675.

MS (EI, 70 eV): m/z (%) = 396 (M^+, 0.08), 213 (16), 212 (100), 187 (12), 185 (18), 183 (42), 169 (14), 156 (12), 115 (67), 103 (27), 87 (39), 78 (11), 77 (21), 75 (25), 59 (21).

HRMS ($C_{19}H_{29}BrO_2Si$, EI): calc.: 396.1120; found: 396.1123 (M^+).

(2,5-Dimethoxyphenyl)(2-(triethylsilyloxy)cyclohex-2-enyl)methanol (3b)



The reaction was performed according to the above procedure using 2,5-dimethoxybenzaldehyde (0.166 g, 1 mmol), leading to the corresponding homoallylic alcohol **3b** in 90% yield (0.34 g) with 92:8 dr as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.13-7.12 (m, 1H), 6.76-6.75 (m, 2H), 5.58 (d, *J* = 2.8 Hz, 1H), 5.10 (ddd, *J* = 4.9, 3.2, 1.7 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 2.70-2.61 (m, 1H), 2.17 (br, s, 1H), 1.71-1.52 (m, 2H), 1.38-1.19 (m, 2H), 1.07-1.02 (m, 9H), 0.78-0.70 (m, 6H).

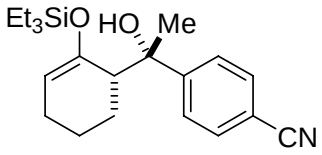
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 153.5, 150.3, 150.0, 132.1, 113.4, 112.0, 110.9, 107.6, 67.7, 55.7, 55.6, 43.6, 24.1, 22.8, 21.6, 6.8, 5.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3477, 2949, 2874, 1697, 1661, 1495, 1463, 1276, 1212, 1177, 1155, 1047, 1007, 902, 802, 729, 715.

MS (EI, 70 eV): m/z (%) = 281 (12), 212 (26), 183 (19), 167 (100), 139 (19), 103 (10), 87 (14), 75 (13), 59 (10).

HRMS ($C_{21}H_{34}O_4Si$, EI): calc.: 378.2226; found: 378.2236 (M^+).

4-(1-Hydroxy-1-(2-(triethylsilyloxy)cyclohex-2-enyl)ethyl)benzonitrile (3c)



The reaction was performed according to the above procedure using 4-acetylbenzonitrile (0.145 g, 1 mmol), leading to the corresponding homoallylic alcohol **3c** in 76% yield (0.272 g) with 95:5 dr as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.57 (s, 4H), 4.94 (s, 1H), 4.91 (ddd, *J* = 5.6, 3.0, 1.4 Hz, 1H), 2.67-2.61 (m, 1H), 1.93-1.64 (m, 3H), 1.59 (s, 3H), 1.50-1.18 (m, 3H), 1.00-0.94 (m, 9H), 0.74-0.65 (m, 6H).

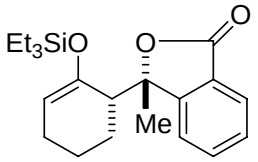
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 151.7, 150.3, 131.2, 127.0, 119.0, 110.1, 107.3, 77.0, 49.3, 28.5, 26.4, 23.7, 21.0, 6.6, 4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3484, 2954, 2876, 2228, 1660, 1166, 1018, 907, 826, 729.

MS (EI, 70 eV): m/z (%) = 260 (16), 213 (18), 212 (100), 211 (10), 184 (10), 183 (53), 169 (16), 156 (13), 146 (37), 130 (21), 116 (11), 115 (95), 103 (37), 102 (13), 87 (59), 79 (12), 75 (34), 59 (31), 47 (100), 43 (42).

HRMS ($C_{21}H_{32}NO_2Si$, EI): calc.: 358.2202; found: 358.2208 (M^++H).

3-Methyl-3-(2-(triethylsilyloxy)cyclohex-2-enyl)isobenzofuran-1(3*H*)-one (3d)



The reaction was performed according to the above procedure using ethyl 2-acetylbenzoate (0.192 g, 1 mmol), leading to the corresponding lactone **3d** in 79% yield (0.282 g) with 98:2 dr as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.77 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.57 (td, *J* = 7.6, 1.2 Hz, 1H), 7.43-7.38 (m, 2H), 4.85 (ddd, *J* = 4.7, 3.5, 1.2 Hz, 1H), 2.70-2.67 (m, 1H), 2.00-1.84 (m, 2H), 1.67 (s, 3H), 1.64-1.51 (m, 2H), 1.33-1.20 (m, 2H), 0.90-0.86 (m, 9H), 0.63-0.57 (m, 6H).

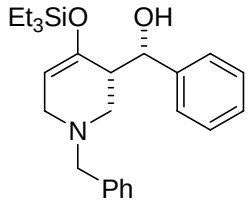
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 170.0, 154.0, 148.9, 133.4, 128.4, 126.3, 125.1, 121.2, 106.4, 89.5, 45.2, 26.4, 26.1, 23.5, 20.3, 6.5, 4.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2934, 2253, 1759, 1466, 1223, 904.

MS (EI, 70 eV): m/z (%) = 358 (M^+, 4), 329 (33), 212 (18), 211 (100), 183 (11), 148 (16), 147 (93), 115 (31), 87 (26).

HRMS ($C_{21}H_{30}O_3Si$, EI): calc.: 358.1964; found: 358.1968 (M^+).

(1-Benzyl-4-(triethylsilyloxy)-1,2,3,6-tetrahydropyridin-3-yl)(phenyl)methanol (3e)



The reaction was performed according to the above procedure using benzaldehyde (0.106 g, 1 mmol), leading to the corresponding homoallylic alcohol **3e** in 69% yield (0.283 g) with 95:5 dr as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.48-7.35 (m, 5H), 7.23-7.14 (m, 3H), 7.03-7.00 (m, 2H), 5.16 (s, 1H), 5.05 (dd, *J* = 5.0, 1.8 Hz, 1H), 3.70 (d, *J* = 12.4 Hz, 1H), 3.43-3.33 (m, 2H), 2.92 (d, *J* = 11.1 Hz, 1H), 2.82 (dt, *J* = 14.9, 1.8 Hz, 1H), 2.18-2.12 (m, 2H), 1.13-1.08 (m, 9H), 0.86-0.78 (m, 6H).

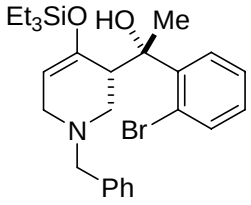
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.4, 144.7, 137.0, 129.8, 128.5, 127.8, 127.5, 126.0, 125.5, 101.9, 73.4, 62.2, 52.1, 49.2, 46.8, 6.7, 5.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3251, 2954, 2875, 1673, 1454, 1369, 1358, 1261, 1238, 1199, 1188, 1126, 1049, 1023, 988, 908, 893, 849, 726, 698.

MS (EI, 70 eV): m/z (%) = 409 (M^+, 3.5), 304 (14), 303 (40), 302 (100), 300 (15), 261 (14), 221 (13), 115 (12), 91 (41), 87 (14).

HRMS ($C_{25}H_{35}NO_2Si$, EI): calc.: 409.2437; found: 409.2445 (M^+).

(1-Benzyl-4-(triethylsilyloxy)-1,2,3,6-tetrahydropyridin-3-yl)-1-(2-bromophenyl)ethanol (3f)



The reaction was performed according to the above procedure using 1-(2-bromophenyl)ethanone (0.199 g, 1 mmol), leading to the corresponding homoallylic alcohol **3f** in 72% yield (0.364 g) with 96:4 dr as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.65 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.50-7.47 (m, 1H), 7.33-7.29 (m, 2H), 7.26-7.21 (m, 2H), 7.06-6.94 (m, 2H), 4.96 (ddd, *J* = 3.3, 2.1, 1.0 Hz, 1H), 3.46 (d, *J* = 12.4 Hz, 1H), 3.40-3.39 (m, 1H), 3.32 (dd, *J* = 15.2, 4.4 Hz, 1H), 3.25 (d, *J* = 12.4 Hz, 1H), 2.71 (d, *J* = 15.2 Hz, 1H), 2.49 (d, *J* = 11.6 Hz, 1H), 2.23 (dd, *J* = 11.6, 3.7 Hz, 1H), 1.77 (s, 3H), 1.06-1.00 (m, 9H), 0.79-0.70 (m, 6H).

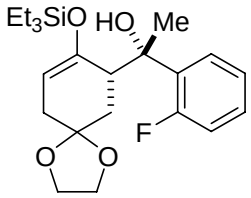
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.5, 147.3, 136.8, 134.8, 129.5, 128.9, 128.4, 127.8, 127.5, 127.2, 119.6, 102.7, 78.3, 62.0, 52.8, 51.5, 43.8, 26.4, 6.8, 5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2875, 2817, 1671, 1455, 1349, 1240, 1190, 1146, 1125, 1014, 1004, 882, 830, 762, 742, 725, 702.

MS (EI, 70 eV): m/z (%) = 501 (M^+, 1.0), 304 (15), 303 (55), 302 (100), 300 (18), 261 (10), 212 (27), 187 (11), 186 (14), 185 (11), 115 (15), 92 (10), 91 (90), 87 (20), 75 (13), 43 (19).

HRMS ($C_{26}H_{36}BrNO_2Si$, EI): calc.: 501.1699; found: 501.1703 (M^+).

1-(8-((Triethylsilyl)oxy)-1,4-dioxaspiro-[4.5]dec-7-ene-9-yl)-1-(2-fluorophenyl)ethanol (3g)



The reaction was performed according to the above procedure using 1-(2-fluorophenyl)ethanone (0.138 g, 1 mmol), leading to the corresponding homoallylic alcohol **3g** in 64% yield (0.262 g) with 95:5 dr as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.65 (td, *J* = 8.0, 2.1 Hz, 1H), 7.23-7.09 (m, 2H), 6.97 (ddd, *J* = 11.9, 7.7, 1.4 Hz, 1H), 4.91 (br, s, 1H), 4.88 (t, *J* = 3.7 Hz, 1H), 3.87-3.78 (m, 2H), 3.66-3.57 (m, 2H), 3.16 (dd, *J* = 4.4, 1.9 Hz, 1H), 2.39-2.20 (m,

2H), 1.79-1.72 (m, 4H), 1.54 (dddd, J = 14.1, 3.2, 1.5, 1.4 Hz, 1H), 1.05-1.00 (m, 9H), 0.79-0.70 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.9 (d, J = 244.3 Hz), 150.0, 135.9 (d, J = 14.3 Hz), 128.1 (d, J = 8.1 Hz), 127.2 (d, J = 5.3 Hz), 123.8 (d, J = 3.1 Hz), 115.5 (d, J = 24.1 Hz), 107.3, 102.7, 75.5 (d, J = 5.3 Hz), 64.3, 64.1, 46.6 (d, J = 4.8 Hz), 34.8, 34.1, 29.1 (d, J = 2.8 Hz), 6.7, 5.0.

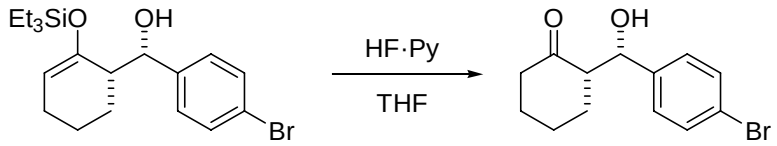
^{19}F NMR (282 MHz, $CDCl_3$): -111.92 ~ -112.01 (m, 1F).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3432, 2956, 2876, 1661, 1448, 1375, 1210, 1190, 1125, 1071, 1040, 1014, 1003, 948, 906, 831, 758, 728.

MS (EI, 70 eV): m/z (%) = 408 (M^+, 0.2), 271 (22), 270 (100), 269 (19), 241 (15), 226 (10), 225 (12), 211 (14), 210 (54), 209 (17), 208 (29), 197 (12), 179 (24), 156 (11), 155 (15), 140 (12), 139 (67), 138 (15), 123 (26), 115 (44), 103 (32), 95 (13), 94 (12), 87 (50), 86 (30), 75 (28), 59 (30), 43 (50).

HRMS ($C_{22}H_{33}FO_4Si$, EI): calc.: 408.2132; found: 408.2120 (M^+).

5. Synthesis of *β*-hydroxy ketone **7** by the de-silylation of homoallylic alcohol **3a**[17c,23]

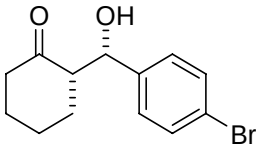


3a **7** : 72%

A solution of hydrogen fluoride pyridine (~70% hydrogen fluoride, 0.2 mL) was added into a solution of homoallylic alcohol **3a** (0.199 g, 0.5 mmol) in THF (4 mL) at -20 °C. The mixture was stirred for 1 h at -20 °C then warmed up to 0 °C with stirring for another 1 h. The mixture was quenched by saturated $NaHCO_3$ (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to provide the *β*-hydroxyl ketone **7** in 72% yield (0.102 g) as a white solid.

[23] (a) K. C. Nicolaou, S. E. Webber, *Synthesis* **1986**, 453. (b) P. Wipf, H. Kim, *J. Org. Chem.* **1993**, *58*, 5592.

(4-Bromophenyl)(hydroxy)methyl)cyclohexanone (7)



^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.49-7.46 (m, 2H), 7.34-7.30 (m, 2H), 5.28 (t, *J* = 3.8 Hz, 1H), 4.09 (d, *J* = 4.1 Hz, 1H), 2.69 (dddd, *J* = 11.5, 6.0, 3.7, 1.1 Hz, 1H), 2.42-2.26 (m, 2H), 2.08-1.96 (m, 1H), 1.86 - 1.52 (m, 5H).

^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 212.3, 144.7, 132.1, 129.5, 121.1, 70.7, 58.2, 43.2, 28.6, 27.3, 25.6.

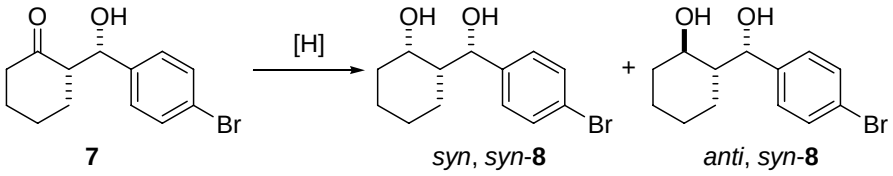
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3431, 2944, 2861, 1696, 1483, 1396, 1364, 1311, 1258, 1130, 1116, 1089, 1063, 1010, 985, 895, 827, 794, 752, 715, 667.

MS (EI, 70 eV): m/z (%) = 284 (12), 282 (M^+, 10), 266 (28), 265 (10), 264 (29), 187 (38), 186 (17), 186 (19), 185 (100), 185 (79), 184 (18), 159 (13), 157 (29), 155 (19), 129 (16), 128 (12), 116 (15), 115 (18), 98 (91), 97 (19), 83 (25), 78 (29), 77 (57), 76 (15), 74 (10), 70 (29), 55 (22), 50 (14), 42 (16), 42 (14), 41 (28).

HRMS ($C_{13}H_{15}BrO_2$, EI): calc.: 282.0255; found: 282.0241 (M^+).

M.P. (^{o}C): 120-122.

6. Diastereoselective reduction of *β*-hydroxy ketone **7** by using various reducing agents.



7 *syn*, *syn*-**8** *anti*, *syn*-**8**

1) L-selectride, THF, -78 ^{o}C, 90% yield, 98:2 dr;
2) DIBAL-H,CH_2Cl_2, -78 ^{o}C, 3 h, 89% yield, 95:5 dr;
3) $Zn(BH_4)_2$, CH_2Cl_2, -78 ^{o}C, 2 h, 99% yield, 94:6 dr;
4) $Me_4NBH(OAc)_3$, HOAc, -40 ^{o}C, 18 h, 92%, 25:75 dr.

(1) L-Selectride reduction[15]

To a solution of *β*-hydroxyl ketone **7** (0.142 g, 0.5 mmol) in dry THF (5 mL) was added L-Selectride (1 mmol, 1 mL, 1.0 M in THF) dropwise at -78 °C under nitrogen

atmosphere. The reaction mixture was stirred for 3 h at -78 °C and then allowed to warm to room temperature for another 1 h. The mixture was then diluted with ethyl acetate (100 mL) and filtered through a pad of silica gel, which was rinsed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give 1,3-diol **8** as white solid (0.128 g, 90% yield, 98:2 dr). The diastereoselectivity of the product was determined by ^{1}H NMR analysis of crude reaction mixture (after workup) by integration of the ratio of the two peaks located at 4.20 ppm (d, J = 2.2 Hz, 1H, for *syn* isomer) and 3.47 ppm (td, J = 10.5, 4.5 Hz, 1H, for *anti* isomer) which belong to the aliphatic (not benzylic) CH attaching to a hydroxyl group.

(2) DIBAL-H reduction[16]

To a solution of *β*-hydroxyl ketone **7** (0.23 g, 0.8 mmol) in anhydrous THF (10 mL) at –78 °C under nitrogen was added DIBAL-H (0.285 g, 0.36 mL, 2 mmol) dropwise. After 2 h, the reaction was quenched by the addition of EtOAc (0.2 mL) and saturated aqueous sodium potassium tartrate (10 mL) and the slurry was warmed to room temperature with vigorous stirring for 12 h. The resulting clear biphase was extracted with ethyl acetate (30 mL x 3) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography using ethyl acetate and isohexane as eluant to provide 1,3-diol **8** as white solid (0.203 g, 89% yield, 95:5 dr).

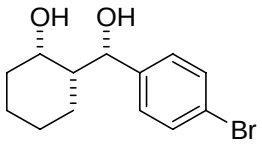
(3) $Zn(BH_4)_2$ reduction[17]

To a stirred solution of *β*-hydroxyl ketone **7** (0.142 g, 0.5 mmol) in anhydrous CH_2Cl_2 (6 mL) at -78 ^{o}C was dropwise added a freshly prepared THF solution of $Zn(BH_4)_2$ (1.5 mmol, 3 mL, 0.5 M) and the solution was stirred at the same temperature for 2 h. Then the reaction mixture was quenched by a saturated aqueous NH_4Cl (10 mL). The resulting solution was allowed to warm to room temperature with stirring for 12 h. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under vacuum. The crude oil was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the 1,3-diol **8** as white solid (0.141 g, 99% yield, 94:6 dr).

(4) Tetramethylammonium triacetoxyborohydride [$Me_4NHB(OAc)_3$] reduction[18]

To a solution of tetramethylammonium triacetoxyborohydride (1.053 g, 4 mmol) in anhydrous CH_3CN (2.2 mL) was added anhydrous CH_3COOH (2.2 mL) and the mixture was stirred at ambient temperature for 30 min. The mixture was cooled to -40 ^oC, and a solution of *β*-hydroxyl ketone **7** (0.142 g, 0.5 mmol) in anhydrous CH_3CN (1 mL) was added dropwise via syringe. The mixture was stirred at -40 ^oC for 18 h. The reaction mixture was quenched with aqueous sodium potassium tartrate (6 mL, 0.5 M) and the mixture was allowed to warm slowly to room temperature. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 for 4 times, and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried with Na_2SO_4 and concentrated *in vacuo*. After concentration under vacuum, the residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give 1,3-diol **8** as white solid (0.132 g, 92% yield; 25:75 dr).

(4-Bromophenyl)(hydroxy)methyl)cyclohexanol (*syn*,*syn*-8)



syn, *syn*-**8**

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.47-7.45 (m, 2H), 7.23-7.21 (m, 2H), 4.95 (d, *J* = 3.0 Hz, 1H), 4.20 (d, *J* = 2.2 Hz, 1H), 2.61 (br, s, 2H), 1.81-1.72 (m, 2H), 1.68-1.46 (m, 5H), 1.29 (dq, *J* = 13.1, 3.2 Hz, 1H), 1.09 (qt, *J* = 13.1, 3.7 Hz, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 142.2, 131.1, 127.6, 120.7, 77.3, 71.6, 47.7, 34.0, 25.5, 19.6, 18.2.

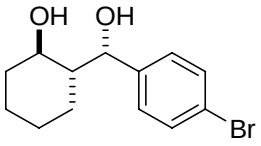
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3254, 2929, 2852, 1485, 1445, 1401, 1329, 1290, 1181, 1087, 1069, 1009, 967, 806, 723.

MS (EI, 70 eV): m/z (%) = 284 (M^+, 0.07), 187 (90), 185 (100), 157 (10), 82 (62), 81 (11), 78 (18), 77 (35), 67 (47), 54 (13), 41 (9).

HRMS ($C_{13}H_{16}BrO_2$, EI): calc.: 283.0334; found: 283.0339 (M^+-H).

M.P. (^{o}C): 155-157.

(4-Bromophenyl)(hydroxy)methyl)cyclohexanol (*anti*,*syn*-8)



anti, *syn*-**8**

^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.49-7.46 (m, 2H), 7.33-7.29 (m, 2H), 5.16 (dd, *J* = 5.2, 2.4 Hz, 1H), 4.60 (d, *J* = 5.5 Hz, 1H), 4.11 (br, s, 1H), 3.55 (t, *J* = 10.1 Hz, 1H), 2.08-1.93 (m, 2H), 1.65-0.99 (m, 7H).

^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 145.5, 131.8, 129.6, 120.7, 73.1, 71.3, 53.0, 37.2, 26.6, 25.9, 24.9.

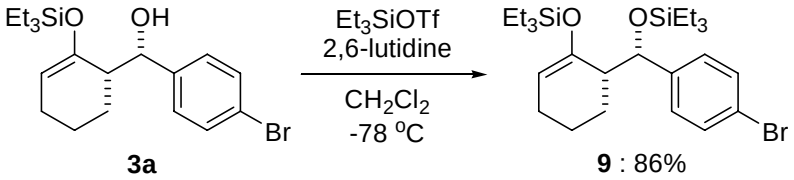
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3414, 3351, 2935, 2922, 2850, 1486, 1446, 1405, 1333, 1226, 1141, 1121, 1081, 1031, 1010, 984, 912, 827, 795, 778, 724, 680, 653.

MS (EI, 70 eV): m/z (%) = 284 (M^+, 0.13), 187 (87), 185 (100), 157 (10), 82 (64), 81 (14), 78 (20), 77 (38), 67 (53), 54 (16), 43 (10), 41 (13).

HRMS ($C_{13}H_{17}BrO_2$, EI): calc.: 284.0412; found: 284.0420 (M^+).

M.P. (^{o}C): 144-146.

7. Synthesis of disilyl protected compound **9**.[21]

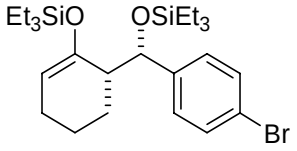


3a **9** : 86%

To a solution of the homoallylic alcohol **3a** (1.192 g, 3 mmol) in CH_2Cl_2 (30 mL) at -78 °C was added 2,6-lutidine (0.643 g, 0.7 mL, 6 mmol) followed by TESOTf (1.19 g, 1.03 mL, 4.5 mmol). The resulting mixture was stirred at -78 °C for 1 h and warmed up to room temperature for 1 h. The mixture was quenched by saturated aqueous NH_4Cl (20 mL) and extracted with diethyl ether (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Further

purification by silica gel column chromatography using isohexane as eluent provided the product **9** as colorless oil (1.32 g, 86% yield).

1-Bromo-4-((triethylsilyloxy)(2-(triethylsilyloxy)cyclohex-2-enyl)methyl)benzene (9)



^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.45-7.40 (m, 2H), 7.21-7.17 (m, 2H), 5.31 (d, *J* = 2.5 Hz, 1H), 4.98 (ddd, *J* = 4.8, 3.5, 1.4 Hz, 1H), 2.15-2.10 (m, 1H), 2.04-1.95 (m, 2H), 1.83-1.66 (m, 2H), 1.36-1.17 (m, 2H), 1.06-1.00 (m, 9H), 0.92-0.87 (m, 9H), 0.75-0.67 (m, 6H), 0.59-0.51 (m, 6H).

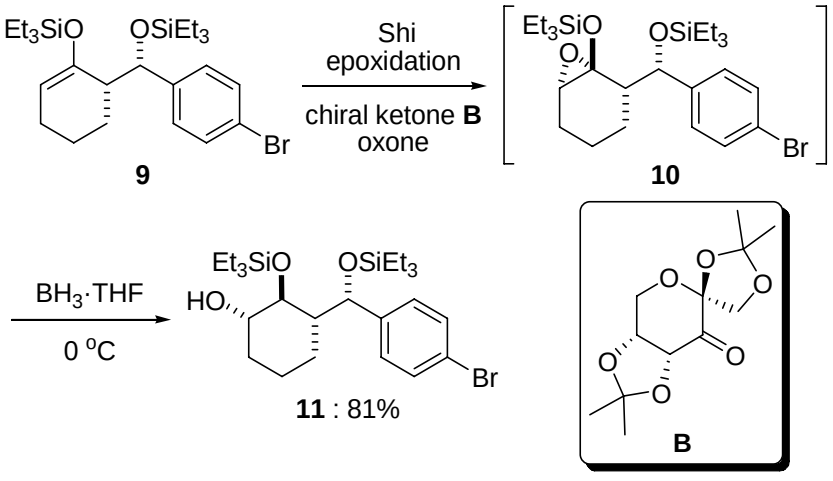
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.9, 144.5, 130.7, 127.7, 120.0, 106.5, 72.3, 48.1, 24.3, 21.6, 21.3, 6.9, 6.8, 5.2, 4.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2874, 1665, 1486, 1457, 1412, 1238, 1213, 1171, 1112, 1085, 1071, 1004, 976, 916, 903, 844, 810, 738, 723, 681.

MS (EI, 70 eV): m/z (%) = 302 (16), 301 (100), 300 (17), 299 (98), 115 (42), 87 (37), 59 (16).

HRMS ($C_{25}H_{43}BrO_2Si_2$, EI): calc.: 510.1985; found: 510.1977 (M^+).

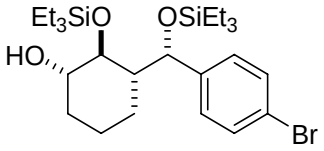
8. Conversion of compound **9** to **11** via Shi-epoxidation followed by ring-opening with BH_3·THF according to Myers' procedure.[20]



Disilyl protected compound **9** (0.266 g, 0.52 mmol, 1.0 equiv) was added to a 100 mL round-bottomed flask and the flask was cooled to 0 °C. CH_3CN (2.5 mL), dimethoxymethane (5.0 mL), and an aqueous stock solution of sodium borate-ethylenediaminetetraacetic acid disodium salt (5.0 mL) were added to the cooled flask. D-Fructose-derived Shi catalyst (40 mg, 0.16 mmol, 0.30 equiv) and tetrabutylammonium bisulfate (7.1 mg, 0.021 mmol, 0.04 equiv) were added in sequence to the stirring mixture at 0 °C. Separately, Oxone (443 mg, 0.72 mmol, 1.38 equiv) was added to an aqueous stock solution of ethylenediaminetetraacetic acid disodium salt (3.2 mL) and the resulting solution was drawn into a 5 mL disposable plastic syringe. A solution of potassium carbonate (418 mg, 3.03 mmol, 5.8 equiv) in water (3.2 mL) was drawn into a second 5 mL disposable plastic syringe. The contents of both syringes were added simultaneously over 90 min using a syringe drive to the ice-cooled, stirring reaction mixture. After the addition was complete, the reaction mixture was stirred for 30 min at 0 °C, then was diluted with ice-cooled pentane (30 mL) and ice-cooled water (30 mL), producing a biphasic mixture. The layers were separated. The aqueous layer was extracted with ice-cooled pentane (70 mL x 2). The organic extracts were combined, washed with brine (100 mL), and dried over Na_2SO_4. After filtration, the filtrate was concentrated to a volume of ca. 5 mL by rotary evaporation.

A solution of borane−tetrahydrofuran complex in THF (1.05 mmol, 1.0 M, 2.0 equiv) was added dropwise by syringe to an ice-cooled, stirring solution of the crude product in pentane (5 mL) in a 100 mL round-bottomed flask. The reaction mixture was stirred for 1 h at 0 °C, followed by the addition of pentane (15 mL). An aqueous solution of tris(hydroxymethyl)aminomethane hydrochloride (10 mL, 1.0 M) was then added carefully, causing vigorous evolution of gas. The biphasic mixture was allowed to warm to 25 °C. After stirring for 30 min at 25 °C, the reaction mixture was partially concentrated by rotary evaporation. Water (25 mL) was added, and the mixture was extracted by ethyl acetate (70 mL x 2). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to provide the desired product **11** as colorless oil in 81% yield (0.222 g).

3-((4-Bromophenyl)(triethylsilyloxy)methyl)-2-(triethylsilyloxy)cyclohexanol (11)



^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.45-7.40 (m, 2H), 7.19-7.14 (m, 2H), 5.24 (s, 3 H), 3.50 (t, *J* = 8.5 Hz, 1H), 3.38 (ddd, *J* = 10.5, 8.3, 4.4 Hz, 1H), 1.94-1.88 (m, 1H), 1.71 (br, s, 1H), 1.62 (dt, *J* = 13.0, 3.5 Hz, 1H), 1.44-1.15 (m, 5H), 1.06-1.01 (m, 9H), 0.93-0.87 (m, 9H), 0.78-0.69 (m, 6H), 0.59-0.51 (m, 6H).

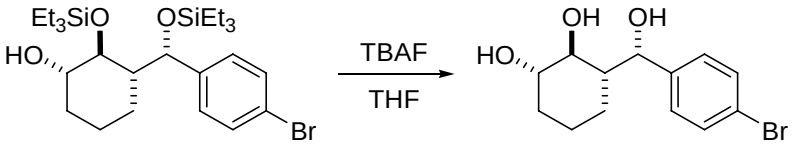
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 144.6, 130.8, 127.8, 120.1, 77.5, 75.7, 71.3, 52.5, 33.4, 22.2, 21.2, 7.3, 6.9, 6.4, 5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3472, 2951, 2874, 1485, 1458, 1404, 1237, 1110, 1093, 1070, 1003, 973, 928, 838, 800, 781, 724, 676.

MS (EI, 70 eV): m/z (%) = 381 (11), 379 (11), 369 (21), 367 (20), 302 (20), 301 (100), 300 (20), 299 (97), 289 (12), 287 (11), 263 (32), 217 (10), 171 (11), 169 (11), 168 (14), 115 (49), 103 (32), 87 (41), 75 (32), 59 (12).

HRMS ($C_{23}H_{40}BrO_3Si_2$, EI): calc.: 499.1699; found: 499.1710 (M^+-C_2H_5).

9. Preparation of triol **12** via the desilylation of compound **11**.[24]



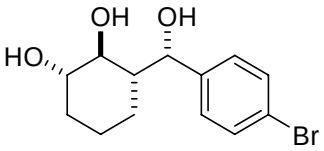
11 **12** : 90%

A solution of TBAF in THF (2.0 mmol, 2 mL, 1.0 M) was slowly added into a solution of compound **11** (0.265 g, 0.5 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min then warmed up to room temperature with stirring for another 4 h. The mixture was quenched by saturated aqueous NH_4Cl (20 mL) and

[24] (a) E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190. (b) *Protective Groups in Organic Synthesis*, 3rd ed.; T. W. Greene, P. G. M. Wuts, Eds.; John Wiley and Sons: New York, **1999**.

extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using ethyl acetate as eluant to provide triol **12** as a white solid (0.136 g, 90% yield).

3-((4-Bromophenyl)(hydroxy)methyl)cyclohexane-1,2-diol (12)



^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.50-7.46 (m, 2H), 7.33-7.30 (m, 2H), 5.19 (dd, *J* = 5.3, 2.2 Hz, 1H), 4.49 (d, *J* = 5.3 Hz, 1H), 4.07 (br, s, 1H), 3.76 (br, s, 1H), 3.40-3.30 (m, 2H), 1.86-1.81 (m, 1H), 1.59-1.55 (m, 2H), 1.30-1.11 (m, 4H).

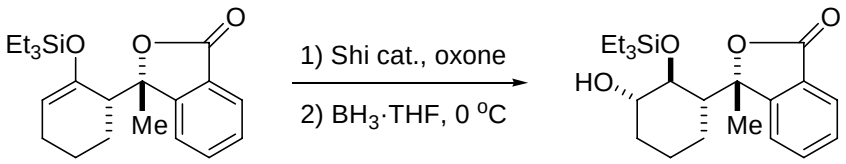
^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 145.9, 132.0, 129.6, 120.8, 77.0, 76.7, 72.2, 51.0, 34.4, 24.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3343, 2945, 2922, 2862, 1486, 1403, 1348, 1242, 1232, 1108, 1071, 1049, 1026, 1010, 992, 879, 845, 830, 793, 725, 675.

MS (EI, 70 eV): m/z (%) = 187 (76), 185 (82), 183 (21), 159 (16), 157 (27), 155 (13), 115 (12), 106 (14), 105 (16), 98 (85), 97 (45), 83 (34), 80 (12), 79 (28), 78 (64), 77 (100), 76 (11), 75 (11), 70 (36), 69 (10), 67 (22), 57 (29), 55 (14), 44 (10), 43 (16), 41 (39).

HRMS ($C_{13}H_{17}BrO_3$, EI): calc.: 300.0361; found: 300.0356 (M^+).

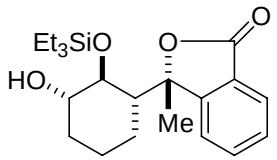
10. Preparation of lactone **13** with four contiguous chiral centers starting from lactone **3d**.[20]



3d **13** : 68%

The reaction was performed according to the above procedure using substrate **3d** (0.186 g, 0.52 mmol), leading to the corresponding product **13** in 68% yield (0.133 g) as colorless oil.

3-(3-Hydroxy-2-(triethylsilyloxy)cyclohexyl)-3-methylisobenzofuran-1(3*H*)-one (13)



^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.85 (d, *J* = 7.5 Hz, 1H), 7.68-7.63 (m, 1H), 7.48 (td, *J* = 7.5, 0.8 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 3.89 (t, *J* = 8.0 Hz, 1H), 3.50-3.43 (m, 1H), 2.09-1.98 (m, 2H), 1.94-1.88 (m, 1H), 1.82 (s, 3H), 1.54-1.12 (m, 4H), 1.03 (t, *J* = 7.7 Hz, 9H), 0.91-0.86 (m, 1H), 0.81-0.73 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 170.1, 155.4, 134.2, 128.7, 125.7, 125.4, 121.0, 89.6, 77.2, 75.2, 48.9, 32.2, 27.2, 25.5, 21.6, 7.1, 5.6.

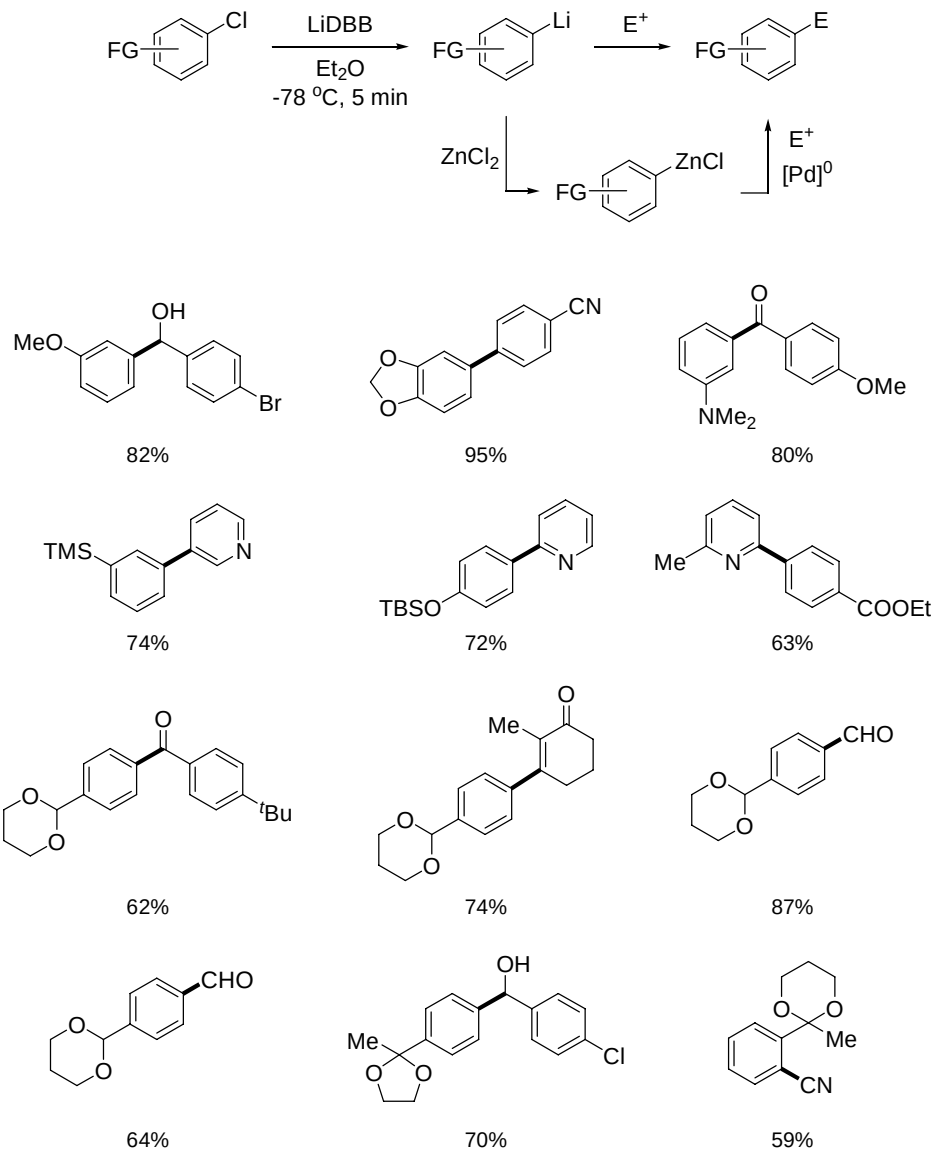
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3391, 2953, 2929, 2874, 1738, 1465, 1286, 1235, 1127, 1056, 1038, 906, 847, 767, 728, 698.

MS (EI, 70 eV): m/z (%) = 376 (M^+, 2), 347 (35), 229 (19), 147 (100), 115 (28), 103 (24), 75 (37), 59 (10).

HRMS ($C_{21}H_{32}O_4Si$, EI): calc.: 376.2070; found: 376.2083 (M^+).

Chapter 8. Summary

8.1 Expedient preparation of aryllithium and arylzinc reagents from aryl chlorides using lithium 4,4'-di-*tert*-butylbiphenylide and $ZnCl_2$



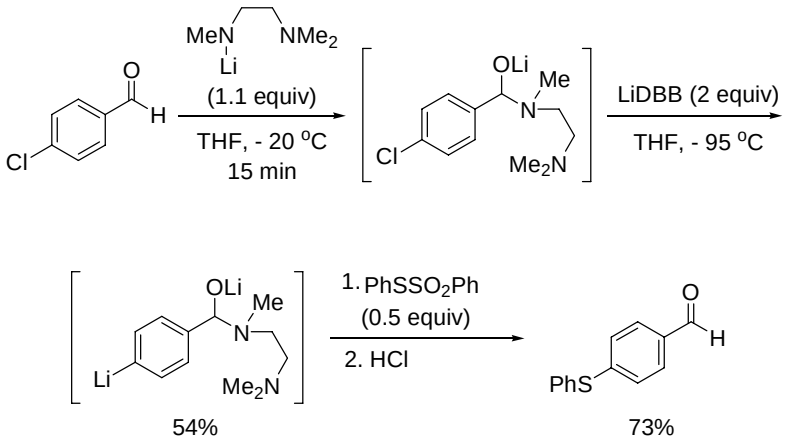
Scheme 1. Preparation of aryllithium and arylzinc reagents from aryl chlorides using lithium 4,4'-di-*tert*-butylbiphenylide and $ZnCl_2$ and subsequent reactions with various electrophiles

In this work, an efficient method for the preparation of aryllithium and zinc reagents from cheap and readily available aryl chlorides by using LiDBB as a lithiation reagent was developed.[1] The resulting organometallic reagents underwent

[1] Z.-L. Shen, K. Sommer, P. Knochel, *Synthesis* **2015**, in press (DOI: 10.1055/s-0034-1380697).

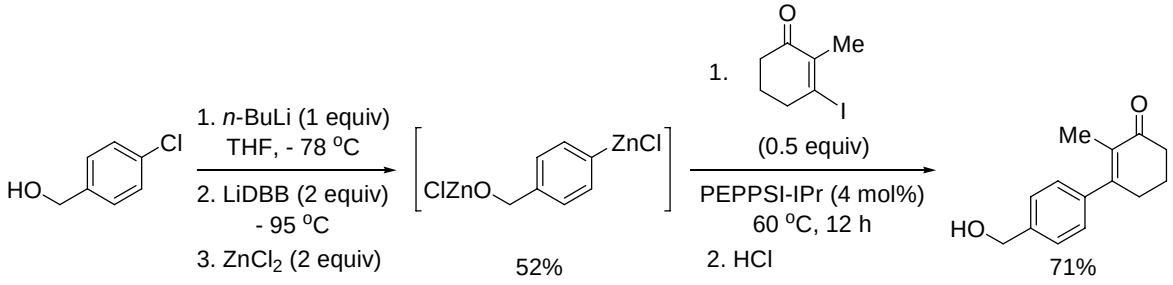
subsequent reactions with a variety of electrophiles, such as an aldehyde, DMF, $PhSSO_2Ph$, TsCN, an aryl halide, or an acid chloride (via Pd-catalyzed cross-coupling). Aryl chlorides bearing substituents, including methoxy, 3,4-methylenedioxy, fluoride, TMS, OTMS, NMe_2, acetal, and ketal, were proven to be appropriate substrates (Scheme 1).

Interestingly, aryl chlorides containing a formyl group can be used as well (Scheme 2), provided that the formyl group was temporarily converted into an *α*-amino alkoxide by using the lithium amide of *N*,*N*,*N*'-trimethylethylenediamine (LiTMDA).



Scheme 2. *In situ* protection of 4-chlorobenzaldehyde as an *α*-amino alkoxide followed by LiDBB-mediated lithiation and subsequent reaction with electrophile leading to the aldehyde

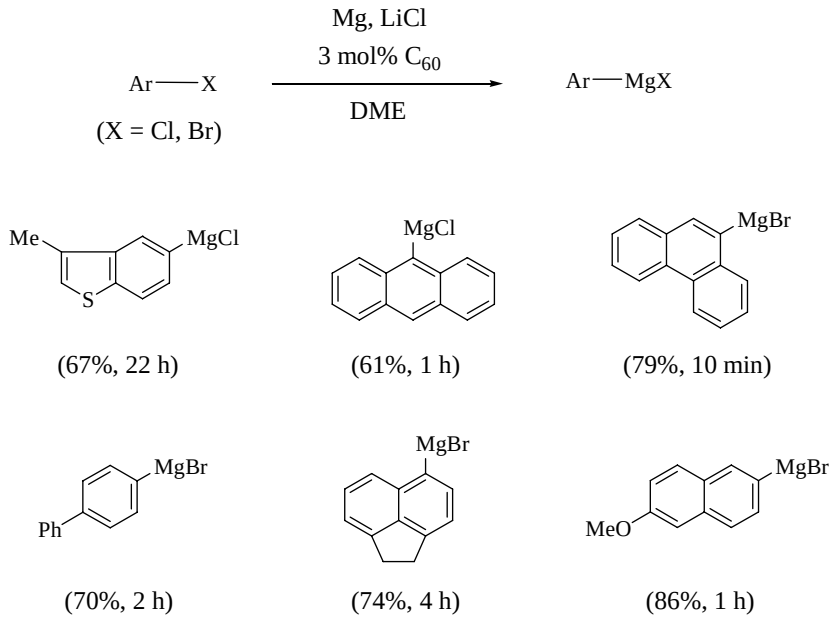
A hydroxyl group is also tolerated if it is deprotonated with *n*-BuLi, prior to the addition of LiDBB (Scheme 3).



Scheme 3. *In situ* deprotonation of 4-chlorobenzyl alcohol by *n*-BuLi followed by LiDBB-mediated lithiation and transmetallation with $ZnCl_2$ and subsequent cross-coupling with electrophile leading to the enone

8.2 C_{60}-catalyzed preparation of aryl and heteroaryl magnesium and zinc reagents using Mg/LiCl

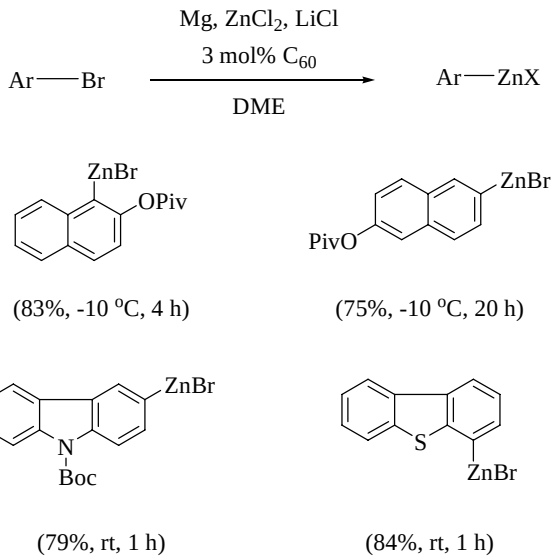
C_{60} fullerene is rarely used as catalyst for organic transformations. We found that the addition of a catalytic amount of C_{60} fullerene (3 mol%) catalyzes the insertion of magnesium into polycyclic aromatic halides allowing the preparation of the corresponding Grignard reagents in good yields (Scheme 4).[2]



Scheme 4. Preparation of polycyclic arylmagnesium reagent by C_{60} fullerene-catalyzed insertion of magnesium into aryl halides

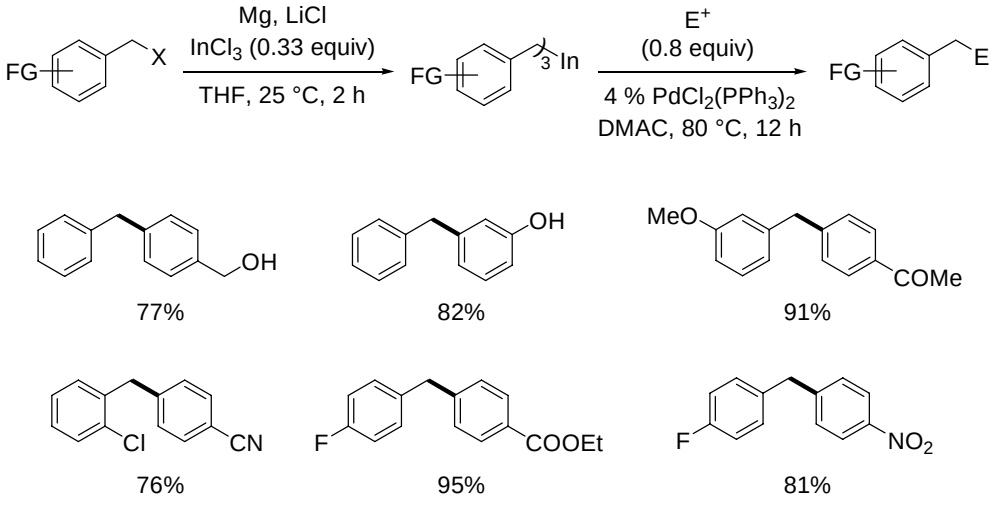
The use of a cocktail of metal and salts (Mg, $ZnCl_2$, LiCl) in the presence of C_{60} fullerene (3 mol%) allows furthermore to prepare some functionalized polyaromatic zinc reagents (Scheme 5). The resulting organomagnesium and organozinc reagents efficiently underwent reactions with electrophiles, such as an aldehyde, an acid chloride, an allylic bromide, or an aryl iodide.

[2] Z.-L. Shen, P. Knochel, *ACS Catalysis* **2015**, *5*, 2324.



Scheme 5. Preparation of functionalized polycyclic arylzinc reagent by C_{60} fullerene-catalyzed insertion of magnesium into aryl halides in the presence of $ZnCl_2$

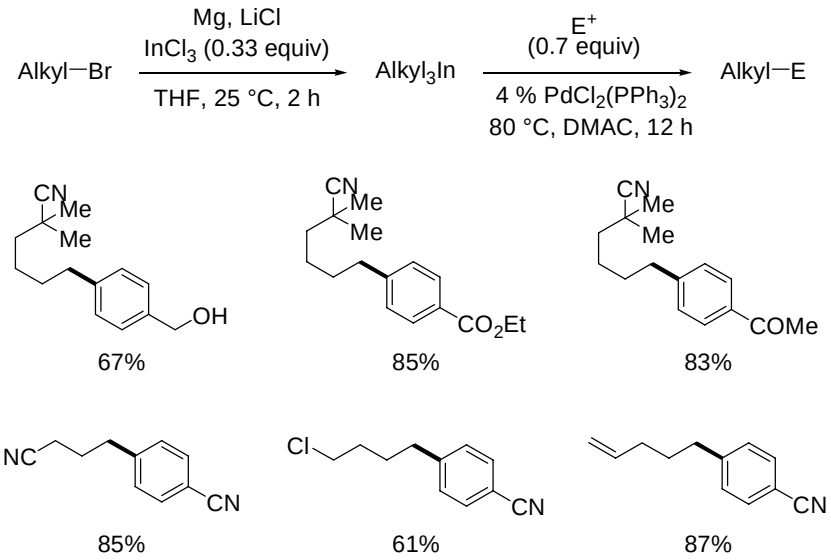
8.3 One-pot preparation of functionalized tribenzylindium and trialkylindium reagents via magnesium insertion into benzyl halides and alkyl halides in the presence of indium trichloride and lithium chloride



Scheme 6. Preparation of functionalized tribenzylindium reagents and their utilities in palladium-catalyzed cross-coupling with various electrophiles

A new and efficient one-pot procedure that enables a direct preparation of triorganoindium reagents from organic halides *via* a magnesium insertion in the

presence of $InCl_3$ and LiCl was developed.[3] Starting from functionalized alkyl bromides as well as benzyl chlorides the corresponding organoindium reagents are accessible at room temperature in good yields (Schemes 6 and 7). Moreover, the obtained organoindium reagents could undergo efficiently Pd-catalyzed cross-coupling reactions with tolerance to various important functional groups such as hydroxyl, carbonyl, cyano, and nitro groups.

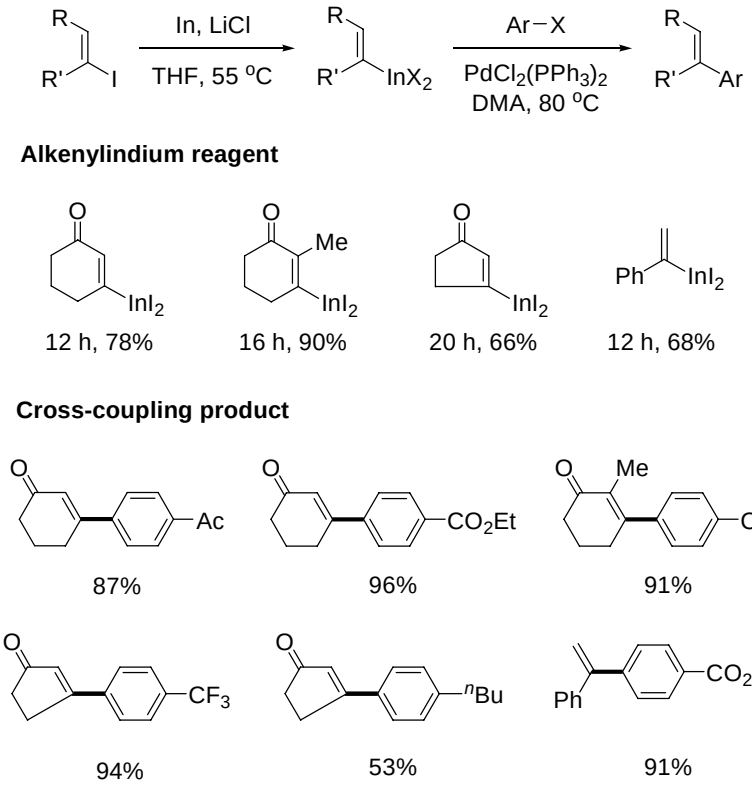


Scheme 7. Preparation of functionalized trialkylindium reagents and their utilities in palladium-catalyzed cross-coupling with various electrophiles

8.4 Stereoselective preparation of polyfunctional alkenylindium(III) halides and their cross-coupling with unsaturated halides

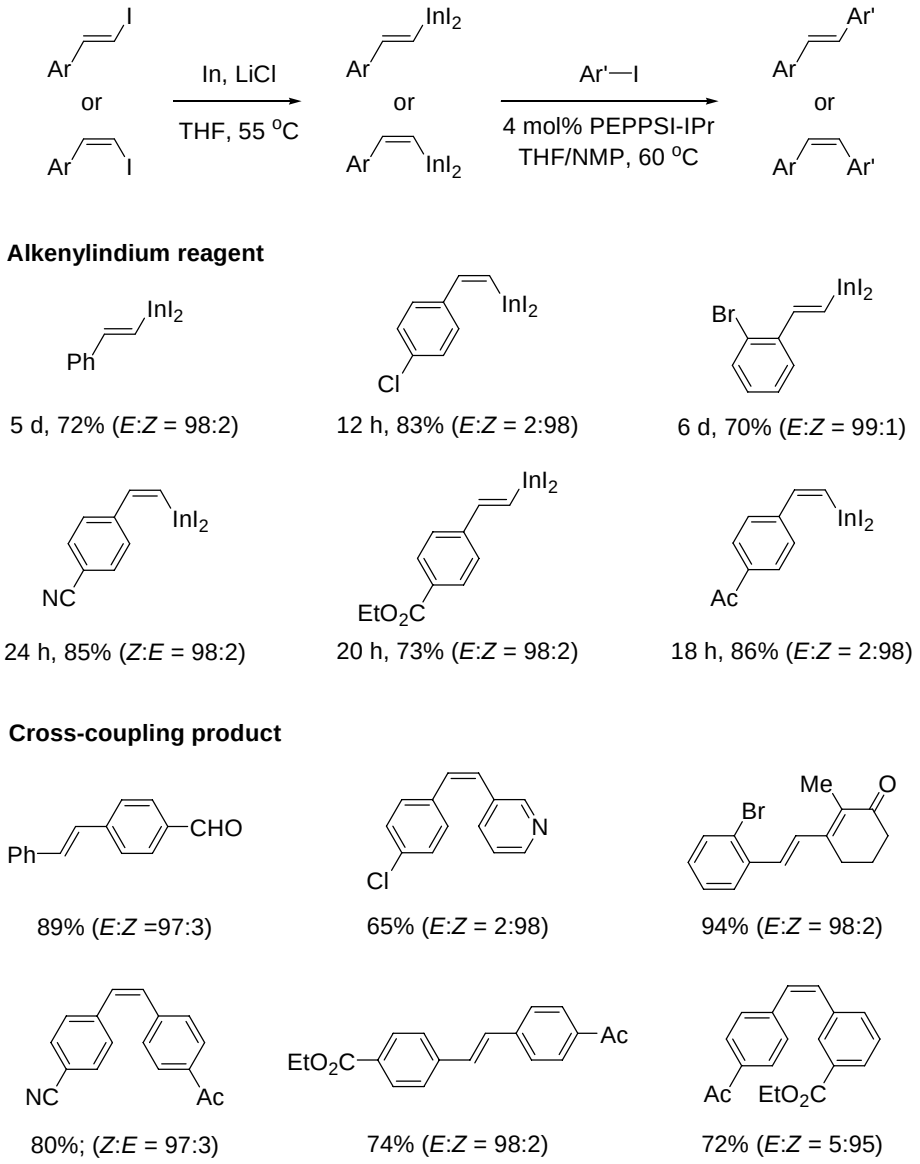
Till now, no direct insertion method is reported for the preparation of alkenylindium(III) reagent. In this project, we developed a convenient method for the synthesis of highly functionalized cycloalkenylindium(III) derivatives by the direct insertion of indium powder to cycloalkenyl iodides in the presence of LiCl in THF (Scheme 8). Poor yield of alkenylindium(III) reagent was obtained when the insertion step was performed in the absence of LiCl. In addition, the insertion step proceeded more efficiently in THF than in other organic solvents.[4]

[3] S. Bernhardt, Z.-L. Shen, P. Knochel, *Chem.-Eur. J.* **2013**, *19*, 828.
[4] Z.-L. Shen, P. Knochel, *Chem.-Eur. J.* **2015**, *21*, 7061.



Scheme 8. Preparation of alkenylindium(III) reagents and subsequent palladium-catalyzed cross-coupling with aryl halides

In addition, we discovered that, in contrast to many metal insertions to alkenyl iodides which proceed with a loss of stereochemistry, the insertion of In/LiCl to stereodefined (*Z*)- and (*E*)-styryl iodides in THF proceeded with high retention of stereochemistry (Scheme 9). After a palladium-catalyzed cross-coupling with a variety of functionalized organic iodides, various polyfunctionalized (*Z*)- and (*E*)-stilbenes were obtained with high stereoselectivity. Wide functional group compatibility was observed both in the insertion step and the subsequent cross-coupling reaction.

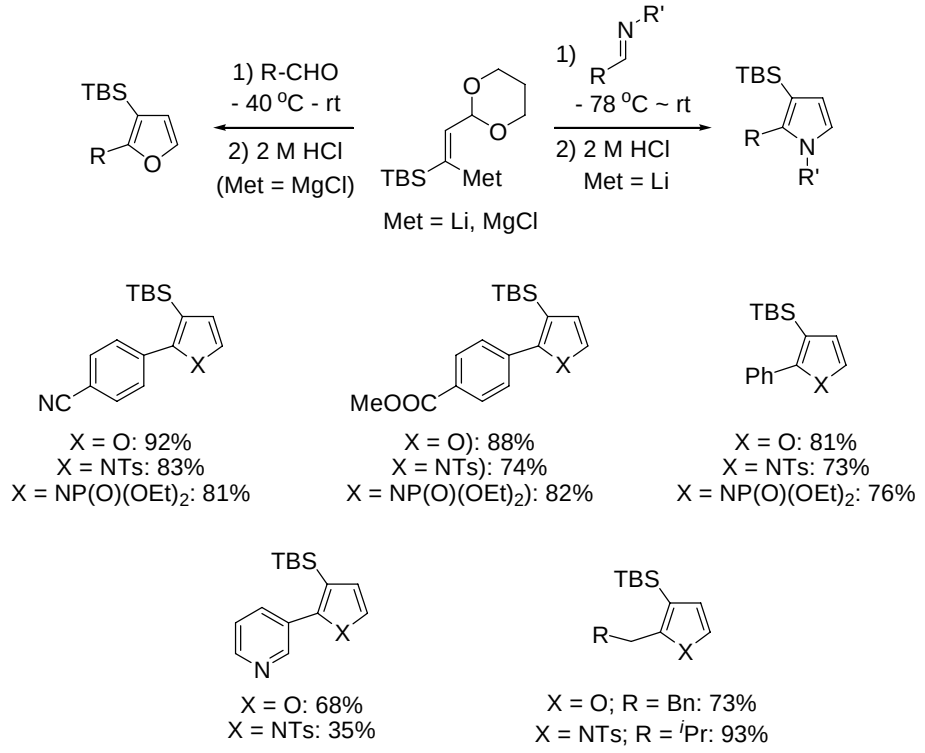


Scheme 9. Preparation of stereodefined *Z*- and *E*-styrylindium reagents and their palladium-catalyzed cross-coupling with aryl halides

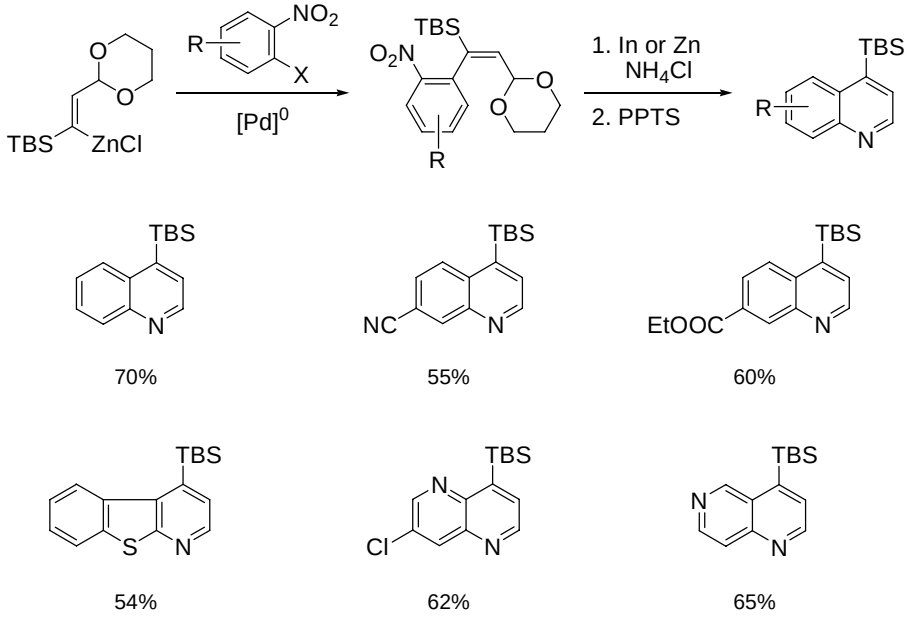
8.5 Polyfunctional alkenyl Li, Mg, or Zn-organometallics as versatile building blocks for the synthesis of complex heterocycles

A multistep synthesis of conjunctive alkenylmetallic reagents starting from TBS-substituted propargyl alcohol was developed. After treating appropriate conjunctive alkenylmetallic reagents (metal = MgX or Li) with aldehydes or aldimines followed by an acidic deacetalization as well as a spontaneous cyclization, a variety of 1,2-disubstituted furans or pyrroles were produced (Scheme 10).[5]

[5] Z.-L. Shen, S. Li, K. Sommer, P. Mayer, P. Knochel, *manuscript under preparation*.



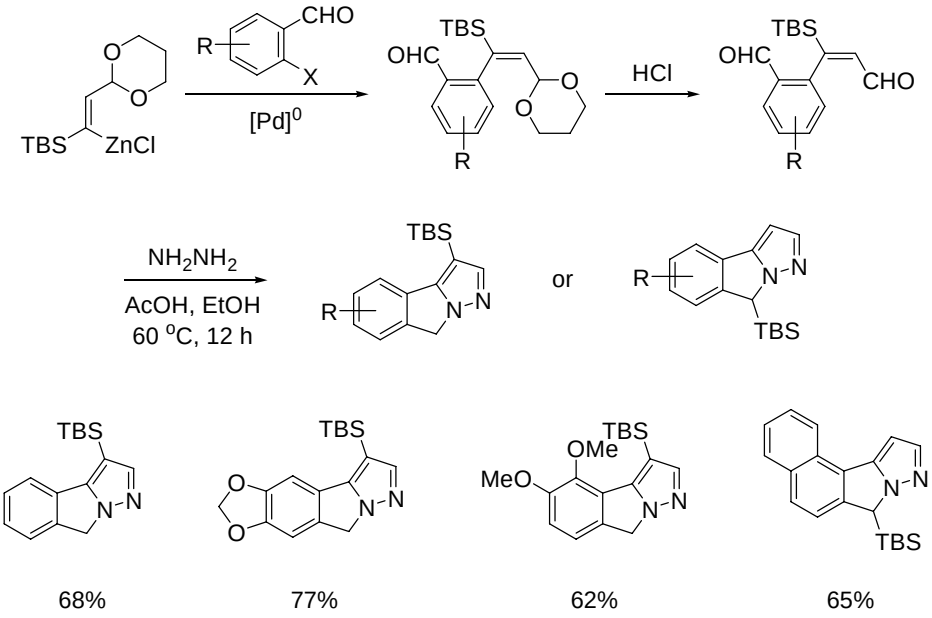
Scheme 10. Preparation of furans and pyrroles by using alkenylmetallic reagents



Scheme 11. Pd-catalyzed cross-coupling of alkenylzinc reagent with 1-halo-2-nitroarene followed by an indium- or zinc-mediated reduction and acidic hydrolysis and *in situ* cyclization leading to annelated pyridine

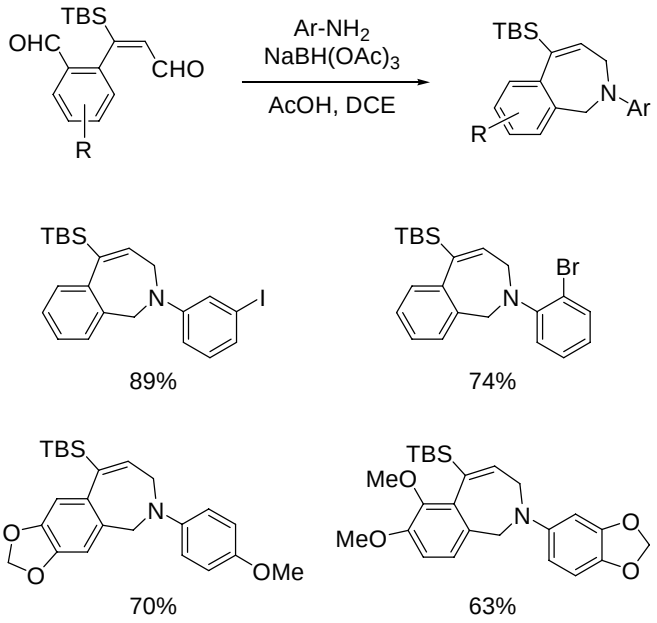
Pd-catalyzed Negishi cross-coupling of the alkenylzinc reagent with various 1-halo-2-nitroarenes provided alkenylated nitroarenes which after indium- or zinc-mediated reduction and acidic acetal cleavage gave the annelated pyridines such as quinolines, naphthyridines, benzo[*b*]thieno[2,3-*b*]pyridine, 1,5- and 1,6-naphthyridine (Scheme 11).

In addition, Pd-catalyzed cross-coupling of alkenylzinc reagent with 1-formyl-2-haloarene followed by an acidic deacetalization and further reaction with hydrazine monohydrate led to interesting tricyclic fused pyrazoles (Scheme 12).



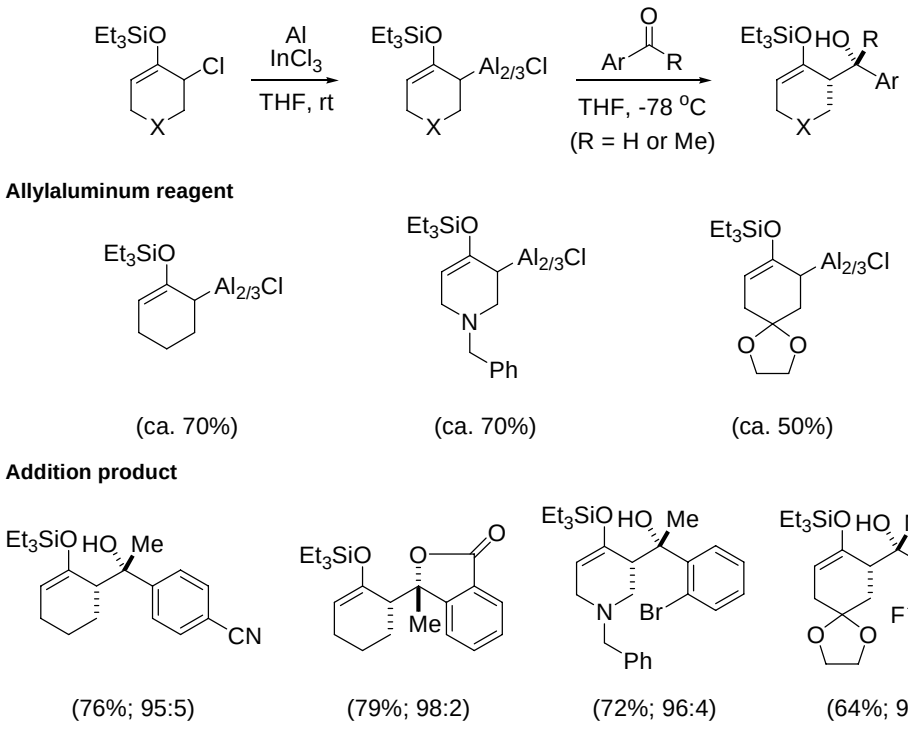
Scheme 12. Pd-catalyzed cross-coupling of alkenylzinc reagent with 1-formyl-2-haloarene followed by an acidic deacetalization and further reaction with hydrazine monohydrate leading to tricyclic fused pyrazoles

In addition, the 1,6-dialdehydes obtained above also can be converted into benzo[*c*]azepine derivative via a double reductive amination using $NaBH(OAc)_3$ and an aniline (Scheme 13). These double reductive aminations proceeded well under mild conditions (AcOH, DCE, rt, 12 h) and produced the corresponding 2,3-dihydro-benzo[*c*]azepines in 63-89% yields.



Scheme 13. $NaBH(OAc)_3$-mediated double reductive amination of 1,6-dialdehyde with aryl amine leading to 7-membered nitrogen-containing heterocycles

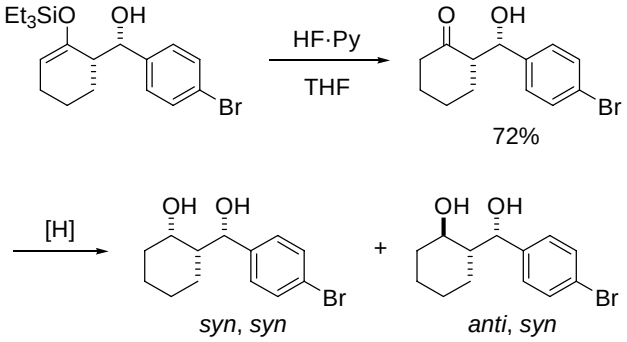
8.6 Highly diastereoselective preparation of aldol products using new functionalized allylic aluminum reagents



Scheme 14. Preparation of allylic aluminum reagents and diastereoselective addition to carbonyl compounds for the synthesis of homoallylic alcohols

In the last project, chloro-substituted triethylsilyl enol ethers derived from cyclohexanone and related ketones were converted with aluminum powder in the presence of indium trichloride to functionalized allylic aluminum reagents which represent a new type of synthetic equivalent of metal enolates.[6] These allylic organometallics undergo highly diastereoselective additions to aldehydes and methyl aryl ketones giving aldol products with a *β*-quaternary center (Scheme 14).

The obtained homoallylic alcohol, after desilylation, could undergo diastereoselective reduction to give either *syn*,*syn*-1,3-diol or *anti*,*syn*-1,3-diol, by choosing appropriate reducing agents (Scheme 15).

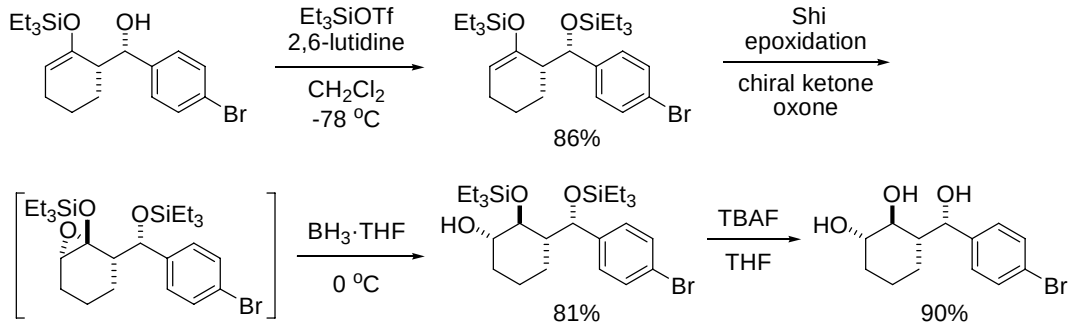


1) L-selectride, THF, -78 ^{o}C, 90% yield, 98:2 dr
2) DIBAL-H,CH_2Cl_2, -78 ^{o}C, 3 h, 89% yield, 95:5 dr
3) $Zn(BH_4)_2$, CH_2Cl_2, -78 ^{o}C, 2 h, 99% yield, 94:6 dr
4) $Me_4NBH(OAc)_3$, HOAc, -40 ^{o}C, 92%, 25:75 dr

Scheme 15. Conversion of homoallylic alcohol to *β*-hydroxy ketone by desilylation and diastereoselective preparation of 1,3-diol bearing three contiguous stereogenic centers starting from *β*-hydroxy ketone

In addition, the homoallylic alcohol can be converted into a triol with four contiguous chiral centers by using a key strategy involving Shi-epoxidation of the silyl enol ether followed by a reductive opening of the epoxide by BH_3·THF (Scheme 16).

[6] Z.-L. Shen, Z. Peng, C.-M. Yang, J. Helberg, P. Mayer, I. Marek, P. Knochel, *Org. Lett.* **2014**, *16*, 956.



Scheme 16. Diastereoselective preparation of triol with four contiguous chiral centers starting from aldol product

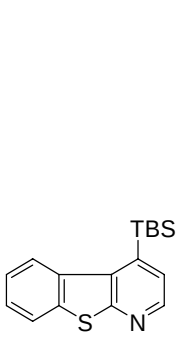
Appendix

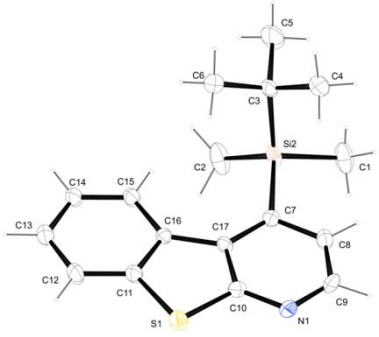
List of abbreviations

Ac	acetyl
AcOH	acetic acid
Alk	alkyl
aq	aqueous
Ar	aryl
Boc	*tert*-butoxycarbonyl
Bu	butyl
calc.	calculated
conc.	concentrated
Cy	cyclohexyl
dba	*trans*,*trans*-dibenzylideneacetone
dist.	distilled
DMAC	dimethylacetamide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
δ	chemical shifts in ppm
E	electrophile
EDG	electron-donating group
EI	electron impact ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
*i*hexane	*iso*-hexane
HRMS	high resolution mass spectrometry
*i*Pr	isopropyl
IR	infra-red
J	coupling constant (NMR)
M	molarity
m	multiplet
m	meta
m.p.	melting point
Me	methyl
Met	metal
min	minute
mmol	millimole
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidine
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
PEPPSI-*i*Pr	[1,3-bis(2,6-di(isopropyl)-phenyl)imidazol-2-ylidene] (3-chloropyridyl)-palladium(II) dichloride
Ph	phenyl
ppm	parts per million
q	quartet
Piv	pivaloyl
R	organic substituent
s	singlet
sat.	saturated
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBAF	tetra-*n*-butylammonium fluoride
*t*Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate
tfp	tris-(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethyl-piperidyl
TMS	trimethylsilyl
TP	typical procedure
Ts	4-toluenesulfonyl
X	halide or pseudohalide

Crystallographic data

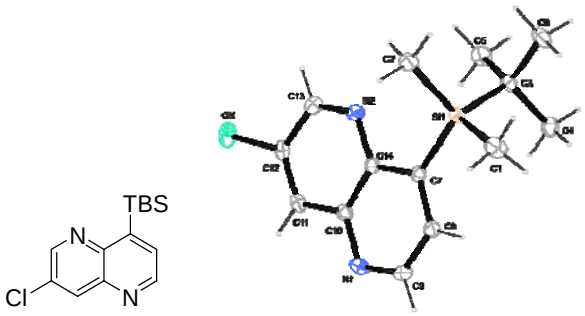
Table 1. Crystallographic data of 4-(*tert*-butyldimethylsilyl)-[*1*]benzothieno[2,3-*b*] pyridine (**11e**, Chapter 6)





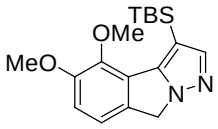
net formula	$C_{17}H_{21}NSSi$
M_r/g mol^{-1}	299.507
crystal size/mm	0.405 × 0.199 × 0.151
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	'P 21/n'
a/Å	7.8930(6)
b/Å	7.7905(6)
c/Å	26.854(2)
α/°	90
β/°	98.368(8)
γ/°	90
V/Å^3	1633.7(2)
Z	4
calc. density/g cm^{-3}	1.21773(15)
μ/mm^{-1}	0.262
absorption correction	'multi-scan'
transmission factor range	0.90942–1.00000
refls. measured	8679
R_{int}	0.0498
mean σ(I)/I	0.0512
θ range	4.314–25.348
observed refls.	2697
x, y (weighting scheme)	0.0000, 6.3332
hydrogen refinement	constr
refls in refinement	2977
parameters	186
restraints	0
$R(F_{obs})$	0.0898
$R_w(F^2)$	0.1927
S	1.314
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.306
min electron density/e Å^{-3}	−0.391

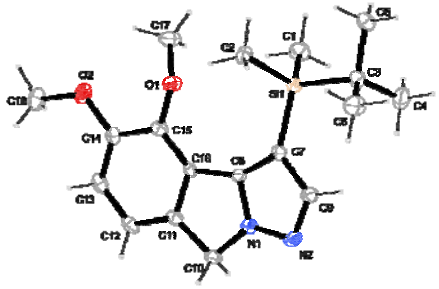
Table 2. Crystallographic data of 8-(*tert*-Butyldimethylsilyl)-3-chloro-1,5-naphthyridine (**11f**, Chapter 6)



net formula	$C_{14}H_{19}ClN_2Si$
M_r/g mol^{-1}	278.852
crystal size/mm	0.478 × 0.268 × 0.188
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	'P 21/n'
a/Å	7.4516(5)
b/Å	15.3869(9)
c/Å	13.0042(9)
α/°	90
β/°	96.246(6)
γ/°	90
V/Å^3	1482.17(16)
Z	4
calc. density/g cm^{-3}	1.24966(13)
μ/mm^{-1}	0.324
absorption correction	'multi-scan'
transmission factor range	0.95064–1.00000
refls. measured	8547
R_{int}	0.0331
mean σ(I)/I	0.0380
θ range	4.244–26.370
observed refls.	2435
x, y (weighting scheme)	0.0415, 0.4297
hydrogen refinement	constr
refls in refinement	3020
parameters	168
restraints	0
$R(F_{obs})$	0.0363
$R_w(F^2)$	0.0969
S	1.053
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.293
min electron density/e Å^{-3}	−0.219

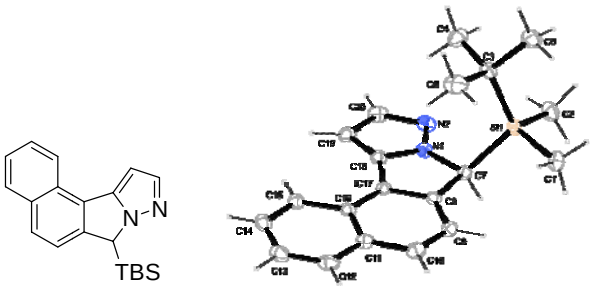
Table 3. Crystallographic data of 3-(*tert*-butyldimethylsilyl)-4,5-dimethoxy-8*H*-pyrazolo[5,1-*a*]isoindole (**15c**, Chapter 6)





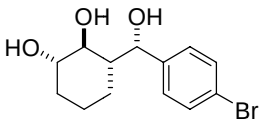
net formula	$C_{18}H_{26}N_2O_2Si$
M_r/g mol^{-1}	330.497
crystal size/mm	0.407 × 0.258 × 0.109
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	'P 21'
a/Å	9.1805(5)
b/Å	7.0642(4)
c/Å	13.9729(7)
α/°	90
β/°	96.388(4)
γ/°	90
V/Å^3	900.56(8)
Z	2
calc. density/g cm^{-3}	1.21882(11)
μ/mm^{-1}	0.142
absorption correction	'multi-scan'
transmission factor range	0.98828–1.00000
refls. measured	4944
R_{int}	0.0241
mean σ(I)/I	0.0373
θ range	4.403–26.370
observed refls.	2501
x, y (weighting scheme)	0.0436, 0.9739
hydrogen refinement	constr
Flack parameter	0.2(4)
refls in refinement	2789
parameters	216
restraints	1
$R(F_{obs})$	0.0539
$R_w(F^2)$	0.1372
S	1.103
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.515
min electron density/e Å^{-3}	−0.297

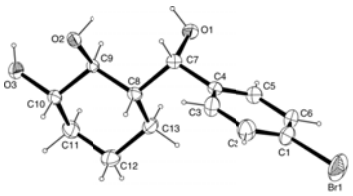
Table 4. Crystallographic data of 7-*(tert*-butyldimethylsilyl)-*b*enzo[*g*]pyrazolo[5,1-*a*] isoindole (**17d**, Chapter 6)



net formula	$C_{20}H_{24}N_2Si$
M_r/g mol^{-1}	320.504
crystal size/mm	0.404 × 0.202 × 0.111
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	'P n a 21'
a/Å	22.3970(7)
b/Å	10.7600(3)
c/Å	7.3662(3)
α/°	90
β/°	90
γ/°	90
V/Å^3	1775.20(10)
Z	4
calc. density/g cm^{-3}	1.19923(7)
μ/mm^{-1}	0.134
absorption correction	'multi-scan'
transmission factor range	0.95374–1.00000
refls. measured	8660
R_{int}	0.0310
mean σ(I)/I	0.0364
θ range	4.202–25.337
observed refls.	2815
x, y (weighting scheme)	0.0368, 0.2228
hydrogen refinement	constr
Flack parameter	0.06(7)
refls in refinement	3061
parameters	213
restraints	1
$R(F_{obs})$	0.0325
$R_w(F^2)$	0.0788
S	1.043
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.195
min electron density/e Å^{-3}	−0.175

Table 5. Crystallographic data of 3-((4-bromophenyl)(hydroxy)methyl)cyclohexane-1,2-diol (**12**, Chapter 7)





net formula	$C_{13}H_{17}BrO_3$
M_r/g mol^{-1}	301.176
crystal size/mm	0.35 × 0.10 × 0.05
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1/c$
a/Å	7.7491(6)
b/Å	32.258(2)
c/Å	10.4006(14)
α/°	90
β/°	90.016(8)
γ/°	90
V/Å^3	2599.8(4)
Z	8
calc. density/g cm^{-3}	1.5390(2)
μ/mm^{-1}	3.156
absorption correction	'multi-scan'
transmission factor range	0.60436–1.00000
refls. measured	16086
R_{int}	0.0373
mean σ(I)/I	0.0434
θ range	4.27–26.36
observed refls.	3920
x, y (weighting scheme)	0.0205, 2.8926
hydrogen refinement	constr
refls in refinement	5285
parameters	313
restraints	0
$R(F_{obs})$	0.0402
$R_w(F^2)$	0.0832
S	1.031
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.697
min electron density/e Å^{-3}	−0.835