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

New Preparation of Polysubstituted Allenes, Benzylic Manganese Chlorides and Protected Aldol Products. Transition Metal Free Benzylation of Unsaturated Cyanides.

von

Pauline Alice Quinio

aus

Saint Brieuc, France

2015

Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 07. Oktober 2011 von Herrn Professor Dr. Paul Knochel betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe bearbeitet.

München, 29. Mai 2015

.....
Pauline Alice Quinio

Dissertation eingereicht am: 08. Juni 2015

1. Gutachter:	Prof. Dr. Paul Knochel
2. Gutachter:	Prof. Dr. Konstantin Karaghiosoff

Mündliche Prüfung am: 29. Juni 2015

This work was carried out from October 2011 to March 2015 under the guidance of Prof. Dr. Paul Knochel at the Department of Chemistry at the Ludwig-Maximilians-Universität Munich.

First of all, I would like to thank Prof. Dr. Paul Knochel for giving me the great opportunity to carry out my PhD thesis in his group, for his support and advice in the course of my scientific research and his interest in this work.

I also would like to express my gratitude to Prof. Dr. Konstantin Karaghiosoff for agreeing to be second reviewer of this thesis and I thank all members of my defense committee – Prof. Dr. Manfred Heuschmann, Dr. Thomas Magauer, Prof. Dr. Franz Bracher, and Prof. Dr. Heinz Langhals – for their interest shown in this manuscript by accepting to be referees.

I am really grateful to Dr. Dorian Didier, Mario Ellwart, Dr. Ilya Makarov, Julia Nafe and Dr. Daniela Sustac Roman for the carefull correction of this manuscript.

I thank every member of the group that I met during my thesis for making this group “breathing” towards activities, meals and parties. Thank you to the best colleagues ever Dr. Annette Frischmuth and Dr. Sophia Manolikakes, we had so much nice moments in and outside the lab. Thanks again to you Annette and Vroni for the very nice trip to Paris. Special thank also goes to my french guys Dr. Dorian Didier and Sarah Fernandez. Thank you for encouraging me and keeping me smiling and laughing, I appreciate our common bad humor.

I deeply thank my labmates in F2.004, for the interesting discussions and the really nice atmosphere: Dr. Sebastian Bernhardt, Peter Dowling, Dr. Christos Stathakis, Dr. Daniela Sustac Roman, Dr. Veronika Werner and Shen Zhi-liang. You made this lab full of life and I appreciate you let me sing and wisthle so bad than I can.

I would like to thank Dr. Cyril François, Dr. Thierry León and Dr. Daniela Sustac Roman for the great collaborations, without forgetting my students Andreas Benischke, Jakob Gaar, Laura Kohout and Sharankini William, I wish you all success and luck in your future scientific research. Laura, I will never thank you enough for your kindness and comprehension, all my thesis long, vielen lieben Dank!

I thank also, Dr. Sebastian Bernhardt, Dr. Tobias Blümke, Dr. Annette Frischmuth, Dr. Thomas Kunz, Dr. Albrecht Metzger and Theresa, Dr. Roland Appel and Claudia for the nice time I had with you on my free time.

Thank you to Peter Dowling, Sophie Hansen, Dr. Vladimir Malakhov and Yulia Tsvik for their huge helps organizing everyday life in the lab and the office. Vladimir, it would now be right to say “Au revoir Monsieur”.

Un très grand merci à mes parents et ma famille pour leur soutien et simplicité, la Bretagne me manque! Je remercie mes amis de Saint Brieuc, mes iutiens de Rennes et mes iupiens de Nantes pour leurs lointains mais pas moindre encouragements tout au long de ma thèse et plus particulièrement Luce et Chris, vous êtes des amours! Endlich, bedanke ich mich vor allem bei dir, Basti, für deine wahnsinnige Unterschützung. Du bist *der beste und liebste Mensch*, und unser Treffen bleibt mir die schönste Erinnerung dieser Zeit.

Parts of this PhD thesis have been published

1. **$Sc(OTf)_3$-Catalysed Addition of Bromomagnesium 2-Vinyloxy Ethoxide to Various Aldehydes leading to Protected Aldol Products**

P. Quinio, L. Kohout, D. Sustac Roman, J. Gaar, K. Karaghiosoff, P. Knochel, **2015** manuscript in preparation.

2. **Transition Metal Free Cross-coupling of Aryl and N-Heteroaryl Cyanides with Benzylic Zinc Reagents**

P. Quinio, D. Sustac Roman, T. León, S. William, K. Karaghiosoff, P. Knochel, **2015** manuscript submitted.

3. **Preparation of Tri- and Tetra-substituted Allenes via Regioselective Lateral Metalation of Benzylic Trimethylsilyl-Alkynes Using TMPZnCl·LiCl**

P. Quinio, C. François, A. Escribano Cuesta, A. K. Steib, F. Achrainer, H. Zipse, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2015**, *17*, 1010.

4. **New preparation of benzylic manganese chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of $MnCl_2$·2LiCl**

P. Quinio, A. D. Benischke, A. Moyeux, G. Cahiez, P. Knochel *Synlett* **2015**, *26*, 514.

5. **BF_3-Mediated Oxidative Cross-Coupling of Pyridines with Alkynyllithium Reagents and Further Reductive Functionalizations of the Pyridine Scaffold**

T. León, P. Quinio, Q. Chen, P. Knochel *Synthesis* **2014**, *46*, 1374.

À mes parents Annick et Pierre
Et mes soeurs Aurélie et Sandrine

“La chance, c’est comme le Tour de France:
on l’attend et ça passe vite.”

Dialogue du film *Le fabuleux Destin d’Amélie Poulain*, de Jean-Pierre JEUNET

TABLE OF CONTENTS

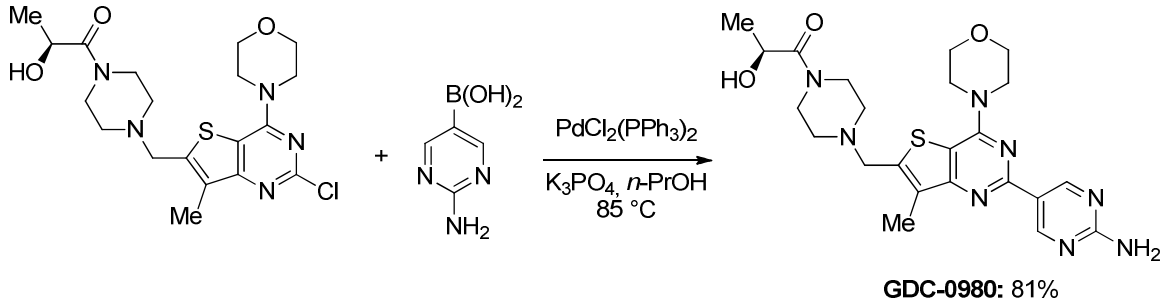
INTRODUCTION

I. Overview

"*In contrast to "Silicon Valley", the term "Carbon Valley" has not yet been commonly applied to describe the many regions around the world where millions of carbon compounds are synthesized every year, some in multiton quantities in the name of basic research concerning materials science, biology, and medicine. It should!*"[1]

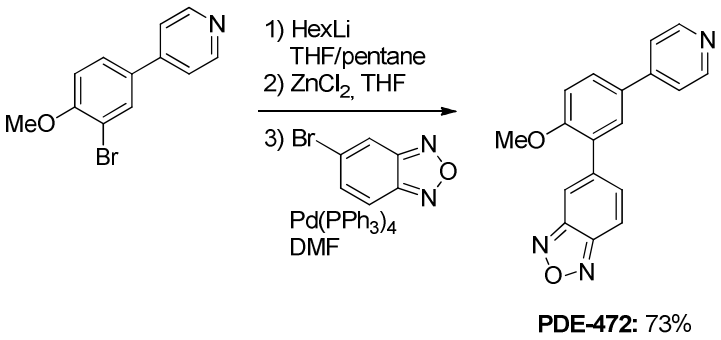
In these words, *K. C. Nicolaou* expressed the worldwide importance of synthetic organic chemistry in our everyday life. As a matter of fact, the global pharmaceutical market is expected to grow to nearly $1.3 trillion by 2018, as the global population aged 65 and over will grow faster than any other age segment, and will account for almost 30% of overall population growth in the next three years.[2] As a consequence of the increasing production of pharmaceuticals, the research in the field of medicinal chemistry is focused on the challenging development of green and sustainable modern technologies.[3] Powerful synthetic methods were developed since the beginning of the 20th century. The formation of the carbon-carbon bonds using organometallic chemistry tools played an unprecedent role for science. In 1912, *V. Grignard* was awarded the Nobel Prize for the discovery of the so-called *Grignard* reagent, which has greatly advanced the progress of organic chemistry.[4,5] One century later, the palladium-catalyzed carbon-carbon bond-forming reactions were recognized through the Nobel Prize laureates *R. F. Heck*, *E. Negishi* and *A. Suzuki*.[6] Palladium-catalyzed cross-coupling reactions have already found numerous applications in the pharmaceutical, agrochemical, and fine chemical industries.[7] For instance, the *Suzuki-Miyaura* cross-coupling reaction has found a wide range of applications in industrial processes, as shown with the recently reported 16-kg scale production of the anticancer agent GDC-0980 in 81% yield by *Genentech* (Scheme 1).[8]

[1] K. C. Nicolaou, E. J. Sorensen, N. Winssinger, *J. Chem. Ed.* **1998**, *75*, 1226.
[2] Source: IMS health.
[3] a) T. Collins, *Science* **2001**, *291*, 48; b) C. Okkerse, H. van Bekkum, *Green Chemistry* **1999**, *1*, 107; c) R. H. Crabtree, *Organometallics* **2011**, *30*, 17; d) K. B. Aubrecht, L. Padwa, X. Shen, G. Bazargan, *J. Chem. Educ.* **2015**, *92*, 631; d) A. Kreimeyer, P. Eckes, C. Fischer, H. Lauke, P. Schuhmacher, *Angew. Chem. Int. Ed.* **2015**, *54*, 3178.
[4] Nobelprize.org. *The Nobel Prize in Chemistry 1912*.
See: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1912/.
[5] a) V. Grignard in *Nobel Lectures: Chemistry 1901–1921*, the Nobel Foundation, Elsevier, New York, **1966**, p 234; b) P. G. Williard in *Comprehensive Organic Synthesis*, Vol. 1, (Ed. S. L. Schreiber), Pergamon, New York, **1991,** p 1; c) D. M. Huryn in *Comprehensive Organic Synthesis*, Vol. 1, (Ed. S. L. Schreiber), Pergamon, New York, **1991**, p 49.
[6] Nobelprize.org. *The Nobel Prize in Chemistry 2010*.
See: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/.
[7] C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027.
[8] Q. Tian, U. Hoffmann, T. Humphries, Z. Cheng, P. Hidber, H. Yajima, M. Guillemot-Plass, J. Li, U. Bromberger, S. Babu, D. Askin, F. Gosselin, *Org. Process Res. Dev.* **2015**, *19*, 416.



Scheme 1. *Suzuki-Miyaura* cross-coupling reaction for the production of GDC-0980.

Interestingly, the more sensitive *Negishi* cross-coupling reaction has also found some industrial applications.[8] In fact, a *Negishi* protocol for the manufacture of the benzoxadiazole PDE-472, used for the treatment of asthma, was reported in 2003 by *Novartis*.[9] In the latter case, the *Negishi* cross-coupling was used as a more efficient alternative to the *Suzuki-Miyaura* reaction, affording the benzoxadiazole PDE-472 in 73% yield on a 4.5-kg scale (Scheme 2).



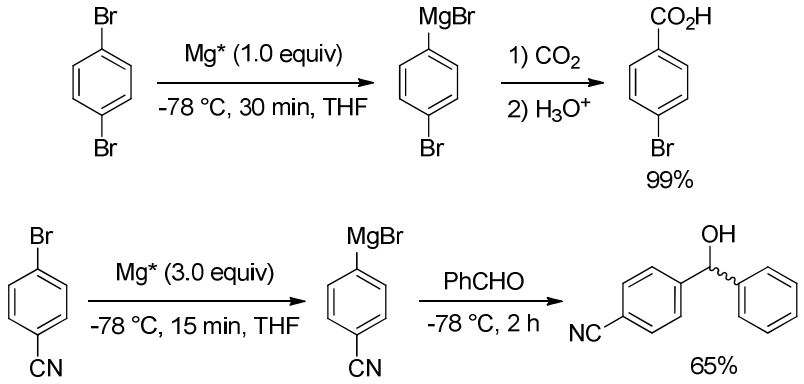
Scheme 2. *Negishi* cross-coupling reaction in the large-scale production of PDE-472.

[9] P. W. Manley, M. Acemoglu, W. Marterer, W. Pachinger, *Org. Process Res. Dev.* **2003**, *7*, 436.

II. Preparation of organometallic reagents

1) Oxidative insertion

The direct insertion of a metal into a carbon-halogen bond was established in the 19th century, when *E. Frankland* discovered the synthesis of diethylzinc *via* the direct insertion of zinc into ethyl iodide.[10] In the beginning of the 20th century, *V. Grignard* discovered the formation of the so-called *Grignard* reagents by the direct insertion of magnesium into methyl iodide.[11] The insertion reaction is assumed to take place *via* a radical pathway.[12] Since harsh conditions (high temperature reactions) are required for the activation of magnesium, *R. D. Rieke* and co-workers developed in 1972 a new method for the preparation of *Grignard* reagents by reducing anhydrous magnesium salts with alkali metal lithium and naphthalene as electron carrier, affording the highly activated, and therefore highly reactive, *Rieke* magnesium (Mg*).[13] The method allowed the generation of organomagnesium reagents at very low temperatures, offering a better regioselectivity and compatibility spectra with functional groups (Scheme 3).[13]

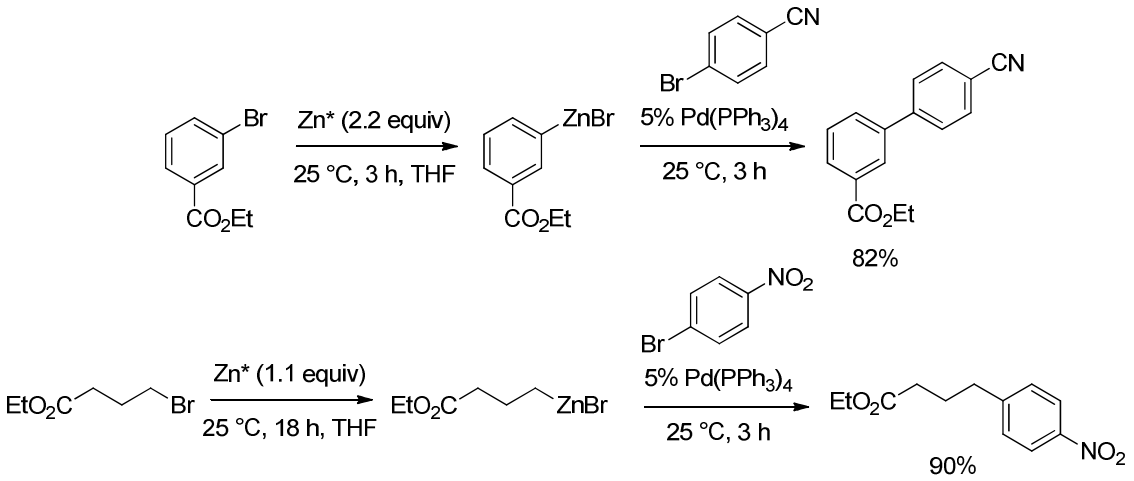


Scheme 3. Preparation of aromatic *Grignard* reagents using highly reactive *Rieke*-magnesium and their reaction with electrophiles.

Similarly, the reduction of zinc chloride by lithium naphtalenide in THF provides highly reactive zinc metal (Zn*),[14] allowing the direct insertion of zinc into the carbon-halogen bond.

[10] a) E. Frankland, *Liebigs Ann. Chem.* **1848**, *71*, 171; b) E. Frankland, *J. Chem. Soc.* **1848**, *2*, 263.
[11] V. Grignard, *Compt. Rend. Acad. Sc. Paris* **1900**, *130*, 1322.
[12] a) H. M. Walborksy, *Acc. Chem. Res.* **1990**, *23*, 286; b) J. F. Garst, *Acc. Chem. Res.* **1991**, *24*, 95; c) J. F. Garst, M. P. Soriaga, *Coord. Chem. Rev.* **2004**, *248*, 623.
[13] a) R. D. Rieke, *Top. Curr. Chem.* **1975**, *59*, 1; b) R. D. Rieke, *Acc. Chem. Res.* **1977**, *10*, 301; c) R. D. Rieke, *Sciences* **1989**, *246*, 1260; d) M. S. Sell, M. V. Hanson, R. D. Rieke *Synth. Commun.* **1994**, *24*, 2379; e) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925; f) J. Lee, R. Verlade-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428; g) R. D. Rieke, *Aldrichchim. Acta* **2000**, *33*, 52.
[14] L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445.

It offers a larger compatibility range with sensitive functional groups such as esters and nitriles (Scheme 4).



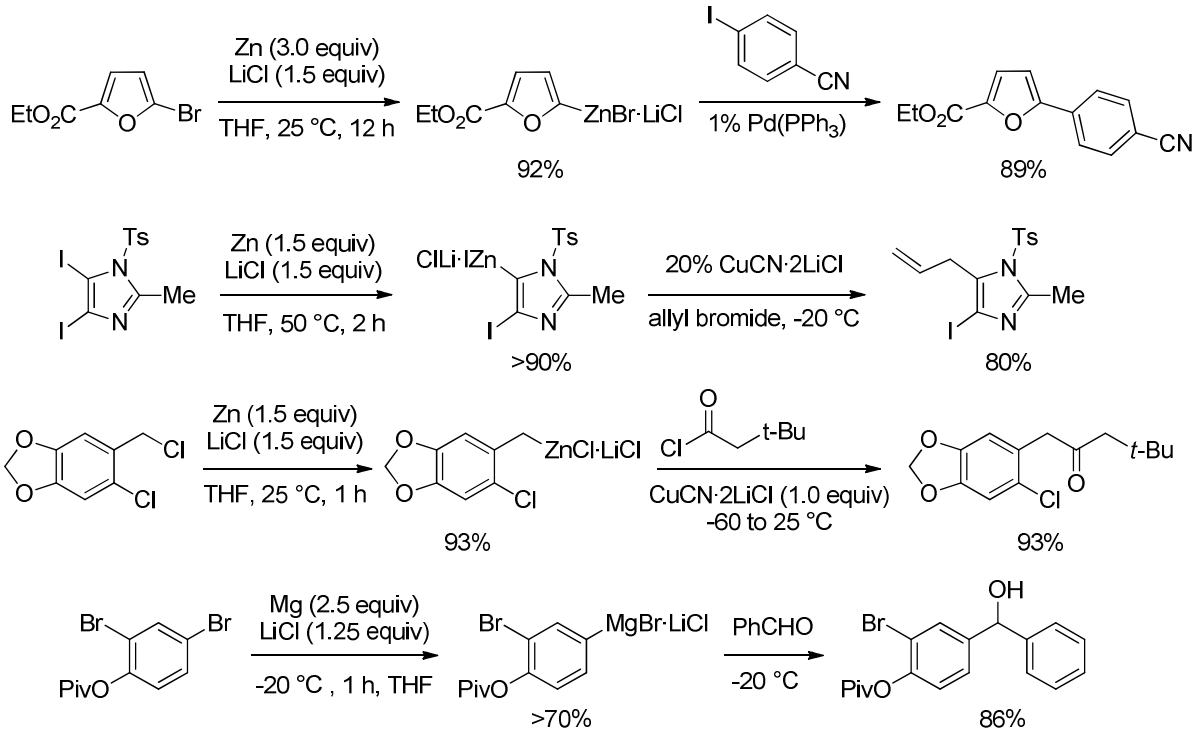
Scheme 4. Preparation of functionalized aromatic and alkyl organozinc reagents using highly reactive *Rieke*-zinc and their *Negishi* cross-coupling reaction with electrophiles.

The necessity of high temperature conditions for the preparation of *Grignard* reagents and, on the contrary, of very low temperature conditions for the activation of the so-called *Rieke* metals, in addition to high dilution, long reaction times and a somewhat reduced scope, motivated *P. Knochel* and co-workers to develop a new strategy for a mild preparation of organometallic reagents. As a matter of fact, a smooth direct zinc insertion into organic halides was achieved at temperatures between 25 and 50 °C, in the presence of stoichiometric amounts of LiCl.[15] The method allowed the successful preparation of a wide range of new hetero- and aryl-zinc reagents from the corresponding iodo- and bromo-compounds (Scheme 5). Similarly, the LiCl-promoted insertion of magnesium metal into organic halides was reported.[16] In both cases, the presence of stoichiometric amount of LiCl salts enhanced the rate of the insertion reaction by improving the solubility of the metal species in THF,[17] thus allowing mild temperatures and short reaction times. Although the zinc insertion is facilitated in the presence of LiCl salts, it still requires in some cases higher temperatures or in other cases, the organozinc species is not reactive enough towards electrophiles.

[15] 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.

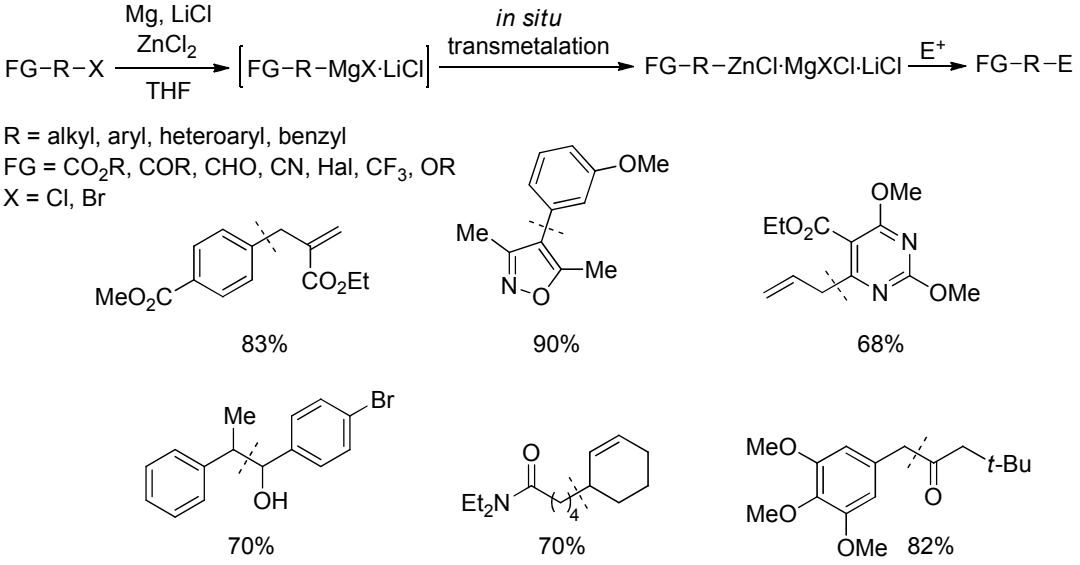
[16] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

[17] a) C.-Y. Liu, X. Wang, T. Furuyama, S. Yasuike, A. Muranaka, K. Morokuma, M. Uchiyama, *Chem. Eur. J.* **2010**, *16*, 1780; b) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771; c) J. E. Fleckenstein, K. Koszinowski, *Organometallics* **2011**, *30*, 5018.



Scheme 5. Selected examples of LiCl-mediated preparation of functionalized organozinc or magnesium reagents.

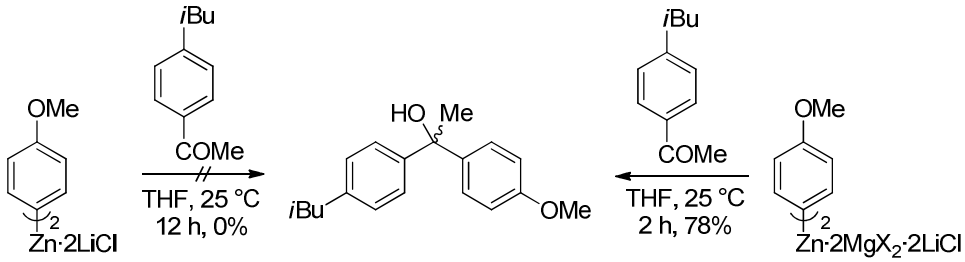
To overcome these weaknesses, *P. Knochel et al.* found that the LiCl-mediated insertion of magnesium in the presence of $ZnCl_2$ permits to extend the scope of the insertion reaction and the reactivity of the *in situ* formed zinc species towards a broad range of substrates (Scheme 6).[18]



Scheme 6. Selected examples of functionalized organozinc reagents prepared using LiCl-mediated Mg-insertion in the presence of $ZnCl_2$ and their reaction with various electrophiles.

[18] a) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824; b) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082.

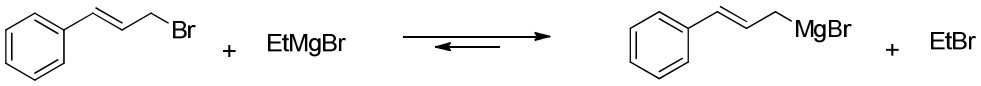
This method further allows the preparation of diorganozinc species in the presence of magnesium salts, resulting in a boost of the reactivity of the organometallic species towards electrophiles (Scheme 7).[19]



Scheme 7. Reactivity of organozinc reagents prepared with or without the presence of MgX_2.

2) Halogen-metal exchange reactions

The first example of a halogen-metal exchange reaction was pioneered in 1931 by *C. Prévost*.[20] He reported a bromine-magnesium exchange between cinnamyl bromide and EtMgBr (Scheme 8). The halogen-magnesium exchange proceeds *via* an equilibrium favoring the most stable organometallic species. In other words, the resulted organomagnesium species has to be more stable than the starting organomagnesium reagent for a successful exchange reaction (organomagnesium stability: sp > sp^2_{vinyl} > sp^2_{aryl} > sp^3_{prim} > sp^3_{sec}).[21]

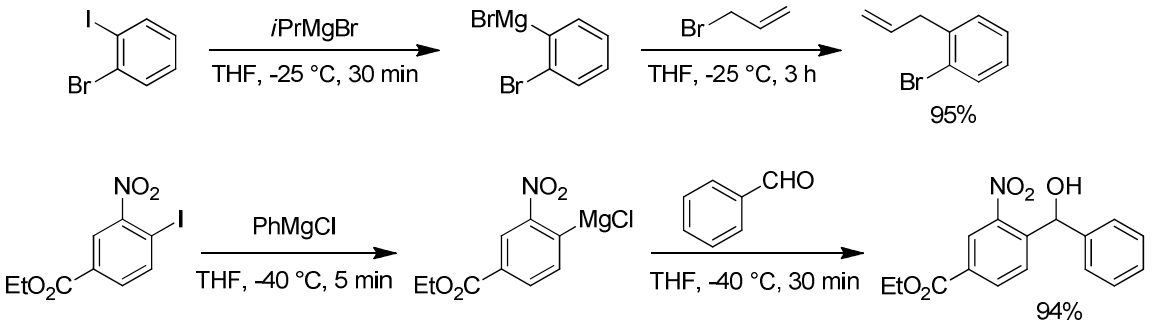


Scheme 8. Pioneer bromine-magnesium exchange reported by *Prévost*.

The halogen-lithium exchange reaction has also been reported by *G. Wittig*[22] and *H. Gilman.*[23] The exchange takes place using iodo- or bromo-compounds and lithium reagents such as *n*BuLi, *t*BuLi or PhLi. However, the high reactivity of lithium species moderates, even at low temperature (-78 °C), the functional-group tolerance; furthermore, their strong basicity leads to undesired side-reactions.[24] To overcome these drawbacks and based on the pioneer work of *J. Villiéras* who reported a general approach to organomagnesium species using *i*PrMgCl,[25] *P. Knochel* and co-workers developed an iodine-magnesium exchange using reagents such as

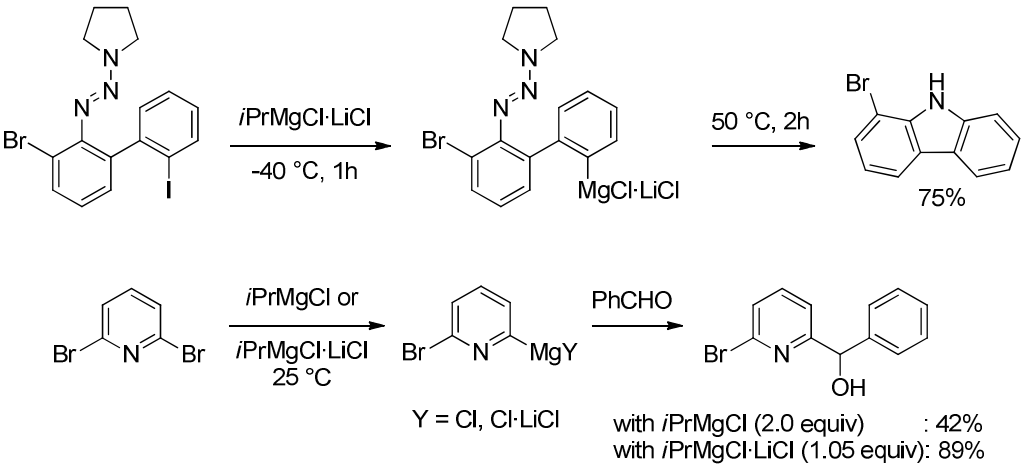
[19] A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665.
[20] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[21] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.
[22] G. Wittig, U. Pockels, H. Dröge, *Chem. Ber.* **1938**, *71*, 1903.
[23] a) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106; b) R. G. Jones, H. Gilman, *Org. Reactions* **1951**, *6*, 339.
[24] P. Pierrat, P. Gros, Y. Fort, *Synlett* **2004**, 2319.
[25] a) J. Villiéras, *Bull. Soc. Chim. Fr.* **1967**, *5*, 1520; b) J. Villiéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Soc. Chim. Fr.* **1986**, *24*, 470.

*i*PrMgBr or PhMgCl.[26] The method allows the formation of various functionalized aromatic *Grignard* reagents under milder conditions (temperature of -40 to -25 °C) than it would be expected with the corresponding lithium reagents (Scheme 9).[26]



Scheme 9. Preparation of functionalized *Grignard* reagents *via* iodine-magnesium exchange and their reactivity towards electrophiles.

A further improvement of the method was the formation of the LiCl-complexed base *i*PrMgCl·LiCl, so-called Turbo-*Grignard*, resulting from the addition of a stoichiometric amount of LiCl to the exchange reagent *i*PrMgCl. The use of *i*PrMgCl·LiCl greatly increases the scope of the halogen-magnesium exchange reaction, and permits the smooth conversion of aromatic and heteroaromatic bromides into their corresponding magnesium reagents, which are more reactive in the reaction with electrophiles than in the absence of LiCl salts (Scheme 10).[27]

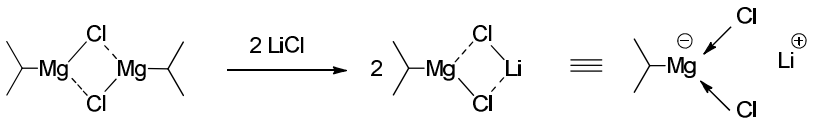


Scheme 10. Preparation of functionalized *Grignard* reagents *via* bromine-magnesium exchange and further reactions.

[26] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; b) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 1610.

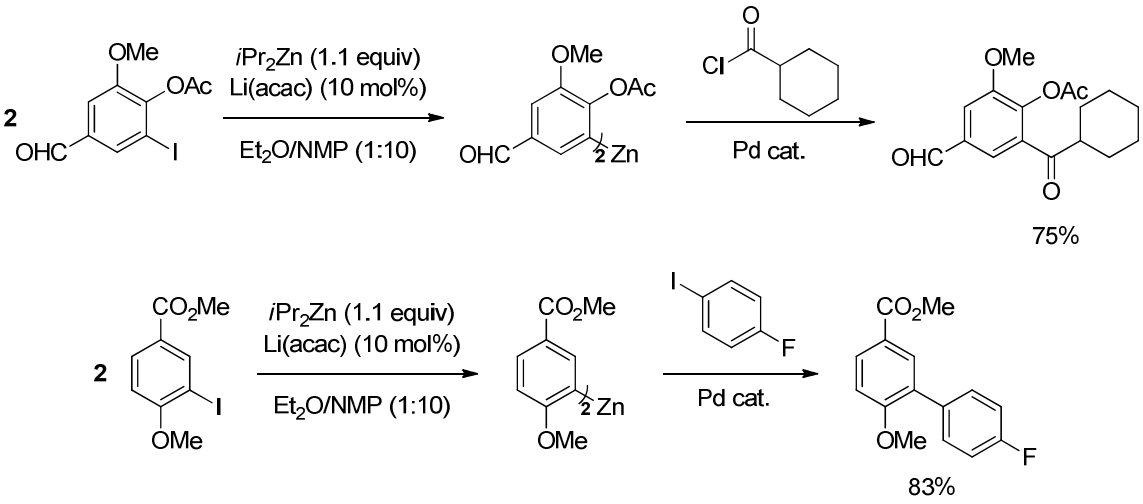
[27] a) F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, 2288; b) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; c) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543, d) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159; e) H. Ren, P. Knochel, *Chem. Commun.* **2006**, 726.

The presence of LiCl salts clearly enhances the solubility and reactivity of the *Grignard* reagent prepared using the Turbo-*Grignard*, as the disaggregation of the magnesium reagent is proposed to form a magnesiate-complex (Scheme 11).[27]



Scheme 11. From magnesium reagent to magnesiate-complex in the presence of LiCl salts.

Zinc reagents have also found some applications in the exchange reaction. As a matter of fact, dialkylzinc species such as *i*Pr_2Zn or Et_2Zn were employed to perform iodine-zinc exchange.[28] The rate of the exchange reaction is improved by the use of catalytic amounts of CuI[29] or Li(acac)[30] (acac = acetylacetonate) salts. Thus, a range of aryl or heteroaryl iodides were successfully converted to the corresponding diarylzinc species and reacted with a wide range of electrophiles. Even sensitive aldehyde groups were tolerated, due to the mild reaction conditions used (Scheme 12).[30]



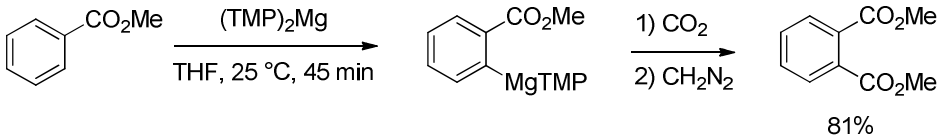
Scheme 12. Preparation and reaction of polyfunctional diaryl zinc reagents with electrophiles in the presence of palladium catalyst.

3) Metalation reactions using amide bases

A clear disadvantage to the exchange methods mentioned above is the necessity for bromine or iodine precursors. A practical alternative is the direct deprotonation using amide bases. Beyond the non-nucleophilic, sterically hindered lithium bases, the more functionalities-

[28] a) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron Lett.* **1966**, *28*, 3353; b) J. Furukawa, N. Kawabata, *Adv. Organomet. Chem.* **1974**, *12*, 83; c)M. J. Rozema, A. Sidduri, P. Knochel, *J. Org. Chem.* **1992**, *57*, 1956.
[29] M. J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 3115.
[30] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.

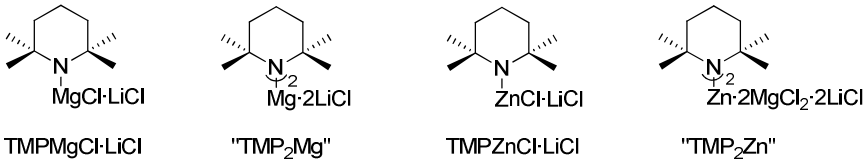
friendly magnesium amides of empirical formula R_2NMgX were first introduced by *L. Meunier* in 1903.[31] Then, in the middle of the 20th century, *C. R. Hauser* and co-workers established bases of type R_2NMgBr, the so-called *Hauser* bases, initially used for the self-condensation of esters.[32] A huge advance in the application of amide bases was achieved by *P. E. Eaton et al.*, who first used the sterically hindered magnesium bis(2,2,6,6-tetramethylpiperamide), $(TMP)_2Mg$, as well as TMPMgBr, as selective metalating reagents (Scheme 13).[33]



Scheme 13. Selective *ortho*-magnesiation of methyl benzoate using *Hauser* base.

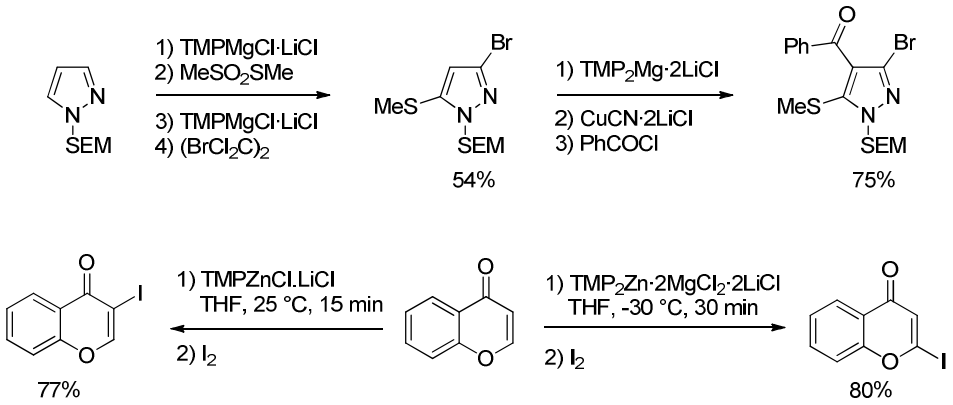
J. Mulzer and co-workers reported a similar magnesium base, TMPMgCl, that found application in the *ortho*-magnesiation of pyridinecarboxamides and carbamates.[34] Even though the magnesium amide bases tolerate many more functionalities than their lithium analogues,[35] their low solubility as a result of aggregation (implying the use of a large excess of the base for a successful metalation) restrict their applications. Inspired by the enhanced reactivity of the Turbo-*Grignard* reagents, *P. Knochel* and co-workers recently developed highly chemoselective TMP mixed metal/Li amides such as TMPMgCl·LiCl[36,37], TMPZnCl·LiCl[38], $TMP_2Mg{\cdot}2LiCl$[39] and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[40] (Scheme 14).

[31] L. Meunier, *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758.
[32] a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295; b) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350.
[33] P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016.
[34] W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.
[35] a) C. L. Kissel, B. Rickborn, *J. Org. Chem.* **1972**, *37*, 2060; b) M. W. Rathke, R. Kow, *J. Am. Chem. Soc.* **1972**, *94*, 6854.
[36] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
[37] P. García-Álvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.
[38] a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; b) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406; c) M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615.
[39] a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681; b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503; c) C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel, *Org. Synth.* **2009**, *86*, 374.
[40] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705.



Scheme 14. TMP-derived, mixed metal/Li amide bases.

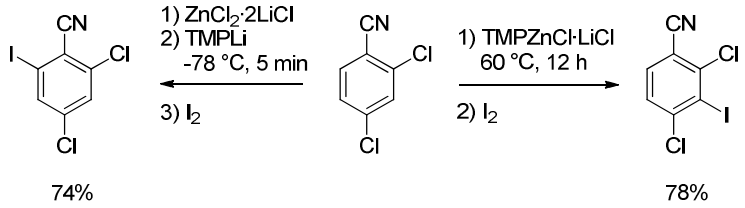
The excellent kinetic basicity, room temperature stability, as well as high solubility of the TMP bases, the so-called Turbo-*Hauser* bases, allow the selective metalation of an unprecedented broad range of sensitive aromatic and heteroaromatic compounds under mild conditions.[41] The metal amide source plays a key role, offering the possibility of switching from one TMP base to the other one, thus adapting to the sensitivity of the electrophile or its C-H acidic character (Scheme 15).[42]



Scheme 15. Selected examples of selective heterocycle metalations using the adapted TMP base and further reactions.

More recently, *P. Knochel* and co-workers reported an *in situ* trapping method of TMPLi with a metal salt such as $MgCl_2$, $ZnCl_2$, or CuCN in the presence of sensitive aromatic or heteroaromatic substrates.[43] The method is a distinguished alternative for providing previously unaccessible organometallic reagents, as well as achieving different regioselectivities in comparison to standard metalations using TMPZnCl·LiCl or TMPMgCl·LiCl (Scheme 16).

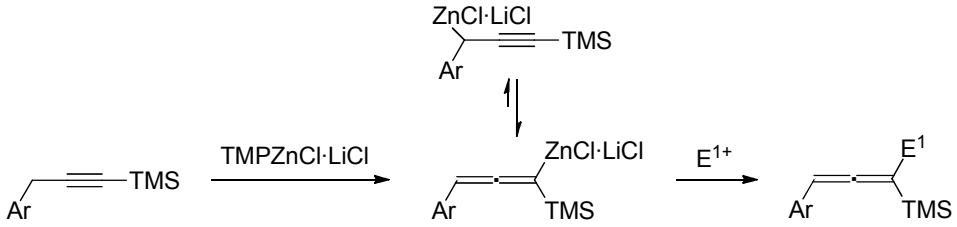
[41] For a review, see: B. A. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed*. **2011**, *50*, 9794.
[42] a) C. Despotopoulou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326; b) L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc*. **2012**, *134*, 13584.
[43] A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed*. **2014**, *53*, 7928.



Scheme 16. Selected examples of the regioselectivity switch in the metalation of polyfunctional aromatics using TMPZnCl·LiCl or TMPLi/$ZnCl_2$.

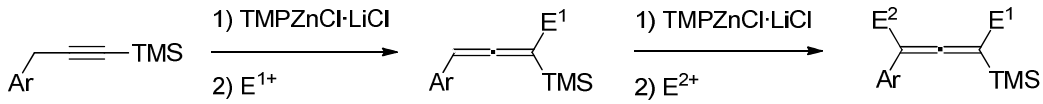
III. Objectives

The aim of the first project was to expand the use of TMPZnCl·LiCl to the metalation of benzylic alkynes. The direct formation of zincated allenes would be possible, as the presence of a TMS group may stabilize the zinc species in the allene form. Further quenching with an electrophile E^{1+} will produce trisubstituted allenes (Scheme 17).



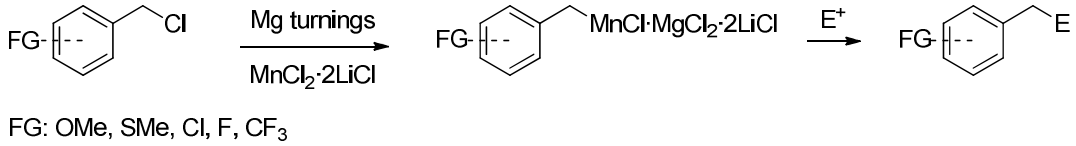
Scheme 17. Lateral metalation of benzylic alkynes with TMPZnCl·LiCl and subsequent reaction with an electrophile.

Furthermore, the method could allow the formation of tetrasubstituted allenes in a one-pot sequence based on successive metalations using TMPZnCl·LiCl followed by reactions with electrophiles (Scheme 18).



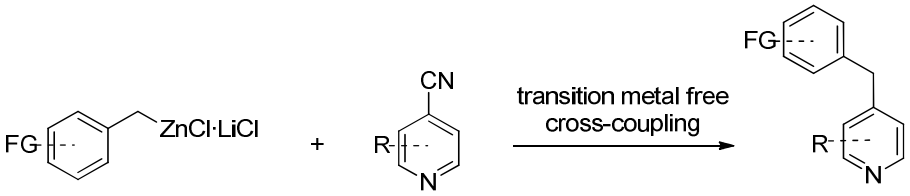
Scheme 18. Successive metalations with TMPZnCl·LiCl and further reactions with electrophiles for the preparation of tetrasubstituted allenes.

In another project, the preparation of benzylic manganese organometallics *via* magnesium insertion in the presence of $MnCl_2$·2LiCl will be investigated. The *in situ* formed *Grignard* reagents will be directly transmetallated to the corresponding organomanganese reagents. Thus, the method should display a higher group tolerance than the organomagnesium analogs, but still a high reactivity in Pd-catalyzed cross-coupling reactions or in reaction with electrophiles (Scheme 19).



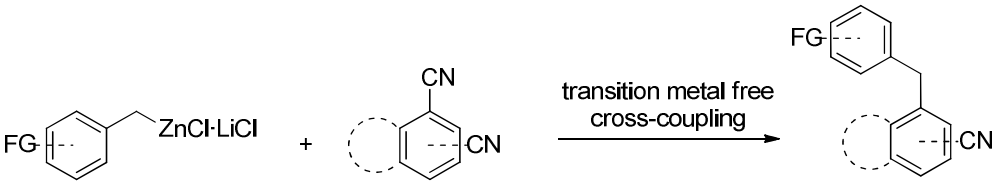
Scheme 19. Preparation of functionalized benzylic manganese reagents from benzylic chlorides *via* magnesium insertion in the presence of $MnCl_2 \cdot 2LiCl$.

Since benzylic zinc reagents are readily prepared and tolerate a range of functionalities, we anticipated that the enhanced ionic character of the benzylic carbon-zinc bond (compared to alkyl or aryl carbon-zinc bonds) may allow transition metal free cross-coupling reactions involving 4-cyanopyridines (Scheme 20).



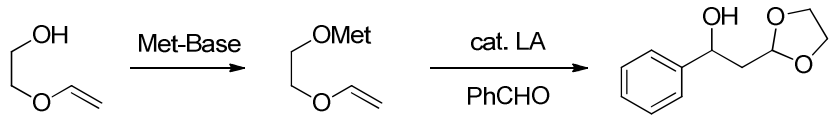
Scheme 20. Transition metal free cross-coupling reactions between benzylic zinc reagents and substituted 4-cyanopyridines.

Moreover, it may be able to promote the benzylation of electron-poor poly-cyano aromatics using the same reaction conditions (Scheme 21).



Scheme 21. Transition metal free cross-coupling reactions between benzylic zinc reagents and poly-cyanoaromatics.

Finally, the preparation of β-hydroxy-1,3-dioxolane derivatives will be investigated. The deprotonation of ethylene glycol vinyl ether to the corresponding alkoxide and its reaction with aldehydes in the presence of catalytic amounts of a Lewis acid is envisioned as a pathway for the formation of protected aldol products (Scheme 22).



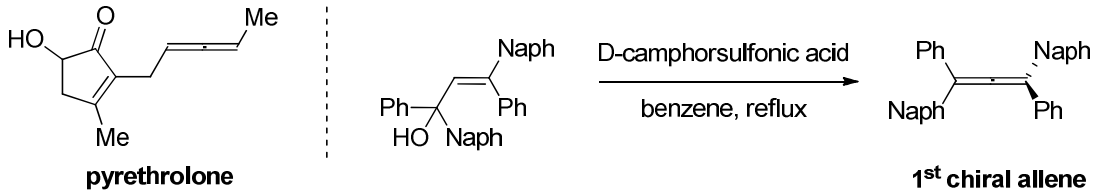
Scheme 22. Strategy for the Lewis acid catalyzed preparation of a broad range of protected aldol products.

RESULTS & DISCUSSION

I. Preparation of Polysubstituted Allenes *via* Regioselective Lateral Metalation of Benzylic Trimethylsilyl-Alkynes using TMPZnCl.LiCl

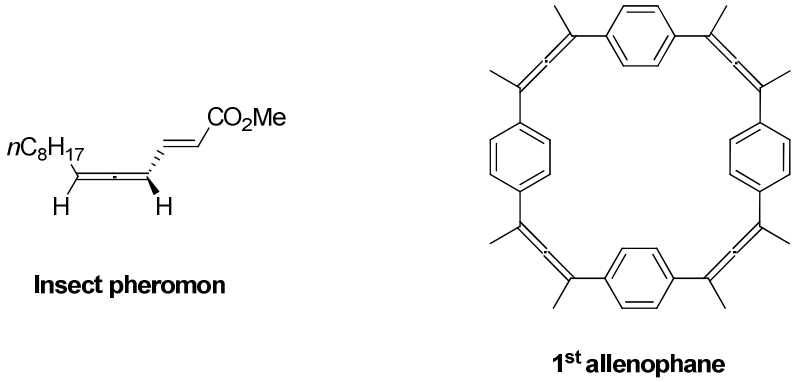
1) Introduction

In 1887, *B. S. Burton* and *H. von Pechmann* reported the hypothetical synthesis of the first allene, glutinic acid.[44] It was one century later, in 1954, when *E. R. H. Jones* and co-workers confirmed its allenic structure.[45] Moreover, the first isolation and characterization of a natural allene, pyrethrolone, were performed by *H. Staudinger* and *L. Ruzicka*,[46] followed by the report of the synthesis of the first chiral allene by *P. Maitland* and *W. H. Mills*[47] (Scheme 23).



Scheme 23. The first isolated allene pyrethrolone and the first synthesis of a chiral allene.

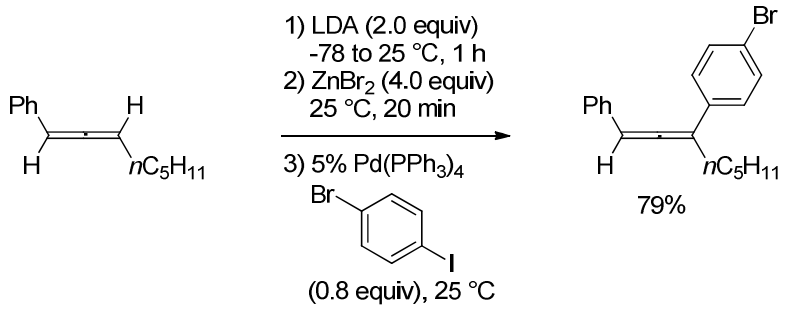
For a long time, allenes were mostly regarded as chemical curiosities,[48] but the interest on their synthesis and application increased considerably the last 15 years. As a matter of fact, allenic structures are found in a number of useful organic molecules such as natural products[49] or materials[50] (Scheme 24).



Scheme 24. Selected examples of natural product (insect pheromon) and material (allenophane) containing an allenic structure.

[44] B. S. Burton, H. von Pechmann, *Chem. Ber.* **1887**, 145.
[45] E. R. H. Jones, G. H. Mansfield, M. C. Whiting, *J. Chem. Soc.* **1954**, 3208.
[46] H. Staudinger, L. Ruzicka, *Helv. Chim. Acta* **1924**, *7*, 177.
[47] a) P. Maitland, W. H. Mills, *Nature* **1935**, 994; b) P. Maitland, W. H. Mills, *J. Chem. Soc.* **1936**, 987.
[48] For a book, see: H. F. Schuster, G. M. Coppola in *Allenes in Organic Synthesis*, Wiley-Interscience, 1st edition, **1984**.
[49] A. Hoffmann-Röder, N. Krause, *Angew. Chem. Int. Ed.* **2004**, *43*, 1196.
[50] a) S. Thorand, F. Vögtle, N. Krause, *Angew. Chem. Int. Ed.* **1999**, *38*, 3721; b) P. Rivera-Fuentes, F. Diederich, *Angew. Chem. Int. Ed.* **2012**, *51*, 2818; c) M. D. Tzirakis, N. Marion, W. B. Schweizer, F. Diederich, *Chem. Commun.* **2013**, *49*, 7605.

Allenes are also important intermediates[51] for carbo- and heterocycle synthesis,[52] as well as natural product synthesis.[49,53] Therefore, the preparation of substituted allenes is a valuable synthetic target[54] and numerous transition-metal catalyzed functionalizations of the allenic moiety have been reported.[55] For instance, *S. Ma* and co-workers reported the preparation of trisubstituted allenes using a Pd-catalyzed arylation of zincated allenes obtained by LDA-deprotonation (LDA= lithium diisopropylamide) of the corresponding disubstituted allenes (Scheme 25).[56] The reaction is highly regioselective (99:1 ratio for the desired allene).



Scheme 25. Selected example of the preparation of a trisubstituted allene by *S. Ma* and co-workers.

Although a broad range of functionalized aryl iodides are compatible with the reaction conditions, the use of an excess of starting material and only aryl iodides (more expensive as coupling partners than aryl bromides and chlorides), as well as a large excess of base and zinc bromide, are clear drawbacks of the method.

[51] a) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067; b) A. S. K. Hashmi in *Science of Synthesis*, Vol. 32 (Ed. J. Mulzer), Thieme, Stuttgart, **2008**, pp 13-52; c) J. Bejjani, C. Botuha, F. Chemla, F. Ferreira, S. Magnus, A. Pérez-Luna, *Organometallics* **2012**, *31*, 4876; d) Q. Xiao, B. Wang, L. Tian, Y. Yang, J. Ma, Y. Zhang, S. Chen, J. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 9305; e) D. R. Williams, A. A. Shah, S. Mazumder, M. Baik, *Chem. Sci.* **2013**, *4*, 238; f) P. Smirnov, J. Mathew, A. Nijs, E. Katan, M. Karni, C. Bolm, Y. Apeloig, I. Marek, *Angew. Chem. Int. Ed.* **2013**, *52*, 13717; g) R. K. Neff, D. E. Frantz, *ACS Catal.* **2014**, *4*, 519.

[52] a) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3590; b) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994; c) H. Clavier, K. Le Jeune, I. de Riggi, A. Tenaglia, G. Buono, *Org. Lett.* **2011**, *13*, 308; d) B. Chen, S. Ma, *Org Lett.* **2013**, *15*, 3884; e) V. R. Sabbasani, D. Lee, Org. *Lett.* **2013**, *15*, 3954; f) Z. He, D. Dobrovolsky, P. Trinchera, A. K. Yudin, *Org. Lett.* **2013**, *15*, 334; g) C. S. Adams, C. D. Weatherly, E. G. Burke, J. M. Schomaker, *Chem. Soc. Rev.* **2014**, *43*, 3136.

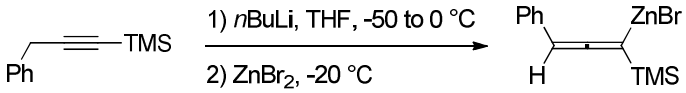
[53] For a review about the use of allenes in the synthesis of natural products, see: a) S. Yu, S. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 3074. For a review about the use of allenes in the synthesis of strained three-membered heterocycles, see: b) C. S. Adams, C. D. Weatherly, E. G. Burke, J. M. Schomaker, *Chem. Soc. Rev.* **2014**, *43*, 3136.

[54] a) B. K. Guitchin, S. Bienz, *Organometallics* **2004**, *23*, 4944; b) B. Bolte, Y. Odabachian, F. Gagosz, *J. Am. Chem. Soc.* **2010**, *132*, 7294; c) S. Yu, S. Ma, *Chem. Commun.* **2011**, *47*, 5384; d) M. A. Schade, S. Yamada, P. Knochel, *Chem Eur. J.* **2011**, *17*, 4232; e) D. A. Mundal, K. E. Lutz, R. J. Thomson, *J. Am. Chem. Soc.* **2012**, *134*, 5782; f) B. Wan, S. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 441; g) Y. Wang, W. Zhang, S. Ma, *J. Am. Chem. Soc.* **2013**, *135*, 11517.

[55] a) L. Schwarz, J. Choi, T. M. Frost, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; b) M. Wu, D. Kumar Rayabarapu, C. Cheng, *J. Am. Chem. Soc.* **2003**, *125*, 12426; c) R. Riveiros, D. Rodriguez, J. P. Sestelo, L. A. Sarandeses, *Org. Lett.* **2006**, *8*, 1403; d) Y. Yu, W. Yang, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2013**, 52, 7586; e) W. Yang, Y. Yu, M. M. Hansmann, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2013**, 52, 1329; f) N. W. Mszar, F. Haeffner, A. H. Hoveyda, *J. Am. Chem. Soc.* **2014**, *136*, 3362; g) X. Shu, M. Zhang, Y. He, H. Frei, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 5844; h) J. Le Bras, J. Muzart, *Chem. Soc. Rev.* **2014**, *43*, 3003; i) S. Kitagaki, F. Inagaki, C. Mukai, *Chem. Soc. Rev.* **2014**, *43*, 2956; j) W. Yang, A. S. K. Hashmi, *Chem. Soc. Rev.*, **2014**, *43*, 2941.

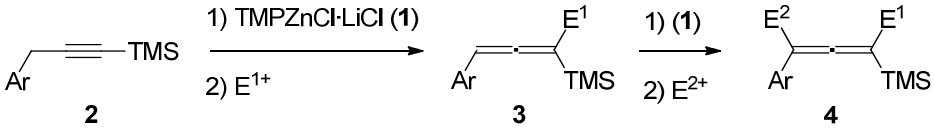
[56] a) S. Ma, Q. He, X. Zhang, *J. Org. Chem.* **2005**, *70*, 3336; b) J. Zhao, Y. Liu, S. Ma, *Org. Lett.* **2008**, *10*, 1521.

Moreover, allenylzinc reagents can also be formed by metalation of benzylic alkynes. Indeed, the lithiation of trimethyl(3-phenylprop-1-yn-1-yl)silane using *n*BuLi, followed by transmetallation with $ZnBr_2$, afforded the corresponding allenyl zinc, which was recently used by *J. Cossy* and co-workers for addition to glyoxylates (Scheme 26).[57]



Scheme 26. Formation of an allenylzinc after metalation of a benzylic alkyne.

As shown in the introduction, TMPZnCl·LiCl (**1**) is an excellent base for the selective metalation of various substrates.[38,41] Thus, the high kinetic basicity of **1** allows the efficient metalation of a range of organic molecules including nitriles, esters and various functionalized unsaturated molecules.[38b,42b,58] Based on the work presented above (Scheme 17 and 18), we have envisioned that lateral metalations[59] of benzylic alkynes of type **2** with TMPZnCl·LiCl (**1**) will produce intermediate allenylzinc reagents, which after quenching with an electrophile E^{1+} will afford trisubstituted allenes of type **3** (Scheme 27).[56]



Scheme 27. Lateral metalation of benzylic alkynes of type **2** with TMPZnCl·LiCl.

A subsequent metalation with TMPZnCl·LiCl (**1**) will give a new zincated intermediate, which after trapping with a second electrophile E^{2+}, will furnish tetrasubstituted allenes (**4**). The reaction sequence could be applied for palladium-[60] or copper-[61] catalyzed reactions of 1-trimethylsilyl-3-aryl-1-propynes (**2**) with electrophiles.

[57] a) J.-F. Poisson, J. F. Normant, *J. Org. Chem.* **2000**, *65*, 6553; b) T. Hameury, J. Guillemont, L. Van Hijfte, V. Bellosta, J. Cossy, *Org. Lett.* **2009**, *11*, 2397.

[58] a) F. Crestey, P. Knochel, *Synthesis* **2010**, 7, 1097; b) G. Monzon, P. Knochel, *Synlett* **2010**, 304; c) T. Bresser, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1914; d) S. Duez, S. Bernhardt, J. Heppekausen, F. F. Fleming, P. Knochel, *Org. Lett.* **2011**, 13, 1690; e) D. Haas, M. Mosrin, P. Knochel, *Org. Lett.* **2013**, *15*, 6162; f) A. Unsinn, M. J. Ford, P. Knochel, *Org. Lett.* **2013**, *15*, 1128.

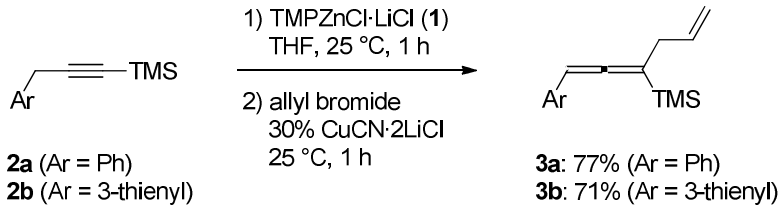
[59] a) S. Duez, A. K. Steib, S. M. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 7686; b) S. Duez, A. K. Steib, P. Knochel, *Org. Lett.* **2012**, *14*, 1951.

[60] a) E. Negishi, M. Kobayashi, *J. Org. Chem.* **1980**, *45*, 5223; b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.

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

2) Preparation of trisubstituted allenes

In preliminary experiments, we have treated the TMS-protected alkyne (**2a**) with TMPZnCl·LiCl (**1**; 1.2 equiv) in THF at 25 °C for 1 h. Adding CuCN·2LiCl (30 mol%) and allyl bromide lead to the allylated allene **3a** in 77% yield, indicating that TMPZnCl·LiCl (**1**) has achieved a smooth deprotonation of the benzylic hydrogen.[62] This result was confirmed by extending the metalation to the heterobenzylic derivative (**2b**), which after allylation, similarly produced the corresponding allene (**3b**) in 71% yield (Scheme 28).



Scheme 28. *In situ* trapping of zinc reagents with CuCN·2LiCl and subsequent allylation reactions.

With these results in hand, we have examined the direct Pd-catalyzed arylation of the TMS-protected alkynes of type **2**. Thus, the reaction of the alkynes (**2a-c**) with TMPZnCl·LiCl (**1**; 1.2 equiv) in THF at 25 °C for 1 h, followed by the addition of an aryl or heteroaryl bromide or iodide (**5a-j**) provides the arylated allenes **3a-p** in 52-92% yield (Table 1). Concerning the palladium catalyst, we have found after an extensive screening, that three catalytic systems gave the best results: (a) 2% $Pd(OAc)_2$/2% DPE-Phos;[63] (b) 2% $Pd(OAc)_2$/4% S-Phos;[64] (c) 2% PEPPSI-*i*Pr.[65] A variety of donor- and acceptor-substituted aryl halides afforded the trisubstituted allenes (**3c-k**) in 57-92% yield (entries 1-9). The thienyl-substituted alkyne (**2b**) behaves similarly to **2a** and produced the allenes (**3l-m**) in 67-76% yield (entries 10-11). Remarkably, an ester-substituent is tolerated under the reaction conditions, as the alkyne (**2c**) leads to the corresponding trisubstituted allenes (**3n-p**) in 52-74% yield (entries 12-14). In all cases, the arylation is regioselective (only allenic derivatives are obtained and no arylated propargylic compounds could be detected).

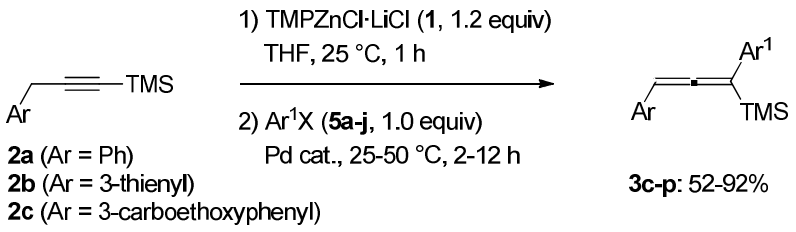
[62] The progress of the zincation of **2a** was difficult to monitor since the iodolysis of the allenylzinc intermediate gave unstable allenic iodides.

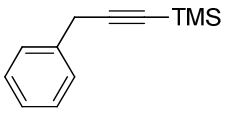
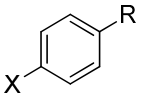
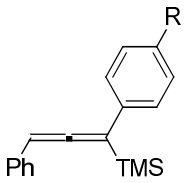
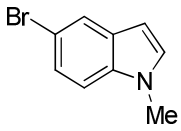
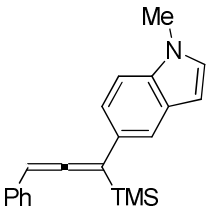
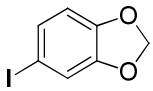
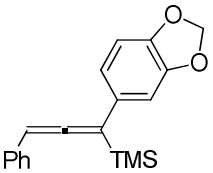
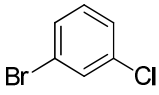
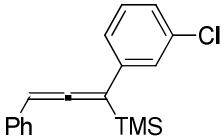
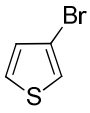
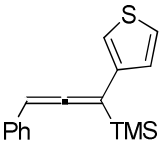
[63] M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, *Organometallics* **1995**, *14*, 3081.

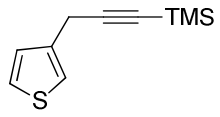
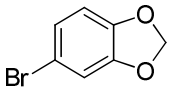
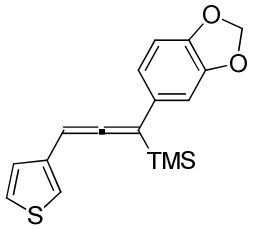
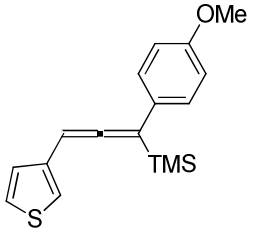
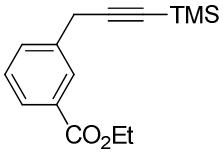
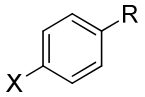
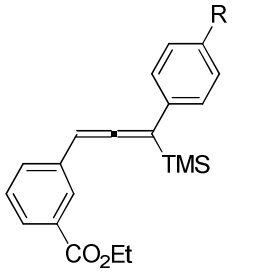
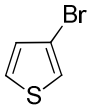
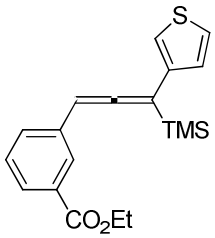
[64] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4865.

[65] a) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749; b) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743; c) S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, *J. Org. Chem.* **2008**, *73*, 7380; d) N. D. Hunter, N. Hadei, V. Blagojevic, P. Patschinski, G. T. Achonduh, S. Avola, D. K. Bohme, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 7845.

Table 1. Zincation with TMPZnCl·LiCl followed by a *Negishi* cross-coupling reaction with various electrophiles.



Entry	Starting material	Electrophile (Ar^1X)	Conditions (°C, h)[a]	Product, yield (%)[b]
				
1	**2a**	**5a** R = H, X = I	25, 4	**3c**: 68[c]
2		**5b** R = OMe, X = I	25, 5	**3d**: 76[c]
3		**5c** R = NMe_2, X = Br	50, 4	**3e**: 66[d]
4		**5d** R = OPiv, X = Br	50, 6	**3f**: 57[e]
5		**5e** R = SMe, X = Br	50, 6	**3g**: 75[e]
6				
		5f	50, 3	**3h**: 64[e]
7				
		5g	25, 4	**3i**: 94[e]
8				
		5h	50, 4	**3j**: 60[e]
9				
		5i	25, 2	**3k**: 73[f]

				
10	**2b**	**5j**	50, 12	**3l**: 65[e]
11				
		5a	50, 2	**3m**: 78[e]
12				
	2c	**5a** R = H, X = I	25, 2	**3n**: 52[c]
13		**5b** R = OMe, X = I	25, 2	**3o**: 59[c]
14				
		5i	25, 3	**3p**: 74[f]

[a] Reaction time at 25 or 50 °C for full conversion. [b] Isolated yield of analytically pure product. [c] Catalyst system: 2% $Pd(OAc)_2$/4% S-Phos. [d] Catalyst system: 4% $Pd(OAc)_2$/4% DPE-Phos. [e] Catalyst system: 2% $Pd(OAc)_2$/2% DPE-Phos. [f] Catalyst system: 2% PEPPSI-*i*Pr.

The structure of compound **3c** has been confirmed by X-ray diffraction analysis (Figure 1),[66] confirming the regioselectivity of the palladium-catalyzed arylation.

[66] X-ray crystal structures described in the entire thesis were performed by Prof. Dr. Konstantin Karaghiosoff, for the crystal structures of this chapter see Supporting Information of: P. Quinio, C. François, A. Escribano Cuesta, A. K. Steib, F. Achrainer, H. Zipse, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2015**, *17*, 1010.

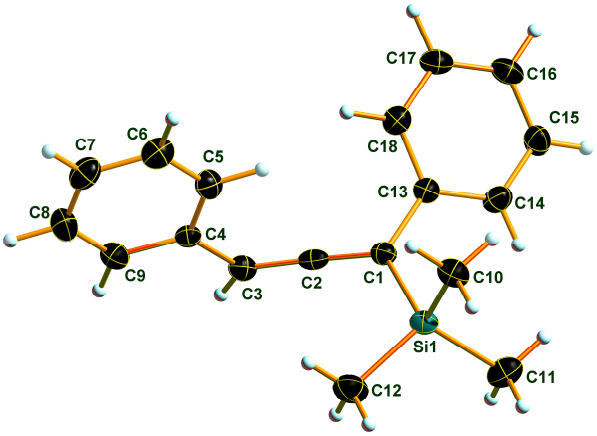
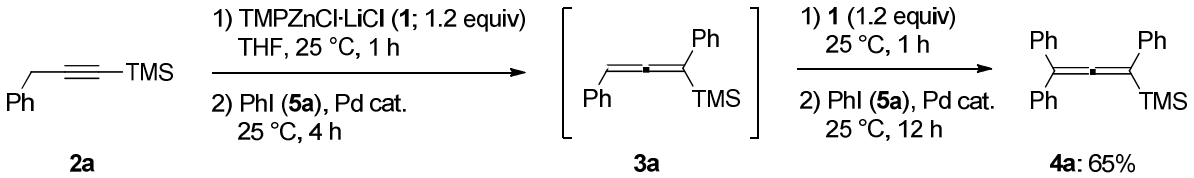


Figure 1. Molecular structure of compound **3c** in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50% probability level.

3) Preparation of tetrasubstituted allenes

We further developed a one-pot procedure allowing a direct conversion of alkyne (**2a**) to tetrasubstituted allenes of type **4** (Scheme 29 and Table 2). Thus, alkyne **2a** was treated as previously described with TMPZnCl·LiCl (**1**, 1.2 equiv) and iodobenzene (**5a**, 1.0 equiv) leading to **3c**, which was not isolated, but directly reacted with TMPZnCl·LiCl (**1**, 1.2 equiv) and iodobenzene (**5a**, 1.0 equiv), affording, in a one-pot process, the tetrasubstituted allene **4a** in 65% isolated yield.

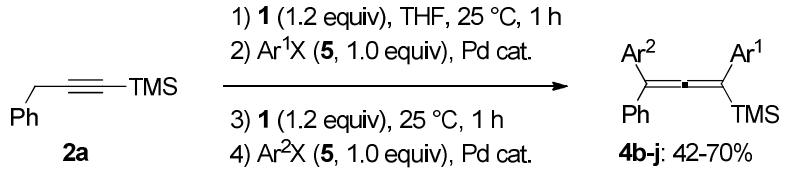


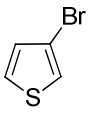
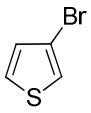
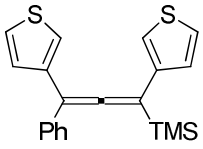
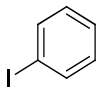
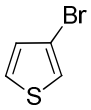
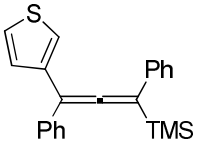
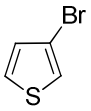
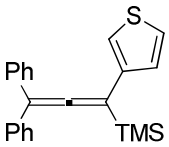
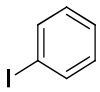
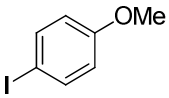
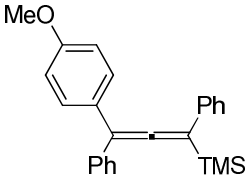
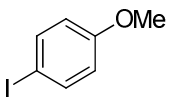
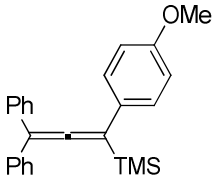
Scheme 29. Successive zincation with TMPZnCl·LiCl and subsequent *Negishi* cross-coupling reactions.

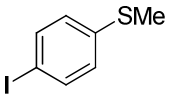
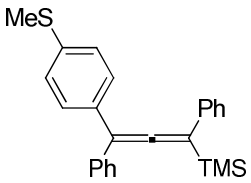
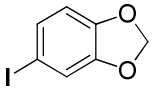
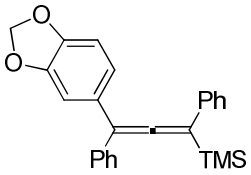
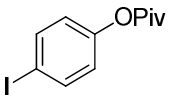
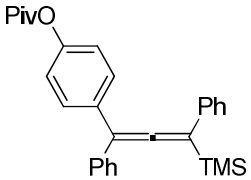
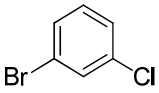
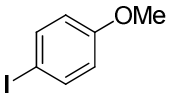
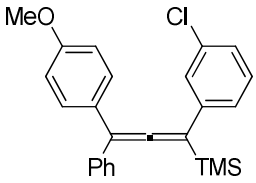
Replacing the aryl iodide (**5a**) by 3-bromothiophene (**5i**) similarly produced the tetrasubstituted allene **4b** in 51% yield (Table 2, entry 1). The use of two different aryl or heteroaryl halides was also possible. Thus, treatment of the alkyne (**2a**) with TMPZnCl·LiCl (**1**), a Pd-catalyst and iodobenzene (**5a**) for 4 h at 25 °C lead to the intermediate allene **3c**, which was directly metalated with TMPZnCl·LiCl (**1**), Pd-catalyst and 3-bromothiophene (**5i**) affording the tetrasubstituted allene **4c** in 63% overall yield (entry 2). Inverting the addition order of the two electrophiles E^{1+} and E^{2+} using first the heterocyclic bromide (**5i**) and then iodobenzene (**5a**) is also possible and the regioisomeric tetrasubstituted allene **4d** was obtained in 47% overall yield (entry 3). The method was also successfully used for the

preparation of the tetrasubstituted allenes (**4e-i**) in 64-70% overall yield (entries 4-8). Remarkably, the tetrasubstituted allene **4j**, bearing four different substituents, was synthesized in 42% overall yield (entry 9).

Table 2. One-pot tetra-functionalization of allenes *via* successive zincation using TMPZnCl·LiCl and *Negishi* cross-coupling reactions with various electrophiles.



Entry	1st electrophile (Ar^1X)[a] (°C, h)[b]	2nd electrophile (Ar^2X) (°C, h)[a]	Product, yield (%)[b]
1	 **5i** (25, 2)	 **5i** (25, 12)	 **4b**: 51[c]
2	 **5a** (25, 4)	 **5i** (25, 12)	 **4c**: 63[c]
3	 **5i** (25, 2)	 **5a** (25, 12)	 **4d**: 47[c]
4	 **5a** (25, 4)	 **5c** (25, 12)	 **4e**: 68[c]
5	 **5c** (25, 5)	 **5a** (25, 12)	 **4f**: 67[c]

6	 **5a** (50, 2)	 **5e** (50, 2)	 **4g**: 64[d]
7	 **5a** (50, 2)	 **5g** (50, 3)	 **4h**: 70[d]
8	 **5a** (50, 2)	 **5d** (50, 12)	 **4i**: 65[d]
9	 **5h** (50, 4)	 **5c** (50, 12)	 **4j**: 42[d]

[a] Reaction time at 25 or 50 °C for full conversion. [b] Isolated yield of analytically pure product. [c] Catalyst system: 2% $Pd(OAc)_2$/4% S-Phos. [d] Catalyst system: 2% $Pd(OAc)_2$/2% DPE-Phos.

The regioselectivity observed in compounds **4c** and **4f** has been confirmed by X-ray diffraction analysis (Figure 2).[66]

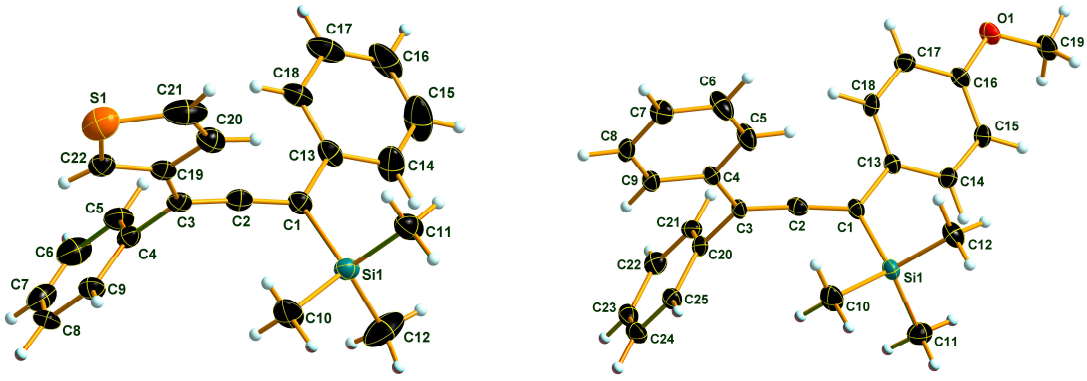
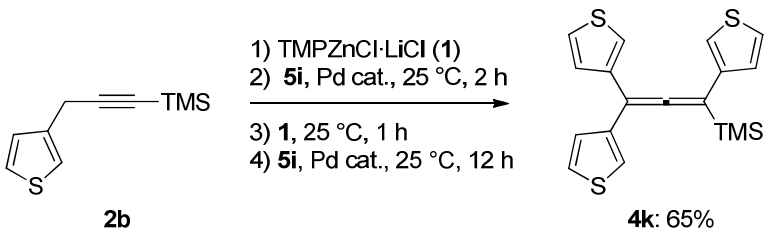


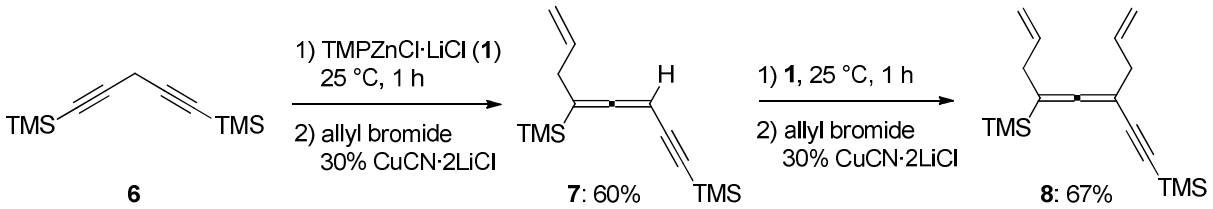
Figure 2. Molecular structure of compound **4c** (left) and **4f** (right) in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50% probability level.

The method allows as well the one-pot synthesis of the *tris*-(3-thienyl) allene **4k** in 65% yield (Scheme 30).



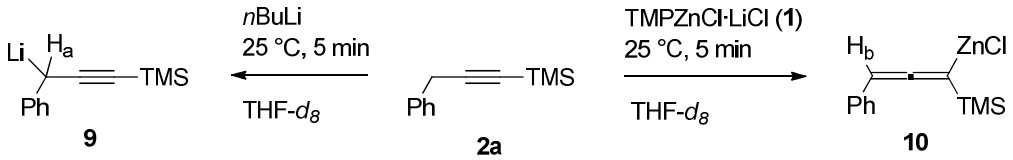
Scheme 30. Preparation of a tri-(3-thienyl)-allene (**4k**).

We have further expanded the scope of these new metalations of alkynes and allenes and found that the related diyne **6** was similarly zincated with TMPZnCl·LiCl (**1**) within 1 h at 25 °C (Scheme 31).[67] After a copper-catalyzed allylation with allyl bromide, the trisubstituted allene **7** was obtained in 60% yield.[68] The unsaturated alkynylallene **7** was cleanly allylated affording the highly unsaturated product **8** in 67% yield.



Scheme 31. Lateral metalation of alkynes (**6**) and (**7**) with TMPZnCl·LiCl and further copper-catalyzed allylation reactions.

In order to establish the nature of the zincated intermediates (allenic or propargylic) occurring during the metalation of **2a**, we performed NMR studies.[69] The reaction of **2a** with *n*BuLi produces only the propargylic lithium species **9**, as seen by the chemical shift of the propargylic proton H_a at 3.33 ppm in the ^{1}H NMR spectra (Scheme 32).



Scheme 32. NMR experiments showed direct formation of allenylzinc reagent.

The zincation of **2a** using TMPZnCl·LiCl (**1**) produces an allenylzinc species **10**, as seen by the allenic ^{13}C signal at 202.8 ppm. No propargyl isomer was observed and the allenic proton

[67] The introduction of a trimethylsilyl acetylene group has a remarkable effect on the acidity of the benzylic hydrogens. For instance, the pKa value in DMSO of diphenylmethane (pKa = +32.3, F. G. Bordwell, W. S. Matthews, N. R. Vanier, *J. Am. Chem. Soc.* **1975**, *97*, 442) is lowered by around 10 for **2a** (pKa = +21.8); calculated by Florian Achrainer using the method published in A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928.

[68] The lateral zincation of 1-butyl-2-trimethylsilylacetylene led to several products showing the limitation of such a metalation.

[69] The most relevant NMR spectra are shown in the Experimental Section.

(H_b) has a chemical shift of 4.99 ppm in the ^{1}H NMR spectra ($CDCl_3$, 400 MHz).[69] From these studies, it becomes clear that the propargyl isomer (**9**) is the most stable organometallic species in the case of the lithium cation, whereas the allenylzinc structure (**10**) is the most stable in case of the zinc cation.[70] Theoretical calculations at MP2 level of theory confirmed a major difference in stability order for the propargyl allenyl isomers of the respective organometallics.[71] An endothermic enthalpy of 1.4 kJ/mol for the two organolithium isomers (**9** and **9a**; Figure 3), in comparison to 7.8 kJ/mol for the zinc species **10** and **10a**.[71]

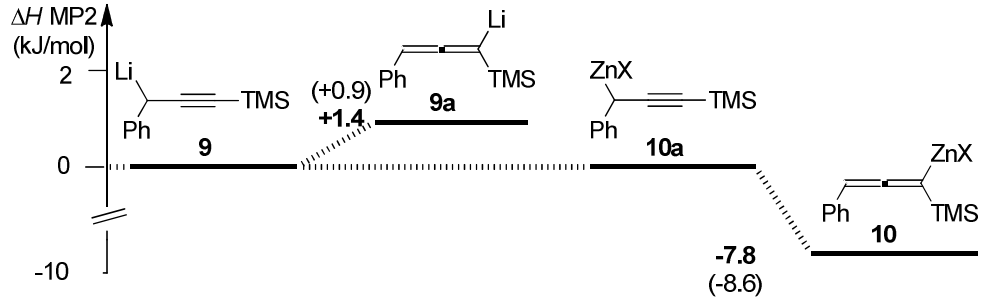


Figure 3. Propargyl allenyl isomerization in THF solution (SMD/B3LYP/6-31G(d)) at MP2(FC)/6-31+G(d,p) level (Li = $Li(THF)_3$, ZnX = $ZnCl(THF)_2$, gas phase values in parenthesis).

In conclusion, we have discovered an efficient and regioselective zincation of various 1-trimethylsilyl-3-aryl-1-propynes using TMPZnCl·LiCl. Subsequent Pd-catalyzed arylation with aromatic bromides or iodides led to a broad range of trisubstituted allenes. Interestingly, we were able to perform a one-pot *bis*-arylation of 1-trimethylsilyl-3-phenyl-1-propyne, accessing with complete regioselectively tetrasubstituted allenes.

[70] a) M. Gaudemar, *Bull. Soc. Chim. Fr.* **1962**, 974.

[71] Theoretical calculations have been performed by Dr. Florian Achrainer and Prof. Dr. Hendrik Zipse, see Supporting Information of: P. Quinio, C. François, A. Escribano Cuesta, A. K. Steib, F. Achrainer, H. Zipse, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2015**, *17*, 1010.

II. New preparation of benzylic manganese chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of $MnCl_2 \cdot 2LiCl$

1) Introduction

The direct insertion of a metal into an organic halide (*Grignard* synthesis) constitutes the most established method for forming organometallic reagents.[11,13,16,72] Since this synthesis requires the use of a metal powder, metal activation is often required for the success of the insertion reaction. *R. D. Rieke* showed in a pioneer work that *in situ* reduction of magnesium chloride with lithium metal produces highly active magnesium, allowing insertions under relatively mild conditions.[13] This methodology has also been applied to other metals such as Ti, Cr, Mn, Fe, Co, Ni, Pd, Pt or Cu.[13c,e] Among the above-noted transition metals, manganese is of high interest, since it is inexpensive[73] and toxicologically benign.[74] Hence, the *in situ* reduction of manganese chloride in the presence of lithium and naphthalene as electron carrier generates highly active manganese (*Rieke* manganese Mn*), used for the preparation of several organomanganese reagents.[75] *G. Cahiez* and co-workers reported the use of 2-phenylpyridine instead of naphthalene as electron carrier, as it was easier to remove during the final work up.[76] Recently, *P. Knochel* and *Z. Peng* found that the use of LiCl allows the efficient insertion of manganese into aryl iodides or bromides (Scheme 33). The advantage of organomanganese reagents is their medium reactivity between organozinc and organomagnesium compounds, allowing the tolerance of more functionalities than the corresponding *Grignard* reagents.[77]

[72] For a review about the preparation and the use of functionalized organometallic reagents, see: T. Klatt, J. Markiewicz, C. Sämann, P. Knochel, *J. Org. Chem.* **2014**, *79*, 4253.

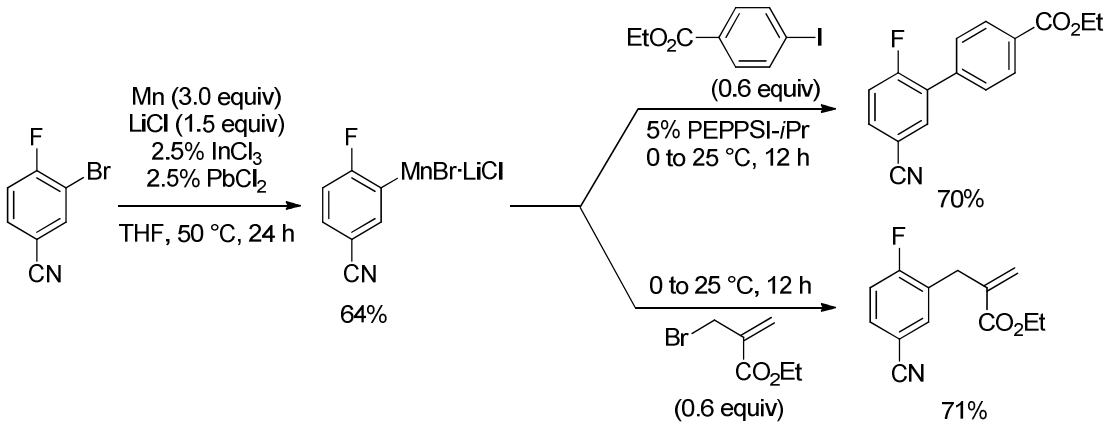
[73] 1 kg Mn chips (99%) 108.40 € in comparison to 167.50 € for 1 kg Mg chips (99.98%), data found on the Sigmaaldrich website, Mai 2015. See: https://www.sigmaaldrich.com/germany.html.

[74] For a book, see: a) G. Cahiez in *Manganese (II) Chloride in Encyclopedia of Reagents for Organic Synthesis*, (Ed. L. Paquette), Wiley, Chichester, **1995**, *5*, 3227. For a review about the chemistry of organomanganese(II) compounds, see: b) G. Cahiez, C. Duplais, J. Buendia, *Chem. Rev.* **2009**, *109*, 1434.

[75] a) S.-H. Kim, M. V. Hanson, R. D. Rieke, *Tetrahedron Lett.* **1996**, *37*, 2197; b) S.-H. Kim, R. D. Rieke, *Tetrahedron Lett.* **1997**, *38*, 993; c) R. D. Rieke, S.-H. Kim, X. Wu, *J. Org. Chem.* **1997**, *62*, 6921; d) S.-H. Kim, R. D. Rieke, *Synth. Commun.* **1998**, *28*, 1065; e) S.-H. Kim, R. D. Rieke, *J. Org. Chem.* **1998**, *63*, 6766; f) S.-H. Kim, M. V. Hanson, R. D. Rieke, *Tetrahedron Lett.* **1999**, *40*, 4931; g) R. D. Rieke, Y. Suh, S.-H. Kim, *Tetrahedron Lett.* **2005**, *46*, 5961.

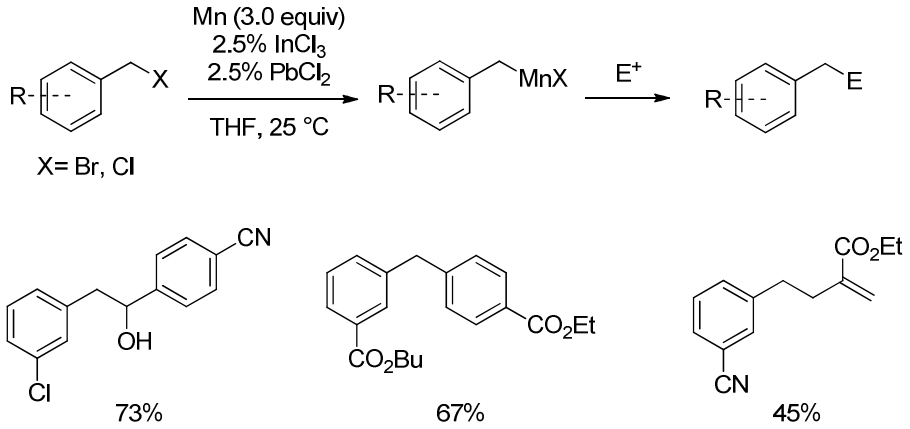
[76] G. Cahiez, A. Martin, T. Delacroix, *Tetrahedron Lett.* **1999**, *40*, 6407.

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



Scheme 33. Selected examples of the preparation of an aryl manganese reagent and its reaction with electrophiles.

P. Knochel and *Z. Peng* also reported that, on contrary to aryl compounds, the manganese insertion reaction into benzylic chlorides or bromides occurrs best in the absence of LiCl salts (Scheme 34).[77]

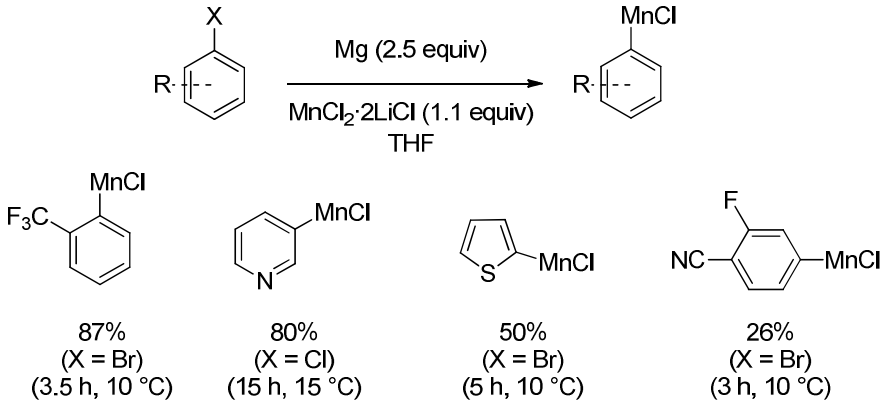


Scheme 34. Selected examples of the preparation of functionalized benzylmanganese halides and subsequent reaction with electrophiles.

In fact, it was observed that the lithium salts generate in this case extensive homocoupling side-reactions. Despite the preparation of a broad range of organomanganese reagents, the method presents some drawbacks such as the use of a large excess of the organomanganese reagent, as well as the use of the highly toxic $PbCl_2$ salts needed for the manganese activation.

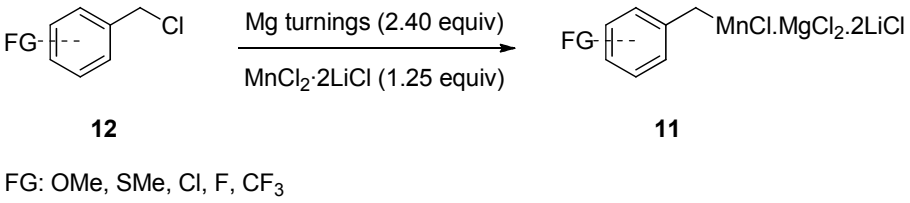
Additionally, *P. Knochel* and co-workers reported the preparation of polyfunctional benzylic zinc chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of LiCl and $ZnCl_2$.[18a] Moreover, *Z. Peng et al.* have reported the use of the high soluble ate-

complex $MnCl_2 \cdot 2LiCl$[78] for the direct *in situ* transmetallation from magnesium to manganese in the preparation of aryl manganese reagents (Scheme 35).[79]



Scheme 35. Preparation of aryl manganese reagents by the insertion of magnesium into aromatic and heteroaromatic halides in the presence of $MnCl_2 \cdot 2LiCl$ (The magnesium and lithium salts complexes were omitted for clarity).

We envisioned the formation of benzylic manganese organometallics of type **11** using magnesium turnings in the presence of $MnCl_2 \cdot 2LiCl$[78] with various benzylic chlorides of type **12** (Scheme 36).



Scheme 36. Magnesium insertion into functionalized benzylic chlorides in the presence of $MnCl_2 \cdot 2LiCl$.

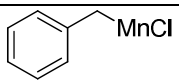
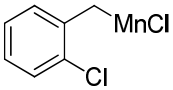
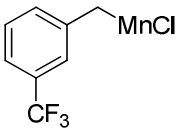
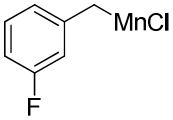
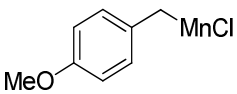
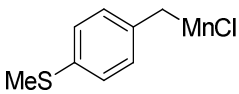
2) Preparation of benzylic manganese chlorides

In preliminary experiments, the treatment of benzyl chloride (**12a**) with Mg turnings (2.4 equiv) and $MnCl_2 \cdot 2LiCl$ (1.25 equiv; prepared as a 1 M solution in THF) at 0 °C produces benzyl manganese chloride (**11a**) within 1 h reaction time with a yield of 85% as determined by iodolysis (Table 3, entry 1). As a general procedure, various substituted benzylic chlorides were converted to the corresponding manganese organometallics **11a-f** in 52-85%. However, in some cases, such as 2-chlorobenzyl chloride (**12b**) and 3-trifluoromethylbenzyl chloride

[78] For the preparation of the complex $MnCl_2 \cdot 2LiCl$, see: G. Cahiez in *Butyl Manganese Chloride and Related Reagents*, Encyclopedia of Reagents for Organic Synthesis, (Ed. L. Paquette), Wiley, Chichester **1995**, 925.
[79] Z. Peng, N. Li, X. Sun, F. Wang, L. Xu, C. Jiang, L. Song, Z. Yan, *Org. Biomol. Chem.* **2014**, *12*, 7800.

(**12c**), extensive amounts of homocoupling products were obtained in THF as solvent. Interestingly, the use of a 2:1 mixture of THF and methyl *t*-butyl ether (MTBE) reduces the amount of homocoupling to less than 10% affording the corresponding manganese reagents (**11b-c**) in 62-65% yield (entries 2 and 3). Also the 3-fluorobenzyl chloride **12d** and 4-methoxybenzyl chloride **12e** gave the corresponding benzylic manganese reagents **11d** and **11e** in 52-67% yield (entries 4 and 5). The presence of a sulfur substituent, like in **12f**, does not inhibit the insertion reactions and benzylic manganese reagent **11f** is produced in 54% yield (entry 6), showing the tolerance of such metalation process.

Table 3. Magnesium insertion into benzylic chlorides in the presence of $MnCl_2 \cdot 2LiCl$.

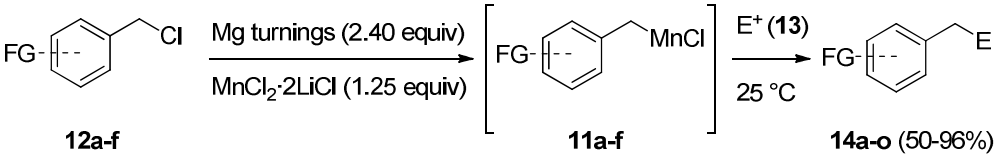
Entry	Benzylic manganese chloride (**11**)	Reactions conditions time (h), T (°C)	Iodolysis yield (%)[a]
1	 **11a**	1, 0	85
2	 **11b**	1.5, 0	62[b]
3	 **11c**	1.5, 0	65[b]
4	 **11d**	1, 0	64
5	 **11e**	1, 0	52
6	 **11f**	1.5, 0	54

[a] The formation of benzylic manganese chlorides is characterized by iodometric titration. [b] A 2:1 mixture of THF and MTBE is used.

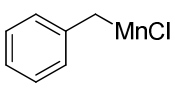
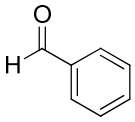
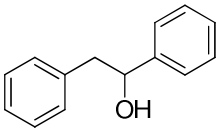
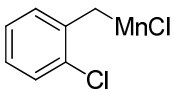
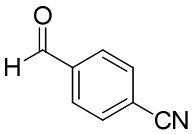
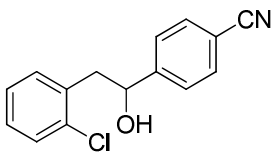
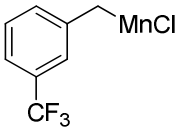
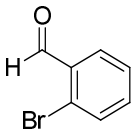
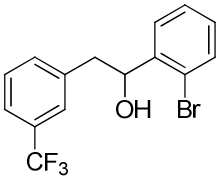
3) Reaction of benzylic manganese chlorides with electrophiles

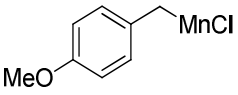
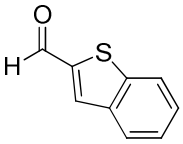
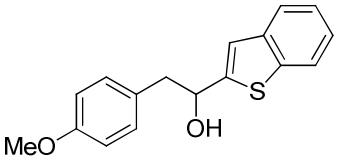
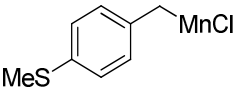
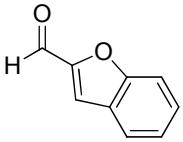
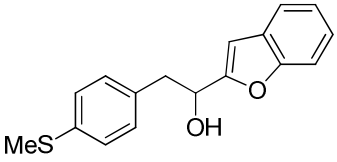
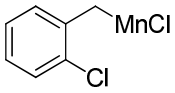
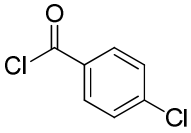
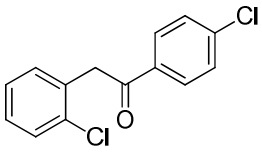
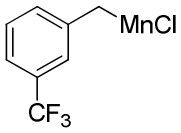
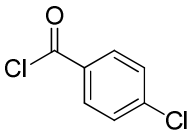
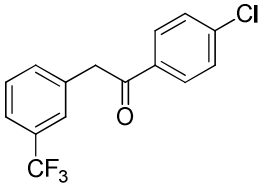
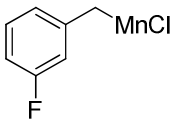
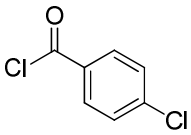
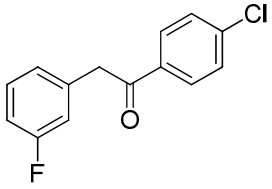
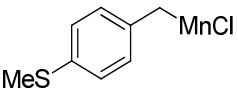
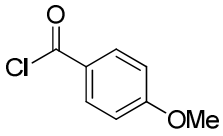
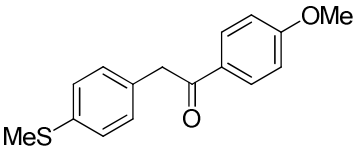
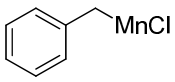
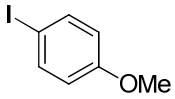
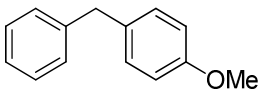
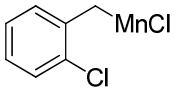
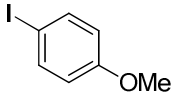
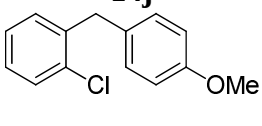
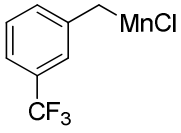
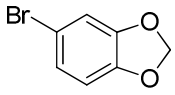
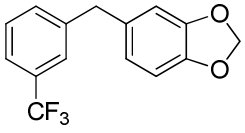
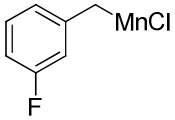
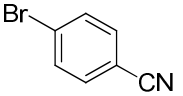
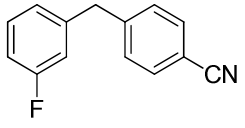
The prepared benzylic manganese reagents **11a-f** react readily with a number of electrophiles **13** (E^+) furnishing products of type **14** (Table 4). The benzylic manganese reagents obtained by our method react with carbonyl groups, in the absence of any additional catalyst. Thus, benzyl manganese chloride (**11a**) adds to benzaldehyde overnight at 25 °C affording the desired alcohol **14a** in 94% yield (entry 1). Similarly, the functionalized benzylic manganese reagents **11b-c**, **11e-f** react with aromatic and heterocyclic aldehydes leading to the products **14b-e** in 76-95% yield (entries 2-5). As expected, the reaction of benzylic manganese reagents (**11**) with acid chlorides furnished the desired ketones **14f-i** without any transition metal catalyst in 72-93% (entries 6-9). Smooth palladium-catalyzed cross-couplings with aryl bromides or iodides take place by treating the benzylic manganese reagent **11a-f** with 2% $Pd(OAc)_2$, 4% S-Phos[64] at 25 °C overnight affording the diaryl methane derivatives **14j-o** in 50-96% (entries 10-15).

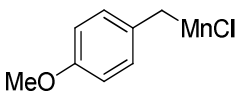
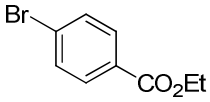
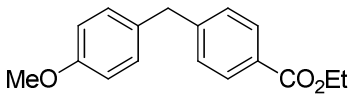
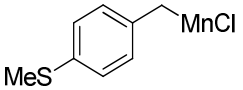
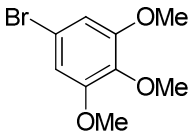
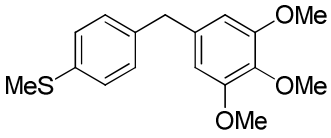
Table 4. Preparation of benzylic manganese reagents and their reactions with electrophiles.



FG: OMe, SMe, Cl, F, CF_3

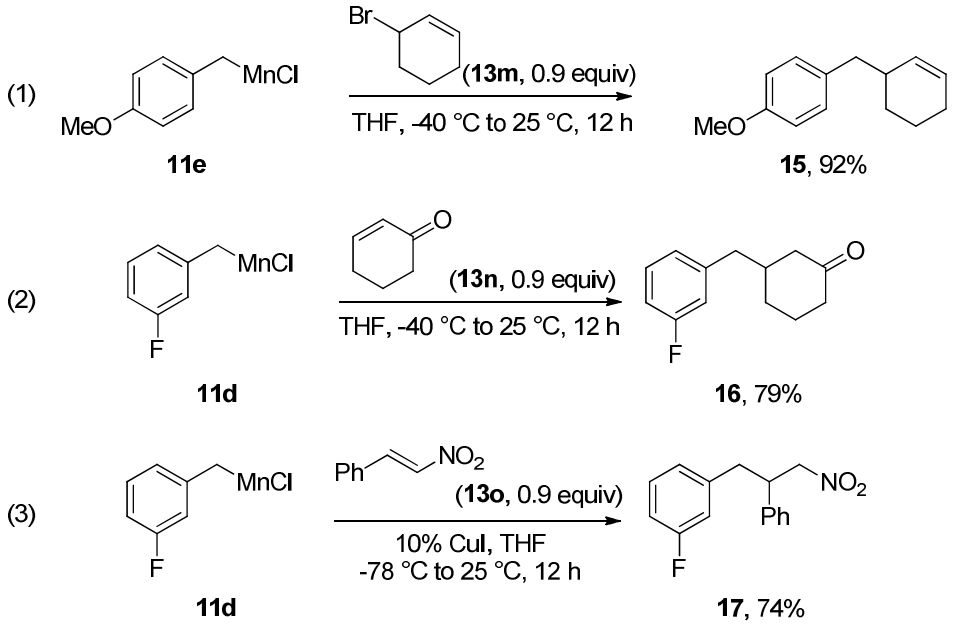
Entry	Benzylic manganese chloride (**11**)	Electrophile[a] (**13**)	Product (**14**)	Yield (%)[b]
1	 **11a**	 **13a**	 **14a**	94
2	 **11b**	 **13b**	 **14b**	95
3	 **11c**	 **13c**	 **14c**	76

4	 **11e**	 **13d**	 **14d**	94
5	 **11f**	 **13e**	 **14e**	94
6	 **11b**	 **13f**	 **14f**	78
7	 **11c**	 **13f**	 **14g**	76
8	 **11d**	 **13f**	 **14h**	72
9	 **11f**	 **13g**	 **14i**	93
10	 **11a**	 **13h**	 **14j**	96[c]
11	 **11b**	 **13h**	 **14k**	94[c]
12	 **11c**	 **13i**	 **14l**	71[c]
13	 **11d**	 **13j**	 **14m**	69[c]

14	 **11e**	 **13k**	 **14n**	88[c]
15	 **11f**	 **13l**	 **14o**	50[c]

[a] 1.1 equiv of benzylic manganese chloride and 1.0 equiv of electrophile are used. [b] Isolated yield of pure product. [c] 2% $Pd(OAc)_2$ and 4% S-Phos are used.

Interestingly, the reaction of benzylic manganese reagents such as **11e** with 3-bromocyclohexene at 25 °C provides the allylated product **15** in 92% yield (Scheme 37, entry 1). Also, the benzylic manganese reagent **11d** undergoes a smooth 1,4-addition to cyclohexenone leading to the ketone **16** in 79 % yield (entry 2). In the presence of 10% CuI, trans-β-nitrostyrene[80] undergoes a conjugated addition providing the nitroalkene **17** in 74% yield (entry 3).



Scheme 37. Further transformations of benzylic manganese reagents.

In summary, we have developed a new convenient preparation of benzylic manganese reagents and have demonstrated their versatility in the presence of various electrophiles such as an allylic bromide, an enone, aldehydes and acid chlorides mostly in the absence of any additional transition metal.

[80] a) C. Juber, P. Knochel, *J. Org. Chem* **1992**, *57*, 5431; b) A. S. B. Prasad, H. Eick, P. Knochel, *J. Organomet. Chem.* **1998**, *562*, 133; c) T. Bresser, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1914.

III. Transition metal free cross-coupling of aryl and *N*-heteroaryl cyanides with benzylic zinc reagents

1) Introduction

Transition metal-catalyzed cross-coupling reactions are standard methods for forming carbon-carbon bonds between aryl and heteroaryl organometallics and electrophiles.[81,82] By far, the most common electrophiles (Ar-X) are organic halides (X= Cl, Br, I) and sulfonates (X= OTf, ONf, OTs or OMs).[83] Nevertheless, other leaving groups such as diazonium salts,[84] trimethylammonium salts,[85] and cyanides[86-88] have been used. Most cross-coupling reactions involving cyanides require either transition metal catalysts,[86] strong Lewis acids[87] or polar organometallics.[88] *J. A. Miller* first reported the coupling of benzonitriles and aryl *Grignard* reagents in the presence of a nickel catalyst (Scheme 38).[86b]

[81] a) N. Miyaura in *Cross-Coupling Reactions, A Practical Guide*, (Ed.: N. Miyaura), Springer, Berlin, **2002**; b) A. de Meijere, F. Diederich in *Metal-Catalyzed Cross-Coupling Reactions, Vol. 1* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; c) J. F. Hartwig in *Organotransition Metal Chemistry: From Bonding to Catalysis*, (Ed.: J. F. Hartwig), University Science Books, Sausalito, CA, **2010**.

[82] a) For the transition-metal-catalyzed direct functionalization of pyridines, see: a) L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020; b) A. Larivée, J. J. Mousseau, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 52; c) Y. Nakao, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2008**, *130*, 2448; d) M. Tobisu, I. Hyodo, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 12070; e) Y. Nakao, Y. Yamada, N. Kashihara, T. Hiyama, *J. Am. Chem. Soc.* **2010**, *132*, 13666; f) M. Wasa, B. T. Worrell, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2010**, *49*, 1275; g) B. Xiao, Z.-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 616.

[83] a) J. Högermeier, H.-U. Reissig, *Adv. Synth. Catal.* **2009**, *351*, 2747; b) J. R. Naber, B. P. Fors, X. Wu, J. T. Gunn, S. L. Buchwald, *Hetereocycles* **2010**, *80*, 1215; c) Z.-J. Quan, F.-Q. Jing, Z. Zhang, Y.-X. Da, X.-C. Wang, *Eur. J. Org. Chem.* **2013**, 7175; d) F. Leng, Y. Wang, H. Li, J. Li, D. Zou, Y. Wu, Y. Wu, *Chem. Commun.* **2013**, *49*, 10697; e) L. W. Sardzinski, W. C. Wertjes, A. M. Schnaith, D. Kalyani, *Org. Lett.* **2015**, *17*, 1256.

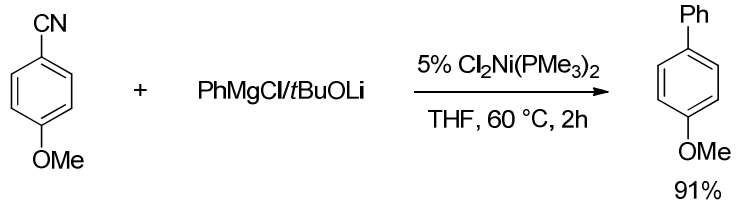
[84] a) S. Darses, G. Michaud, J.-P. Genêt, *Tetrahedron Lett.* **1998**, *39*, 5045; b) S. Darses, G. Michaud, J.-P. Genêt, *Eur. J. Org. Chem.* **1999**, 1875; c) M. B. Andrus, C. Song, J. Zhang, *Org. Lett.* **2002**, *4*, 2079; d) R. H. Taylor, F.-X. Felpin, *Org. Lett* **2007**, *9*, 2911; e) C.-Y. Liu, A. Gavryushin, P. Knochel, *Chem. Asian. J.* **2007**, *2*, 1020; f) E. Fouquet, F.-X. Felpin, *Adv. Synth. Catal.* **2008**, *350*, 863.

[85] a) S. B. Blakey, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 6046; b) K. R. Buszeck, N. Brown, *Org. Lett.* **2007**, *9*, 707; c) X.-Q. Zhang, Z.-X. Wang, *J. Org. Chem.* **2012**, *77*, 3658; d) P. Maity, D. M. Shacklady-McAtee, G. P. A. Yap, E. R. Sirianni, M. P. Watson, *J. Am. Chem. Soc.* **2013**, *135*, 280.

[86] a) For a review, see: Q, Wen, P. Lu, Y. Wang, *RSC Adv.* **2014**, *4*, 47806. For Ni-catalyzed cross-couplings, see: b) J. A. Miller, *Tetrahedron Lett.* **2001**, *42*, 6991; c) J. J. Garcia, N. M. Brunkan, W. D. Jones, *J. Am. Chem. Soc.* **2002**, *124*, 9547; d) J. A. Miller, J. W. Dankwardt *Tetrahedron Lett.* **2003**, *44*, 1907; e) J. M. Penney, J. A. Miller, *Tetrahedron Lett.* **2004**, *45*, 4989; f) Y. Nakao, S. Oda, T. Hiyama, *J. Am. Chem. Soc.* **2004**, *126*, 13904; g) Y. Nakao, A. Yada, S. Ebata, T. Hiyama, *J. Am. Chem. Soc.* **2007**, *129*, 2428; h) D.-G. Yu, M. Yu, B.-T. Guan, B.-J. Li, Y. Zheng, Z.-H. Wu, Z.-J. Shi, *Org. Lett.* **2009**, *11*, 3374; i) K. Nakai, T. Kurahashi, S. Matsubara, *J. Am. Chem. Soc.* **2011**, *133*, 11066. For a Pd-catalyzed cross-coupling, see: j) S. Tang, S.-H. Li, W. Yan, *Tetrahedron Lett.* **2012**, 53, 6743. For Rh-catalyzed cross-couplings, see: k) M. Tobisu, Y. Kita, Y. Ano, N. Chatani, *J. Am. Chem. Soc.* **2008**, *130*, 15982; l) Y. Kita, M. Tobisu, N. Chatani, *Org. Lett.* **2010**, *12*, 1864.

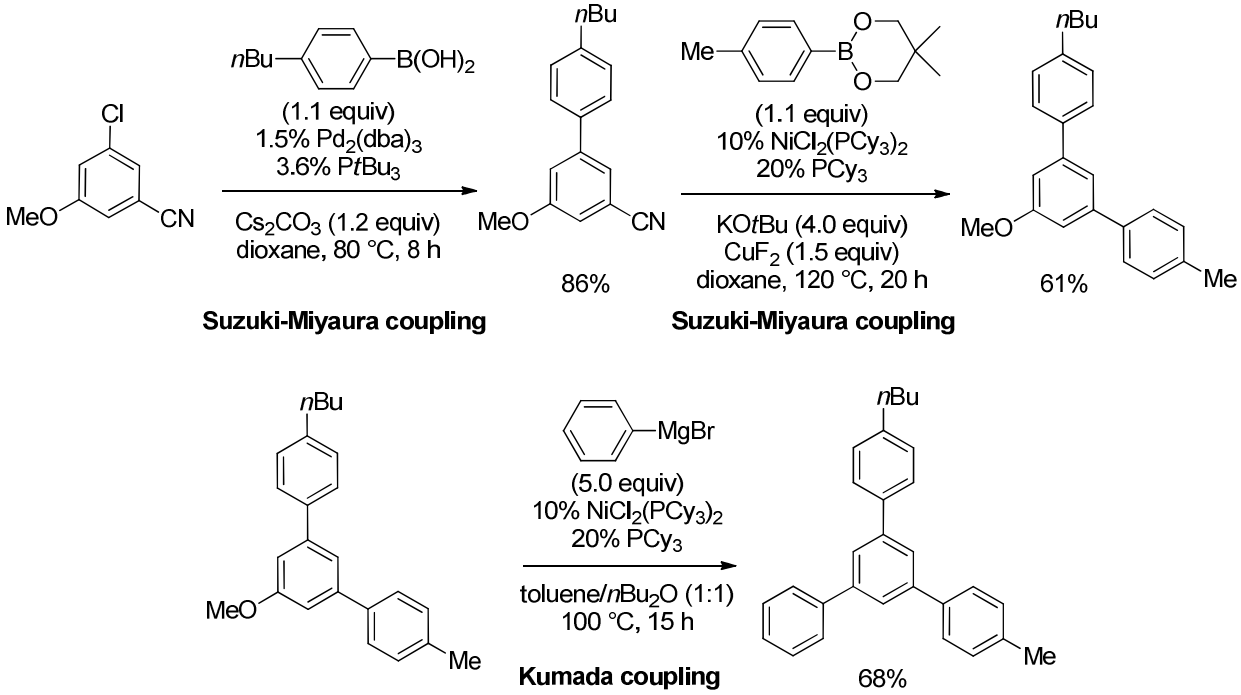
[87] Q. Chen, T. León, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 8746.

[88] a) N. Picci, M. Pocci, A. Gugliuzza, F. Puoci, A. De Munno, F. Iemma, V. Bertini, *Heterocycles* **2001**, *55*, 2075; b) J. M. Penney, *Tetrahedron Lett.* **2004**, *45*, 2667; c) A. D. Thompson, M. P. Huestis, *J. Org. Chem.* **2013**, *78*, 762.



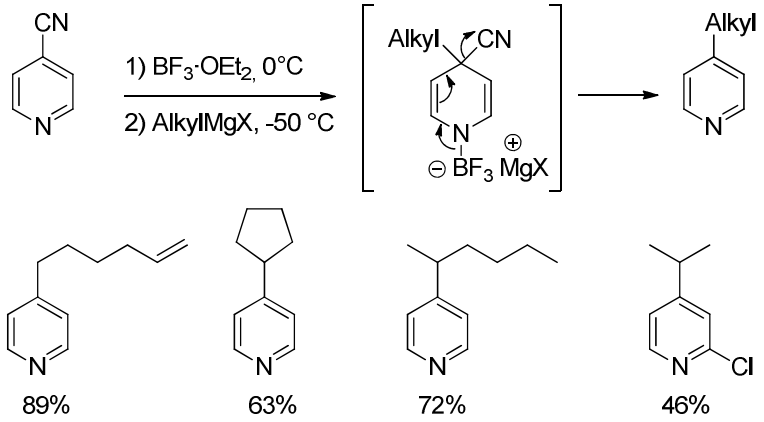
Scheme 38. Nickel catalyzed cross-coupling of an aryl nitrile with an aryl *Grignard* reagent.

Another interesting nickel catalyzed cross-coupling of aryl cyanides and boronic esters was described by *Z.-J. Shi* and co-workers, who reported its application to the orthogonal synthesis of a triarylbenzene, taking advantage of the relative reactivity of C-Cl, C-CN or C-OMe bond activations (Scheme 39).[86h]



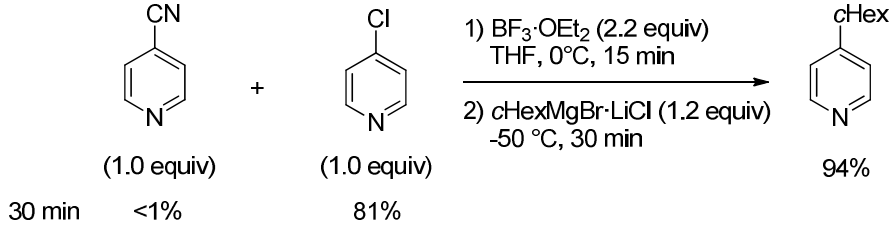
Scheme 39. Orthogonal synthesis of triarylbenzene based on relative reactivity by *Z.-J. Shi*.

Among cross-coupling reactions involving cyanides as leaving groups,[86] *P. Knochel* and co-workers recently developed the transition metal free, BF_3-mediated cross-coupling of 4-substituted pyridines and alkylmagnesium reagents (Scheme 40).[87]



Scheme 40. Transition metal free BF_3-mediated cross-couplings of 4-cyanopyridine with various alkyl *Grignard* reagents.

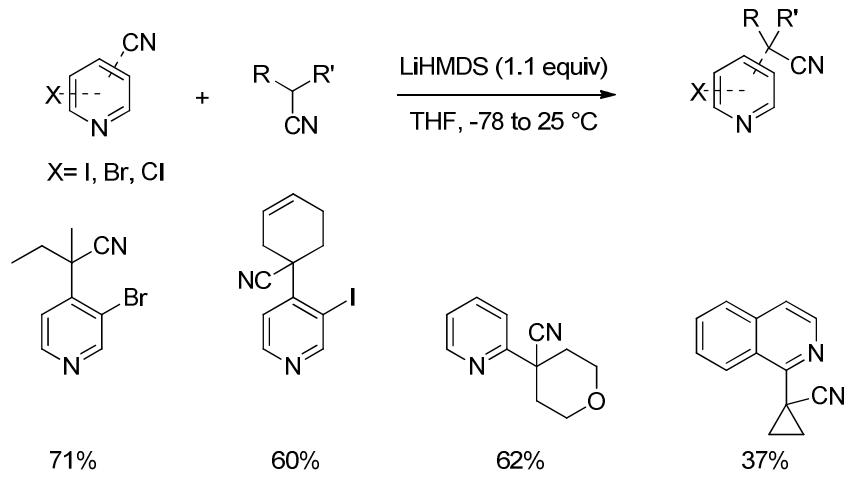
The method allows the chemoselective reaction of a cyano group versus a chloro substituent. This reactivity may be explained by the mesomeric acceptor properties of the cyano group compared to the mesomeric donor properties of the chloro substituent; acid cyanides are also more electrophilic than acid chlorides[89] (Scheme 41).[87]



Scheme 41. Competition reaction between the 4-cyanopyridine and 4-chloropyridine in the transition metal free BF_3-mediated cross-coupling with the cyclohexyl *Grignard* reagent.

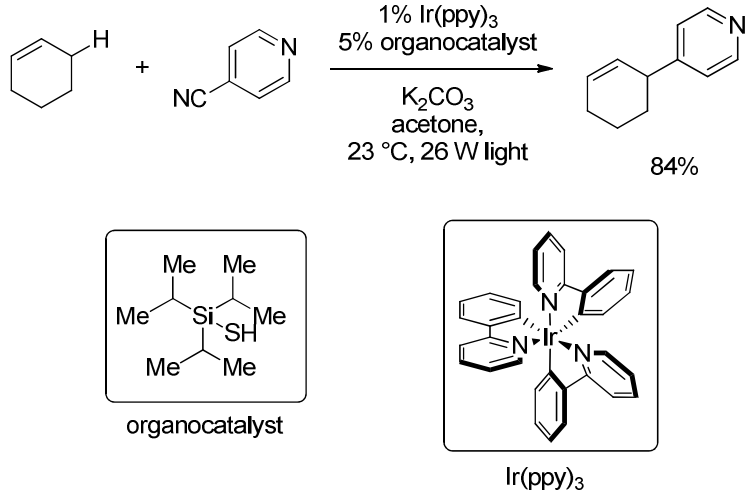
Moreover, nucleophilic aromatic substitutions using cyanide anion as leaving group were also reported by *A. D. Thompson* and *M. P Huestis* from *Genentech*.[90] The use of polar organometallics such as LiHMDS (HMDS = hexamethyldisilazane) or KHMDS permits the synthesis of quaternary centers at azine heterocycles (Scheme 42).

[89] a) S. R. Crabtree, W. L. A. Chu, L. N. Mander, *Synlett* **1990**, 169; b) C. Duplais, F. Bures, I. Sapountzis, T. J. Korn, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 2968.
[90] A. D. Thompson, M. P. Huestis, *J. Org. Chem.* **2013**, *78*, 762.



Scheme 42. S_NAr of aliphatic α,α-disubstituted nitriles with cyanoazines.

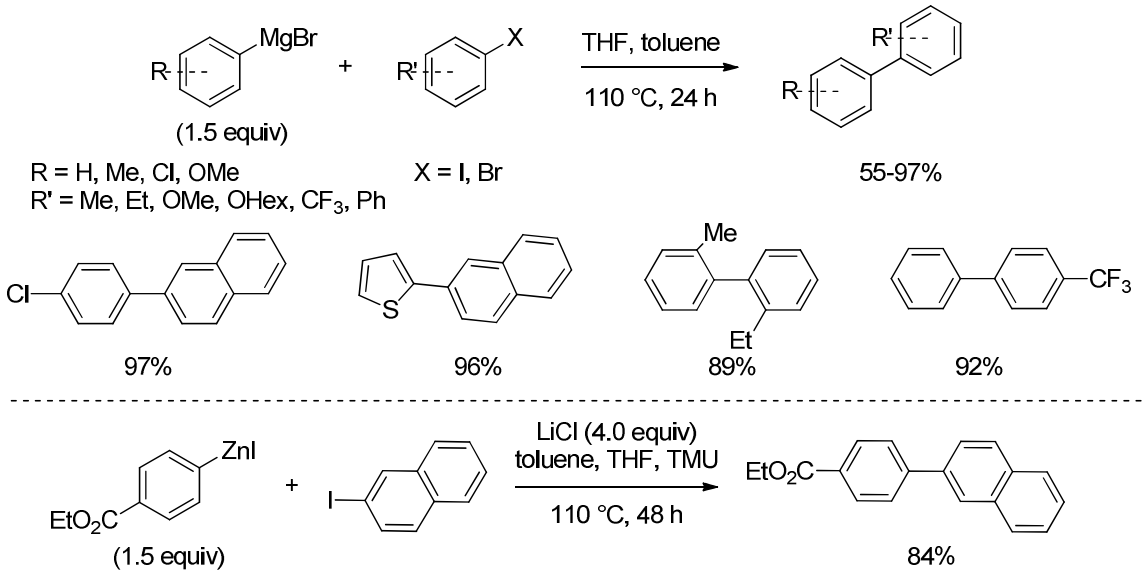
Additionally, photo-redox and photo-induced substitution reactions of aryl and N-heteroaryl cyanides have been reported.[91] For example *D. W. C. MacMillan* and co-workers reported the Ir-catalyzed photoredox arylation of allylic sp^3 C-H bonds using 4-cyanopyridine (Scheme 43).[91b]



Scheme 43. Catalyzed photoredox direct allylic arylation reaction.

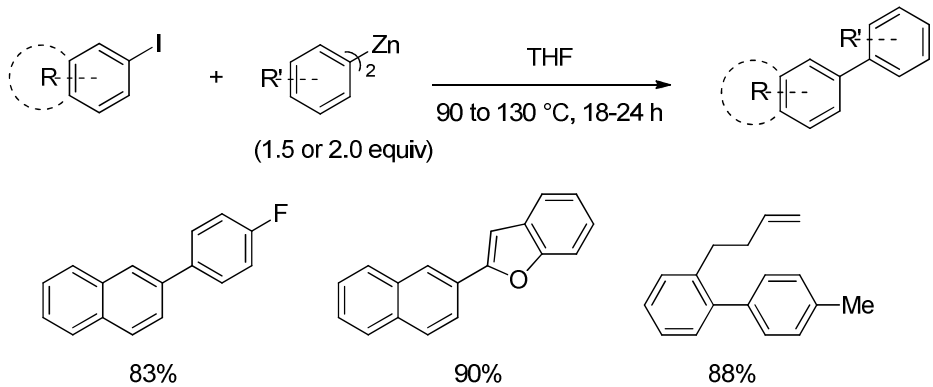
[91] For photoredox catalysis, see: a) A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114; b) J. D. Cuthbertson, D. W. C. MacMillan, *Nature* **2015**, *519*, 74. For photoinitiated substitutions, see: c) A. Yoshino, K. Yamasaki, T. Yonezawa, M. Ohashi, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 735; d) R. Bernadi, T. Caronna, S. Morrocchi, P. Traldi, B. M. Vittimberga, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 1607; e) J. Y. Lan, G. B. Schuster, *J. Am. Chem. Soc.* **1985**, *107*, 6710. f) K. Tsujimoto, N. Nakao, M. Ohashi, *J. Chem. Soc., Chem. Commun.* **1992**, 366; g) Y. Ito, S. Endo, *J. Am. Chem. Soc.* **1997**, *119*, 5974; h) W. M. Horspool, G. Hynd, U. Ixkes, *Tetrahedron Lett.* **1999**, *40*, 8295; i) M. Tsuji, K. Higashiyama, T. Yamauchi, H. Kubo, S. Ohmiya, Heterocycles **2001**, *54*, 1027; j) J. Tang, J.-J. Yue, F.-F. Tao, G. Grampp, B.-X. Wang, F. Li, X.-Z. Liang, Y.-M. Shen, J.-H. Xu, *J. Org. Chem.* **2014**, *79*, 7572.

The performance of transition metal free cross-couplings is a valuable synthetic goal and pioneer advances were reported by *E. Shirakawa* and *T. Hayashi*.[92] Thus, various aryl *Grignard* reagents undergo cross-coupling reactions with a range of aryl halides through a $S_{RN}1$ pathway (Scheme 44).[92a] The authors further reported the single electron transfer induced coupling of arylzinc reagents with a range of aryl and alkenyl halides.[92b]



Scheme 44. Transition metal free cross-coupling reactions of aryl *Grignard* and arylzinc reagents with various aryl halides reported by *Shirakawa* and *Hayashi*.

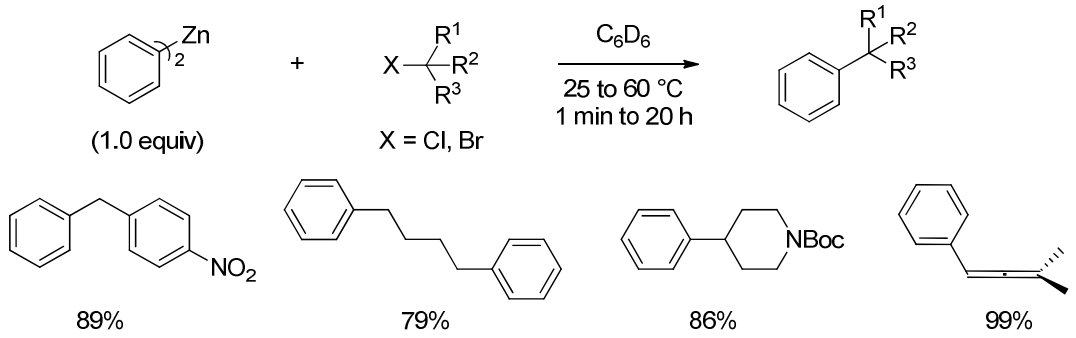
Moreover, *M. Uchiyama* and co-workers reported the use of *bis*-arylzinc reagents in transition metal free cross-coupling reactions enabling the diversified synthesis of biaryl compounds (Scheme 45).[93]



Scheme 45. Coupling of *bis*-arylzinc reagents with various aryl halides in absence of external catalysts reported by *Uchiyama*.

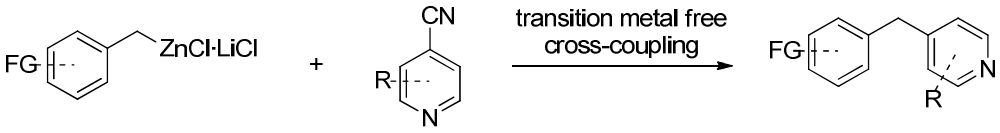
[92] a) E. Shirakawa, Y. Hayashi, K. Itoh, R. Watabe, N. Uchiyama, W. Konagaya, T. Hayashi, *Angew. Chem. Int. Ed.* **2012**, *51*, 218; b) E. Shirakawa, F. Tamakuni, E. Kusano, N. Uchiyama, W. Konagaya, R. Watabe, T. Hayashi, *Angew. Chem. Int. Ed.* **2014**, *53*, 521.
[93] H. Minami, X. Wang, C. Wang, M. Uchiyama, *Eur. J. Org. Chem.* **2013**, 7891.

More recently, *M. J. Ingleson* and co-workers also showed the feasibility and significance of such transition metal free reactions.[94] In fact, benzylic, primary, secondary and tertiary alkyl halides were reacted with *bis*-arylzinc reagents affording the corresponding cross-coupling products (Scheme 46).[94] Preliminary mechanistic studies suggest that Lewis acidity of zinc is important, and that the coupling involves radical species.



Scheme 46. Cross-coupling reaction of *bis*-phenylzinc reagent with benzylic, tertiary propargylic, primary and secondary halides in the absence of a catalyst.

Previous results on $BF_3 \cdot OEt_2$-mediated substitutions of cyanopyridines with alkylmagnesium reagents have demonstrated that a cyano group may be a better leaving group compared to a chloride.[87] Since benzylic zinc reagents are readily prepared and tolerate a range of functionalities,[95] we anticipated that the enhanced ionic character of the benzylic carbon-zinc bond (compared to alkyl or aryl carbon-zinc bonds)[96] may allow transition metal free cross-coupling reactions involving 4-cyanopyridines (Scheme 47).



Scheme 47. Strategy for the transition metal free cross-coupling reactions between benzylic zinc reagents and substituted 4-cyanopyridines.

2) Transition metal free benzylation of 4-cyanopyridines

Preliminary results show that the treatment of 4-cyanopyridine (**18a**) with 3-(trifluoromethyl)benzylzinc chloride **20a**[95b] in THF did not provide any substitution product

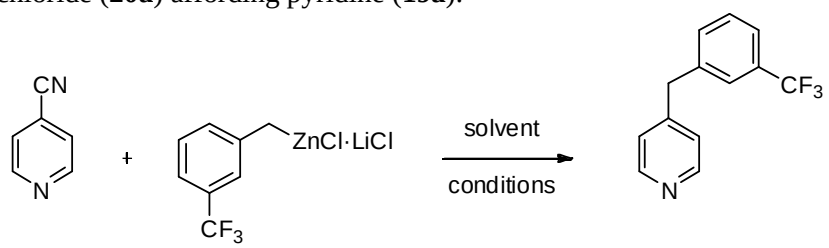
[94] J. J. Dunsford, E. R. Clark, M. J. Ingleson, *Angew. Chem. Int. Ed.* **2015**, *54*, 5688.

[95] a) A. Metzger, M. A. Schade, G. Manolikakes, P. Knochel, *Chem. Asian J.* **2008**, *3*, 1678; b) A. Metzger, C. Argyo, P. Knochel, *Synthesis* **2010**, *5*, 882; c) K.-H. Cho, S.-H. Kim, *Bull. Korean Chem. Soc.* **2013**, *34*, 983; d) N. M. Barl, E. Sansiaume-Dagousset, G. Monzon, A. J. Wagner, P. Knochel, *Org. Lett.* **2014**, *16*, 2422.

[96] a) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2001**, *58*, 417; b) P. Knochel, H. Leuser, L.-Z. Gong, S. Perrone, F. F. Kneisel in *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH: Weinheim, **2005**; c) P. Knochel, J. J. Almena Perea, P. Jones, *Tetrahedron* **1998**, *54*, 8275; d) P. Knochel, P. Jones in *Organozinc Reagents*, (Eds.: P. Knochel, P. Jones), Oxford University Press, New York, **1999**; e) P. Knochel, F. Langer, M. Rottländer, T. Stüdemann, *Chem. Ber.* **1997**, *130*, 1021; f) P. Knochel, S. Vettel, C. Eisenberg, *Appl. Organomet. Chem.* **1995**, *9*, 175.

(25 °C, 16 h; entry 1 of Table 5). However, the use of a polar solvent such as DMPU[97] (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) led to the formation of the 4-benzylated pyridine (**19a**) in 43% yield (as determined by ^{1}H NMR analysis; entry 2). Variation of the solvent mixture allowed boosting the reaction yield up to 81% (entries 3-5). In addition, the reaction time could be considerably shortened by microwave irradiation,[98,99] (μW, 40 °C, 30 min; entry 6)[100] leading to the 4-benzylated pyridine (**19a**) in 94% isolated yield.

Table 5. Optimization of the reaction conditions for the cross-coupling of 4-cyanopyridine (**18a**) with the benzylic zinc chloride (**20a**) affording pyridine (**19a**).



18a (1.0 equiv) **20a** (1.5 equiv) **19a**

Entry	Solvent (ratio)[a]	Conditions (°C, h)	Yield[b] [%]
1	THF	25, 16	<1
2	DMPU	25, 16	43
3	THF/DMPU (1:1)	25, 16	57
4	THF/DMPU (1:2)	25, 16	81
5	THF/TMU (1:2)	25, 16	52
6	THF/DMPU (1:2)	μW, 40, 0.5 h	>95 (94)[c]

[a] For clarity, the ratio is given before the addition of the benzylic zinc reagent. [b] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield. (TMU = tetramethylurea, μW = microwave irradiation).

[97] T. Mukhopadhyay, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 385.

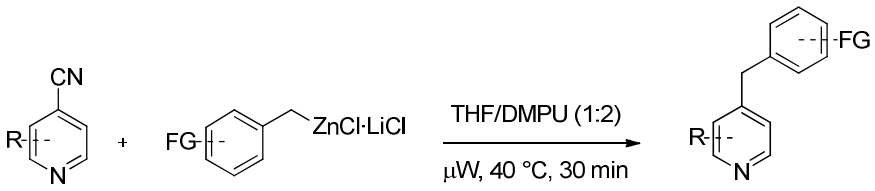
[98] For the use of microwaves in organic synthesis, see: a) R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, J. Rousell, *Tetrahedron Lett.* **1986**, *27*, 279; b) R. J. Giguere, T. L. Bray, S. M. Duncan, G. Majetich, *Tetrahedron Lett.* **1986**, *27*, 4945; c) B. L. Hayes in *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, **2002**. d) P. Lidström, J. P. Tierney in *Microwave-Assisted Organic Synthesis*, (Eds.: P. Lidström, J. P. Tierney), Wiley-Blackwell, **2009**. e) A. de la Hoz, A. Loupy in *Microwaves in Organic Synthesis, 3rd ed.*, (Ed.: A. Loupy), Wiley-VCH, Weinheim, **2012**. f) M. Larhed, K. Olofsson in *Microwave Methods in Organic Synthesis*; (Eds: M. Larhed, K. Olofsson), Springer, Berlin, **2006**.

[99] For a review about organometallic reactions under microwave irradiation, see: a) D. Dallinger, C. O. Kappe, *Chem. Rev.* **2007**, *107*, 2563. b) C. O. Kappe, *Angew. Chem.* **2004**, *116*, 6408-6443; *Angew. Chem. Int. Ed.* **2004**, *43*, 6250; c) H. Tsukamoto, T. Matsumoto, Y. Kondo, *J. Am. Chem. Soc.* **2008**, *130*, 388; d) G. Shore, S. Morin, M. G. Organ, *Angew. Chem. Int. Ed.* **2006**, *45*, 2761; e) S. Fustero, D. Jiménez, M. Sánchez-Roselló, C. del Pozo, *J. Am. Chem. Soc.* **2007**, *129*, 6700; f) S. Constant, S. Tortoioli, J. Müller, D. Linder, F. Buron, J. Lacour, *Angew. Chem. Int. Ed.* **2007**, *46*, 8979; g) S. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705-4707.

[100] Heating the reaction mixture at 40 °C for 30 min without microwave irradiation led to 46% of **2a** and 21% of recovered **1a** suggesting that some decomposition has occurred.

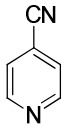
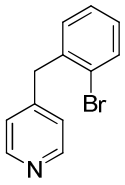
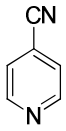
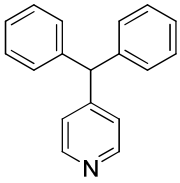
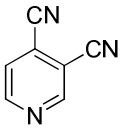
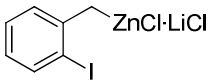
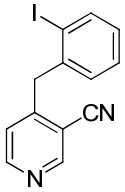
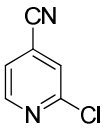
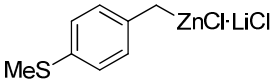
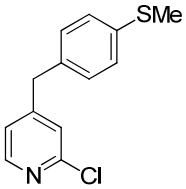
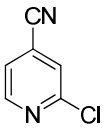
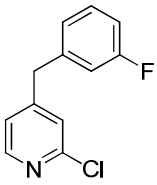
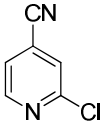
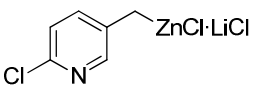
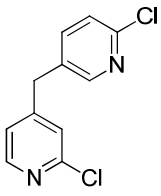
Since a broad range of benzylic zinc reagents are available,[95] a variety of 4-substituted pyridines of type **19** were readily prepared (Table 6). Thus, 2-bromobenzylzinc chloride (1.5 equiv) adds to 4-cyanopyridine (**18a**) in a 1:2 mixture of THF:DMPU within 0.5 h at 40 °C using microwave irradiation and leading to the pyridine (**19b**) in 92% yield (entry 1). Similarly, the addition of benzhydrylzinc chloride (**20c**) provides the 4-substituted pyridine (**19c**) in 80% yield (entry 2). Substitution at the C(4)-position of the pyridine ring is strongly favored. Thus, the reaction of 3,4-dicyanopyridine (**18b**) with 2-iodobenzylzinc chloride (**20d**) furnishes the 4-benzylic pyridine (**19d**) as sole product in 83% yield (entry 3). Remarkably, the substitution of the 4-cyano group is highly preferred compared to the 2-chloro substituent. This is a rather unusual selectivity, since 2-chloropyridines readily undergo substitution reactions.[101] Hence, 2-chloro-4-cyanopyridine (**18c**) reacts with various benzylic zinc reagents (**20e-f**) and a heterobenzylic zinc chloride[95d] (**20g**) leading to the corresponding 4-substituted pyridines (**19e-g**) in 67-78% yield (entries 4-6). Even 2,6-dichloro-4-cyanopyridine (**18d**) prefers to undergo a substitution of the 4-cyano group with benzylic zinc reagents (**20e**, **20h**) affording 4-benzylated pyridines (**19h-i**) in 60-82% yield (entries 7-8). Furthermore, the reaction of 3,5-dichloro-4-cyanopyridine (**18e**) with benzylic zinc chlorides **20a** and **20i** furnishes the expected pyridines (**19j-k**) in 62-79% yield (entries 9-10). A smooth addition of benzylic zinc reagent (**20j**) occurs also to 3-trimethylsilyl-4-cyanopyridine (**18f**) leading almost quantitatively (96% yield) to the desired pyridine **19l** (entry 11).

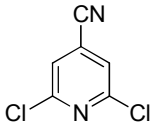
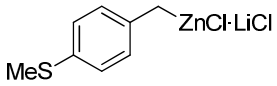
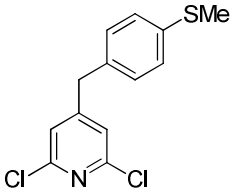
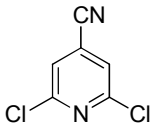
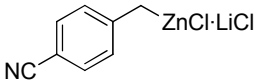
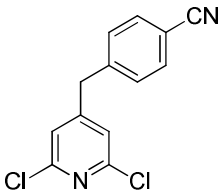
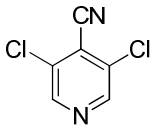
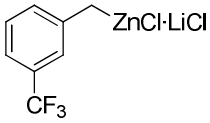
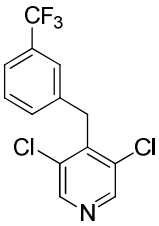
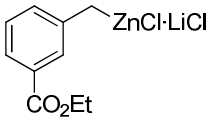
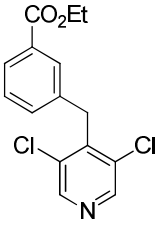
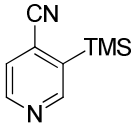
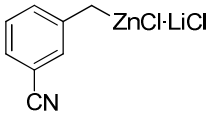
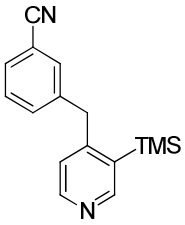
Table 6. Cross-coupling between functionalized 4-cyanopyridines of type **18** and various benzylic zinc chloridesof type **20** using microwave irradiation.



18a-f (1.0 equiv) **20a-j** (1.5 equiv) **19b-l**, 60-96% yield

[101] a) V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner, P. Knochel, *Tetrahedron* **2002**, *58*, 4429; b) T. Tagata, M. Nishida, *J. Org. Chem.* **2003**, *68*, 9412; c) T. J. Korn, G. Cahiez, P. Knochel, *Synlett* **2003**, *12*, 1892; d) M. Schlosser, T. Rausis, *Helv. Chim. Acta* **2005**, *88*, 1240; e) O. M. Kuzmina, A. K. Steib, D. Flubacher, P. Knochel, *Org. Lett.* **2012**, *14*, 4818; f) A. K. Steib, S. Fernandez, O. M. Kuzmina, M. Corpet, C. Gosmini, P. Knochel *Synlett* **2015**, DOI: 10.1055/s-0034-1380178.

Entry	Electrophile	Benzylic zinc chloride	Product, Yield[a]
1	 **18a**	 **20b**	 **19b**: 92%
2	 **18a**	 **20c**	 **19c**: 80%
3	 **18b**	 **20d**	 **19d**: 83%
4	 **18c**	 **20e**	 **19e**: 71%
5	 **18c**	 **20f**	 **19f**: 67%
6	 **18c**	 **20g**	 **19g**: 78%[b]

			
7	**18d**	**20e**	**19h**: 60%
			
8	**18d**	**20h**	**19i**: 82%
			
9	**18e**	**20a**	**19j**: 62%
			
10	**18e**	**20i**	**19k**: 79%
			
11	**18f**	**20j**	**19l**: 96%

[a] Isolated yield. [b] The reaction was heated for 1 h.

The structure of compound **19g** was confirmed by X-ray diffraction analysis (Figure 4).[102]

[102] X-ray crystal structures described in the entire thesis were performed by Prof. Dr. Konstantin Karaghiosoff; for the crystal structures of this chapter see the Appendix.

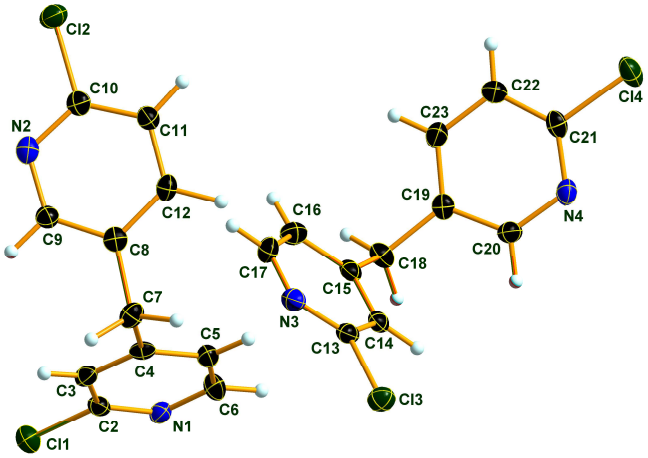
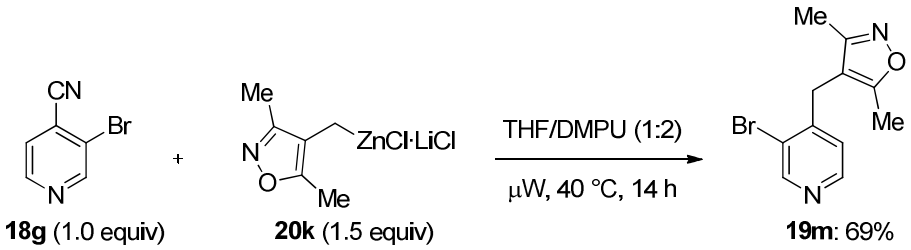


Figure 4. Molecular structure of compound **19g** in the crystal, DIAMOND representation of the two crystallographically independent molecules; thermal ellipsoids are drawn at 50% probability level.

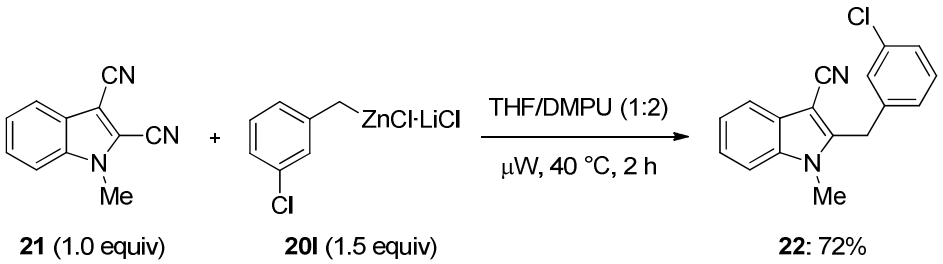
In addition, the substitution reaction allows linking two heterocyclic scaffolds in an efficient manner, avoiding the necessity of transition metal catalysis. Thus, 3-bromo-4-cyanopyridine (**18g**) reacts with the heterobenzylic zinc chloride (**20k**) prepared from 4-(chloromethyl)-3,5-dimethyl-isoxazole[103] providing the isoxazole (**19m**) in 69% isolated yield (Scheme 48).



Scheme 48. Synthesis of isoxazole **19m** *via* cross-coupling of 3-bromo-4-cyanopyridine **18g** with the corresponding benzylic zinc reagent **20k** under microwave irradiation.

In addition, the 2,3-dicyano-indole **21** reacts regioselectively at the C(2)-position with the benzylic zinc chloride (**20l**) leading to 3-cyanoindole **22** in 72% yield (Scheme 49). The presence of the two cyano groups of **21** is necessary since both 2-cyano- and 3-cyano-N-methylindoles did not undergo the reaction with benzylic zinc reagents.

[103] L. Klier, C. R. Diène, M. Schickinger, A. Metzger, A. J. Wagner, K. Karaghiosoff, I. Marek, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 14096.



Scheme 49. Regioselective preparation of indole **22** *via* cross-coupling of indole **21** with benzylic zinc reagent **20l** under microwave irradiation.

The regioselectivity observed in compound **22** has been confirmed by X-ray diffraction analysis (Figure 5).[102]

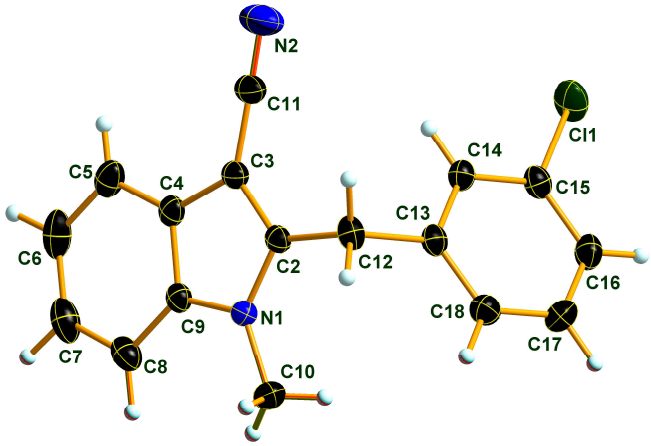


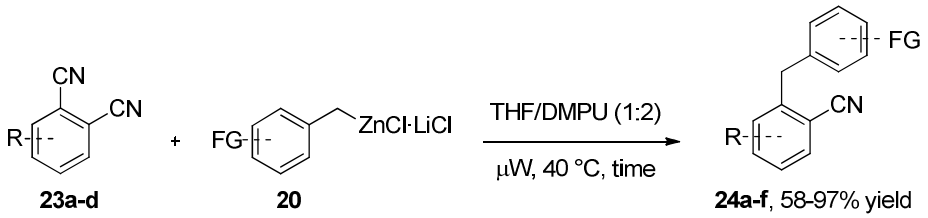
Figure 5. Molecular structure of compound **22** in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50% probability level.

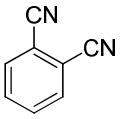
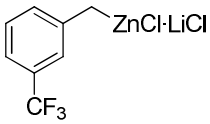
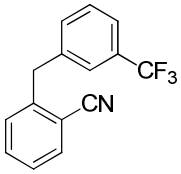
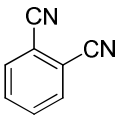
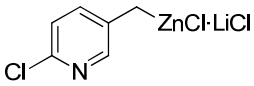
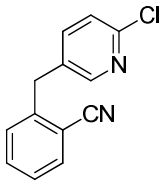
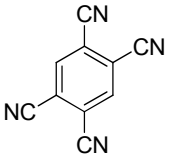
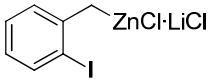
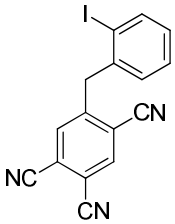
3) Transition metal free benzylation of polycyano-aromatics

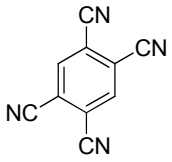
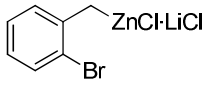
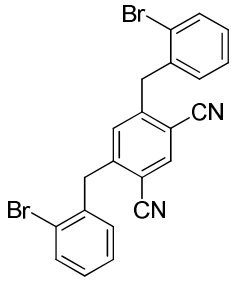
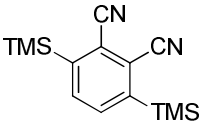
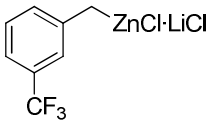
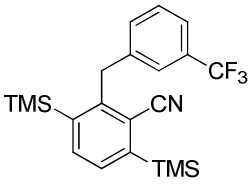
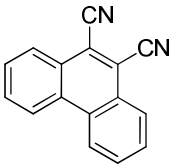
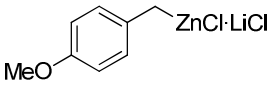
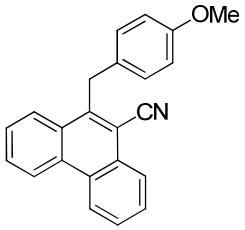
In order to expand the reaction scope, substitutions on various polycyano-aromatics were examined. It was found that 1,2-dicyanobenzene (**23a**) undergoes a smooth substitution with benzylic and heterobenzylic reagents **20a** and **20h** providing the products of monocyano substitution (**24a-b**) in 97 and 91% yield respectively (Table 7, entries 1 and 2). In addition, the reaction of tetracyanobenzene (**23b**) with benzylic zinc chloride (**20c**; 1.0 equiv) furnishes solely the monosubstituted product (**24c**) in 91% yield (entry 3). However, by treating **23b** with an excess of benzylic zinc reagent (**20b**; 3.0 equiv; 1.5 h), 1,3-disubstituted dicyanide (**24d**) is obtained as major product in 58% yield (entry 4). The structures of **24c** and **24d** have been established unambiguously by X-ray diffraction analysis (Figure 6).[102] The regioselectivity obtained in the second substitution in the synthesis of **24d** can be rationalized by considering the stability of the mesomeric structures obtained after nucleophilic addition

(Scheme 50). The readily prepared 1,4-bis-trimethylsilyl-2,3-dicyanobenzene (**23c**) undergoes a smooth benzylation with **20a** leading to the 1,2,3,4-tetrasubstituted aryl cyanide (**24e**) in 84% yield (Table 7, entry 5). Finally, 9,10-dicyanophenanthrene (**23d**) reacts with 4-methoxybenzylzinc chloride (**20n**) affording the corresponding substituted product (**24f**) in 74% yield (entry 6).

Table 7. Cross-coupling between aromatic nitriles of type **23** and various benzylic zinc chlorides of type **20** under microwave irradiation.



Entry	Electrophile	Benzylic zinc chloride (equiv, time)	Product, Yield[a]
1	 **23a**	 **20a** (1.5, 30 min)	 **24a**: 97%
2	 **23a**	 **20g** (1.5, 30 min)	 **24b**: 91%
3	 **23b**	 **20d** (1.0, 30 min)	 **24c**: 91%

			
4	**23b**	**20b** (3.0, 1.5 h)	**24d**: 58%
			
5	**23c**	**20a** (1.5, 45 min)	**24e**: 84%
			
6	**23d**	**20m** (1.5, 1 h)	**24f**: 74%

[a] Isolated yield of analytically pure product.

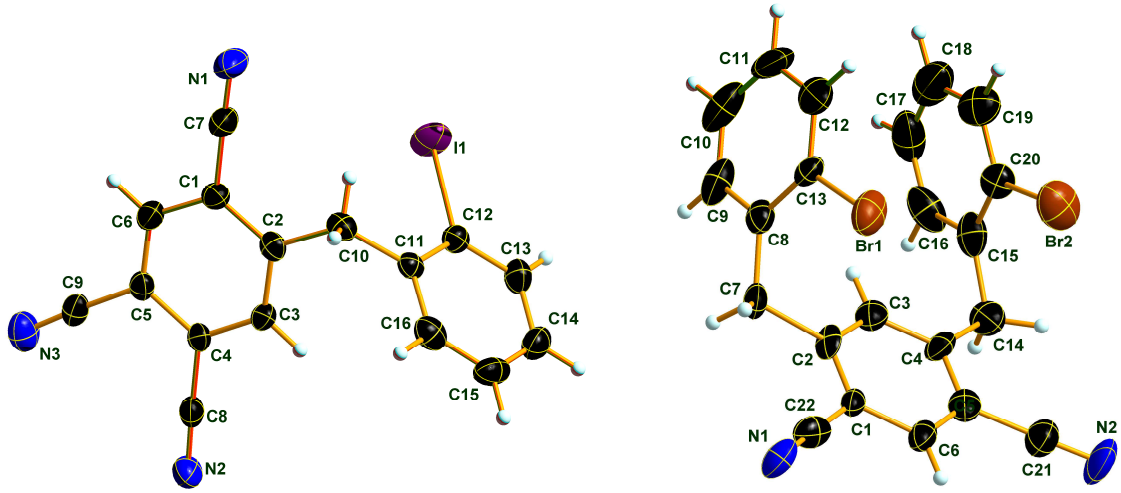
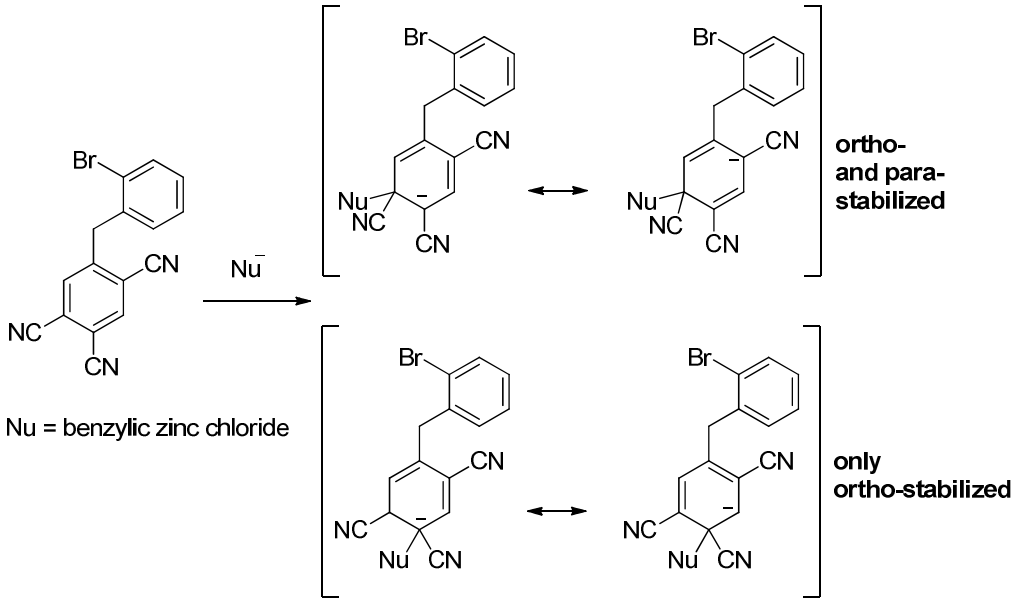
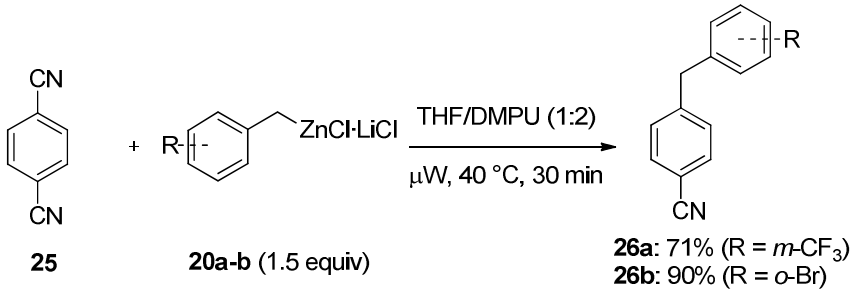


Figure 6. Molecular structures of compounds **24c** and **24d** in the crystal, DIAMOND representation (only one of the four crystallographically independent molecules is shown for **24d**); thermal ellipsoids are drawn at 50% probability level.



Scheme 50. Mesomeric structures explaining the regioselectivity of the cyano-susbtitution in the case of 1,2,4,5-tetracyanobenzene **23b**.

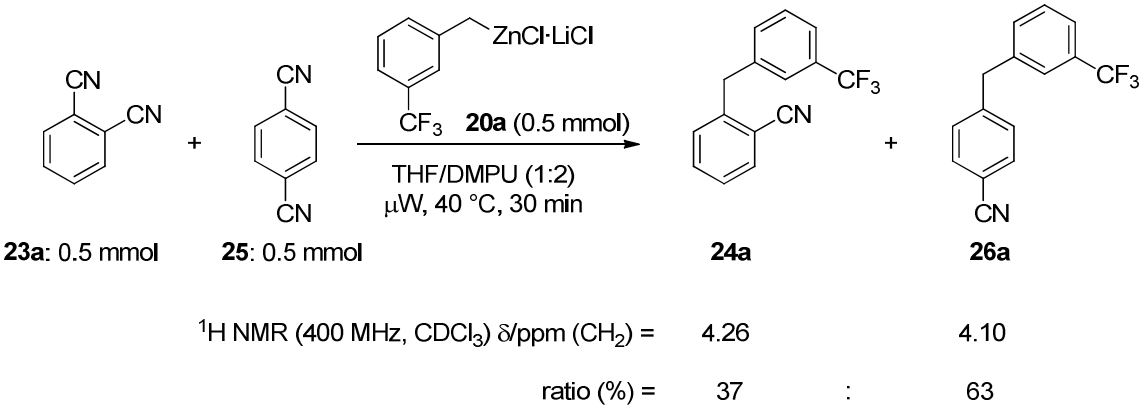
Whereas Table 7 demonstrates that 1,2-dicyanoarenes readily undergo the benzylation, we next examined the influence of the substitution pattern of cyano groups on the reaction outcome. It was found that 1,4-dicyanobenzene **25** also undergoes the selective monosubstitution leading to the benzonitriles (**26a-b**) in 71 and 90% yields, respectively (Scheme 51).



Scheme 51. Cross-coupling reactions between 1,4-dicyanobenzene (**25**) and benzylic zinc chlorides of type **20**.

An intermolecular competition reaction shows that 1,4-dicyanobenzene (**25**) reacts preferentially to 1,2-dicyanobenzene (**23a**) with benzylic zinc chloride **20a** (Scheme 52).[104] The observed selectivity may be a result of sterical hindrance of the addition.

[104] See ^{1}H NMR spectra in the Experimental Section.

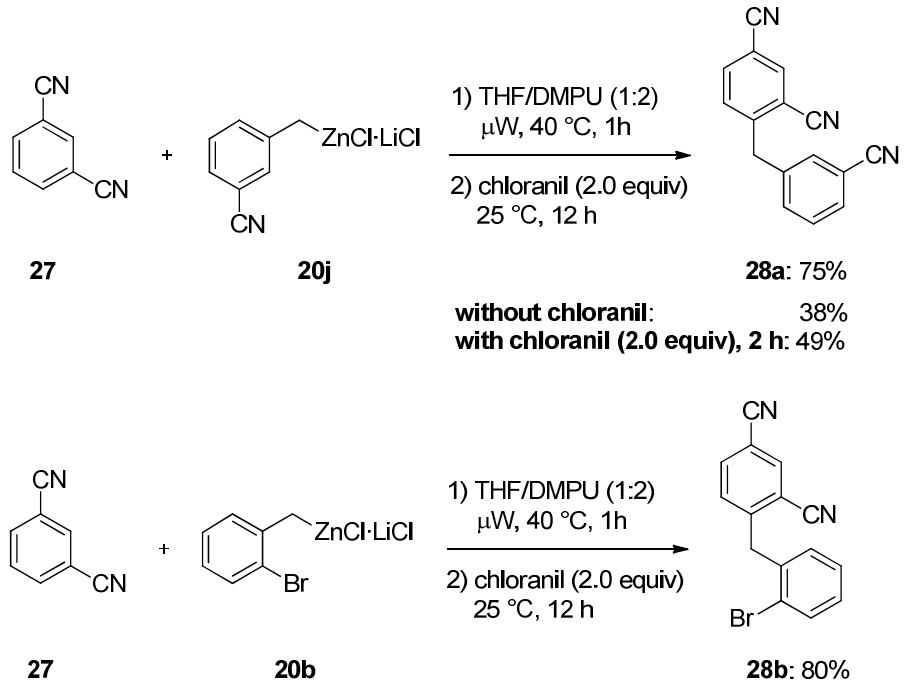


^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm (CH_2) =	4.26		4.10
ratio (%) =	37	:	63

Scheme 52. Competition reaction of 1,2-dicyanobenzene (**23a**) and 1,4-dicyanobenzene (**25**) with benzylic zinc reagent (**20a**).

Surprisingly, 1,3-dicyanobenzene (**27**) did not undergo a cyano substitution, but the addition product **28a** was isolated in 38% yield (Scheme 53). Increasing the reaction time did not improve the product yield but the use of the oxidative agent chloranil, particularly useful for rearomatisation,[105] permit to increase the yield to 49% after 2 h. After further optimisation, the reaction of 1,3-dicyanobenzene (**27**) with the benzylic zinc species **20j** and subsequent chloranil oxidation (2.0 equiv, 12 h) afforded the desired product **28a** in 75% yield. Similarly, the 1,3,4-trisubstituted product **28b** was successfully isolated in 80% yield. The exact structure of compound **28b** was confirmed by X-Ray diffraction analysis (Figure 7).[102] Thus, the addition proceeds at the *ortho*- and *para*-activated position and not at the doubly *ortho*-activated position, which may be too hindered.

[105] a) A. Krasovskiy, A. Tishkov, V. del Amo, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 5010; b) V. del Amo, S. R. Dubbaka, A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 7838.



Scheme 53. Cross-coupling reactions between 1,3-dicyanobenzene (**27**) and benzylic zinc chlorides of type **20** affording products 28a and 28b.

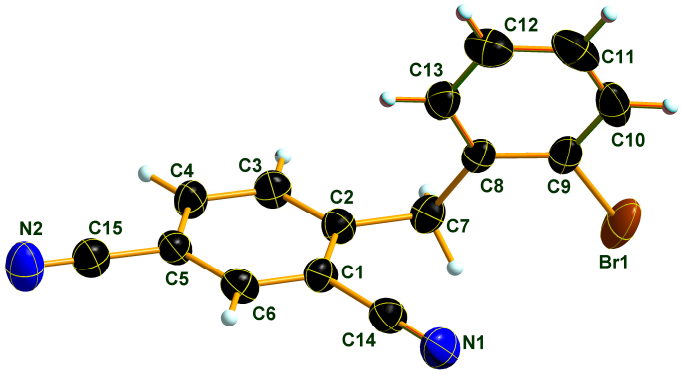
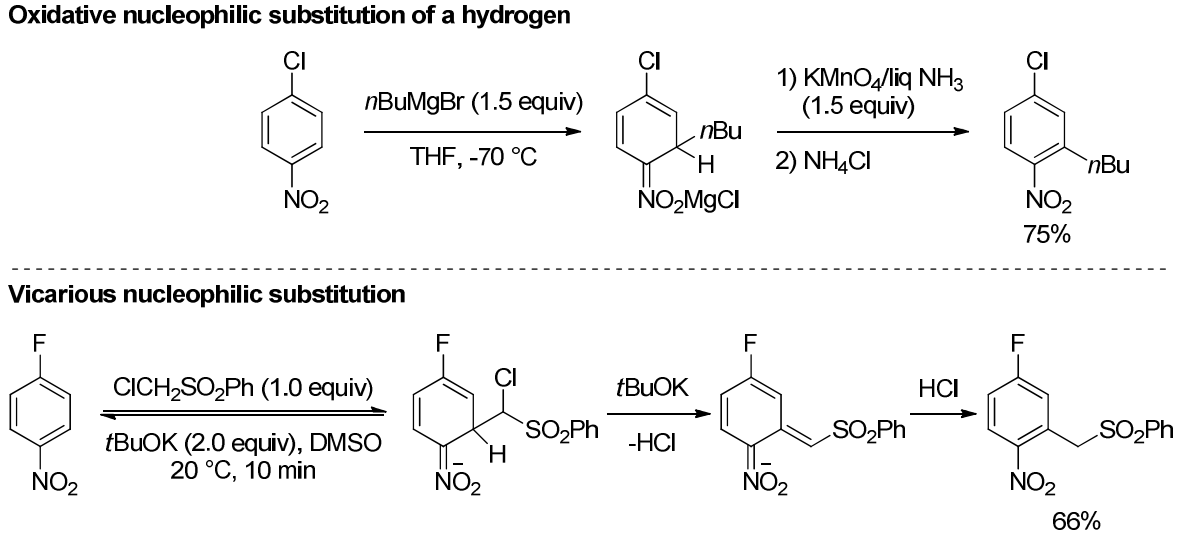


Figure 7. Molecular structure of compound **28b** in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50% probability level.

The reaction of 1,3-dicyanobenzene **27** may be described as a new oxidative type of vicarious nucleophilic substitution.[106] *M. Makosza* and co-workers pioneered the nucleophilic substitution of hydrogen in electron-deficient arenes, relegating the conventional nucleophilic substitution of halogens, S_NAr reaction,[107] as a secondary process. *M. Makosza* and co-workers reported that the direct alkylation of nitroarenes *via* nucleophilic replacement of hydrogen can be executed on two principal ways, the vicarious nucleophilic substitution (VNS) or oxidative nucleophilic substitution of hydrogen (ONSH).[106]The VNS reaction takes

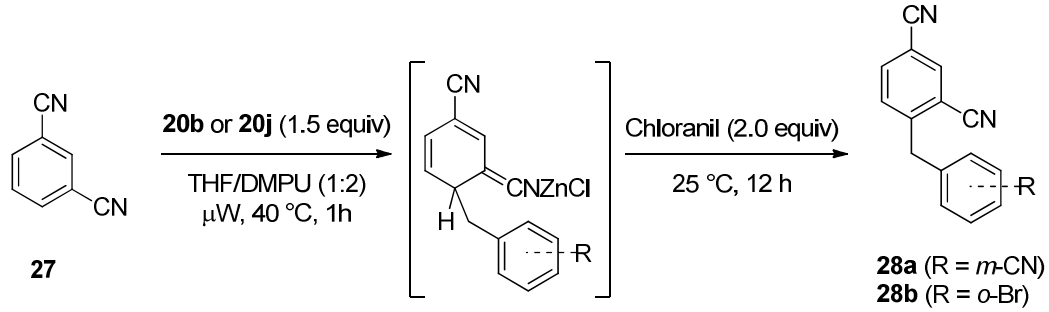
[106] K. Wojciechowski, M. Makosza, *Heterocycles* **2014**, *88*, 75.
[107] a) J. F. Bunnett,; R. E. Zahler, *Chem. Rev.* **1951**, *49*, 273; b) E. Buncel, J. M. Dust, F. Terrier, *Chem. Rev.* **1995**, *95*, 2261.

place when the nucleophile is bearing a leaving group at the carbanion center, whereas ONSH occurs when the addition product requires to be oxidized with external oxidants (Scheme 54).[106,108]



Scheme 54. Illustrated examples of an oxidative nucleophilic substitution (ONSH) and a vicarious nucleophilic substitution (VNS).

In our case, the reaction of 1,3-dicyanobenzene **27** with benzylic zinc chlorides **20b** and **20j** is proposed to follow an oxidative nucleophilic substitution, since the yield was increased in the presence of an oxidant (Scheme 55).



Scheme 55. Proposed mechanism for the oxidative nucleophilic substitution of benzylic zinc reagents **20b** or **20j** to 1,3-dicyanobenzene **27**.

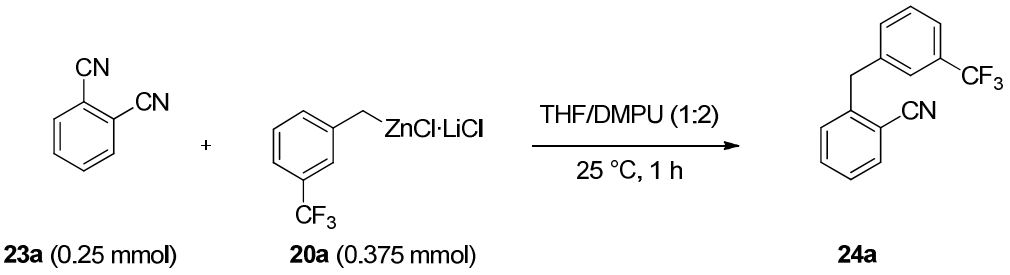
ICP-AES analysis of zinc powder and lithium chloride excluded the presence of transition metal impurities as catalysts for the substitutions.[109] Compared to the work of *E. Shirakawa* and *T. Hayashi*,[92] where the addition of catalytic single electron-donors such as SmI_2 or

[108] For the oxidative nucleophilic substitution of hydrogen, see: a) G. Bartoli, *Acc. Chem. Res.* **1984**, *17*, 109; b) M. Makosza, M. Surowiec, *J. Org. Chem.* **2001**, *624*, 167. For the vicarious nucleophilic substitution, see: c) M. Makosza, T. Glinka, *Acc. J. Org. Chem.* **1983**, *48*, 3681; d) M. Makosza, J. Winiarski, *Acc. Chem. Res.* **1987**, *20*, 282; e) S. Blazej, M. Makosza, *Chem. Eur. J.* **2008**, *14*, 11113.

[109] ICP-AES analysis of zinc powder and LiCl showed that there were less than the respective detection limits of the following metals: Fe (1.5 ppm), Cu (2.0 ppm), Ag (3.0 ppm), Ir (3.5 ppm), Co, Rh (5.0 ppm), Au, Ni, Ru (5.5 ppm).

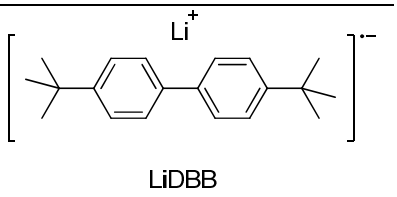
LiDBB (lithium di-*tert*-butylbiphenyl) provided a significant increase in the product yield, this effect was not observed in our reaction. In contrast, a slight yield decrease was observed when catalytic amounts of SmI_2 or LiDBB were added to the reaction of 1,2-dicyanobenzene (**23a**) with benzylic zinc reagent **20a** (Table 8).

Table 8. Addition of catalytic SET donor (*^{1}H NMR yield were determined using 1,3,5-trimethoxybenzene as internal standard).

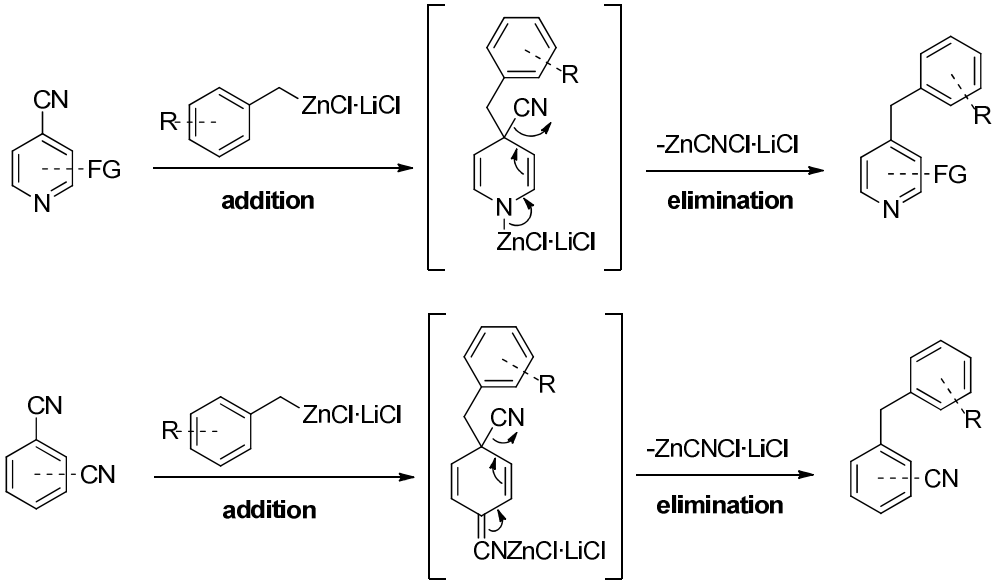


23a (0.25 mmol) **20a** (0.375 mmol) **24a**

Entry	Additive	Yield (^{1}H NMR)*
1	none	83%
2	20% LiDBB	55%
3	20% SmI_2	71%



Our results are better mechanistically rationalized by assuming an addition-elimination pathway typical of an S_NAr reaction (Scheme 56).[107] Additionally, a high electrophilicity of the aromatic or heteroaromatic substrates seems to be required for this new benzylic substitution,[91a] since substrates bearing an electron-donating group react poorly under our reaction conditions.



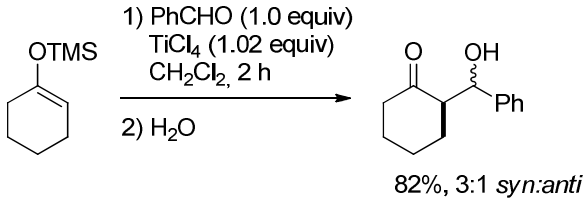
Scheme 56. Proposed mechanism for the reaction of various 4-cyanopyridines and polycyano-aromatics with a range of benzylic zinc reagents *via* an S_NAr pathway.

In summary, the use of a THF/DMPU mixture allows an unprecedented transition metal free benzylation of 4-cyanopyridines and polycyano-aromatics using readily prepared benzylic zinc reagents under microwave irradiation. In addition, a novel oxidative nucleophilic substitution of hydrogen on 1,3-dicyanobenzene was accomplished.

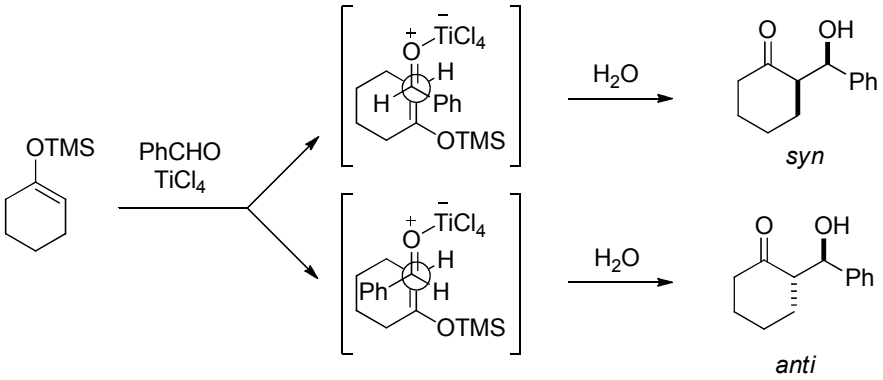
IV. $Sc(OTf)_3$-catalyzed addition of bromomagnesium 2-vinyloxy ethoxide to various aldehydes leading to protected aldol products

1) Introduction

The aldol reaction is one the most famous carbon-carbon bond formation processes, and also one of the oldest ones. Since *C. A. Wurtz* and *A. B. Borodin* discovered independently the first aldol reaction in 1872,[110] its prominence as a classical transformation in organic synthesis is evident.[111] In 1973, *T. Mukaiyama* and co-workers reported a "new aldol type reaction".[112] Thus, in the presence of $TiCl_4$, trimethylsilyl enol ethers of ketones react smoothly with ketones or aldehydes at room temperature to give aldol type addition products, β-hydroxyketones, in good yields (Scheme 57).[112a] The reaction requires activation by the Lewis acid $TiCl_4$ and proceeds *via* an open transition state (Scheme 58).



Scheme 57. Selected example of a *Mukaiyama* aldol reaction.

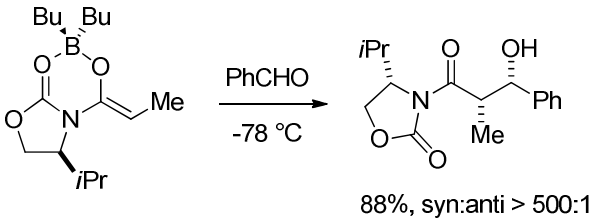


Scheme 58. *Mukaiyama* aldol reaction proceeds *via* an open transition state (*Felkin* representation).

Inspired by the *Mukaiyama* aldol reaction, *D. A. Evans* and co-workers reported in 1981 enantioselective aldol condensations using boron enolates.[113] For example, the boron (Z)-

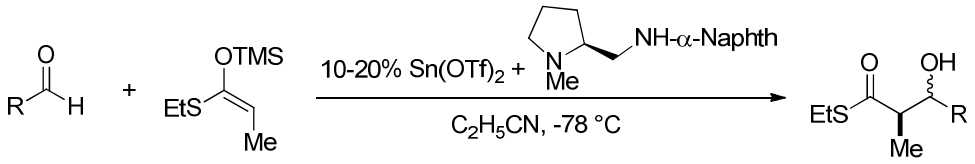
[110] C. A. Wurtz, *Bull. Soc. Chim. Fr.* **1872**, *17*, 436.
[111] *Comprehensive Organic Synthesis*, Vol. 2 (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**.
[112] a) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, 1011; b) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503; c) For a minireview, see: G. L. Beutner, S. E. Denmark, *Angew. Chem. Int. Ed.* **2013**, *52*, 9086; d) R. Threlfall, *Asian. J. Org. Chem.* **2013**, *2*, 888.
[113] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127.

enolate of *N*-propionyloxazolidone was condensed with benzaldehyde affording the aldol product with high diastereoselectivity (Scheme 59).



Scheme 59. Selected example of the *Evans* aldol condensation.

Since the enantioselective *Evans* aldol condensation requires the preparation of boron enolates and the use of stoichiometric amount of chiral oxaziolidininone, the challenge to develop a catalytic and enantioselective aldol reaction was of high interest. After the report of the first catalytic *Mukaiyama* aldol reaction by *C. H. Heathcock*,[114] *S. Kobayashi*, *T. Mukaiyama* and co-worker disclosed the first enantioselective catalysis of the *Mukaiyama* aldol reaction.[115] Thus, the catalytic asymmetric aldol reaction of silyl enol ether with several aldehydes including aromatic, aliphatic and α,β-unsaturated aldehydes in the presence of chiral diamine coordinated to tin(II) triflate afforded in high optical purities the desired aldol products (Scheme 60).[115]



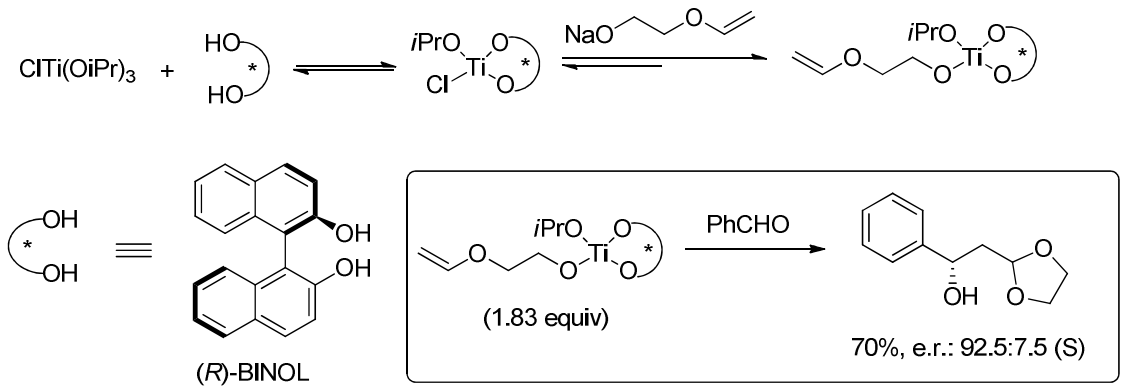
R	Yield	*syn*:*anti*	ee
Ph	77%	93:7	90%
p-MePh	75%	89:11	91%
octyl	80%	100:0	>98%

Scheme 60. The first enantioselective and catalytic *Mukaiyama* aldol reaction.

Among the broad reaction spectra enabling the synthesis of racemic or enantiopure aldol products, *H. Redlich* and co-workers reported the relatively high enantio- and diastereo-selective preparation of protected aldol products resulting from the addition of chiral vinyloxy ethoxides to aldehydes.[116] Thus, a (*R*)-BINOL complexed titanium alcoholate reacts with

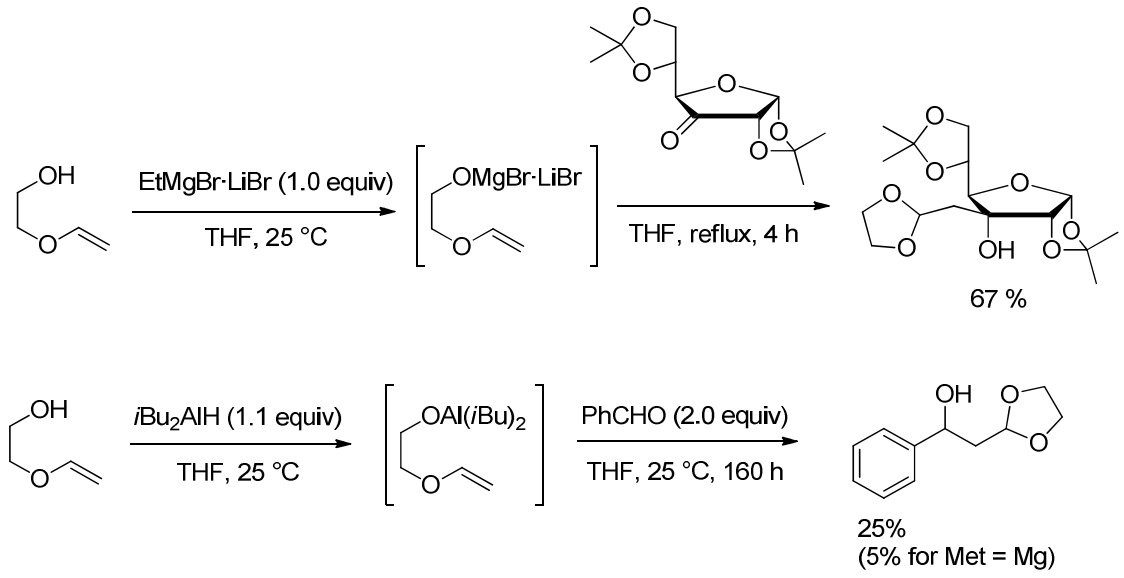
[114] G. A. Slough, R. G. Bergman, C. H. Heathcock, *J. Am. Chem. Soc* **1989**, *111*, 938.
[115] S. Kobayashi, Y. Fujishita, T. Mukaiyama, *Chem. Lett.* **1990**, 1455.
[116] P. Maier, H. Redlich, J. Richter, *Tetrahedron. Asymmetry* **2005**, 16, 3848.

benzaldehyde affording the corresponding chiral protected aldol product with an enantiomeric ratio of 92.5:7.5 (Scheme 61).[116]



Scheme 61. Selected example of the enantioselective synthesis of protected aldol product by *Redlich.*

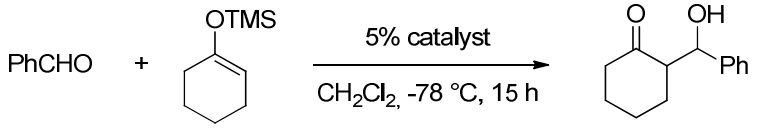
Moreover, *H. Redlich* and co-workers reported the use of the bromomagnesium-2-vinyloxy ethoxide reagent for the addition to carbonyl compounds affording branched chain carbohydrate derivatives (Scheme 62).[117] However, the reaction using bromomagnesium-2-vinyloxy ethoxide has a limited scope and is almost inefficient towards aldehydes in comparison to the previously mentioned enantiomeric addition reaction (Scheme 61).[116] Even the replacement of magnesium by aluminum, formed by deprotonation of the alcohol with DIBAL (diisobutylaluminium hydride), only afford the product of reaction with benzaldehyde in 25% yield after 160 h.[117b]



Scheme 62. Examples of the addition reaction of vinyloxy ethoxide organometallic reagents to a carbohydrate derivative or benzaldehyde discovered by *Redlich.*

[117] a) M. Schmeichel, H. Redlich, *Synthesis* **1996**, 1002; b) P. Maier, H. Redlich, *Synlett* **2000**, *2*, 257.

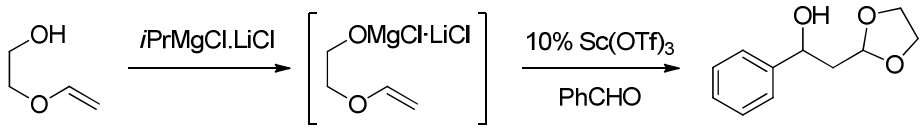
With the goal of expanding the scope of the addition of bromomagnesium-2-vinyloxy ethoxide to various aldehydes, we envisioned that the addition of a catalytic amount of Lewis acid could enhance the electrophilic character of the aldehyde. Among the broad range of highly active Lewis acids reported to catalyze additions to carbonyl derivatives,[118] $Sc(OTf)_3$ is an excellent Lewis acid catalyst.[119] In fact, $Sc(OTf)_3$ was found to be an effective catalyst in *Mukaiyama* type aldol reactions (addition of silyl enol ethers to aldehydes; Scheme 63).[120] The aldol adduct was obtained in 81% in the presence of $Sc(OTf)_3$, whereas catalysts $Y(OTf)_3$ or $Yb(OTf)_3$ only provide the product in trace amounts.



catalyst	yield
$Sc(OTf)_3$	81%
$Y(OTf)_3$	trace
$Yb(OTf)_3$	trace

Scheme 63. $Sc(OTf)_3$-catalyzed *Mukaiyama* aldol reaction and the effect of catalysts.

Cognizant of the good performance of $Sc(OTf)_3$ as a catalyst in the *Mukaiyama* type aldol reactions, we persued the preparation of chloromagnesium-2-vinyloxy ethoxide using the readily available Turbo-*Grignard*, followed by its $Sc(OTf)_3$-catalyzed addition to various aldehydes (Scheme 64).



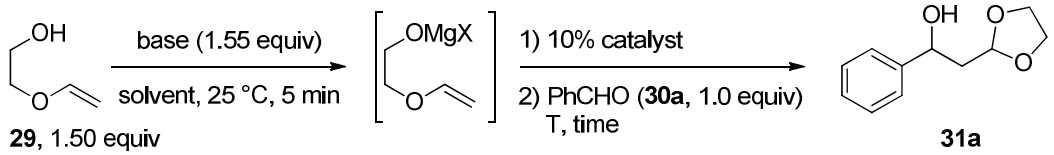
Scheme 64. Strategy for the $Sc(OTf)_3$-catalyzed preparation of a broad range of protected aldol products.

[118] E. Marcantoni, M. Petrini in *Comprehensive Organic Synthesis* (2nd Edition), Vol. 1 (Eds.: P. Knochel, G. A. Molander), **2014**, pp 344-364.
[119] S. Kobayashi, *Eur. J. Org. Chem.* **1999**, 15.
[120] S. Kobayashi, I. Hachiya, H. Ishitani, M. Araki, *Synlett* **1993**, 472.

2) Preparation of the protected aldol products

Preliminary experiments show that the treatment of ethylene glycol vinyl ether (**29**) with *i*PrMgCl·LiCl (Turbo-*Grignard*) in THF and further addition to benzaldehyde **30a** provide only a small conversion to the desired aldol product **31a** (60 °C, 9 h, 9% yield; entry 1 of Table 9). Replacing *i*PrMgCl·LiCl with *i*PrMgCl, permits to increase the reaction yield (60 °C, 7 h, 21% yield; entry 2), indicating that the reaction performs better in the absence of LiCl salts. Further investigations show that the treatment of ethylene glycol vinyl ether (**29**) with *i*PrMgBr in THF give the best result in comparison to previous *iso*propylmagnesium derivatives affording the desired aldol product **31a** in 38% yield (entry 3). This result reveals the importance of a bromomagnesium 2-vinyloxy ethoxide intermediate instead of the corresponding chloro-analog. Nevertheless, the results were unsatisfactory since the conversion of benzaldehyde was less than 40%. In an attempt to improve the conversion of benzaldehyde, catalytic amounts of $Sc(OTf)_3$ were added to the reaction mixture, which considerably improved its conversion since the desired aldol product **31a** could be isolated in 80% yield after 4 h (entry 4). Remarkably, performing the reaction in Et_2O instead of THF allows the synthesis of the desired aldol product **31a** in 91% yield (entry 5). Finally, decreasing the reaction temperature (25 °C instead of 40 °C) leads to an inefficient reaction (entry 6).

Table 9. Optimization of the reaction conditions for the synthesis of protected aldol product **31a**.



29, 1.50 equiv

31a

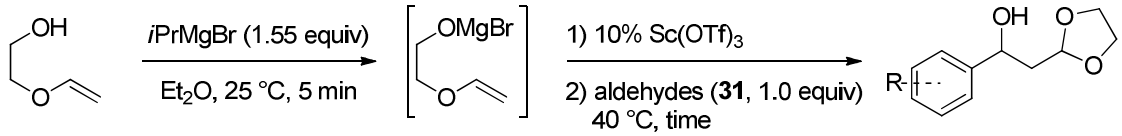
Entry	Base	Solvent	Catalyst	T (°C), Time[c] (h)	Yield[d] (%)
1	*i*PrMgCl·LiCl[a]	THF	-	60, 9	9
2	*i*PrMgCl[a]	THF	-	60, 7	21
3	*i*PrMgBr[b]	THF	-	60, 6	38
4	***i*PrMgBr[b]**	**THF**	**$Sc(OTf)_3$**	**60, 4**	**80**
5	***i*PrMgBr[b]**	**Et_2O**	**$Sc(OTf)_3$**	**40, 4**	**91**
6	*i*PrMgBr[b]	Et_2O	$Sc(OTf)_3$	25, 12	5

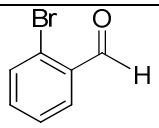
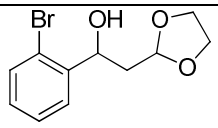
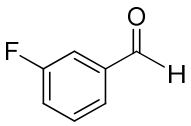
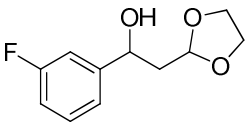
[a] Solution commercially available titrated prior use. [b] *i*PrMgBr was prepared from direct magnesium insertion to *i*PrBr and was titrated prior to use. [c] The reaction progress was monitored by gas chromatography using decane as an internal standard and a hydrolyzed aliquot of the reaction. [d] Yield of isolated analytically pure product.

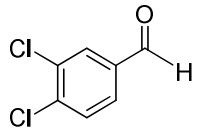
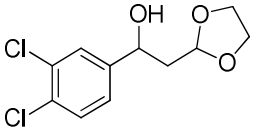
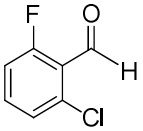
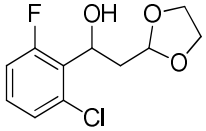
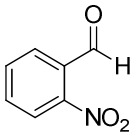
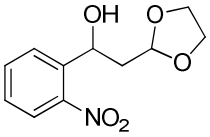
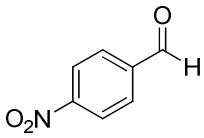
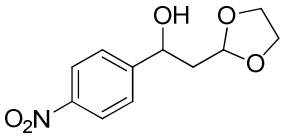
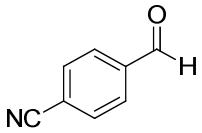
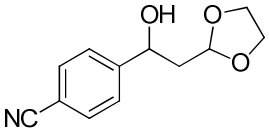
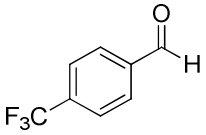
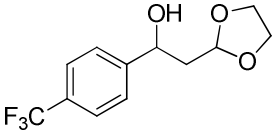
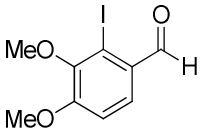
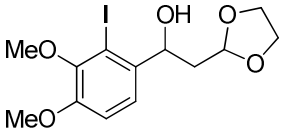
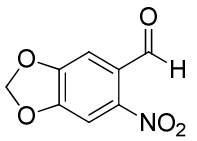
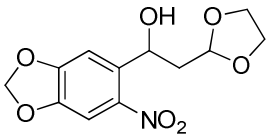
With these optimized reaction conditions in hand, we examined the reaction scope. Thus, the reaction of bromomagnesium 2-vinyloxy ethoxide **30**, prepared from ethylene glycol vinyl

ether **29,** with 2-bromobenzaldehyde (**31b**) in the presence of $Sc(OTf)_3$ afforded the protected aldol compound **32b** in 86% yield after 3 h at 40 °C (Table 10, entry 1). Similarly, the 3-fluorobenzylalcohol derivative **32c** was obtained in 90% yield (entry 2). The $Sc(OTf)_3$-catalyzed reaction of the chloro-substituted aldehyde **31d** with bromomagnesium 2-vinyloxy ethoxide (**30**) gives the corresponding protected aldol product **32d** in 84% after 3 h (entry 3). The highly electron-poor aldehyde **31e** easily reacts under the same conditions affording the aldol product **32e** in 87% yield after 2 h (entry 4). Remarkably, the nitro-substituted aldehydes **31f** and **31g** are tolerated in our reaction conditions and permit the synthesis of the nitrobenzylalcohol derivatives **32f** and **32g** in 90% and 61%, respectively (entries 5 and 6). The 4-cyanobenzaldehyde (**31h**) reacts similarly with bromomagnesium 2-vinyloxy ethoxide (**30**) affording the addition product **32h** in 81% yield (entry 7). In the same way, the reaction of **30** with 4-(trifluoromethyl)benzaldehyde **31i** led to the protected aldol compound **32i** in 72% yield (entry 8). The electron-rich benzaldehyde **31j** also reacts in our reaction conditions giving the highly functionalized aldol derivative **32j** in 88% yield after 10 h (entry 9). Moreover, the $Sc(OTf)_3$-catalyzed reaction of bromomagnesium 2-vinyloxy ethoxide with 6-nitropiperonal (**31k**) affords the protected aldol compound **32k** in 80% yield (entry 10). In a general way, the reaction proceeds within 2 to 4 h using electron-poor aldehydes, whereas the use of electron-rich aldehydes requires longer reaction time.

Table 10. $Sc(OTf)_3$-catalyzed preparation of protected aldol products of type **32**.



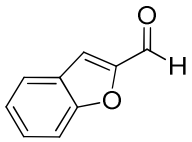
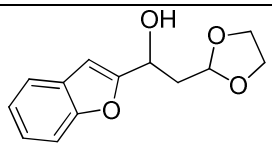
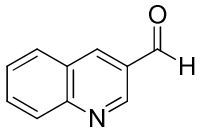
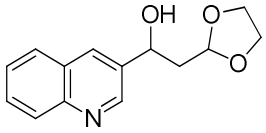
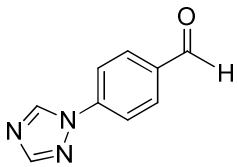
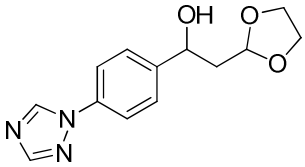
Entry	aldehyde	Time[a]	Product, Yield[b]
			
1	**31b**	3 h	**32b**: 86%
			
2	**31c**	3 h	**32c**: 90%

				
3	**31d**	3 h	**32d**: 84%	
				
4	**31e**	2 h	**32e**: 87%	
				
5	**31f**	3 h	**32f**: 90%	
				
6	**31g**	2 h	**32g**: 61%	
				
7	**31h**	4 h	**32h**: 81%	
				
8	**31i**	3 h	**32i**: 63% (72%)[c]	
				
9	**31j**	10 h	**32j**: 88%	
				
10	**31k**	5 h	**32k**: 80%	

[a] The reaction progress was monitored by gas chromatography using decane as an internal standard and a hydrolyzed aliquot of the reaction. [b] Isolated yield of analytically pure product. [c] The reaction was done with 10 mmol of aldehyde **30k**.

To further expand the scope of our reaction to heteroaromatic aldehydes, 2-benzofurancarboxaldehyde (**31l**) was reacted with bromomagnesium 2-vinyloxy ethoxide and 10% $Sc(OTf)_3$ affording the desired heterocyclic product **32l** in 94% yield (Table 11, entry 1). The addition requires slightly longer reaction times than for electron-rich aromatic aldehydes (12 h). 3-Quinolinecarboxaldehyde **31m** also undergoes the addition reaction, enabling the synthesis of heteroaromatic protected aldol product **32m** in 76% (entry 2). Furthermore, the triazole derivative **32n** was successfully prepared in 94% yield after 20 h at 40 °C (entry 3).

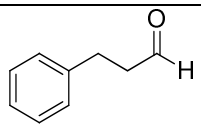
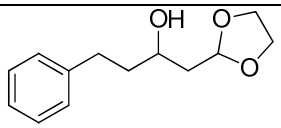
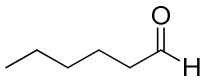
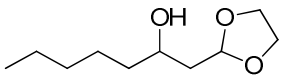
Table 11. $Sc(OTf)_3$-catalyzed preparation of heteroaromatic protected aldol products **32l-n**.

Entry	aldehyde	Time[a]	Product, Yield[b]
1	 **31l**	12 h	 **32l**: 94%
2	 **31m**	12 h	 **32m**: 76%
3	 **31n**	20 h	 **32n**: 94**%**

[a] The reaction progress was controlled by gas chromatography using decane as an internal standard and a hydrolyzed aliquot of the reaction. [b] Isolated yield of analytically pure product.

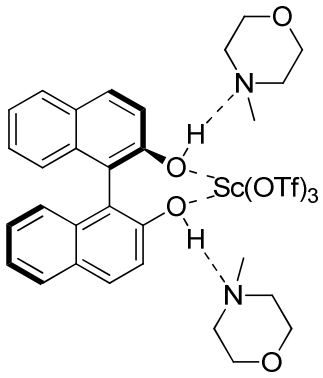
We have extended the reaaction scope to aliphatic aldehydes. The addition reactions to 3-phenylpropionaldehyde (**31o**) and hexanal (**31p**) afford the desired protected aldol products **32o** and **32p** in modest 46% and 44% yields, respectively (Table 11, entries 1 and 2). The use of 20% $Sc(OTf)_3$ did not permit to increase the yield of the reactions. Unfortunatly, our attempt to extend the scope of the addition reaction to ketones did not succeed, since no reaction occurred. Nonetheless, our extended scope of aldehyde electrophiles complements the work of *Redlich*.[117]

Table 12. $Sc(OTf)_3$-catalyzed preparation of aliphatic protected aldol products **32o-p**.

Entry	aldehyde	Time[a]	Product, Yield[b]
1	 **31o**	22 h	 **32o**: 46%
2	 **31p**	2 h	 **32p**: 44%

[a] The reaction progress was controlled by gas chromatography using decane as an internal standard and a hydrolyzed aliquot of the reaction. [b] Isolated yield of analytically pure product.

An enantioselective synthesis of compound **32a** having already been reported by *H. Redlich* and co-workers by adding stoichiometric amount of a (*R*)-BINOL complexed titanium alcoholate to benzaldehyde (Scheme 61),[116] we decided to investigate the feasibility of synthesizing the chiral version of the 4-(trifluoromethyl)-aldol compound **32i**. Unfortunately, the use of a previously reported chiral $Sc(OTf)_3$ catalyst[121] under our reaction conditions did not induce any chirality to the protected aldol product **32i** (Scheme 65).



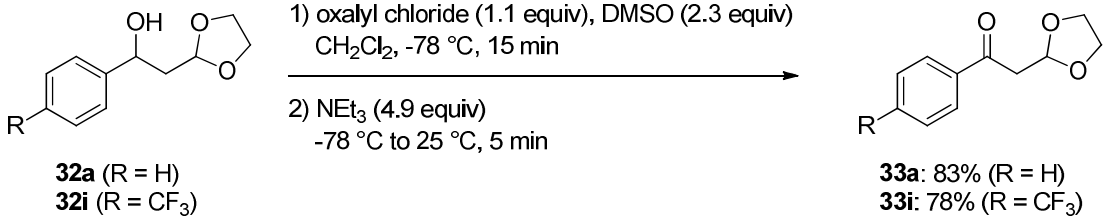
Scheme 65. (*R*)-BINOL chiral scandium complex.

With the goal to enantioselectively prepare protected aldol products of type **32**, we envisioned a simple reaction sequence of a *Swern* oxidation followed by a *CBS*-reduction (*Corey-Bakshi-Shibata*-reduction). Thus, the readily prepared protected aldol product **32a** was reacted under typical *Swern* oxidation[122] conditions affording the desired ketone **33a** in 75% (Scheme

[121] a) S. Kobayashi, H. Ishitani, M. Araki, I. Hachiya, *Tetrahedron Lett.* **1994**, *35*, 6325; b) G. V. More, B. M. Bhanage, *Eur. J. Org. Chem.* **2013**, 6900.

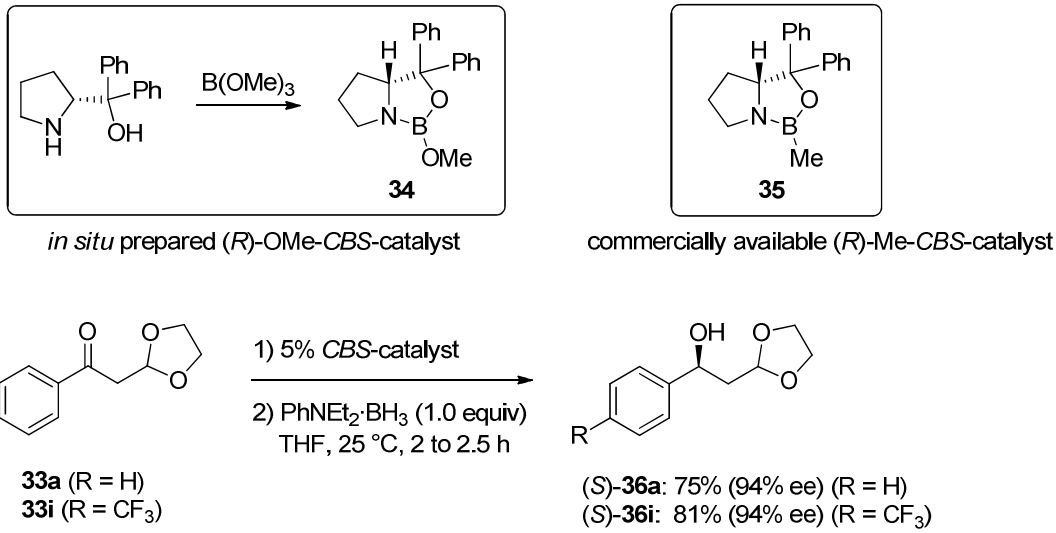
[122] a) K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651; b) A. J. Mancuso, S.-L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480; c) A. J. Mancuso, D. S. Brownfain, D. Swern, *J. Org. Chem.* **1979**, *44*, 4148.

66).[123] Similarly, ketone **33i**, prepared from the protected aldol product **32i**, was synthesized in 83% yield.[123]



Scheme 66. Preparation of ketones **33a** and **33i** using typical *Swern*-oxidation conditions.

The readily prepared ketones **33a** and **33i** were then submitted in a *CBS*-reduction step using catalytic amounts of an oxazaborolidine *CBS*-catalyst.[124] Thus, the use of the *in situ* prepared (*R*)-OMe-*CBS*-catalyst **34** as well as the commercially available (*R*)-Me-*CBS* catalyst **35** allow the highly enantioselective preparation of β-hydroxy-1,3-dioxolanes **36a** and **36i** in 75% and 81% yield, respectively, in an enantiomeric excess of 94% (Scheme 67).[123,125]



Scheme 67. Highly enantioselective preparation of β-hydroxy-1,3-dioxolanes **36a** and **36i** *via* a *CBS*-reduction.

Since the chiral protected aldol product **36a** is already known in the literature,[116] the absolute configuration of compound **36a** was determined by comparison of the measured specific rotation and the reported one.[116,126] Per analogy, we deduced the (*S*)-configuration of the protected aldol product **36i**. The structure of compound **36i** was confirmed by X-ray

[123] These experiments were performed in collaboration with Laura Kohout in the frame of her Master thesis and Dr. Daniela Sustac Roman.
[124] D. Soorukram, P. Knochel, *Org. Lett.* **2007**, *9*, 1021.
[125] The enantiomeric excesses of **35a** and **35i** were determined using chiral HPLC measurements, see experimental part.
[126] For the specific rotation results, see the Experimental Section.

diffraction analysis corroborating the (S)-configuration since every single structure is showing the alcohol substituent at the front, and the large group (phenyl ring) on the left (Figure 8).[127]

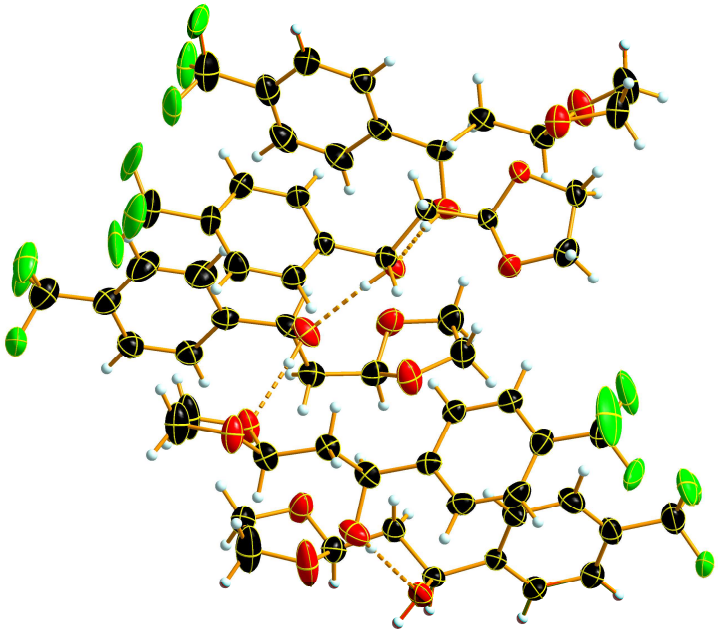


Figure 8. Molecular structure of compound **36i** in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50% probability level.

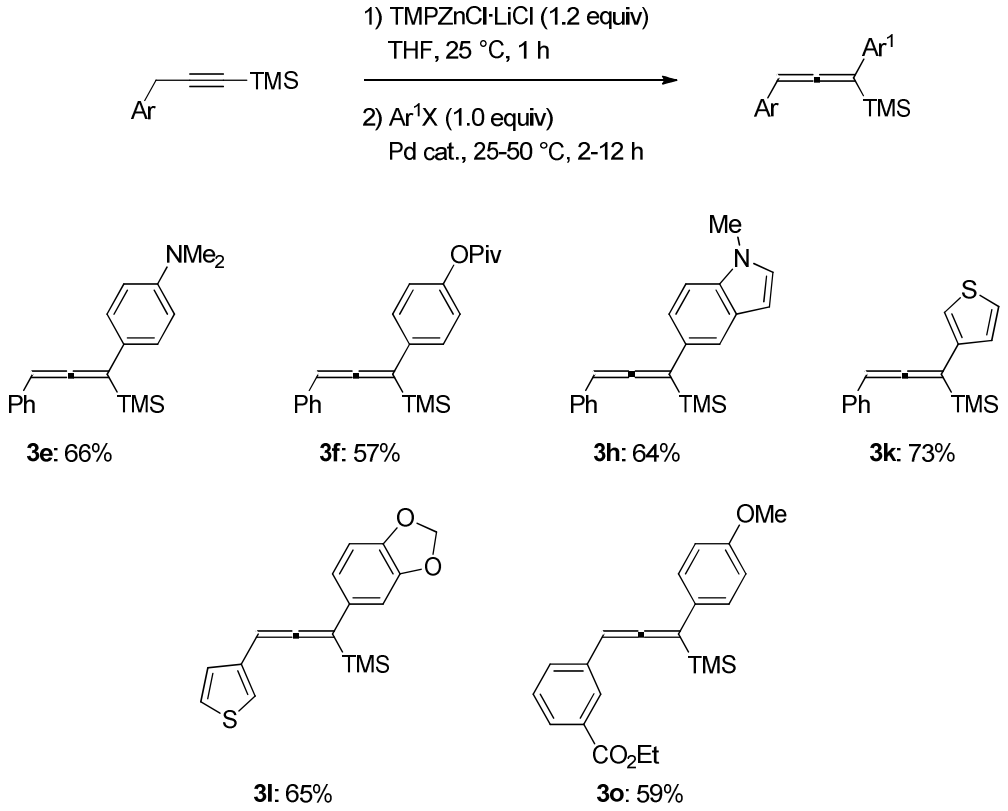
To summarize, we developed an efficient catalytic method for accessing β-hydroxy-1,3-dioxolane derivatives of type **32** by reacting bromomagnesium-2-vinyl ethoxide **30** with a broad range of aldehydes of type **31** in the presence of 10% $Sc(OTf)_3$. We further proved the feasibility of easily preparing enantiomerically pure β-hydroxy-1,3-dioxolane products **36a** and **36i** using the well-established *Swern* oxidation and *CBS*-reduction procedures. Additional extensions of our process to the synthesis of diastereoselective compounds are further studied in our laboratories.

[127] X-ray crystal structures described in the all thesis were performed by Prof. Dr. Konstantin Karaghiosoff, for the crystal structures of this chapter see the Appendix.

V. Summary

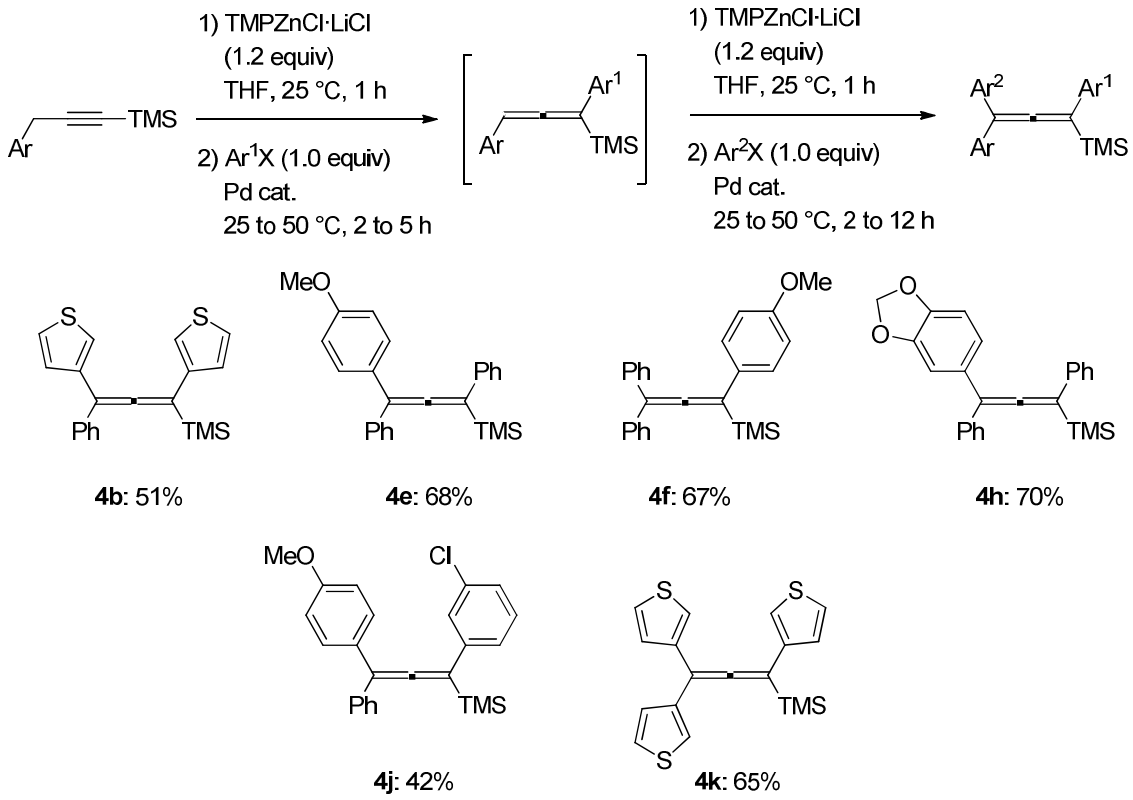
1) Preparation of polysubstituted allenes via regioselective lateral metalation of benzylic trimethylsilyl-alkynes using TMPZnCl·LiCl

The metalation of benzylic trimethylsilyl-alkynes using TMPZnCl·LiCl successfully permits the regioselective formation of allenyl zinc species. Thus, the zincated allenes react with a broad range of aryl or heteroaryl bromides or iodides in *Negishi* cross-coupling reactions producing trisubstituted allenes (Scheme 68).



Scheme 68. Lateral metalation of benzylic alkynes with TMPZnCl·LiCl and subsequent *Negishi* cross-coupling reactions affording a broad range of .trisubstituted allenes.

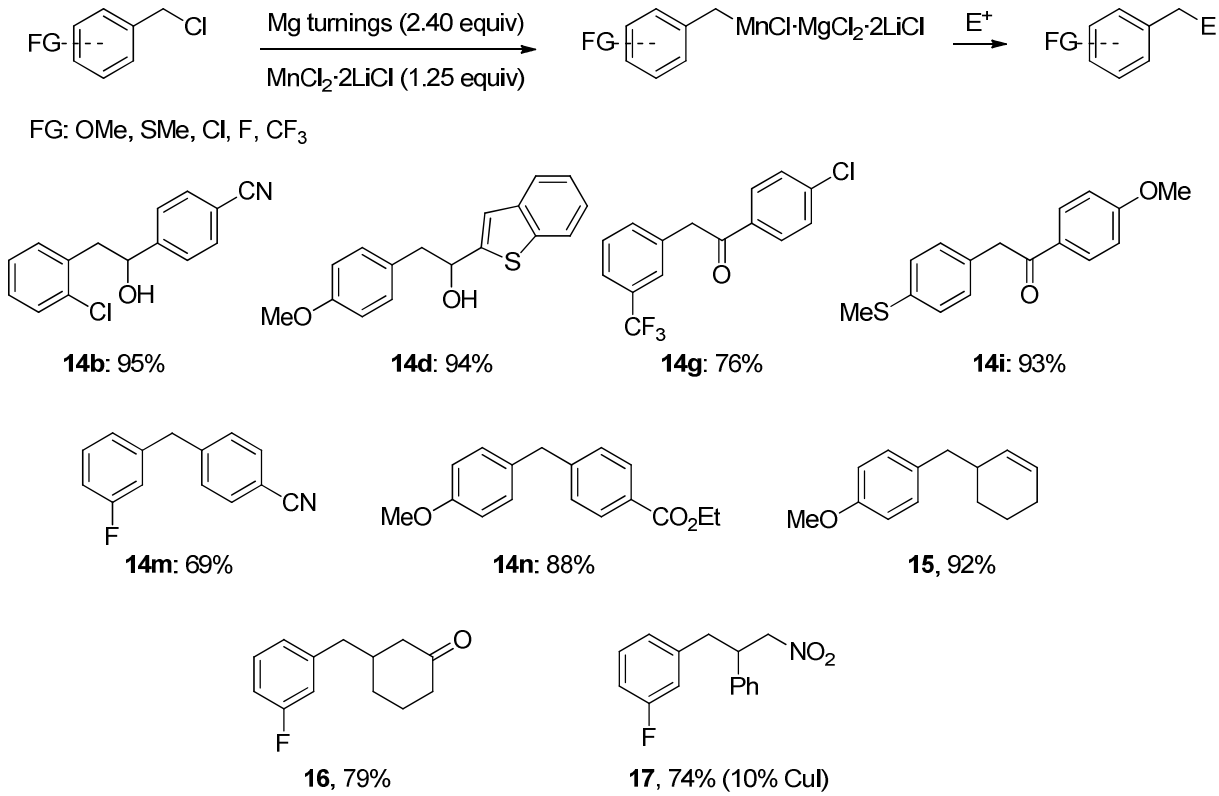
Furthermore, the method allows for the formation of tetrasubstituted allenes in a one-pot sequence based on successive metalations using TMPZnCl·LiCl followed by *Negishi* cross-coupling reactions (Scheme 69).



Scheme 69. Successive metalations with TMPZnCl·LiCl followed by *Negishi* cross-coupling reactions for the preparation of tetrasubstituted allenes.

2) <u>New preparation of benzylic manganese chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of $MnCl_2 \cdot 2LiCl$</u>

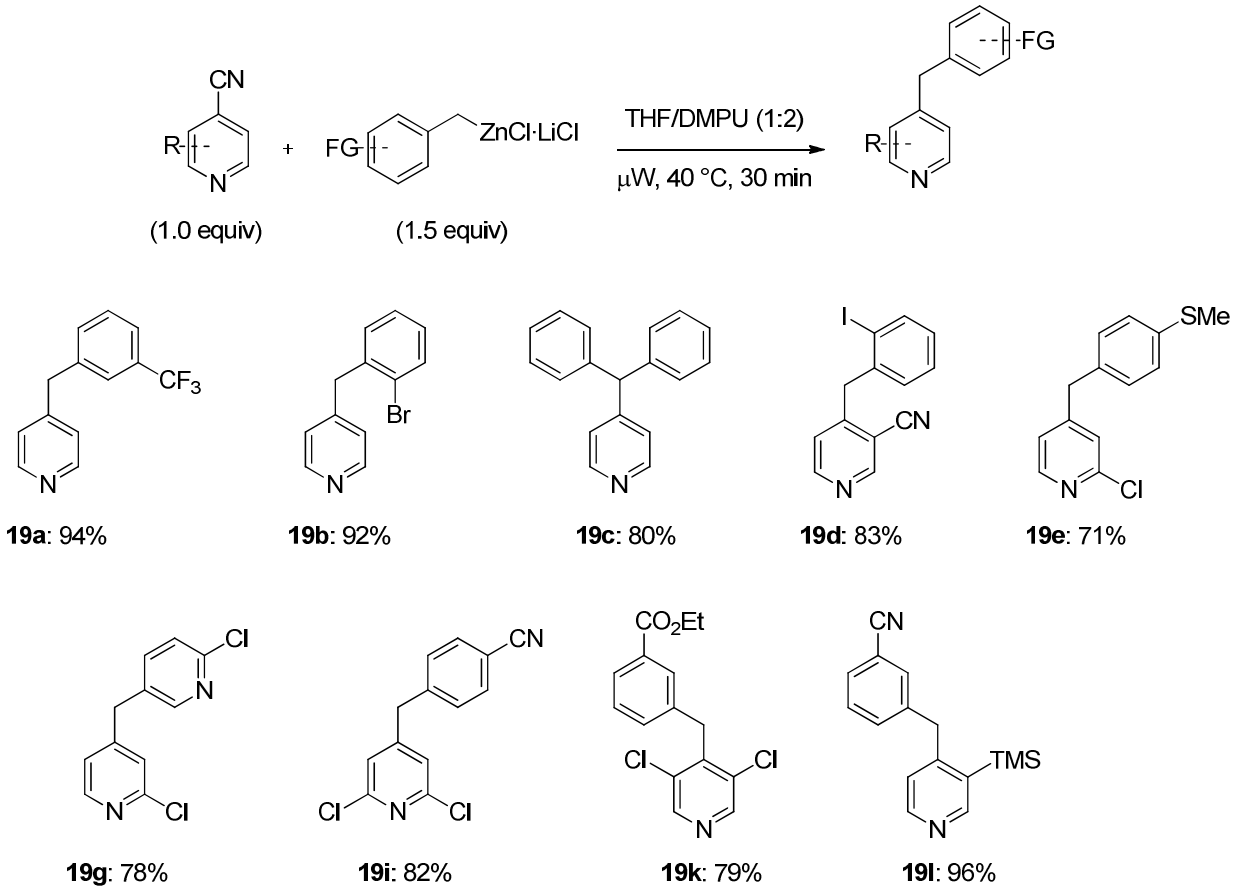
An efficient method for the preparation of benzylic manganese organometallics *via* magnesium insertion in the presence of $MnCl_2 \cdot 2LiCl$ was developed. The *in situ* formed *Grignard* reagents were directly transmetallated to the corresponding benzylic manganese reagents. We have demonstrated their versatility in the presence of various electrophiles such as an allylic bromide, an enone, aldehydes and acid chlorides mostly in the absence of additional transition metal (Scheme 70).



Scheme 70. Preparation of functionalized benzylic manganese reagents from benzylic chlorides *via* magnesium insertion in the presence of $MnCl_2 \cdot 2LiCl$ and subsequent reaction with electrophiles.

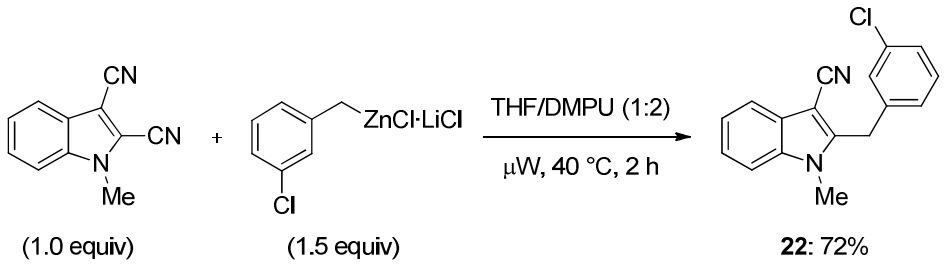
3) Transition metal free cross-coupling of aryl and *N*-heteroaryl cyanides with benzylic zinc reagents

The efficient transition metal free benzylation of 4-cyanopyridines in a THF/DMPU mixture under microwave irradiation was developed. The cyano substitutions occur under mild conditions (40 °C, 0.5-1.5 h) using readily available benzylic zinc chlorides and without the use of transition metal catalysts or Lewis acids (Scheme 71).



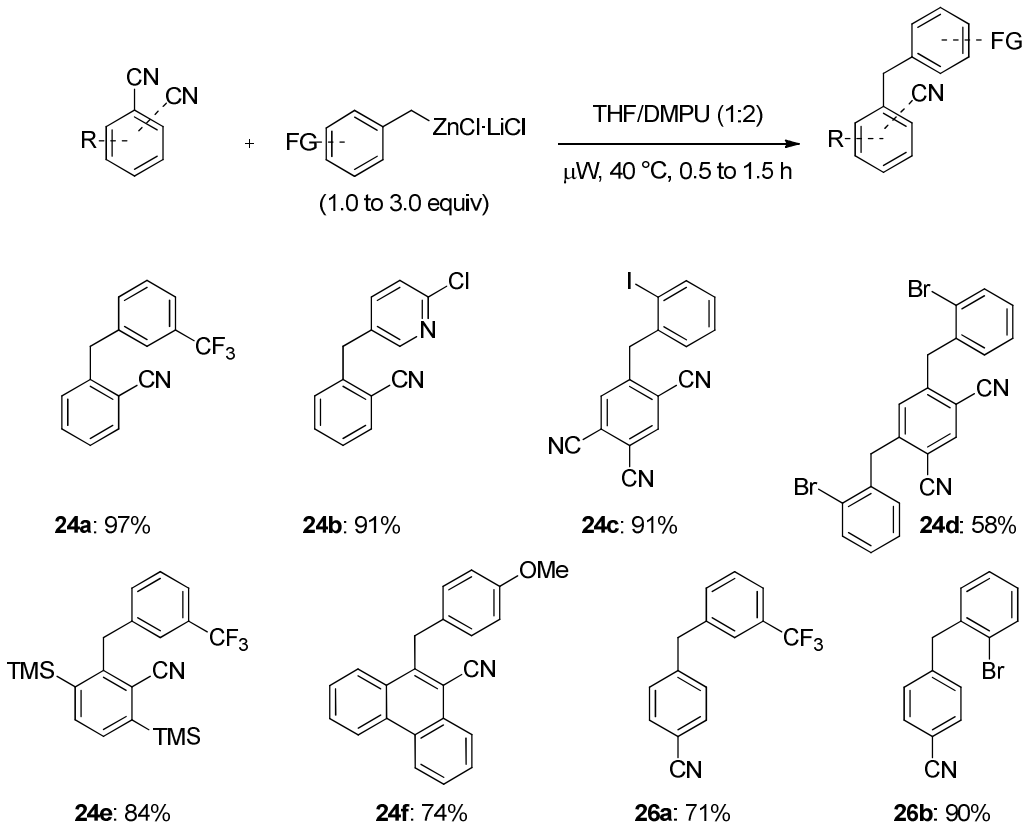
Scheme 71. Transition metal free cross-coupling reactions between benzylic zinc reagents and substituted 4-cyanopyridines.

Furthermore, the transition metal free benzylation using benzylic zinc chloride reagents is also regioselective, as illustrated in the reaction with a dicyano-substituted indole (Scheme 72).



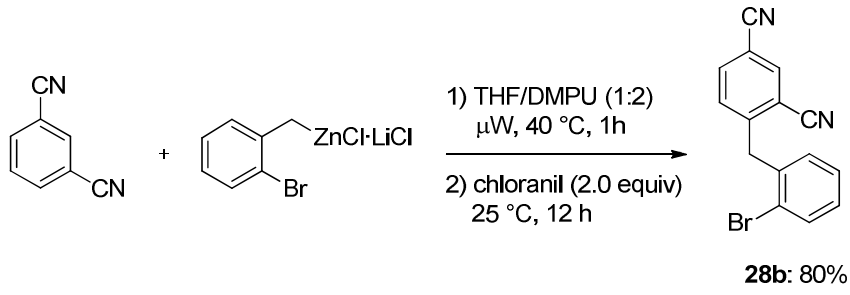
Scheme 72. Regioselective transition metal free cross-coupling reaction affording indole **22**.

The developed method could be successfully applied to the benzylation of various polycyano-aromatics (Scheme 73).



Scheme 73. Cross-coupling between aromatic nitriles and various benzylic zinc chlorides under microwave irradiation.

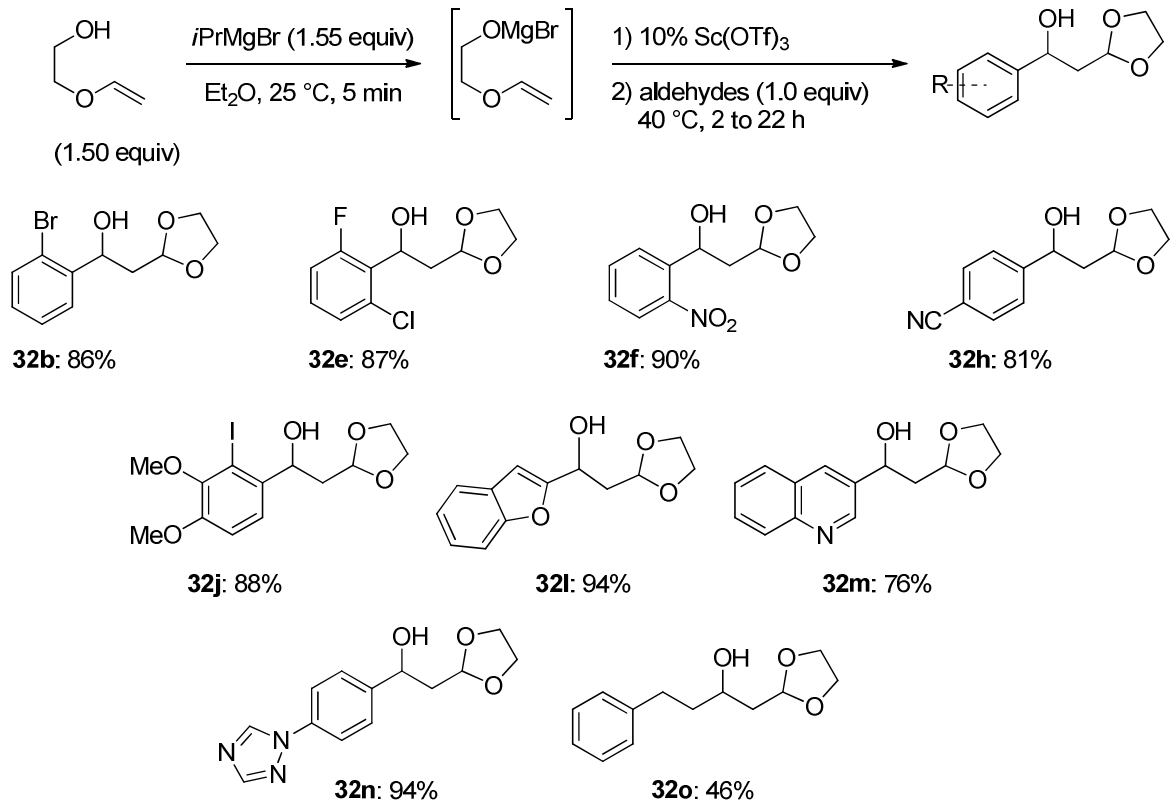
In addition, a novel oxidative nucleophilic substitution of hydrogen on 1,3-dicyanobenzene was successfully accomplished (Scheme 74).



Scheme 74. Novel oxidative nucleophilic substitution of hydrogen on 1,3-dicyanobenzene.

4) Sc(OTf)$_3$-catalyzed addition of bromomagnesium 2-vinyloxy ethoxide to various aldehydes leading to protected aldol products

Finally, the Sc(OTf)$_3$-catalyzed preparation of β-hydroxy-1,3-dioxolane derivatives was developed. The deprotonation of ethylene glycol vinyl ether using *i*PrMgBr affords the corresponding bromomagnesium 2-vinyloxy ethoxide, which reacts with aldehydes in the presence of 10% Sc(OTf)$_3$ allowing the preparation of a broad range of protected aldol products (Scheme 75).



Scheme 75. $Sc(OTf)_3$-catalyzed preparation of a broad range of protected aldol products.

EXPERIMENTAL SECTION

I. 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.

1) Solvents

Solvents were dried according to standard procedures by distillation over drying agents and stored under argon.

CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2.
Et_2O was predried over CaH_2 and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.
DMPU was freshly distilled over CaH_2 prior to use and kept under argon over molecular sieves (4 Å).
MTBE was freshly distilled from sodium benzophenone ketyl under nitrogen.
Solvents for column chromatography were distilled on a rotary evaporator prior to use.
THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and kept under argon over molecular sieves (4 Å).

2) Reagents

Commercially available starting materials were purchased from commercial sources and used without further purification.

***i*PrMgCl·LiCl** solution in THF was purchased from Rockwood Lithium.
***i*PrMgCl** solution in THF was purchased from Rockwood Lithium.
***i*PrMgBr:** A dry and argon-flushed 10 mL *Schlenk* tube, equipped with a stirring bar and septum, was charged with Mg turnings (2.43 g, 100 mmol, 2.5 equiv) and heated with a heat gun (450 °C) under high vacuum. After cooling to 25 °C, THF (20 mL) and DBE (1,2-dibromoethane, few drops; as activator) were added and the solution was heated with heat gun (50 °C). A solution of *i*PrBr (3.76 mL, 40.0 mmol, 1.0 equiv) in THF (20 mL) was added dropwise at 0 °C. The mixture was allowed to warm to 25 °C. The solids were allowed to sediment overnight and giving *Grignard* reagent *i*PrMgBr as a grey solution.

***n*BuLi** solution in hexane was purchased from Rockwood Lithium.

CuCN·2LiCl (1.0 M solution in THF): A *Schlenk*-flask was charged with LiCl (16.96 g, 0.40 mol), predried under high vacuum ($5 \cdot 10^{-2}$ mbar; dry stirring). CuCN (17.95 g, 0.20 mol) was added and the mixture was dried for 6 h at 150 °C under high vacuum ($5 \cdot 10^{-2}$ mbar; dry stirring). After cooling, careful addition of THF (200 mL) under an argon atmosphere and stirring overnight furnished a slightly yellow to green solution. A dark green to black color indicates the presence of Cu(II), this solution should not be used.

$MnCl_2$·2LiCl (1.0 M in THF): A dry and argon-flushed 250 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a glass stopper, was charged with LiCl (6.8 g, 160 mmol) and heated up to 150 °C under high vacuum for 3 h. After cooling to room temperature under argon, $MnCl_2$ (10.1 g, 80 mmol, 99 % pure) was added under inert atmosphere. The *Schlenk*-flask was further heated to 130 °C for 3 h under high vacuum, cooled to room temperature and charged with freshly distilled THF (80 mL) under argon with vigorous stirring. The mixture was stirred for at least 24 h at 25 °C. The reagent $MnCl_2$·2LiCl (1.0 M in THF) appears as a yellow solution.

TMPZnCl·LiCl: A dry and argon-flushed *Schlenk*-flask was charged with TMPH (10.2 mL, 60 mmol) and THF (60 mL). The solution was cooled to -40 °C and *n*BuLi-solution (2.3 M in hexane; 26 mL, 60 mmol) was added dropwise at this temperature. The solution was slowly warmed to -10 °C over 1 h before the addition of a $ZnCl_2$-solution (1.0 M in THF; 66 mL, 66 mmol). The solution was maintained at this temperature for 30 min and warmed to 25 °C for another 30 min. All the volatiles were removed under high vacuum before the addition of THF (30-35 mL) and stirring overnight furnishes a slightly yellowish solution.

$ZnCl_2$ (1.0 M solution in THF): A *Schlenk*-flask was charged with $ZnCl_2$ (27.2 g, 0.20 mol) and dried for 6 h at 150 °C under high vacuum ($5 \cdot 10^{-2}$ mbar, dry stirring). After cooling, careful addition of THF (200 mL) under an argon atmosphere and stirring overnight furnishes a clear, colorless solution which is kept over molecular sieves (4 Å).

3) Content Determination of Organometallic Reagents

Organozinc and organomagnesium reagents were titrated with I_2 in THF.[128]

[128] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890.

Organolithium reagents were titrated with anhydrous 2-propanol and 1,10-phenanthroline as indicator in THF.[129]

TMPZnCl·LiCl was titrated with benzoic acid and 4-(phenylazo)diphenylamine as indicator in THF at 25 °C.

4) Chromatography

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from MERCK.

Thin layer chromatography was performed using SiO_2 pre-coated aluminium plates (Merck 60, F-254). The chromatograms were examined under 254 nm UV irradiation or by staining of the TLC plate with a solution of $KMnO_4$ (3.0 g), 5 drops of conc. H_2SO_4 in water (300 mL), followed by heating with a heat gun.

5) Analytical Data

^{1}H NMR and **^{13}C NMR** spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the solvent peak. NMR spectra were recorded in a solution of $CDCl_3$ (residual chloroform: δ = 7.27 ppm for ^{1}H NMR and δ = 77.0 ppm for ^{13}C NMR). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, brought.

Mass spectroscopy: High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an ionization energy of 70 eV.

For coupled gas chromatography/mass spectrometry, a HEWLETT-PACKARD HP 6890/MSD 5973 GC/MS system was used. Molecular fragments are reported starting at a relative intensity of 10%.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSampl*IR* II Diamond ATR sensor was used. Wavenumbers are reported in cm^{-1} starting at an absorption of 10%.

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

[129] H.-S. Lin, A. Paquette, *Synth. Commun*. **1994**, *24*, 2503.

II. Typical Procedures

1) Typical Procedure for the preparation of allenylzinc reagents and subsequent allylation (**TP1**):

A dry and argon-flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a rubber septum, was charged with alkynes **2a-c** (1.0 mmol), followed by dry THF (2 mL). A freshly titrated solution of TMPZnCl·LiCl in THF (**1**, 1.2 equiv) was added dropwise at 25 °C. After 1 h stirring, a solution of CuCN·2LiCl (0.3 equiv; 1.0 M in THF) was added at 25 °C and the resulting solution was stirred 15 min at this temperature before addition of allyl bromide (1.5 equiv). The solution was stirred at 25 °C for 1 h and quenched with aq. ammonia solution (NH_4Cl/NH_3 25 %, 4:1; 2 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and purification by flash column chromatography (Al_2O_3) afforded the expected trisubstituted allenes.

2) Typical Procedure for the direct cross-coupling reactions of allenylzinc reagents (**TP2**):

A dry and argon-flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a rubber septum, was charged with alkynes **2a-c** (1.0 mmol), followed by dry THF (2 mL). A freshly titrated solution of TMPZnCl·LiCl in THF (**1**, 1.2 equiv) was added dropwise at 25 °C. After 1 h stirring, electrophile (1.0 equiv) was added, followed by a mixture of $Pd(OAc)_2$ (0.02 equiv) and DPE-Phos (0.02 equiv) or $Pd(OAc)_2$ (0.02 equiv) and S-Phos (0.04 equiv) or PEPPSI-iPr (0.02 equiv). The reaction mixture was stirred at 25 or 50 °C until the GC analysis of hydrolyzed reaction aliquots (quenched with aq. sat. NH_4Cl) showed complete conversion of the alkyne (> 98 %). After complete conversion the reaction mixture was quenched with aq. sat. NH_4Cl (2 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and purification by flash column chromatography (SiO_2) afforded the expected trisubstituted allenes.

3) Typical Procedure for the one-pot double direct cross-coupling reactions of allenylzinc reagents (**TP3**):

A dry and argon-flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a rubber septum, was charged with alkyne **2a** (1.0 mmol), followed by dry THF (2 mL). A freshly titrated solution of TMPZnCl·LiCl in THF (1.2 equiv) was added dropwise at 25 °C. After 1 h

stirring, electrophile (1.0 equiv) was added, followed by a mixture of $Pd(OAc)_2$ (0.02 equiv) and DPE-Phos (0.02 equiv) or $Pd(OAc)_2$ (0.02 equiv) and S-Phos (0.04 equiv). The reaction mixture was stirred at 25 or 50 °C until the GC analysis of hydrolyzed reaction aliquots (quenched with aq. sat. NH_4Cl) showed complete conversion of the alkyne (> 98 %). After complete conversion, a freshly titrated solution of TMPZnCl·LiCl in THF (1.2 equiv) was added dropwise at 25 °C. After 1 h stirring, electrophile (1.0 equiv) was added, followed by a mixture of $Pd(OAc)_2$ (0.02 equiv) and DPE-Phos (0.02 equiv) or $Pd(OAc)_2$ (0.02 equiv) and S-Phos (0.04 equiv). The reaction mixture was stirred at 25 or 50 °C until the GC analysis of hydrolyzed reaction aliquots (quenched with aq. sat. NH_4Cl) showed complete conversion of the tri-substituted allene (> 98 %). After complete conversion the reaction mixture was quenched with aq. sat. NH_4Cl (2 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and purification by flash column chromatography (SiO_2) afforded the expected tetrasubstituted allenes.

4) Typical Procedure for the preparation of benzyl manganese chlorides **11a-f** (**TP4**):

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum was charged with magnesium (175 mg, 2.40 equiv), followed by dry THF (1 mL) or MTBE (1.9 mL) and a solution of $MnCl_2$·2LiCl (3.75 mL, 1.25 equiv; 1.0 M in THF). The mixture was cooled to 0 °C, the benzyl chloride (3.0 mmol, 1.0 equiv) was added at once and the reaction was maintained at 0 °C until complete conversion of the starting material was observed (reaction of aliquots with iodine followed by GC analysis).
When the insertion reaction was completed, the solution of benzyl manganese chloride was separated from the resulting salts *via* a syringe equipped with a filter and transferred to another *Schlenk*-flask, dry and argon flushed, before being titrated against iodine.

Titration procedure of the benzyl manganese chloride solutions:

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum was charged with iodine (note the exact mass), followed by dry THF (3 mL) to give a deep red solution. The benzyl manganese chloride solution was added dropwise at 25 °C to the iodine solution until the red coloration went to colorless (note the exact volume). Then, the concentration of the benzyl manganese chloride solution could be calculated. The yield of the benzyl manganese reagent was calculated using the volume of the resulting solution (after filtration) and the concentration as determined prior.

5) Typical Procedure for the reaction of benzyl manganese chlorides with electrophiles (**TP5**):

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum was charged with the electrophile (1.0 equiv), followed by dry THF (1 mL). The benzyl manganese chloride solution (1.05-1.10 equiv) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Sat. aq. NH_4Cl (4 mL) and water (2 mL) were added and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and purification by flash column chromatography (SiO_2) afforded the expected products.

6) Typical Procedure for the preparation of 4-benzylated pyridines (**TP6**):

A dry and argon-flushed microwave reaction vial, equipped with a magnetic stirring bar and a rubber septum, was charged with pyridine **18a-g** (0.25 mmol or 0.50 mmol), followed by dry THF (0.5 M) and DMPU (0.25 M). A freshly titrated solution of benzylic zinc chloride **20a-k** (1.5 equiv) was added at 25 °C and the microwave reaction vial was closed with an adapted microwave vial cap septum. The microwave vial was heated at 40 °C for 30 min under microwave irradiation (Biotage© microwave, max.: 15 Watt). Then, the reaction mixture was quenched with sat. aq. NH_4Cl (4 mL), transferred to an extraction funnel where additional sat. aq. NH_4Cl (20 mL) was added. The aqueous phase was extracted with Et_2O (6 x 20 mL). The organic layers were combined, dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and purification by flash column chromatography (SiO_2) afforded the expected pyridines **19a-m**.

7) Typical Procedure for the benzylation of aryl cyanides (**TP7**):

A dry and argon-flushed microwave reaction vial, equipped with a magnetic stirring bar and a rubber septum, was charged with aryl cyanides **23a-d** or **25** (0.5 or 1.0 mmol), followed by dry THF (1 mL) and dry DMPU (2 mL). A freshly titrated solution of benzylic zinc chloride (**20**, 1.5 equiv) was added at 25 °C and the microwave reaction vial was closed with an adapted microwave vial cap septum. The microwave vial was heated at 40 °C for the given reaction time under microwave irradiation and the reaction mixture was quenched with sat. aq. NH_4Cl (4 mL). After transfer to an extraction funnel, additional sat. aq. NH_4Cl (20 mL) was added and the aqueous phase was extracted with Et_2O (6 x 20 mL). The organic layers were combined, dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and

purification by flash column chromatography (SiO_2) afforded the expected benzylated aromatics **24a-f** and **26a-b**.

8) Typical Procedure for the benzylation of 1,3-dicyanobenzene **27** (**TP8**):

A dry and argon-flushed microwave reaction vial, equipped with a magnetic stirring bar and a rubber septum, was charged with 1,3-dicyanobenzene **27** (0.5 mmol), followed by dry THF (1 mL) and dry DMPU (2 mL). A freshly titrated solution of benzylic zinc chloride **20b** or **20j** (1.5 equiv) was added at 25 °C and the microwave reaction vial was closed with an adapted microwave vial cap septum. The microwave vial was heated at 40 °C for 1 h under microwave irradiation. Then, chloranil (2.0 equiv) was added to the reaction mixture and it was stirred at 25 °C under argon for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl (4 mL), transferred to an extraction funnel and additional sat. aq. NH_4Cl (20 mL) was added. The aqueous phase was extracted with Et_2O (6 x 20 mL). The organic layers were combined, dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and purification by flash column chromatography (SiO_2) afforded the benzylated aromatics **28a-b**.

9) Typical Procedure for the preparation of protected aldol products 32a-p (TP9):

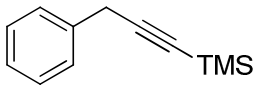
A dry and argon-flushed 10 mL *Schlenk* tube, equipped with a stirring bar and septum, was charged with 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, *i*PrMgBr (1.55 mmol, 1.55 equiv) was added dropwise at 25 °C. After 5 min stirring, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and aldehyde **31a-p** (1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred at 40 °C for the given time. After a full conversion was detected by GC-analysis, sat. aq. NH_4Cl (15 mL) was added and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered and solvent was evaporated in *vacuo*. Purification by column chromatography (SiO_2) afforded expected products **32a-p**.

III. Preparation of polysubstituted allenes via regioselective lateral metalation of benzylic trimethylsilyl-alkynes using TMPZnCl·LiCl

Some compounds of this chapter were prepared by Dr. Cyril François.

1) Preparation of the starting materials

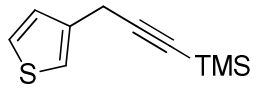
a. Trimethyl(3-phenylprop-1-yn-1-yl)silane (2a)



A dry and argon flushed *Schlenk*-flask was charged with TMS-acetylene (4.26 mL, 30 mmol) and THF (60 mL). The solution was cooled to 0 °C and *i*PrMgCl·LiCl (25.4 mL, 32 mmol; 1.26 M in THF) was added. The resulting solution was stirred at 25 °C for 2 h and added to a solution of benzyl chloride (2.23 mL, 20 mmol) and $Co(acac)_3$ (200 mg, 0.56 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 5 h and quenched with aq. sat. NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (*i*hexane) to yield compound **2a** (3.23 g, 86 %) as a brown liquid.

The analytical data matches the reported one in the literature.[130]

b. Trimethyl(3-(thiophen-3-yl)prop-1-yn-1-yl)silane (2b)



A dry and argon-flushed *Schlenk*-flask was charged with TMS-acetylene (4.26 mL, 30 mmol) and THF (60 mL). The solution was cooled to 0 °C and *i*PrMgCl·LiCl (25.4 mL, 32 mmol; 1.26 M in THF) was added. The resulting solution was stirred at 25 °C for 2 h and added to a solution of 3-(chloromethyl)thiophene[131] (2.13 mL, 20 mmol) and $Co(acac)_3$ (200 mg, 0.56 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 5 h and quenched with aq. sat. NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and purification by flash chromatography (SiO_2, *i*hexane) afforded the desired product **2b** (3.4 g, 88 %) as a brown liquid.

[130] Kuno, A.; Saino, N.; Kamachi, T.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 2591
[131] Shang, R.; Huang, Z.; Xiao, X.; Lu, X.; Fu, Y.; Liu, L. *Adv. Synth. Catal.* **2012**, *354*, 2465 – 2472

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.27 (dd, *J* = 4.8, 3.0 Hz, 1 H), 7.15 (dd, *J* = 3.0, 1.5 Hz, 1 H), 7.00 (dd, *J* = 4.8, 1.5 Hz, 1 H), 3.62 (s, 1 H), 3.61 (s, 1 H), 0.19 (s, 9 H).

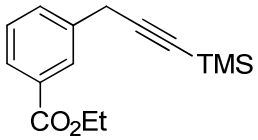
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 136.8, 127.7, 126.0, 121.4, 104.2, 86.5, 21.5, 0.2 (3 C).

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 2950, 2174, 1248, 1024, 832.

MS (EI, 70 eV) *m/z* (%) = 42 (100), 73 (80), 179 (21), 194 (7).

HRMS (EI): *m/z* (M^+) for **$C_{10}H_{14}SSi$**: calc. 194.0585; found 194.0563.

c. Ethyl 3-(3-(trimethylsilyl)prop-2-yn-1-yl)benzoate (2c)



A dry and argon-flushed 2-necked round-bottom flask equipped with a condenser was charged with ethyl 3-(chloromethyl)benzoate[132] (990 mg, 5.0 mmol), TMS-acetylene (3.55 mL, 25 mmol), cesium carbonate (1.95 g, 5.5 mmol), $Pd(OAc)_2$ (30 mg, 0.125 mmol), X-Phos (150 mg, 0.30 mmol) and THF (10 mL). The resulting mixture was refluxed for 5 h and quenched with aq. sat. NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 50:1) afforded the desired product **2c** (825 mg, 63 %) as a brown liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.03 (s, 1 H), 7.92 (d, *J* = 7.2 Hz, 1 H), 7.54 (d, *J* = 7.2 Hz, 1 H), 7.40 (dd, 1 H), 4.38 (q, *J* = 7.5 Hz, 2 H), 3.70 (s, 2 H), 1.40 (t, *J* = 7.5 Hz, 3 H), 0.20 (s, 9 H).

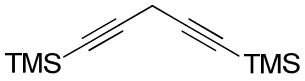
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 166.6, 136.8, 132.4, 130.9, 129.1, 128.6, 128.0, 103.7, 87.8, 61.1, 26.1, 14.5, 0.2 (3 C).

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 2957, 2177, 1717, 1276, 1248, 837.

MS (EI, 70 eV) *m/z* (%) = 201 (100), 215 (12), 245 (35), 260 (13).

HRMS (EI): *m/z* (M^+) for **$C_{15}H_{20}O_2Si$**: calc. 260.1233; found 260.1216.

d. 1,5-bis(trimethylsilyl)penta-1,4-diyne (6)



A dry and argon-flushed 2-necked round-bottom flask equipped with a condenser was charged with THF (20 mL) and CH_3MgCl (6.04 mL, 16.5 mmol; 2.73 M in THF). TMS-acetylene (2.83 mL, 20 mmol) was added dropwise over a period of 15 min, just fast enough

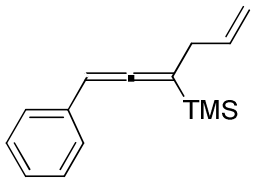
[132] Duez, S.; Bernhardt, S.; Heppekausen, J.; Fleming. F. F.; Knochel. P. *Org. Lett.* **2011**, *13*, 1690

to keep the solution at reflux. The catalyst CuCl (50 mg, 0.51 mmol) was added and the mixture was refluxed for 1 h. A solution of propargyl chloride[133] (1.06 g, 1.03 mL, 14.25 mmol) in THF (2.5 mL) was added to the refluxing solution and the mixture was heated for 1 h. The reaction mixture was poured into 25 mL ice water and acidified with 1.25 mL of concentrated H_2SO_4, extracted with Et_2O (3 x 15 mL), and the organic phase was neutralized with sat. $NaHCO_3$ solution, washed with water, and dried over Na_2SO_4. Vacuum fractional distillation under argon gave compound **6** (2.00 g, 67 %) as a colorless liquid.

The analytical data matches the reported one in the literature.[134]

2) Preparation of trisubstituted allenes

a. Trimethyl(1-phenylhexa-1,2,5-trien-3-yl)silane (3a)



According to **TP1,** trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), THF (2 mL) and freshly titrated TMPZnCl·LiCl (**1**, 1.02 mL, 1.2 mmol; 1.18 M in THF) were used. After stirring the reaction mixture for 1 h at 25 °C, a solution of CuCN·2LiCl (0.30 mL, 0.30 equiv; 1.0 M in THF) was added at 25 °C and the reaction mixture was stirred 15 min at this temperature, followed by the addition of allyl bromide (181 mg , 0.13 mL, 1.50 mmol). The reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (Al_2O_3, *i*hexane) afforded the desired product **3a** (176 mg, 77 %) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.34-7.25 (m, 4 H), 7.20-7.14 (m, 1 H), 6.00-5.87 (m, 1 H), 5.95 (t, *J* = 3.0 Hz, 1 H), 5.17-5.10 (m, 1 H), 5.07-5.03 (m, 1 H), 2.96-2.91 (m, 2 H), 0.20 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 206.4, 137.1, 136.0, 128.7 (2 C), 126.0 (3 C), 115.6, 99.8, 90.2, 34.4, -1.1 (3 C).

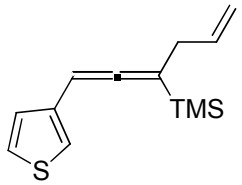
IR (Diamond-ATR, neat) ν/cm^{-1} = 2956, 1922, 1598, 1249, 832.

MS (EI, 70 eV) *m/z* (%) = 43 (100), 45 (15), 61 (18), 70 (12), 73 (29), 228 (3).

HRMS (EI): *m/z* (M^+) for **$C_{15}H_{20}Si$**: calc. 228.1334; found 228.1338.

[133] Verkruijsse, H.D., Brandsma, L. *Synth. Commun.* **1990** 20, 3375.
[134] Du, B.; Farona, M.F. *Tetrahedron* **1995**, *51*, 4359.

b. Trimethyl(1-(thiophen-3-yl)hexa-1,2,5-trien-3-yl)silane (3b)



According to **TP1,** trimethyl(3-(thiophen-3-yl)prop-1-yn-1-yl)silane (**2b**, 194 mg, 1.00 mmol), THF (2 mL) and freshly titrated TMPZnCl·LiCl (**1**, 1.02 mL, 1.2 mmol; 1.18 M in THF) were used. After stirring the reaction mixture for 1 h at 25 °C, a solution of CuCN·2LiCl (0.30 mL, 0.30 equiv; 1.0 M in THF) was added at 25 °C and the reaction mixture was stirred 15 min at this temperature, followed by the addition of allyl bromide (181 mg, 0.13 mL, 1.50 equiv). The reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (Al_2O_3, *i*hexane) afforded the desired product **3b** (166 mg, 71 %) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.22 (dd, *J* = 5.1, 3.0 Hz, 1 H), 6.99 (dd, *J* = 5.1, 1.2 Hz, 1 H), 6.94 (dd, *J* = 3.0, 1.2 Hz, 1 H), 5.98 (t, *J* = 3.0 Hz, 1 H), 5.95-5.81 (m, 1 H), 5.12-4.98 (m, 2 H), 2.88-2.85 (m, 2 H), 0.14 (s, 9 H).

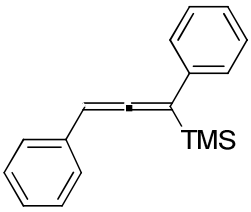
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 207.1, 137.1, 137.0, 126.2, 125.7, 118.6, 115.5, 99.1, 84.9, 34.5, -1.1 (3 C).

IR (Diamond-ATR, neat) ν/cm^{-1} = 2954, 1922, 1637, 1246, 832.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 165 (18), 234 (20).

HRMS (EI): *m/z* (M^+) for **$C_{13}H_{18}SSi$**: calc. 234.0898; found 234.0881.

c. (1,3-diphenylpropa-1,2-dien-1-yl)trimethylsilane (3c)



According to **TP2**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 0.96 mL, 1.2 mmol; 1.25 M in THF), iodobenzene (204 mg, 0.11 mL, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / S-Phos (16.4 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 4 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane) afforded the desired product **3c** (180 mg, 68 %) as a white solid.

M.p. (°C): 78-80.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.38-7.28 (m, 8 H), 7.23-7.16 (m, 2 H), 6.21 (s, 1 H), 0.30 (s, 9 H).

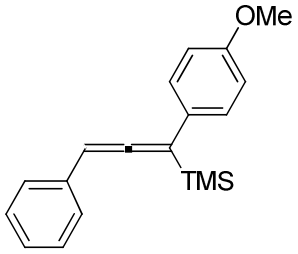
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.6, 136.8, 134.9, 128.8 (2 C), 128.7 (2 C), 127.0 (2 C), 126.7, 126.5, 126.3 (2 C), 107.8, 91.5, 0.0 (3 C).

IR (Diamond-ATR, neat) ν/cm^{-1} = 2966, 1910, 1488, 1242, 833.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 189 (9), 264 (6).

HRMS (EI): *m/z* (M^+) for **$C_{18}H_{20}Si$**: calc. 264.1334; found 264.132.

d. (1-(4-methoxyphenyl)-3-phenylpropa-1,2-dien-1-yl)trimethylsilane (3d)



According to **TP2**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 0.96 mL, 1.2 mmol; 1.25 M in THF), 4-iodoanisole (234 mg, 1.00 mmol) and the catalytic system [PEPPSI-*i*Pr (13.6 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 5 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane) afforded the desired product **3d** (223 mg, 76 %) as a yellow solid.

M.p. (°C): 95-97.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.31-7.27 (m, 6 H), 7.18-7.14 (m, 1 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 6.20 (s, 1 H), 3.79 (s, 3 H), 0.29 (s, 9 H).

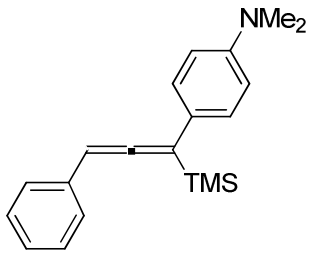
^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm = 209.2, 158.6, 135.1, 129.0 (2 C), 128.9 (2 C), 128.7, 126.4, 126.3 (2 C), 114.2 (2 C), 104.0, 91.5, 55.4, 0.0 (3 C).

IR (Diamond-ATR, neat) ν/cm^{-1} = 2959, 1905, 1508, 1245, 828.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 178 (14), 221 (21), 279 (100), 294 (14).

HRMS (EI): *m/z* (M^+) for **$C_{19}H_{22}OSi$**: calc. 294.1440; found 294.1429.

e. *N*,*N*-dimethyl-4-(3-phenyl-1-(trimethylsilyl)propa-1,2-dien-1-yl)aniline (3e)



According to **TP2**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.07 mL, 1.2 mmol; 1.12 M in THF), 4-bromo-*N*,*N*-dimethylaniline (200 mg, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (9.0 mg, 0.04 mmol) / DPE-Phos (21.5 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 4 h at 50 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:1) afforded the desired product **3e** (203 mg, 66 %) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.30-7.26 (m, 6 H), 7.17-7.14 (m, 1 H), 6.70 (d, *J* = 8.4 Hz, 2 H), 6.20 (s, 1 H), 2.94 (s, 6 H), 0.30 (s, 9 H).

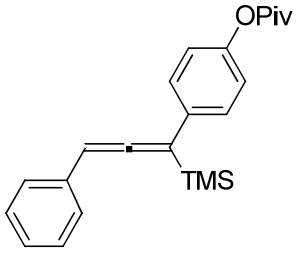
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.0, 149.6, 135.6, 128.77 (2 C), 128.75 (2 C), 126.24 (2 C), 126.20 (2 C), 123.8, 112.9, 104.0, 91.6, 40.7 (2 C), 0.1 (3 C).

IR (Diamond-ATR, neat) ν/cm^{-1} = 2952, 1904, 1606, 1515, 1247, 833.

MS (EI, 70 eV) *m/z* (%) = 73 (54), 189 (12), 218 (24), 234 (100), 307 (26).

HRMS (EI): *m/z* (M^+) for **$C_{20}H_{25}NSi$**: calc. 307.1756; found 307.1737.

f. 4-(3-phenyl-1-(trimethylsilyl)propa-1,2-dien-1-yl)phenyl pivalate (3f)



According to **TP2**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.07 mL, 1.2 mmol; 1.12 M in THF), 4-bromophenylpivalate[135] (257 mg, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 6 h at 50 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:2) afforded the desired product **3f** (208 mg, 57 %) as a yellow oil.

[135] J.-S. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.34 (d, *J* = 9.0 Hz, 2 H), 7.31-7.27 (m, 4 H), 7.19-7.16 (m, 1 H), 6.99 (d, *J* = 9.0 Hz, 2 H), 6.21 (s, 1 H), 1.35 (s, 9 H), 0.29 (s, 9 H).

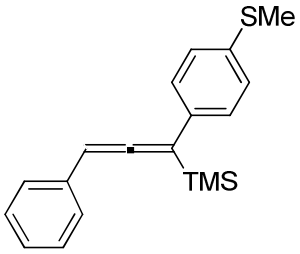
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.7, 177.2, 149.9, 134.8, 134.1, 128.9 (2 C), 128.8 (2 C), 126.6, 126.3 (2 C), 121.7 (2 C), 104.1, 91.6, 39.2, 27.3 (3 C), -0.1 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2961, 1911, 1751, 1108, 835.

MS (EI, 70 eV) *m/z* (%) = 57 (53), 73 (100), 190 (44), 279 (77), 364 (5).

HRMS (EI): *m/z* (M^+) for **$C_{23}H_{28}O_2Si$**: calc. 364.1859; found 364.1854.

g. Trimethyl(1-(4-(methylthio)phenyl)-3-phenylpropa-1,2-dienyl)silane (3g)



According to **TP2**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.11 mL, 1.2 mmol; 1.08 M in THF), 4-bromothioanisole (203 mg, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 6 h at 50 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:1) afforded the desired product **3g** (233 mg, 75 %) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.29-7.24 (m, 6 H), 7.17-7.13 (m, 3 H), 6.20 (s, 1 H), 2.45 (s, 3 H), 0.27 (s, 9 H).

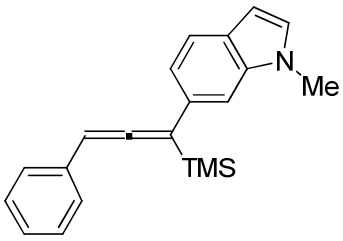
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 209.7, 136.7, 134.8, 133.5, 128.9 (2 C), 128.4 (2 C), 127.1 (2 C), 126.6, 126.3 (2 C), 104.2, 91.7, 16.2, 0.0 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2954, 1907, 1486, 1248, 835.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 295 (13), 310 (18).

HRMS (EI): *m/z* (M^+) for **$C_{19}H_{22}SSi$**: calc. 310.1211; found 310.1206.

h. 1-methyl-5-(3-phenyl-1-(trimethylsilyl)propa-1,2-dien-1-yl)-1*H*-indole (3h)



According to **TP2**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.07 mL, 1.2 mmol; 1.12 M in THF), 5-bromo-*N*-methylindole (230 mg, 1.10 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:2) afforded the desired product **3h** (202 mg, 64 %) as a yellow solid.

M.p. (°C): 76-78.

^{1}H NMR (400 MHz, C_6D_6) δ/ppm = 8.00 (d, *J* = 1.6 Hz, 1 H), 7.60 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.43 (d, *J* = 1.6 Hz, 2 H), 7.22-7.17 (m, 4 H), 6.57 (d, *J* = 2.8 Hz, 1 H), 6.50 (dd, *J* = 3.2, 0.8 Hz, 1 H), 6.28 (s, 1 H), 2.94 (s, 3 H), 0.04 (s, 9 H).

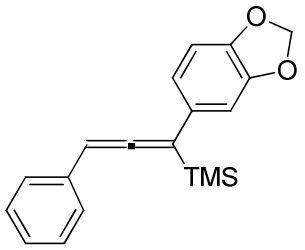
^{13}C NMR (75 MHz, C_6D_6) δ/ppm = 209.6, 136.4, 135.9, 129.7, 129.11 (2 C), 129.08, 128.2, 126.6 (2 C), 126.6 (2 C), 120.5, 109.8, 105.8, 101.6, 91.7, 32.0, 0.2 (3 C).

IR (Diamond-ATR, neat) υ / cm^{-1} = 2922, 1909, 1488, 1244, 834.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 244 (54), 317 (29).

HRMS (EI): *m/z* (M^+) for **$C_{21}H_{23}NSi$**: calc. 317.1600; found: 317.1575.

i. (1-(benzo[*d*][1,3]dioxol-5-yl)-3-phenylpropa-1,2-dien-1-yl)trimethylsilane (3i)



According to **TP2**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.11 mL, 1.2 mmol; 1.08 M in THF), 3-iodobenzodioxole (248 mg, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 4 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 50:1) afforded the desired product **3i** (290 mg, 94 %) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.28-7.24 (m, 4 H), 7.18-7.13 (m, 1 H), 6.85 (d, *J* = 1.8 Hz, 1 H), 6.80 (dd, *J* = 7.8, 1.8 Hz, 1 H), 6.74 (d, *J* = 7.8 Hz, 1 H), 6.18 (s, 1 H), 5.91 (s, 2 H), 0.27 (s, 9 H).

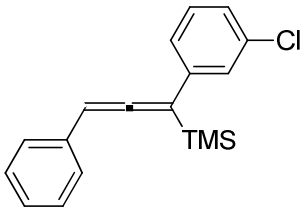
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 209.3, 148.0, 146.6, 134.9, 130.5, 128.9 (2 C), 126.5, 126.3 (2 C), 121.2, 108.4 (2 C), 104.5, 101.1, 91.7, 0.0 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2954, 2892, 1907, 1479, 1236, 1037, 833.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 276 (15), 278 (11), 308 (15).

HRMS (EI): *m/z* (M^+) for **$C_{19}H_{20}O_2Si$**: calc. 308.1233; found 308.1237.

j. (1-(3-chlorophenyl)-3-phenylpropa-1,2-dien-1-yl)trimethylsilane (3j)



According to **TP2**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.07 mL, 1.2 mmol; 1.12 M in THF), 3-chlorobromobenzene (191 mg, 0.12 mL, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 4 h at 50 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:0.5) afforded the desired product **3j** (180 mg, 60 %) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.32-7.28 (m, 5 H), 7.24-7.18 (m, 4 H), 6.24 (s, 1 H), 0.30 (s, 9 H).

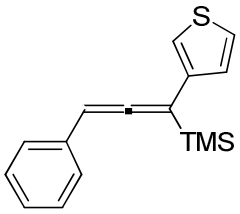
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.9, 138.9, 134.6, 134.4, 129.8, 128.9 (2 C), 127.9, 126.8 (2 C), 126.4 (2 C), 126.0, 104.1, 91.8, -0.1 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2955, 1914, 1588, 1249, 835.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 189 (23), 285/283 (5), 298 (5).

HRMS (EI): *m/z* (M^+) for **$C_{18}H_{19}ClSi$**: calc. 298.0945; found 298.0948.

k. Trimethyl(3-phenyl-1-(thiophen-3-yl)propa-1,2-dien-1-yl)silane (3k)



According to **TP2**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.02 mL, 1.2 mmol; 1.18 M in THF), 3-bromothiophene (163 mg, 0.09 mL, 1.00 mmol) and the catalytic system [PEPPSI-*i*Pr (13.6 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane) afforded the desired product **3k** (197 mg, 73 %) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.30-7.27 (m, 4 H), 7.26-7.25 (m, 1 H) 7.19-7.16 (m, 1 H), 7.14-7.13 (m, 1 H), 7.12 (dd, *J* = 5.4, 1.8 Hz, 1 H), 6.19 (s, 1 H), 0.31 (s, 9 H).

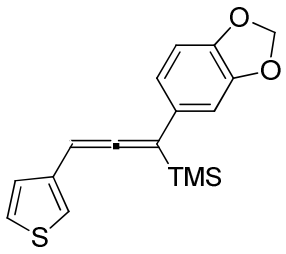
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.9, 136.4, 134.9, 128.8 (2 C), 128.0, 126.5, 126.4 (2 C), 125.3, 120.8, 99.5, 91.4, -0.2 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2960, 1907, 1245, 830.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 197 (5), 270 (7).

HRMS (EI): *m/z* (M^+) for **$C_{16}H_{18}SSi$**: calc. 270.0898; found: 270.0887.

l. (1-(benzo[*d*][1,3]dioxol-5-yl)-3-(thiophen-3-yl)propa-1,2-dien-1-yl)trimethylsilane (3l)



According to **TP2**, trimethyl(3-(thiophen-3-yl)prop-1-yn-1-yl)silane (**2b**, 194 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.11 mL, 1.2 mmol; 1.08 M in THF), 3-bromobenzodioxole (0.12 mL, 207.2 mg, 1 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 12 h at 50 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:1) afforded the desired product **3l** (203 mg, 65 %) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.27 (dd, *J* = 7.8, 0.4 Hz, 1 H), 7.05 (s, 1 H), 7.05-7.04 (m, 1 H), 6.87 (d, *J* = 1.8 Hz, 1 H), 6.83-6.81 (ddd, *J* = 8.0, 1.8, 0.4 Hz, 1 H), 6.78-6.76 (dd, *J* = 8.0, 0.4 Hz, 1 H), 6.29 (s, 1 H), 5.94 (d, *J* = 0.8 Hz, 2 H), 0.29 (s, 9 H).

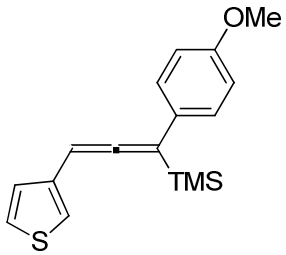
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.8, 147.9, 146.4, 135.7, 130.5, 125.9 (2 C), 121.0, 119.4, 108.2 (2 C), 103.7, 101.0, 86.3, -0.21 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2957, 2893, 1910, 1482, 1237, 1038, 836.

MS (EI, 70 eV) m/z (%) = 73 (100), 283 (12), 285 (10), 313 (12), 314 (31).

HRMS (EI): *m/z* (M^+) for **$C_{17}H_{18}O_2SSi$**: calc. 314.0797; found 314.0792.

m. (1-(4-methoxyphenyl)-3-(thiophen-3-yl)propa-1,2-dien-1-yl)trimethylsilane (3m)



According to **TP2**, trimethyl(3-(thiophen-3-yl)prop-1-yn-1-yl)silane (**2b**, 190 mg, 0.98 mmol), TMPZnCl·LiCl (**1**, 1.02 mL, 1.2 mmol; 1.18 M in THF), 4-iodoanisole (229 mg, 0.98 mmol) and the catalytic system and the catalytic system [$Pd(OAc)_2$ (4.4 mg, 0.02 mmol) / DPE-Phos (10.6 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:1) afforded the desired product **3m** (233 mg, 78 %) as an orange solid.

M.p. (°C): 44-46.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.28 (d, *J* = 8.4 Hz, 2 H), 7.25 (ddd, *J* = 4.8, 3.0, 0.6 Hz, 1 H), 7.05 (dd, *J* = 4.8, 1.2 Hz, 1 H), 7.04 (ddd, *J* = 3.0, 1.2, 0.6 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 6.28 (s, 1 H), 3.80 (s, 3 H), 0.29 (s, 9 H).

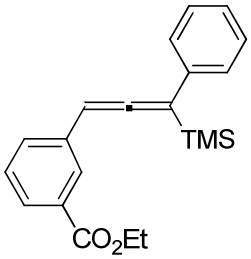
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.6, 158.4, 135.9, 128.9 (2 C), 128.7, 126.0, 125.8, 119.2, 114.0 (2 C), 103.2, 86.1, 55.3, -0.2 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2953, 1909, 1505, 1244, 830.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 227 (14), 285 (50), 300 (18).

HRMS (EI): *m/z* (M^+) for **$C_{17}H_{20}OSSi$**: calc. 300.1004; found 300.1000.

n. Ethyl 3-(3-phenyl-3-(trimethylsilyl)propa-1,2-dien-1-yl)benzoate (3n)



According to **TP2**, ethyl 3-(3-(trimethylsilyl)prop-2-yn-1-yl)benzoate (**2c**, 215 mg, 0.83 mmol), TMPZnCl·LiCl (**1**, 1.11 mL, 1.0 mmol; 1.08 M in THF), iodobenzene (169 mg, 0.09 mL, 0.83 mmol) and the catalytic system [$Pd(OAc)_2$ (3.7 mg, 0.02 mmol) / S-Phos (13.6 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:2) afforded the desired product **3n** (145 mg, 52 %) as a yellow oil.

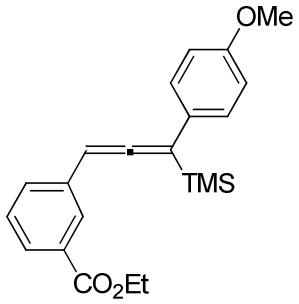
^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.94 (t, *J* = 1.8 Hz, 1 H), 7.84 (dt, *J* = 7.8, 1.2 Hz, 1 H), 7.47 (dt, *J* = 7.8, 1.8 Hz, 1 H), 7.37-7.30 (m, 5 H), 7.22 (dt, *J* = 7.2, 1.8 Hz, 1 H), 6.24 (s, 1 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 1.39 (t, *J* = 7.2 Hz, 3 H), 0.30 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.4, 166.7, 136.4, 135.5, 131.2, 130.3, 128.8 (3 C), 128.0 (2 C), 127.6, 127.4, 126.7, 105.2, 90.8, 61.1, 14.5, -0.1 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2956, 1911, 1716, 1276, 1248, 834.

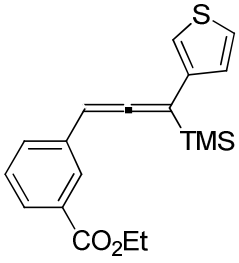
MS (EI, 70 eV) *m/z* (%) = 73 (58), 190 (100), 218 (75), 307 (96), 336 (34).
HRMS (EI): *m/z* (M^+) for **$C_{21}H_{24}O_2Si$**: calc. 336.1546; found 336.1528.

o. Ethyl 3-(3-(4-methoxyphenyl)-3-(trimethylsilyl)propa-1,2-dien-1-yl)benzoate (3o)



According to **TP2**, ethyl 3-(3-(trimethylsilyl)prop-2-yn-1-yl)benzoate (**2c**, 200 mg, 0.77 mmol), TMPZnCl·LiCl (**1**, 1.07 mL, 0.9 mmol; 1.12 M in THF), 4-iodoanisole (162 mg, 0.77 mmol) and the catalytic system [$Pd(OAc)_2$ (3.4 mg, 0.02 mmol) / S-Phos (12.6 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:2) afforded the desired product **3o** (165 mg, 59 %) as a yellow oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.93 (s, 1 H), 7.84 (d, *J* = 7.8 Hz, 1 H), 7.47 (d, *J* = 7.8 Hz, 1 H), 7.35 (t, *J* = 7.8 Hz, 1 H), 7.28 (d, *J* = 9.0 Hz, 2 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 6.23 (s, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 3.80 (s, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H), 0.03 (s, 9 H).
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.0, 166.7, 158.7, 135.2, 131.1, 130.3, 129.1 (2 C), 128.8, 128.3, 127.5, 127.3, 114.3 (2 C), 104.4, 90.9, 61.1, 55.4, 14.5, 0.0 (3 C).
IR (Diamond-ATR, neat) υ/cm^{-1} = 2955, 1909, 1715, 1506, 1277, 1244, 834.
MS (EI, 70 eV) *m/z* (%) = 73 (30), 220 (61), 248 (41), 293 (9), 337 (100), 366 (19).
HRMS (EI): *m/z* (M^+) for **$C_{22}H_{26}O_3Si$**: calc. 366.1651; found 336.1639.

p. Ethyl 3-(3-(thiophen-3-yl)-3-(trimethylsilyl)propa-1,2-dien-1-yl)benzoate (3p)



According to **TP2**, ethyl 3-(3-(trimethylsilyl)prop-2-yn-1-yl)benzoate (**2c**, 260 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.18 mL, 1.2 equiv; 1.02 M in THF), 3-bromothiophene (163 mg, 0.09 mL, 1.00 mmol) and the catalytic system [PEPPSI-*i*Pr (13.6 mg, 0.02 mmol)] were used.

The reaction mixture was stirred for 2 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:2) afforded the desired product **3p** (252 mg, 74 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.91 (t, *J* = 1.6 Hz, 1 H), 7.84 (dt, *J* = 8.0, 1.6 Hz, 1 H), 7.45 (dt, *J* = 8.0, 1.6 Hz, 1 H), 7.35 (t, *J* = 8.0 Hz, 1 H), 7.26 (dd, *J* = 4.8, 3.2 Hz, 1 H), 7.15-7.14 (m, 1 H), 7.10 (dd, *J* = 4.8, 1.6 Hz, 1 H), 6.22 (s, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 0.30 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm = 209.7, 166.7, 136.0, 135.4, 131.1, 130.4, 128.8, 127.9, 127.6, 127.5, 125.5, 121.1, 99.9, 90.7, 61.1, 14.5, -0.3 (3 C).

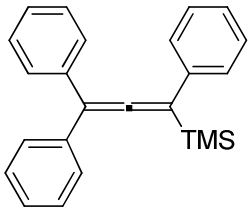
IR (Diamond-ATR, neat) υ/cm^{-1} = 2957, 1907, 1716, 1275, 1248, 832.

MS (EI, 70 eV) *m/z* (%) = 73 (36), 196 (67), 224 (56), 313 (100), 342 (34).

HRMS (EI): *m/z* (M^+) for **$C_{19}H_{22}O_2SSi$**: calc. 342.1110; found 342.1109.

3) Preparation of tetrasubstituted allenes

a. Trimethyl(1,3,3-triphenylpropa-1,2-dienyl)silane (4a)



According to **TP3**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 184 mg, 0.98 mmol), TMPZnCl·LiCl (**1**, 1.05 mL, 1.18 mmol, 1.2 equiv; 1.12 M in THF), iodobenzene (200 mg, 0.11 mL, 0.98 mmol) and the catalytic system [$Pd(OAc)_2$ (4.4 mg, 0.02 mmol) / S-Phos (16.1 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 4 h at 25 °C. Then, TMPZnCl·LiCl (**1**, 1.05 mL, 1.18 mmol, 1.2 equiv; 1.12 M in THF), iodobenzene (200 mg, 0.11 mL, 0.98 mmol) and the catalytic system [$Pd(OAc)_2$ (4.4 mg, 0.02 mmol) / S-Phos (16.1 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 12 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane) afforded the desired product **4a** (216 mg, 65 %) as a white solid.

M.p. (°C): 78-80.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.42-7.30 (m, 12 H), 7.27-7.26 (m, 1 H), 7.25-7.19 (m, 2 H), 0.31 (s, 9 H).

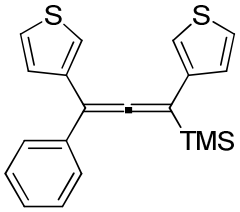
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.6, 136.9, 136.8, 128.8 (2 C), 128.6 (4 C), 128.2 (4 C), 128.0 (2 C), 126.9, (2 C), 126.8 (2 C), 106.7, 103.8, 0.1 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2956, 1898, 1489, 1246, 835.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 165 (12), 267 (12), 340 (9).

HRMS (EI): *m/z* (M^+) for **$C_{24}H_{24}Si$**: calc. 340.1647; found 340.1638.

b. Trimethyl(3-phenyl-1,3-di(thiophen-3-yl)propa-1,2-dien-1-yl)silane (4b)



According to **TP3**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.14 mL, 1.2 mmol; 1.05 M in THF), 3-bromothiophene (164 mg, 0.09 mL, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / S-Phos (16.4 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 2 h at 25 °C. Then, TMPZnCl·LiCl (**1**, 1.14 mL, 1.2 mmol; 1.05 M in THF), 3-bromothiophene (164 mg, 0.09 mL, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / S-Phos (16.4 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 12 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane) afforded the desired product **4b** (180 mg, 51 %) as a yellow solid.

M.p. (°C): 71-73.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.48-7.12 (m, 11 H), 0.34 (s, 9 H).

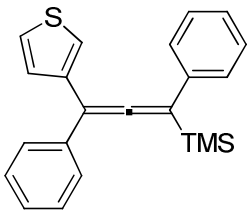
^{13}C NMR (75 MHz, $CDCl_3$) δ/ ppm = 210.1, 137.2, 136.8, 136.4, 128.5 (2 C), 127.9, 127.8 (2 C), 127.7, 127.0, 125.4, 125.3, 121.4, 120.9, 102.3, 98.5, -0.3 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2951, 1898, 1490, 1247, 829.

MS (EI, 70 eV) m/z (%) = 73 (100), 279 (11), 352 (14).

HRMS (EI): *m/z* (M^+) for **$C_{20}H_{20}S_2Si$**: calc. 352.0776; found: 352.0767.

c. (1,3-diphenyl-3-(thiophen-3-yl)propa-1,2-dien-1-yl)trimethylsilane (4c)



According to **TP3**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.14 mL, 1.2 mmol; 1.05 M in THF), iodobenzene (204 mg, 0.11 mL, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / S-Phos (16.4 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 4 h at 25 °C. Then, TMPZnCl·LiCl (**1**, 1.14 mL, 1.2 mmol; 1.05 M in THF), 3-bromothiophene (204 mg, 0.11 mL, 1.00 mmol)

and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / S-Phos (16.4 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 12 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane) afforded the desired product **4c** (219 mg, 63 %) as a yellow solid.

M.p. (°C): 83.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.47-7.46 (m, 2 H), 7.43-7.41 (m, 2 H), 7.38-7.32 (m, 5 H), 7.29-7.27 (m, 1 H), 7.24-7.22 (m, 1 H), 7.15-7.12 (m, 2 H), 0.33 (s, 9 H).

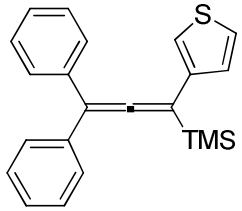
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.8, 137.3, 136.9, 136.7, 128.8 (2 C), 128.6 (2 C), 128.0 (2 C), 127.9 (2 C), 127.8, 127.1, 126.8, 125.6, 121.5, 103.6, 102.4, -0.1 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2952, 1900, 1489, 1247.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 273 (13), 346 (18).

HRMS (EI): *m/z* (M^+) for **$C_{22}H_{22}SSi$**: calc. 346.1211; found 346.1205.

d. (3,3-diphenyl-1-(thiophen-3-yl)propa-1,2-dien-1-yl)trimethylsilane (4d)



According to **TP3**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 145 mg, 0.77 mmol), TMPZnCl·LiCl (**1**, 0.82 mL, 0.92 mmol; 1.12 M in THF), 3-bromothiophene (126 mg, 0.07 mL, 0.77 mmol) and the catalytic system [$Pd(OAc)_2$ (3.5 mg, 0.02 mmol) / S-Phos (12.6 mg, 0.03 mmol)] were used. The reaction mixture was stirred for 2 h at 25 °C. Then, TMPZnCl·LiCl (**1**, 0.82 mL, 0.92 mmol; 1.12 M in THF), iodobenzene (157 mg, 0.08 mL, 0.77 mmol) and the catalytic system [$Pd(OAc)_2$ (3.5 mg, 0.02 mmol) / S-Phos (12.6 mg, 0.03 mmol)] were used. The reaction mixture was stirred for 12 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane) afforded the desired product **4d** (125 mg, 47 %) as a yellow solid.

M.p. (°C): 74.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.38-7.33 (m, 8 H), 7.28-7.25 (m, 3 H), 7.22-7.20 (m, 1 H), 7.18-7.17 (m, 1 H), 0.33 (s, 9 H).

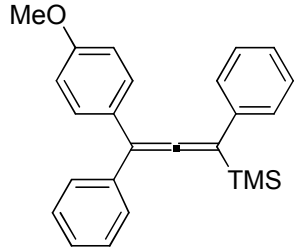
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 210.0, 136.9, 136.6, 128.6 (4 C), 128.2 (4 C), 128.0 (2 C), 127.0 (2 C), 125.4, 120.9, 106.5, 98.6, 0.1 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2950, 1897, 1490, 1248, 829.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 165 (9), 273 (9), 346 (6).

HRMS (EI): *m/z* (M^+) for **$C_{22}H_{22}SSi$**: calc. 346.1211; found 346.1205.

e. (3-(4-methoxyphenyl)-1,3-diphenylpropa-1,2-dien-1-yl)trimethylsilane (4e)



According to **TP3**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.07 mL, 1.2 mmol; 1.12 M in THF), iodobenzene (204 mg, 0.11 mL, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / S-Phos (16.4 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 4 h at 25 °C. Then, TMPZnCl·LiCl (**1**, 1.07 mL, 1.2 mmol; 1.12 M in THF), 4-iodoanisole (234 mg, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / S-Phos (16.4 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 12 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane) afforded the desired product **4e** (251 mg, 68 %) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.41-7.39 (m, 2 H), 7.38-7.36 (m, 2 H), 7.34-7.28 (m, 6 H), 7.26-7.23 (m, 1 H), 7.22-7.19 (m, 1 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 3.82 (s, 3 H), 0.30 (s, 9 H).

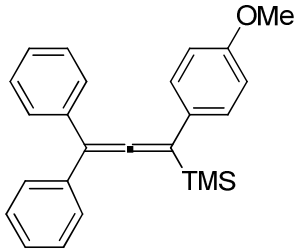
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 209.7, 158.8, 137.2, 137.0, 129.3 (2 C), 129.1, 128.7 (2 C), 128.6 (2 C), 128.1 (2 C), 128.0 (2 C), 126.9, 126.7, 114.1 (2 C), 106.3, 103.6, 55.4, 0.1 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2952, 1901, 1506, 1244, 832.

MS (EI, 70 eV) m/z (%) = 73 (40), 252 (19), 297 (24), 355 (100), 370 (7).

HRMS (EI): *m/z* (M^+) for **$C_{25}H_{26}OSi$**: calc. 370.1753; found 370.1744.

f. (1-(4-methoxyphenyl)-3,3-diphenylpropa-1,2-dien-1-yl)trimethylsilane (4f)



According to **TP3**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 162 mg, 0.86 mmol), TMPZnCl·LiCl (**1**, 0.92 mL, 1.03 mmol; 1.12 M in THF), 4-iodoanisole (201 mg, 0.86 mmol) and the catalytic system [$Pd(OAc)_2$ (3.9 mg, 0.02 mmol) / S-Phos (14.1 mg, 0.03 mmol)] were used. The reaction mixture was stirred for 5 h at 25 °C. Then, TMPZnCl·LiCl (**1**, 0.92 mL, 1.03 mmol, 1.2 equiv; 1.12 M in THF), iodobenzene (175 mg, 0.09 mL, 1.86 mmol) and the

catalytic system [$Pd(OAc)_2$ (3.9 mg, 0.02 mmol) / S-Phos (14.1 mg, 0.03 mmol)] were used. The reaction mixture was stirred for 12 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:1) afforded the desired product **4f** (213 mg, 67 %) as a yellow solid.

M.p. (°C): 104.

^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm = 7.40-7.24 (m, 12 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 3.80 (s, 3 H), 0.30 (s, 9 H).

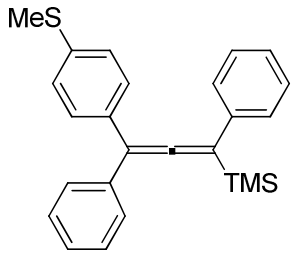
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.3, 158.7, 137.1 (2 C), 129.1 (2 C), 128.7, 128.6 (4 C), 128.2 (4 C), 126.9 (2 C), 114.3 (2 C), 106.8, 103.0, 55.4, 0.1 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2960, 1895, 1507, 1244, 833.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 165 (14), 252 (23), 297 (32), 355 (91), 370 (12).

HRMS (EI): *m/z* (M^+) for **$C_{25}H_{26}OSi$**: calc. 370.1753; found 370.1740.

g. Trimethyl(3-(4-(methylthio)phenyl)-1,3-diphenylpropa-1,2-dien-1-yl)silane (4g)



According to **TP3**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.14 mL, 1.2 mmol; 1.05 M in THF), iodobenzene (204 mg, 0.11 mL, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 2 h at 50 °C. Then, TMPZnCl·LiCl (**1**, 1.14 mL, 1.2 mmol; 1.05 M in THF), 4-bromothioanisole (203 mg, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 2 h at 50 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:1) afforded the desired product **4g** (247 mg, 64 %) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.41-7.27 (m, 11 H), 7.25-7.21 (m, 3 H), 2.50 (s, 3 H), 0.31 (s, 9 H).

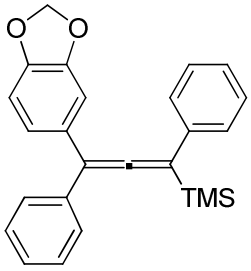
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.6, 136.9, 136.8, 136.7, 133.8, 128.8 (2 C), 128.6 (2 C), 128.5 (2 C), 128.2 (2 C), 128.0 (2 C), 127.0, 126.9 (2 C), 126.8, 106.3, 103.9, 16.1, 0.1 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2953, 1899, 1487, 1247, 832, 693.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 265 (14), 313 (14), 371 (16), 386 (13).

HRMS (EI): *m/z* (M^+) for **$C_{25}H_{26}SSi$**: calc. 386.1524; found 386.1508.

h. (3-(benzo[*d*][1,3]dioxol-5-yl)-1,3-diphenylpropa-1,2-dien-1-yl)trimethylsilane (4h)



According to **TP3**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.14 mL, 1.2 mmol; 1.05 M in THF), iodobenzene (204 mg, 0.11 mL, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 2 h at 50 °C. Then, TMPZnCl·LiCl (**1**, 1.14 mL, 1.2 mmol; 1.05 M in THF), 3-iodobenzodioxole (248 mg, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 3 h at 50 °C. Purification by flash chromatography (SiO_2, *i*-hexane/EtOAc = 100:1) afforded the desired product **4h** (268 mg, 70 %) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.43-7.39 (m, 4 H), 7.37-7.32 (m, 4 H), 7.28-7.22 (m, 2 H), 6.90 (d, *J* = 1.8 Hz, 1 H), 6.85 (dd, *J* = 8.4, 1.8 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 5.98 (A of AB system, *J* = 1.8 Hz, 1 H), 5.97 (B of AB system, *J* = 1.8 Hz, 1 H), 0.34 (s, 9 H).

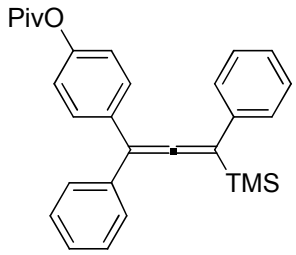
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.5, 147.9, 146.7, 137.0, 136.8, 130.8, 128.8 (2 C), 128.6 (2 C), 128.1 (2 C), 128.0 (2 C), 127.0, 126.8, 121.7, 108.6, 108.4, 106.5, 103.8, 101.2, 0.1 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 1955, 1901, 1438, 1224, 1037, 833.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 252 (31), 311 (22), 356 (18), 384 (14).

HRMS (EI): *m/z* (M^+) for **$C_{25}H_{24}O_2Si$**: calc. 384.1546; found 384.1551.

i. 4-(1,3-diphenyl-3-(trimethylsilyl)propa-1,2-dien-1-yl)phenyl pivalate (4i)



According to **TP3**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.14 mL, 1.2 mmol; 1.05 M in THF), iodobenzene (204 mg, 0.11 mL, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 2 h at 50 °C. Then, TMPZnCl·LiCl (**1**, 1.14 mL, 1.2 mmol; 1.05 M in THF), 4-bromophenylpivalate (257 mg, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 12 h at 50 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:2) afforded the desired product **4i** (287 mg, 65 %) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.40-7.36 (m, 6 H), 7.34-7.31 (m, 4 H), 7.27-7.21 (m, 2 H), 7.03 (d, *J* = 8.4 Hz, 2 H), 1.36 (s, 9 H), 0.30 (s, 9 H).

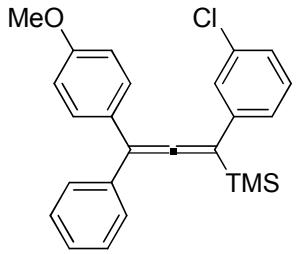
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.5, 177.3, 150.1, 136.8, 136.7, 134.3, 129.1 (2 C), 128.8 (2 C), 128.6 (2 C), 128.1 (2 C), 128.0 (2 C), 127.0, 126.8, 121.6 (2 C), 106.0, 104.0, 39.2, 27.3 (3 C), 0.0 (3 C).

IR (Diamond-ATR, neat) υ / cm^{-1} = 2959, 1901, 1752, 1108, 834.

MS (EI, 70 eV) *m/z* (%) = 57 (73), 73 (100), 266 (44), 355 (82), 440 (4).

HRMS (EI): *m/z* (M^+) for **$C_{29}H_{32}O_2Si$**: calc. 440.2172; found 440.2170.

j. (1-(3-chlorophenyl)-3-(4-methoxyphenyl)-3-phenylpropa-1,2-dien-1-yl)trimethylsilane (4j)



According to **TP3**, trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**, 188 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.07 mL, 1.2 equiv; 1.12 M in THF), 3-chlorobromobenzene (191 mg, 0.12 mL, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos

(10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 4 h at 50 °C. Then, TMPZnCl·LiCl (**1**, 1.07 mL, 1.2 mmol; 1.12 M in THF), 4-iodoanisole (234 mg, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / DPE-Phos (10.8 mg, 0.02 mmol)] were used. The reaction mixture was stirred for 12 h at 50 °C. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 100:1) afforded the desired product **4j** (170 mg, 42 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.36-7.16 (m, 11 H), 6.89 (d, *J* = 9.2 Hz, 2 H), 3.81 (s, 3 H), 0.29 (s, 9 H).

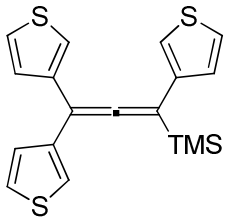
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 209.9, 158.9, 139.1, 136.8, 134.6, 129.9, 129.3 (2 C), 128.65 (2 C), 128.59, 128.1 (2 C), 127.9, 127.1, 126.7, 126.1, 114.2 (2 C), 106.7, 102.9, 55.4, 0.0 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2954, 1907, 1507, 1245, 830.

MS (EI, 70 eV) *m/z* (%) = 73 (50), 252 (13), 296 (19), 331 (14), 389 (100), 391 (35), 404 (11).

HRMS (EI): *m/z* (M^+) for **$C_{25}H_{25}ClOSi$**: calc. 404.1363; found 404.1362.

k. Trimethyl(1,3,3-tri(thiophen-3-yl)propa-1,2-dien-1-yl)silane (4k)



According to **TP3**, trimethyl(3-(thiophen-3-yl)prop-1-yn-1-yl)silane (**2b**, 194 mg, 1.00 mmol), TMPZnCl·LiCl (**1**, 1.14 mL, 1.2 mmol; 1.05 M in THF), 3-bromothiophene (164 mg, 0.09 mL, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / S-Phos (16.4 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 2 h at 25 °C. Then, TMPZnCl·LiCl (**1**, 1.14 mL, 1.2 mmol; 1.05 M in THF), 3-bromothiophene (164 mg, 0.09 mL, 1.00 mmol) and the catalytic system [$Pd(OAc)_2$ (4.5 mg, 0.02 mmol) / S-Phos (16.4 mg, 0.04 mmol)] were used. The reaction mixture was stirred for 12 h at 25 °C. Purification by flash chromatography (SiO_2, *i*hexane) afforded the desired product **4k** (233 mg, 65 %) as a white solid.

M.p. (°C): 71.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.30 (dd, *J* = 5.1, 3.0 Hz, 2 H), 7.27-7.25 (m, 1 H), 7.22 (dd, *J* = 3.0, 1.2 Hz, 2 H), 7.16-7.12 (m, 4 H), 0.31 (s, 9 H).

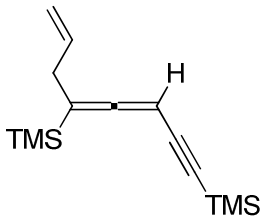
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 210.5, 137.1 (2 C), 136.3, 128.0, 127.6 (2 C), 125.4 (2 C), 125.3, 121.1 (2 C), 121.0, 98.7, 98.0, -0.3 (3 C).

IR (Diamond-ATR, neat) υ/cm^{-1} = 2955, 1900, 1248, 829.

MS (EI, 70 eV) *m/z* (%) = 73 (100). 285 (13), 358 (19).

HRMS (EI): *m/z* (M^+) for **$C_{18}H_{18}S_3Si$**: calc. 358.0340; found 358.0331.

l. Preparation of octa-3,4,7-trien-1-yne-1,5-diylbis(trimethylsilane) (7)



According to **TP1,** 1,5-bis(trimethylsilyl)penta-1,4-diyne (**6**, 208 mg, 1.00 mmol), THF (2 mL) and TMPZnCl·LiCl (**1**, 1.10 mL, 1.2 mmol; 1.09 M in THF) were used. After stirring the reaction mixture for 1 h at 25 °C, a solution of CuCN·2LiCl (0.30 mL, 0.30 mmol, 1.0 M in THF) was added at 25 °C and the reaction mixture was stirred 15 min at this temperature, followed by the addition of allyl bromide (181 mg , 0.13 mL, 1.50 mmol). The reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (Al_2O_3, *i*hexane) afforded the desired product **7** (149 mg, 60 %) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 5.82 (ddt, *J* = 17.2, 10.2, 6.5 Hz, 1 H), 5.08 (t, *J* = 2.9 Hz, 1 H), 5.05 (ddt, *J* = 1.8 Hz, 2 H), 2.83 (A of AB system, *J* = 15.9, 6.9, 1.2 Hz, 1 H), 2.75 (B of AB system, *J* = 15.9, 6.9, 1.2 Hz, 1 H), 0.14 (s, 9 H), 0.12 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 211.8, 136.2, 115.8, 99.1, 97.3, 94.3, 70.4, 33.6, 0.07 (3C), -1.5 (3C).

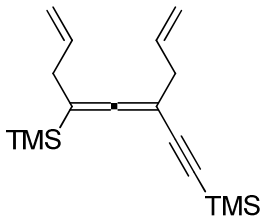
^{29}Si NMR (79 MHz, $CDCl_3$) δ/ppm = -1.65, -18.5.

IR (Diamond-ATR, neat) υ/cm^{-1} = 3080, 2959, 2899, 2151, 1924, 1639, 1407, 1370, 1248, 1044.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 159 (11), 160 (47), 248 (7).

HRMS (EI): *m/z* (M^+) for **$C_{14}H_{24}Si_2$**: calc. 248.1417; found 248.1409.

m. Preparation of (3-allylocta-3,4,7-trien-1-yne-1,5-diyl)bis(trimethylsilane) (8)



According to **TP1,** octa-3,4,7-trien-1-yne-1,5-diylbis(trimethylsilane) (**7**, 124 mg, 0.50 mmol), THF (1 mL) and TMPZnCl·LiCl (**1**, 0.55 mL, 0.60 mmol; 1.09 M in THF) were used. After stirring the reaction mixture for 1 h at 25 °C, a solution of CuCN·2LiCl (0.15 mL, 0.14 mmol; 1.0 M in THF) was added at 25 °C and the reaction mixture was stirred 15 min at this temperature, followed by the addition of allyl bromide (91 mg, 0.07 mL, 0.75 mmol). The reaction mixture was stirred for 1 h at 25 °C. Purification by flash chromatography (Al_2O_3, *i*hexane) afforded the desired product **8** (193 mg, 67 %) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 5.66 (tdd, *J* = 17.0, 10.1, 6.8, 6.4 Hz, 1 H), 5.63 (tdd, *J* = 17.0, 10.1, 6.9 Hz, 1 H), 4.90 (d, *J* = 17.0 Hz, 2 H), 4.85 (d, *J* = 10.1 Hz, 2 H), 2.66 (A of AB system, *J* = 15.8, 6.9, 1.4 Hz, 1 H), 2.64-2.62 (m, 2 H), 5.59 (B of AB system, *J* = 15.8, 6.4, 1.4 Hz, 1 H), 0.00 (s, 9 H), - 0.05 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 210.1, 136.6, 135.2, 116.0, 115.5, 101.8, 98.3, 95.8, 83.9, 37.8, 34.0, 0.10 (3 C), -1.31 (3 C).

^{29}Si NMR (79 MHz, $CDCl_3$) δ/ppm = -1.65, -18.5.

IR (Diamond-ATR, neat) υ/cm^{-1} = 3080, 2958, 2899, 2143, 1923, 1639, 1432, 1409, 1360, 1248, 1162, 1014, 990.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 159 (9), 200 (11), 288 (2).

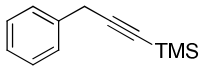
HRMS (EI): *m/z* (M^+) for **$C_{17}H_{28}Si_2$**: calc. 288.1730; found 288.1703.

4) NMR studies

Only the most relevant spectra are shown. Full analytical data are available in the Supporting Information of P. Quinio, C. François, A. Escribano Cuesta, A. K. Steib, F. Achrainer, H. Zipse, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2015**, *17*, 1010.

The propargyl isomer (**9**) is the most stable organometallic species in the case of the lithium cation, whereas the allenylzinc structure (**10**) is the most stable in case of the zinc cation.

a. Starting material (2a)

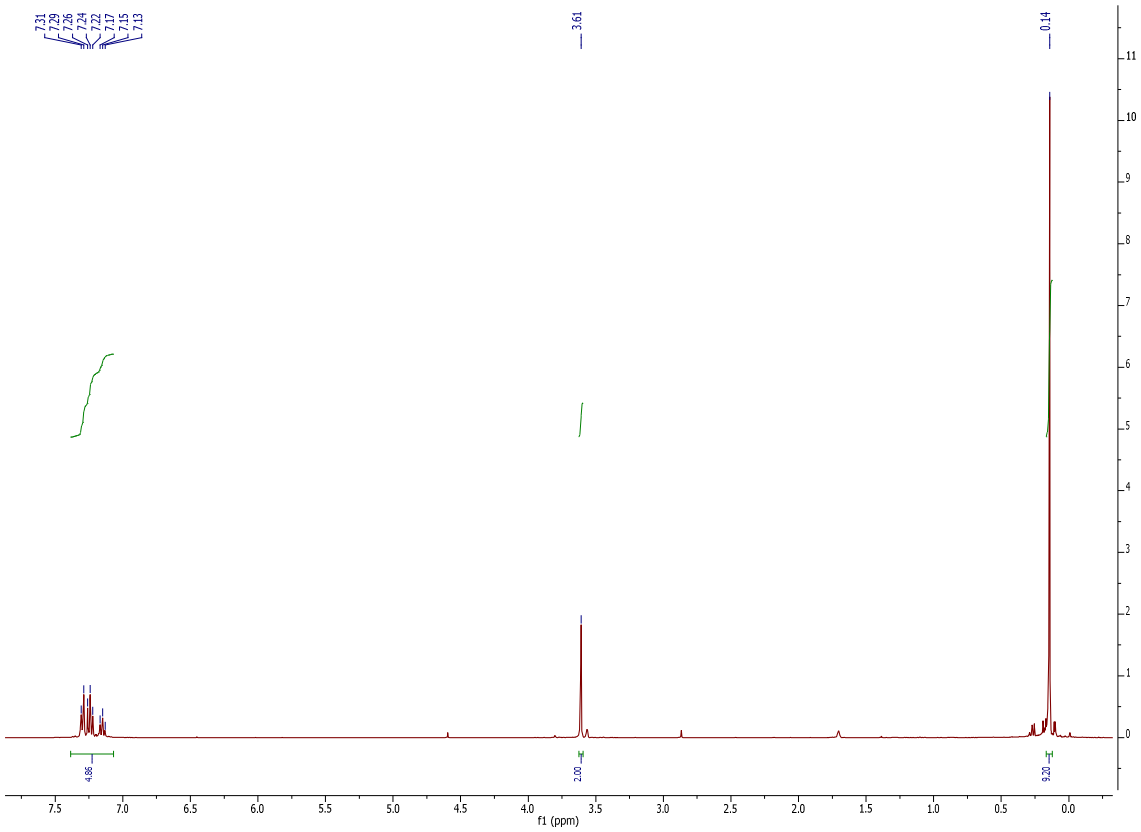


^{1}H NMR (400 MHz, THF-d_8) δ/ppm = 7.30 (2 H, dd, 2-H_{meta}), 7.24 (2 H, d, 2-H_{ortho}), 7.15 (1 H, t, 1-H_{para}), 3.61 (1 H, s, CH_2), 0.03 (9 H, s, CH_3).

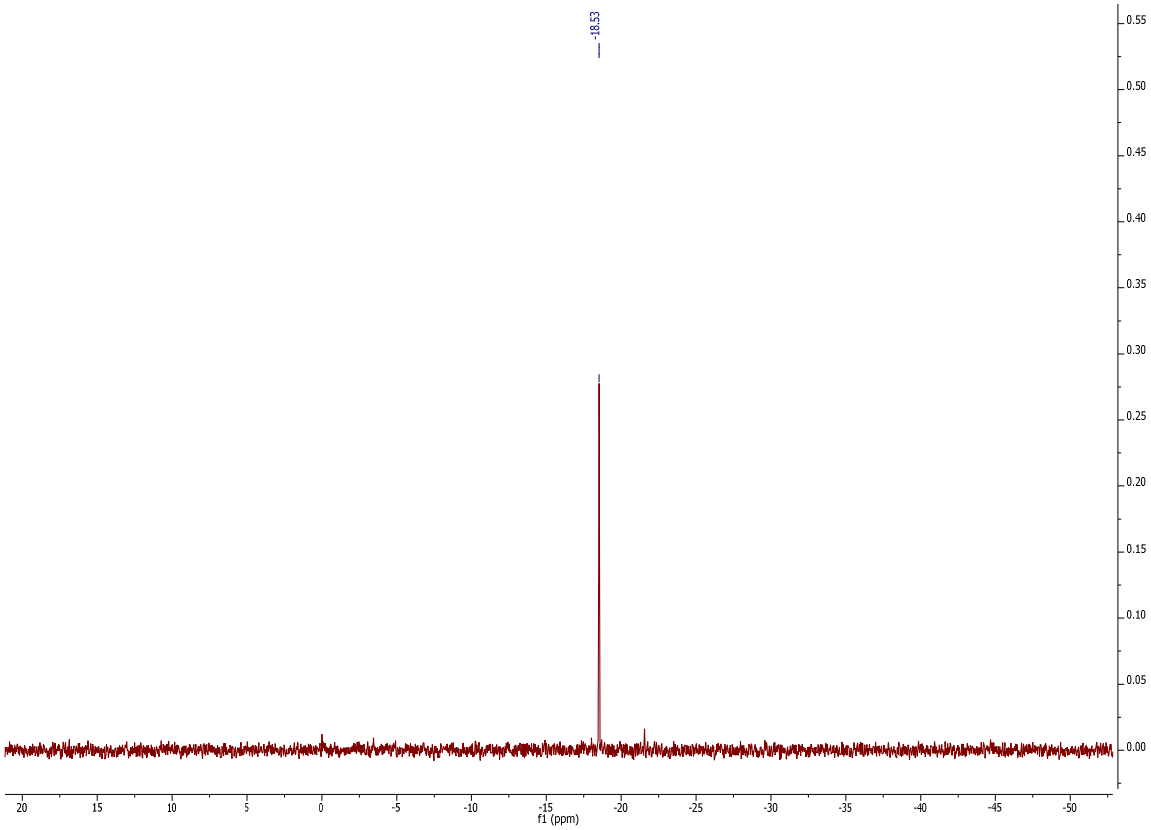
^{13}C NMR (100 MHz, THF-d_8) δ/ppm = 104.5 (-C≡), 136.6 (C_{ipso}), 128.2 ($2C_{meta}$) 127.7 ($2C_{ortho}$), 126.3 (C_{para}), 85.8 (≡C-Si), 25.5 (CH_2), -0.71 (CH_3).

^{29}Si NMR (79 MHz, THF-d_8) δ/ppm = -18.53.

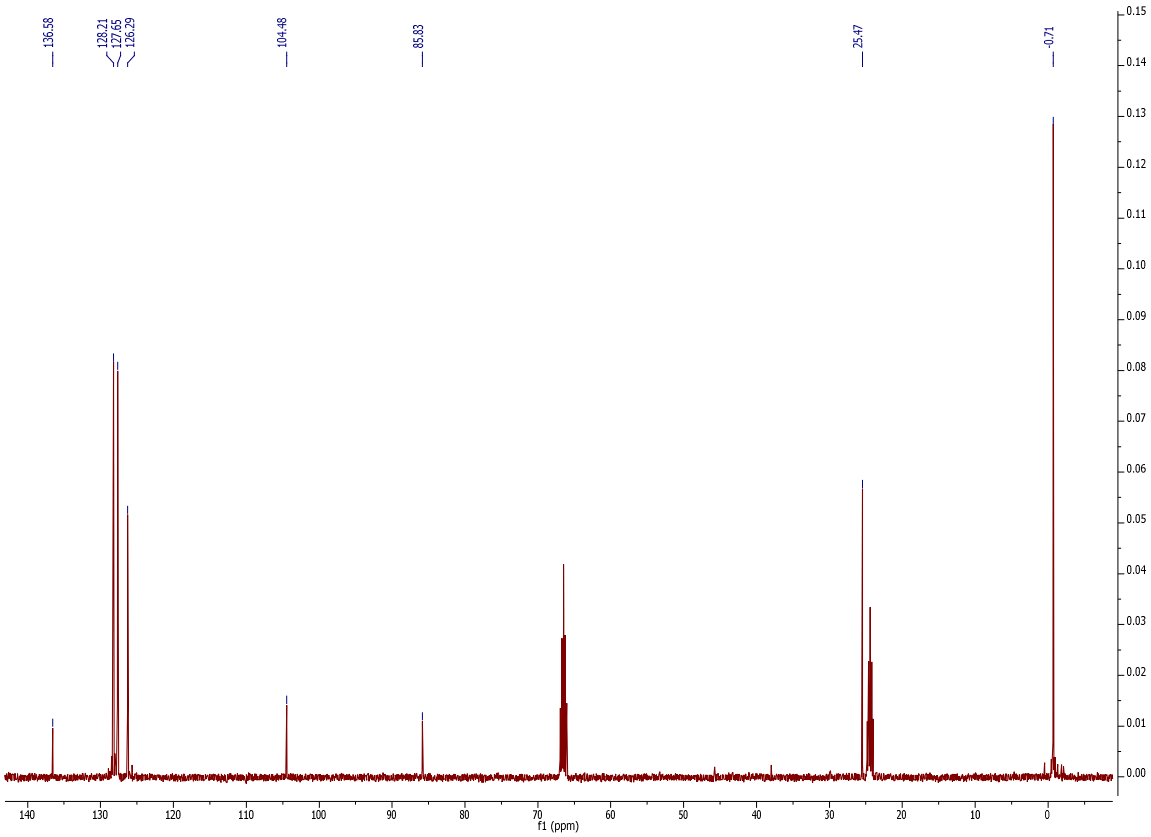
^{1}H NMR (400 MHz, THF-d_8)



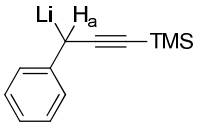
^{29}Si NMR (79 MHz, THF-d_8)



^{13}C NMR (100 MHz, THF-d_8)



b. NMR studies of the metalated intermediate 9



In order to provide structural information on the metalated TMS-alkyne of type **9,** we investigated the metalation of trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**) with *n*BuLi at 25°C. Therefore trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**; 47.0 mg, 0.25 mmol) and THF-d_8 (0.5 mL) were charged in a dry, argon flushed NMR tube. The NMR tube was cooled to 0°C and *n*BuLi (0.10 mL, 0.25 mmol; 2.45 M in hexanes) was slowly added and the tube was shaken once. The NMR tube was warmed up to 25 °C and NMR studies were performed at 25 °C, including ^{1}H, ^{13}C, ^{29} Si, ^{7}Li and 2D NMR.

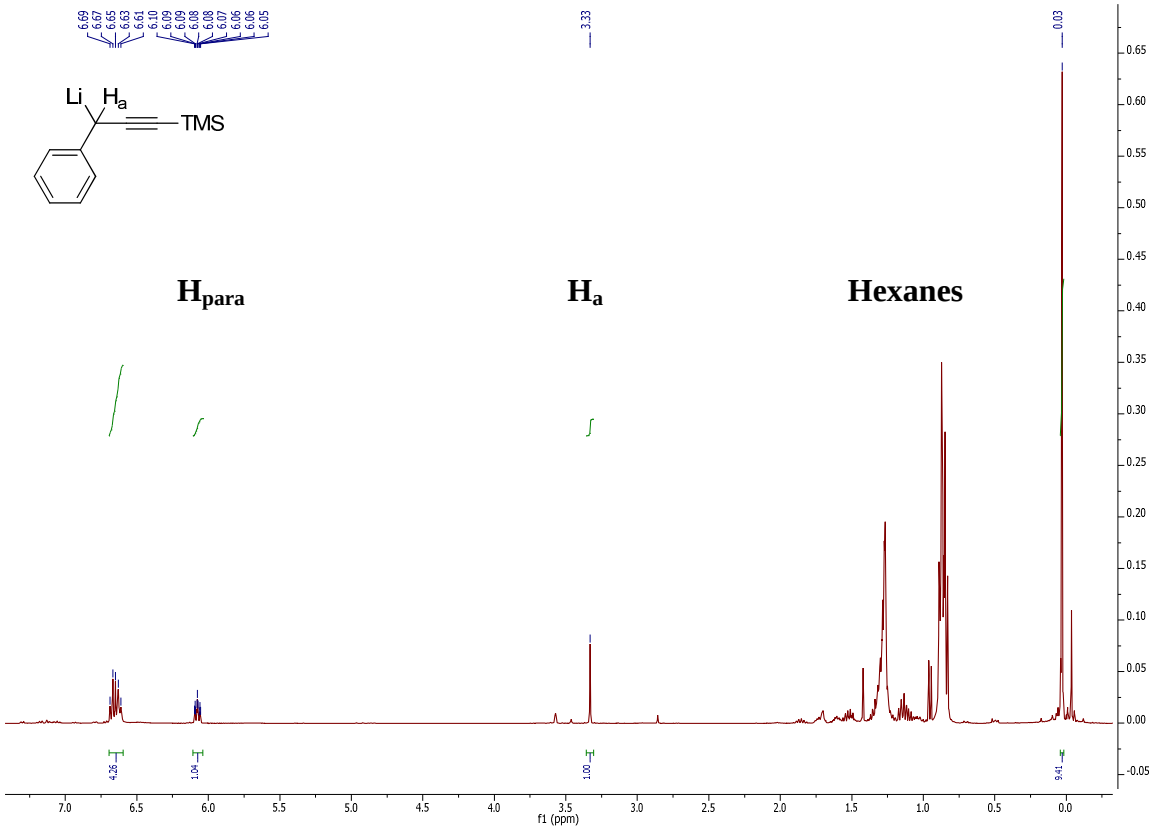
^{1}H NMR (400 MHz, THF-d_8) δ/ppm = 6.67 (2H, dd, 2-H_{meta}), 6.63 (2H, d, 2-H_{ortho}), 6.07 (1H, t, 1-H_{para}), 3.33 (1H, s, H_a), 0.03 (9H, s, CH_3).

^{13}C NMR (100 MHz, THF-d_8) δ/ppm = 151.4 (-C≡), 149.9 (C_{ipso}), 127.2 ($2C_{meta}$) 118.9 ($2C_{ortho}$), 112.9 (C_{para}), 95.0 (≡C-Si), 51.9 (C-H_a), 1.71 (CH_3).

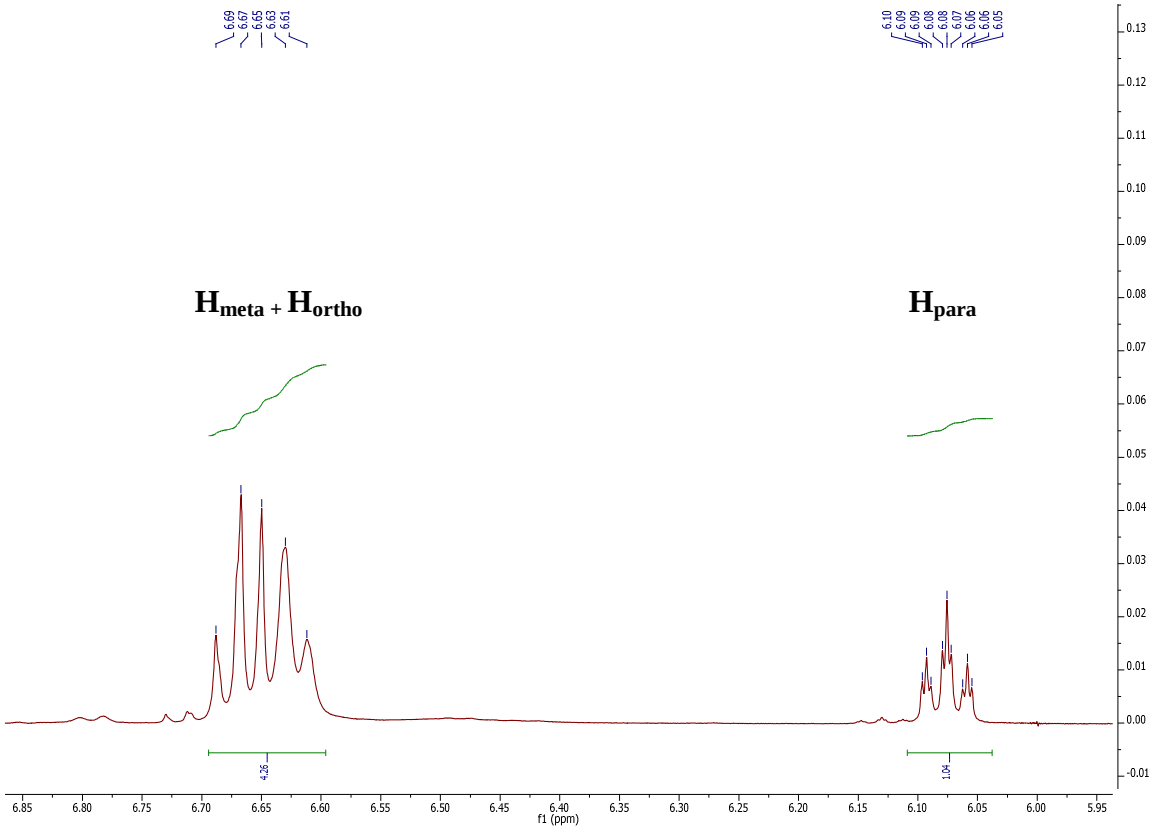
^{29}Si NMR (79 MHz, THF-d_8) δ/ppm = -18.83.

^{7}Li NMR (155 MHz, THF-d_8) δ/ppm = 2.87.

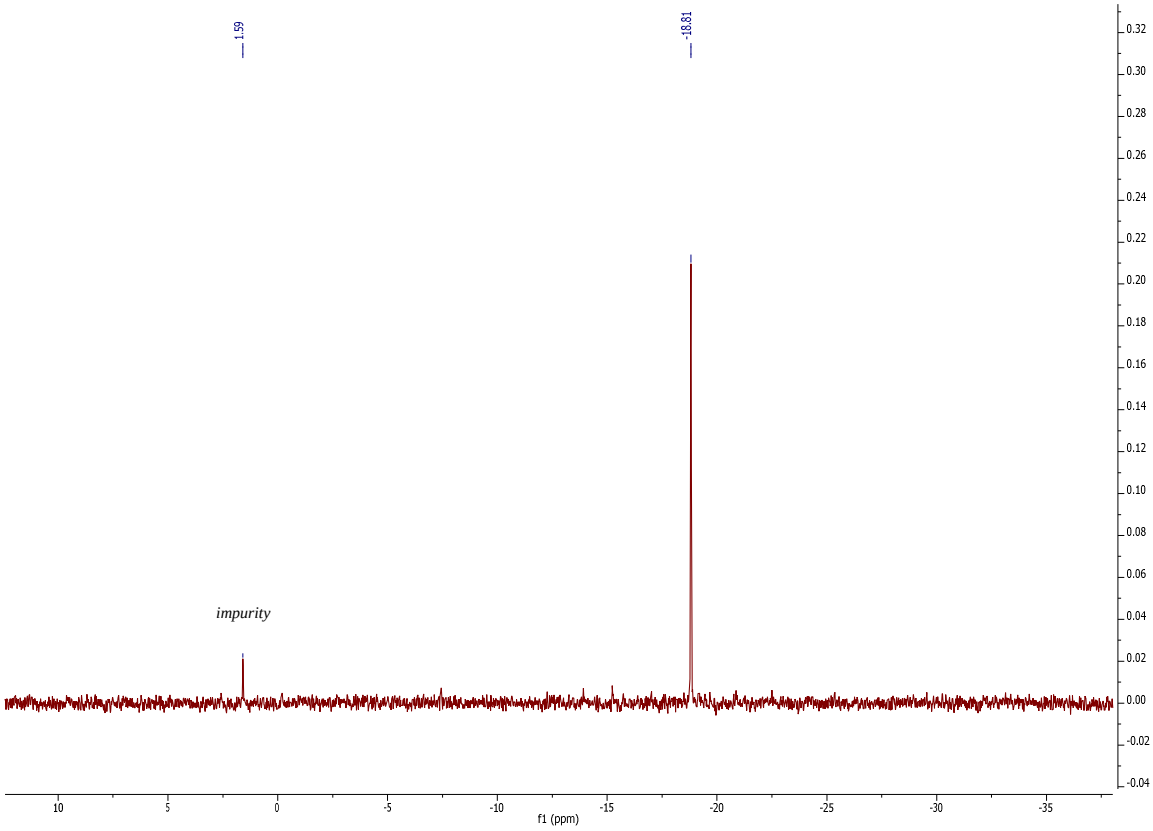
^{1}H NMR (400 MHz, THF-d_8)



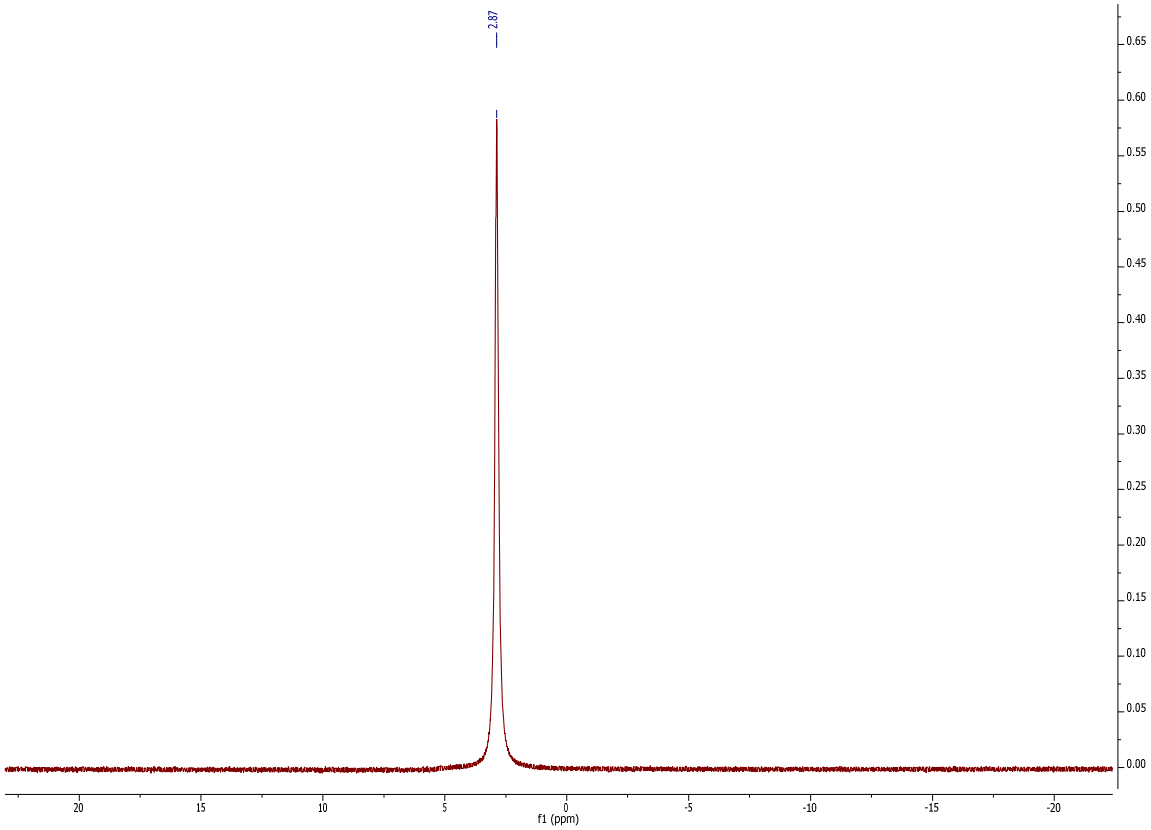
^{1}H NMR (400 MHz, THF-d_8),zoom on aromatic region



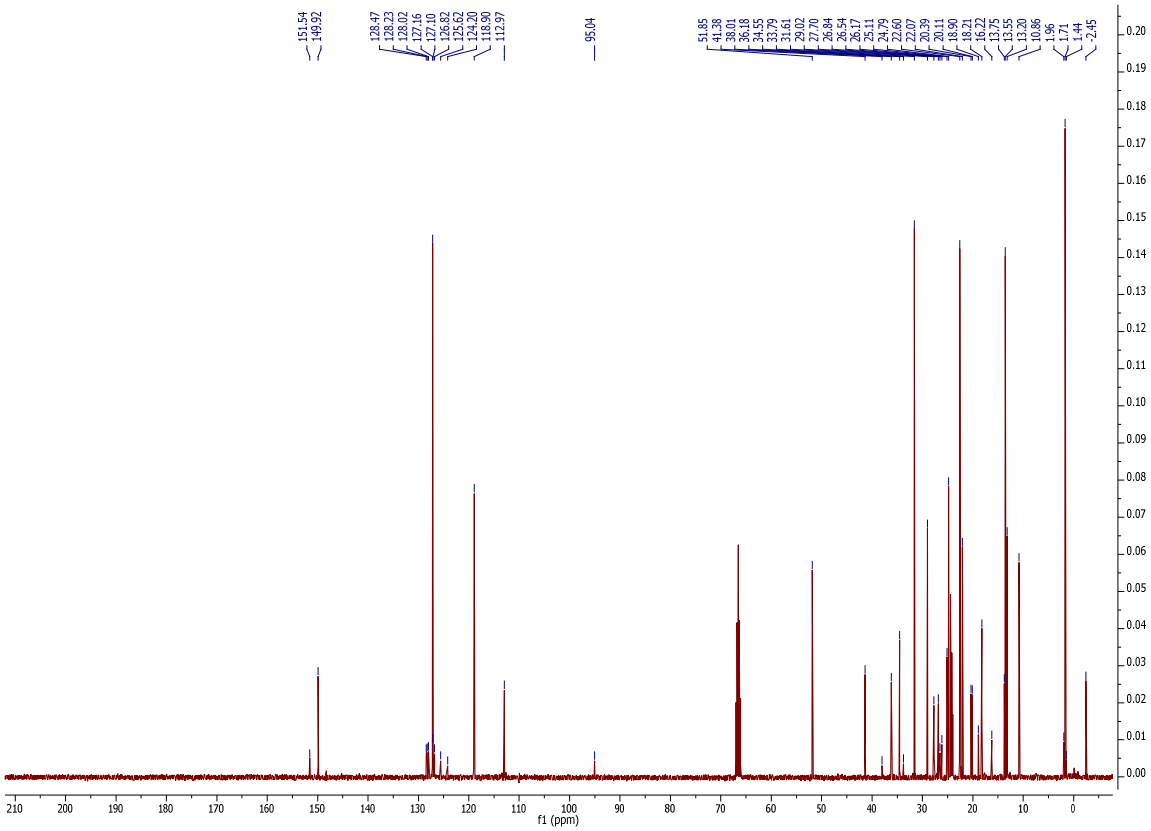
^{29}Si NMR (79 MHz, THF-d_8)



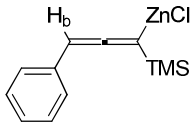
^{7}Li NMR (155 MHz, THF-d_8)



^{13}C NMR (100 MHz, THF-d_8)



c. NMR studies of the metalated intermediate 10



In order to provide structural information on the metalated allene of type **10,** we investigated the metalation of trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**) with TMPZnCl·LiCl at 25°C. Therefore trimethyl(3-phenylprop-1-yn-1-yl)silane (**2a**; 47.0 mg, 0.25 mmol) and THF-d_8 (0.5 mL) were charged in a dry, argon flushed NMR tube. TMPZnCl·LiCl (0.27 mL, 1.2 mmol; 1.10 M in THF-d_8) was slowly added and the tube was shaken once. The NMR tube was kept at 25 °C and NMR studies were performed at 25 °C, including ^{1}H, ^{13}C, ^{29} Si and 2D NMR.

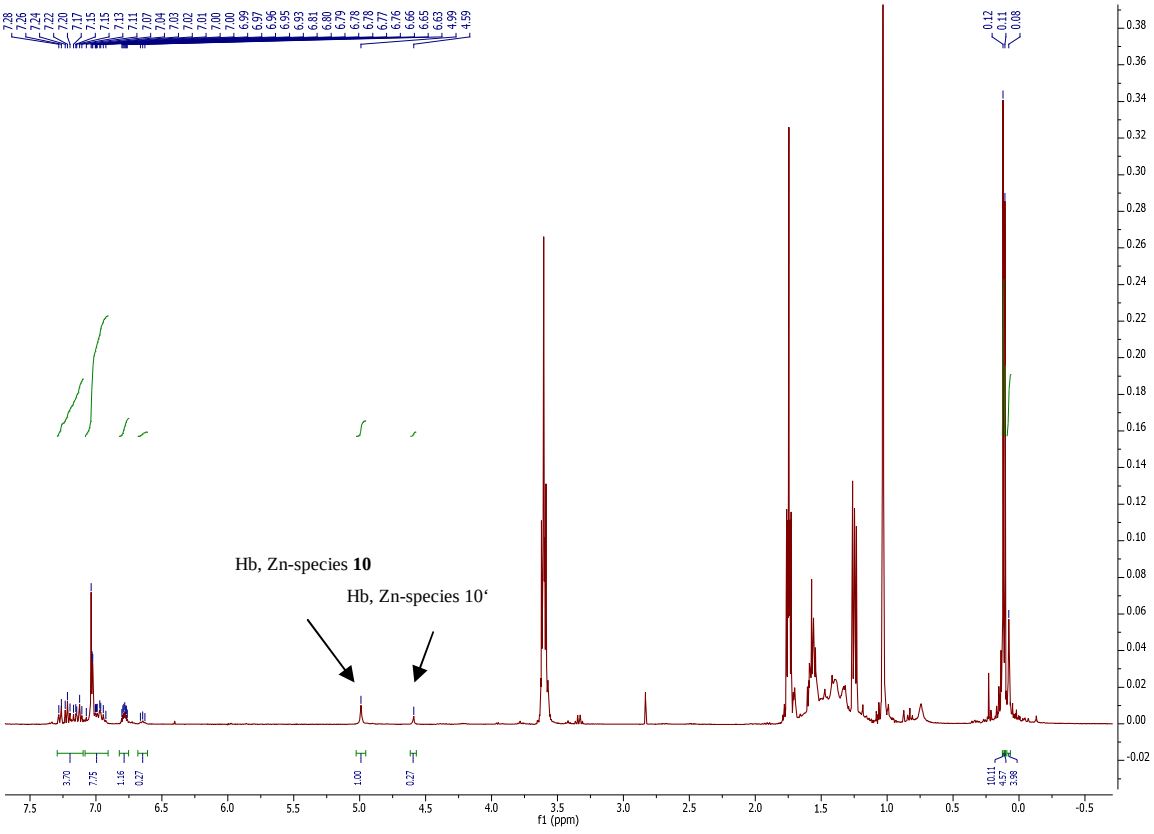
^{1}H NMR (400 MHz, THF-d_8) δ/ppm = 7.04 (2H, dd, 2-H_{ortho}), 7.03 (2H, d, 2-H_{meta}), 6.78 (1H, t, 1-H_{para}), 4.99 (1H, s, H_b), 0.12 (9H, s, CH_3).

^{13}C NMR (100 MHz, THF-d_8) δ/ppm = 202.8 (=C=), 139.4 (C_{ipso}), 127.9 ($2C_{meta}$) 124.0 ($2C_{ortho}$), 122.7 (C_{para}), 94.0 (C-Zn), 73.4 (C-H_b), - 0.13 (CH_3).

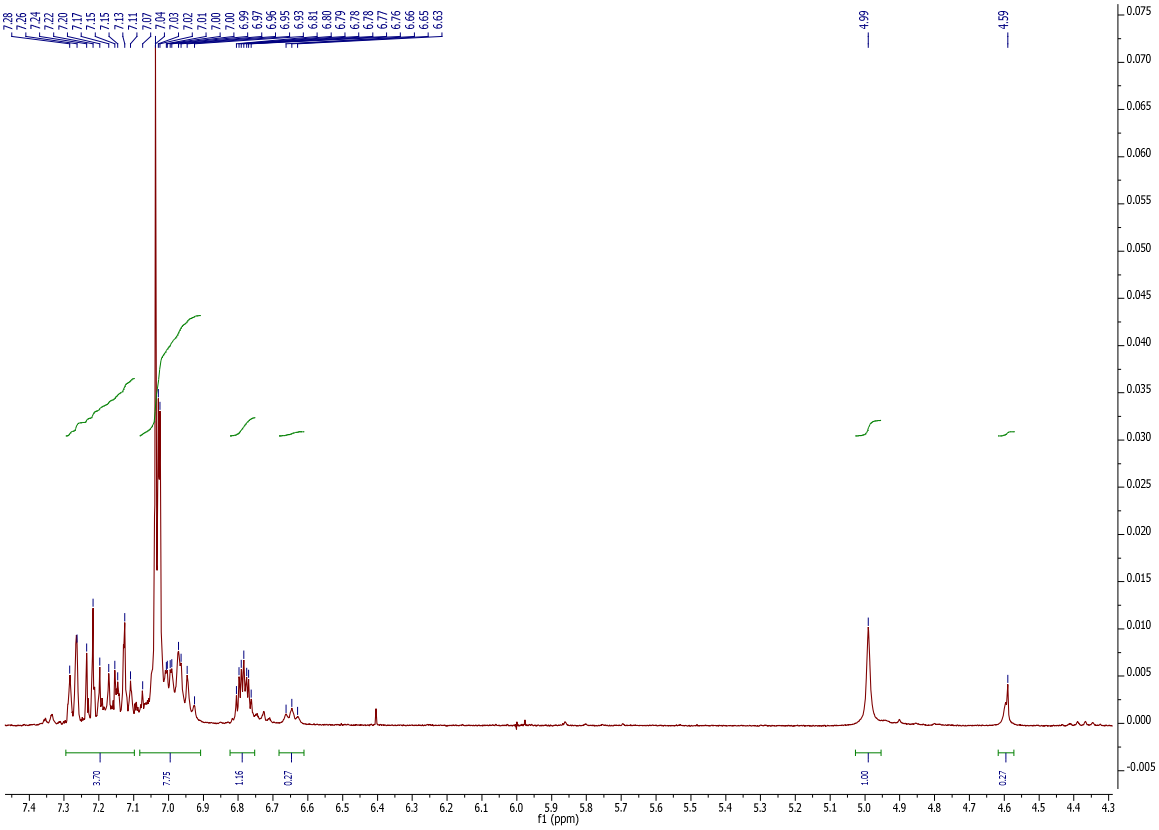
^{29}Si NMR (79 MHz, THF-d_8) δ/ppm = -4.59.

NMR studies of the metalated intermediate **10** were done again after 3 and 6 days measuring the same NMR tube (under argon) to show that the zinc species **10** equilibrates to another allenylzinc species.

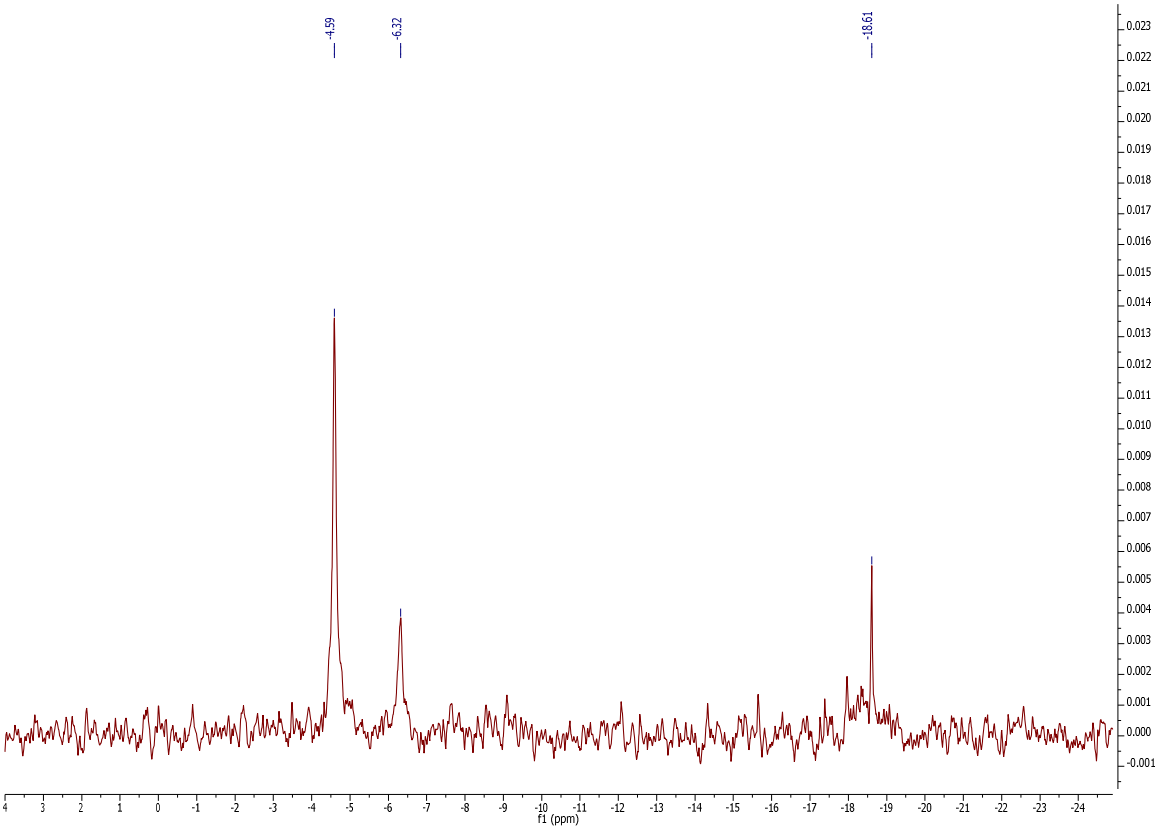
^{1}H NMR (400 MHz, THF-d_8)



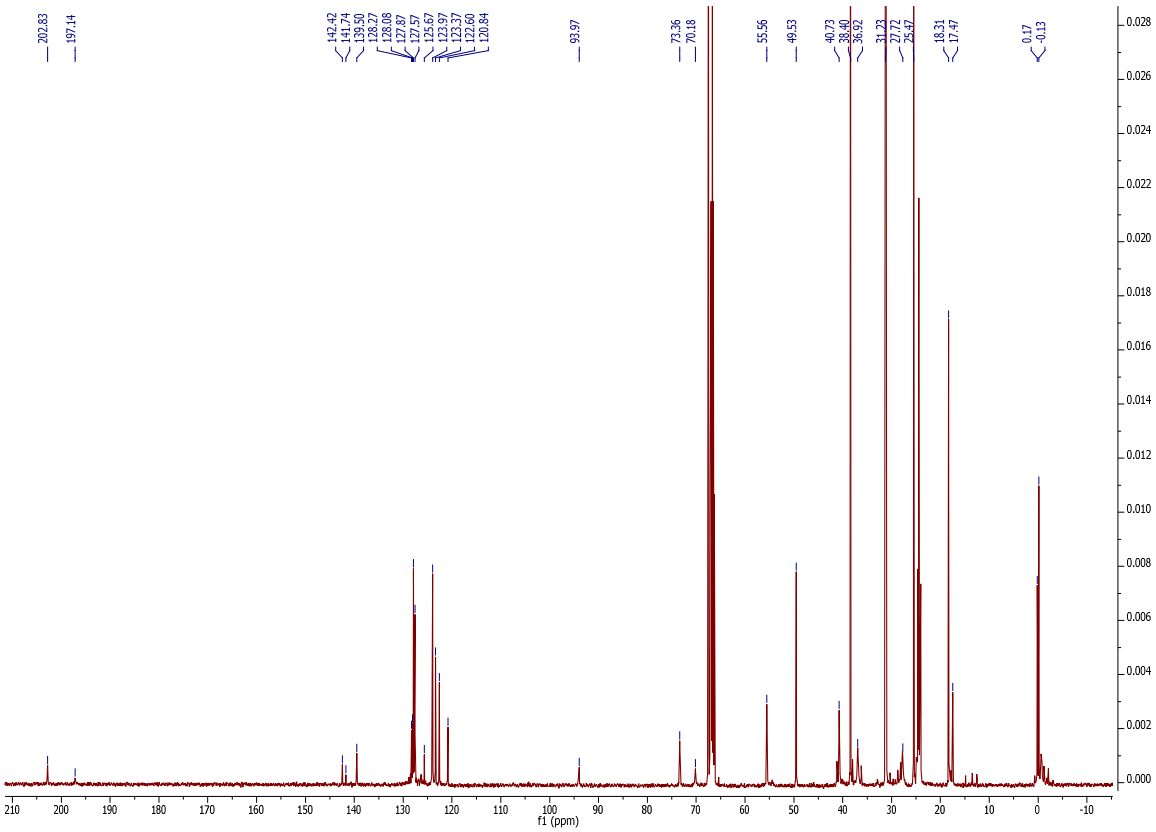
^{1}H NMR (400 MHz, THF-d_8), zoom on aromatic and allenic region



^{29}Si NMR (79 MHz, THF-d_8)

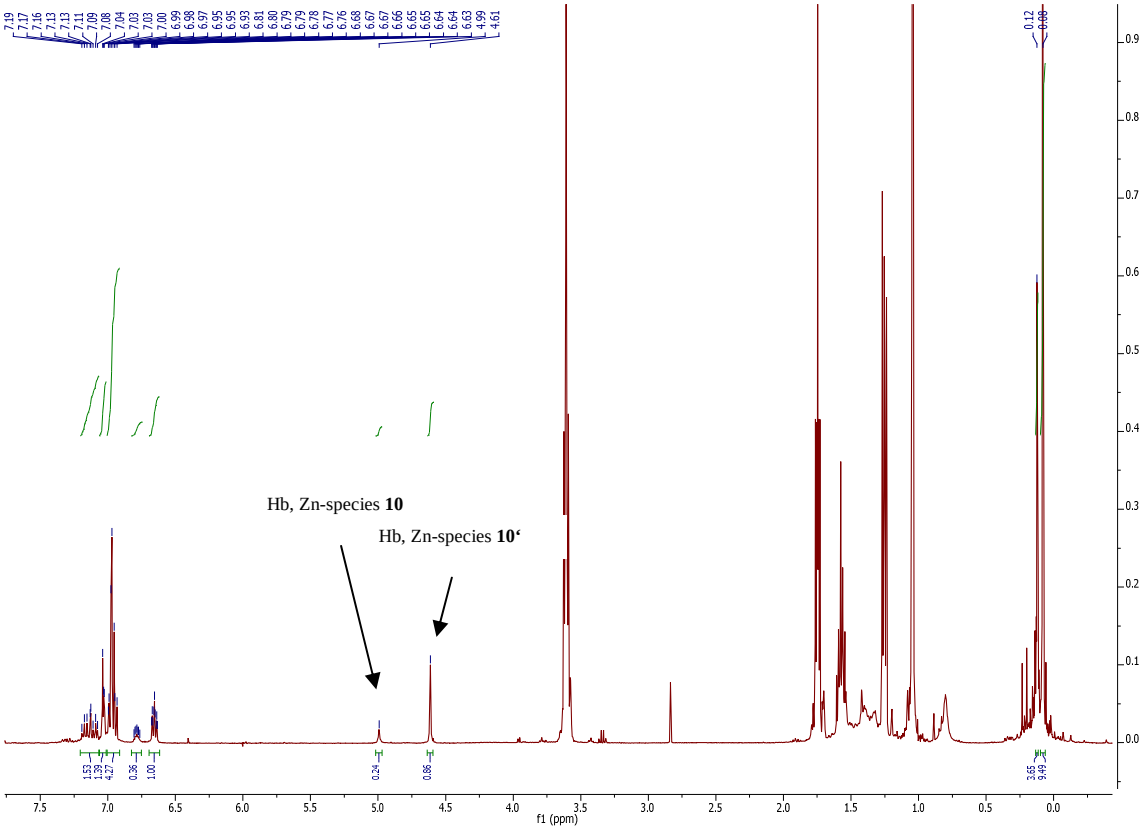


^{13}C NMR (100 MHz, THF-d_8)

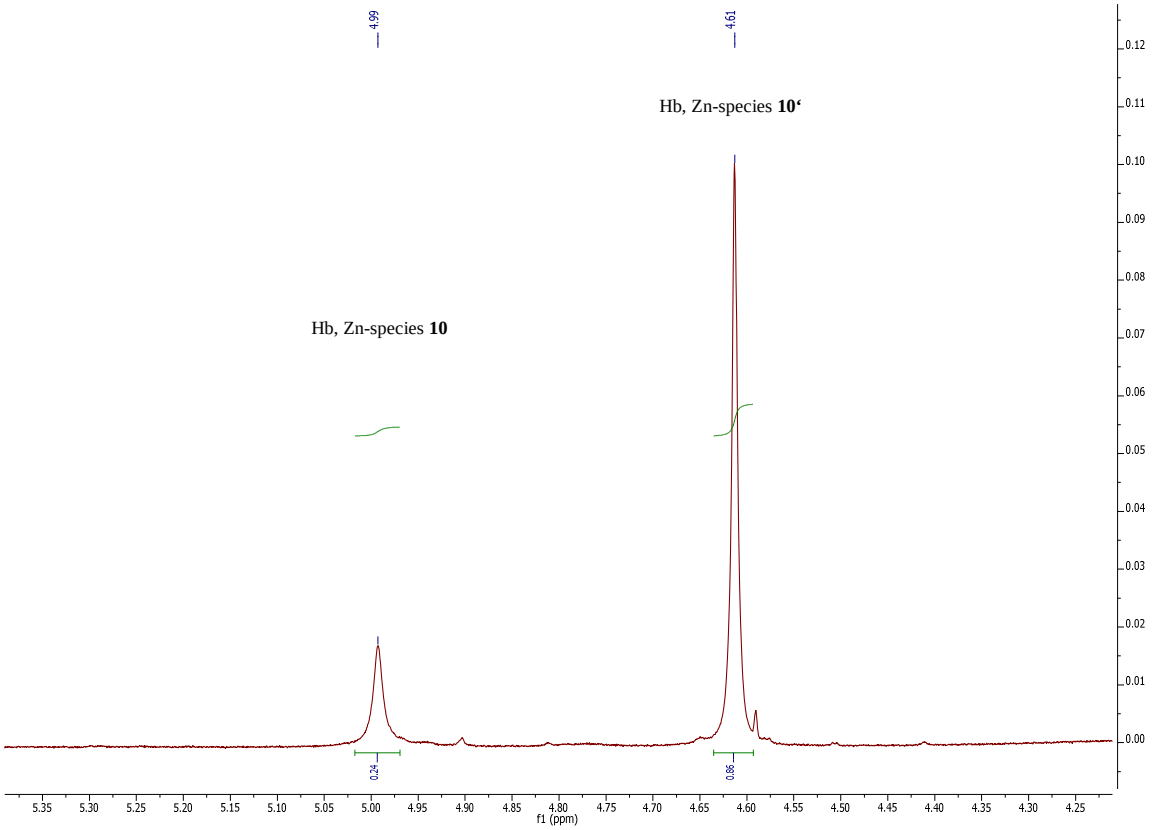


NMR studies of the metalated intermediate **10** after 3 and 6 days at 25°C under argon.

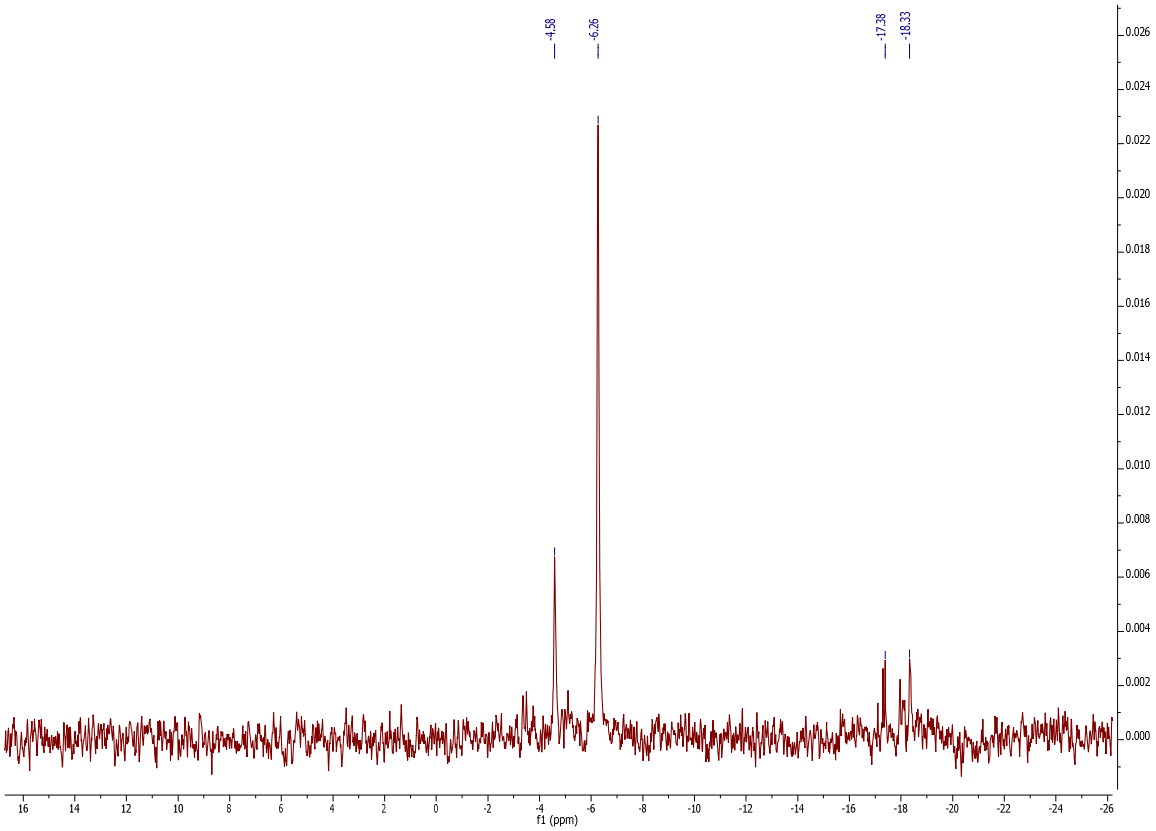
After 3 days, **^{1}H NMR (400 MHz, THF-d_8)**



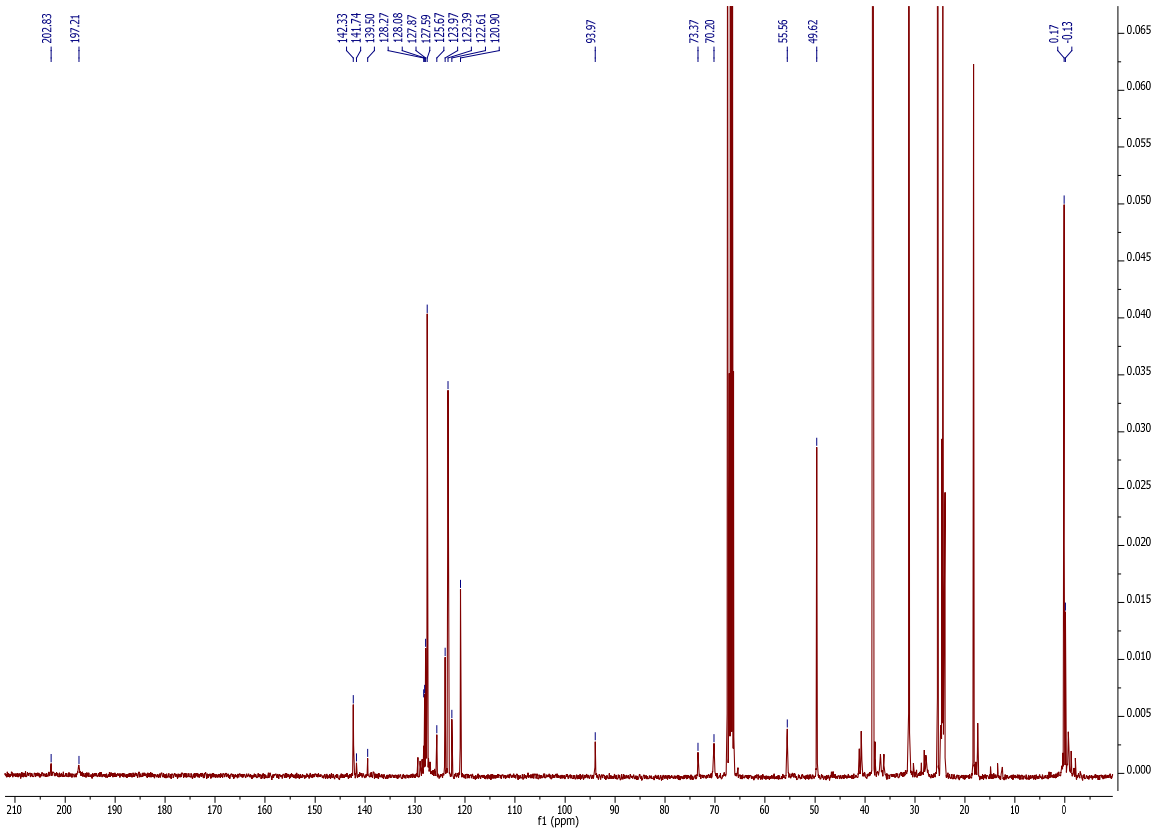
After 3 days, **^{1}H NMR (400 MHz, THF-d_8), zoom on allenic region**



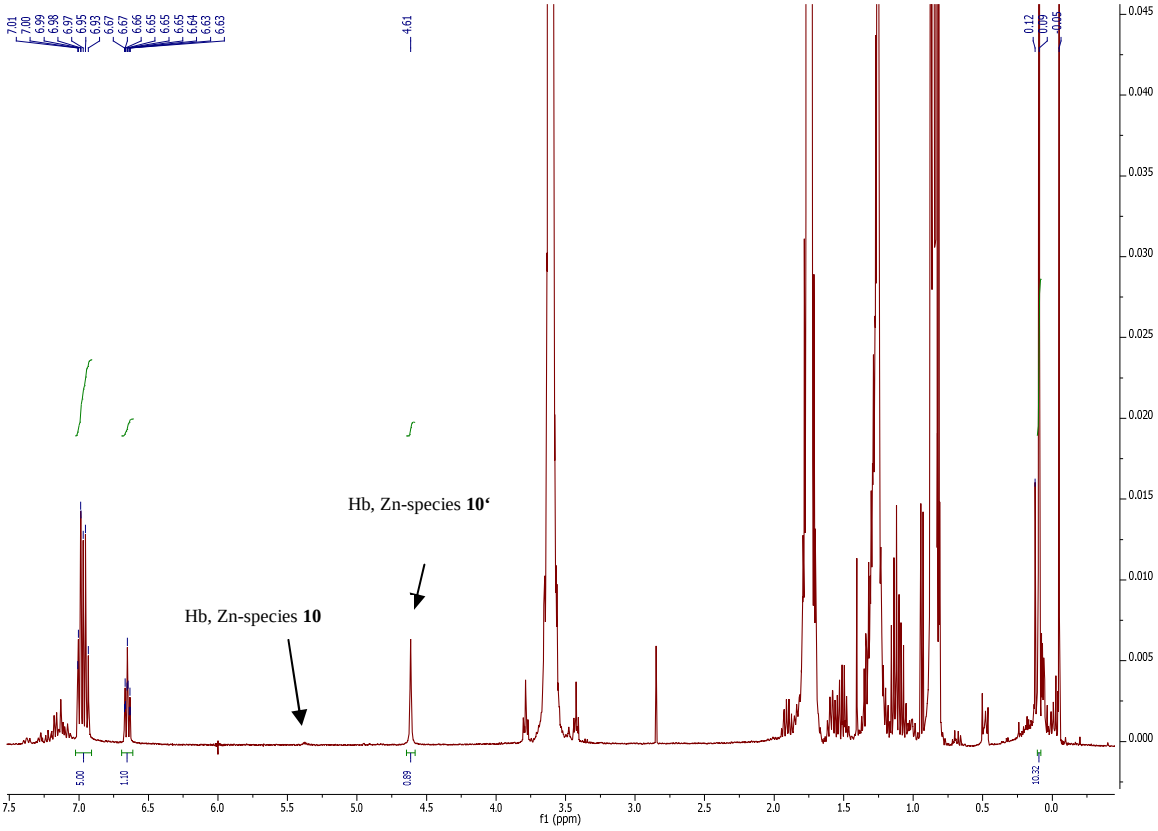
After 3 days, **^{29}Si NMR (79 MHz, THF-d_8)**



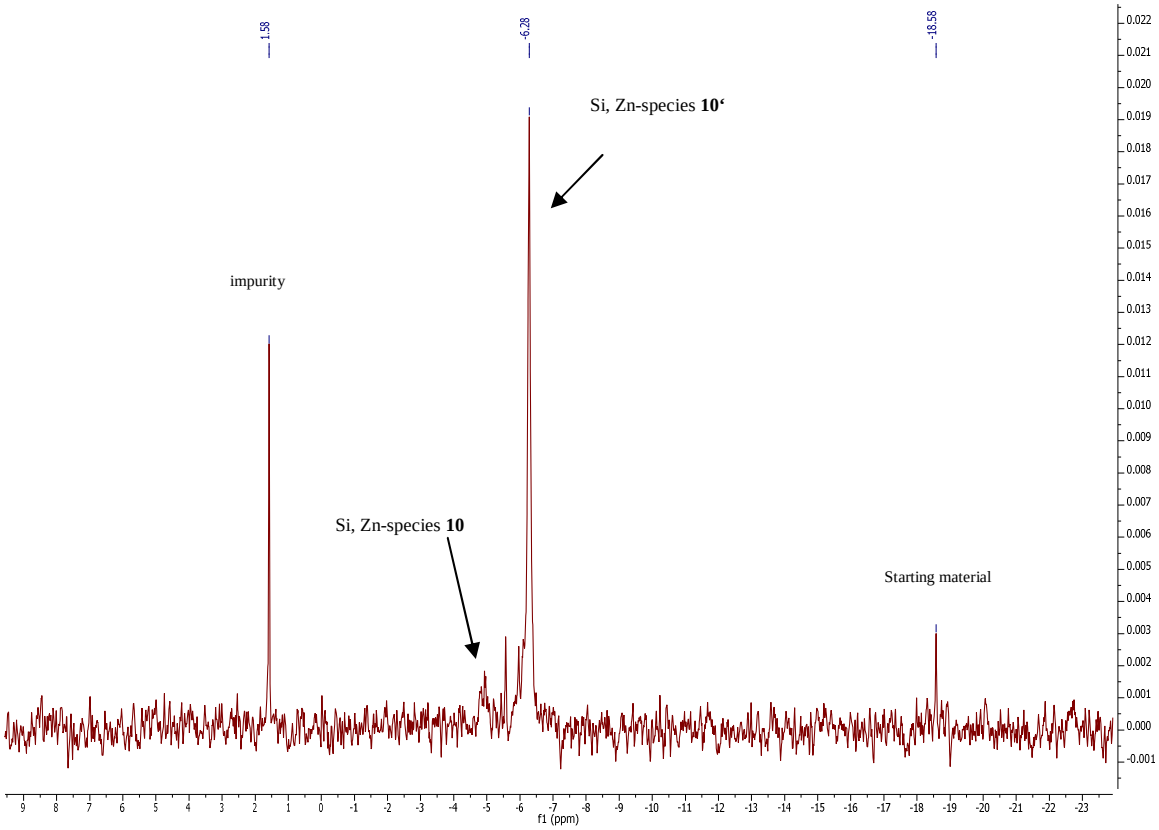
After 3 days, **^{13}C NMR (100 MHz, THF-d_8)**



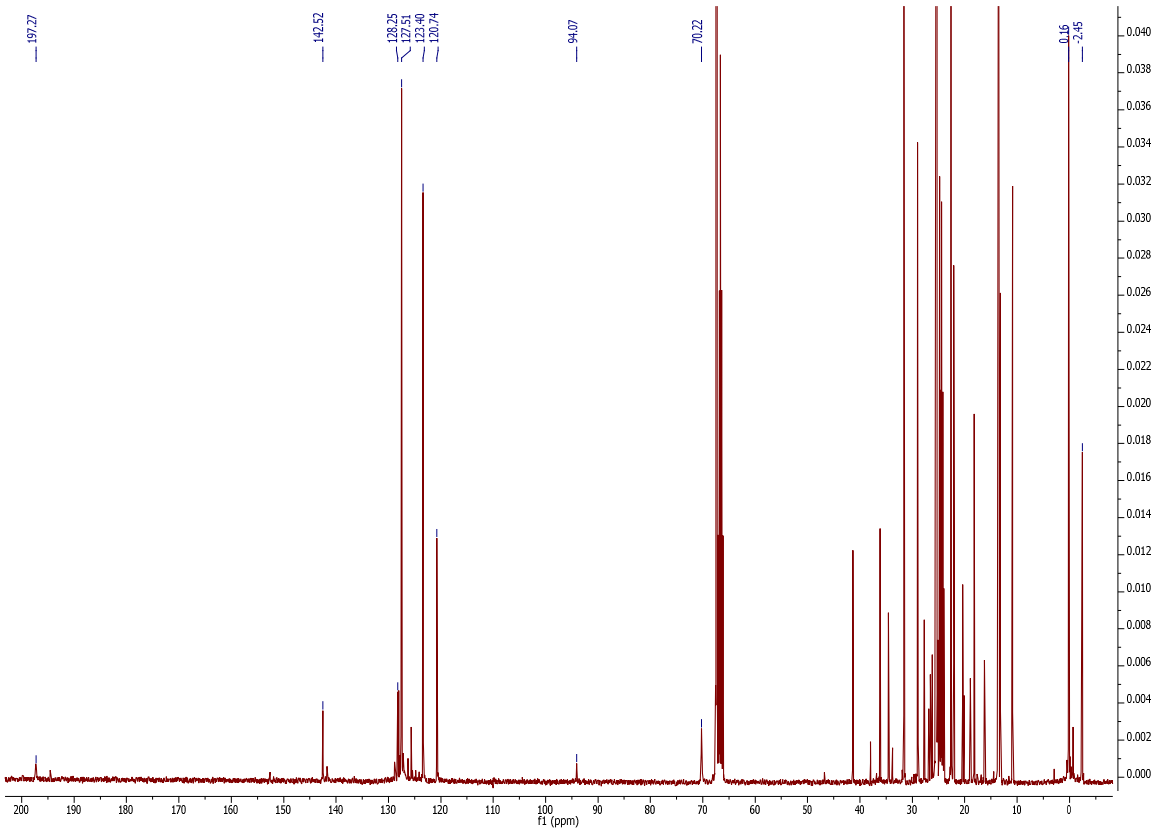
After 6 days, **^{1}H NMR (400 MHz, THF-d_8), overall and zoom on aromatic region**



^{29}Si NMR (79 MHz, THF-d_8)



^{13}C NMR (100 MHz, THF-d_8)

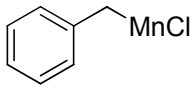


IV. New preparation of benzylic manganese chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of $MnCl_2 \cdot 2LiCl$

Some compounds of this chapter were prepared by Andreas Benischke in the frame of his Master thesis.

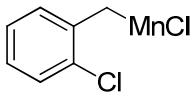
1) Preparation of benzylic manganese reagents

a. Benzylic manganese chloride (11a)



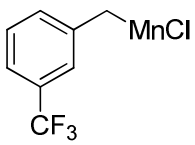
According to **TP4**, magnesium turnings (175 mg, 7.20 mmol), THF (1 mL) and $MnCl_2 \cdot 2LiCl$ (3.75 mL, 3.75 mmol; 1.0 M solution in THF) were used. Benzyl chloride (380 mg, 0.35 mL, 3.0 mmol) was added at once at 0 °C and the reaction was stirred for 1 h at this temperature. The concentration of the benzyl manganese reagent was determined as 0.50 M by the described titration method. Yield: 85 %.

b. 2-Chlorobenzylic manganese chloride (11b)



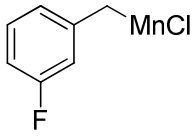
According to **TP4**, magnesium turnings (175 mg, 7.20 mmol), MTBE (1.9 mL) and $MnCl_2 \cdot 2LiCl$ (3.75 mL, 3.75 mmol; 1.0 M solution in THF) were used. 2-Chlorobenzyl chloride (483 mg, 0.38 mL, 3.0 mmol) was added at once at 0 °C and the reaction was stirred for 1.5 h at this temperature. The concentration of the benzyl manganese reagent was determined as 0.37 M by the described titration method. Yield: 62 %.

c. 3-(Trifluoromethyl)benzylic manganese chloride (11c)



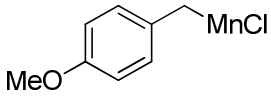
According to **TP4**, magnesium turnings (175 mg, 7.20 mmol), MTBE (1.9 mL) and $MnCl_2 \cdot 2LiCl$ (3.75 mL, 3.75 mmol; 1.0 M solution in THF) were used. 3-Trifluoromethylbenzyl chloride (584 mg, 0.47 mL, 3.0 mmol) was added at once at 0 °C and the reaction was stirred for 1.5 h at this temperature. The concentration of the benzyl manganese reagent was determined as 0.44 M by the described titration method. Yield: 65 %.

d. 3-Fluororobenzylic manganese chloride (11d)



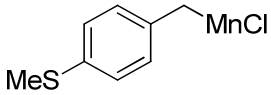
According to **TP4**, magnesium turnings (175 mg, 7.20 mmol), THF (1 mL) and $MnCl_2 \cdot 2LiCl$ (3.75 mL, 3.75 mmol; 1.0 M solution in THF) were used. 3-Fluorobenzyl chloride (434 mg, 0.36 mL, 3.0 mmol) was added at once at 0 °C and the reaction was stirred for 1 h at this temperature. The concentration of the benzyl manganese reagent was determined as 0.44 M by the described titration method. Yield: 64 %.

e. 4-methoxybenzylic manganese chloride (11e)



According to **TP4**, magnesium turnings (175 mg, 7.20 mmol), THF (1 mL) and $MnCl_2 \cdot 2LiCl$ (3.75 mL, 3.75 mmol; 1.0 M solution in THF) were used. 4-Methoxybenzyl chloride (470 mg, 0.41 mL, 3.0 mmol) was added at once at 0 °C and the reaction was stirred for 50 min at this temperature. The concentration of the benzyl manganese reagent was determined as 0.39 M by the described titration method. Yield: 52 %.

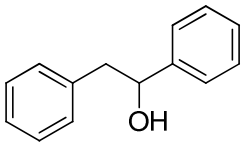
f. 4-(Methylthio)benzylic manganese chloride (11f)



According to **TP4**, magnesium turnings (175 mg, 7.20 mmol), THF (1 mL) and $MnCl_2 \cdot 2LiCl$ (3.75 mL, 3.75 mmol; 1.0 M solution in THF) were used. 4-(Methylthio)benzyl chloride (518 mg, 0.44 mL, 3.0 mmol) was added at once at 0 °C and the reaction was stirred for 1.5 h at this temperature. The concentration of the benzyl manganese reagent was determined as 0.35 M by the described titration method. Yield: 54 %.

2) Preparation of the title compounds

a. 1,2-Diphenylethanol (14a)



According to **TP5**, benzaldehyde (**13a**, 159 mg, 0.15 mL, 1.5 mmol) and THF (1 mL) were used. The benzyl manganese chloride solution **11a** (3.15 mL, 2.25 mmol; 0.50 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 9:1 + 1 % NEt_3) afforded the desired product **3a** (280 mg, 94 %) as a white solid.

M.p. (°C): 65-66.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 7.40-7.37 (m, 4 H), 7.35-7.30 (m, 3 H), 7.27 (t, *J* = 1.4 Hz, 1 H), 7.23 (dd, *J* = 8.2, 1.4 Hz, 2 H), 4.92 (dd, *J* = 8.5, 4.7 Hz, 1 H), 3.11-2.98 (m, 2 H), 2.06 (br. s., 1 H, OH).

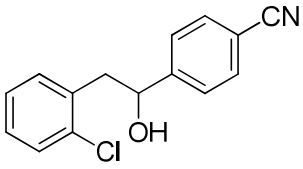
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 143.8, 138.0, 129.5 (2 C), 128.5 (2 C), 128.4 (2 C), 127.6, 126.6, 125.9 (2 C), 75.3, 46.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3301, 3026, 2922, 2857, 1601, 1495, 1453, 1445, 1316, 1272, 1208, 1149, 1071, 1039, 1026, 1016.

MS (70 eV, EI): *m/z* (%) = 51 (11), 65 (12), 77 (32), 79 (55), 92 (100), 107 (81), 198 (1).

HRMS (EI): *m/z* (M^+) for **$C_{14}H_{14}O$**: calcd. 198.1045; found 198.1031.

b. 4-(2-(2-Chlorophenyl)-1-hydroxyethyl)benzonitrile (14b)



According to **TP5**, 4-cyanobenzaldehyde (**13b**, 66 mg, 0.5 mmol) and THF (1 mL) were used. The benzyl manganese chloride solution **11b** (1.49 mL, 0.55 mmol; 0.37 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 7:3 + 1 % NEt_3) afforded the desired product **14b** (122 mg, 95 %) as a white solid.

M.p. (°C): 90-92.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.63 (d, *J* = 8.0 Hz, 2 H), 7.49 (d, *J* = 8.2 Hz, 2 H), 7.40 (d, *J* = 7.2 Hz, 1 H), 7.26-7.12 (m, 3 H), 5.09 (dd, *J* = 8.5, 4.6, 3.9 Hz, 1 H), 3.12 (ddd, *J* = 13.7, 8.7, 4.5 Hz, 2 H), 2.18 (br. s., 1 H, OH).

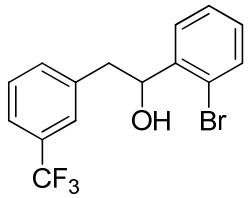
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 149.3, 135.2, 134.6, 132.5 (2 C), 132.3, 130.0, 128.8, 127.2, 126.7 (2 C), 119.1, 111.6, 73.0, 44.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3556, 3064, 2953, 2925, 2360, 2340, 2225, 1946, 1700, 1606, 1573, 1504, 1471, 1444, 1412, 1374, 1355, 1318, 1308, 1270, 1173, 1048.

MS (70 eV, EI): *m/z* (%) = 77 (15), 89 (13), 91 (30), 102 (10), 104 (49), 125 (28), 126 (84), 127 (17), 128 (27), 132 (100), 239 (2).

HRMS (EI): *m/z* (M^+) for **$C_{15}H_{12}NOCl$**: calcd. 257.0607; found 239.0486 (-H_2O).

c. 1-(2-Bromophenyl)-2-(3-(trifluoromethyl)phenyl)ethanol (14c)



According to **TP5**, 2-bromobenzaldehyde (**13c**, 93 mg, 0.06 mL, 0.5 mmol) and THF (1 mL) were used. The benzyl manganese chloride solution **11c** (1.25 mL, 0.55 mmol; 0.44 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 9:1 + 1 % NEt_3) afforded the desired product **14c** (131 mg, 76 %) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.60-7.32 (m, 7 H), 7.18 (td, *J* = 8.02, 1.94 Hz, 1 H), 5.29 (dd, *J* = 8.9, 3.3 Hz, 1 H), 3.22 (dd, *J* = 13.8, 3.3 Hz, 1 H), 2.88 (dd, *J* = 13.8, 8.9 Hz, 1 H), 2.01 (br. s., 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 142.5, 139.1, 133.0, 133.0, 132.94, 132.67,130.67 (q, ^2J(C,F) = 32 Hz), 129.08, 128.75, 127.79, 127.26, 126.3 (q, ^3J(C,F) = 3.65 Hz), 124.2 (d, ^1J(C,F) = 272 Hz), 123.5 (q, ^3J(C,F) = 3.93 Hz), 121.67, 73.7, 43.8.

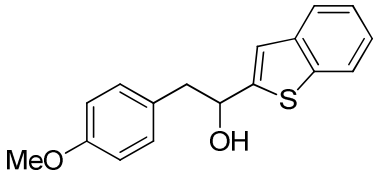
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -62.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3417, 3066, 3017, 2926, 2361, 2338, 1738, 1706, 1615, 1595, 1568, 1491, 1466, 1449, 1440, 1356, 1327, 1228, 1200, 1160, 1130, 1094, 1072, 1022.

MS (70 eV, EI) *m/z* (%) = 51 (15), 76 (10), 77 (100), 78 (34), 105 (31), 109 (15), 140 (12), 157 (51), 159 (47), 160 (15), 178 (14), 183 (22), 186 (35), 188 (28), 325 (11).

HRMS (EI): *m/z* (M^+) for **$C_{15}H_{12}OBrF_3$**: calcd. 344.0024; found 325.0035 (-F).

d. 1-(Benzo[b]thiophen-2-yl)-2-(4-methoxyphenyl)ethanol (14d)



According to **TP5**, benzo[*b*]thiophene-2-carboxaldehyde (**13d**, 195 mg, 1.2 mmol) and THF (1 mL) were used. The benzyl manganese chloride solution **11e** (3.38 mL, 1.32 mmol, 0.39 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 8:2 + 1 % NEt_3) afforded the desired product **14d** (321 mg, 94 %) as a white solid.

M.p. (°C): 114-115.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.89-7.79 (m, 1 H), 7.76-7.68 (m, 1 H), 7.39-7.29 (m, 1 H), 7.17 (ddd, *J* = 8.6, 2.9, 2.0 Hz, 3 H), 6.86 (dd, *J* = 8.8, 2.2 Hz, 2 H), 5.18 (t, *J* = 5.5 Hz, 1 H), 3.80 (s, 3 H), 3.15 (td, *J* = 13.7, 5.1 Hz, 2 H), 2.32 (d, *J* = 2.7 Hz, 1 H, OH).

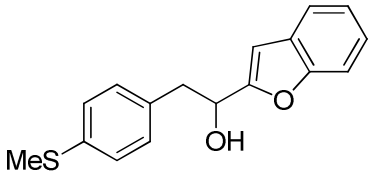
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 158.5, 148.3, 139.4, 139.3, 130.5 (2 C), 129.1, 124.2, 124.1, 123.4, 122.4, 120.3, 114.0 (2 C), 71.8, 55.2, 44.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3533, 3501, 3388, 3014, 2912, 2853, 1888, 1608, 1583, 1510, 1441, 1301, 1242, 1176, 1114, 1053, 1031.

MS (70 eV, EI): *m/z* (%) = 78 (10), 91 (28), 122 (100), 134 (12), 135 (25), 163 (59), 284 (1).

HRMS (EI): *m/z* (M^+) for **$C_{17}H_{16}O_2S$**: calcd. 284.0871; found 284.0859.

e. 1-(Benzofuran-2-yl)-2-(4-(methylthio)phenyl)ethanol (14e)



According to **TP5**, 2-benzofurancarboxaldehyde (**14d**, 73 mg, 0.06 mL, 0.5 mmol) and THF (1 mL) were used. The benzyl manganese chloride solution **11f** (1.57 mL, 0.55 mmol; 0.35 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 8:2 + 1 % NEt_3) afforded the desired product **14e** (134 mg, 94 %) as a white solid.

M.p. (°C): 115-116.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.57-7.47 (m, 2 H), 7.32-7.13 (m, 6 H), 6.60 (t, *J* = 0.8 Hz, 1 H), 5.10–4.99 (m, 1 H), 3.21 (dq, *J* = 18.3, 14.1, 5.5 Hz, 1 H), 2.47 (s, 3 H), 2.10 (d, *J* = 4.7 Hz, 1 OH).

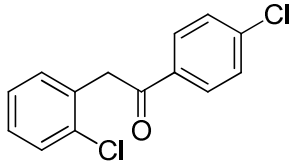
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 158.3, 154.8, 136.8, 133.8, 130.0 (2 C), 128.1, 127.0 (2 C), 124.2, 122.8, 121.1, 111.2, 103.2, 69.2, 41.6, 16.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3552, 3546, 3398, 2917, 2363, 2356, 1492, 1453, 1436, 1404, 1301, 1254, 1165, 1134, 1065, 1003.

MS (70 eV, EI): *m/z* (%) = 91 (27), 122 (11), 123 (14), 137 (45), 138 (75), 147 (100), 148 (11), 284 (4), 285 (1).

HRMS (EI): *m/z* (M^+) for **$C_{17}H_{16}O_2S$**: calcd. 284.0871; found 284.0862.

f. 2-(2-Chlorophenyl)-1-(4-chlorophenyl)ethanone (14f)



According to **TP5**, 4-chlorobenzoyl chloride (**13f**, 140 mg, 0.10 mL, 0.8 mmol) and THF (1 mL) were used. The benzyl manganese chloride solution **11b** (2.38 mL, 0.88 mmol; 0.37 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/Et_2O = 9:1) afforded the desired product **14f** (165 mg, 78 %) as a white solid.

M.p. (°C): 102-103.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 8.01–7.97 (m, 2 H), 7.49-7.45 (m, 2 H), 7.42 (ddd, *J* = 4.4, 3.6, 2.7 Hz, 1 H), 7.27-7.24 (m, 3 H), 4.41 (s, 2 H).

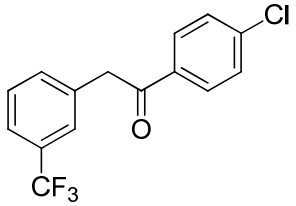
^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 195.4, 140.0, 135.1, 134.6, 133.0, 131.8, 130.0 (2 C), 129.7, 129.2 (2 C), 128.9, 127.2, 43.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3853, 3365, 3053, 2914, 2854, 1944, 1723, 1688, 1588, 1571, 1474, 1398, 1326, 1212, 1197, 1085, 1048.

MS (70 eV, EI): *m/z* (%) = 111 (16), 125 (11), 139 (100), 141 (29), 265 (27), 267 (17).

HRMS (EI): *m/z* (M^+) for **$C_{14}H_{10}OCl_2$**: calcd. 264.0109; found 265.0189.

g. 4-(4-Chlorophenyl)-2-(3-(trifluoromethyl)phenyl)ethanone (14g)



According to **TP5**, 4-chlorobenzoyl chloride (**13f**, 88 mg, 0.07 mL, 0.5 mmol) and THF (0.5 mL) were used. The benzyl manganese chloride solution **11c** (1.25 mL, 0.55 mmol; 0.44 M in

THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/Et_2O = 9:1) afforded the desired product **14g** (114 mg, 76 %) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.96 (dt, *J* = 8.6, 1.9 Hz, 2 H), 7.58-7.41 (m, 6 H), 4.33 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 195.4, 140.0, 135.0, 134.6, 133.0 (q, ^4J(C,F) = 1.4 Hz) , 131.0 (q, ^2J(C,F) = 32 Hz), 129.8, 129.1 (2 C), 126.3 (q, ^3J(C,F) = 4 Hz), 125.80, 124.0 (q, ^3J(C,F) = 4 Hz), 124.0 (q, ^1J(C,F) = 272 Hz), 44.9.

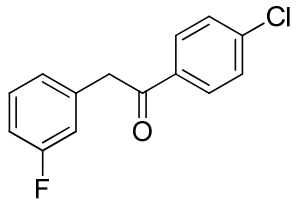
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -62.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3094, 3051, 2925, 2840, 2727, 2675, 2558, 1931, 1799, 1677, 1591, 1574, 1491, 1424, 1400, 1321, 1304, 1295, 1281, 1213, 1175, 1126, 1091, 1015.

MS (70 eV, EI): *m/z* (%) = 75 (16), 111 (32), 139 (100), 298 (1).

HRMS (EI): *m/z* (M^+) for **$C_{15}H_{10}OClF_3$**: calcd. 298.0372; found 298.0365.

h. 1-(4-Chlorophenyl)-2-(3-fluorophenyl)ethanone (14h)



According to **TP5**, 4-chlorobenzoyl chloride (**13f**, 140 mg, 0.10 mL, 0.8 mmol) and THF (0.5 mL) were used. The benzyl manganese chloride solution **11d** (1.91 mL, 0.88 mmol; 0.44 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/Et_2O = 9:1) afforded the desired product **14h** (143 mg, 72 %) as a pale yellow solid.

M.p. (°C): 51-52.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.94 (dt, *J* = 8.6, 1.9 Hz, 2 H), 7.45 (dt, *J* = 8.4, 1.7 Hz, 2 H), 7.36-7.25 (m, 1 H), 7.07–6.91 (m, 3 H), 4.26 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 195.7, 162.9 (d, ^1J(C-F) = 246 Hz), 139.8, 136.4 (d, ^3J(C-F) = 8 Hz), 134.7, 130.2, 130.1, 129.9, 129.03, 125.1 (d, ^4J(C-F) = 3 Hz), 116.5 (d, ^2J(C-F) = 22 Hz), 114.0 (d, ^2J(C-F) = 21 Hz), 45.0 (d, ^4J(C-F) = 2 Hz).

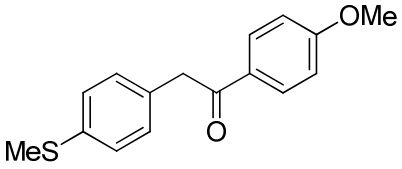
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -112.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3351, 3061, 2908, 2855, 2569, 1933, 1790, 1738, 1681, 1618, 1587, 1487, 1446, 1398, 1328, 1250, 1207, 1171, 1143, 1089.

MS (70 eV, EI): *m/z* (%) = 111 (16), 139 (100), 219 (3), 249 (1).

HRMS (EI): *m/z* (M^+) for **$C_{14}H_{10}OClF$**: calcd. 248.0404; found 249.0481.

i. 1-(4-Methoxyphenyl)-2-(4-(methylthio)phenyl)ethanone (14i)



According to **TP5**, 4-methoxybenzoyl chloride (**13g**, 85 mg, 0.07 mL, 0.5 mmol) and THF (1 mL) were used. The benzyl manganese chloride solution **11f** (1.57 mL, 0.55 mmol; 0.35 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 9:1) afforded the desired product **14i** (127 mg, 93 %) as a white solid.

M.p. (°C): 138-140.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (dd, *J* = 9.1, 1.4 Hz, 2 H), 7.26-7.16 (m, 4 H), 6.94 (dd, *J* = 8.5, 0.9 Hz, 2 H), 4.20 (s, 2 H), 3.87 (s, 3 H), 2.47 (s, 3 H).

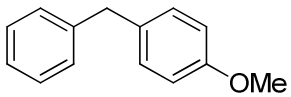
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 196.0, 163.6, 136.8, 131.8, 130.9 (2 C), 129.9 (2 C), 129.6, 127.1 (2 C) 113.8 (2 C), 55.5, 44.7, 16.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3019, 2960, 2915, 2837, 2361, 2339, 1677, 1599, 1574, 1506, 1494, 1458, 1443, 1417, 1330, 1306, 1253, 1226, 1202, 1174, 1108, 1087, 1028.

MS (70 eV, EI): *m/z* (%) = 135 (100), 272 (6), 273 (1).

HRMS (EI): *m/z* (M^+) for **$C_{16}H_{16}O_2S$**: calcd. 272.0871; found 272.0861.

j. 1-Benzyl-4-methoxybenzene (14j)



According to **TP5**, 4-iodoanisole (**13h**, 234 mg, 1.0 mmol) and THF (1 mL) were used. Then, 2 % $Pd(OAc)_2$ (4.5 mg) and 4 % S-Phos (16.4 mg) were added to the solution. The benzyl manganese chloride solution **11a** (2.20 mL, 1.1 mmol; 0.50 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/Et_2O = 99:1) afforded the desired product **14j** (190 mg, 96 %) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.43-7.28 (m, 5 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 6.98-6.90 (m, 2 H), 4.03 (s, 2 H), 3.86 (s, 3 H).

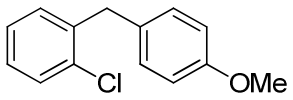
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 157.9, 141.5, 133.2, 129.8 (2 C), 128.8 (2 C), 128.4 (2 C), 125.9, 113.8 (2 C), 55.1, 41.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3061, 3027, 3001, 2906, 2834, 1947, 1884, 1610, 1584, 1509, 1493, 1462, 1452, 1439, 1300, 1243, 1174, 1106, 1073, 1033.

MS (70 eV, EI): *m/z* (%) = 57 (43), 69 (31), 83 (32), 91 (41), 97 (36), 109 (18), 111 (27), 125 (17), 153 (13), 165 (26), 167 (32), 183 (14), 197 (46), 198 (100), 199 (15).

HRMS (EI): *m/z* (M$^+$) for **C$_{14}$H$_{14}$O**: calcd. 198.1045; found 198.1040.

k. 1-Chloro-2-(4-methoxybenzyl)benzene (14k)



According to **TP5**, 4-iodoanisole (**13h**, 234 mg, 1.0 mmol) and THF (1 mL) were used. Then, 2 % Pd(OAc)$_2$ (4.5 mg) and 4 % S-Phos (16.4 mg) were added to the solution. The benzyl manganese chloride solution **11b** (2.97 mL, 1.1 mmol; 0.37 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO$_2$, *i*hexane/Et$_2$O = 99:1) afforded the desired product **14k** (219 mg, 94 %) as a colourless liquid.

^{1}H NMR (300 MHz, CDCl$_3$) δ/ppm = 7.47-7.41 (m, 1 H), 7.26-7.16 (m, 5 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 4.12 (s, 2 H), 3.84 (s, 3 H).

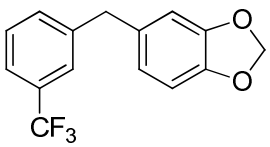
^{13}C NMR (75 MHz, CDCl$_3$) δ/ppm = 158.0, 139.1, 134.1, 131.5, 130.8, 129.9 (2 C), 129.4, 127.5, 126.7, 113.8 (2 C), 55.1, 38.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3062, 2999, 2953, 2931, 2834, 1612, 1584, 1571, 1509, 1470, 1441, 1301, 1243, 1175, 1105, 1049, 1035.

MS (70 eV, EI): *m/z* (%) = 121 (20), 125 (12), 152 (33), 153 (19), 166 (10), 181 (13), 197 (51), 231 (24), 232 (100), 233 (22), 234 (34).

HRMS (EI): *m/z* (M$^+$) for **C$_{14}$H$_{13}$OCl**: calcd. 232.0655; found 232.0652.

l. 5-(3-(Trifluoromethyl)benzyl)benzo[d][1,3]dioxole (14l)



According to **TP5**, 5-bromo-1,3-benzodioxole (**13i**, 101 mg, 0.06 mL, 0.5 mmol) and THF (0.5 mL) were used. Then, 2 % Pd(OAc)$_2$ (2.3 mg) and 4 % S-Phos (8.2 mg) were added to the solution. The benzyl manganese chloride solution **11c** (1.25 mL, 0.55 mmol; 0.44 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C

and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/EtOAc = 98:2) afforded the desired product **14l** (100 mg, 71 %) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.51-7.33 (m, 4 H), 6.77 (dd, *J* = 0.8 Hz, 2 H), 6.67 (dd, *J* = 1.1, 0.6 Hz, 2 H), 5.94 (s, 3 H), 3.96 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 147.9, 146.2, 142.2, 133.8, 132.1, 132.1, 130.8 (q, ^2J(C,F) = 32 Hz), 128.9, 125.4 (q, ^3J(C,F) = 4 Hz), 124.2 (q, ^1J(C,F) = 272 Hz), 123.0 (q, ^3J(C,F) = 4 Hz), 109.3, 108.3, 101.0, 41.3.

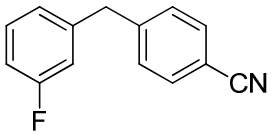
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -62.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3017, 2896, 2778, 2361, 1846, 1714, 1610, 1597, 1503, 1488, 1442, 1360, 1329, 1244, 1160, 1120, 1092, 1072, 1038.

MS (70 eV, EI): *m/z* (%) = 135 (33), 152 (18), 153 (11), 159 (11), 181 (26), 201 (10), 242 (24), 249 (11), 261 (11), 279 (23), 280 (100), 281 (15).

HRMS (EI): *m/z* (M^+) for **$C_{15}H_{11}O_2F_3$**: calcd. 280.0711; found 280.0704.

m. 4-(3-Fluorobenzyl)benzonitrile (14m)



According to **TP5**, 4-bromobenzonitrile (**13j**, 216 mg, 1.2 mmol) and THF (1 mL) were used. Then, 2 % $Pd(OAc)_2$ (5.4 mg) and 4 % S-Phos (19.7 mg) were added to the solution. The benzyl manganese chloride solution **11d** (3.0 mL, 1.3 mmol; 0.44 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/Et_2O = 9:1) afforded the desired product **14m** (175 mg, 69 %) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.57 (dt, *J* = 8.2, 1.7 Hz, 2 H), 7.28 (m, 3 H), 7.01-6.81 (m, 3 H), 4.03 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 162.9 (d, ^1J(C-F) = 246 Hz), 145.7, 141.7 (d, ^3J(C-F) = 7 Hz), 132.2 (2 C), 130.1 (d, ^3J(C-F) = 8 Hz), 129.5 (2 C), 124.5 (d, ^4J(C-F) = 3 Hz), 118.7, 115.7 (d, ^2J(C-F) = 21 Hz), 113.5 (d, ^2J(C-F) = 21 Hz), 110.2, 41.4 (d, ^4J(C-F) = 2 Hz).

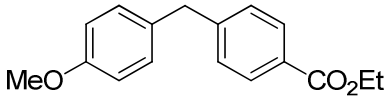
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -112.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3061, 2925, 2227, 1929, 1606, 1588, 1505, 1486, 1448, 1414, 1246, 1136, 1021.

MS (70 eV, EI): *m/z* (%) = 109 (10), 190 (16), 208 (14), 210 (34), 211 (100), 212 (31).

HRMS (EI): *m/z* (M^+) for **$C_{14}H_{10}FN$**: calcd. 211.0797; found 211.0784.

n. Ethyl 4-(4-methoxybenzyl)benzoate (14n)



According to **TP5**, ethyl 4-bromobenzoate (**13k** 275 mg, 0.20 mL, 1.2 mmol) and THF (1 mL) were used. Then, 2 % $Pd(OAc)_2$ (5.4 mg) and 4 % S-Phos (19.7 mg) were added to the solution. The benzyl manganese chloride solution **11e** (3.38 mL, 1.3 mmol; 0.39 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/Et_2O = 9:1) afforded the desired product **14n** (285 mg, 88 %) as a pale yellow solid.

M.p. (°C): 42-43.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.98 (dd, *J* = 8.6, 1.9 Hz, 2 H), 7.25 (dd, *J* = 8.0, 2.2 Hz, 2 H), 7.10 (dd, *J* = 8.9, 2.2 Hz, 2 H), 6.85 (dd, *J* = 8.9, 2.2 Hz, 2 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 3.98 (s, 2 H), 3.80 (s, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H).

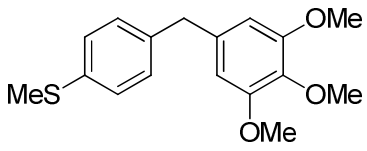
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 166.6, 158.1, 146.8, 132.2, 129.9 (2 C), 129.7 (2 C), 128.7 (2 C), 128.3, 114.0 (2 C), 60.8, 55.2, 41.0, 14.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3001, 2972, 2910, 2837, 1946, 1889, 1710, 1609, 1512, 1471, 1414, 1364, 1286, 1268, 1244, 1174, 1126, 1106, 1032, 1018.

MS (70 eV, EI): *m/z* (%) = 121 (27), 152 (14), 153 (15), 165 (19), 197 (65), 198 (11), 241 (17), 270 (100), 271 (21).

HRMS (EI): *m/z* (M^+) for **$C_{17}H_{18}O_3$**: calcd. 270.1256; found 270.1244.

o. Methyl(4-(3,4,5-trimethoxybenzyl)phenyl)sulfane (14o)



According to **TP5**, 5-bromo-1,2,3-trimethoxybenzene (**13l**, 247 mg, 1.0 mmol) and THF (1 mL) were used. Then, 2 % $Pd(OAc)_2$ (4.5 mg) and 4 % S-Phos (16.4 mg) were added to the solution. The benzyl manganese chloride solution **11f** (3.14 mL, 1.1 mmol; 0.35 M in THF) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Purification by flash chromatography (SiO_2, *i*hexane/Et_2O = 8:2) afforded the desired product **14o** (152 mg, 50 %) as a yellow solid.

M.p. (°C): 56-57.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.21 (dt, *J* = 8.2, 1.8 Hz, 2 H), 7.13 (dt, *J* = 8.2, 1.8 Hz, 2 H), 6.40 (s, 2 H), 3.89 (s, 2 H), 3.82 (s, 9 H), 2.48 (s, 3 H).

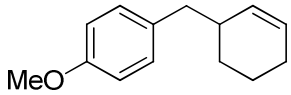
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 152.9 (2 C), 137.6, 136.2, 136.1, 135.5, 129.1, 129.0 (2 C), 128.6, 128.5, 126.7 (2 C), 105.6 (2 C), 60.5, 55.7 (2 C), 41.3, 15.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 2999, 2959, 2920, 2836, 2820, 1914, 1731, 1652, 1588, 1505, 1493, 1459, 1449, 1431, 1421, 1327, 1316, 1236, 1118, 1089, 1009.

MS (70 eV, EI) *m/z* (%) = 128 (11), 137 (10), 289 (10), 304 (100), 305 (19).

HRMS (EI): *m/z* (M^+) for **$C_{17}H_{20}O_3S$**: calcd. 304.1133; found 304.1123.

p. 1-(Cyclohex-2-en-1-ylmethyl)-4-methoxybenzene (15)



A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum was charged with 3-bromocyclohexene (**13m**, 161 mg, 0.11 mL, 1.0 mmol), followed by dry THF (1 mL). The benzyl manganese chloride solution **11e** (2.82 mL, 1.1 mmol; 0.39 M) was added dropwise at -40 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Sat. aq. NH_4Cl (4 mL) and water (2 mL) were added and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and purification by flash column chromatography (SiO_2, *i*hexane/Et_2O = 9:1) afforded the desired product **15** (186 mg, 92 %) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.14 (d, *J* = 8.6 Hz, 2 H), 6.92-6.84 (m, 2 H), 5.79-5.59 (m, 2 H), 3.83 (s, 3 H), 2.69-2.49 (m, 2 H), 2.45-2.31 (m, 1 H), 2.09–1.98 (m, 2 H), 1.84-1.70 (m, 2 H), 1.66-1.51 (m, 1 H), 1.39-1.22 (m, 1 H).

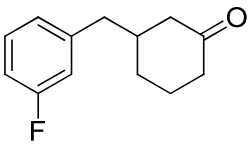
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 157.7, 132.9, 131.3, 129.9 (2 C), 127.2, 113.5 (2 C), 77.4, 76.6, 55.1, 41.8, 37.3, 28.8, 25.4, 21.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3014, 2919, 2834, 1648, 1611, 1583, 1510, 1463, 1441, 1299, 1242, 1175, 1107, 1036.

MS (70 eV, EI) *m/z* (%) = 77 (8), 121 (100), 202 (1).

HRMS (EI): *m/z* (M^+) for **$C_{14}H_{18}O$**: calcd. 202.1358; found 202.1350.

q. 3-(3-Fluorobenzyl)cyclohexanone (16)



A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum was charged with cyclohexenone (**13n**, 96 mg, 0.10 mL, 1.0 mmol), followed by dry THF (1 mL). The benzyl manganese chloride solution **11d** (2.5 mL, 1.1 mmol, 0.44 M in THF) was added dropwise at -40 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Sat. aq. NH_4Cl (4 mL) and water (2 mL) were added and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and purification by flash column chromatography (SiO_2, *i*hexane/EtOAc = 9:1 + 1 % NEt_3) afforded the desired product **16** (163 mg, 79 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.25-7.17 (m, 1 H), 6.90-6.83 (m, 2 H), 6.80 (dd, *J* = 10.0, 1.6 Hz, 1 H), 2.66-2.51 (m, 2 H), 2.38-2.17 (m, 3 H), 2.07-1.95 (m, 3 H), 1.89-1.79 (m, 1 H), 1.66-1.55 (m, 1 H), 1.41-1.28 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 211.2, 162.8 (d, ^1J(C-F) = 246 Hz), 141.9 (d, ^3J(C-F) = 7 Hz), 129.7 (d, ^3J(C-F) = 8 Hz), 124.7 (d, ^4J(C-F) = 3 Hz), 115.8 (d, ^2J(C-F) = 21 Hz), 113.1 (d, ^2J(C-F) = 21 Hz), 47.6, 42.6 (d, ^4J(C-F) = 2 Hz), 41.3, 40.6, 30.8, 25.0.

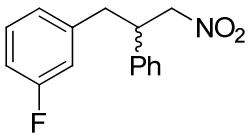
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -113.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 2933, 2866, 1708, 1614, 1587, 1486, 1448, 1346, 1311, 1249, 1225, 1139, 1056.

MS (70 eV, EI): *m/z* (%) = 41 (54), 42 (10), 55 (41), 69 (38), 83 (33), 97 (42), 109 (100), 133 (19), 135 (20), 147 (33), 148 (94), 206 (9), 207 (5).

HRMS (EI): *m/z* (M^+) for **$C_{13}H_{15}FO$**: calcd. 206.1107; found 206.1102.

r. 1-Fluoro-3-(3-nitro-2-phenylpropyl)benzene (17)



A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum was charged with trans-β-nitrostyrene (**13o**, 224 mg, 1.5 mmol), followed by dry THF (1.5 mL). The benzyl manganese chloride solution **11d** (0.44 M, 3.75 mL, 1.1 equiv) was added dropwise at - 78 °C and the reaction mixture was slowly warmed up to 25 °C and stirred overnight. Sat. aq. NH_4Cl (4 mL) and water (2 mL) were added and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and purification by flash column

chromatography (SiO_2, *i*hexane/Et_2O = 9:1) afforded the desired product **17** (288 mg, 74 %) as a slight yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm = 7.36 - 7.13 (m, *J* = 8.04, 7.67, 2.06, 1.50 Hz, 5 H), 6.96 - 6.74 (m, *J* = 8.42, 2.43 Hz, 3 H), 4.70 - 4.53 (m, *J* = 8.23, 2.62, 1.50 Hz, 2 H), 3.78 (quin, *J* = 7.62 Hz, 1 H), 3.01 (d, *J* = 7.48 Hz, 2 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm = 162.7 (d, ^1J(C-F) = 246 Hz), 140.3 (d, ^3J(C-F) = 7 Hz), 138.5, 129.9 (d, ^3J(C-F) = 8 Hz), 128.8 (2 C), 127.7, 127.4 (2 C), 124.7 (d, ^4J(C-F) = 3 Hz), 115.8 (d, ^2J(C-F) = 21 Hz), 113.6 (d, ^2J(C-F) = 21 Hz), 79.4, 45.7, 39.4 (d, ^4J(C-F) = 2 Hz).

^{19}F-NMR (282 MHz, $CDCl_3$) δ/ppm = -113.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1} = 3064, 3032, 2923, 2361, 1614, 1588, 1548, 1487, 1450, 1431, 1377, 1249, 1141, 1075.

MS (70 eV, EI) *m/z* (%) = 83 (12), 91 (38), 103 (12), 104 (89), 109 (100), 198 (23), 212 (15).

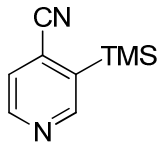
HRMS (EI): *m/z* (M^+) for **$C_{15}H_{14}FNO_2$**: calcd. 259.1009; found 259.1024.

V. Transition Metal Free Cross-coupling of Aryl and N-Heteroaryl Cyanides with Benzylic Zinc Reagents

Some compounds of this chapter were prepared by Dr. Daniela Sustac Roman.

1) Preparation of the starting materials

a. 3-(Trimethylsilyl)isonicotinonitrile (18f)



A dry and argon-flushed tube was charged with 3-iodoisonicotinonitrile (**18a**, 460 mg, 2.0 mmol) and THF (4 mL). A freshly titrated solution of *i*PrMgCl·LiCl[136] (1.74 mL, 2.2 mmol, 1.26 M in THF) was added dropwise at 0 °C and the reaction was stirred for 30 min at this temperature. Then, TMSOTf (0.43 mL, 222 mg, 2.4 mmol) was added and the reaction mixture was stirred at 25 °C for 3.5 h. The reaction mixture was then quenched with sat. aq. NH_4Cl (20 mL) and extracted with Et_2O (4 x 20 mL). The organic layers were combined, dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* and purification by flash column chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/Et_2O = 8:2) afforded the expected pyridine **18f** (208 mg, 59 %) as a yellow oil.

[136] Purchased from Rockwood Lithium and titrated against iodine prior to use.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.85 (d, *J* = 0.8 Hz, 1 H), 8.75 (d, *J* = 5.0 Hz, 1 H), 7.52 (dd, *J* = 5.1, 1.0 Hz, 1 H), 0.48 (s, 9 H).

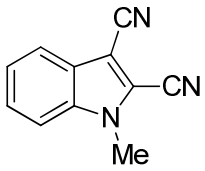
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 155.0, 150.6, 137.3, 126.2, 125.4, 117.6, -1.58 (3 C).

IR (Diamond-ATR, neat) ν/cm^{-1} = 3044, 2959, 2907, 2230, 1568, 1531, 1462, 1395, 1279, 1252, 1204, 1117, 1036, 912.

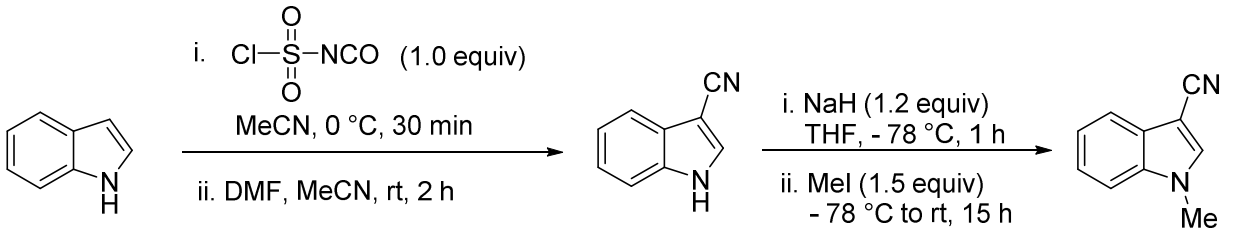
MS (EI, 70 eV) *m/z* (%) = 107 (15), 134 (15), 161 (100), 162 (26), 176 (31).

HRMS (EI): *m/z* (M^+) for **$C_9H_{12}N_2Si$**: calc. 176.0770; found 176.0770.

b. 1-Methyl-1*H*-indole-2,3-dicarbonitrile (21)



1. 3-Cyanoindole



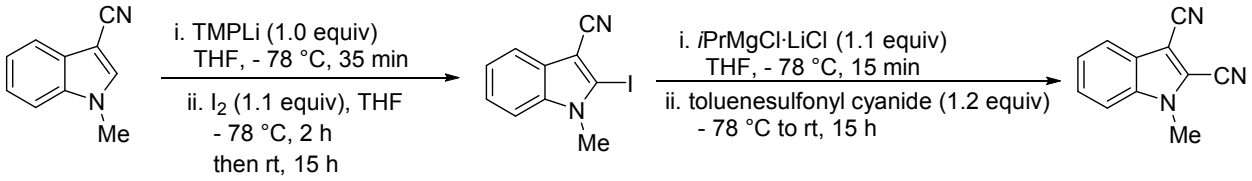
61% (2 steps)

3-Cyanoindole is commercially available, but can be alternatively prepared via the reported literature procedure[137] (the reaction was performed on a 12 mmol scale). The resulting crude 3-cyanoindole was dissolved in THF (30 mL) in a 250 mL round-bottom flask and cooled to -78 °C (under argon). NaH (60%, 576 mg, 14.4 mmol, 1.2 equiv) was added in one portion and the reaction was stirred for 1 h at -78 °C. Iodomethane (1.12 mL, 18 mmol, 1.5 equiv) was added *via* syringe and the reaction was allowed to warm up to room temperature overnight. The reaction was quenched with H_2O (15 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated. The crude was purified by flash chromatography (*i*hexane/EtOAc = 8:2) affording 3-cyanoindole over two steps (1.136 g, 7.2 mmol, 61 %) as brown solid.

The compound was previously reported in the literature[138] and matches reported spectral data.

[137] G. Mehta, *Synthesis* **1978**, 374.
[138] Y. Nakao, K. S. Kanyiva, S. Oda, T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 8146.

2. 1-methyl-1H-indole-2,3-dicarbonitrile (21)



Adapted from a literature procedure,[139] a solution of 1-methyl-1*H*-indole-3-carbonitrile (625 mg, 4.0 mmol, 1.0 equiv) in THF (2 mL) was added dropwise to a solution of freshly prepared TMPLi (8.7 mL, 4.0 mmol, 1.0 equiv; 0.46 M in THF) at -78 °C. After stirring for 35 min at -78 °C, a solution of iodine (1.24 g, 4.4 mmol, 1.1 equiv) in THF (2 mL) was added dropwise (ensuring proper stirring of the resulting precipitate). The reaction mixture was stirred for 2 h at -78 °C, then overnight at room temperature. The reaction mixture was quenched with a sat. aq. solution of $Na_2S_2O_3$ (15 mL), then extracted with EtOAc (20 mL). The organic layer was dried (Na_2SO_4) and concentrated to give 1.074 g of a brown solid, which was used without further purification for the next step.

2-Iodo-1-methyl-1*H*-indole-3-carbonitrile (846 mg, 3.0 mmol, 1.0 equiv) was dissolved in THF (3 mL) and cooled to -78 °C. *i*PrMgCl·LiCl (2.62 mL, 3.3 mmol, 1.1 equiv; 1.26 M in THF) was added dropwise. After 15 min of stirring at -78 °C, a solution of *p*-toluenesulfonyl cyanide (652.5 mg, 3.6 mmol, 1.2 equiv) in THF (3 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight, and then quenched with sat. aq. NH_4Cl (15 mL), extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude was purified by flash chromatography (*i*hexane/Et_2O/$CHCl_3$ = 6:3:1). The resulting insoluble solid was further purified by hot filtration from Et_2O affording indole **4** (233 mg 1.28 mmol, 43%) as white solid.

M.p. (°C): 201-202.

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm = 7.80 (dd, *J* = 15.3, 8.6 Hz, 2 H), 7.59 (ddd, *J* = 8.5, 7.2, 1.2 Hz, 1 H), 7.48 - 7.40 (m, 1 H), 4.00 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6) δ/ppm = 136.7, 127.3, 125.2, 124.2, 119.8, 116.0, 113.0, 112.6, 110.7, 93.1, 33.0.

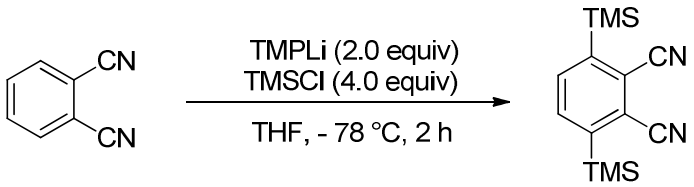
IR (Diamond-ATR, neat) ν/cm^{-1} = 2223, 1518, 1477, 1402, 1338, 1251, 1129, 1008, 808.

MS (EI, 70 eV) *m/z* (%) = 40 (17), 42 (18), 43 (35), 55 (21), 56 (11), 57 (34), 69 (25), 70 (13), 71 (24), 82 (10), 83 (19), 85 (10), 97 (16), 153 (12), 180 (42), 181 (100), 182 (12).

HRMS (EI): *m/z* (M^+) for **$C_{11}H_7N_3$** calc. 181.0640; found 181.0633.

[139] A. A. Pletnev, Q. Tian, R. C. Larock, *J. Org. Chem.* **2002**, *67*, 9276.

c. 1,4-bis-trimethylsilyl-2,3-dicyanobenzene (23c)



A solution of 1,2-dicyanobenzene (**23a**, 487 mg, 3.8 mmol, 1.0 equiv) and TMSCl (1.93 mL, 15.2 mmol, 4.0 equiv) in THF (3 mL) was added dropwise to a solution of freshly prepared TMPLi (14.1 mL, 7.6 mmol, 2.0 equiv; 0.61 M in THF) at -78 °C. The reaction mixture was stirred for 2 h at -78 °C, and then allowed to warm to room temperature overnight. The reaction mixture was quenched with sat. aq. NH_4Cl (15 mL), extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude was purified by flash chromatography (SiO_2, *i*hexane/Et_2O = 95:5) affording compound **23c** (730 mg, 2.67 mmol, 70 %) as white solid.

M.p. (°C): 123-125.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.78 (s, 2 H), 0.45 (s, 18 H).

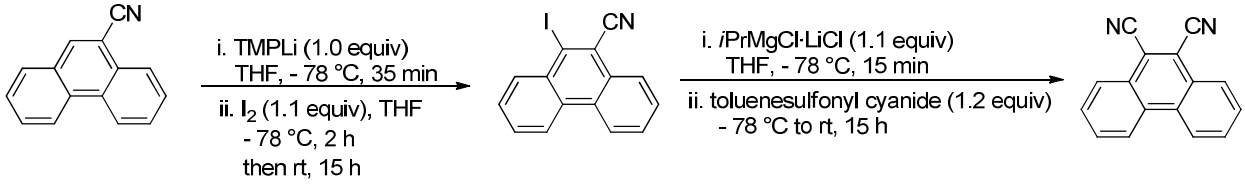
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 147.0 (2 C), 136.7 (2 C), 121.5 (2 C), 116.9 (2 C), -1.71 (6 C).

IR (Diamond-ATR, neat) ν/cm^{-1} = 2955, 2897, 2221, 1514, 1412, 1351, 1249, 1211, 1172, 837.

MS (EI, 70 eV) *m/z* (%) = 43 (15), 44 (14), 257 (100), 258 (24), 259 (10).

HRMS (EI): *m/z* (M^+) for **$C_{14}H_{20}N_2Si_2$** calc. 272.1165; found 272.1153.

d. 9,10-dicyanophenanthrene (23d)



Adapted from a literature[140] a solution of 9-cyanophenanthrene (610 mg, 3.0 mmol, 1.0 equiv) in THF (1.5 mL) was added dropwise to a solution of freshly prepared TMPLi (6.85 mL, 3.0 mmol, 1.0 equiv; 0.44 M in THF) at -78 °C. After stirring for 35 min at -78 °C, a solution of iodine (838 g, 3.3 mmol, 1.1 equiv) in THF (1.5 mL) was added dropwise (ensuring proper stirring of the resulting precipitate). The reaction mixture was stirred for 2 h at -78 °C, then overnight at room temperature. The reaction mixture was quenched with a sat. aq. solution of

[140] Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276-9287.

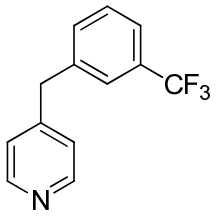
$Na_2S_2O_3$ (15 mL), then extracted with EtOAc (20 mL). The organic layer was dried (Na_2SO_4) and concentrated to give 415 mg of 10-iodophenanthrene-9-carbonitrile as white solid, which was used without further purification for the next step.

To a suspension of 10-iodophenanthrene-9-carbonitrile (415 mg, 1.26 mmol, 1.0 equiv) in THF (1 mL) at -78 °C was added *i*PrMgCl·LiCl (1.1 mL, 1.39 mmol, 1.1 equiv; 1.26 M in THF) dropwise. After 15 min of stirring at -78 °C, a solution of p-toluenesulfonyl cyanide (274 mg, 1.51 mmol, 1.2 equiv) in THF (1 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight, then quenched with sat. aq. NH_4Cl (15 mL), extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The resulting insoluble solid was further purified by hot filtration from toluene affording compound **23d** (121 mg, 0.53 mmol, 18 % yield over two steps, 95 % purity) as white solid.

The compound was previously characterized in the literature[141] and matches the reported spectral data.

2) Preparation of benzylic pyridines

a. 4-(3-(trifluoromethyl)benzyl)pyridine (19a)



According to **TP6**, isonicotinonitrile (**18a**, 52 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20a**, 0.82 mL, 0.75 mmol; 0.92 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/Et_2O/CH_2Cl_2 = 20/1/1) afforded the desired product **19a** (111 mg, 94 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.53 (d, *J* = 6.1 Hz, 2 H), 7.56-7.32 (m, 4 H), 7.12 (d, *J* = 5.5 Hz, 2 H), 4.04 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 149.8 (2 C), 149.2, 139.6, 132.4 (q, ^4J(C,F) = 1 Hz), 131.1 (q, ^2J(C,F) = 32 Hz), 129.2 (2 C), 125.7 (q, ^3J(C,F) = 4 Hz), 124.2, 124.0 (q, ^1J(C,F) = 272 Hz), 123.7 (q, ^3J(C,F) = 4 Hz), 40.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -62.7.

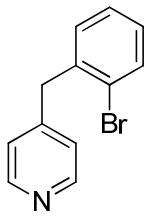
[141] M. Hanack, G. Renz, *Chem. Ber.* **1990**, *123*, 1105-1110.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3409, 3029, 2926, 1711, 1659, 1599, 1561, 1495, 1449, 1416, 1361, 1329, 1270, 1221, 1162, 1123, 1095, 1073, 1001, 994.

MS (EI, 70 eV) *m/z* (%) = 43 (22), 51 (10), 69 (15), 145 (18), 159 (23), 167 (23), 168(17), 173 (26), 236 (35), 237 (100), 238 (18).

HRMS (EI): *m/z* (M^+) for **$C_{13}H_{10}F_3N$**: calc. 237.0765; found 237.0758.

b. 4-(2-bromobenzyl)pyridine (19b)



According to **TP6**, isonicotinonitrile (**18a**, 52 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20b**, 0.63 mL, 0.75 mmol; 1.19 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/Et_2O/CH_2Cl_2 = 20/1/1) afforded the desired product **19b** (114 mg, 92 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.50 (d, *J* = 4.4, 1.7 Hz, 2 H), 7.60 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.29 (td, *J* = 7.7, 1.4 Hz, 1 H), 7.17 (td, *J* = 7.3, 1.9 Hz, 2 H), 7.11 (d, *J* = 4.4 Hz, 2 H), 4.13 (s, 2 H).

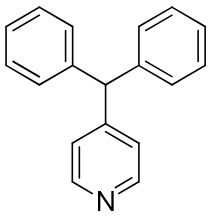
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 149.8 (2 C), 148.5, 138.2, 133.1, 131.2, 128.6, 127.7, 124.9, 124.1 (2 C), 41.1.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3068, 3027, 2923, 2359, 1934, 1656, 1598, 1559, 1495, 1469, 1438, 1414, 1344, 1288, 1219, 1116, 1069, 1045, 1024, 994.

MS (EI, 70 eV) *m/z* (%) = 115 (10), 139 (19), 167 (62), 168 (100), 169 (12), 247 (39).

HRMS (EI): *m/z* (M^+) for **$C_{12}H_{10}BrN$**: calc. 246.9997; found 246.9983.

c. 4-benzhydrylpyridine (19c)



According to **TP6**, isonicotinonitrile (**18a**, 52 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20c**, 2.50 mL, 0.75 mmol; 0.30 M in

THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 9:1) afforded the desired product **19c** (98 mg, 80 %) as a white solid.

M.p. (°C): 129-131.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.41 (d, *J* = 4.9 Hz, 2 H), 7.26-7.12 (m, 6 H), 7.00 (d, *J* = 7.6 Hz, 4 H), 6.95 (d, *J* = 4.9 Hz, 2 H), 5.41 (s, 1 H).

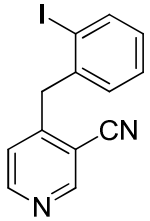
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 152.7, 149.8 (2 C), 142.0 (2 C), 129.3 (4 C), 128.6 (4 C), 126.8 (2 C), 124.6 (2 C), 56.2.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3081, 3060, 3025, 2923, 2897, 2849, 1951, 1659, 1591, 1558, 1492, 1446, 1415, 1387, 1317, 1277, 1218, 1179, 1155, 1090, 1068, 1030, 994.

MS (EI, 70 eV) *m/z* (%) = 139 (11), 152 (14), 165 (32), 166 (18), 167 (85), 168 (17), 244 (35), 245 (100), 246 (23).

HRMS (EI): *m/z* (M^+) for **$C_{18}H_{15}N$**: calc. 245.1204; found 245.1199.

d. 4-(2-iodobenzyl)nicotinonitrile (19d)



According to **TP6**, pyridine-3,4-dicarbonitrile (**18b**, 65 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20d**, 0.71 mL, 0.75 mmol; 1.05 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/ Et_2O/CH_2Cl_2 = 6/1/1) afforded the desired product **19d** (133 mg, 83 %) as a slightly yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.86 (s, 1 H), 8.62 (d, *J* = 5.3 Hz, 1 H), 7.91 (dd, *J* = 7.9, 1.0 Hz, 1 H), 7.37 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.21 (dd, *J* = 7.7, 1.7 Hz, 1 H), 7.03 (td, *J* = 7.5, 1.5 Hz, 1 H), 6.96 (dd, *J* = 5.3, 0.8 Hz, 1 H), 4.35 (s, 2 H).

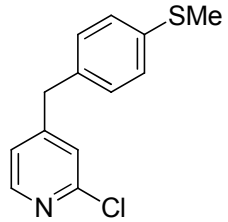
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 152.9, 152.8, 152.2, 140.1, 139.4, 130.8, 129.3, 128.9, 123.6, 115.8, 110.7, 101.0, 44.2.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3050, 3007, 2921, 2854, 2226, 1924, 1694, 1584, 1563, 1554, 1483, 1466, 1435, 1418, 1403, 1332, 1297, 1275, 1224, 1191, 1161, 1111, 1055, 1046, 1011, 947.

MS (EI, 70 eV) *m/z* (%) = 50 (16), 51 (10), 63 (17), 89 (11), 139 (18), 140 (13), 164 (22), 165 (15), 166 (32), 192 (58), 193 (100), 194 (20), 320 (14).

HRMS (EI): *m/z* (M^+) for **$C_{13}H_9IN_2$**: calc. 319.9810; found 320.9869 $[M+H]^+$.

e. 2-chloro-4-(4-(methylthio)benzyl)pyridine (19e)



According to **TP6**, 2-chloroisonicotinonitrile (**18c**, 69 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20e**, 0.83 mL, 0.75 mmol; 0.903 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/ Et_2O/CH_2Cl_2 = 8/1/1) afforded the desired product **19e** (89 mg, 71 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.26 (d, *J* = 5.3 Hz, 1 H), 7.22 (dt, *J* = 8.3, 1.9 Hz, 2 H), 7.10 (m, 3 H), 7.01 (dd, *J* = 5.0, 1.4 Hz, 1 H), 3.91 (s, 2 H), 2.47 (s, 3 H).

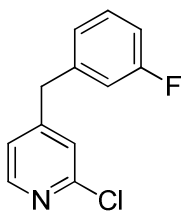
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 153.3, 151.7, 149.5, 137.1, 134.7, 129.4 (2 C), 127.0 (2 C), 124.3, 122.8, 40.3, 15.8.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3052, 3020, 2984, 2919, 2839, 1901, 1710, 1587, 1545, 1493, 1463, 1435, 1425, 1404, 1383, 1315, 1284, 1239, 1216, 1197, 1119, 1084, 1050, 1015, 989.

MS (EI, 70 eV) *m/z* (%) = 137 (30), 166 (30), 167 (18), 202 (25), 249 (100), 250 (13), 251 (33).

HRMS (EI): *m/z* (M^+) for **$C_{13}H_{12}ClNS$**: calc. 249.0379; found 249.0375.

f. 2-chloro-4-(3-fluorobenzyl)pyridine (19f)



According to **TP6**, 2-chloroisonicotinonitrile (**18c**, 69 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20f**, 0.86 mL, 0.75 mmol;

0.87 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/ Et_2O/CH_2Cl_2 = 12/1/1) afforded the desired product **19f** (74 mg, 67 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.29 (d, *J* = 5.0 Hz, 1 H), 7.30 (td, *J* = 8.0, 6.1 Hz, 1 H), 7.13 (s, 1 H), 7.05 – 6.91 (m, 3 H), 6.86 (dt, *J* = 9.7, 2.1 Hz, 1 H), 3.95 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 163.0 (d, ^1J(C-F) = 247 Hz), 152.5, 151.8, 149.7, 140.3 (d, ^3J(C-F) = 8 Hz), 130.3 (d, ^3J(C-F) = 8 Hz), 124.6 (d, ^4J(C-F) = 3 Hz), 124.4, 122.8, 115.9 (d, ^2J(C-F) = 22 Hz),113.9 (d, ^2J(C-F) = 21 Hz), 40.5 (d, ^4J(C-F) = 2 Hz).

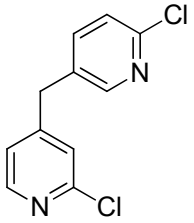
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -112.5.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3057, 2925, 2849, 1936, 1712, 1616, 1586, 1547, 1487, 1465, 1448, 1383, 1318, 1251, 1217, 1137, 1120, 1085, 1004, 990.

MS (EI, 70 eV) *m/z* (%) = 83 (14), 109 (30), 133 (16), 157 (19), 158 (17), 159 (15), 184 (23), 185 (59), 186 (80), 187 (15), 220 (21), 221 (100), 222 (18).

HRMS (EI): *m/z* (M^+) for **$C_{12}H_9ClFN$** calc. 221.0408; found 221.0414.

g. 2-chloro-4-((6-chloropyridin-3-yl)methyl)pyridine (19g)



According to **TP6**, 2-chloroisonicotinonitrile (**18c**, 69 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20g**, 1.90 mL, 0.75 mmol; 0.40 M in THF) were used. The reaction mixture was stirred for 1 h at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/ Et_2O/CH_2Cl_2 = 2/1/1) afforded the desired product **19g** (93 mg, 78 %) as a white solid.

M.p. (°C): 56-59.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.32 (d, *J* = 5.0 Hz, 1 H), 8.28 (dd, *J* = 2.5, 0.6 Hz, 1 H), 7.43 (dd, *J* = 8.2, 2.6 Hz, 1 H), 7.33 - 7.28 (m, 1 H), 7.13 (dd, *J* = 1.5, 0.7 Hz, 1 H), 7.03 – 6.99 (m, 1 H), 3.95 (s, 2 H).

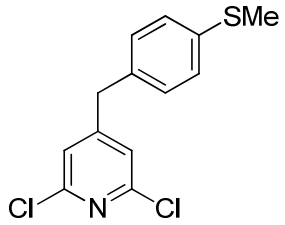
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 152.2, 151.3, 150.4, 150.0, 149.8, 139.2, 132.5, 124.5, 124.3, 122.6, 37.2.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3051, 2922, 1669, 1590, 1565, 1546, 1457, 1378, 1314, 1286, 1252, 1205, 1137, 1120, 1104, 1085, 1023, 990.

MS (EI, 70 eV) *m/z* (%) = 63 (15), 126 (25), 140 (20), 167 (24), 168 (24), 202 (14), 203 (60), 204 (12), 205 (19), 238 (100), 239 (25), 240 (65).

HRMS (EI): *m/z* (M^+) for **$C_{11}H_8Cl_2N_2$** calc. 238.0065; found 238.0052.

h. 2,6-dichloro-4-(4-(methylthio)benzyl)pyridine (19h)



According to **TP6**, 2,6-dichloroisonicotinonitrile (**18d**, 86 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20e**, 0.83 mL, 0.75 mmol; 0.90 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/Et_2O/CH_2Cl_2 = 16/1/1) afforded the desired product **19h** (85 mg, 60 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.26-7.22 (dt, *J* = 8.6, 2.2 Hz, 2 H), 7.11–7.07 (m, 2 H), 7.06 (t, *J* = 0.7 Hz, 2 H), 3.90 (s, 2 H), 2.49 (s, 3 H).

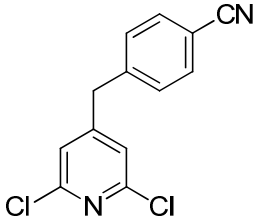
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 155.9, 150.6 (2 C), 137.6, 133.8, 129.5 (2 C), 127.1 (2 C), 123.0 (2 C), 40.1, 15.8.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3071, 3019, 2983, 2919, 2844, 1901, 1578, 1538, 1493, 1435, 1405, 1374, 1311, 1241, 1224, 1204, 1164, 1102, 1091, 1016, 986.

MS (EI, 70 eV) *m/z* (%) = 121 (18), 122 (26), 137 (100), 138 (12), 139 (12), 164 (17), 165 (13), 166 (26), 200 (94), 201 (57), 202 (35), 203 (19), 284 (40), 286 (27).

HRMS (EI): *m/z* (M^+) for **$C_{13}H_{11}Cl_2NS$** calc. 282.9989; found 284.0058 $[M + H]^+$.

i. 4-((2,6-dichloropyridin-4-yl)methyl)benzonitrile (19i)



According to **TP6**, 2,6-dichloroisonicotinonitrile (**18d**, 86 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20h**, 0.66 mL, 0.75

mmol; 1.13 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/Et_2O/CH_2Cl_2 = 8/1/1) afforded the desired product **19i** (108 mg, 82 %) as a white solid.

M.p. (°C): 177-179.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.65 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.05 (s, 2 H), 4.01 (s, 2 H).

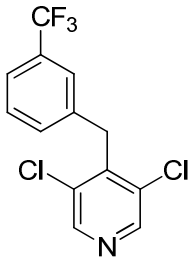
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 154.0, 150.9 (2 C), 142.5, 132.8 (2 C), 129.8 (2 C), 123.1 (2 C), 118.4, 111.4, 40.5.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3118, 3080, 2923, 2860, 2231, 1924, 1789, 1681, 1607, 1574, 1543,1511, 1502, 1448, 1414, 1378, 1284, 1236, 1221, 1195, 1166, 1104, 1020, 987.

MS (EI, 70 eV) *m/z* (%) = 73 (40), 89 (14), 116 (31), 135 (19), 139 (18), 164 (43), 191 (66), 192 (48), 207 (39), 208 (12), 226 (12), 227 (62), 228 (12), 229 (28), 231 (26), 262 (100), 263 (18).

HRMS (EI): *m/z* (M^+) for **$C_{13}H_8Cl_2N_2$** calc. 262.0065; found 262.0074.

j. 3,5-dichloro-4-(3-(trifluoromethyl)benzyl)pyridine (19j)



According to **TP6**, 3,5-dichloroisonicotinonitrile (**18e**, 86 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20a**, 0.64 mL, 0.75 mmol; 1.17 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/Et_2O/CH_2Cl_2 = 50/1/1) afforded the desired product **19j** (95 mg, 62 %) as a white solid.

M.p. (°C): 47-50.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.53 (s, 2 H), 7.54 - 7.47 (m, 2 H), 7.45 - 7.34 (m, 2 H), 4.37 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 147.9 (2 C), 144.2, 137.1, 133.1, 131.7 (q, ^4J(C-F) = 1 Hz), 131.0 (d, ^2J(C-F) = 32 Hz), 129.1 (2 C), 125.3 (d, ^3J(C-F) = 4 Hz), 123.9 (d, ^1J(C-F) = 272 Hz), 123.8 (d, ^3J(C-F) = 4 Hz), 35.8.

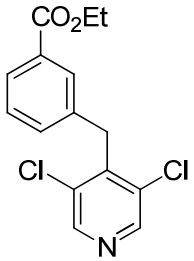
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -62.7.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3049, 2925, 2855, 1969, 1828, 1723, 1613, 1597, 1563, 1526, 1491, 1447, 1392, 1330, 1256, 1212, 1190, 1147, 1121, 1090, 1074, 1002, 934.

MS (EI, 70 eV) *m/z* (%) =.63 (13), 109 (11), 159 (19), 166 (13), 173 (10), 200 (29), 201 (31), 202 (10), 203 (10), 206 (14), 207 (17), 234 (55), 235 (17), 236 (16), 250 (10), 269 (22), 270 (100), 271 (20), 272 (30), 305 (81).

HRMS (EI): *m/z* (M^+) for **$C_{13}H_8Cl_2F_3N$** calc. 304.9986; found 304.9985.

k. ethyl 3-((3,5-dichloropyridin-4-yl)methyl)benzoate (19k)



According to **TP6**, 3,5-dichloroisonicotinonitrile (**18e**, 86 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20i**, 1.09 mL, 0.75 mmol; 0.69 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc: 97:3) afforded the desired product **19k** (122 mg, 79 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.51 (s, 2 H), 7.96-7.87 (m, 2 H), 7.35 (d, *J* = 4.7 Hz, 2 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 4.36 (s, 2 H), 1.39 (t, *J* = 7.1 Hz, 3 H).

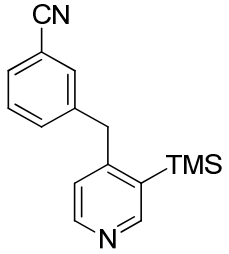
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 166.3, 147.8 (2 C), 144.5, 136.5, 133.2, 132.6 (2 C), 130.9, 129.7, 128.6, 128.0, 61.0, 35.8, 14.2.

IR (Diamond-ATR, neat) ν/cm^{-1} = 2980, 2939, 1715, 1606, 1587, 1560, 1528, 1443, 1391, 1366, 1272, 1212, 1184, 1105, 1088, 1021, 944.

MS (EI, 70 eV) *m/z* (%) = 139 (11), 166 (31), 200 (17), 201 (32), 202 (21), 203 (11), 264 (100), 265 (17), 266 (64), 268 (11), 281 (41), 309 (31), 311 (21).

HRMS (EI): *m/z* (M^+) for **$C_{15}H_{13}Cl_2NO_2$** calc. 309.0323; found 309.0314.

l. 3-((3-(trimethylsilyl)pyridin-4-yl)methyl)benzonitrile (19l)



According to **TP6**, 3-(trimethylsilyl)isonicotinonitrile (**18f**, 44 mg, 0.25 mmol), THF (0.5 mL), DMPU (1 mL) and a freshly titrated solution of benzylic zinc chloride (**20j**, 0.56 mL, 0.38mmol; 0.67 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 9:1) afforded the desired product **19l** (64 mg, 96 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.74 (br. s., 1 H), 8.54 (br. s., 1 H), 7.59-7.49 (m, 1 H), 7.43 (t, *J* = 8.0 Hz, 1 H), 7.39-7.35 (m, 1 H), 7.35-7.29 (m, 1 H), 6.85 (br. s., 1 H), 4.13 (s, 2 H), 0.35 (s, 9 H).

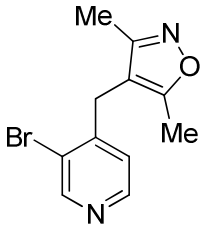
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 154.9, 153.3, 150.6, 140.8, 133.9, 133.5, 132.5, 130.4, 129.4, 124.7, 118.6, 112.8, 40.6, -0.03 (3 C).

IR (Diamond-ATR, neat) ν/cm^{-1} = 2956, 2891, 2230, 1576, 1542, 1482, 1433, 1396, 1299, 1252, 1219, 1143, 1115, 1094, 1042, 908.

MS (EI, 70 eV) *m/z* (%) = 235 (21), 251 (100), 252 (21).

HRMS (EI): *m/z* (M^+) for **$C_{16}H_{18}N_2Si$** calc. 266.1239; found 265.1153 $[M-H]^+$.

m. 4-((3-bromopyridin-4-yl)methyl)-3,5-dimethylisoxazole (19m)



According to **TP6**, 3-bromoisonicotinonitrile (**18g**, 92 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20k**, 0.95 mL, 0.75 mmol; 0.67 M in THF) were used. The reaction mixture was stirred for 14 h at 40 °C under microwave irradiations. Purification by flash chromatography (SiO_2, loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc: 4:1) afforded the desired product **19m** (92 mg, 69 %) as a white solid.

M.p. (°C): 90-92.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.71 (s, 1 H), 8.40 (d, *J* = 5.0 Hz, 1 H), 6.85 (d, *J* = 5.0 Hz, 1 H), 3.74 (s, 2 H), 2.29 (s, 3 H), 2.09 (s, 3 H).

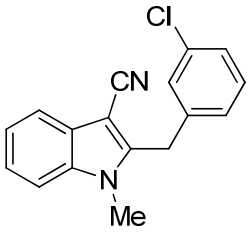
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 166.5, 159.7, 151.9, 148.5, 146.8, 124.0, 122.9, 109.3, 28.0, 11.1, 10.2.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3044, 2949, 2923, 2849, 1949, 1645, 1580, 1470, 1452, 1416, 1396, 1374, 1277, 1259, 1220, 1196, 1160, 1085, 1034, 1016, 900.

MS (EI, 70 eV) *m/z* (%) = 41 (15), 43 (100), 44 (98), 50 (12), 55 (11), 57 (14), 58 (19), 68 (12), 69 (14), 71 (13), 75 (10), 110 (12), 117 (11), 145 (36), 146 (15), 182 (10), 187 (77), 225 (10), 266 (47), 268 (59).

HRMS (EI): *m/z* (M^+) for **$C_{11}H_{11}BrN_2O$** calc. 266.0055; found 266.0047.

n. Preparation of 2-(3-chlorobenzyl)-1-methyl-1H-indole-3-carbonitrile (22)



A dry and argon-flushed microwave reaction vial, equipped with a magnetic stirring bar and a rubber septum, was charged with functionalized indole (**21**, 91 mg, 0.50 mmol), followed by dry THF (1 mL) and DMPU (2 mL). A freshly titrated solution of benzyl zinc chloride (**20l**; 0.51 mL, 0.75 mmol, 1.48 M in THF) was added at 25 °C and the microwave reaction vial was closed with an adapted microwave cap septum. The microwave vial was heated at 40 °C for 2 h under microwave irradiation (Biotage© microwave, max.: 15 Watt). The reaction mixture was evaporated and the crude directly purified by flash column chromatography (SiO_2; *i*hexane/EtOAc = 9:1), affording indole **22** (101 mg, 72 %) as an off-white solid.

M.p. (°C): 108-110.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.71-7.65 (m, 1 H), 7.30-7.15 (m, 5 H), 7.11 (s, 1 H), 7.04-6.98 (m, 1 H), 4.25 (s, 2 H), 3.52 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 146.0, 138.0, 136.6, 134.8, 130.2, 128.2, 127.4, 126.8, 126.4, 123.6, 122.2, 119.4, 116.2, 110.0, 86.3, 31.8, 30.6.

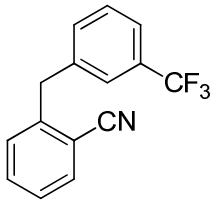
IR (Diamond-ATR, neat) ν/cm^{-1} = 3044, 2923, 2849, 2210, 1588, 1530, 1476, 1425, 1364, 1253, 1190, 1187, 1087, 1074, 1012, 882.

MS (EI, 70 eV) *m/z* (%) = 169 (90), 170 (11), 229 (11), 279 (17), 280 (100), 281 (26), 282 (37).

HRMS (EI): *m/z* (M^+) for **$C_{17}H_{13}ClN_2$** calc. 280.0767; found 280.0761.

3) Preparation of cyano-substituted aromatics

a. 2-(3-(trifluoromethyl)benzyl)benzonitrile (24a)



According to **TP7**, phthalonitrile (**23a**, 64 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20a**, 0.54 mL, 0.75 mmol; 1.38 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/Et_2O = 9:1) afforded the desired product **24a** (127 mg, 97 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.68 (d, *J* = 8.3 Hz, 1 H), 7.58-7.47 (m, 3 H), 7.45 (d, *J* = 5.0 Hz, 2 H), 7.39-7.28 (m, 2 H), 4.28 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 143.7, 139.6, 133.1 (2 C), 132.3 (q, ^4J(C-F) = 1 Hz, 1 C), 131.1 (q, ^2J(C-F) = 32 Hz, 1 C), 130.0, 129.2, 127.2, 124.0 (q, ^1J(C-F) = 272, 1 C), 125.6 (q, ^3J(C-F) = 4 Hz, 1 C), 123.7 (q, ^3J(C-F) = 4 Hz), 117.9, 112.7, 39.9.

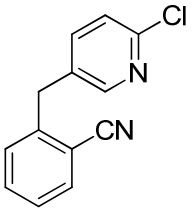
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -62.7.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3076, 2927, 2860, 2225, 1713, 1598, 1487, 1448, 1328, 1221, 1161, 1116, 1072, 1002, 957.

MS (EI, 70 eV) *m/z* (%) = 165 (14), 190 (25), 191 (11), 221 (44), 222 (15), 240 (23), 241 (91), 242 (24), 261 (100), 262 (16).

HRMS (EI): *m/z* (M^+) for **$C_{15}H_{10}F_3N$** calc. 261.0765; found 261.1690.

b. 2-((6-chloropyridin-3-yl)methyl)benzonitrile (24b)



According to **TP7**, phthalonitrile (**23a**, 64 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20h**, 1.90 mL, 0.75 mmol; 0.39 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent:

pentane/Et_2O/CH_2Cl_2 = 6:1:1) afforded the desired product **24b** (104 mg, 91 %) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.30 (s, 1 H), 7.67 (d, *J* = 7.7 Hz, 1 H), 7.60-7.48 (m, 2 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.32-7.23 (m, 2 H), 4.19 (s, 2 H).

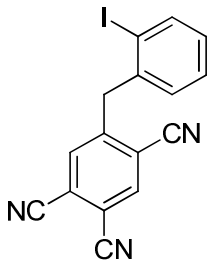
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 150.2, 150.1, 149.8, 143.0, 139.2, 133.3, 133.2, 129.9, 127.5, 124.3, 117.8, 112.7, 36.6.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3092, 3060, 2949, 2931, 2854, 2223, 1595, 1584, 1565, 1483, 1464, 1443, 1383, 1297, 1204, 1154, 1135, 1103, 1087, 1024, 959.

MS (EI, 70 eV) *m/z* (%) = 164 (15), 165 (15), 166 (23), 191 (14), 192 (18), 193 (25), 207 (14), 227 (37), 228 (100), 229 (32), 230 (35).

HRMS (EI): *m/z* (M^+) for **$C_{13}H_9ClN_2$** calc. 228.0454; found 228.0430.

c. 5-(2-iodobenzyl)benzene-1,2,4-tricarbonitrile (24c)



According to **TP7**, benzene-1,2,4,5-tetracarbonitrile (**23b**, 90 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20c**, 0.49 mL, 0.50 mmol; 1.03 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/Et_2O = 7:3) afforded the desired product **24c** (157 mg, 91 %) as a white solid.

M.p. (°C): 185-186.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.10 (s, 1 H), 7.95 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.44 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.38 (s, 1 H), 7.25 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.11 (td, *J* = 7.7, 1.5 Hz, 1 H), 4.45 (s, 2 H).

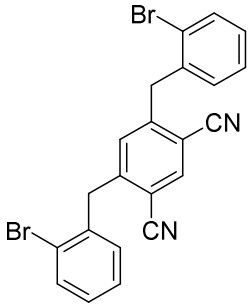
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 149.7, 140.5, 138.3, 136.9, 134.1, 131.1, 130.1, 129.3, 119.4, 118.2, 114.7, 114.5, 114.1, 113.6, 100.9, 44.8.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3041, 2925, 2238, 1631, 1602, 1523, 1488, 1464, 1429, 1383, 1317, 1272, 1249, 1046, 1011, 929.

MS (EI, 70 eV) *m/z* (%) = 188 (11), 213 (15), 214 (19), 215 (57), 216 (14), 240 (25), 241 (21), 242 (100), 243 (20), 370 (1).

HRMS (EI): *m/z* (M^+) for $\mathbf{C_{16}H_8IN_3}$ calc. 368.9763; found 370.9915.

d. 4,6-bis(2-bromobenzyl)isophthalonitrile (24d)



According to **TP7**, benzene-1,2,4,5-tetracarbonitrile (**23b**, 90 mg, 0.5 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20b**, 1.56 mL, 1.50 mmol; 0.96 M in THF) were used. The reaction mixture was stirred for 1.5 h at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/Et_2O = 8:2) afforded the desired product **24d** (136 mg, 58 %) as a white solid.

M.p. (°C): 141-143.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.94 (s, 1 H), 7.52 (dd, *J* = 7.9, 1.2 Hz, 2 H), 7.28-7.20 (m, 2 H), 7.17-7.07 (m, 4 H), 6.81 (s, 1 H), 4.28 (s, 4 H).

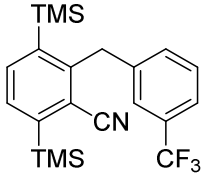
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 148.1 (2 C), 136.6, 136.4 (2 C), 133.2 (2 C), 131.3 (2 C), 131.1, 129.0 (2 C), 127.8 (2 C), 124.8 (2 C), 115.9 (2 C), 111.9 (2 C), 40.2 (2 C).

IR (Diamond-ATR, neat) ν/cm^{-1} = 3061, 2908, 2854, 2226, 1957, 1929, 1728, 1694, 1606, 1568, 1489, 1470, 1440, 1419, 1388, 1274, 1181, 1154, 1116, 1045, 1023, 949.

MS (EI, 70 eV) *m/z* (%) = 89 (14), 125 (12), 126 (15), 138 (20), 139 (22), 140 (12), 152 (10), 153 (25), 169 (73), 202 (11), 215 (16), 216 (13), 228 (15), 229 (34), 277 (22), 278 (16), 303 (15), 305 (24), 306 (24), 385 (81), 386 (26), 387 (85), 388 (25), 464 (51), 465 (13), 466 (100), 467 (25), 468 (56), 469 (12).

HRMS (EI): *m/z* (M^+) for $\mathbf{C_{22}H_{14}Br_2N_2}$ calc. 463.9524; found 463.9513.

e. 2-(3-(trifluoromethyl)benzyl)-3,6-bis(trimethylsilyl)benzonitrile (24e)



According to **TP7**, 3,6-bis(trimethylsilyl)phthalonitrile (**23c**, 272 mg, 1.0 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20a**, 1.27 mL,

1.5 mmol; 1.185 M in THF) were used. The reaction mixture was stirred for 45 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2; eluent: *i*hexane/Et_2O = 97:3) afforded the desired product **24e** (341 mg, 84 %) as a white solid.

M.p. (°C): 90-92.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.76 (d, *J* = 7.6 Hz, 1 H), 7.55 (d, *J* = 7.6 Hz, 1 H), 7.50-7.43 (m, 1 H), 7.38 (t, *J* = 7.7 Hz, 1 H), 7.17 (s, 1 H), 7.13 (d, *J* = 7.8 Hz, 1 H), 4.49 (s, 2 H), 0.41 (s, 9 H), 0.24 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 147.7, 146.8, 142.1, 140.4, 137.8, 132.2, 131.6, 130.6 (q, ^2J(C-F) = 32 Hz), 128.8, 124.9 (q, ^3J(C-F) = 4 Hz), 124.1 (q, ^1J(C-F) = 272 Hz), 123.2 (q, ^3J(C-F) = 4 Hz), 119.0, 118.8, 39.9, 0.2 (3 C), -1.5 (s, 3 C).

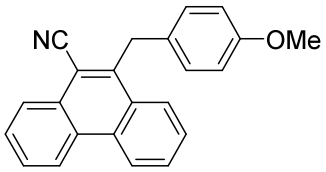
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -62.7.

IR (Diamond-ATR, neat) ν/cm^{-1} = 2960, 2221, 1443, 1331, 1317, 1250, 1159, 1115, 1069, 831.

MS (EI, 70 eV) *m/z* (%) = 43 (17), 44 (22), 73 (57), 77 (20), 202 (42), 298 (67), 299 (17), 390 (100), 391 (33), 392 (11).

HRMS (EI): *m/z* (M^+) for **$C_{21}H_{26}F_3NSi_2$** calc. 405.1556; found 404.1478 $[M-H]^+$.

f. 10-(4-Methoxybenzyl)phenanthrene-9-carbonitrile (24f)



According to **TP7**, 9,10-phenanthrene (**23d**, 57 mg, 0.25 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20n**, 0.36 mL, 0.75 mmol; 1.05 M in THF) were used. The reaction mixture was stirred for 1 h at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2; eluent: *i*hexane/Et_2O = 9:1) afforded the desired product **24f** (60 mg, 74 %) as a white solid.

M.p. (°C): 167-169.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.75-8.69 (m, 2 H), 8.41-8.36 (m, 1 H), 8.16 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.79-7.72 (m, 3 H), 7.61 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.18-7.14 (m, 2 H), 6.83-6.77 (m, 2 H), 4.80 (s, 2 H), 3.75 (s, 3 H).

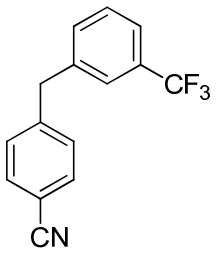
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 158.2, 144.4, 132.0, 130.6, 129.5, 129.3 (2 C), 129.1 (2 C), 129.0, 128.2, 127.8, 127.6, 126.8, 126.3, 123.3, 122.8, 117.6, 114.1 (2 C), 110.5, 55.2, 37.5.

IR (Diamond-ATR, neat) ν/cm^{-1} = 2927, 2828, 2218, 1610, 1579, 1510, 1493, 1438, 1372, 1325, 1299, 1277, 1251, 1171, 1156, 1109, 1033, 954.

MS (EI, 70 eV) *m/z* (%) = 121 (13), 278 (10), 280 (21), 290 (11), 308 (35), 322 (20), 323 (100), 324 (26).

HRMS (EI): *m/z* (M^+) for **$C_{23}H_{17}NO$** calc. 323.1310; found 323.1308.

g. 4-(3-(Trifluoromethyl)benzyl)benzonitrile (26a)



According to **TP7**, terephthalonitrile (**25**, 64 mg, 0.50 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20a**, 0.54 mL, 0.75 mmol; 1.38 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/Et_2O = 9:1) afforded the desired product **26a** (93 mg, 71 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.63-7.59 (m, 2 H), 7.54-7.50 (m, 1 H), 7.47-7.42 (m, 2 H), 7.34 (d, *J* = 7.6 Hz, 1 H), 7.29 (d, *J* = 8.6 Hz, 2 H), 4.10 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 145.5, 140.2, 132.5 (2 C), 132.3 (q, ^4J(C-F) = 2 Hz), 131.1 (q, ^2J(C-F) = 32 Hz), 129.6 (2 C), 129.2, 125.6 (q, ^3J(C-F) = 4 Hz), 124.0 (q, ^1J(C-F) = 272 Hz), 123.7 (q, ^3J(C-F) = 4 Hz), 118.8, 110.6, 41.7.

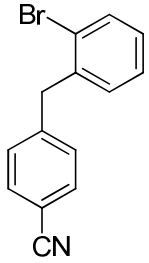
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -62.7.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3097, 3053, 2925, 2229, 1607, 1504, 1448, 1414, 1327, 1276, 1161, 1119, 1093, 1073, 1021, 1002, 919.

MS (EI, 70 eV) *m/z* (%) = 57 (16), 71 (10), 128 (11), 165 (20), 190 (30), 191 (17), 192 (75), 193 (12), 221 (13), 240 (14), 241 (41), 242 (15), 260 (10), 261 (100), 262 (18).

HRMS (EI): *m/z* (M^+) for **$C_{15}H_{10}F_3N$** calc. 261.0765; found 261.0760.

h. 4-(2-Bromobenzyl)benzonitrile (26b)



According to **TP7**, terephthalonitrile (**25**, 128 mg, 1.0 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20b**, 1.20 mL, 1.5 mmol; 1.25 M in THF) were used. The reaction mixture was stirred for 30 min at 40 °C under microwave irradiation. Purification by flash chromatography (SiO_2; eluent: pentane/Et_2O = 95:5) afforded the desired product **26b** (244 mg, 90 %) as an off-white solid.

M.p. (°C): 68-70.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.62-7.55 (m, 3 H), 7.32-7.25 (m, 3 H), 7.19-7.11 (m, 2 H), 4.19 (s, 2 H).

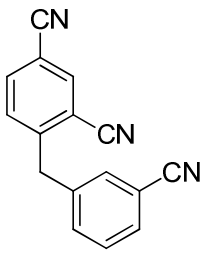
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 145.1, 138.6, 133.1, 132.2 (2 C), 131.1, 129.5 (2 C), 128.5, 127.7, 124.8, 118.9, 110.1, 41.8.

IR (Diamond-ATR, neat) ν/cm^{-1} = 2921, 2849, 2226, 1736, 1604, 1464, 1435, 1169, 1021, 913.

MS (EI, 70 eV) *m/z* (%) = 41 (32), 42 (13), 43 (62), 44 (83), 55 (38), 56 (18), 57 (92), 67 (11), 69 (33), 70 (19), 71 (80), 81 (12), 82 (11), 83 (31), 84 (13), 85 (53), 89 (14), 95 (15), 96 (10), 97 (27), 99 (23), 111 (18), 113 (20), 127 (15), 141 (12), 163 (14), 164 (15), 165 (61), 169 (10), 190 (100), 191 (48), 271 (58), 273 (52).

HRMS (EI): *m/z* (M^+) for **$C_{14}H_{10}BrN$** calc. 270.9997; found 270.9976.

i. 4-(3-Cyanobenzyl)isophthalonitrile (28a)



According to **TP8**, 1,3-dicyanobenzene (**27**, 64 mg, 0.5 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20j**, 1.12 mL, 0.75 mmol; 0.65 M in THF) were used. The reaction mixture was stirred for 1 h at 40 °C under microwave irradiation. Chloranil (246 mg, 1.0 mmol) was added and the reaction was stirred for 12 h at

25 °C. Purification by flash chromatography (SiO_2, loaded with pentane containing 2 % NEt_3; eluent: pentane/Et_2O/CH_2Cl_2 = 2:1:1) afforded the desired product **28a** (91 mg, 75 %) as a white solid.

M.p. (°C): 151-153.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.98 (d, *J* = 1.7 Hz, 1 H), 7.84 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.62-7.56 (m, 1 H), 7.52-7.39 (m, 4 H), 4.31 (s, 2 H).

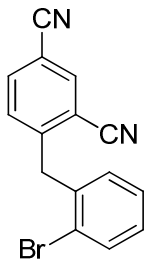
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 148.1, 138.5, 136.4, 136.2, 133.4, 132.3, 131.2, 131.1, 129.9, 118.2, 116.4, 115.7, 114.4, 113.3, 112.4, 39.8.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3078, 3044, 2934, 2227, 1599, 1582, 1484, 1452, 1433, 1401, 1261, 1232, 1090, 1027, 920.

MS (EI, 70 eV) *m/z* (%) = 215 (24), 242 (10), 243 (100), 244 (17).

HRMS (EI): *m/z* (M^+) for **$C_{16}H_9N_3$** calc. 243.0796; found 243.0795.

j. 4-(2-Bromobenzyl)isophthalonitrile (28b)



According to **TP8**, 1,3-dicyanobenzene (**27**, 64 mg, 0.5 mmol), THF (1 mL), DMPU (2 mL) and a freshly titrated solution of benzylic zinc chloride (**20b**, 0.60 mL, 0.75 mmol; 1.25 M in THF) were used. The reaction mixture was stirred for 1 h at 40 °C under microwave irradiation. Chloranil (246 mg, 1.0 mmol) was added and the reaction was stirred for 12 h at 25 °C. Purification by flash chromatography (SiO_2; eluent: *i*hexane/Et_2O = 9:1) afforded the desired product **28b** (119 mg, 80 %) as an off-white solid.

M.p. (°C): 109-110.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.97 (d, *J* = 1.6 Hz, 1 H), 7.73 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.63 (d, *J* = 8.2 Hz, 1 H), 7.37-7.30 (m, 1 H), 7.25-7.18 (m, 3 H), 4.42 (s, 2 H).

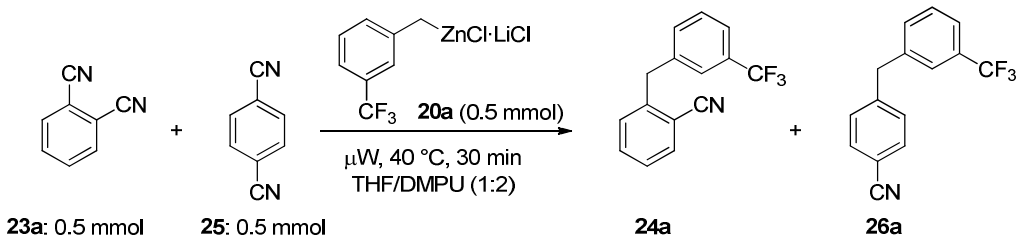
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 148.5, 136.5, 136.0, 135.8, 133.4, 131.5, 130.5, 129.3, 128.0, 124.9, 116.7, 115.8, 114.4, 111.7, 40.4.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3069, 2234, 1687, 1606, 1568, 1490, 1471, 1439, 1401, 1278, 1157, 1111, 1046, 1025, 910.

MS (EI, 70 eV) *m/z* (%) = 108 (10), 188 (12), 189 (13), 190 (45), 215 (39), 216 (21), 217 (100), 218 (19), 296 (53).

HRMS (EI): *m/z* (M^+) for $\mathbf{C_{15}H_9BrN_2}$ calc. 295.9949; found 295.9939.

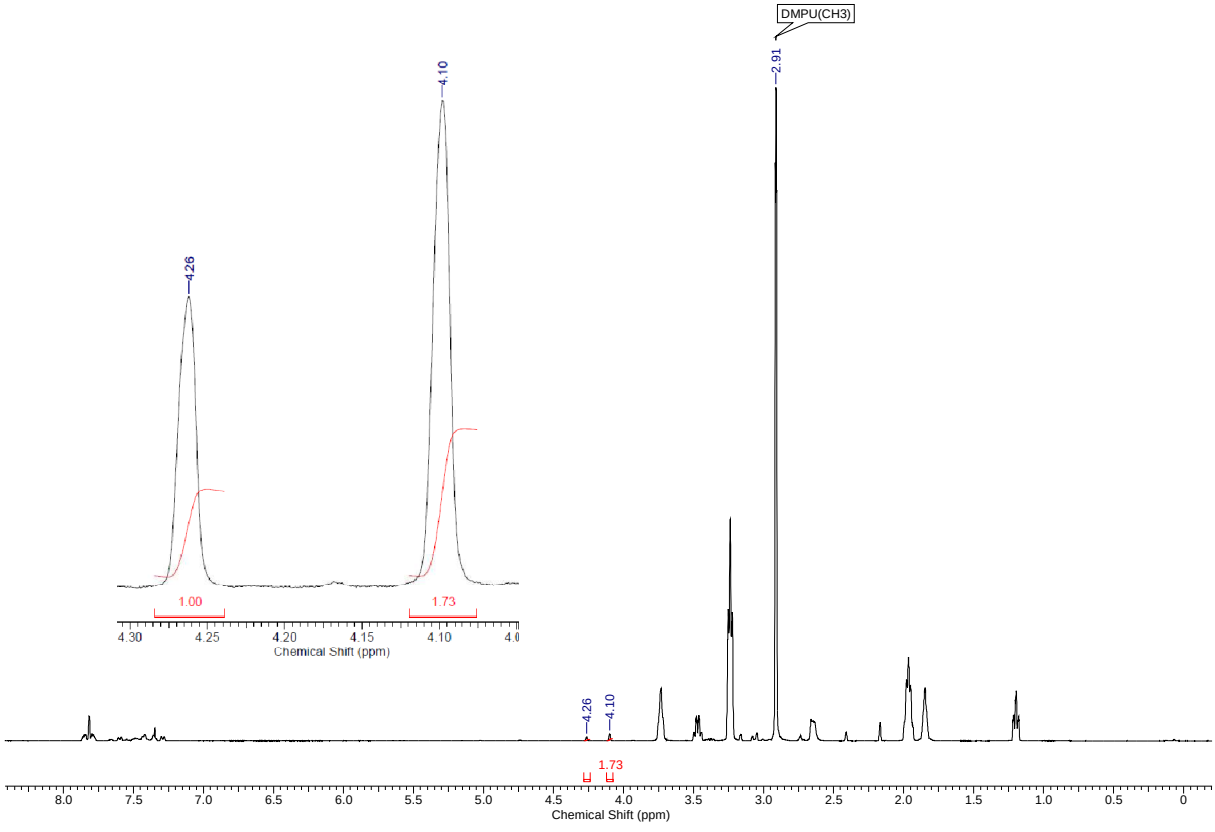
4) <u>Competition reaction of 1,2-dicyanobenzene (**23a**) and 1,4-dicyanobenzene (**25**) with benzylic zinc reagent (**20a**)</u>



23a: 0.5 mmol **25**: 0.5 mmol **24a** **26a**

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm (CH_2) =	4.26		4.10
ratio (%) =	37	:	63

^{1}H NMR (400 MHz, $CDCl_3$)



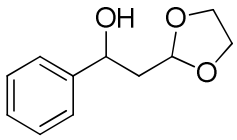
An intermolecular competition reaction shows that 1,4-dicyanobenzene (**25**) reacts preferentially to 1,2-dicyanobenzene (**23a**) with benzylic zinc chloride **20a**.

VI. $Sc(OTf)_3$-Catalyzed Addition of Bromomagnesium 2-Vinyloxy Ethoxide to Various Aldehydes leading to Protected Aldol Products

Some compounds of this chapter were prepared by Jakob Gaar in the frame of his F-Praktikum, Laura Kohout in the frame of her Master thesis and Dr. Daniela Sustac Roman.

1) Preparation of the protected aldol products

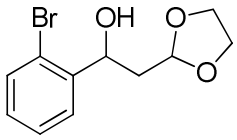
a. 2-(1,3-Dioxolan-2-yl)-1-phenylethanol (32a)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and benzaldehyde (**31a**, 106 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 4 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 6:4) afforded the desired product **32a** (177 mg, 91 %) as a colorless oil.

The compound was previously characterized in the literature[142] and matches the reported analytical data.

b. 1-(2-Bromophenyl)-2-(1,3-dioxolan-2-yl)ethanol (32b)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and 2-bromobenzaldehyde (**31b**, 155 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 3 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 6:4) afforded the desired product **32b** (235 mg, 86 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.65 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.51 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.34 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.12 (td, *J* = 7.6, 1.8 Hz, 1 H), 5.33 (dt, *J* = 9.5, 2.1

[142] C. N. Eid Jr., J. P. Konopelski, *Tetrahedron* **1991**, *47*, 975-992.

Hz, 1 H), 5.12 (dd, *J* = 5.2, 3.8 Hz, 1 H), 4.14-4.01 (m, 2 H), 3.98-3.87 (m, 2 H), 3.59 (d, *J* = 2.2 Hz, 1 H), 2.25 (ddd, *J* = 14.6, 3.8, 2.2 Hz, 1 H), 1.95 (ddd, *J* = 14.6, 9.5, 5.2 Hz, 1 H).

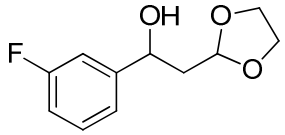
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 142.6, 132.6, 128.7, 127.6, 127.4, 121.4, 103.3, 69.3, 65.0, 64.8, 40.5.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3457, 3060, 2957, 2884, 1736, 1590, 1567, 1466, 1438, 1409, 1360, 1308, 1270, 1192, 1119, 1076, 1019.

MS (EI, 70 eV) *m/z* (%) = 44 (22), 73 (100), 77 (22), 87 (16), 116 (20), 181 (11), 183 (14), 184 (19), 186 (11), 274 (1).

HRMS (EI): *m/z* (M^+) for **$C_{11}H_{13}BrO_3$** calc. 274.0048; found: 274.0027.

c. 2-(1,3-Dioxolan-2-yl)-1-(3-fluorophenyl)ethanol (32c)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and 3-fluorobenzaldehyde (**31c**, 124 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 3 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 7:3) afforded the desired product **32c** (190 mg, 90 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.33-7.26 (m, 1 H), 7.16-7.10 (m, 2 H), 6.95 (dd, *J* = 8.2, 1.0 Hz, 1 H), 5.09 - 4.97 (m, 2 H), 4.12 - 4.02 (m, 2 H), 3.96 - 3.86 (m, 2 H), 3.42 (d, *J* = 2.4 Hz, 1 H), 2.10 (ddd, *J* = 5.5, 4.3, 1.6 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 163.0 (d, ^{1}J(C,F) = 246 Hz), 146.6 (d, ^{3}J(C,F) = 7 Hz), 129.9 (d, ^{3}J(C,F) = 8 Hz), 121.2 (d, ^{4}J(C,F) = 3 Hz), 114.2 (d, ^{2}J(C,F) = 21 Hz), 112.7 (d, ^{2}J(C,F) = 22 Hz), 103.1, 69.7 (d, ^{4}J(C,F) = 2 Hz), 65.0, 64.9, 42.3.

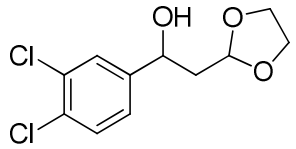
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -113.1.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3451, 2959, 2888, 1615, 1590, 1484, 1449, 1411, 1362, 1244, 1091, 1060, 1024.

MS (EI, 70 eV) *m/z* (%) = 43 (20), 44 (18), 45 (50), 73 (100), 87 (26), 95 (12), 97 (21), 194 (1).

HRMS (EI): *m/z* (M^+) for **$C_{11}H_{13}FO_3$** calc. 212.0849; found 194.0768 ([M-H_2O]$^+$).

d. 1-(3,4-Dichlorophenyl)-2-(1,3-dioxolan-2-yl)ethanol (32d)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and 3,4-dichlorobenzaldehyde (**31d**, 175 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 3 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 6:4) afforded the desired product **32d** (221 mg, 84 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.51 (d, *J* = 1.9 Hz, 1 H), 7.40 (d, *J* = 8.3 Hz, 1 H), 7.20 (dd, *J* = 8.3, 1.9 Hz, 1 H), 5.04 (t, *J* = 4.2 Hz, 1 H), 4.99 (t, *J* = 5.9 Hz, 1 H), 4.12-4.01 (m, 2 H), 3.98-3.85 (m, 2 H), 3.55 (d, *J* = 2.2 Hz, 1 H), 2.06 (dd, *J* = 5.9, 4.2 Hz, 2 H).

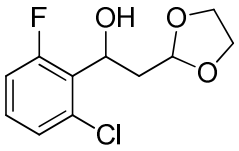
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 144.1, 132.5, 131.1, 130.3, 127.8, 125.0, 102.9, 69.0, 65.1, 64.9, 42.1.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3447, 2957, 2887, 1591, 1564, 1467, 1388, 1361, 1300, 1195, 1127, 1076, 1053.

MS (EI, 70 eV) *m/z* (%) = 43 (12), 45 (24), 73 (100), 87 (24), 111 (29), 147 (12), 172 (11), 173 (23), 174 (9), 174 (22), 176 (7), 177 (15), 200 (13), 202 (13), 262 (1).

HRMS (EI): *m/z* (M^+) for **$C_{11}H_{12}Cl_2O_3$** calc. 262.0163; found 262.0179.

e. 1-(2-Chloro-6-fluorophenyl)-2-(1,3-dioxolan-2-yl)ethanol (32e)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and 2-chloro-6-fluorobenzaldehyde (**31e**, 158 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 2 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 1:4) afforded the desired product **32e** (215 mg, 87 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.23-7.13 (m, 2 H), 6.99 (ddd, *J* = 10.9, 7.1, 2.3 Hz, 1 H), 5.54 (ddd, *J* = 9.7, 6.0, 3.6 Hz, 1 H), 5.10 (t, *J* = 4.5 Hz, 1 H), 4.09-3.99 (m, 2 H), 3.96-

3.84 (m, 2 H), 3.09 (dd, *J* = 6.1, 2.4 Hz, 1 H), 2.53 (dddd, *J* = 14.4, 9.7, 4.7, 1.7 Hz, 1 H), 2.12 (dt, *J* = 14.5, 4.0 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -113.1.

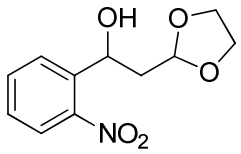
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 161.9 (d, ^{1}J(C,F) = 240 Hz), 133.6 (d, ^{3}J(C,F) = 7 Hz), 129.3 (d, ^{3}J(C,F) = 11 Hz), 128.4 (d, ^{2}J(C,F) = 13 Hz), 125. 8, 115.1 (d, ^{2}J(C,F)= 15 Hz), 102.9, 66.1 (d, ^{3}J(C,F) = 1 Hz), 65.0, 64.8, 39.3 (d, ^{4}J(C,F) = 3 Hz).

IR (Diamond-ATR, neat) ν/cm^{-1} = 3452, 3083, 2963, 2886, 1604, 1575, 1454, 1411, 1360, 1317, 1239, 1189, 1174, 1132, 1067, 1024.

MS (EI, 70 eV) *m/z* (%) = 45 (17), 73 (100), 159 (14), 228 (4).

HRMS (EI): *m/z* (M^+) for **$C_{11}H_{12}ClFO_3$** calc. 246.0459; found 228.0349 $[M-H_2O]^+$.

f. 2-(1,3-Dioxolan-2-yl)-1-(2-nitrophenyl)ethanol (32f)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and 2-nitrobenzaldehyde (**31f**, 151 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 3 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 6:4) afforded the desired product **32f** (216 mg, 90 %) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.94 (dd, *J* = 3.2, 1.2 Hz, 1 H), 7.91 (dd, *J* = 3.0, 1.4 Hz, 1 H), 7.69-7.61 (m, 1 H), 7.48-7.38 (m, 1 H), 5.55 (ddd, *J* = 9.3, 1.9, 1.8 Hz, 1 H), 5.16 (dd, *J* = 5.5, 3.6 Hz, 1 H), 4.13-4.00 (m, 2 H), 4.00-3.86 (m, 2 H), 3.77 (d, *J* = 2.2 Hz, 1 H), 2.34 (ddd, *J* = 14.4, 3.5, 2.1 Hz, 1 H), 2.02 (ddd, *J* = 14.5, 9.3, 5.5 Hz, 1 H).

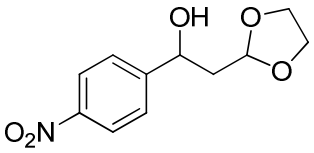
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 147.4, 139.3, 133.5, 128.2, 128.1, 124.3, 103.3, 66.0, 65.1, 64.8, 41.5.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3426, 2961, 2886, 1719, 1609, 1577, 1480, 1475, 1444, 1409, 1344, 1301, 1187, 1130, 1091, 1062, 1014.

MS (EI, 70 eV) *m/z* (%) = 45 (17), 73 (100), 77 (13), 104 (11), 238 (1).

HRMS (EI): *m/z* (M^+) for **$C_{11}H_{13}NO_5$** calc. 239.0794; found 238.0728 $[M-H]^+$.

g. 2-(1,3-Dioxolan-2-yl)-1-(4-nitrophenyl)ethanol (32g)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and 4-nitrobenzaldehyde (**31g**, 151 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 2 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 1:1) afforded the desired product **32g** (145 mg, 61 %) as yellow crystals.

M.p. (°C): 96-98.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.21 (d, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 9.0 Hz, 2 H), 5.18-5.11 (m, 1 H), 5.07 (t, *J* = 4.0 Hz, 1 H), 4.13-4.03 (m, 2 H), 3.99-3.88 (m, 2 H), 3.69 (d, *J* = 2.2 Hz, 1 H), 2.13-2.07 (m, 2 H).

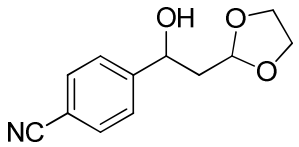
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 151.2, 147.2, 126.5 (2 C), 123.7 (2 C), 102.9, 69.4, 65.1, 65.0, 42.1.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3434, 3108, 3082, 2958, 2900, 2879, 1607, 1598, 1501, 1483, 1470, 1424, 1393, 1351, 1317, 1294, 1254, 1229, 1195, 1140, 1120, 1104, 1081, 1060, 1013.

MS (EI, 70 eV) *m/z* (%) = 45 (12), 73 (100), 77 (10), 238 (1).

HRMS (EI): *m/z* (M^+) for **$C_{11}H_{13}NO_5$** calc. 239.0794; found 238.0703 $[M-H]^+$.

h. 4-(2-(1,3-Dioxolan-2-yl)-1-hydroxyethyl)benzonitrile (32h)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and 4-cyanobenzaldehyde (**31h**, 131 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 4 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 6:4) afforded the desired product **32h** (177 mg, 81 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.64 (d, *J* = 8.3 Hz, 2 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 5.12-5.01 (m, 2 H), 4.12-4.01 (m, 2 H), 3.99-3.85 (m, 2 H), 3.62 (d, *J* = 2.2 Hz, 1 H), 2.11-2.05 (m, 2 H).

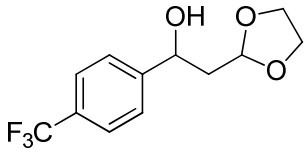
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 149.2, 132.2 (2 C), 126.4 (2 C), 118.8, 111.1, 102.9, 69.5, 65.1, 64.9, 42.1.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3463, 2958, 2887, 2226, 1608, 1503, 1474, 1406, 1361, 1303, 1197, 1173, 1131, 1075, 1030.

MS (EI, 70 eV) *m/z* (%) = 43 (16), 44 (17), 45 (47), 73 (100), 77 (11), 104 (10), 220 (1).

HRMS (EI): *m/z* (M^+) for **$C_{12}H_{13}NO_3$** calc. 219.0895; found 220.1013 $[M+H]^+$.

i. 2-(1,3-Dioxolan-2-yl)-1-(4-(trifluoromethyl)phenyl)ethanol (32i)



The reaction was performed like usual on a 1 mmol scale but also on a 10 mmol scale.

According to **TP9**, *i*PrMgBr (17.8 mL, 15.5 mmol, 1.55 equiv; 0.87 M in THF) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (15 mL). Then, $Sc(OTf)_3$ (492 mg, 1.00 mmol, 0.10 equiv) and 4-(trifluoromethyl)benzaldehyde (**31i**, 1.37 mL, 10.0 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 3 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 8:2) afforded the desired product **32i** (1.89 g, 72 %; 165 mg, 63% on 1 mmol scale) as a white solid.

M.p. (°C): 60-61.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.61 (d, *J* = 8.3 Hz, 2 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 5.13-5.02 (m, 2 H), 4.12-4.01 (m, 2 H), 3.97-3.85 (m, 2 H), 3.55 (d, *J* = 2.2 Hz, 1 H), 2.14-2.07 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 147.8, 129.6 (q, ^2J(C-F) = 32 Hz), 126.7 (q, ^1J(C-F) = 272 Hz), 126.0 (2 C), 125.3 (q, ^3J(C-F) = 4 Hz, 2 C), 103.0, 69.6, 65.1, 64.9, 42.2.

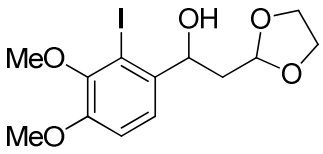
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -62.5.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3395, 2899, 1618, 1477, 1418, 1328, 1199, 1162, 1078, 1068, 1032, 1016.

MS (EI, 70 eV) *m/z* (%) = 45 (14), 73 (100), 87 (12), 127 (54), 145 (21), 172 (16), 173 (30), 175 (25), 200 (25), 262 (1).

HRMS (EI): *m/z* (M^+) for $\mathbf{C_{12}H_{13}F_3O_3}$ calc. 262.0817; found 262.0798.

j. 2-(1,3-Dioxolan-2-yl)-1-(2-iodo-3,4-dimethoxyphenyl)ethanol (32j)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and 2-iodo-3,4-dimethoxybenzaldehyde (**31j**, 292 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 12 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 7:3) afforded the desired product **32j** (332 mg, 87 %) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.31 (dd, *J* = 8.6, 0.6 Hz, 1 H), 6.92 (d, *J* = 8.6 Hz, 1 H), 5.18 (dt, *J* = 9.7, 1.9 Hz, 1 H), 5.12 (dd, *J* = 5.1, 3.7 Hz, 1 H), 4.14-4.00 (m, 2 H), 3.99-3.88 (m, 2 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.56 (d, *J* = 2.2 Hz, 1 H), 2.21 (ddd, *J* = 14.5, 3.7, 2.2 Hz, 1 H), 1.87 (ddd, *J* = 14.7, 9.6, 5.3 Hz, 1 H).

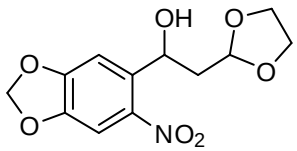
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 151.7, 148.1, 138.3, 122.5, 112.5, 103.3, 96.2, 73.5, 65.0, 64.7, 60.2, 56.0, 40.9.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3470, 2958, 2934 2886, 2836, 1734, 1587, 1478, 1445, 1432, 1392, 1288, 1269, 1253, 1203, 1166, 1133, 1090, 1060.

MS (EI, 70 eV) *m/z* (%) = 45 (25), 73 (86), 87 (51), 138 (25), 139 (21), 151 (30), 165 (22), 166 (49), 208 (54), 289 (31), 290 (39), 291 (100), 292 (97), 293 (92), 380 (39).

HRMS (EI): *m/z* (M^+) for $\mathbf{C_{13}H_{17}IO_5}$ calc. 380.0121; found 380.0108.

k. 2-(1,3-Dioxolan-2-yl)-1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethanol (32k)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and 6-nitropiperional (**31k**, 195 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 6 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 6:4) afforded the desired product **32k** (226 mg, 80 %) as yellow crytals.

M.p. (°C): 122-123.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.49 (s, 1 H), 7.36 (s, 1 H), 6.11 (s, 2 H) 5.57 (dt, *J* = 9.3, 1.6 Hz, 1 H), 5.16 (dd, *J* = 5.8, 3.3 Hz, 1 H), 4.14-4.01 (m, 2 H), 4.00-3.86 (m, 2 H), 3.82 (d, *J* = 1.9 Hz, 1 H), 2.32 (ddd, *J* = 14.3, 3.5, 1.8 Hz, 1 H), 1.92 (ddd, *J* = 14.4, 9.1, 5.8 Hz, 1 H).

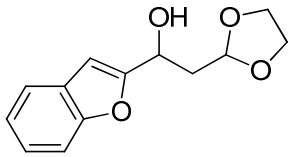
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 152.4 (2 C), 146.9, 137.4, 107.0, 105.1, 103.3, 102.9, 66.2, 65.1, 64.7, 41.6.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3065, 2888, 2166, 2024, 1726, 1618, 1513, 1503, 1489, 1418, 1392, 1369, 1323, 1267, 1199, 1139, 1074, 1012.

MS (EI, 70 eV) *m/z* (%) = 44 (27), 73 (100), 87 (24), 120 (17), 121 (11), 135 (18,) 148 (31), 149 (17), 151 (15), 165 (16), 179 (19), 194 (11), 195 (11), 282 (1).

HRMS (EI): *m/z* (M^+) for **$C_{12}H_{13}NO_7$** calc. 283.0692; found 282.0655 $[M-H]^+$.

l. 1-(Benzofuran-2-yl)-2-(1,3-dioxolan-2-yl)ethanol (32l)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and 2-benzofurancarboxaldehyde (**31l**, 146 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 12 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 6:4) afforded the desired product **32l** (219 mg, 93 %) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.54 (d, *J* = 7.8 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.28-7. 18 (m, 2 H), 6.66 (s, 1 H), 5.17 (dt, *J* = 7.8, 4.0 Hz, 1 H), 5.11 (t, *J* = 4.4 Hz, 1 H), 4.12-4.00 (m, 2 H), 3.97-3.85 (m, 2 H), 3.42 (d, *J* = 3.9 Hz, 1 H), 2.43-2.25 (m, 2 H).

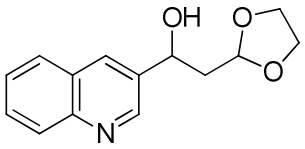
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 158.6, 154.8, 128.1, 124.0, 122.7, 121.0, 111.2, 102.8, 102.5, 65.0, 64.9, 64.8, 38.7.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3428, 3062, 2962, 2886, 2249, 1782, 1600, 1585, 1473, 1453, 1413, 1360, 1300, 1279, 1253, 1170, 1130, 1105, 1066, 1022.

MS (EI, 70 eV) *m/z* (%) = 43 (28), 44 (14), 45 (52), 63 (14), 65 (12), 73 (100), 87 (30), 89 (24), 91 (48), 115 (37), 116 (26), 118 (17), 131 (10), 144 (17), 145 (40), 146 (18), 147 (50), 234 (15).

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

m. 2-(1,3-Dioxolan-2-yl)-1-(quinolin-3-yl)ethanol (32m)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and quinoline-3-carboxaldehyde (**31m**, 157 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 12 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 2:8) afforded the desired product **32m** (185 mg, 75 %) as a yellow solid.

M.p. (°C): 122 – 123.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.90 (d, *J* = 2.2 Hz, 1 H), 8.19 (s, 1 H), 8.09 (d, *J* = 8.6 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.73-7.65 (m, 1 H), 7.58-7.50 (m, 1 H), 5.34-5.20 (m, 1 H), 5.11 (t, *J* = 4.2 Hz, 1 H), 4.16-4.03 (m, 2 H), 4.00-3.87 (m, 2 H), 3.86 (s, 1 H), 2.30-2.16 (m, 2 H).

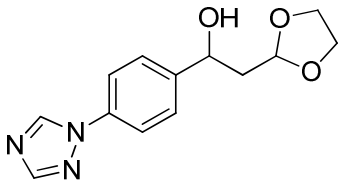
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 149.3, 147.6, 136.4, 132.4, 129.2, 129.1, 127.8 (2 C), 126.7, 103.0, 68.3, 65.1, 64.9, 42.1.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3172, 2959, 288 , 1622, 1578, 1500, 1478, 1425, 1403, 1371, 1361, 1318, 1264, 1209, 1168, 1130, 1084, 1070, 1034.

MS (EI, 70 eV) *m/z* (%) = 43 (23), 44 (24), 45 (67), 73 (100), 77 (24), 87 (40), 103 (17), 116 (18), 128 (32), 130 (64), 156 (34), 158 (44), 182 (30), 245 (1).

HRMS (EI): *m/z* (M^+) for **$C_{14}H_{15}NO_3$** calc. 245.1052; found: 245.1055.

n. 1-(4-(1*H*-1,2,4-Triazol-1-yl)phenyl)-2-(1,3-dioxolan-2-yl)ethanol (32n)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and 4-(1*H*-1,2,4-triazol-1-yl)benzaldehyde (**31n**, 173 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 20 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: EtOAc) afforded the desired product **32n** (246 mg, 94 %) as yellow crystals.

M.p. (°C): 115-117.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.53 (s, 1 H), 8.09 (s, 1 H), 7.65 (dd, *J* = 8.6, 2.0 Hz, 2 H), 7.54 (dd, *J* = 8.8, 2.2 Hz, 2 H), 5.13-5.03 (m, 2 H), 4.13-4.02 (m, 2 H), 3.97-3.86 (m, 2 H), 3.58 (d, *J* = 2.2 Hz, 1 H), 2.12 (ddd, *J* = 4.5, 3.5, 3.1 Hz, 2 H).

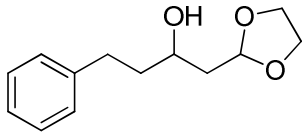
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 152.5, 144.2, 140.8, 136.1, 127.1 (2 C), 120.1 (2 C), 103.03, 69.6, 65.1, 64.9, 42.3.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3228, 3109, 2865, 1608, 1521, 1409, 1360, 1319, 1283, 1245, 1226, 1196, 1147, 1128, 1067, 1050, 1035.

MS (EI, 70 eV) *m/z* (%) = 45 (23), 65 (14), 73 (100), 77 (10), 87 (16), 90 (11), 91 (17), 92 (11), 116 (29), 117 (14), 119 (20), 120 (12), 146 (32), 171 (15), 172 (63), 173 (20), 174 (75), 175 (12), 199 (47), 200 (13), 128 (13), 231 (10), 261 (7).

HRMS (EI): *m/z* (M^+) for **$C_{13}H_{15}N_3O_3$** calc. 261.1113; found 261.1100.

o. 1-(1,3-Dioxolan-2-yl)-4-phenylbutan-2-ol (32o)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$ (49.2 mg, 0.10 mmol, 0.10 equiv) and 3-phenylpropionaldehyde (**31o**, 134 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 22 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 6:4) afforded the desired product **32o** (101 mg, 45 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.33-7.14 (m, 5 H), 5.04 (dd, *J* = 5.3, 3.9 Hz, 1 H), 4.01-3.81 (m, 4 H), 3.03 (s, 1 H), 2.89-2.60 (m, 3 H), 1.93-1.72 (m, 4 H).

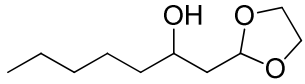
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 142.1, 128.4 (2 C), 128.3 (2 C), 125.7, 103.5, 67.2, 64.9, 64.7, 40.1, 39.0, 31.8.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3447, 3023, 2885, 1602, 1495, 1453, 1411, 1095, 1029.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 91 (43), 92 (19), 99 (14), 105 (10), 117 (16), 221 (1).

HRMS (EI): *m/z* (M^+) for **$C_{13}H_{18}O_3$** calc. 222.1256; found 221.1167 $(M-H)^+$.

p. 1-(1,3-Dioxolan-2-yl)heptan-2-ol (32p)



According to **TP9**, *i*PrMgBr (1.91 mL, 1.55 mmol, 1.55 equiv) was added to a solution of 2-(vinyloxy)ethanol (**29**, 132 mg, 1.50 mmol, 1.50 equiv) in Et_2O (1.5 mL). Then, $Sc(OTf)_3$

(49.2 mg, 0.10 mmol, 0.10 equiv) and hexanal (**31p**, 100 mg, 1.00 mmol, 1.00 equiv) were added. The reaction mixture was stirred for 2 h at 40 °C. Purification by flash column chromatography (SiO_2 loaded with *i*hexane containing 2 % NEt_3; eluent: *i*hexane/EtOAc = 6:4) afforded the desired product **32p** (82 mg, 44 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 5.03 (dd, *J* = 5.1, 3.8 Hz, 1 H), 4.06-3.94 (m, 2 H), 3.93-3.81 (m, 3 H), 2.90 (s, 1 H), 1.94-1.84 (m, 1 H), 1.82-1.70 (m, 1 H), 1.54-1.20 (m, 8 H), 0.95-0.82 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 103.7, 67.8, 64.9, 64.7, 40.1, 37.3, 31.8, 25.1, 22.6, 14.0.

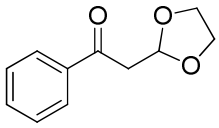
IR (Diamond-ATR, neat) ν/cm^{-1} = 3430, 2952, 2925, 2871, 2859, 1729, 1643, 1467, 1414, 1379, 1311, 1209, 1093.

MS (EI, 70 eV) *m/z* (%) = 73 (100), 187 (1).

HRMS (EI): *m/z* (M^+) for **$C_{10}H_{20}O_3$** calc. 188.1412; found 187.1323 $[M-H]^+$.

2) Preparation of the ketones

a. 2-(1,3-Dioxolan-2-yl)-1-phenylethanone (33a)



A dry and argon-flushed *Schlenk* flask, equipped with a stirring bar and a septum, was charged with DMSO (0.33 mL, 4.6 mmol, 2.3 equiv) and DCM (2 mL). Then, oxalyl chloride (0.19 mL, 2.2 mmol, 1.1 equiv) was added dropwise at -78 °C. After complete addition, a solution of alcohol **32a** (389 mg, 2.0 mmol, 1.0 equiv) in DCM (2 mL) was added over 20 min. After stirring for 15 min at -78 °C, NEt_3 (1.37 mL, 9.8 mmol, 4.9 equiv) was added and the reaction was placed at 25 °C for 8 min. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. Purification by flash column chromatography (SiO_2, eluent: *i*hexane/EtOAc = 8:2) afforded the desired product **33a** yield (317 mg, 83%) as a white solid.

M.p. (°C): 63-64.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.01-7.93 (m, 2 H), 7.62-7.42 (m, 3 H), 5.45 (t, *J* = 5.0 Hz, 1 H), 4.05-3.87 (m, 4 H), 3.35 (d, *J* = 4.9 Hz, 2 H).

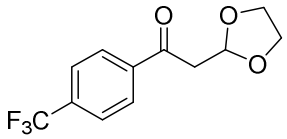
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 196.5, 136.9, 133.3, 128.6 (2 C), 128.3 (2 C), 101.4, 65.0 (2 C), 43.4.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3056, 2880, 1685, 1595, 1578, 1451, 1419, 1389, 1361, 1333, 1304, 1239, 1210, 1165, 1140, 1050, 1009.

MS (EI, 70 eV) *m/z* (%) = 45 (24), 73 (65), 77 (42), 105 (100), 120 (12), 192 (1).

HRMS (EI): *m/z* (M^+) for **$C_{11}H_{12}O_3$** calc. 192.0786; found 192.0788.

b. 2-(1,3-Dioxolan-2-yl)-1-(4-(trifluoromethyl)phenyl)ethanone (33i)



A dry and argon-flushed *Schlenk* flask, equipped with a stirring bar and a septum, was charged with DMSO (0.66 mL, 9.30 mmol, 2.3 equiv) and DCM (4 mL). Then, oxalyl chloride (0.39 mL, 4.55 mmol, 1.1 equiv) was added dropwise at -78 °C. After complete addition, a solution of alcohol **32i** (1.09 g, 4.14 mmol, 1.0 equiv) in DCM (4 mL) was added over 20 min. After stirring for 15 min at -78 °C, NEt_3 (2.90 mL, 20.1 mmol, 4.9 equiv) was added and the reaction was placed at 25 °C for 8 min. Then, the reaction mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated in *vacuo*. Purification by flash column chromatography (SiO_2, eluent: *i*hexane/EtOAc = 8:2) afforded the desired product **33i** (840 g, 78 %) as an off-white solid.

M.p. (°C): 76-80.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.07 (d, *J* = 8.1 Hz, 2 H), 7.74 (d, *J* = 8.2 Hz, 2 H), 5.43 (t, *J* = 4.9 Hz, 1 H), 4.05-3.88 (m, 4 H), 3.36 (d, *J* = 4.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 195.8, 139.7, 134.7 (q, ^2J(C-F) = 32 Hz), 128.9 (2 C), 125.8 (q, ^3J(C-F) = 3 Hz, 2 C), 123.7 (q, ^1J(C-F) = 272 Hz), 101.3, 65.2 (2 C), 43.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -63.2.

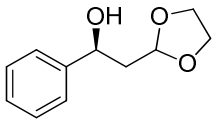
IR (Diamond-ATR, neat) ν/cm^{-1} = 2895, 1687, 1580, 1511, 1478, 1422, 1408, 1387, 1366, 1322, 1216, 1153, 1109, 1063.

MS (EI, 70 eV) *m/z* (%) = 45 (30), 73 (100), 260 (1).

HRMS (EI): *m/z* (M^+) for **$C_{12}H_{11}F_3O_3$** calc. 260.2122; found 260.0651.

3) Preparation of chiral protected aldol products

a. (*S*)-2-(1,3-dioxolan-2-yl)-1-phenylethanol (36a)



To a solution of (*R*)-2-methyl-CBS-oxazaborolidine (7.0 mg, 0.025 mmol) in THF (0.75 mL) was added dropwise *N*,*N*-diethylaniline borane (0.18 mL, 1.0 mmol) at 25 °C. Then, a solution of ketone **33a** (96 mg, 0.5 mmol) in THF (0.75 mL) was added *via* a syringe pump over 1 h. The reaction was further stirred for 1.5 h at 25 °C, and then slowly quenched with MeOH (0.5 mL). Water (5 mL) and Et_2O (10 mL) were added and the reaction was transferred to a 50 mL separation funnel. The layers were separated, and the aq. layer was further extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, *i*hexane/EtOAc = 8:2, 1 % NEt_3, visualized with $KMnO_4$ stain) afforded the desired product **36a** (73 mg, 75 % yield; 94 % ee) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.44-7.22 (m, 5 H), 5.11-4.97 (m, 2 H), 4.13-3.84 (m, 4 H), 3.29 (br. s., 1 H), 2.22-2.04 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 143.8, 128.4 (2 C), 127.4, 125.7 (2 C), 103.2, 70.3, 65.0, 64.8, 42.4.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3444, 3030, 2958, 2886, 1603, 1494, 1453, 1411, 1360, 1307, 1195, 1131, 1090, 1063, 1022.

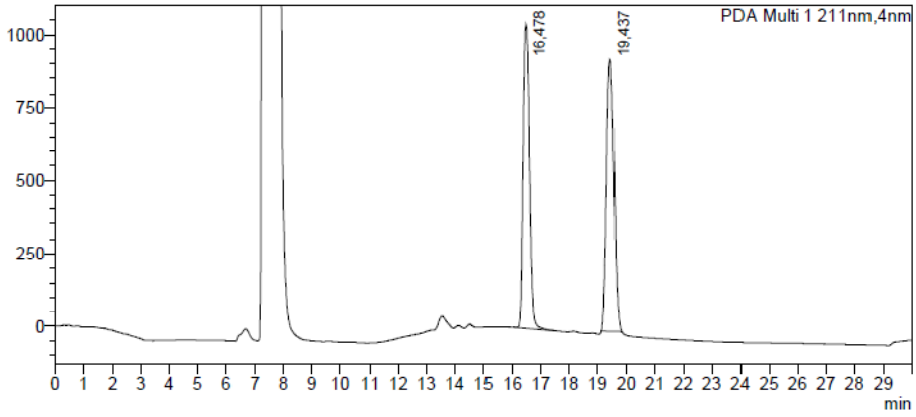
MS (EI, 70 eV) *m/z* (%) = 43 (11), 44 (14), 45 (40), 51 (10), 73 (100), 77 (34), 79 (30), 87 (25), 104 (14), 105 (16), 107 (19), 132 (13), 194 (1).

HRMS (EI): *m/z* (M^+) for **$C_{11}H_{14}O_3$** calc. 194.0643; found 194.0935.

$[\alpha]_D^{23}$ = -6.7 (*c* 1.0, MeOH).

HPLC: (Chiralpak OD-H, heptane / *i*propanol = 90:10 to 20:80, 0.1 mL/min; t_R (min) = 16.4 (minor), 19.2 (major).

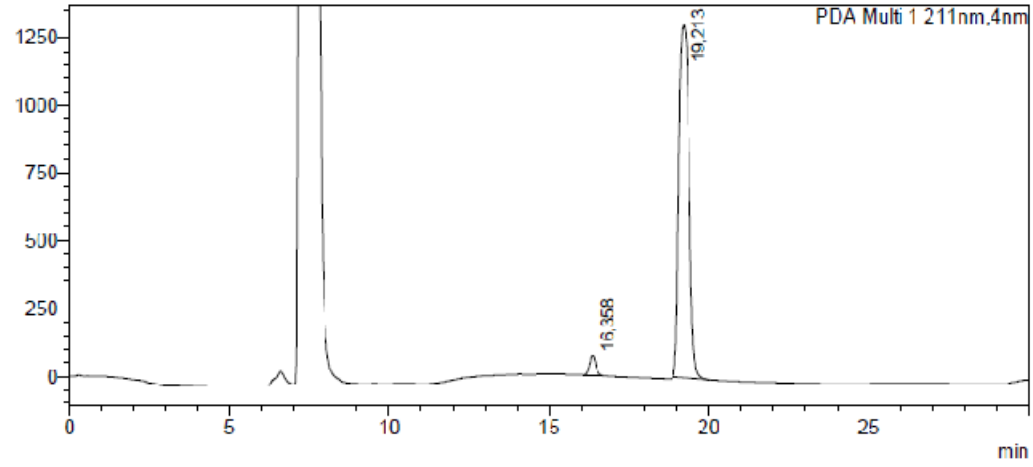
Racemic:



PDA Ch1 211nm

Peak#	Ret. Time	Area	Height	Conc.
1	16,478	16285546	1044518	49,489
2	19,437	16621725	933292	50,511
Total		32907272	1977810	

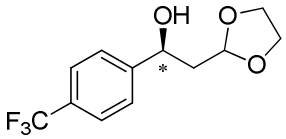
Chiral:



PDA Ch1 211nm

Peak#	Ret. Time	Area	Height	Conc.
1	16,358	895805	69698	3,064
2	19,213	28343935	1298531	96,936
Total		29239739	1368229	

b. (*S*)-2-(1,3-Dioxolan-2-yl)-1-(4-(trifluoromethyl)phenyl)ethanol (36i)



A dry and argon-flushed *Schlenk* flask, equipped with a magnetic stirring bar and a septum, was charged with (*R*)-diphenylprolinol (25 mg, 0.10 mmol), THF (1.9 mL) and $B(OMe)_3$ (11 µL, 0.1 mmol). The reaction mixture was stirred for 1 h at 25 °C, followed by the slow addition of *N*,*N*-diethylaniline borane (0.36 mL, 2.0 mmol). To the reaction mixture was then

added a solution of ketone **33i** (520 mg, 2.0 mmol) in THF (1.9 mL) over 20 min. The reaction mixture was stirred at 25 °C for 2 h at 25 °C and then carefully quenched with MeOH (0.9 mL). The solvents were removed under reduced pressure and the remainder was partitioned between Et_2O (5 mL) and H_2O (10 mL). The organic phase was separated and the aq. layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, *i*hexane/EtOAc = 8:2) afforded the desired product **36i** (425 mg, 81 %; 94 % ee) as a colorless solid.

M.p. (°C): 64-67.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.60 (d, J = 8.1 Hz, 2 H), 7.51 (d, J = 8.1 Hz, 2 H), 5.16–4.96 (m, 2 H), 4.17–4.01 (m, 2 H), 4.01–3.80 (m, 2 H), 3.55 (d, J = 4.0 Hz, 1 H), 2.20–2.01 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 148.0, 129.7 (q, ^2J(C-F) = 32 Hz), 126.1 (2 C), 125.5 (q, ^3J(C-F) = 3 Hz, 2 C), 124.3 (q, ^1J(C-F) = 272 Hz), 103.2, 69.8, 65.2, 65.1, 42.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -62.4.

IR (Diamond-ATR, neat) ν/cm^{-1} = 3383, 2956, 2895, 1617, 1598, 1506, 1415, 1328, 1222, 1087, 1109, 1066, 1048, 1036, 1016.

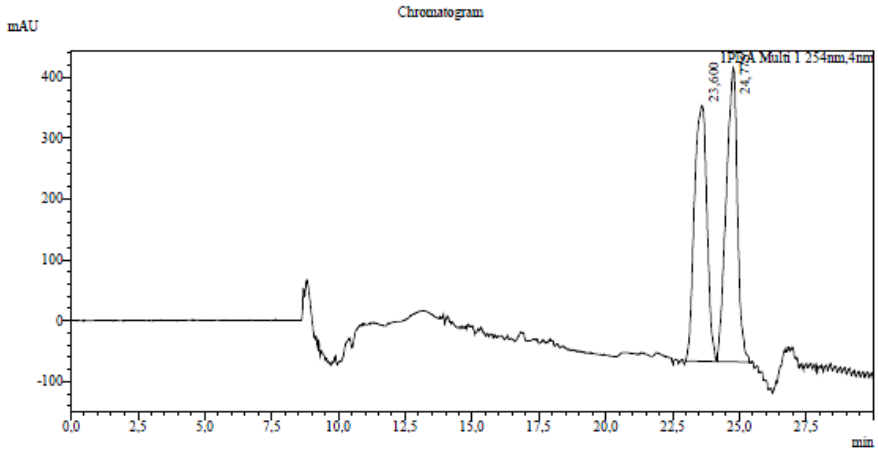
MS (EI, 70 eV) *m/z* (%) = 45 (26), 73 (100), 127 (20), 262 (1).

HRMS (EI): *m/z* (M^+) for $\mathbf{C_{12}H_{13}F_3O_3}$ calc. 262.2282; found: 262.1843.

$[\alpha]_D^{23}$ = -9.6 (*c* 0.55, MeOH).

HPLC: (Chiralpak AD-H, heptane/*i*propanol = 90:10 to 20:80, 0.1 mL/min; t_R (min) = 23.61 (major), 24.69 (minor).

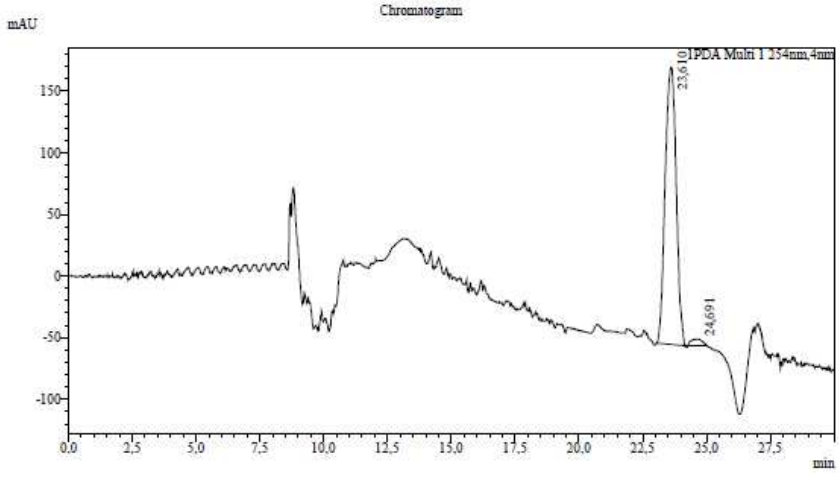
Racemic:



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	23,600	13756818	421179	49,398		M	
2	24,775	14091933	481634	50,602		V M	
Total		27848751	902813				

Chiral:



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	23,610	6750063	225013	97,478		M	
2	24,691	174643	5538	2,522		M	
Total		6924706	230551				

APPENDIX

I. List of abbreviations

Ac	acetyl
acac	acetylacetonate
Alk	alkyl
aq.	aqueous
Ar	aryl
ATR	attenuated total reflection (IR)
BINOL	1,1'-bi-2-naphthol
Bu	butyl
*i*Bu	*iso*butyl
calc.	calculated
CBS catalyst	*Corey-Bakshi-Shibata* catalyst
*c*Hex	cyclohexyl
conc.	Concentrated
Cy	cyclohexyl
d	doublet (NMR) / day
dba	*trans,trans*-dibenzylideneacetone
DBB	di-tert-butylbiphenyl
DBE	1,2-dibromoethane
DCM	dichloromethane
dist.	distilled
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
DPE-Phos	(oxydi-2,1-phenylene) bis(diphenylphosphine)
E^+	electrophile
EI	electron ionization
Et	ethyl
equiv	equivalent
FG	functional group
GC	gas chromatography
h	hour
Hal	halogen
Hex	hexyl

*i*hexane	*iso*hexane
HMDS	hexamethyldisilazane
HRMS	high resolution mass spectroscopy
Hz	Hertz
ICP-AES	Inductively coupled plasma atomic emission spectroscopy
IR	infrared
J	coupling constant (NMR)
L	ligand
LDA	lithium *N*,*N*-di*iso*propylamide
m	*meta*
Me	methyl
min	minute
mmol	millimole
M.p.	melting point
MS	mass spectroscopy
*n*Bu	*n*-butyl
*n*Pr	*n*-propyl
NMP	*N*-methylpyrrolidin-2-one
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
PEPPSI-*i*Pr	[1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Ph	phenyl
Piv	pivaloyl
ppm	parts per million
ppy	Tris[2-phenylpyridinato-C^2,*N*]
*i*Pr	*iso*-propyl
R	organic substituent
rpm	revolutions per minute
sat.	saturated
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
*t*Bu	*tert*-butyl
T	temperature

t	reaction time
TLC	thin layer chromatography
THF	tetrahydrofuran
TMP	2,2,6,6-tetramethylpiperidyl
TMPH	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Ts	4-toluenesulfonyl / tosylate
TP	typical procedure
X	halide or pseudohalide
μW	microwave irradiation

II. Single Crystal X-Ray Diffraction Studies[143]

Single crystals of compounds **19g, 22, 24c, 24d, 28b** and **36i** suitable for X-ray diffraction, were obtained by slow evaporation of pentane/dichloromethane solutions. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection was performed with the CrysAlis CCD software;[a)] CrysAlis RED software[b)] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method[c)] was applied. The structures were solved with SHELXS-97,[d)] refined with SHELXL-97[e)] and finally checked using PLATON.[f)] Details for data collection and structure refinement are summarized in Table 1.

CCDC-1061698 (for **22**), CCDC-1061699 (for **24c**), CCDC-1061700 (for **24d**), CCDC-1061701 (for **19g**) and CCDC-1061697 (for **28b**) contain supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. Compound **36i** was submitted to The Cambridge Crystallographic Data Centre.

[143] Single Crystal X-Ray Diffraction Studies were performed by Prof. Dr. Konstantin Karaghiosoff.

Table 1. Details for X-ray data collection and structure refinement for compounds **19g, 22, 24c, 24d, 28b**

	22	**24c**	**24d**	**19g**	**28b**
Empirical formula	$C_{17}H_{13}ClN_2$	$C_{16}H_8IN_3$	$C_{22}H_{14}Br_2N_2$	$C_{11}H_8Cl_2N_2$	$C_{15}H_9BrN_2$
Formula mass	280.74	369.15	466.17	239.09	297.15
T[K]	173(2)	173(2)	173(2)	120(2)	173(2)
Crystal size [mm]	0.45 × 0.30 × 0.12	0.49 × 0.47 × 0.34	0.30 × 0.22 × 0.11	0.29 × 0.13 × 0.06	0.43 × 0.17 × 0.05
Crystal description	colorless block	colorless block	colorless block	colorless block	colorless platelet
Crystal system	triclinic	orthorhombic	triclinic	monoclinic	triclinic
Space group	*P*-1	*Pna*21	*P*-1	*Pn*	*P*-1
a [Å]	8.3281(5)	14.7600(5)	10.6482(8)	6.2036(3)	7.8204(4)
b [Å]	8.3937(5)	12.3515(3)	12.4536(6)	12.1213(6)	8.2301(4)
c [Å]	11.3279(6)	7.8266(2)	29.1059(15)	14.0379(8)	11.0711(5)
α [°]	82.383(5)	90	96.762(4)	90	81.489(4)
β [°]	73.299(5)	90	95.631(5)	99.077(5)	74.012(5)
γ [°]	65.480(6)	90	92.756(5)	90	67.896(5)
V [Å^3]	689.98(7)	1426.85(7)	3807.4(4)	1042.37(9)	633.87(5)
Z	2	4	8	4	2
$\rho_{calcd.}$ [g cm^{-3}]	1.351	1.718	1.627	1.524	1.557
μ [mm^{-1}]	0.267	2.236	4.266	0.586	3.224
F(000)	292	712	1840	488	296
Θ range [°]	4.17 – 30.50	4.42 – 30.03	4.13 – 25.35	4.19 – 26.36	4.11 – 27.48
Index ranges	$-11 \le h \le 11$	$-20 \le h \le 20$	$-12 \le h \le 12$	$-7 \le h \le 7$	$-10 \le h \le 10$
	$-11 \le k \le 11$	$-17 \le k \le 16$	$-14 \le k \le 14$	$-15 \le k \le 15$	$-10 \le k \le 10$
	$-16 \le l \le 16$	$-11 \le l \le 9$	$-35 \le l \le 35$	$-17 \le l \le 17$	$-14 \le l \le 14$
Reflns. collected	13962	15394	27999	6932	10314
Reflns. obsd.	3133	2767	6865	3295	2187
Reflns. unique	4171 (R_{int} = 0.0329)	3389 (R_{int} = 0.0336)	13815 (R_{int} = 0.0495)	3723 (R_{int} = 0.0338)	2886 (R_{int} = 0.0348)
R_1, wR_2 (2σ data)	0.0459, 0.1147	0.0308, 0.0582	0.0701, 0.1452	0.0407, 0.0821	0.0346, 0.0782
R_1, wR_2 (all data)	0.0670, 0.1253	0.0464, 0.0636	0.1512, 0.1821	0.0493, 0.0867	0.0538, 0.0851
GOOF on F^2	1.084	1.035	1.015	1.016	1.027
Peak/hole [e Å^{-3}]	0.358 / -0.263	0.662 / -0.518	1.413 / -0.950	0.429 / -0.243	0.353 / -0.524

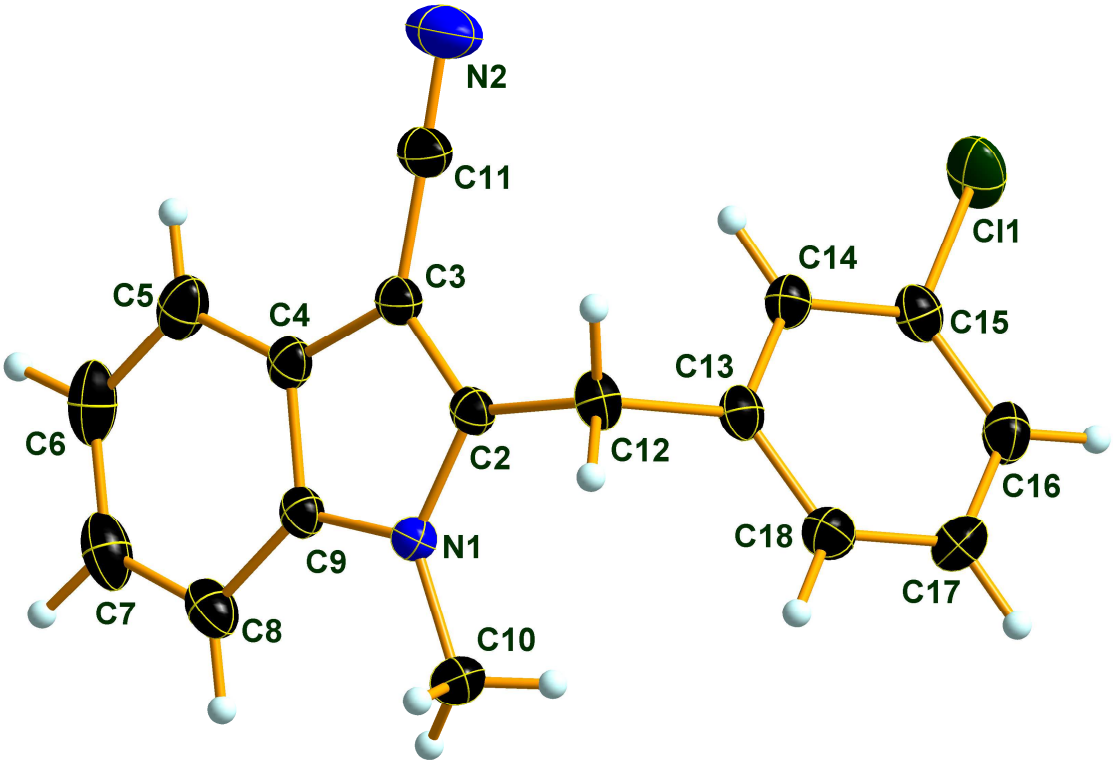


Figure 1. Molecular structure of compound **22** in the crystal, DIAMOND[g)] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 2. Selected bond lengths (Å) of compound **22**.

Cl1 – C15	1.742(2)	N1 – C10	1.454(2)
C14 – C15	1.382(2)	C13 – C18	1.390(2)
C14 – C13	1.394(2)	C13 – C12	1.518(2)
C4 – C5	1.401(2)	C15 – C16	1.383(2)
C4 – C9	1.403(2)	C11 – N2	1.148(2)
C4 – C3	1.434(2)	C11 – C3	1.415(2)
C9 – N1	1.384(2)	C18 – C17	1.388(2)
C9 – C8	1.397(2)	C8 – C7	1.382(2)
C2 – N1	1.368(2)	C6 – C5	1.378(2)
C2 – C3	1.381(2)	C6 – C7	1.392(3)
C2 – C12	1.498(2)	C16 – C17	1.387(2)

Table 3. Selected bond angles (°) of compound **22**.

C15 – C14 – C13	119.6(1)	C14 – C15 – C16	122.1(1)
C5 – C4 – C9	119.5(1)	C14 – C15 – Cl1	118.9(1)
C5 – C4 – C3	134.5(1)	C16 – C15 – Cl1	119.0(1)
C9 – C4 – C3	106.0(1)	N2 – C11 – C3	179.0(2)
N1 – C9 – C8	129.5(1)	C17 – C18 – C13	120.7(1)
N1 – C9 – C4	108.2(1)	C7 – C8 – C9	116.8(2)
C8 – C9 – C4	122.3(1)	C2 – C3 – C11	125.1(1)
N1 – C2 – C3	108.5(1)	C2 – C3 – C4	107.9(1)
N1 – C2 – C12	123.4(1)	C11 – C3 – C4	127.0(1)
C3 – C2 – C12	128.1(1)	C5 – C6 – C7	121.5(2)
C2 – N1 – C9	109.4(1)	C2 – C12 – C13	112.8(1)
C2 – N1 – C10	126.6(1)	C8 – C7 – C6	121.7(2)
C9 – N1 – C10	124.0(1)	C15 – C16 – C17	118.1(1)
C18 – C13 – C14	118.8(1)	C6 – C5 – C4	118.2(2)
C18 – C13 – C12	121.4(1)	C16 – C17 – C18	120.7(1)
C14 – C13 – C12	119.8(1)		

Table 4. Selected torsion angles (°) of compound **22**.

C5 – C4 – C9 – N1	-179.7(1)	C12 – C2 – C3 – C11	-3.9(2)
C3 – C4 – C9 – N1	-0.4(1)	N1 – C2 – C3 – C4	-0.1(1)
C5 – C4 – C9 – C8	0.5(2)	C12 – C2 – C3 – C4	178.3(1)
C3 – C4 – C9 – C8	179.7(1)	C5 – C4 – C3 – C2	179.4(1)
C3 – C2 – N1 – C9	-0.1(1)	C9 – C4 – C3 – C2	0.3(1)
C12 – C2 – N1 – C9	-178.6(1)	C5 – C4 – C3 – C11	1.7(2)
C3 – C2 – N1 – C10	-178.9(1)	C9 – C4 – C3 – C11	-177.4(1)
C12 – C2 – N1 – C10	2.6(2)	N1 – C2 – C12 – C13	84.8(2)
C8 – C9 – N1 – C2	-179.8(1)	C3 – C2 – C12 – C13	-93.4(2)
C4 – C9 – N1 – C2	0.3(1)	C18 – C13 – C12 – C2	-110.0(1)
C8 – C9 – N1 – C10	-1.0(2)	C14 – C13 – C12 – C2	70.3(2)
C4 – C9 – N1 – C10	179.2(1)	C9 – C8 – C7 – C6	0.4(2)
C15 – C14 – C13 – C18	0.4(2)	C5 – C6 – C7 – C8	0.3(2)

C15 – C14 – C13 – C12	-179.9(1)	C14 – C15 – C16 – C17	0.1(2)
C13 – C14 – C15 – C16	-0.2(2)	Cl1 – C15 – C16 – C17	179.0(1)
C13 – C14 – C15 – Cl1	-179.1(1)	C7 – C6 – C5 – C4	-0.7(2)
C14 – C13 – C18 – C17	-0.6(2)	C9 – C4 – C5 – C6	0.3(2)
C12 – C13 – C18 – C17	179.8(1)	C3 – C4 – C5 – C6	-178.7(1)
N1 – C9 – C8 – C7	179.3(1)	C15 – C16 – C17 – C18	-0.2(2)
C4 – C9 – C8 – C7	-0.8(2)	C13 – C18 – C17 – C16	0.4(2)
N1 – C2 – C3 – C11	177.7(1)		

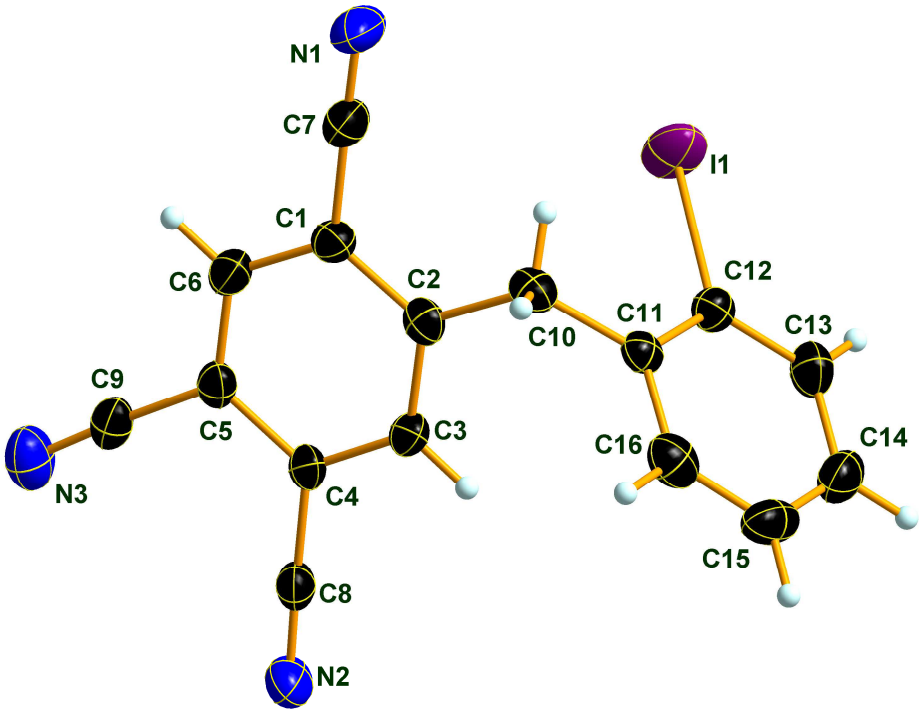


Figure 2. Molecular structure of compound **24c** in the crystal, DIAMOND[g)] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 5. Selected bond lengths (Å) of compound **24c**.

I1 – C12	2.102(3)	C7 – C1	1.446(4)
C2 – C3	1.385(4)	C10 – C11	1.511(4)
C2 – C1	1.399(4)	C5 – C6	1.377(5)
C2 – C10	1.516(4)	C5 – C9	1.445(4)
C4 – C3	1.393(4)	C6 – C1	1.401(5)
C4 – C5	1.411(4)	C9 – N3	1.143(4)

C4 – C8	1.432(4)	C11 – C12	1.381(4)
C14 – C15	1.386(5)	C11 – C16	1.399(4)
C14 – C13	1.387(6)	C12 – C13	1.384(4)
N2 – C8	1.145(4)	C16 – C15	1.370(5)
N1 – C7	1.149(5)		

Table 6. Selected bond angles (°) of compound **24c**.

C3 – C2 – C1	117.6(3)	C2 – C1 – C6	121.9(3)
C3 – C2 – C10	120.1(3)	C2 – C1 – C7	119.1(3)
C1 – C2 – C10	122.2(3)	C6 – C1 – C7	119.0(3)
C3 – C4 – C5	120.1(3)	N3 – C9 – C5	177.3(4)
C3 – C4 – C8	119.1(3)	C12 – C11 – C16	116.9(3)
C5 – C4 – C8	120.9(3)	C12 – C11 – C10	123.3(3)
C15 – C14 – C13	119.1(4)	C16 – C11 – C10	119.8(3)
N1 – C7 – C1	178.6(4)	C11 – C12 – C13	121.9(3)
C11 – C10 – C2	113.9(2)	C11 – C12 – I1	120.9(2)
C6 – C5 – C4	119.2(3)	C13 – C12 – I1	117.2(2)
C6 – C5 – C9	122.4(3)	C15 – C16 – C11	122.1(3)
C4 – C5 – C9	118.3(3)	C12 – C13 – C14	120.0(3)
C5 – C6 – C1	119.7(3)	C2 – C3 – C4	121.4(3)
N2 – C8 – C4	177.7(3)	C16 – C15 – C14	120.0(3)

Table 7. Selected torsion angles (°) of compound **24c**.

C3 – C2 – C10 – C11	34.9(4)	C16 – C11 – C12 – C13	-1.2(4)
C1 – C2 – C10 – C11	-147.6(3)	C10 – C11 – C12 – C13	-179.0(3)
C3 – C4 – C5 – C6	-0.1(4)	C16 – C11 – C12 – I1	178.2(2)
C8 – C4 – C5 – C6	179.1(3)	C10 – C11– C12 – I1	0.3(4)
C3 – C4 – C5 – C9	-178.8(3)	C12 – C11 – C16 – C15	0.8(4)
C8 – C4 – C5 – C9	0.4(4)	C10 – C11 – C16 – C15	178.7(3)
C4 – C5 – C6 – C1	0.0(4)	C11 – C12 – C13 – C14	0.9(5)
C9 – C5 – C6 – C1	178.6(3)	I1 – C12 – C13 – C14	-178.5(2)
C3 – C2 – C1 – C6	0.7(4)	C15 – C14 – C13 – C12	-0.1(5)

C10 – C2 – C1 – C6	-176.8(3)	C1 – C2 – C3 – C4	-0.8(4)
C3 – C2 – C1 – C7	179.9(3)	C10 – C2 – C3 – C4	176.8(3)
C10 – C2 – C1 – C7	2.3(4)	C5 – C4 – C3 – C2	0.5(4)
C5 – C6 – C1 – C2	-0.3(4)	C8 – C4 – C3 – C2	-178.7(3)
C5 – C6 – C1 – C7	-179.5(3)	C11 – C16 – C15 – C14	-0.1(5)
C2 – C10 – C11 – C12	87.4(4)	C13 – C14 – C15 – C16	-0.3(5)
C2 – C10 – C11 – C16	-90.4(3)		

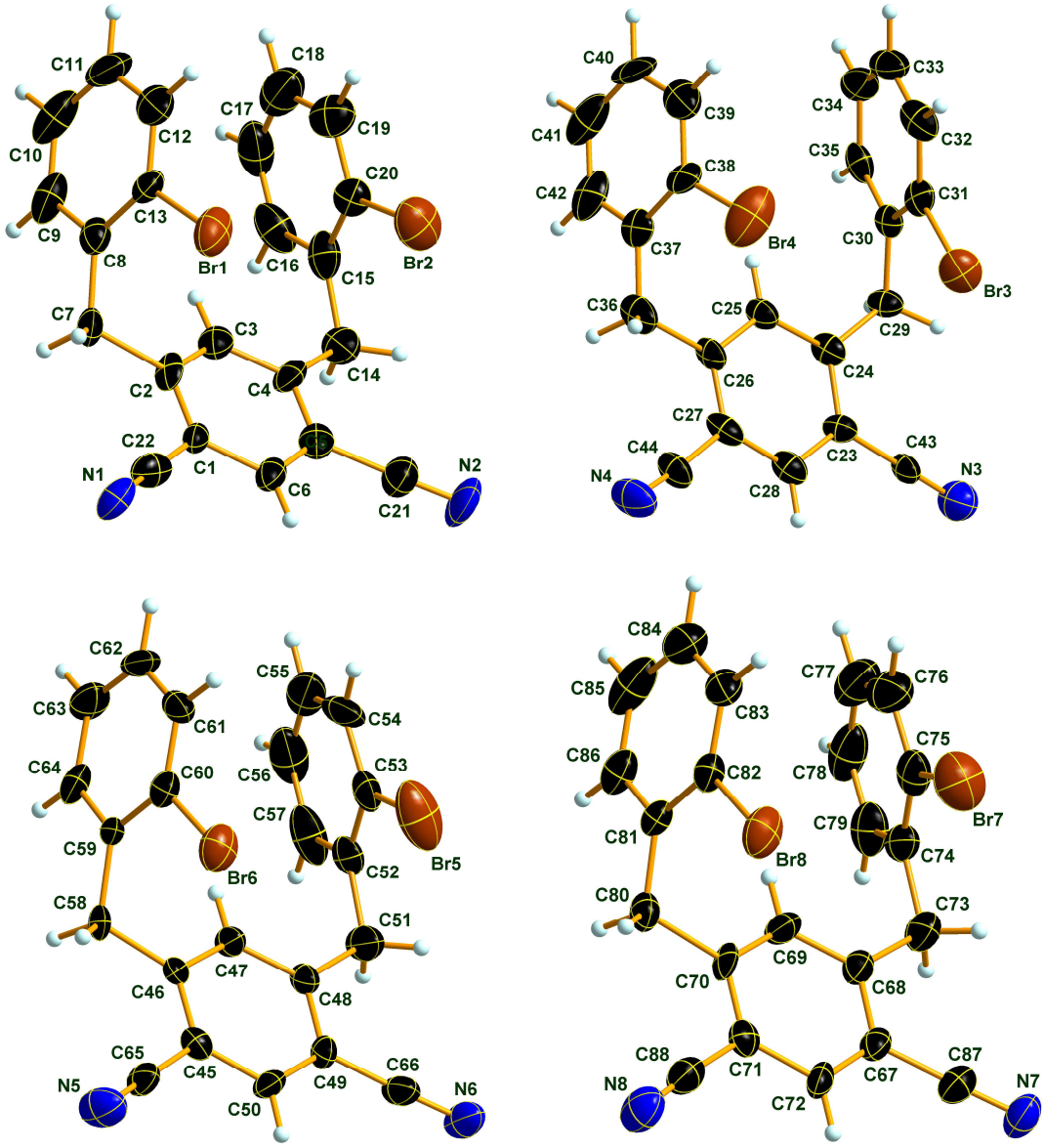


Figure 3. Molecular structure of compound **24d** in the crystal, DIAMOND[g] representation of the four crystallographically independent molecules; thermal ellipsoids are drawn at 50 % probability level.

Table 8. Selected bond lengths (Å) of compound **24d**.

Br6 – C60	1.900(7)	Br3 – C31	1.866(7)
Br5 – C53	1.890(7)	Br4 – C38	1.878(7)
N6 – C66	1.150(8)	N4 – C44	1.149(8)
N5 – C65	1.135(8)	N3 – C43	1.152(8)
C48 – C47	1.391(8)	C26 – C27	1.358(9)
C48 – C49	1.426(9)	C26 – C25	1.398(8)
C48 – C51	1.518(8)	C26 – C36	1.534(9)
C49 – C50	1.371(8)	C25 – C24	1.408(8)
C49 – C66	1.428(9)	C24 – C23	1.410(9)
C50 – C45	1.384(8)	C24 – C29	1.508(8)
C45 – C46	1.393(9)	C23 – C28	1.383(8)
C45 – C65	1.457(9)	C23 – C43	1.434(9)
C46 – C47	1.390(8)	C28 – C27	1.411(9)
C46 – C58	1.515(8)	C27 – C44	1.439(9)
C58 – C59	1.511(8)	C29 – C30	1.492(8)
C59 – C64	1.395(9)	C30 – C31	1.403(8)
C59 – C60	1.404(8)	C30 – C35	1.411(9)
C64 – C63	1.376(9)	C35 – C34	1.423(9)
C63 – C62	1.355(9)	C34 – C33	1.362(10)
C62 – C61	1.381(10)	C33 – C32	1.378(10)
C61 – C60	1.370(9)	C32 – C31	1.404(9)
C51 – C52	1.500(9)	C36 – C37	1.511(10)
C52 – C57	1.375(9)	C37 – C42	1.359(9)
C52 – C53	1.412(9)	C37 – C38	1.407(9)
C57 – C56	1.364(12)	C42 – C41	1.346(11)
C56 – C55	1.353(12)	C41 – C40	1.371(11)
C55 – C54	1.363(11)	C40 – C39	1.383(11)
C54 – C53	1.384(10)	C39 – C38	1.382(10)
Br8 – C82	1.911(7)	Br1 – C13	1.904(7)
Br7 – C75	1.906(7)	Br2 – C20	1.885(7)
N7 – C87	1.149(8)	N2 – C21	1.131(9)

N8 – C88	1.138(8)	N1 – C22	1.154(8)
C70 – C71	1.380(9)	C2 – C1	1.362(9)
C70 – C69	1.389(8)	C2 – C3	1.400(9)
C70 – C80	1.532(8)	C2 – C7	1.543(8)
C71 – C72	1.396(8)	C1 – C6	1.407(8)
C71 – C88	1.467(9)	C1 – C22	1.435(10)
C72 – C67	1.364(9)	C6 – C5	1.411(9)
C67 – C68	1.400(9)	C5 – C4	1.37(1)
C67 – C87	1.452(9)	C5 – C21	1.509(10)
C68 – C69	1.367(8)	C4 – C3	1.380(9)
C68 – C73	1.526(8)	C4 – C14	1.524(9)
C73 – C74	1.513(9)	C14 – C15	1.53(1)
C74 – C75	1.372(9)	C15 – C20	1.372(9)
C74 – C79	1.402(9)	C15 – C16	1.411(10)
C79 – C78	1.346(11)	C16 – C17	1.352(11)
C78 – C77	1.384(11)	C17 – C18	1.356(11)
C77 – C76	1.365(11)	C18 – C19	1.396(11)
C76 – C75	1.398(10)	C19 – C20	1.382(10)
C80 – C81	1.496(9)	C7 – C8	1.522(9)
C81 – C86	1.378(9)	C8 – C9	1.397(10)
C81 – C82	1.403(8)	C8 – C13	1.398(8)
C86 – C85	1.383(10)	C9 – C10	1.362(11)
C85 – C84	1.388(11)	C10 – C11	1.383(11)
C84 – C83	1.39(1)	C11 – C12	1.385(11)
C83 – C82	1.367(9)	C12 – C13	1.364(9)

Table 9. Selected bond angles (°) of compound **24d**.

C47 – C48 – C49	116.7(6)	C27 – C26 – C25	119.6(6)
C47 – C48 – C51	122.2(6)	C27 – C26 – C36	119.7(6)
C49 – C48 – C51	121.0(6)	C25 – C26 – C36	120.7(6)
C50 – C49 – C48	120.9(6)	C26 – C25 – C24	121.5(6)
C50 – C49 – C66	120.2(6)	C25 – C24 – C23	117.6(6)

C48 – C49 – C66	118.9(6)	C25 – C24 – C29	120.2(6)
C49 – C50 – C45	119.9(6)	C23 – C24 – C29	122.3(6)
C50 – C45 – C46	121.7(6)	C28 – C23 – C24	120.8(6)
C50 – C45 – C65	117.1(6)	C28 – C23 – C43	118.5(6)
C46 – C45 – C65	121.2(6)	C24 – C23 – C43	120.7(6)
C47 – C46 – C45	117.2(6)	C23 – C28 – C27	119.7(7)
C47 – C46 – C58	120.1(6)	C26 – C27 – C28	120.7(6)
C45 – C46 – C58	122.6(6)	C26 – C27 – C44	120.5(6)
C46 – C47 – C48	123.4(6)	C28 – C27 – C44	118.8(7)
N6 – C66 – C49	177.7(8)	N4 – C44 – C27	175.2(8)
N5 – C65 – C45	178.9(8)	N3 – C43 – C23	178.4(7)
C59 – C58 – C46	113.2(5)	C30 – C29 – C24	112.8(5)
C64 – C59 – C60	116.1(6)	C31 – C30 – C35	116.8(6)
C64 – C59 – C58	122.1(6)	C31 – C30 – C29	122.4(6)
C60 – C59 – C58	121.7(6)	C35 – C30 – C29	120.8(6)
C63 – C64 – C59	121.7(6)	C30 – C35 – C34	121.2(6)
C62 – C63 – C64	120.7(7)	C33 – C34 – C35	120.0(7)
C63 – C62 – C61	119.6(7)	C34 – C33 – C32	120.0(7)
C60 – C61 – C62	120.1(7)	C33 – C32 – C31	121.0(7)
C61 – C60 – C59	121.8(7)	C30 – C31 – C32	121.0(6)
C61 – C60 – Br6	118.8(5)	C30 – C31 – Br3	120.3(5)
C59 – C60 – Br6	119.5(5)	C32 – C31 – Br3	118.8(5)
C52 – C51 – C48	114.0(6)	C37 – C36 – C26	115.0(6)
C57 – C52 – C53	117.4(7)	C42 – C37 – C38	117.3(7)
C57 – C52 – C51	120.9(7)	C42 – C37 – C36	119.8(7)
C53 – C52 – C51	121.6(7)	C38 – C37 – C36	122.9(7)
C56 – C57 – C52	120.5(8)	C41 – C42 – C37	122.5(8)
C55 – C56 – C57	122.1(9)	C42 – C41 – C40	120.8(9)
C56 – C55 – C54	119.5(9)	C41 – C40 – C39	119.3(8)
C55 – C54 – C53	119.8(7)	C38 – C39 – C40	119.3(8)
C54 – C53 – C52	120.7(7)	C39 – C38 – C37	120.8(7)
C54 – C53 – Br5	119.6(6)	C39 – C38 – Br4	118.4(6)

C52 – C53 – Br5	119.7(6)	C37 – C38 – Br4	120.8(6)
C71 – C70 – C69	118.3(6)	C1 – C2 – C3	119.2(6)
C71 – C70 – C80	122.3(6)	C1 – C2 – C7	121.4(6)
C69 – C70 – C80	119.4(6)	C3 – C2 – C7	119.4(7)
C70 – C71 – C72	121.2(6)	C2 – C1 – C6	120.5(6)
C70 – C71 – C88	120.3(6)	C2 – C1 – C22	121.9(6)
C72 – C71 – C88	118.5(6)	C6 – C1 – C22	117.5(7)
C67 – C72 – C71	118.4(7)	C1 – C6 – C5	117.7(7)
C72 – C67 – C68	122.1(6)	C4 – C5 – C6	123.0(7)
C72 – C67 – C87	118.2(6)	C4 – C5 – C21	121.1(7)
C68 – C67 – C87	119.6(6)	C6 – C5 – C21	115.7(7)
C69 – C68 – C67	117.7(6)	C5 – C4 – C3	116.7(7)
C69 – C68 – C73	123.2(6)	C5 – C4 – C14	119.8(6)
C67 – C68 – C73	119.0(6)	C3 – C4 – C14	123.5(7)
C68 – C69 – C70	122.2(6)	C4 – C3 – C2	122.8(7)
N8 – C88 – C71	176.1(8)	N2 – C21 – C5	178.5(10)
N7 – C87 – C67	178.9(8)	N1 – C22 – C1	177.7(8)
C74 – C73 – C68	113.4(6)	C4 – C14 – C15	109.9(6)
C75 – C74 – C79	116.3(7)	C20 – C15 – C16	116.5(8)
C75 – C74 – C73	123.2(7)	C20 – C15 – C14	121.2(7)
C79 – C74 – C73	120.5(7)	C16 – C15 – C14	122.2(7)
C78 – C79 – C74	122.4(8)	C17 – C16 – C15	121.8(7)
C79 – C78 – C77	119.6(9)	C16 – C17 – C18	121.3(9)
C76 – C77 – C78	120.7(9)	C17 – C18 – C19	118.6(9)
C77 – C76 – C75	118.3(8)	C20 – C19 – C18	120.0(8)
C74 – C75 – C76	122.5(7)	C15 – C20 – C19	121.7(7)
C74 – C75 – Br7	121.0(6)	C15 – C20 – Br2	122.0(6)
C76 – C75 – Br7	116.5(7)	C19 – C20 – Br2	116.4(5)
C81 – C80 – C70	112.8(5)	C8 – C7 – C2	112.1(5)
C86 – C81 – C82	115.7(7)	C9 – C8 – C13	117.2(7)
C86 – C81 – C80	121.1(6)	C9 – C8 – C7	121.8(6)
C82 – C81 – C80	123.2(6)	C13 – C8 – C7	121.1(6)

C81 – C86 – C85	121.2(7)	C10 – C9 – C8	120.5(7)
C86 – C85 – C84	120.9(8)	C9 – C10 – C11	121.2(8)
C85 – C84 – C83	119.8(8)	C10 – C11 – C12	119.4(8)
C82 – C83 – C84	117.1(7)	C13 – C12 – C11	119.1(8)
C83 – C82 – C81	125.2(6)	C12 – C13 – C8	122.5(7)
C83 – C82 – Br8	116.6(5)	C12 – C13 – Br1	116.9(6)
C81 – C82 – Br8	118.2(5)	C8 – C13 – Br1	120.5(5)

Table 10. Selected torsion angles (°) of compound **24d**.

C47 – C48 – C49 – C50	1.9(9)	C27 – C26 – C25 – C24	0.4(10)
C51 – C48 – C49 – C50	179.7(6)	C36 – C26 – C25 – C24	-179.9(6)
C47 – C48 – C49 – C66	-177.2(6)	C26 – C25 – C24 – C23	2.0(9)
C51 – C48 – C49 – C66	0.7(10)	C26 – C25 – C24 – C29	-175.9(6)
C48 – C49 – C50 – C45	-3.1(9)	C25 – C24 – C23 – C28	-2.3(9)
C66 – C49 – C50 – C45	176.0(6)	C29 – C24 – C23 – C28	175.6(6)
C49 – C50 – C45 – C46	1.2(9)	C25 – C24 – C23 – C43	179.2(6)
C49 – C50 – C45 – C65	-177.5(6)	C29 – C24 – C23 – C43	-2.9(9)
C50 – C45 – C46 – C47	1.8(9)	C24 – C23 – C28 – C27	0.2(9)
C65 – C45 – C46 – C47	-179.5(5)	C43 – C23 – C28 – C27	178.7(6)
C50 – C45 – C46 – C58	-176.1(6)	C25 – C26 – C27 – C28	-2.7(10)
C65 – C45 – C46 – C58	2.5(9)	C36 – C26 – C27 – C28	177.7(6)
C45 – C46 – C47 – C48	-3.0(9)	C25 – C26 – C27 – C44	176.9(6)
C58 – C46 – C47 – C48	174.9(6)	C36 – C26 – C27 – C44	-2.7(10)
C49 – C48 – C47 – C46	1.3(9)	C23 – C28 – C27 – C26	2.4(10)
C51 – C48 – C47 – C46	-176.6(6)	C23 – C28 – C27 – C44	-177.2(6)
C47 – C46 – C58 – C59	-33.1(8)	C25 – C24 – C29 – C30	30.6(8)
C45 – C46 – C58 – C59	144.7(6)	C23 – C24 – C29 – C30	-147.3(6)
C46 – C58 – C59 – C64	109.2(7)	C24 – C29 – C30 – C31	69.2(8)
C46 – C58 – C59 – C60	-67.3(8)	C24 – C29 – C30 – C35	-109.4(7)
C60 – C59 – C64 – C63	-0.7(10)	C31 – C30 – C35 – C34	-1.2(9)
C58 – C59 – C64 – C63	-177.4(6)	C29 – C30 – C35 – C34	177.4(6)
C59 – C64 – C63 – C62	0.6(11)	C30 – C35 – C34 – C33	0.8(10)
C64 – C63 – C62 – C61	-0.4(11)	C35 – C34 – C33 – C32	-0.1(11)
C63 – C62 – C61 – C60	0.3(11)	C34 – C33 – C32 – C31	0.0(11)
C62 – C61 – C60 – C59	-0.4(10)	C35 – C30 – C31 – C32	1.1(9)
C62 – C61 – C60 – Br6	179.5(5)	C29 – C30 – C31 – C32	-177.5(6)
C64 – C59 – C60 – C61	0.6(10)	C35 – C30 – C31 – Br3	-179.8(4)
C58 – C59 – C60 – C61	177.3(6)	C29 – C30 – C31 – Br3	1.6(8)
C64 – C59 – C60 – Br6	-179.3(5)	C33 – C32 – C31 – C30	-0.5(10)
C58 – C59 – C60 – Br6	-2.6(8)	C33 – C32 – C31 – Br3	-179.6(5)

C47 – C48 – C51 – C52	14.9(10)	C27 – C26 – C36 – C37	167.7(6)
C49 – C48 – C51 – C52	-162.8(6)	C25 – C26 – C36 – C37	-11.9(10)
C48 – C51 – C52 – C57	-101.1(8)	C26 – C36 – C37 – C42	106.2(8)
C48 – C51 – C52 – C53	74.6(8)	C26 – C36 – C37 – C38	-72.7(8)
C53 – C52 – C57 – C56	-0.4(10)	C38 – C37 – C42 – C41	0.7(10)
C51 – C52 – C57 – C56	175.5(7)	C36 – C37 – C42 – C41	-178.3(7)
C52 – C57 – C56 – C55	-0.2(13)	C37 – C42 – C41 – C40	0.4(12)
C57 – C56 – C55 – C54	-1.0(13)	C42 – C41 – C40 – C39	-1.5(13)
C56 – C55 – C54 – C53	2.8(12)	C41 – C40 – C39 – C38	1.4(12)
C55 – C54 – C53 – C52	-3.5(10)	C40 – C39 – C38 – C37	-0.3(11)
C55 – C54 – C53 – Br5	179.9(6)	C40 – C39 – C38 – Br4	-179.7(6)
C57 – C52 – C53 – C54	2.3(9)	C42 – C37 – C38 – C39	-0.7(10)
C51 – C52 – C53 – C54	-173.6(6)	C36 – C37 – C38 – C39	178.2(6)
C57 – C52 – C53 – Br5	178.9(5)	C42 – C37 – C38 – Br4	178.6(5)
C51 – C52 – C53 – Br5	3.0(8)	C36 – C37 – C38 – Br4	-2.4(9)
C69 – C70 – C71 – C72	2.8(9)	C3 – C2 – C1 – C6	2.5(9)
C80 – C70 – C71 – C72	-176.7(6)	C7 – C2 – C1 – C6	-175.8(6)
C69 – C70 – C71 – C88	180.0(6)	C3 – C2 – C1 – C22	179.7(5)
C80 – C70 – C71 – C88	0.5(9)	C7 – C2 – C1 – C22	1.4(9)
C70 – C71 – C72 – C67	-0.8(9)	C2 – C1 – C6 – C5	-0.6(9)
C88 – C71 – C72 – C67	-178.1(6)	C22 – C1 – C6 – C5	-178.0(6)
C71 – C72 – C67 – C68	-0.9(9)	C1 – C6 – C5 – C4	-1.6(10)
C71 – C72 – C67 – C87	175.6(6)	C1 – C6 – C5 – C21	174.2(6)
C72 – C67 – C68 – C69	0.6(10)	C6 – C5 – C4 – C3	1.8(10)
C87 – C67 – C68 – C69	-175.9(6)	C21 – C5 – C4 – C3	-173.8(6)
C72 – C67 – C68 – C73	-179.1(6)	C6 – C5 – C4 – C14	-177.6(6)
C87 – C67 – C68 – C73	4.5(9)	C21 – C5 – C4 – C14	6.8(10)
C67 – C68 – C69 – C70	1.5(10)	C5 – C4 – C3 – C2	0.2(10)
C73 – C68 – C69 – C70	-178.8(6)	C14 – C4 – C3 – C2	179.6(6)
C71 – C70 – C69 – C68	-3.2(10)	C1 – C2 – C3 – C4	-2.4(10)
C80 – C70 – C69 – C68	176.3(6)	C7 – C2 – C3 – C4	176.0(6)
C69 – C68 – C73 – C74	9.1(10)	C5 – C4 – C14 – C15	-152.8(6)

C67 – C68 – C73 – C74	-171.2(6)	C3 – C4 – C14 – C15	27.9(9)
C68 – C73 – C74 – C75	75.5(8)	C4 – C14 – C15 – C20	72.0(8)
C68 – C73 – C74 – C79	-104.7(7)	C4 – C14 – C15 – C16	-103.7(8)
C75 – C74 – C79 – C78	-2.0(11)	C20 – C15 – C16 – C17	-0.8(11)
C73 – C74 – C79 – C78	178.1(7)	C14 – C15 – C16 – C17	175.0(7)
C74 – C79 – C78 – C77	-0.7(12)	C15 – C16 – C17 – C18	-0.7(13)
C79 – C78 – C77 – C76	1.6(13)	C16 – C17 – C18 – C19	2.1(13)
C78 – C77 – C76 – C75	0.3(12)	C17 – C18 – C19 – C20	-1.9(12)
C79 – C74 – C75 – C76	4.(1)	C16 – C15 – C20 – C19	1.(1)
C73 – C74 – C75 – C76	-176.1(6)	C14 – C15 – C20 – C19	-174.9(6)
C79 – C74 – C75 – Br7	-179.0(5)	C16 – C15 – C20 – Br2	179.4(5)
C73 – C74 – C75 – Br7	0.9(9)	C14 – C15 – C20 – Br2	3.5(9)
C77 – C76 – C75 – C74	-3.2(12)	C18 – C19 – C20 – C15	0.4(11)
C77 – C76 – C75 – Br7	179.7(6)	C18 – C19 – C20 – Br2	-178.2(6)
C71 – C70 – C80 – C81	147.7(6)	C1 – C2 – C7 – C8	146.0(6)
C69 – C70 – C80 – C81	-31.8(8)	C3 – C2 – C7 – C8	-32.4(8)
C70 – C80 – C81 – C86	110.7(7)	C2 – C7 – C8 – C9	111.3(7)
C70 – C80 – C81 – C82	-66.6(8)	C2 – C7 – C8 – C13	-67.0(8)
C82 – C81 – C86 – C85	0.3(10)	C13 – C8 – C9 – C10	-1.3(11)
C80 – C81 – C86 – C85	-177.2(6)	C7 – C8 – C9 – C10	-179.7(7)
C81 – C86 – C85 – C84	-0.6(12)	C8 – C9 – C10 – C11	1.7(12)
C86 – C85 – C84 – C83	0.1(12)	C9 – C10 – C11 – C12	-1.6(13)
C85 – C84 – C83 – C82	0.7(11)	C10 – C11 – C12 – C13	1.1(12)
C84 – C83 – C82 – C81	-1.1(11)	C11 – C12 – C13 – C8	-0.8(11)
C84 – C83 – C82 – Br8	-179.7(5)	C11 – C12 – C13 – Br1	-179.7(6)
C86 – C81 – C82 – C83	0.6(10)	C9 – C8 – C13 – C12	0.9(10)
C80 – C81 – C82 – C83	178.1(6)	C7 – C8 – C13 – C12	179.3(6)
C86 – C81 – C82 – Br8	179.2(5)	C9 – C8 – C13 – Br1	179.8(5)
C80 – C81 – C82 – Br8	-3.4(8)	C7 – C8 – C13 – Br1	-1.8(9)

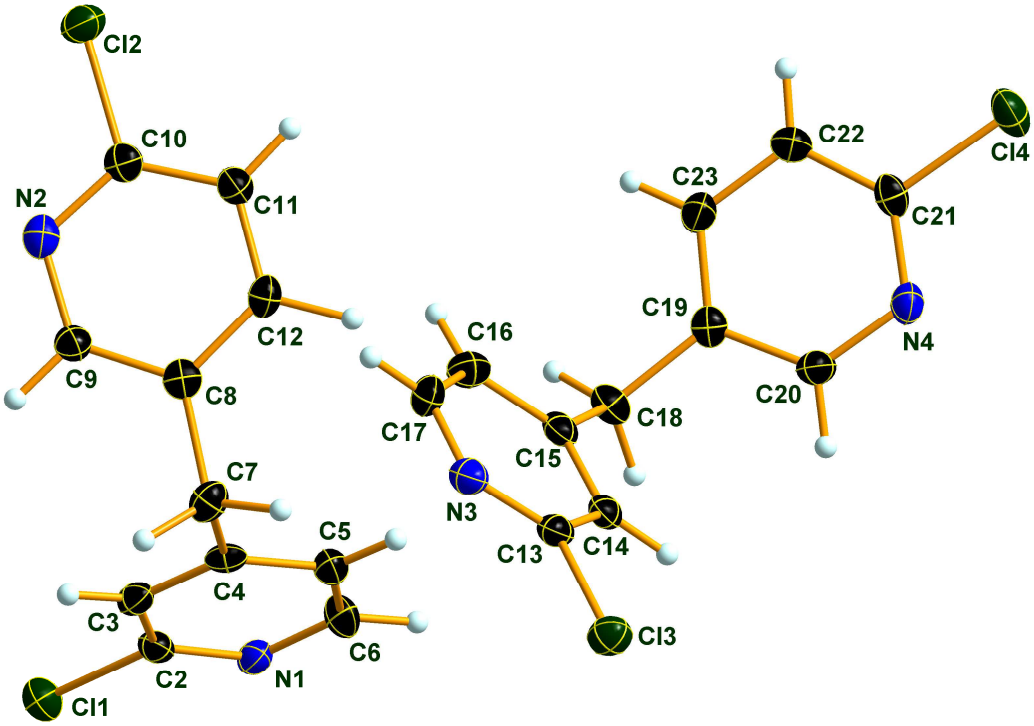


Figure 4. Molecular structure of compound **19g** in the crystal, DIAMOND[g)] representation of the two crystallographically independent molecules; thermal ellipsoids are drawn at 50 % probability level.

Table 11. Selected bond lengths (Å) of compound **19g**.

Cl1 – C2	1.754(3)	Cl3 – C13	1.747(4)
Cl2 – C10	1.753(3)	Cl4 – C21	1.750(3)
N1 – C2	1.322(4)	N3 – C13	1.315(4)
N1 – C6	1.347(5)	N3 – C17	1.340(5)
N2 – C10	1.323(4)	N4 – C21	1.312(4)
N2 – C9	1.350(4)	N4 – C20	1.344(4)
C2 – C3	1.380(5)	C13 – C14	1.387(5)
C6 – C5	1.385(5)	C17 – C16	1.368(5)
C5 – C4	1.386(5)	C16 – C15	1.399(5)
C4 – C3	1.383(5)	C15 – C14	1.393(5)
C4 – C7	1.521(5)	C15 – C18	1.507(5)
C7 – C8	1.503(5)	C18 – C19	1.507(5)
C8 – C9	1.388(5)	C19 – C23	1.377(5)

C8 – C12	1.396(5)	C19 – C20	1.389(5)
C10 – C11	1.375(5)	C21 – C22	1.371(5)
C11 – C12	1.387(5)	C22 – C23	1.380(5)

Table 12. Selected bond angles (°) of compound **19g**.

C2 – N1 – C6	115.1(3)	C13 – N3 – C17	114.8(3)
C10 – N2 – C9	115.4(3)	C21 – N4 – C20	116.2(3)
N1 – C2 – C3	126.3(3)	N3 – C13 – C14	126.0(3)
N1 – C2 – Cl1	115.2(3)	N3 – C13 – Cl3	115.7(3)
C3 – C2 – Cl1	118.5(3)	C14 – C13 – Cl3	118.3(3)
N1 – C6 – C5	123.5(4)	N3 – C17 – C16	125.0(3)
C6 – C5 – C4	119.6(3)	C17 – C16 – C15	119.3(3)
C3 – C4 – C5	117.6(3)	C14 – C15 – C16	116.6(3)
C3 – C4 – C7	120.6(3)	C14 – C15 – C18	120.9(3)
C5 – C4 – C7	121.8(3)	C16 – C15 – C18	122.4(3)
C2 – C3 – C4	117.9(3)	C13 – C14 – C15	118.3(3)
C8 – C7 – C4	111.1(3)	C19 – C18 – C15	112.4(3)
C9 – C8 – C12	116.5(3)	C23 – C19 – C20	116.7(3)
C9 – C8 – C7	120.8(3)	C23 – C19 – C18	122.6(3)
C12 – C8 – C7	122.7(3)	C20 – C19 – C18	120.6(3)
N2 – C9 – C8	125.1(3)	N4 – C20 – C19	124.2(3)
N2 – C10 – C11	125.8(3)	N4 – C21 – C22	125.2(3)
N2 – C10 – Cl2	115.6(3)	N4 – C21 – Cl4	115.8(3)
C11 – C10 – Cl2	118.6(3)	C22 – C21 – Cl4	119.0(3)
C10 – C11 – C12	117.3(3)	C21 – C22 – C23	117.4(3)
C11 – C12 – C8	119.9(3)	C19 – C23 – C22	120.2(4)

Table 13. Selected torsion angles (°) of compound **19g**.

C6 – N1 – C2 – C3	0.0(5)	C17 – N3 – C13 – C14	-0.6(5)
C6 – N1 – C2 – Cl1	-180.0(2)	C17 – N3 – C13 – Cl3	-179.5(3)
C2 – N1 – C6 – C5	0.1(5)	C13 – N3 – C17 – C16	0.9(5)
N1 – C6 – C5 – C4	0.0(6)	N3 – C17 – C16 – C15	-0.3(6)

C6 – C5 – C4 – C3	-0.4(5)	C17 – C16 – C15 – C14	-0.8(5)
C6 – C5 – C4 – C7	-178.3(3)	C17 – C16 – C15 – C18	-179.4(3)
N1 – C2 – C3 – C4	-0.3(5)	N3 – C13 – C14 – C15	-0.4(5)
Cl1 – C2 – C3 – C4	179.6(2)	Cl3 – C13 – C14 – C15	178.5(2)
C5 – C4 – C3 – C2	0.5(5)	C16 – C15 – C14 – C13	1.1(5)
C7 – C4 – C3 – C2	178.4(3)	C18 – C15 – C14 – C13	179.7(3)
C3 – C4 – C7 – C8	-85.7(4)	C14 – C15 – C18 – C19	-83.2(4)
C5 – C4 – C7 – C8	92.2(4)	C16 – C15 – C18 – C19	95.3(4)
C4 – C7 – C8 – C9	87.0(4)	C15 – C18 – C19 – C23	-91.5(4)
C4 – C7 – C8 – C12	-92.0(4)	C15 – C18 – C19 – C20	86.6(4)
C10 – N2 – C9 – C8	-0.8(5)	C21 – N4 – C20 – C19	-1.5(5)
C12 – C8 – C9 – N2	1.3(5)	C23 – C19 – C20 – N4	2.5(5)
C7 – C8 – C9 – N2	-177.8(3)	C18 – C19 – C20 – N4	-175.7(3)
C9 – N2 – C10 – C11	0.0(5)	C20 – N4 – C21 – C22	-0.9(5)
C9 – N2 – C10 – Cl2	-179.9(3)	C20 – N4 – C21 – Cl4	179.6(3)
N2 – C10 – C11 – C12	0.3(6)	N4 – C21 – C22 – C23	2.3(6)
Cl2 – C10 – C11 – C12	-179.8(3)	Cl4 – C21 – C22 – C23	-178.3(3)
C10 – C11 – C12 – C8	0.3(5)	C20 – C19 – C23 – C22	-1.0(5)
C9 – C8 – C12 – C11	-1.0(5)	C18 – C19 – C23 – C22	177.1(3)
C7 – C8 – C12 – C11	178.1(3)	C21 – C22 – C23 – C19	-1.2(6)

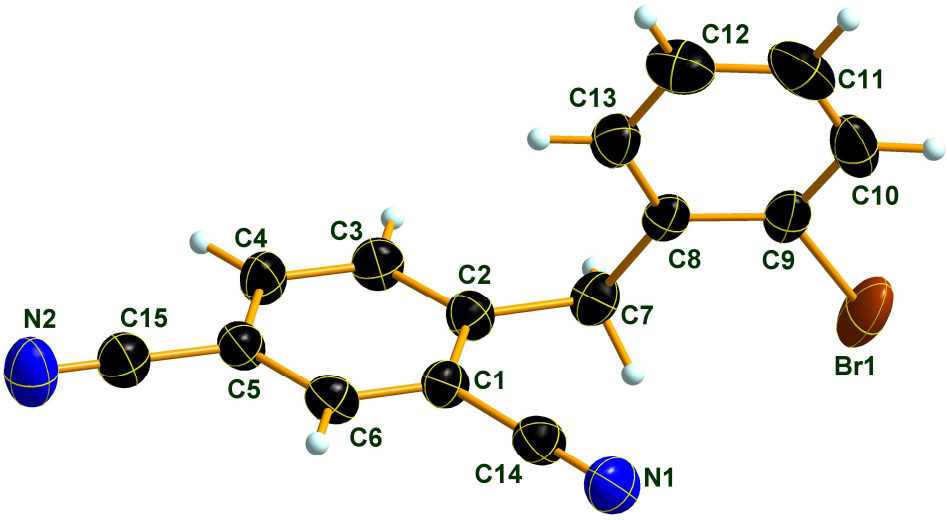


Figure 5. Molecular structure of compound **28b** in the crystal, DIAMOND[g)] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 14. Selected bond lengths (Å) of compound **28b**.

Br1 – C9	1.895(2)	C1 – C14	1.450(3)
C9 – C10	1.378(4)	C5 – C4	1.391(3)
C9 – C8	1.390(3)	C5 – C15	1.441(3)
C3 – C2	1.382(3)	C2 – C7	1.510(3)
C3 – C4	1.389(3)	C15 – N2	1.142(3)
C6 – C1	1.383(3)	N1 – C14	1.131(3)
C6 – C5	1.388(3)	C10 – C11	1.377(4)
C13 – C12	1.376(3)	C12 – C11	1.388(4)
C13 – C8	1.386(3)	C1 – C2	1.407(3)
C8 – C7	1.512(3)		

Table 15. Selected bond angles (°) of compound **28b**.

C10 – C9 – C8	122.3(2)	C3 – C2 – C7	121.7(2)
C10 – C9 – Br1	117.7(2)	C1 – C2 – C7	120.5(2)
C8 – C9 – Br1	120.0(2)	N2 – C15 – C5	179.4(3)
C2 – C3 – C4	121.9(2)	C3 – C4 – C5	119.1(2)
C1 – C6 – C5	119.3(2)	C2 – C7 – C8	114.6(2)
C12 – C13 – C8	122.3(2)	C11 – C10 – C9	119.8(2)
C13 – C8 – C9	116.4(2)	N1 – C14 – C1	179.5(3)
C13 – C8 – C7	122.4(2)	C13 – C12 – C11	119.7(3)
C9 – C8 – C7	121.1(2)	C10 – C11 – C12	119.3(3)
C6 – C1 – C2	121.4(2)	C6 – C5 – C15	119.0(2)
C6 – C1 – C14	118.8(2)	C4 – C5 – C15	120.5(2)
C2 – C1 – C14	119.9(2)	C3 – C2 – C1	117.8(2)
C6 – C5 – C4	120.6(2)		

Table 16. Selected torsion angles (°) of compound **28b**.

C12 – C13 – C8 – C9	-0.3(3)	C6 – C1 – C2 – C7	179.2(2)
C12 – C13 – C8 – C7	-179.9(2)	C14 – C1 – C2 – C7	-0.8(3)
C10 – C9 – C8 – C13	2.2(3)	C2 – C3 – C4 – C5	0.2(4)
Br1 – C9 – C8 – C13	-176.4(2)	C6 – C5 – C4 – C3	-0.8(3)
C10 – C9 – C8 – C7	-178.2(2)	C15 – C5 – C4 – C3	178.7(2)
Br1 – C9 – C8 – C7	3.2(3)	C3 – C2 – C7 – C8	105.4(2)
C5 – C6 – C1 – C2	0.0(3)	C1 – C2 – C7 – C8	-74.4(3)
C5 – C6 – C1 – C14	180.0(2)	C13 – C8 – C7 – C2	-17.4(3)
C1 – C6 – C5 – C4	0.7(3)	C9 – C8 – C7 – C2	163.1(2)
C1 – C6 – C5 – C15	-178.8(2)	C8 – C9 – C10 – C11	-2.2(4)
C4 – C3 – C2 – C1	0.5(3)	Br1 – C9 – C10 – C11	176.4(2)
C4 – C3 – C2 – C7	-179.3(2)	C8 – C13 – C12 – C11	-1.6(4)
C6 – C1 – C2 – C3	-0.6(3)	C9 – C10 – C11 – C12	0.3(4)
C14 – C1 – C2 – C3	179.4(2)	C13 – C12 – C11 – C10	1.6(4)

References

a) CrysAlis CCD, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).

b) CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).

c) SCALE3 ABSPACK – An Oxford Diffraction Program (1.0.4, gui:1.0.3) (C), Oxford Diffraction, Ltd., 2005.

d) Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.

e) Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.

f) Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

g) DIAMOND, Crystal Impact GbR., Version 3.2i.