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New Preparations and Reactions of Organometallic Reagents of Mg, Zn and B for the Functionalization of Aromatics and Heteroaromatics, Allylic and Vinylic Compounds as well as for Adamantyl Derivatives

von

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Erklärung

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

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe bearbeitet.

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Christoph Sämann

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<u>Parts of this PhD thesis have been published</u>

<u>Communications and Full Papers</u>

1. B. A. Haag, C. Sämann, A. Jana, P. Knochel: "Practical One-Pot Preparation of Magnesium Di(hetero)aryl- and Magnesium Dialkenylboronates for Suzuki-Miyaura Cross-Coupling Reactions" *Angew. Chem. Int. Ed.* **2011**, *50*, 7290; *Angew. Chem.* **2011**, *123*, 7428.
2. C. Sämann, B. A. Haag, P. Knochel: "Highly Regioselective Preparation of Heteroaryl-Magnesium Reagents using a Br/Mg-Exchange", *Chem. Eur. J.* **2012**, *18*, 16145.
3. C. Sämann, M. A. Schade, S. Yamada, P. Knochel: "Functionalized Alkenyl-zinc Reagents Bearing Carbonyl Groups: Preparation by Direct Metal Insertion and Reaction with Electrophiles", *Angew. Chem. Int. Ed.* **2013**, *52*, 9495; *Angew. Chem.* **2013**, *125*, 9673.
   (The publication was rated as *Hot Paper*)
4. C. Sämann, P. Knochel: "A Convenient Synthesis of α-Substituted β,γ-Unsaturated Ketones and Esters *via* the Direct Addition of Substituted Allylic Zinc Reagents Prepared by Direct Insertion", *Synthesis*, **2013**, *45*, 1870.
5. C. Sämann, E. Coya, P. Knochel, "Full Functionalization of the Imidazol Scaffold by Selective Metalation and Sulfoxide/Magnesium Exchange", *Angew. Chem. Int. Ed.* **2013**, DOI: 10.1002/anie.201309217; *Angew. Chem.* **2013**, DOI: 10.1002/ange.201309217.
6. C. Sämann, V. Dhayalan, P. Knochel, "Synthesis of Functionalized Adamantylzinc Reagents Using a Br/Mg-Insertion in the Presence of $ZnCl_2$", *manuscript in preparation*.

<u>Reviews</u>

1. P. Knochel, C. Sämann, S. Bernhardt, T. Kunz: "Auf den Spuren zweier Chemie-Nobelpreisträger – Verbesserte Metallorganische Intermediate für Kreuzkupplungs-reaktionen", *GIT Laborfachzeitschrift* **2011**, *11*, 799.
2. S. M. Manolikakes, N. M. Barl, C. Sämann, P. Knochel: "Regioselective Functionalization of Pyridines Using a Directed Metalation or a Halogen/Metal Exchange", *Z. Naturforsch.* **2013**, *68b*, 411.

3. P. Knochel, N. M. Barl, V. Werner, C. Sämann, “The Halogen/Magnesium Exchange Using *i*PrMgCl·LiCl and Related Exchange Reagents”, *Heterocycles*, *Heterocycles*, **2014**, *88*, 827.

Meiner Familie

“We choose to go to the Moon in this decade and do the other things, not because they are easy, but because they are hard!“

- John F. Kennedy -

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A. INTRODUCTION

1. OVERVIEW

"*In the 21st century, the field of chemistry will face more than just academic challenges. Indeed, our ability to devise straightforward and practical chemical syntheses is indispensable to the survival of our species.*"[1]

With this statement, *Ryoji Noyori* precisely summarizes the rising challenges chemical and pharmaceutical industry has to face nowadays. Increasing concerns about climate change, resource depletion, and environmental degradation has created new targets for the scientific community.[2] Advanced chemical processes must be economical, safe, environmentally benign, and resource- and energy-saving.[3] Thus, production of the myriad of substances that are required to serve the needs of society, stretching from the world of material science to health care, must address synthetic efficiency not only in terms of selectivity (chemo-, regio-, diastereo- and enantioselectivity) but increasingly in terms of atom economy, that is, in terms of maximizing the number of atoms of all raw materials that end up in the product.[4] Organometallic chemistry has already proven its potential to play an important role in the development of green chemistry.2 A plethora of very versatile reagents and synthetic transformations are provided and synthetic organic chemists can choose from an ever growing toolbox of organometallic derivatives, each possessing a unique reactivity and selectivity depending on the nature of the metal used.[5]

The reactivity of organometallic reagents is strongly determined by the polarity of the incorporated carbon-metal bond. An appropriate selection of the metal atom and the organic moiety creates versatile tools for specific synthetic applications.5 Due to their strongly polarized carbon-metal bond, organolithium reagents represent a highly reactive class of organometallics but are incompatible with sensitive functional groups.[6] In contrast, organoboron reagents have been established as air- and moisture-stable building blocks with a high functional group tolerance. However, their almost covalent carbon-boron bond enforces harsh conditions and highly developed catalytic systems for the reaction with electrophiles.[7] Organomagnesium, -copper and -zinc reagents can be considered as a compromise between these two extremes. Although *Grignard* reagents

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[1] R. Noyori, *Chem. Commun.* **2005**, 1807.
[2] R. H. Crabtree, *Organometallics* **2011**, *30*, 17.
[3] R. Noyori, *Green Chem.* **2003**, *5*, G37.
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[6] G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596.
[7] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

are highly reactive towards electrophiles, they show an excellent functional group tolerance at appropriate low temperatures.[8] Also organocopper reagents possess a well-balanced reactivity. They undergo smoothly reactions with various electrophilic substrates but still tolerate various versatile functional groups.[9] A main drawback is the thermal instability as well as the need of the preparation from other organometallic species such as organolithium or organomagnesium reagents.[10] The big advantages of organozinc reagents are their stability at elevated temperatures8 and the outstanding functional group tolerance.[11] The slightly lower reactivity compared to other organometallic reagents can readily be overcome by suitable transition metal catalysts readily facilitating reactions with electrophiles.[12] The availability of empty low-energy *p*-orbitals in organozinc reagents enables readily the interaction with *d*-orbitals of transition metals and thus leads to smooth transmetalation reactions.5[a,11a] For this reason, Pd-catalyzed *Negishi* coupling reactions usually proceed much faster and under milder conditions than the corresponding *Stille* or *Suzuki cross*-coupling reactions.5[b,13]

An elegant example for the utility of the *Negishi* cross-coupling is demonstrated with the stereoselective synthesis of β-carotene (Scheme 1). The key feature of this approach is the regio- and stereoselective zirconium-catalyzed methylalumination of terminal alkyne precursors, followed by transmetalation with $ZnCl_2$ and subsequent *Negishi* cross-coupling of the resulting vinylzinc intermediates with the appropriate vinyl halide electrophiles furnishing β-carotene in >99% stereoisomeric purity.[14]

[8] P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.
[9] a) P. Knochel, M. J. Rozema, C. E. Tucker, *Preparation of Highly Functionalized Copper Reagents* in *Practical Approach Series in Chemistry - Organocopper Reagents*, (Ed.: R. J. K. Taylor), Oxford University Press, **1993**, 348. b) *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**.
[10] a) *Organometallics in Organic Synthesis* (Ed.: E.-i. Negishi), Wiley, New York, **1980**. b) For halogen-copper exchange reactions, see: i) X. Yang, T. Rotter, C. Piazza, P. Knochel, *Org. Lett.* **2003**, *8*, 1229. ii) X. Yang, P. Knochel, *Synlett* **2004**, *1*, 81. iii) M. I. Calaza, X. Yang, D. Soorukram, P. Knochel, *Org. Lett.* **2004**, *8*, 1229. iv) X. Yang, A. Althammer, P. Knochel, *Org. Lett.* **2004**, *6*, 1665. c) For direct insertion of highly reactive copper, see: i) G. W. Ebert, R. D. Rieke, *J. Org. Chem.* **1984**, *49*, 5280. ii) R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 5056. iii) G. W. Ebert, R. D. Rieke, *J. Org. Chem.* **1988**, *53*, 4482.
[11] a) P. Knochel, N. Millot, A. L. Rodriguez, *Org. React.* **2001**, *58*, 417. b) *Organozinc Reagents* (Eds.: P. Knochel, P. Jones), Oxford University Press, New York, **1999**.
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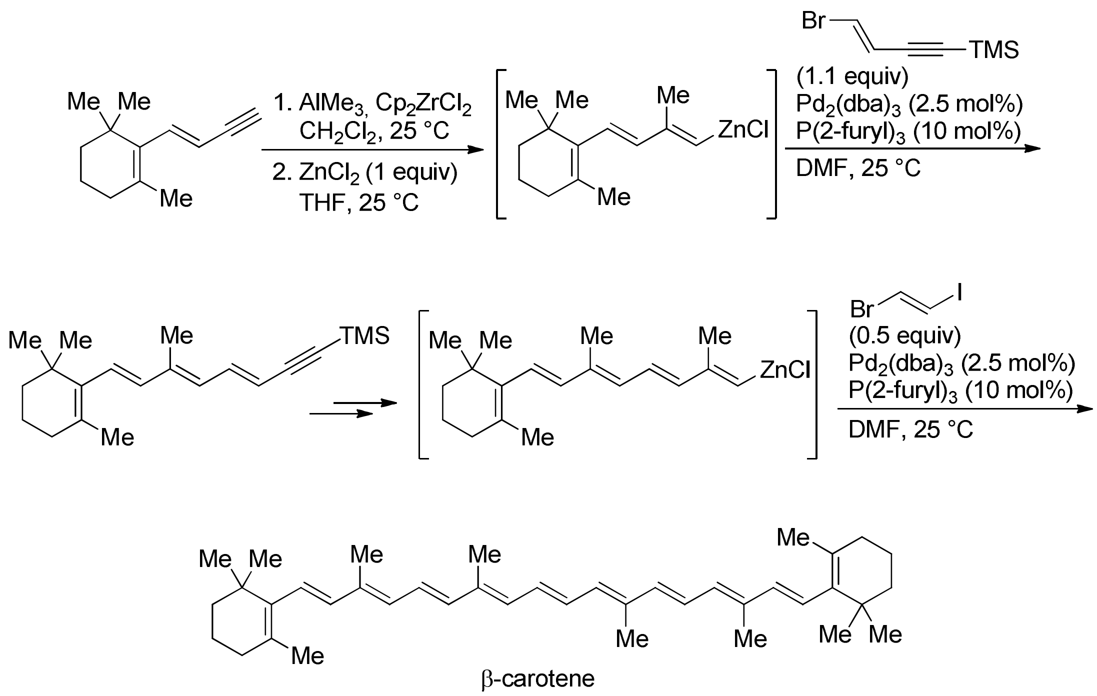
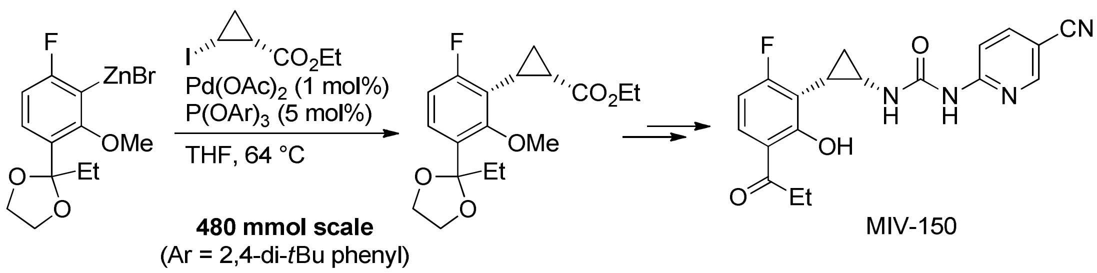
[13] a) E. Negishi, *Angew. Chem Int. Ed.* **2011**, *50*, 673. b) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem Int. Ed.* **2012**, *51*, 5062. c) V. F. Slagt, A. H. M. de Vries, J. G. de Vries, R. M. Kellog, *Org. Process Res. Dev.* **2010**, *14*, 30.
[14] F. Xeng, E.-i. Negishi, *Org. Lett.* **2001**, *3*, 719.



Scheme 1: Total synthesis of β-carotene using *Negishi* cross-couplings.

An impressive industrial application of a *Negishi* cross-coupling reaction is the synthesis of the HIV-reverse transcriptase inhibitor MIV-150 (Scheme 2) by the *Chiron* Corporation.[15] The reaction of the aryl zinc reagent with the enantiopure cyclopropyl iodide affords stereoselectively the key intermediate in 85 % yield.



Scheme 2: *Negishi* cross-coupling in the synthesis of HIV-reverse trancriptase inhibitor MIV-150.

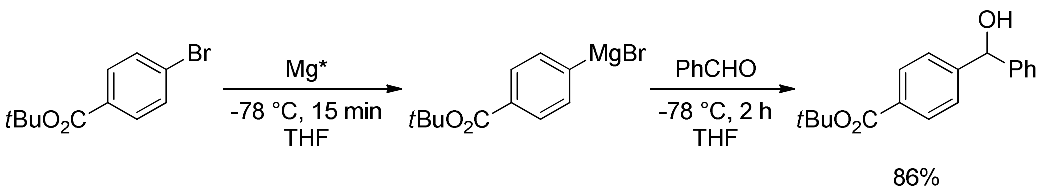
[15] S. Cai, M. Dimitroff, T. McKennon, M. Reider, L. Robarge, D. Ryckman, X. Shang, J. Therrien, *Org. Process Res. Dev.* **2004**, *8*, 353.

2. ORGANOMAGNESIUM REAGENTS

More than 100 years ago, *Victor Grignard* prepared organomagnesium compounds for the very first time.[16] These so called *Grignard* reagents turned out to be exceptionally versatile nucleophiles and are nowadays widely used in chemical laboratories and have even found their way into chemical industry.[17]

The direct insertion of magnesium metal into carbon-halogen bonds is still the most straightforward approach for the preparation of organomagnesium compounds.[17] The exact mechanism of this reaction is still not entirely elucidated, but radical pathways are generally accepted.[18] Despite the efficiency of the magnesium insertion in terms of atom economy4 the reaction suffers from a limited functional group tolerance since the standard protocol for the insertion is highly exothermic and normaly performed at the boiling point of the solvent (e.g. Et_2O or THF). Therefore the preparation in plant scale is accompanied with serious safety risks.[19]

These drawbacks have been elegantly bypassed by *Rieke* and coworkers using highly reactive magnesium powder (Mg*) prepared by the reduction of magnesium salts with lithium naphthalide. This methodology allowed the preparation of the organomagnesium reagents at very low temperatures and thus enabled the tolerance of very sensitive groups like nitriles and esters (Scheme 3).[20]

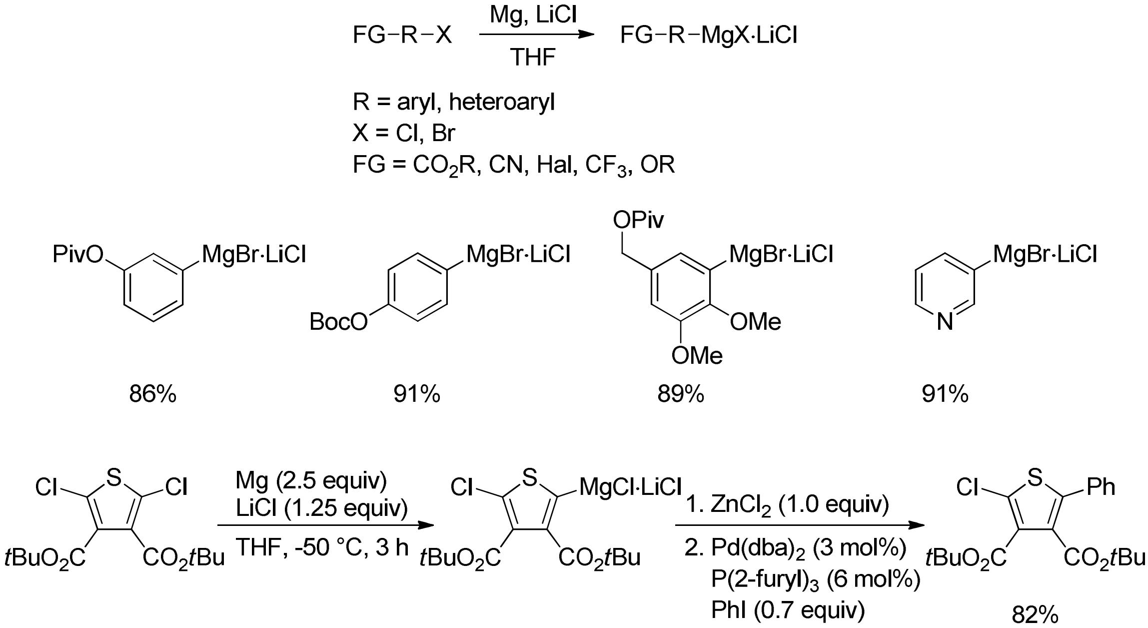


Scheme 3: Preparation and reactivity of a functionalized *Grignard* reagent using highly reactive *Rieke*-Mg (Mg*).

In order to avoid the drawback of the prior preparation of the highly active magnesium, *Knochel* and coworkers developed a methodology applying stoichiometric amounts of LiCl in the insertion reaction (Scheme 4).[21] This gives access to a range of

[16] V. Grignard, *Compt. Rend. Acad. Sci. Paris*, **1900**, *130*, 1322.
[17] a) *Handbook of Grignard Reagents* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **2000**. b) *Grignard Reagents, New Developments* (Ed.: H. G. Richey Jr.), Wiley-VCH, New York, **2000**. c) J. Wiss, M. Länzlinger, M. Wermuth, *Org. Proc. Res. Dev.* **2005**, *9*, 365.
[18] 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.
[19] M. C. Jones, *Plant and Operations Progress* **1989**, *8*, 200.
[20] a) R. D. Rieke, *Science* **1989**, *246*, 1260. b) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925. b) J. Lee, R. Verlade-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428. d) R. D. Rieke, *Aldrichchim. Acta* **2000**, *33*, 52.
[21] a) F. M. Piller, P. Appukuttan, 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.

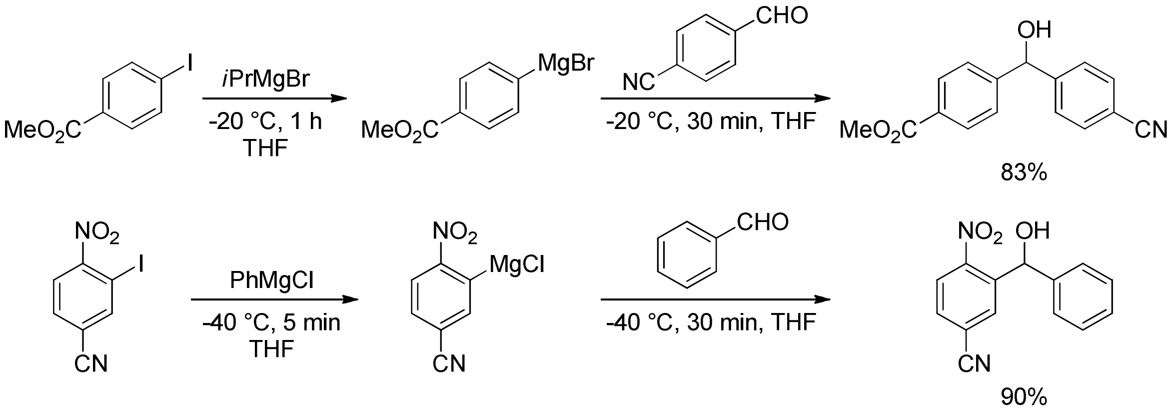
new functionalized aryl and heteroaryl magnesium species from the corresponding chlorides and bromides under mild reaction conditions.



Scheme 4: Preparation of functionalized organomagnesium reagents using Mg in the presence of LiCl.

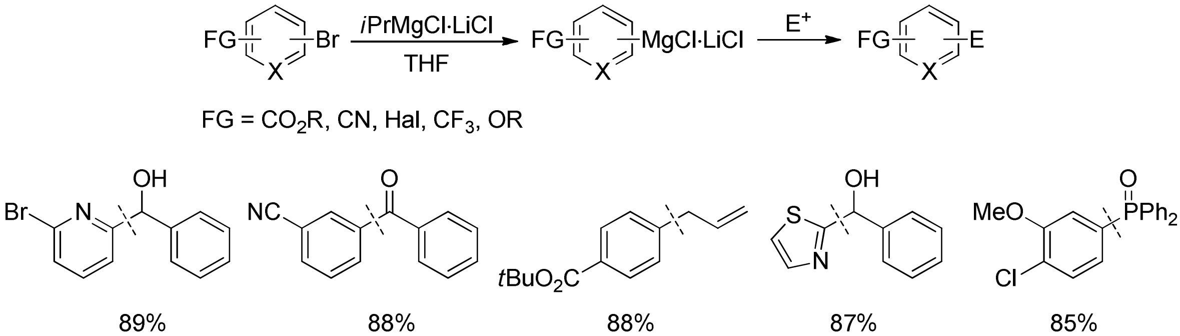
A more convenient preparation of organomagnesium compounds with high functional group tolerance, avoiding many of the flaws of the direct insertion, is the halogen-magnesium exchange reaction. The driving force for this reaction class is the formation of an organometallic reagent possessing a higher stability than the exchange reagent itself ($sp > sp^2_{vinyl} > sp^2_{aryl} > sp^3_{prim} > sp^3_{sec}$).[22] Based on the preliminary work of *Prévost*[23] and *Villieras*,[24] *Knochel* could impressively demonstrate the potential of the iodine-magnesium exchange with *i*PrMgBr and PhMgCl on substrates bearing sensitive functionalities (Scheme 5).[25]

[22] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.
[23] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[24] a) J. Villiéras, *Bull. Chem. Soc. Fr.* **1967**, *5*, 1520. b) J. Villiéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Chem. Soc. Fr.* **1986**, *24*, 470.
[25] 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.



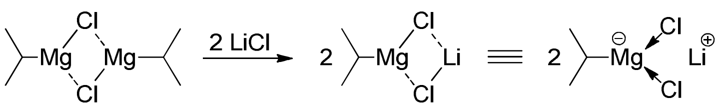
Scheme 5: Preparation and reactivity of functionalized *Grignard* reagents by iodine-magnesium exchange using *i*PrMgBr or PhMgCl.

This method could further be improved by the addition of stoichiometric amounts of LiCl to the exchange reagent *i*PrMgCl resulting in the formation of an organomagnesium species with the formal composition *i*PrMgCl·LiCl. Noteworthy, this so called Turbo-*Grignard* reagent shows a remarkably higher reactivity, broadening the scope of the exchange reaction. A huge variety of aromatic and heteroaromatic bromides could now be converted into the corresponding magnesium reagents. However, the increased reactivity does not limitate the functional group tolerance (Scheme 6).[26]



Scheme 6: Preparation and reactivity of functionalized *Grignard* reagents by bromine-magnesium exchange using the Turbo-*Grignard* reagent (*i*PrMgCl·LiCl).

The formation of a magnesium-lithium ate complex as intermediate of the Turbo-*Grignard* reagent leads to deaggregation of the organometal species and is assumed to be responsible for the higher solubility and the enhanced reactivity of the *Grignard* reagent (Scheme 7).[26]

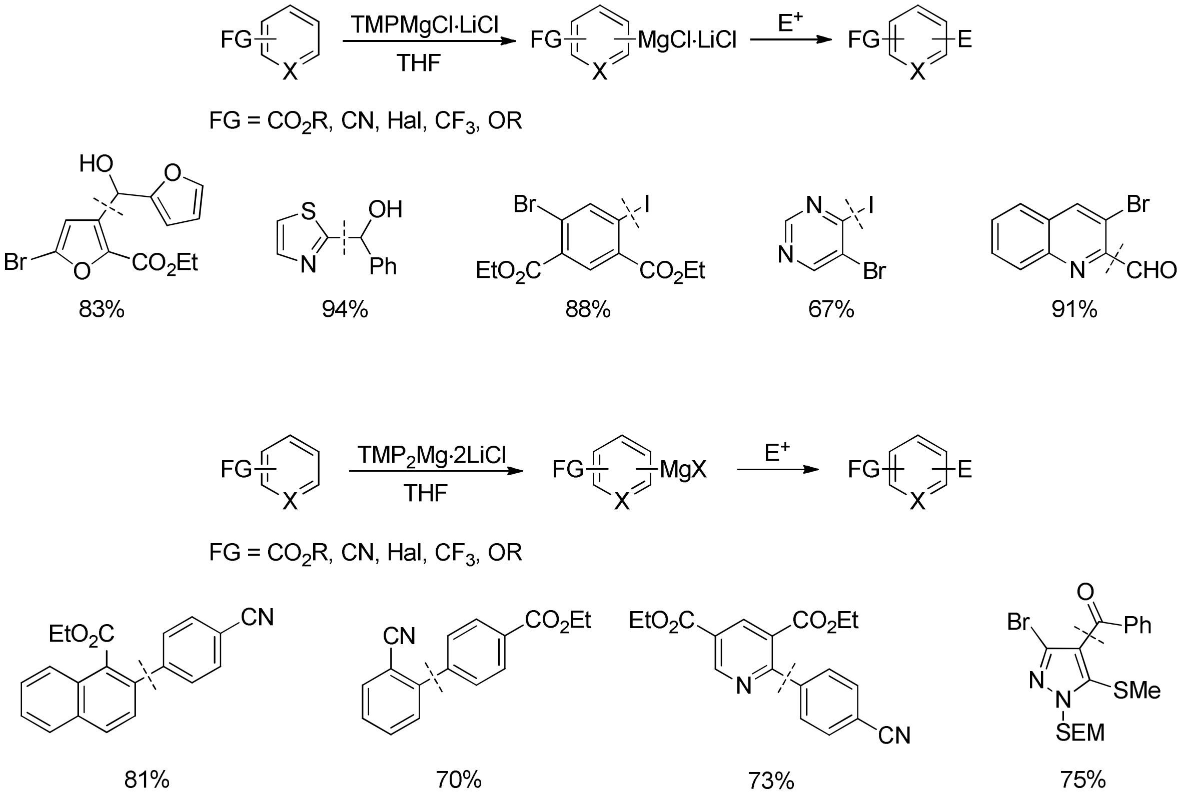


Scheme 7: Effect of LiCl on *Grignard* reagents.

[26] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *41*, 1610. b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159. c) H. Ren, P. Knochel, *Chem. Commun.* **2006**, 726. d) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543. e) F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, 2288.

Since electron-rich aromatic compounds resisted to undergo a bromine-magnesium exchange, reagents of type RMg_2•LiCl had been developed.[26b] Quantum calculations on exchange reactions indicated that the reaction becomes more likely when the exchange reagent's ate character is increased. Thus, *bis*-magnesium reagents of type RMg_2•LiCl complete the exchange reaction methodology on substrates where *i*PrMgCl•LiCl fails.[26b]

Besides these two halogen-metal interconversions, a direct metalation using magnesium amide bases is the third major pathway to magnesium organometallics.[27] The recently developed mixed lithium-magnesium amide bases TMPMgCl·LiCl and TMP_2Mg·2LiCl (Turbo-*Hauser* bases) give access to a large number of functionalized aromatic, heteroaromatic and vinylic organomagnesium reagents (Scheme 8).[28,29]



Scheme 8: Direct magnesiation using Turbo-*Hauser* bases TMPMgCl·LiCl and TMP_2Mg·2LiCl.

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27 a) L. Meunier, *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758. b) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295. c) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350. d) A. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.

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29 For a recent review article about metalation reactions using hindered amide bases, see: B. A. Haag, M. Mosrin, H. Ila, V. Malakhov, P Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.

3. ORGANOBORON REAGENTS

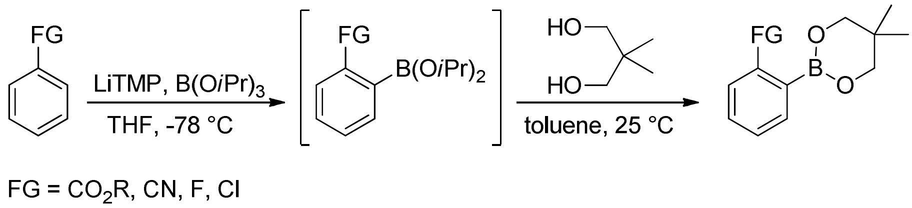
From the first isolation of an organoboron compound by *Frankland* in 1860[30] to the report of their palladium-catalyzed cross-coupling reactions with organic halides by *Suzuki* and *Miyaura* in 1979,[31] the chemistry of organoboron compounds has experienced a tremendous development. *Brown* and coworkers intensively explored the preparation and application of boron-containing compounds in organic synthesis.[32] For his pioneering work in this field, *Brown* received the *Nobel Prize* in 1979.

One of the most significant reasons for the success and the extensive use of organoboron compounds in modern organic synthesis is the highly covalent character of the carbon-boron bond and their high compatibility with a broad range of functional groups,[33] their water stability as well as their relatively low toxicity.[32] Hence, these reagents have emerged to a versatile class of synthons in organic chemistry.7[,32,34]

The most general route for the generation of organoboron reagents is the transmetalation reaction of various metalorganic species with trihalogenboranes or trialkoxyboranes like BCl_3 or $B(OMe)_3$.[35,36] Organoboron compounds with all kinds of organic groups, whether alkyl, aryl, alkenyl, or alkynyl can be obtained in this way. The first preparation of an organoborane by *Frankland* over a century ago used triethoxyborane and diethylzinc,[30,32] which was later superseded by the more readily prepared *Grignard* reagents. For metals significantly more electropositive than boron, the equilibrium of the transmetalation reactions lies entirely on the side of the organoborane

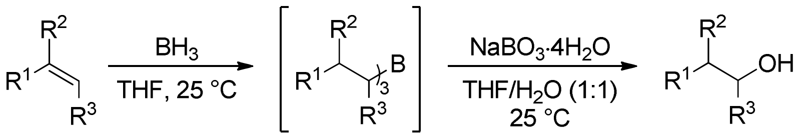
[30] a) E. Frankland, B. Duppa, *Proc. Royal Soc.* **1860**, *10*, 568. b) E. Frankland, *J. Chem. Soc.* **1862**, *15*, 363.
[31] N. Miyaura, A. Suzuki, *J. Chem. Soc., Chem. Commun.* **1979**, 866. b) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437.
[32] a) H. C. Brown, in *Boranes in Organic Chemistry*, Cornell University Press, New York, **1972**. b) A. Pelter, K. Smith, H. C. Brown, in *Borane Reagents*, Academic Press, New York, **1988**. c) D. S. Matteson, in *Stereodirected Synthesis with Organoboranes*, Springer, New York, **1995**. d) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879. e) T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2000**, *611*, 392. f) E. Tyrell, P. Brookes, *Synthesis* **2003**, 469. g) T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2003**, *680*, 3.
[33] a) S. Darses, T. Jeffery, J.-P. Gênet, J.-L. Brayer, J.-P. Demoute, *Tetrahedron Lett.* **1996**, *37*, 3857. b) D. Willis, R. M. Strongin, *Tetrahedron Lett.* **2000**, *41*, 6271. c) G. Manickam, A. D. Schluter, *Synthesis* **2000**, 442. d) J. W. Goodby, M. Hird, R. A. Lewis, K. J. Toyne, *Chem. Commun.* **1996**, 2719. e) B. U. Maes, R. Lemiere, R. Dommisse, K. Augustyns, A. Haemers, *Tetrahedron* **2000**, *56*, 1777. f) D. Ren, R. A. McClelland, *Can. J. Chem.* **1998**, *76*, 78.
[34] a) A. Suzuki, in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, 49. b) S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263. c) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147. d) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544. e) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176. f) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633. g) A. Suzuki, *J. Organomet. Chem.* **2002**, *653*, 83. h) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.
[35] J. Kristensen, M. Lysén, P. Vedsø, M. Begtrup, *Org. Lett.* **2001**, *3*, 1435.
[36] a) A. Michaelis, P. Becker, *Chem. Ber.* **1880**, *13*, 59. b) E. Krause, R. Nitsche, *Chem. Ber.* **1921**, *54*, 2784.

and the metal halide (order of reactivity: K, Na > Li > Mg > Al > Zn, Cd > Pb, Hg, Sn).[37] The ease of displacement of various groups X of BX_3 follows the order Hal > OR > NR_2.[38] Recently, *Vedsø* and *Begtrup* reported an efficient method for the synthesis of *ortho*-substituted arylboronic esters *via ortho*-lithiation and in *situ* trapping of the corresponding lithium species with triisopropyl borate (Scheme 9).[35]



Scheme 9: Preparation of organoboron reagents *via* transmetalation.

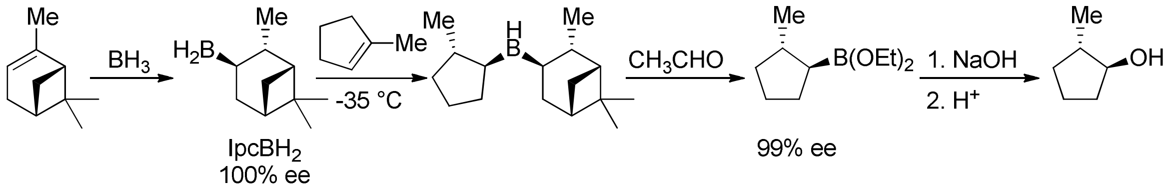
A very efficient method for the preparation of organoboron reagents is the hydroboration of unsaturated compounds.[39] The first hydroboration was reported by *Brown et al.* using diborane (B_2H_6) generated from BF_3 and $NaBH_4$.[40] With the years the hydroboration proved to be one of the most important transformations for the synthesis of complex molecules due to its high regioselectivity and the excellent functional group tolerance. The *syn*-addition of hydroboranes to unsaturated compounds occurs with predictable selectivity, wherein the boron adds preferentially to the least hindered carbon. This selectivity is enhanced if sterically demanding boranes like pinacolborane or 9-borabicyclo[3.3.1]nonane (9-BBN) are used. Combining the hydroboration with a subsequent oxidation of the newly formed borane gives readily access to *anti-Markovnikov* alcohols. The hydroboration/oxidation sequence constitutes a powerful method for the regio- and stereoselective synthesis of alcohols (Scheme 10).[41]



Scheme 10: Hydroboration and subsequent oxidation for the regio- and stereoselective synthesis of alcohols.

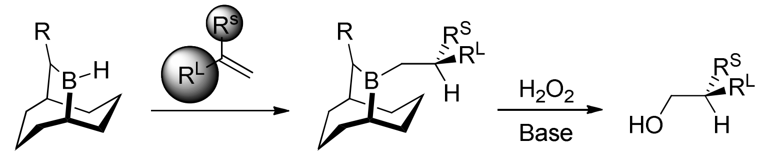
[37] G. E. Coates, M. L. H. Green, P. Powell, K. Wade, in *Principles of Organometallic Chemistry*, Methuen, London, **1968**.
[38] M. F. Lappert, M. K. Majumdar, *J. Organometallic Chem.,* **1966**, *6,* 316.
[39] H. C. Brown, *Organoboran Compounds in Organic Synthesis*, in *Comprehensive Organometallic Chemistry* (Ed.: G. Wilkinson), Pergamon Press, Oxford, **1982**, 111.
[40] a) H. C. Brown, B. C. Subba Rao, *J. Am. Chem. Soc.* **1956**, *78*, 5694. b) H. C. Brown, B. C. Subba Rao, *J. Org. Chem.* **1957**, *22*, 1136.
[41] G. W. Kabalka, T. M. Shoup, N. M. Goudgaon, *J. Org. Chem.* **1989**, 5930.

For the synthesis of chiral, enantiomerically enriched stereocenters in organoboron species, hydroboration is by far the most general method.[42] In the early days of organoboron chemistry, chirality was introduced *via* chiral auxiliaries obtained from the chiral pool.[43] Isopinene for instance can be converted into a chiral hydroborating reagent $IpcBH_2$ by addition of BH_3. A drawback of this methodology is the attachment of the chiral auxiliary *via* a boron-carbon bond, complicating its recycling. The chiral auxiliary needs to be removed prior subsequent carbon-carbon bond forming chemistry limitating this otherwise elegant chemistry (Scheme 11).



Scheme 11: Preparation and application of $IpcBH_2$.

Soderquist and coworkers developed an improved stoichiometric chiral auxiliary derived from 9-BBN-related derivatives for the hydroboration of a broad variety of olefins proceeding with extremely high selectivity.[44] Most importantly, transformation of the resulting boron-carbon bond can be accomplished without removal of the chiral auxiliary (Scheme 12).



R = Ph, TMS

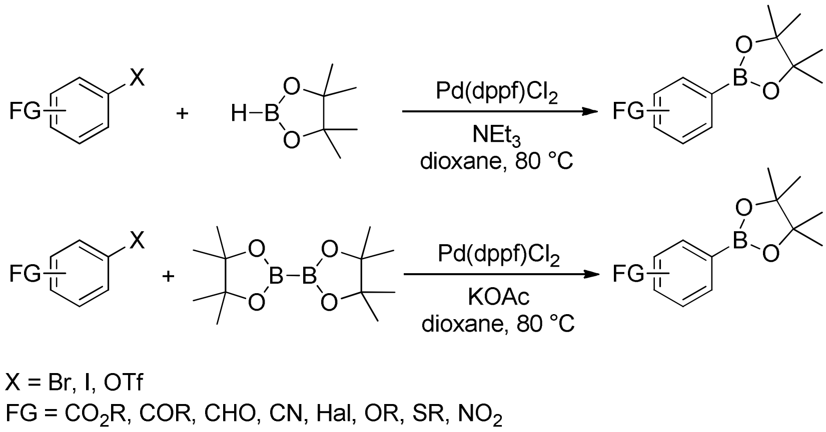
Scheme 12: Stereoselective hydroboration with *Soderquist's* chiral borane and subsequent oxidation.

In terms of a catalytic enantioselective process, *Hayashi et al.* described the use of catechol borane (1,3,2-benzodioxaborole, HBCat) as achiral hydroborating reagent in combination with a rhodium catalyst and the chiral ligand BINAP.[45]

Another convenient approach for the preparation of organoboron reagents is the transition metal-catalyzed borylation of aryl halides and triflates. The cross-coupling

[42] a) I. Beletskaya, A. Pelter, *Tetrahedron* **1997**, *53*, 4957. b) K. Burgess, M. J. Ohlmeyer, *Chem. Rev.* **1991**, *91*, 1179. c) A. M. Carroll, T. P. O'Sullivan, P. J. Guiry, *Adv. Synth. Catal.* **2005**, *347*, 609. d) H. C. Brown, in *Organic Syntheses via Boranes*, Wiley-VCH, London, **1975**.
[43] H. C. Brown, P. V. Ramachandran, *J. Organomet. Chem.* **1995**, *500*, 1.
[44] A. Z. Gonzalez, J. G. Roman, E. Gonzalez, J. Martinez, J. R. Medina, K. Matos, J. A. Soderquist, *J. Am. Chem. Soc.* **2008**, *130*, 9218.
[45] a) T. Hayashi, Y. Matsumoto, Y. Ito, *J. Am. Chem. Soc.* **1989**, *111*, 3426. b) T. Hayashi, Y. Matsumoto, Y. Ito, *Tetrahedron: Asymmetry* **1991**, *2*, 601.

reaction of these aryl derivatives with pinacolborane[46] or bis(pinacolato)diboron[47] in the presence of a palladium catalyst and a base enables readily the synthesis of highly functionalized arylboron compounds containing sensitive groups such as carbonyl, cyano or nitro (Scheme 13). By using more active catalytic systems *Miyaura* and *Fürstner* could also employ aryl chlorides as precursors.[48]

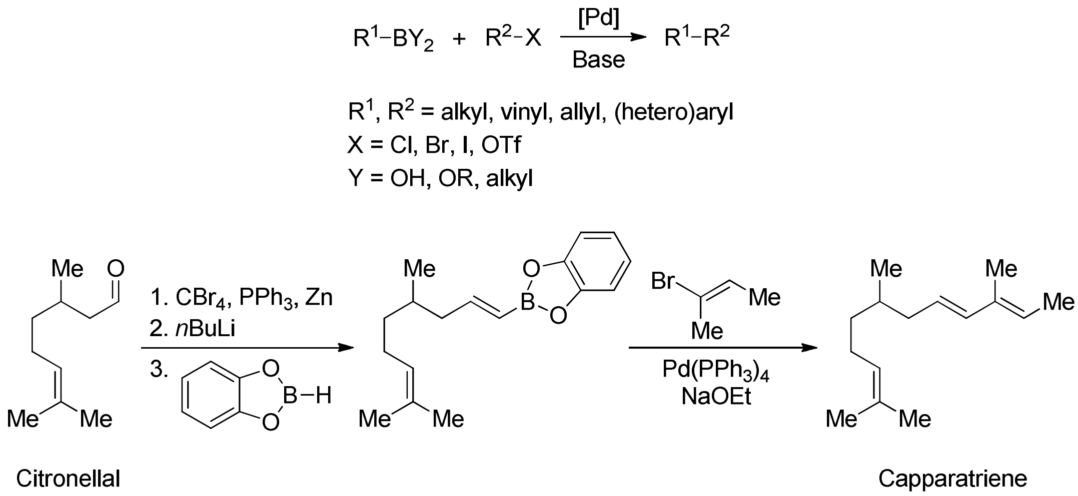


Scheme 13: Preparation of organoboron reagents *via* Pd-catalysed borylation of aryl halides and triflates.

Since *Suzuki* and *Miyaura* introduced in 1979 organoboron reagents into the realm of cross-coupling chemistry by demonstrating a palladium-catalysed reaction of 1-alkenyl-boranes with aryl and alkynyl halides in presence of a base,[31] this reaction has seen significant advancement and has become one of the most powerful carbon-carbon bond forming methods in organic synthesis (Scheme 14).[7,34,49] The availability of the reagents and the mild reaction conditions all contribute to the versatility of this reaction. The coupling reaction offers several additional advantages, such as being largely unaffected by the presence of water, tolerating a broad range of functional groups and proceeding generally regio- and stereoselective. Moreover, the inorganic by-product of the reaction is non-toxic and easily removed from the reaction mixture thereby making this reaction suitable not only for laboratories but also for industrial processes.[50] For instance, the

[46] a) M. Murata, S. Watanabe, Y. Masuda, *J. Org. Chem.* **1997**, *62*, 6458. b) M. Murata, T. Oyama, S. Watanabe, Y. Masuda, *J. Org. Chem.* **2000**, *65*, 164.
[47] a) T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508. b) T. Ishiyama, Y. Itoh, T. Kitano, N. Miyaura, *Tetrahedron Lett.* **1997**, *38*, 3447.
[48] a) T. Ishiyama, K. Ishida, N. Miyaura, *Tetrahedron* **2001**, *57*, 9813. b) A. Fürstner, G. Seidel, *Org. Lett.* **2002**, *4*, 541.
[49] a) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11. b) F.-X. Felpin, T. Ayad, S. Mitra, *Eur. J. Org. Chem.* **2006**, 2679. c) A. Suzuki, *Heterocycles* **2010**, *80*, 15. d) *Cross-Coupling Reactions – A Practical Guide* (Ed.: N. Miyaura), Springer, New York, **2002**. e) C. Torborg, M. Beller, *Adv. Synth.Catal.* **2009**, *351,* 3027. f) L. Ackermann, R. Born, *Angew. Chem. Int. Ed.* **2005**, *44*, 2444. g) L. Ackermann, *Synlett* **2007**, *4*, 507.
[50] A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147.

Suzuki-Miyaura coupling has been used in the total synthesis of Caparratriene, a natural product that is highly active against leukemia (Scheme 14).[51]

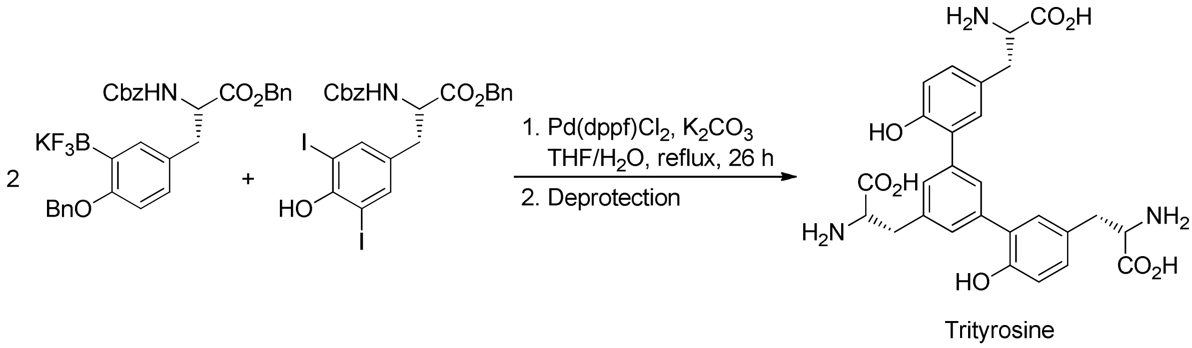


Scheme 14: Standard *Suzuki-Miyaura* cross-coupling and its application in the total synthesis of Capparatriene.

Until now, organoboronic acids[52] are the most frequently used reagents in the *Suzuki-Miyaura* cross-coupling reaction although they are far from ideal. For example, though there are currently over 450 boronic acids commercially available, many of these reagents are difficult to purify due to their waxy constitution. Moreover, boronic acids tend to form trimeric cyclic anhydrides (boroxines) which can influence the reaction stoichiometry. Thus, it is difficult to determine the concentration of boronic acid *versus* boroxine in a mixture. Consequently, many literature protocols for *Suzuki-Miyaura* cross-couplings employ excess of the boronic acid to ensure a complete conversion of the electrophilic component in the reaction.[53] Therefore, various boronic derivatives, such as trifluoroborates,[53,54] MIDA boronates[55] or DAN reagents[56] have been developed to overcome these drawbacks. The reagents exist as monomeric complexes with defined structures aiding for precise adjustment of stoichiometry.

[51] J. R. Vyvyan, E. A. Peterson, M. L. Stephan, *Tetrahedron Lett.* **1999**, *40*, 4947.
[52] a) N. Miyaura, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513. b) T. Ohe, N. Miyaura, A. Suzuki, *J. Org. Chem.* **1993**, *58*, 2201. c) D. Badone, M. Baroni, R. Cardamone, A. Ielmini, U. Guzzi, *J. Org. Chem.* **1997**, *62*, 7170. d) A. Zapf, M. Beller, *Chem. Eur. J.* **2000**, *6*, 1830.
[53] G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007,** *40*, 275.
[54] a) G. A. Molander, B. Canturk, *Angew. Chem. Int. Ed.* **2009**, *48*, 9240. b) A. Darses, J.-P. Genet, *Chem. Rev.* **2008**, *108*, 288.
[55] a) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961. b) E. P. Gillis, M. D. Burke. *Aldrichimica Acta*, **2009**, *42*, 17. c) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716.
[56] a) H. Noguchi, K. Hojo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 758. b) H. Noguchi, T. Shioda, C.-M. Chou, M. Suginome, *Org. Lett.* **2008**, *10*, 377. c) N. Iwadate, M. Suginome, *Org. Lett.* **2009**, *11*, 1899.

An impressive demonstration of biaryl synthesis employing trifluoroborates was disclosed with the preparation of Trityrosine.[57] The analogous boronic acid gave none of the double coupling product while the aryltrifluoroborate afforded the desired product in 74% overall yield (Scheme 15).



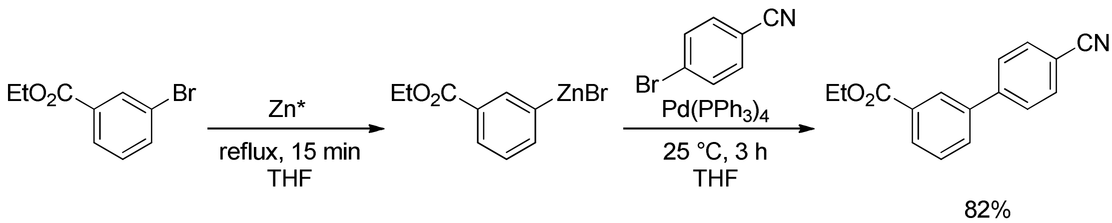
Scheme 15: Synthesis of Trityrosine employing trifluoroborates as nucleophile.

4. ORGANOZINC REAGENTS

In the first years after the discovery of the carbon-zinc bond by *Frankland*,[58] organozinc reagents found only little attention due to the excellent accessibility of organolithium compounds and the well-established procedures for the preparation of organomagnesium reagents described by *Grignard*.[16,59] Since organozinc compounds possess an intrinsically lower reactivity compared to the aforementioned analogs, they found only few applications in organic synthesis, such as the *Simmons-Smith* cyclopropanation reaction[60] or the *Reformatsky* reaction of zinc enolates.[61] However, one of the main advantages of organozinc reagents is the significantly higher tolerance of functional groups present in both the organometallic substrate and the electrophile. This can be explained by the higher covalent character of the carbon-zinc bond in comparison to the carbon-magnesium or carbon-lithium bond. For this reason, organozinc reagents can be handled at elevated temperatures not tolerated by the corresponding *Grignard* or organolithium reagents.5[a,11,62]

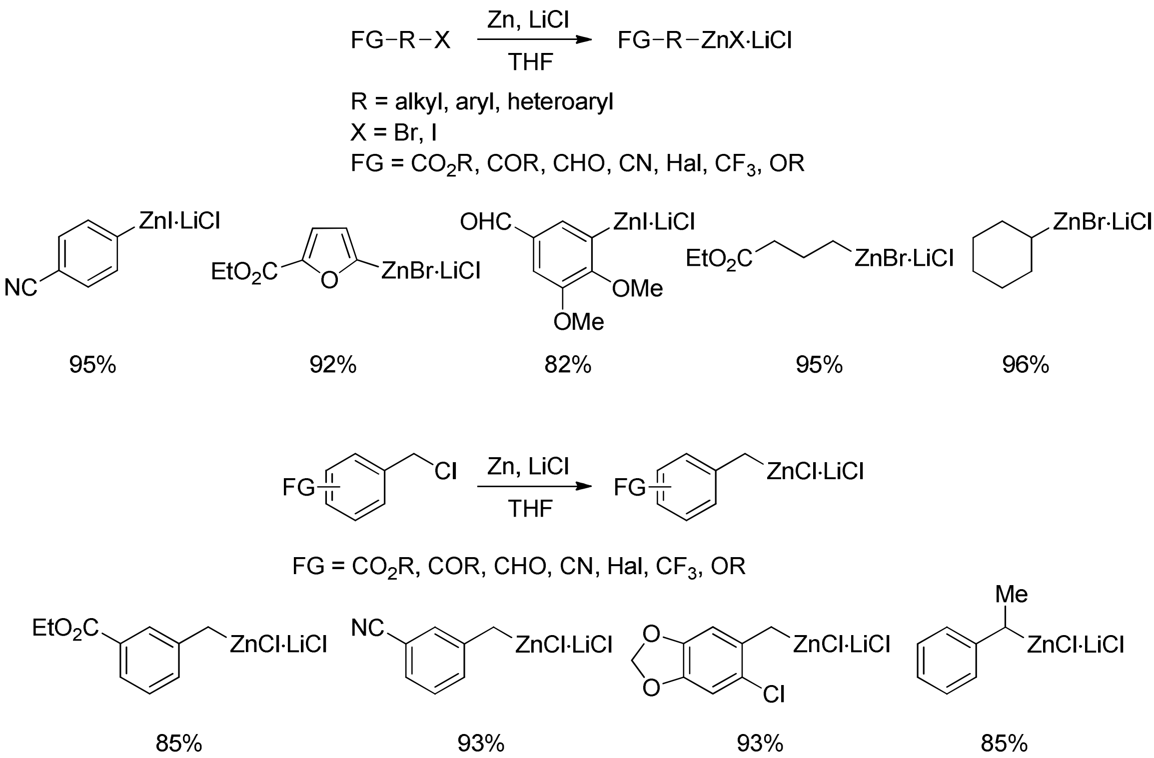
[57] O. Skaff, K. A. Jollioffe, C. A. Hutton, *J. Org. Chem.* **2005**, *70*, 7353.
[58] a) E. Frankland, *Liebigs Ann. Chem.* **1848**, *71*, 171. b) E. Frankland, *J. Chem. Soc.* **1848**, *2*, 263.
[59] V. Grignard, *Ann. Chim.* **1901**, *24*, 433.
[60] a) H. E. Simmons, T. L. Cairns, A. Vladiuchick, C. M. Hoiness, *Org. React.* **1972**, *20*, 1. b) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323. c) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 5323. d) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977.
[61] a) S. Reformatsky, *Chem. Ber.* **1887**, *20*, 1210, b) S. Reformatsky, *Chem. Ber.* **1895**, *28*, 2842. c) R. Ocampo, *Tetrahedron* **2004**, *60*, 9325. d) A, Fürstner, *Angew. Chem. Int. Ed.* **1993**, *32*, 164.
[62] a) P. Knochel, F. Langer, M. Rottländer, T. Stüdemann, *Chem. Ber.* **1997**, *130*, 387. b) P. Knochel, J. J. Almena Perea, P. Jones, P. *Tetrahedron* **1998**, *54*, 8275.

Similarly to organomagnesium compounds, the most common method for the direct synthesis of organozinc reagents is the insertion of zinc powder into organic halides.[11,62c] However, the reaction suffers from the use of expensive organic iodides and elevated reaction temperatures. To avoid these drawbacks, *Rieke et al.* used highly active zinc (Zn*), prepared by reduction of $ZnCl_2$ with lithium naphthalide to obtain functionalized organozinc reagents from less reactive arylbromides (Scheme 16).[20b-d,63]



Scheme 16: Preparation and reactivity of a functionalized organozinc reagent using highly reactive *Rieke*-Zn (Zn*).

In 2006, *Knochel* and coworkers reported a LiCl-facilitated insertion of zinc metal into organic halides.[64] Besides aromatic and heteroaromatic bromides and iodides, the presence of stoichiometric amounts of LiCl enabled also the use of alkyl bromides and benzyl chlorides in insertion reactions (Scheme 17).

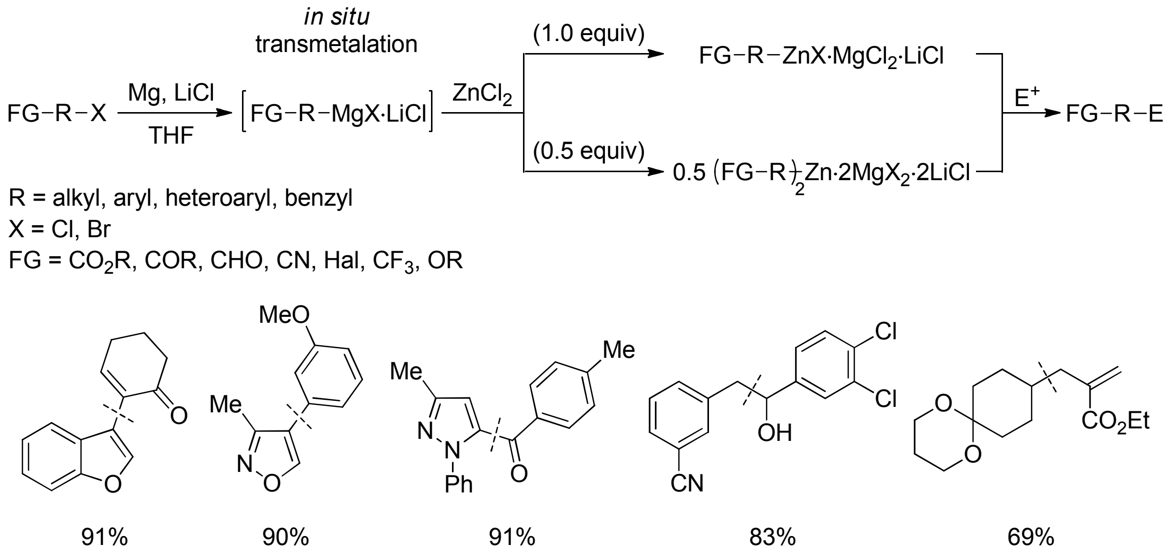


Scheme 17: Preparation of functionalized organozinc reagents using Zn in the presence of LiCl.

[63] a) R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4324. b) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445.

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

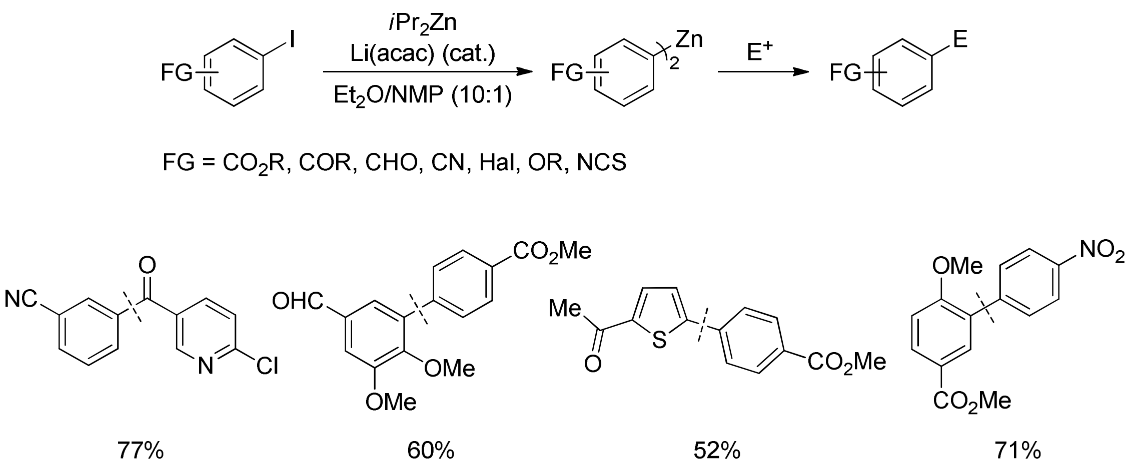
By using a LiCl-mediated magnesium insertion in the presence of $ZnCl_2$ *Knochel et al.* were able to further improve the aforementioned insertion reaction.[21,65] Due to the higher reduction potential of magnesium, the insertion times could be shortened and aryl bromides as well as heteroaryl bromides and chlorides replaced the corresponding iodides as cheaper starting materials. Furthermore, by using only 0.5 equivalents of $ZnCl_2$ more reactive diorganozinc reagents could be obtained (Scheme 18).



Scheme 18: Preparation and reactivity of functionalized organozinc reagents using LiCl-mediated Mg-insertion in the presence of $ZnCl_2$.

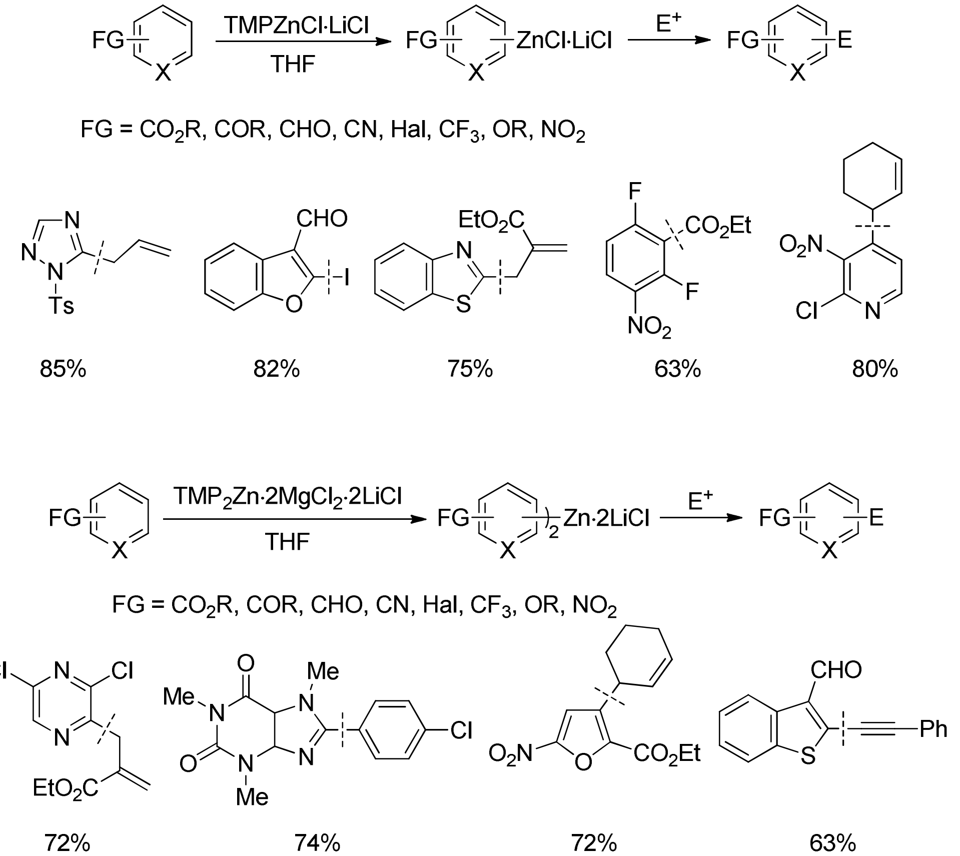
Another convenient approach for the preparation of diorganozinc reagents is the iodine-zinc exchange reaction using dialkylzinc species such as diethylzinc or diisopropylzinc. A range of alkyl iodides reacted with diethylzinc in the presence of Cu(I) salts to the corresponding dialkylzinc reagents.[66] Moreover, this methodology could be improved by using Li(acac) as catalytic additive. Thus, highly functionalized aryl and heteroaryl iodides could be converted into the corresponding diorgano zinc species and trapped with a broad range of electrophiles (Scheme 19).[67]

[65] 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.
[66] a) M. J. Rozema, A. Sidduri, P. Knochel, *J. Org. Chem.* **1992**, *57*, 1956. b) M. J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 3115.
[67] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.



Scheme 19: Preparation and reactivity of functionalized zinc reagents by iodine-zinc exchange using *i*Pr_2Zn.

Inspired by the work on the Turbo-*Hauser* bases, *Knochel et al.* developed the mild and chemoselective bases $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ and TMPZnCl·LiCl for hydrogen-metal interconversion on sensitive substrates. A variety of sensitive aromatic and heteroaromatic compounds could be smoothly zincated and subsequently functionalized. (Scheme 20).[29,68]



Scheme 20: Direct zincation using TMPZnCl·LiCl and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.

[68] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685. b) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837. c) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406. d) A. Unsinn, P. Knochel, *Chem. Commun.* **2012**, *48*, 2680.

5. ADAMANTANE AND ITS CHEMISTRY

The originality of adamantane structure showing also in the properties of its derivatives is the main factor governing the constant interest to the chemistry of this compound.[69] The development of the adamantane chemistry makes it possible both to solve a series of theoretical problems and to design molecules of substances promising for the practical application in the fields of medicine, supramolecular chemistry, nanotechnologies, etc.[70] Thus, adamantane derivatives found numerous applications in medicinal chemistry and drug development. No other singular hydrocarbon moiety (apart from the methyl group) is as successful as adamantane in improving or providing pharmacological activity for pharmaceuticals. Having the "lipophilic bullet" (adamantane is assumed to provide the critical lipophilicity) readily available as an "add-on" for known pharmacophors, it was used for example in the modification of hypoglycemic sulfonylureas,[71] anabolic steroids,[72] and nucleosides.[73] The adamantane modifications were chosen to enhance lipophilicity and stability of the drugs, thereby improving their pharmacokinetics. Aminoadamantanes, such as Amantadine,[74] Rimantadine,[75] or Tromantadine,[76] are *anti-Influenza A* agents and were among the first compounds on the pharmaceutical market containing an adamantyl moiety (Figure 1).[77]

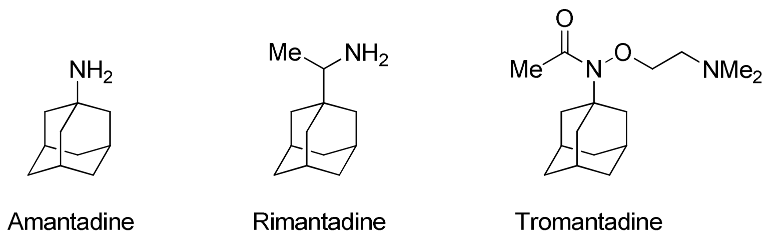


Figure 1: Pharmaceutical active substances containing an adamantyl moiety.

The aminoadamantanes are synthetic drugs that have not been inspired by natural products like numerous other drugs. There are, however, also natural products that incorporate the adamantane skeleton, showing interesting biological properties (Figure 2).

[69] G. A. Mansoori, *Adv. Chem. Phys.* **2007**, *136*, 207.
[70] E. A. Shokova, V. V. Kovalev, *Russ. J. Org. Chem.* **2012**, *48*, 1007.
[71] K. Gerzon, E. V. Krumalns, R. L. Brindle, F. J. Marshall, M. A. Root, *J. Med. Chem.* **1963**, *6*, 760.
[72] R. T. Rapala, R. J. Kraay, K. Gerzon, *J. Med. Chem.* **1965**, *8*, 580.
[73] K. Gerzon, D. Kau, *J. Med. Chem.* **1967**, *10*, 189.
[74] W. L. Davies, R. R. Grunert, R. F. Haff, J. W. McGahen, E. M. Neumayer, M. Paulshock, J. C. Watts, T. R. Wood, E. C. Hermann, C. E. Hoffmann, *Science* **1964**, *144*, 862.
[75] A. Tsunoda, H. F. Maassab, K. W. Cochran, W. C. Eveland, *Antimicrob. Agents Chemother.* **1965**, 553.
[76] a) D. Fanta, *Wien. Med. Wochenschr.* **1976**, *126*, 315. b) K. S. Rosenthal, M. S. Sokol, R. L. Ingram, R. Subramanian, R. C. Fort, *Antimicrob. Agents Chemother.* **1982**, *22*, 1031.
[77] L. Wanka, K. Iqbal, P. R. Schreiner, *Chem. Rev.* **2013**, *113*, 3516.

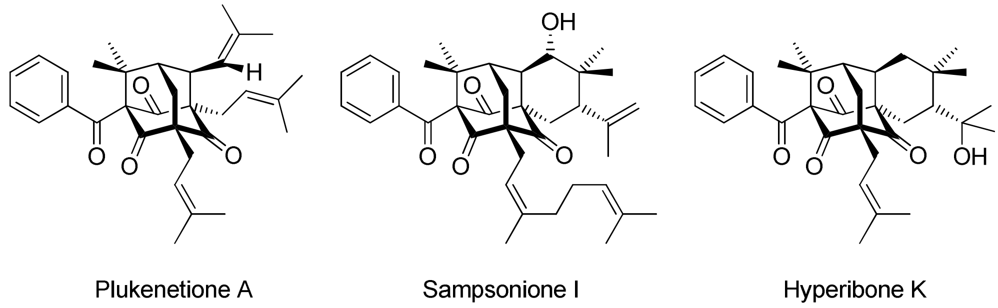


Figure 2: Naturally occurring substrates bearing an adamantyl moiety.

Plukenetione A for example was first isolated from *Clusia plukenetii* in 1996[78] and displayed cytotoxicity in a panel of cell lines for different cancer entities.[79] Also Sampsonione I, isolated from *Hypericum sampsonii*, showed cytotoxicity toward a P388 cell line.[80] However, Hyperibone K, isolated from the Uzbek medicinal plant *Hypericum scrabum*, provided only moderate cytotoxicity in two human cancer cell lines,[81] and no *anti*-HIV activity.

Noteworthy, the addition of adamantane moieties increases the permeability of the modified compounds through the blood-brain barrier.[82] Therefore, targets of the central nervous system are today most promising both academically and commercially. With the discovery that Amantadine gives symptomatic benefits in *Parkinson* disease[83] and the application of Memantine for the treatment of *Alzheimer* disease,[84] two neurodegenerative diseases of increasing importance in the aging society are being addressed with structurally remarkably simple adamantane derivatives (Figure 3).

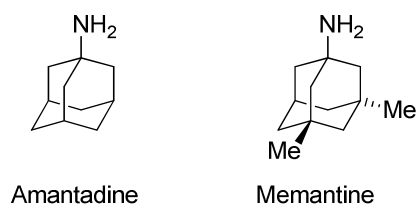


Figure 3: Simple adamantane derivatives as pharmaceuticals against *Parkinson* and *Alzheimer* disease.

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[78] G. E. Henry, H. Jacobs, C. M. S. Carrington, S. McLean, W. F. Reynolds, *Tetrahedron Lett.* **1996**, *37*, 8663.
[79] D. Diaz-Carballo, S. Malak, W. Bardenheuer, M. Freistuehler, H. Peter Reusch, *Bioorg. Med. Chem.* **2008**, *16*, 9635.
[80] L. H. Hu, K. Y. Sim, *Org. Lett.* **1999**, *1*, 879.
[81] N. Tanaka, Y. Takaishi, Y. Shikishima, Y. Nakanishi, K. Bastow, K.-H. Lee, G. Honda, M. Ito, Y. Takeda, O. K. Kodzhimatov, O. Ashurmetov, *J. Nat. Prod.* **2004**, *67*, 1870.
[82] a) K. Gerzon, D. J. Tobias, R. E. Holmes, R. E. Rathbun, R. W. Kattau, *J. Med. Chem.* **1967**, *10*, 603. b) P. A. Swift, M. L. Stagnito, G. B. Mullen, G. C. Palmer, V. S. Georgiev, *Eur. J. Med. Chem.* **1988**, *23*, 465.
[83] R. S. Schwab, A. C. England, Jr., D. C. Poskanzer, R. R. Young, *J. Am. Med. Assoc.* **1969**, *208*, 1168.
[84] a) S. K. Sonkusare, C. L. Kaul, P. Ramarao, *Pharmacol. Res.* **2005**, *51*, 1. b) S. A. Lipton, *Nat. Rev. Drug Discovery* **2006**, *5*, 160. c) C. G. Parsons, W. Danysz, G. Quack, *Amino Acids* **2000**, *19*, 157. d) W. Danysz, C. G. Parsons, G. Quack, *Amino Acids* **2000**, *19*, 167.

An emerging field with respect to the application of adamantane derivatives is the inhibition of enzymes using adamantane based scaffolds. Most important are the DPP-IV inhibitors Vildagliptin and Saxagliptin,[85] that currently enter the multibillion dollar market of diabetes management (Figure 4).

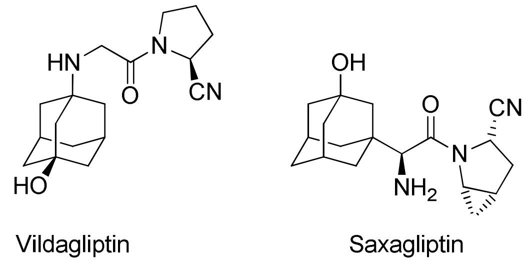


Figure 4: Adamantane derivatives as pharmaceuticals against diabetes.

Moreover, there are three classes of adamantane derivatives of relevance in cancer research. The add-on strategy is followed by adamantane derivatives of cisplatin (e.g. LA-12) and Adaphostin. Adamantyl retinoids (e.g. CD437) however represent an alternative strategy to fight cancer cell proliferation (Figure 5).

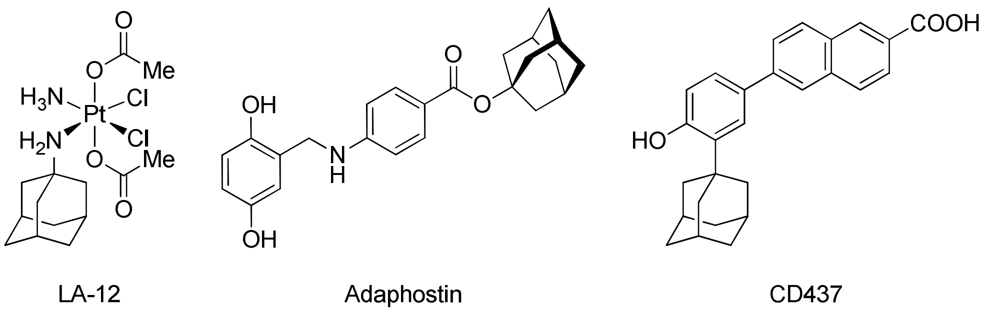


Figure 5: Adamantane derivatives as pharmaceutically active substrates against cancer.

LA-12 was found to provide a higher degree of cytotoxicity against both cisplatin-sensitive and cisplatin-resistant ovarian cancer cells compared to other cisplatin-analogous substrates.[86] Furthermore, Adaphostin is the adamantyl ester of the protein tyrosine kinase inhibitor AG957.[87] Both AG957 and Adaphostin are classified as tyrphostins (tyrosine phosphorylation inhibitors) and were shown to induce chronic

[85] a) E. B. Villhauer, J. A. Brinkman, G. B. Naderi, B. F. Burkey, B. E. Dunning, K. Prasad, B. L. Mangold, M. E. Russell, T. E. Hughes, *J. Med. Chem.* **2003**, *46*, 2774. b) D. J. Augeri, J. A. Robl, D. A. Betebenner, D. R. Magnin, A. Khanna, J. G. Robertson, A. Wang, L. M. Simpkins, P. Taunk, Q. Huang, S.-P. Han, B. Abboa-Offei, M. Cap, L. Xin, L. Tao, E. Tozzo, G. E. Welzel, D. M. Egan, J. Marcinkeviciene, S. Y. Chang, S. A. Biller, M. S. Kirby, R. A. Parker, L. G. Hamann, *J. Med. Chem.* **2005**, *48*, 5025. c) A. Barnett, *Int. J. Clin. Pract.* **2006**, *60*, 1454.

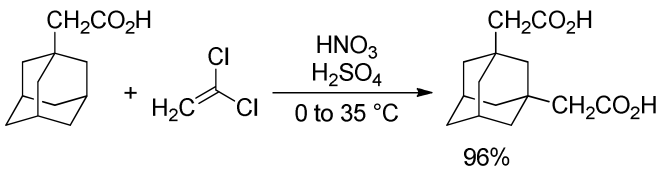
[86] A. Kozubik, V. Horvath, L. Svihalkova-Sindlerova, K. Soucek, J. Hofmanova, P. Sova, A. Kroutil, F. Zak, A. Mistr, J. Turanek, *Biochem. Pharmacol.* **2005**, *69*, 373.

[87] A. Levitzki, E. Mishani, *Annu. Rev. Biochem.* **2006**, *75*, 93.

myelogenous leukemia cell death.[88] The adamantyl-based retinoid CD437 shows high activity against a broad spectrum of cancers, including lung, prostate, ovarian, breast, melanoma and leukemia.[89]

The synthesis of adamantane derivatives is commonly based on the application of well known efficient procedures of selective monofunctionalization of adamantane and on the availability of its polyfunctional derivatives with the same substituents at the bridgehead positions.[90] The synhesis of adamantyl derivatives includes mainly two approaches: selective functionalization of tertiary C–H bonds in mono- and polysubstituted adamantanes and the selective modification of functional groups on adamantane derivatives.

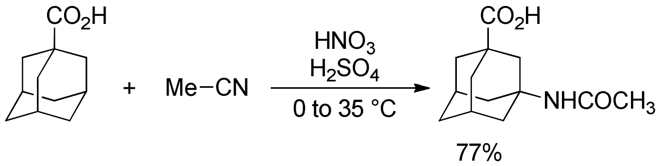
Among the methods of activation of the tertiary C–H bond in substituted adamantane derivatives with the use of nitric acid, the application of the nitrating mixture HNO_3/H_2SO_4 found the widest spread. In this mixture an efficient single-electron oxidant NO_2^+ is generated *in situ*. The reaction most probably proceeds *via* a single-electron transfer mechanism (SET mechanism) with the formation of adamantyl cation-radicals that can be trapped by various nucleophiles. Thus, the use of 1,1-dichloroethene as a nucleophile introduces a fragment of the acetic acid onto the bridgehead position of the adamantane frame in almost quantitative yield (Scheme 21).[91]



Scheme 21: Functionalization of 1-adamantlyacetic acid *via* SET and subsequent trapping with 1,1-dichloroethene as electrophile.

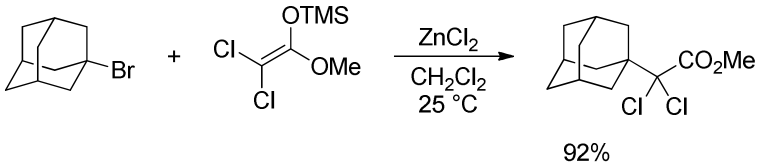
Under similar conditions, 1-adamantanecarboxylic acid can be converted to the corresponding acetylamino derivative by using acetonitrile as nucleophile in the HNO_3–H_2SO_4 medium. The bifunctional derivative has been obtained in 77% yield (Scheme 22).[92]

[88] P. A. Svingen, A. Tefferi, T. J. Kottke, G. Kaur, V. L. Narayanan, E. A. Sausville, S. H. Kaufmann, *Clin. Cancer Res.* **2000**, *6*, 237.
[89] a) B. Charpentier, J. M. Bernardon, J. Eustache, C. Millois, B. Martin, S. Michel, B. Shroot, *J. Med. Chem.* **1995**, *38*, 4993. b) L. Altucci, H. Gronemeyer, *Nat. Rev. Cancer* **2001**, *1*, 181. c) L. Altucci, M. D. Leibowitz, K. M. Ogilvie, A. R. de Lera, H. Gronemeyer, *Nat. Rev. Drug Discov.* **2007**, *6*, 793.
[90] a) R. C. Fort, in *Adamantane. The Chemistry of Diamond Molecules*, Marcel Dekker, New York, **1976**. b) I. K. Moiseev, N. V. Makarova, M. N. Zemtsova, *Usp. Khim.* **1999**, *68*, 1102.
[91] a) L. N. Butenko, P. A. Protopopov, V. E. Derbisher, A. P. Khardin, *Synth. Commun.* **1984**, *14*, 113. b) S. S. Novikov, A. P. Khardin, L. N. Butenko, I. A. Novakov, S. S. Radchenko, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, *25*, 2597.
[92] S. S. Novikov, A. P. Khardin, L. N. Butenko, I. A. Kulev, I. A. Novakov, S. S. Radchenko, S. S. Burdenko, *Zh. Org. Khim,***1980**, *16*, 1433.



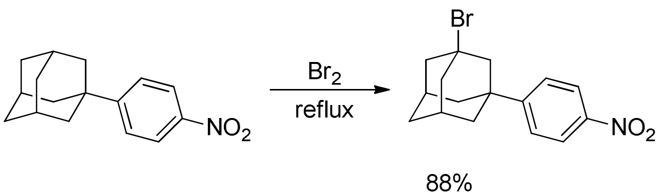
Scheme 22: Functionalization of 1-adamantanecarboxylic acid *via* SET and subsequent trapping with acetonitrile as electrophile.

Moreover, the treatment of 1-bromoadamantane with 1,2-diethoxy-1,2-bis(trimethyl-siloxy)ethene in dry CH_2Cl_2 in the presence of catalytic amounts of $ZnCl_2$ gives the desired α,α-dichloroester in excellent yield (Scheme 23).



Scheme 23: $ZnCl_2$-promoted addition of 1,2-diethoxy-1,2-bis(trimethylsiloxy)ethene to 1-bromo-adamantane.

Adamantane is readily brominated at elevated temperatures with liquid bromine forming 1-bromoadamantane.[93] The major drawback of this methodology is the poor functional group tolerance. The bromination of functionalized adamantane derivatives succeded without catalysts only with a few compounds such as 1-adamantylacetic acid,[94] 1-(4-nitrophenyl)adamantane,[95] or 1-(α-acetylamino)ethyladamantane[96] (Scheme 24).

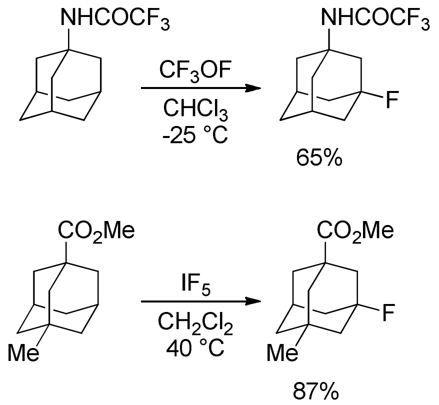


Scheme 24: Bromination of 1-(4-nitrophenyl)adamantane.

However, bromination of the 1-adamantanecarboxylic acid requires already a catalyst to furnish the corresponding bromo-derivative in good yield. 3-Bromo-1-adamantane-carboxylic acid has been obtained in 68% yield by treating 1-adamantane-carboxylic acid with anhydrous bromine in the presence of $AlBr_3$.[97]

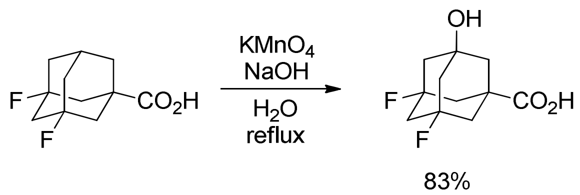
[93] H. Stetter, M. Schwarz, A. Hirschhorn, *Chem. Ber.* **1959**, *92*, 1629.
[94] K. Bott, *Chem. Ber*. **1968**, *101*, 564.
[95] a) F. N. Stepanov, E. I. Dikolenko, G. I. Danilenko, *Zh. Org. Khim.* **1966**, *2*, 640. b) W. Fisher, C. F. Grob, H. Katayama, *Helv. Shim. Acta* **1976**, *59*, 1953.
[96] P. S. Manchand, R. L. Cerruti, J. A. Martin, C. H. Hill, J. H. Merrett, E. Keech, R. B. Belshe, E. V. Connell, I. S. Sim, *J. Med. Chem.* **1990**, *33*, 1992.
[97] H. Stetter, J. Mayer, *Chem. Ber.* **1962**, *95*, 667.

Furthermore, by treating adamantane derivatives with fluorooxytrifluoromethane (CF_3OF) under conditions preventing radical processes (in the dark or in the presence of radical inhibitors) the tertiary position of the adamantane framework undergoes a selective fluorination.[98] Besides CF_3OF, also IF_5 proved to be an effective fluorinating agent.[99] Substituted adamantane derivatives are only monofluorinated, whereas the unsubstituted adamantane reacts with IF_5 to both mono- and difluoro derivatives depending on the amount of the fluorinating reagent (Scheme 25).



Scheme 25: Fluorination of adamantane derivatives using CF_3OF, and IF_5.

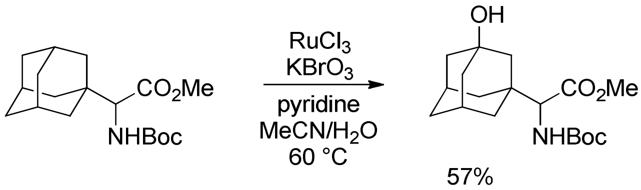
The hydroxylation of the tertiary C–H bonds in functionalized adamantane derivatives can be performed with oxidation systems containing metal complexes or salts. Thus, potassium permanganate in a 2% NaOH solution converts 3,5-difluoroadamantane-1-carboxylic acid to the corresponding hydroxyl derivative in 83% yield (Scheme 26).[94]



Scheme 26: Hydroxylation of adamantane derivatives using $KMnO_4$/NaOH.

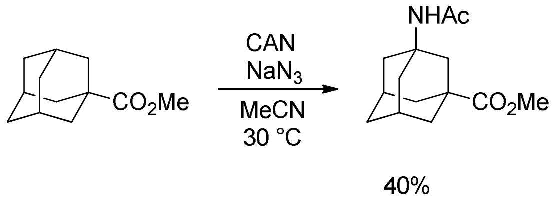
Recently an efficient procedure has been developed for the selective hydroxylation of tertiary C–H bonds applying RuO_4 as oxidant.[100] The latter is generated *in situ* under the reaction conditions and is responsible for the selectivity of the process. The generation of RuO_4 from catalytic amounts of $RuCl_3$ is performed by stoichiometric amounts of the cheap oxidant $KBrO_3$. The procedure permits the hydroxylation of substrates with various functional groups like ester, oxazolidine, carbamate or sulfamate (Scheme 27).

[98] D. H. R. Barton, R. H. Hesse, R. E. Markwell, M. M. Pechet, H. T. Toh, *J. Am. Chem. Soc.* **1976**, *98*, 3034.
[99] S. Hara, M. Aoyama, *Synthesis* **2008**, 2510.
[100] E. McNeill, J. Du Bois, *J. Am. Chem. Soc.* **2010**, *132*, 10202.



Scheme 27: Hydroxylation of adamantane derivatives using RuO_4.

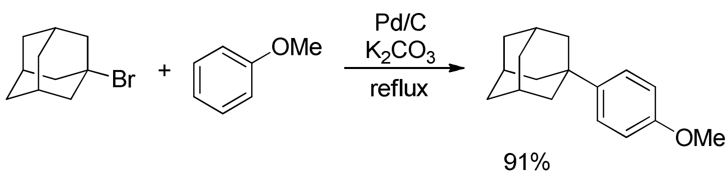
An efficient system for the preparation adamantylacetamides proved to be a mixture of cerium ammonium nitrate (CAN) with sodium azide in acetonitrile (Scheme 28).[101] The corresponding alcohols are formed as side products.



Scheme 28: Amidation of adamantane derivatives using CAN/NaN_3.

Friedel-Crafts alkylation of aromatics with diverse alkylating agents including tertiary alkyl halides has been extensively investigated.[102] Also the related adamantylation of aromatics is of great interest since an increasing variety of pharmaceuticals containing the phenyladamantane moiety have been discovered.

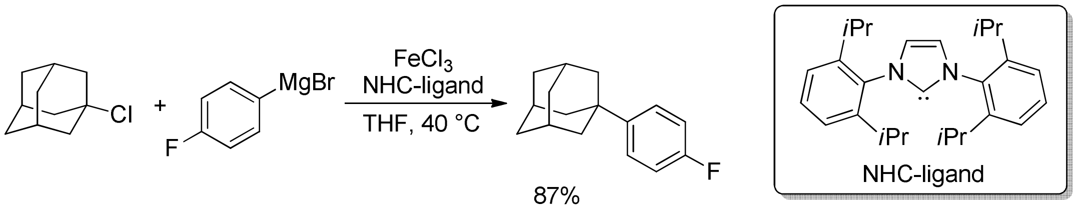
De Meijere et al. for instance use Pd/C as catalyst for *Friedel-Crafts* type arylation reactions of adamantane. The reaction of 1-bromoadamantane with different arenes in the presence of Pd/C furnishes the corresponding 1-aryladamantane derivatives in excellent yields (Scheme 29).[103] Noteworthy, *Stetter et al.* have discovered earlier that donor-substituted arenes like toluene and acetanilide can be easily adamantylated by heating with 1-bromoadamantane in the presence of water.[104]



Scheme 29: *Friedel-Crafts* type arylation of 1-bromoadamantane.

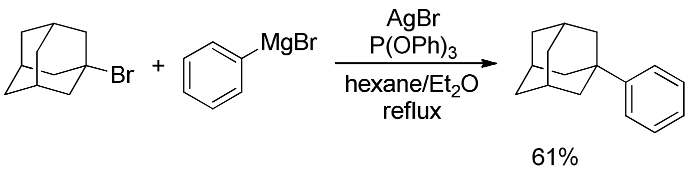
[101] V. Nair, T. D. Suja, K. Mohanan, *Tetrahedron Lett.* **2005**, *46*, 3217.
[102] a) G. A. Olah, in *Friedel-Crafts Chemistry*, Wiley-VCH, New York, **1973**. b) R. M. Roberts, A. A. Khalaf, in *Friedel-Crafts Alkylation Chemistry*, Marcel Dekker, New York, **1984**.
[103] S. Bräse, B. Waegell, A. de Meijere, *Synthesis* **1997**, 148.
[104] H. Stetter, J. Weber, C. Wulff, *Chem. Ber.* **1964**, *97*, 3488.

Furthermore, the arylation of 1-bromoadamantane with the use of substoichiometric (35 mol%) or even stoichiometric amounts of $FeCl_3$[105] or $AlCl_3$[106] has been known much longer, and is well documented. However, recently *Nakamura* and coworkers developed an efficient cross-coupling reaction of 1-chloroadamantane with aryl *Grignard* reagents using catalytic amounts of an *N*-heterocyclic carbene ligand (NHC-ligand) and $FeCl_3$ (Scheme 30).[107]



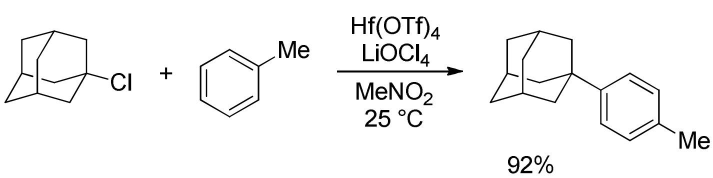
Scheme 30: $FeCl_3$-catalyzed cross-coupling reaction of 1-chloroadamantane and an aryl *Grignard* reagent.

Also the silver-catalysed reaction of tertiary alkyl bromides with aryl *Grignard* reagents in dichloromethane affords the corresponding cross-coupling products in reasonable yields (Scheme 31).[108]



Scheme 31: Silver-catalyzed phenylation of 1-bromoadamantane.

Hafnium(IV) trifluoromethanesulfonate has been found to be an efficient catalyst for *Friedel-Crafts* alkylation. The adamantylation of toluene with 1-chloroadamantane in the presence of 5 mol% $Hf(OTf)_4$ furnishes the corresponding product in 92% yield (Scheme 32).[109]



Scheme 32: $Hf(OTf)_4$-catalyzed *Friedel-Crafts* arylation of 1-chloroadamantane.

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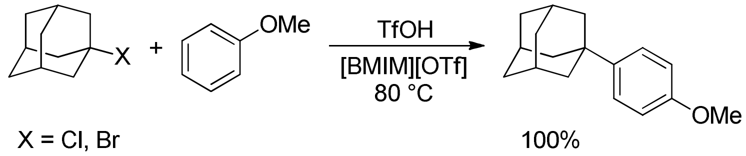
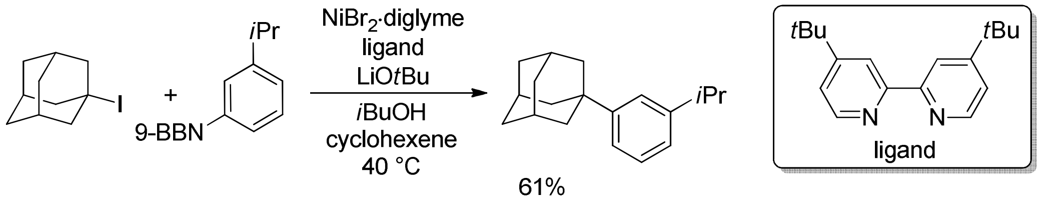
[105] T. J. Broxton, G. Capper, L. W. Deady, A. Lenko, R. D. Topsom, *J. Chem. Soc., Perkin Trans. 2* **1972**, 1237.
[106] a) H. Stetter, M. Schwarz, A. Hirschhorn, *Chem. Ber.* **1959**, *92*, 1629. b) H. Stetter, E. Rauscher, *Chem. Ber.* **1960**, *93*, 1161.
[107] S. K. Ghorai, M. Jin, T. Hatakeyama, M. Nakamura, *Org. Lett.* **2012**, *14*, 1066.
[108] H. Someya, H. Yorimitsu, K. Oshima, *Tetrahedron Lett.* **2009**, *50*, 3270.
[109] I. Hachiya, M. Moriwaki, S. Kobayashi, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2053.

Furthermore, *Laali et al.* have reported a TfOH-promoted adamantylation of aromatic substrates using the ionic liquid *n*-butylmethylimidazolium triflate ([BMIM][OTf]) as solvent (Scheme 33).[110]



Scheme 33: TfOH-promoted adamantylation of anisol in the ionic liquid *n*-butylmethyl-imidazolium triflate ([BMIM][OTf]).

Recently, a method for *Suzuki-Miyaura* cross-coupling reactions of tertiary alkyl bromides, using the commercially available catalyst components $NiBr_2$·diglyme and 4,4′-di-*tert*-butyl-2,2′-bipyridine, was disclosed.[111] Thus, the reaction of 1-iodo-adamantane with the isopropylphenyl-substituted 9-borabicyclo[3.3.1]nonane (9-BBN) furnished the desired product in 61% yield (Scheme 34).



Scheme 34: *Susuzki-Miyaura* cross-coupling of 1-iodoadamantane with the isopropylphenyl-substituted 9-borabicyclo[3.3.1]nonane.

6. IMIDAZOLE AND ITS CHEMISTRY

The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine or nucleic acid. Due to its polarity and its ionisable aromatic character, it leads to improved pharmacokinetic characteristics of lead molecules and is therefore used as a remedy to optimize solubility and bioavailability parameters of proposed poorly soluble molecules.[112]

Marine sponges produce a plethora of structurally diverse secondary metabolites usually containing both imidazole and pyrrole moieties.[113] Since the discovery in 1971 of the first alkaloid of this family, Oroidin,[114] many hundreds of such compounds have been isolated. Members of this family range from relatively simple compounds containing

[110] K. K. Laali, V. D. Sarca, T. Okazaki, A. Brock, P. Der, *Org . Biomol. Chem* . **2005**, *3*, 1034.
[111] S. L. Zultanski, G. C. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 624.
[112] K. Shalini, P. K. Sharma, N. Kumar, *Der Chemica Sinica* **2010**, *1*, 36.
[113] Z. Jin, *Nat. Prod. Rep.* **2006**, *23*, 464.
[114] S. Forenza, L. Minale, R. Riccio and E. Fattorusso, *J. Chem. Soc. D* **1971**, 1129.

intact imidazole systems such as Hymenidine, Parazoanthoxanthin A and Cribrostatin 6 to considerably more complex metabolites such as Palau'amine or Axinellamine A (Figure 6).

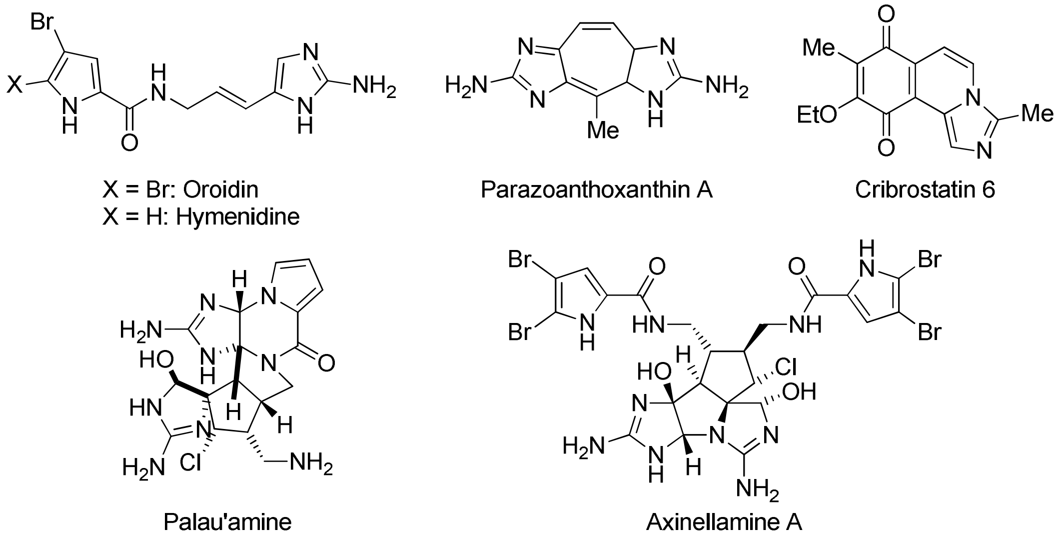


Figure 6: Natural products occurring in marine sponges containing the imidazole moiety.

However, the most important natural product derived from imidazole is the proteinogenic amino acid histidine. With its physiological pH value of 7.4, the histidine acts in protein building blocks as a free base and as a conjugated acid (pK_a = 7.00) due to a regulating acid-base equilibrium. Especially in enzymes, imidazole acts as *Brønsted* base or *Brønsted* acid. Moreover it also has the possibility to form complexes with metal ions. These properties are unique among the proteinogenic amino acids (Figure 7).[115] Histamine is formed by enzymatic decarboxylation of histidine. It acts as a vasodilator and thus lowers the blood pressure. Moreover, it can contract smooth muscles and regulate the gastric acid secretion. Too high histamine level in the blood can cause allergic reactions like hay fever, which can be surpressed by antihistamines blocking the allergy-causing histamine receptors (H_1 receptors).[116] Cimetidine is used for treatment of duodenal and gastric ulcers. By blocking the histamine receptors stimulating the gastric acid secretion (H_2 receptors), it reduces the gastric acid production (Figure 7).[116]

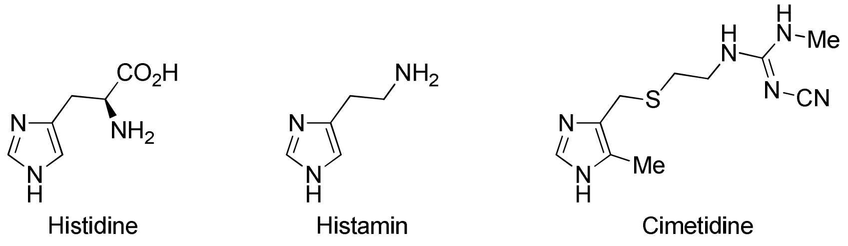


Figure 7: Natural products containing the imidazole moiety.

[115] R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 317.
[116] *The Chemistry of Heterocycles* (Eds.: S. Hauptmann, T. Eicher), Wiley-VCH, New York, **2003**.

Among imidazole derivatives a huge variety of pharmacological activite molecules can be found.[112] Metronidazole is a nitroimidazole antibiotic medication used particularly for anaerobic bacteria and protozoa. Metronidazole is an antibiotic, amebicide, and antiprotozoal and the drug of choice for first episodes of mild-to-moderate *Clostridium difficile* infection.[117] Bifonazole shows antifungal activity. It has dual mode of action. It blocks transformation of 24-methylendihydrolanosterol to desmethylsterol in fungi together with inhibition of HMG-CoA. This enables fungicidal properties against dermatophytes and distinguishes bifonazole from other antifungal drugs.[116] Eprosartan is an Angiotensin II receptor antagonist used for the treatment of high blood pressure. It blocks the binding of Angiotensin II to AT_1 receptors in vascular smooth muscle, causing vascular dilatation and inhibits sympathetic norepinephrine production (Figure 8).[116]

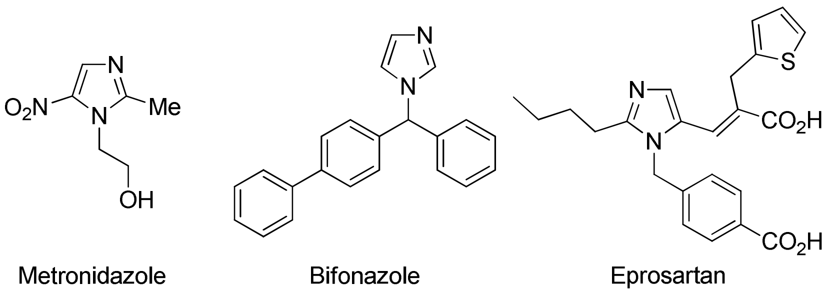


Figure 8: Pharmaceutically relevant imidazole derivatives.

Ionic liquids have received attention in recent years for their various desirable properties. Imidazolium-based ionic liquids and ionic liquid monomers are becoming increasingly popular in a variety of areas including biphasic reaction catalysis,[118] electromechanical actuator membranes and diluents,[119] separation science membranes,[120] as well as water purification agents[121] or green solvents (Figure 9).[122] Imidazole was targeted for its ability to form cationic compounds, which are molten salts at low molar mass. Ionic liquids offer several beneficial attributes including fixed charge, potential as green solvents, and relatively high thermal stability. The imidazole ring has gained much attention for its ability to tune the properties of the resulting ionic liquid. The type of substituents on any of the positions in the ring and exchange of the counteranion influences many physical properties such as the melting point, the boiling point, and the

[117] S. H. Cohen, D. N. Gerding, S. Johnson, C. P. Kelly, V. G. Loo, L. C. McDonald, J. Pepin, M. H. Wilcox, *Infect. Control Hosp. Epidemiol.* **2010**, *31*, 431.
[118] S. Ding, M. Radosz, Y. Shen, *Macromolecules* **2005**, *38*, 5921.
[119] A. J. Duncan, D. J. Leo, T. E. Long, *Macromolecules* **2008**, *41*, 7765.
[120] T. H. Maugh, *Science* **1983**, *222*, 259.
[121] J. G. Huddleston, A. E. Visser, W. M. Reichert, H. D. Willauer, G. A. Broker, R. D. Rogers, *Green Chem.* **2001**, *3*, 156.
[122] D. S. Jacob, S. Makhluf, I. Brukental, R. Lavi, L. A. Solovyov, I. Felner, I. Nowik, R. Persky, H. E. Gottlieb, A. Gedanken, *Eur. J. Inorg. Chem.* **2005**, *13*, 2669.

viscosity. Furthermore, imidazolium ionic liquids utilize two of their unique properties in biphasic catalysis, i.e. their ability to coordinate transition metals and their hydrophilic ionic nature. Several imidazolium-based ionic liquid molecules have displayed the ability to catalyze atom transfer radical polymerization and facilitate the synthesis of polymers with a narrow molecular weight distribution.[123]

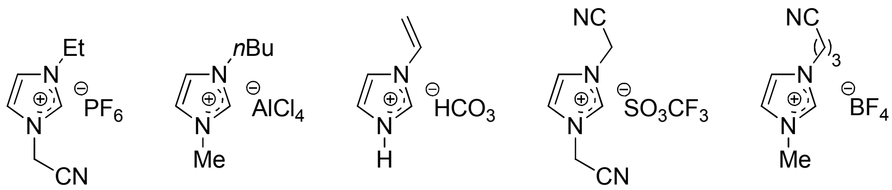
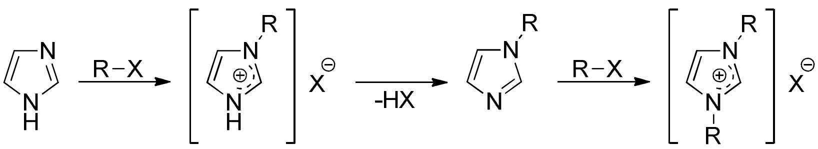


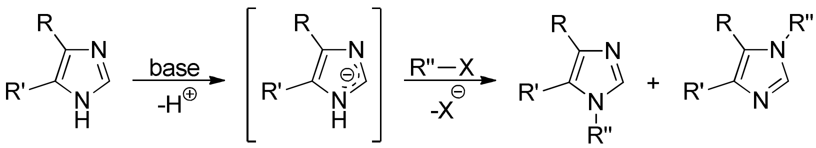
Figure 9: Imidazole-based ionic liquids.

Imidazoles react with electrophilic reagents like halogenoalkanes *via* the nucleophilic pyridine-like *N*-atom to give quarternary salts as primary products. These salts readily undergo deprotonation and react with a second halogenoalkane to afford 1,3-dialkylimidazolium salts (Scheme 35).[116]



Scheme 35: Reaction with electrophilic reagents.

In the presence of strong bases, imidazoles form the corresponding imidazolyl anion and easily undergo 1-alkylation with halogenoalkanes and dialkyl sulfates.[124] Due to the ambient character of unsymmetrical imidazolyl anions, base-induced alkylation of substituted imidazoles furnishes product mixtures (Scheme 36). Imidazolyl anions also react with acid chlorides, sulfonyl chlorides and trialkylchlorosilanes to give the corresponding 1-substituted imidazoles.[125]



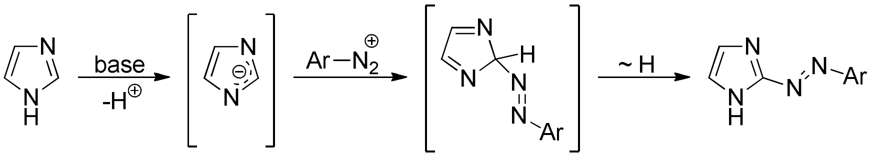
R'' = alkyl, acyl, silyl, sulfonyl

Scheme 36: Base-induced reaction with electrophilic reagents leading to product mixtures.

S_EAr reactions like halogenations or azo couplings are mostly performed in neutral or basic medium. Chlorination with SO_2Cl_2 furnishes 4,5-dichloroimidazole[116] whereas

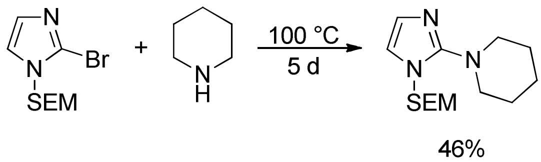
[123] M. D. Green, T. E. Long, *J. Macromol. Sci., Polym. Rev.* **2009**, *49*, 291.
[124] M. Begtrup, P. Larsen, *Acta. Chem. Scand.* **1990**, *44*, 1050.
[125] J. A. Joule, K. Mills, in *Heterocyclic Chemistry*, Blackwell Science, Oxford, **2010**.

bromination with Br_2 in water or HOAc/NaOAc[126] and iodination with I_2 in H_2O/NaOH[127] produce the corresponding 2,4,5-trihalogenated imidazoles. Azo couplings in aqueous alkaline solution lead to 2-substituted products, since the negative charge of the intermediate imidazolyl anion is delocalized over positions 1-3 of the ring (Scheme 37).[128]



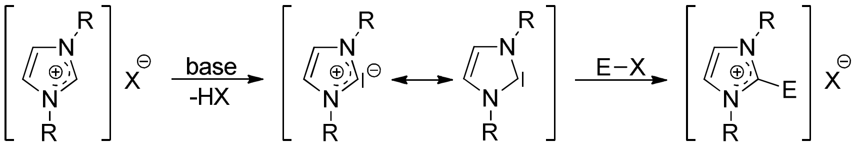
Scheme 37: Azo coupling of imidazole in basic medium.

Reactions of *N*-substituted imidazole derivatives with nucleophiles occur rather slowly and demand vigorous conditions. For instance, the S_NAr reaction of 2-halogeno-1-alkylimidazoles require high temperatures (Scheme 38).[129]



Scheme 38: S_NAr reaction of *N*-substituted imidazol derivatives.

The treatment of 1,3-dialkylimidazolium salts with strong bases leads to deprotonation at position 2 generating 1,3-dialkylimidazolium ylides. Due to their electronic distribution, these ylides exhibit the behavior of nucleophilic carbenes and undergo electrophilic reactions like alkylation, acylation, halogenations, etc. at position 2 (Scheme 39).[130]

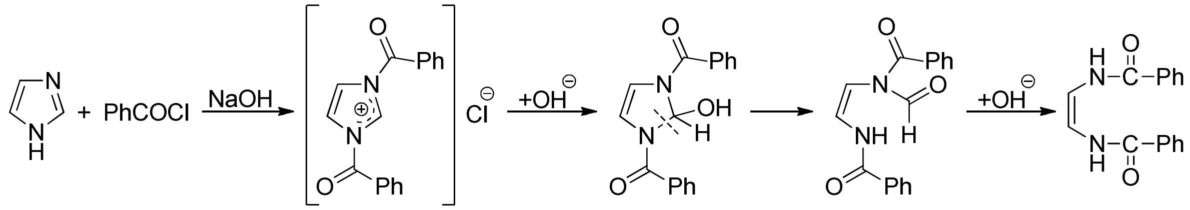


Scheme 39: Preparation of 1,3-dialkylimidazolium ylides and there subsequent reaction with electrophiles.

1,3-dialkyl- and 1,3-diacylimidazolium ions show high reactivity against OH-ions, usually with addition at position 2 followed by ring-cleavage. For instance, the reaction

[126] T. Mukai, K. Nishikawa, *Chem. Lett.* **2009**, *38*, 402.
[127] A. Schmidt, T. Mordhorst, *Heterocycles* **2006**, *68*, 1393.
[128] St. Bernt, M. Feyand, A. Modrow, J. Wack, J. Senker, N. Stock, *Eur. J. Inorg. Chem.* **2011**, 5378.
[129] J. M. Joo, B. B. Touré, D. Sames, *J. Org. Chem.* **2010**, *75*, 4911.
[130] a) M. Begtrup, *J. Chem. Soc., Chem. Commun.* **1975**, 334. b) C. A. Zificzak, D. J. Hlasta, *Tetrahedron Lett.* **2005**, *46*, 4789.

of imidazole with PhCOCl in NaOH/H_2O leads to the cleaved product 1,2-(dibenzoylamido)ethane and formate (Scheme 40).[131]

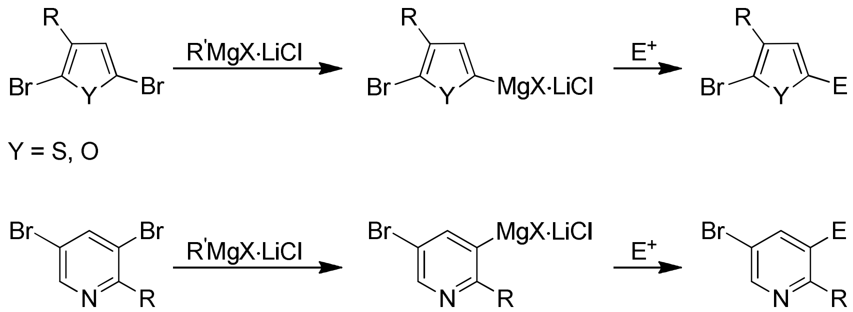


Scheme 40: Ring cleavage of 1,3-diacylimidazolium ions under basic conditions.

[131] P. Ruggli, R. Ratti, E. Henzi, *Helv. Chim. Acta* **1929**, *12*, 332.

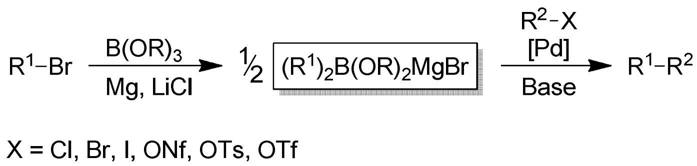
7. OBJECTIVES

As functionalized five- and six-membered heterocycles are highly important building blocks for the synthesis of pharmaceuticals, agrochemicals and materials (e.g. regio-regular polymers), a simple and general method for the regioselective preparation of metalated heterocycles would be highly desirable. Hence, a selective Br/Mg-exchange reaction of unsymmetrically substituted five- and six-membered dibromo-heterocycles should be developed (Scheme 41).[132]



Scheme 41: Regioselective Br/Mg-exchange on unsymmetrically substituted dibromoheterocycles and subsequent functionalization.

Arylboron derivatives have found broad applications for the performance of *Suzuki-Miyaura* cross-couplings. In general, most arylboronic compounds are prepared *via* lithium or magnesium organometallics in a two-step process. The aim of the project lay on the development of a convenient, general and atom-economical method for the one-pot preparation of boronic derivatives using inexpensive starting materials with little toxicity and their subsequent use in *Suzuki-Miyaura* cross-coupling reactions (Scheme 42).[133]

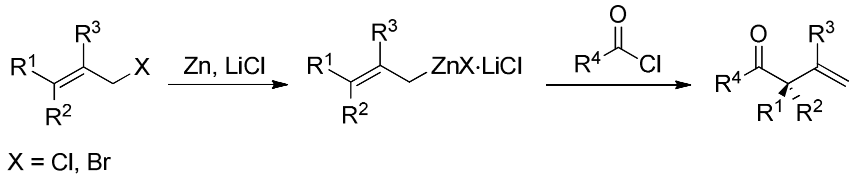


Scheme 42: One-pot preparation and subsequent cross-coupling of magnesium diarylboronates.

β,γ-Unsaturated ketones and esters are versatile building blocks in organic chemistry. Although a number of synthetic methods for β,γ-unsaturated ketones have been disclosed, only a few have been proven practical and useful. Moreover, the direct preparation of β,γ-unsaturated esters is entirely unknown in literature. Therefore, a

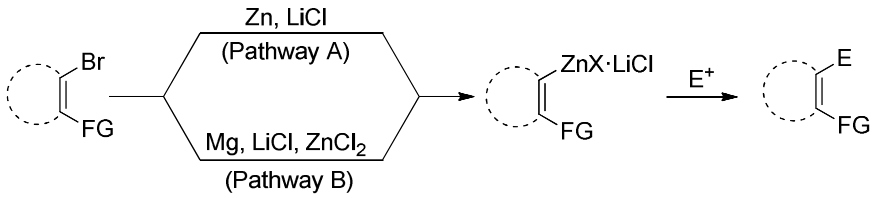
[132] Project was developed in cooperation with B. A. Haag (see: Dissertation, LMU-München, **2010**).
[133] Project was developed in cooperation with B. A. Haag (see: Dissertation, LMU-München, **2010**) and A. Jana.

procedure involving the reaction of substituted allylic zinc reagents, prepared *via* direct metal insertion into substituted allylic halides, with a broad range of acid chlorides and chloroformates was envisioned to furnish the corresponding α-substituted β,γ-unsaturated ketones and esters (Scheme 43).



Scheme 43: Preparation of α-substituted β,γ-unsaturated ketones and esters *via* addition of allylic zinc reagents to various acid chlorides and chloroformates.

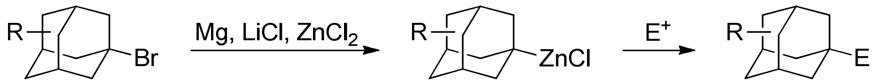
Functionalized alkenes bearing aldehyde, keto or ester functions are found in a plethora of naturally occurring products as well as in pharmaceutically active substances. This makes functionalized alkenyl organometallics bearing such sensitive carbonyl groups important intermediates in organic synthesis. Since the addition of LiCl to various insertion reactions allows the simple preparation of alkyl, aryl, and benzylic zinc reagents, this method should be extended to alkenyl zinc reagents starting from their corresponding unsaturated bromides (Scheme 44).[134]



Scheme 44: Preparation of alkenylzinc reagents and subsequent functionalization.

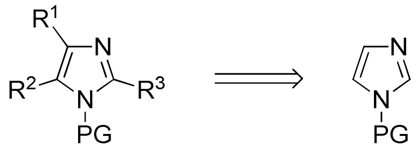
Adamantane derivatives found numerous applications in medicinal chemistry and drug development. The development of the adamantane chemistry allows it to design molecules of substances promising for the practical application in the fields of medicine, supramolecular chemistry, nanotechnologies, etc. Until now, no general methodology has been reported for the selective synthesis of adamantyl organometalic reagents. Hence, a mild and convenient procedure for the selective synthesis of adamantyl organometallics was envisioned also tolerating functional groups on the adamantyl scaffold (Scheme 45).[135]

[134] Project was developed in cooperation with M. A. Schade (see: Dissertation, LMU-München, **2011**) and S. Yamada.
[135] Project was developed in cooperation with V. Dhayalan.



Scheme 45: Preparation of adamantylzinc reagents and subsequent functionalization.

The imidazole scaffold can be found in a plethora of naturally occuring products. Moreover, among imidazole derivatives a huge variety of pharmacological active molecules can be found and are therefore important targets in pharmaceutical industry. For this reason, a methodology for the selective and predictable functionalization of all positions of the imidazole ring starting from simple imidazole by directed metalation and sulfoxide/magnesium exchange is highly desirable (Scheme 46).[136]



Scheme 46: Fully functionalization of imidazole scaffold starting from plain *N*-protected imidazole.

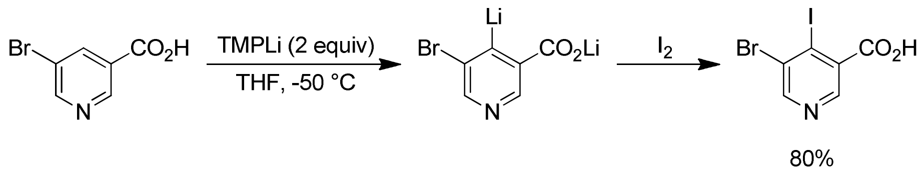
[136] Project was developed in cooperation with E. Coya.

B. RESULTS AND DISCUSSION

1. HIGHLY REGIOSELECTIVE PREPARATION OF HETEROARYL-MAGNESIUM REAGENTS USING A Br/Mg-EXCHANGE

1.1 INTRODUCTION

The functionalization of heterocycles is of key importance for the preparation of pharmaceuticals, agrochemicals and materials (regioregular polymers) and has attracted a lot of attention in recent years.[137] Especially important is the regioselective preparation of metalated five- and six-membered heterocycles. Substituted pyridines react with a variety of metallic bases leading to the corresponding metalated intermediates. Using a proper set of reaction conditions and an appropriate metal base enables the performance of a range of selective metalations. The nature of the substituents attached to the pyridine scaffold deeply influences the regioselectivity and the rate of the metalation. The deprotonation of 5-bromonicotinic acid with lithium 2,2,6,6-tetramethylpiperidide (TMPLi)[138] for example proceeds smoothly leading regioselectively after iodolysis to the desired product with the iodo-substituent in position 4 (Scheme 47).[139]



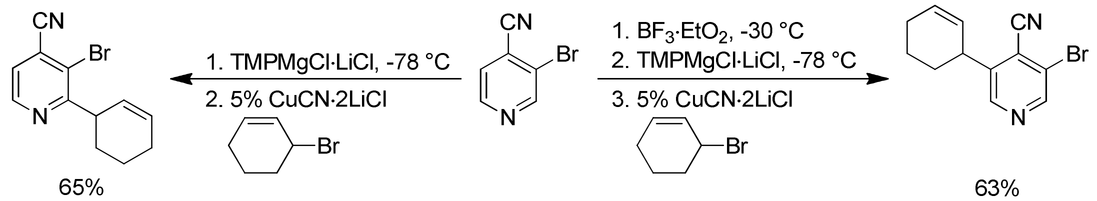
Scheme 47: Regioselective deprotonation on 5-bromonicotinic acid with TMPLi.

[137] a) *Heterocylic Chemistry* (Ed.: T. L. Gilchrist), Longman, London, **1998**. b) J. F. Miller, A. Termin, K. Koch, A. D. Piscopio, *J. Org. Chem.* **1998**, *63*, 3158. c) M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 7449. d) *Organolithiums: Selectivity for Synthesis. Tetrahedron Organic Chemistry Series* (Ed.: J. Clayden), Pergamon, Oxford, **2002**. e) H. Ila, O. Baron, A. J. Wagner, P. Knochel, *Chem. Comm.* **2006**, 583. f) K. L. Tan, A. Vasudevan, R. G. Bergman, J. A. Ellman, A. J. Souers, *Org. Lett.* **2003**, *5*, 2131. g) J. P. Wolfe, J. S. Thomas, *Curr. Org. Chem.* **2005**, *9*, 625. h) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173. i) I. J. S. Fairlamb, *Chem. Soc. Rev.* **2007**, *36*, 1036. j) C. Schmuck, D. Rupprecht, *Synthesis* **2007**, 3095. k) S. J. Hwang, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 16158. l) R. Ponce Ortiz, J. Casado, V. Hernández, J. T. López Navarrete, J. A. Letizia, M. A. Ratner, A. Facchetti, T. J. Marks, *Chem. Eur. J.* **2009**, *15*, 5023. m) P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874. n) F. M. Piller, P. Knochel, *Org. Lett.* **2009**, *11*, 445. o) P. Thansandote, C. Gouliaras, M.-O. Turcotte-Savard, M. Lautens, *J. Org. Chem.* **2009**, *74*, 1791. p) C. J. O'Connor, M. D. Roydhouse, A. M. Przybył, M. D. Wall, J. M. Southern, *J. Org. Chem.* **2010**, *75*, 2534. q) M. Jeganmohan, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 8520. r) F. Miege, C. Meyer, J. Cossy, *Angew. Chem. Int. Ed.* **2011**, *50*, 5932. s) S. Benetti, C. De Risi, G. P. Pollini, V. Zanirato, *Chem. Rev.* **2012**, *112*, 2129. t) D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil, B. M. Stoltz, *Nature Chem.* **2012**, *4*, 130.

[138] a) R. A. Olofson, C. M. Dougherty, *J. Am. Chem. Soc.* **1973**, *95*, 582. b) E. J. Corey, A. Gross, *Tetrahedron Lett.* **1984**, *25*, 495. c) N. Plé, A. Turck, P. Martin, S. Barbey, G. Quéginer, *Tetrahedron Lett.* **1993**, *34*, 1605. d) M. Iwao, T. Kuraishi, *Tetrahedron Lett.* **1983**, *24*, 2649.

[139] J. Lazaar, A.-S. Rebstock, F. Mongin, A. Godard, F. Trécourt, F. Marsais, G. Quéginer, *Tetrahedron* **2002**, *58*, 6723.

Another way of controlling the regioselectivity in metalation reactions of pyridine derivatives is the addition of strong *Lewis* acids such as $BF_3{\cdot}OEt_2$. It turns out that the sterically hindered base TMPMgCl·LiCl reacts reversibly with $BF_3{\cdot}OEt_2$ at temperatures below -20 °C leading to the frustrated *Lewis* pair TMPMgCl·BF_3.[140] This adduct decomposes only at temperatures above -10 °C.[141] Through a coordination of the BF_3 group at the *N*-heterocyclic nitrogen the acidity of the pyridyl hydrogens increases and the deprotonation of even electron-rich pyridines such as 2-methoxypyridine proceeds readily. Moreover, the addition of $BF_3{\cdot}OEt_2$ also changes dramatically the direction of the deprotonation. Thus, 3-bromoisonicotinonitrile is magnesiated with TMPMgCl·LiCl in position 2 providing the corresponding 2-allylated pyridine in 65% yield after Cu(I)-catalyzed allylation. In the presence of $BF_3{\cdot}OEt_2$, a complete switch of regioselectivity is observed and the 4-allylated pyridine is obtained after a Cu(I)-catalyzed allylation in 63% yield (Scheme 48).[142]

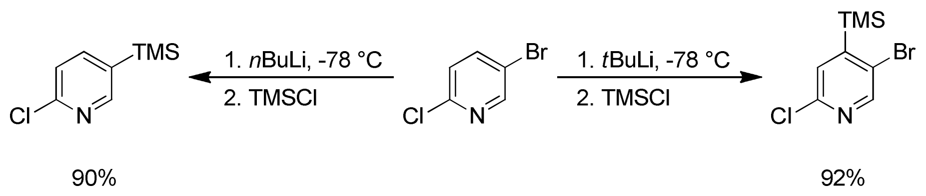


Scheme 48: Effect of $BF_3{\cdot}OEt_2$ on the deprotonation of 3-bromoisonicotinonitrile with TMPMgCl·LiCl.

The presence of a bromo or an iodo substituent attached to the pyridine ring allows the performance of halogen/metal exchange. The use of alkyllithium reagents leads to fast exchange reactions. However, the reaction conditions and the nature of the lithium reagent used are of special importance since lithiation of the pyridine ring may be a competitive process.

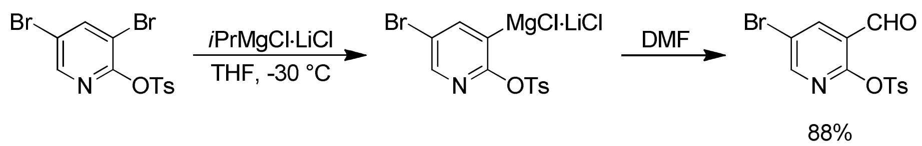
In the reaction with 5-bromo-2-chloropyridine *t*BuLi plays the role of a base and the *ortho*-lithiation leads selectively after addition of TMSCl to the trisubstituted product 5-bromo-2-chloro-4-(trimethylsilyl)pyridine in 92% yield. In contrast, *n*BuLi selectively exchanges the bromine of 5-bromo-2-chloropyridine and furnishes, after addition of TMSCl, selectively the disubstituted heterocycle 2-chloro-5-(trimethylsilyl)pyridine in 90% yield (Scheme 49).[143]

[140] D.W. Stefan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46.
[141] M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.
[142] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 1501.
[143] P. Pierrat, P. Gros, Y. Fort, *Synlett* **2004**, 2319.



Scheme 49: Br/Li exchange *versus ortho*-lithiation depending on the nature of the lithium reagent.

Furthermore, *Knochel et al.* found that a tosyloxy substituent in position 2 of 3,5-dibromopyridine allows a highly regioselective Br/Mg exchange reaction using *i*PrMgCl·LiCl.[26c] The bromine substituent in position 3 undergoes a Br/Mg exchange with 99:1 regioselectivity, showing the strong influence of the tosyloxy group. The reaction of the pyridylmagnesium reagent with DMF affords the corresponding pyridylaldehyde in 88% yield (Scheme 50).

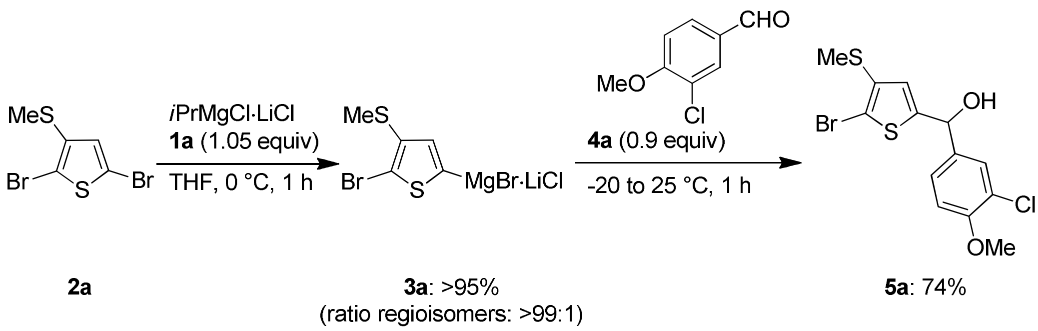


Scheme 50: Regioselective Br/Mg exchange on 3,5-dibromopyridin-2-yl 4-tosylate with *i*PrMgCl·LiCl.

Based on these results, we envisioned a convenient and general regioselective Br/Mg-exchange reaction for unsymmetrically substituted dibromoheterocycles allowing the preparation of various thienyl-, furyl- and pyridyl-magnesium derivatives.

1.2 REGIOSELECTIVE Br/Mg-EXCHANGE ON UNSYMMETRICAL DIBROMO-HETEROCYCLES USING iPrMgCl·LiCl

Preliminary experiments have shown that the treatment of unsymmetrically substituted dibromo-heterocycles like 2,5-dibromo-3-(methylthio)thiophene (**2a**) with *i*PrMgCl·LiCl (**1a**) (1.05 equiv) in THF at 0 °C leads within 1 h to the corresponding magnesium reagent **3a** in >95% yield and with a regioselectivity of >99:1. Its addition to 3-chloro-4-methoxybenzaldehyde (**4a**, 0.9 equiv) at -20 °C provides the corresponding alcohol **5a** in 74% yield (Scheme 51). With these conditions in hand, several unsymmetrically substituted dibromo-thiophenes and -benzo[*b*]thiophenes have been converted into their corresponding magnesium species (Table 1) and subsequently functionalized using a broad range of electrophiles, such as aldehydes, aryl iodides or acyl chlorides in the presence of an appropriate catalyst.



Scheme 51: Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromothiophene **2a** using *i*PrMgCl·LiCl (**1a**).

This regioselective exchange has been performed with a number of unsymmetrically substituted dibromothiophenes in excellent regioselectivities. Thio-substituents such as MeS, PhS or PyrS on the dibromothiophene direct the Br/Mg-exchange in position 5 with a regioselectivity of >99:1 (Table 1).[144] Subsequent functionalization reactions furnish the corresponding products in excellent yields. Hence, (5-bromo-4-(methylthio)thiophen-2-yl)magnesium bromide (**3a**) has been transmetalated with $ZnCl_2$ and submitted to a Pd-catalysed *Negishi* cross-coupling[145] with electrophiles **4b** and **4c** furnishing the highly functionalized products **5b** and **5c** in 82% and 84% yield respectively (entries 1 and 2). The reaction of organomagnesium compound **3a** with di-*tert*-butyl dicarbonate (**4d**) produces the ester-substituted thiophene **5d** in 82% yield (entry 3). Furthermore, the magnesium reagent **3b** of the PhS-substituted dibromothiophene smoothly adds to anisaldehyde (**4e**) furnishing the corresponding alcohol in 91% yield (entry 4). Also Pd-catalyzed *Negishi* cross-couplings of **3b** after transmetalation with an electron-poor as well as an electron-rich electrophile (**4f** and **4g**) proceed well and lead to the desired products **5f** and **5g** in high yields (entries 5 and 6). Noteworthy, the exchange reaction as well as the subsequent cross-coupling with **4g** has been carried out in a 15 mmol scale without any loss in regioselectivity or yield. Finally, also Mg-species **3c** of the PyrS-substituted dibromothiophene has been successfully submitted to a *Negishi* cross-coupling with ethyl 4-iodobenzoate (**4h**) producing thiophene **5h** in 92% yield (entry 7).

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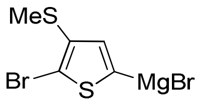
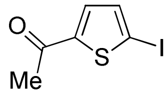
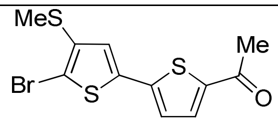
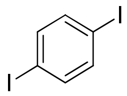
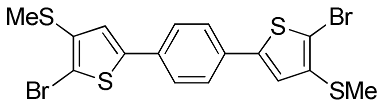
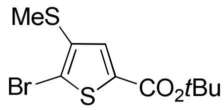
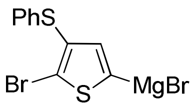
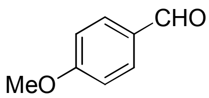
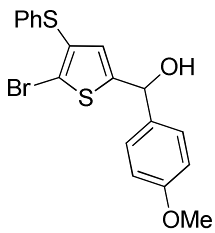
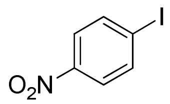
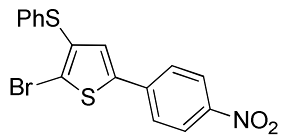
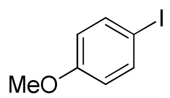
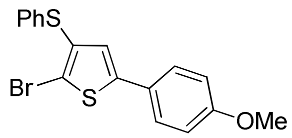
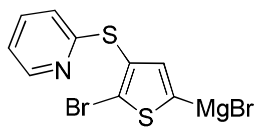
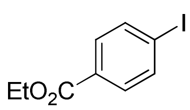
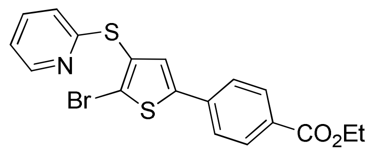
144 The corresponding regioisomers of **3a-e** and **3h** were not observed in ^{1}H NMR measurements of the hydrolyzed crude reaction mixtures (HOAc, 10 equiv, -20 to 25 °C).

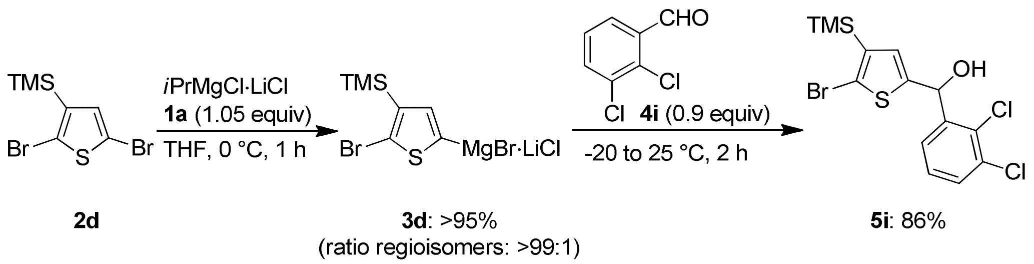
145 a) A. King, N. Okukado, E.-i. Negishi, *J. Org. Chem.* **1977**, *42*, 1821. b) E.-i. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298. c) E.-i. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340. d) Ø. Rist, M. Begtrup, *J. Chem. Soc., Perkin Tran. 1* **2001**, 1566. e) X. Zeng, M. Quian, Q. Hu, E.-i. Negishi, *Angew. Chem. Int. Ed.* **2004**, *43*, 2259. f) E.-i. Negishi, X. Zeng, Z. Tan, M. Qian, Q. Hu, Z. Huang, in *Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, 815. g) A. de Meijere, P. von Zezschwitz, S. Braese, *Acc. Chem. Res.* **2005**, *38*, 413. h) J.-X. Wang, J. McCubbin, M. Jin, R. Laufer, Y. Mao, A. Crew, M. Mulvihill, V. Snieckus, *Org. Lett.* **2008**, *10*, 2923. i) G. Manolikakes, M. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765. j) Z. Dong, G. Manolikakes, J. Li, P. Knochel, *Synthesis* **2009**, 681. k) G. Wang, N. Yin, E.-i. Negishi, *Chem. Eur. J.* **2011**, *17*, 4118.

Table 1: Preparation of functionalized thiophenes *via* regioselectively generated heteroaryl-magnesium reagents of type **3**.

Entry	Mg-Reagent[a]	Electrophile	Product, Yield[b]
1	 **3a**: >99:1	 **4b**	 **5b**: 82%[c]
2	**3a**: >99:1	 **4c**	 **5c**: 84%[c]
3	**3a**: >99:1	(tBuO$_2$C)$_2$O **4d**	 **5d**: 82%
4	 **3b**: >99:1	 **4e**	 **5e**: 91%
5	**3b**: >99:1	 **4f**	 **5f**: 86%[c]
6	**3b**: >99:1	 **4g**	 **5g**: 96%[c],[d]
7	 **3c**: >99:1	 **4h**	 **5h**: 92%[c]

[a] Obtained after exchange reaction with *i*PrMgCl·LiCl (**1a**; 1.05 equiv) in THF at 0 °C in 1 h. Ratio of regioisomers determined by ^{1}H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after a *Negishi* cross-coupling ($ZnCl_2$ (1 equiv); then 4% $Pd(PPh_3)_4$) with ArI (0.9 or 1.1 equiv). [d] Reaction was performed on a 15 mmol scale.

Also the TMS-substituted dibromothiophene **2d** undergoes readily the Br/Mg-exchange with *i*PrMgCl·LiCl (**1a**) (1.05 equiv) in THF at 0 °C and leads within 1 h to the corresponding magnesium reagent **3d** in >95% yield and with a regioselectivity of >99:1. Its addition to 2,3-dichlorobenzaldehyde (**4i**, 0.9 equiv) at -20 °C provides the corresponding alcohol **5i** in 86% yield (Scheme 52).



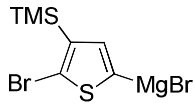
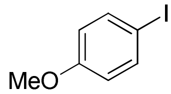
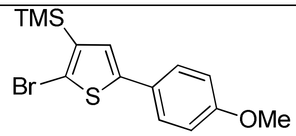
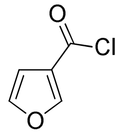
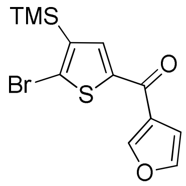
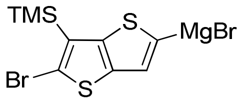
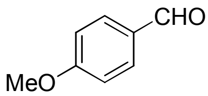
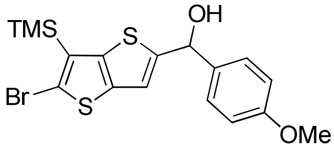
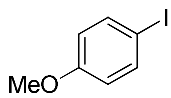
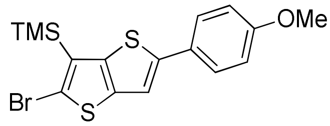
Scheme 52: Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromothiophene **2d** using *i*PrMgCl·LiCl (**1a**).

After transmetalation with $ZnCl_2$ (1 equiv), the *Negishi* cross-coupling reaction of magnesium species **3d** with 4-iodoanisol (**4g**) using 4% $Pd(PPh_3)_4$ as catalyst furnishes the corresponding arylated thiophene **5j** in 87% yield (Table 2, entry 1). Moreover, transmetalation of **3d** with $ZnCl_2$ (1 equiv) followed by a Cu(I)-catalyzed[146] acylation (10% CuCN·2LiCl) with furan-3-carbonyl chloride (**4j**) gives access to the functionalized ketone **5k** in 72% yield (entry 2). Since benzo[*b*]thiophenes are important building blocks for the preparation of organic materials,[147] regioselective functionalizations of this scaffold have been performed with *i*PrMgCl·LiCl (**1a**). The Br/Mg-exchange of dibromo-thienothiophene **2e** leads to the corresponding magnesium reagent **3e** in >95% and >99:1 regioselectivity. Its subsequent addition to anisaldehyde (**4e**) proceeds readily and furnishes the expected alcohol **5l** in 81% yield (entry 3). The arylated thienothiophene **5m** has been obtained in almost quantitative yield after Pd-catalysed cross-coupling of magnesium reagent **3e** with 4-iodoanisol (**4g**).

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

[147] a) A. R. Katritzky, L. Serdyuk, L. Xie, I. Ghiviriga, *J. Org. Chem.* **1997**, *62*, 6215. b) S. S. Mandal, S. S. Samanta, C. Deb, A. De, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2559. c) T. Kunz, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 866. d) M. Raduan, J. Padrosa, A. Pla-Quintana, T. Parella, A. Roglans, *Adv. Synth. Catal.* **2011**, *353*, 2003. e) T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 1958.

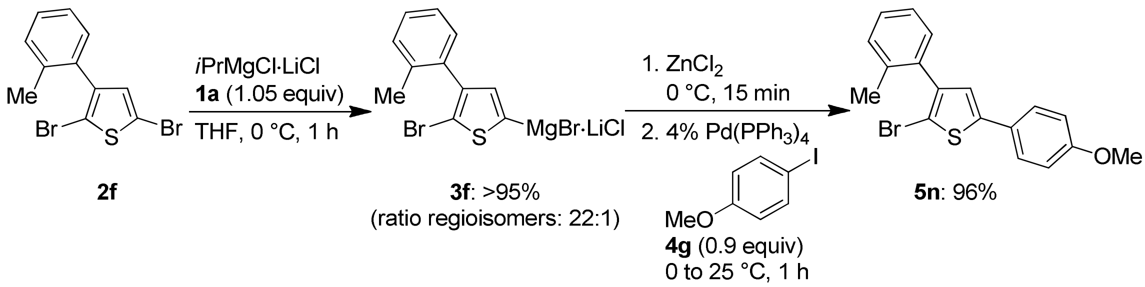
Table 2: Preparation of functionalized thiophenes and benzo[*b*]thiophenes *via* regioselectively generated heteroarylmagnesium reagents of type **3**.

Entry	Mg-Reagent[a]	Electrophile	Product, Yield[b]
1	 **3d**: >99:1	 **4g**	 **5j**: 87%[c],[d]
2	**3d**: >99:1	 **4j**	 **5k**: 72%[e]
3	 **3e**: >99:1	 **4e**	 **5l**: 81%
4	**3e**: >99:1	 **4g**	 **5m**: 96%[c]

[a] Obtained after exchange reaction with *i*PrMgCl·LiCl (**1a**; 1.05 equiv) in THF at 0 °C in 1 h. Ratio of regioisomers determined by ^{1}H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after a *Negishi* cross-coupling ($ZnCl_2$ (1 equiv); then 4% $Pd(PPh_3)_4$) with ArI (0.9 or 1.1 equiv). [d] Reaction was performed on a 10 mmol scale. [e] Obtained after acylation ($ZnCl_2$ (1 equiv); then 10% CuCN·2LiCl) with ArCOCl (0.9 equiv).

Besides thio- and TMS-substituted thiophenes, also other substituents on the dibromothiophene have been tested. Interestingly, by using 2,5-dibromo-3-phenyl-thiophene, no regioselective Br/Mg-exchange could be achieved under various conditions. However by introducing a substituent at the *ortho* position of the phenyl group like Me, MeO or Me_2N selectivities from 20:1 up to >99:1 could be obtained. This effect may be explained by assuming a conformation change by moving the aryl group out of plane due to the substituent on position 2' of the aryl ring and therefore shielding the bromine at position 2.

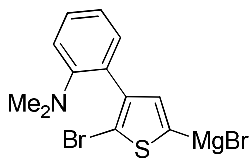
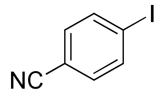
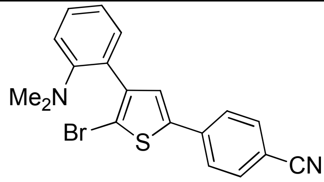
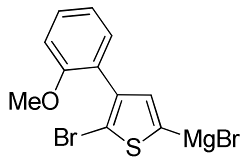
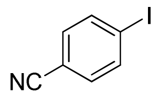
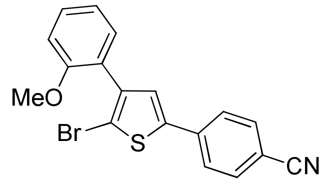
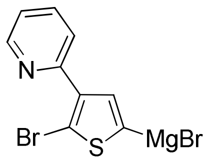
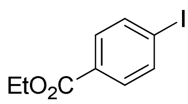
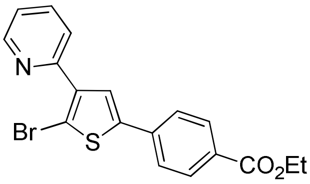
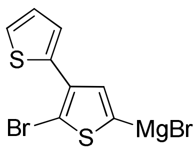
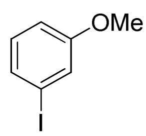
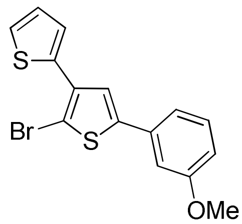
The Br/Mg-exchange of 2,5-dibromo-3-(*o*-tolyl)thiophene (**2f**) with *i*PrMgCl·LiCl (**1a**) (1.05 equiv) in THF at 0 °C leads within 1 h to the corresponding magnesium reagent (**3f**) in >95% yield and with a regioselectivity of 22:1. After transmetalation with $ZnCl_2$, the *Negishi* cross-coupling with 4-iodoanisol (**4g**) furnishes the highly functionalized thiophene **5n** in almost quantitative yield (Scheme 53).



Scheme 53: Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromothiophene **2f** using *i*PrMgCl·LiCl (**1a**).

Employing 2-*N*,*N*-dimethylaniline as substituent on the dibromothiophene, the ratio of the regioisomers of the Br/Mg-exchange could be increased and the corresponding magnesium reagent **3g** has been obtained in a regioselectivity of 39:1 (Table 3, entry 1). The subsequent *Negishi* cross-coupling with 4-iodobenzonitrile (**4k**) furnished the desired bisarylated bromothiophene **5o** in 91% yield. Furthermore, a 2-anisyl-substituent on the dibromothiophene directs the Br/Mg-exchange in position 5 with a regioselectivity of >99:1 (entry 2). The cross-coupling product **5p** is obtained after a *Negishi* cross-coupling of the magnesium species **3h** with 4-iodobenzonitrile (**4k**) in 90% yield. Noteworthy, a satisfactory regioselectivity of 20:1 has also been achieved with heterocyclic substituents like a 2-pyridyl or a 2-thienyl group (entries 3 and 4). The subsequent cross-coupling reactions of the magnesium reagents **3i** and **3j** with the electrophiles **4h** and **4l** lead to the expected products **5q** and **5r** in 89% and 83% yield respectively. It is worth mentioning, that no chelating effect with the MeO- or Me_2N-substituent of the phenyl ring as well as with the pyridyl- or the thienyl-substituent could be observed. It is assumed that this might be a result of the too long distance between the bromine in position 2 of the thiophene ring and the heteroatom of the MeO- or Me_2N-group of the phenyl ring or the pyridyl- and the thienyl-substituent caused by the almost perpendicular orientation of the thiophene ring and the substituents in position 3.

Table 3: Preparation of functionalized thiophenes *via* regioselectively generated heteroaryl-magnesium reagents of type **3**.

Entry	Mg-Reagent[a]	Electrophile	Product, Yield[b]
			
1	**3g**: 39:1	**4k**	**5o**: 91%[c]
			
2	**3h**: >99:1	**4k**	**5p**: 90%[c]
			
3	**3i**: 20:1	**4h**	**5q**: 89%[c]
			
4	**3j**:[d] 20:1	**4l**	**5r**: 83%[c]

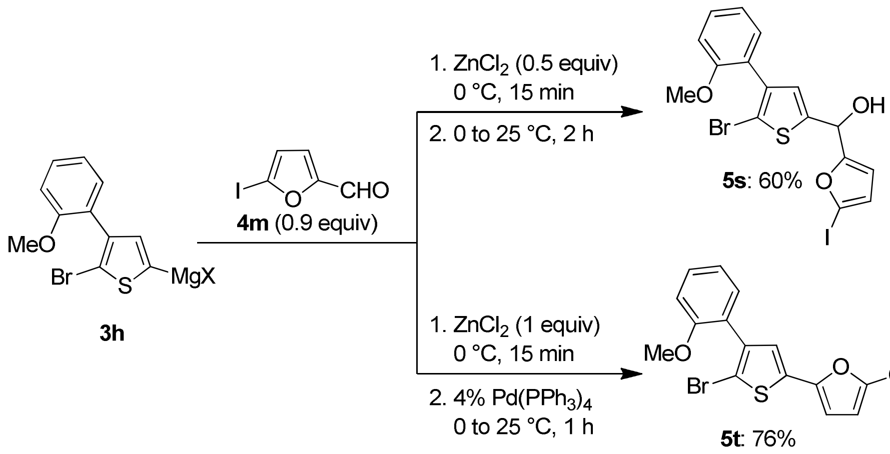
[a] Obtained after exchange reaction with *i*PrMgCl·LiCl (**1a**; 1.05 equiv) in THF at 0 °C in 1 h. Ratio of regioisomers determined by ^{1}H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after a *Negishi* cross-coupling ($ZnCl_2$ (1 equiv); then 4% $Pd(PPh_3)_4$) with ArI (0.9 or 1.1 equiv). [d] Exchange reaction performed at -20 °C in 1 h.

1.2.1 *TUNABLE REACTIVITY OF THIENYLMAGNESIUM REAGENTS TOWARDS CARBONYL DERIVATIVES*

By the reaction of magnesium species like **3h** with formyl-substituted heterocyclic iodides, it has been possible to either perform an addition to the aldehyde-group or a *Negishi* cross-coupling using the iodide substituent (Scheme 54). After transmetalation with $ZnCl_2$ (0.5 equiv), the reaction with 5-iodofuran-2-carbaldehyde (**4m**) produces rapidly the corresponding alcohol **5s** in 60% yield.[148] By the addition of 4% $Pd(PPh_3)_4$

[148] Preliminary transmetalation with $ZnCl_2$ (0.5 equiv) proved to be necessary for performing the addition to the carbonyl group. Otherwise only a I/Mg-exchange was observed.

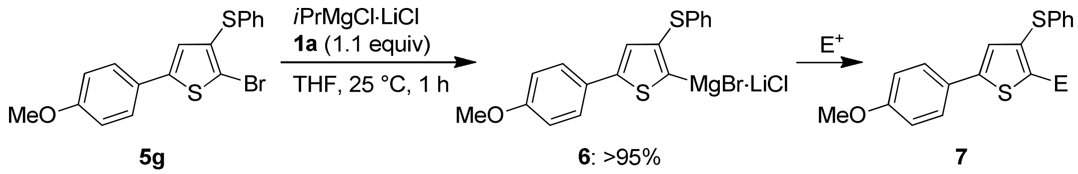
the formyl group remains untouched and the *Negishi* cross-coupling takes place leading to **5t** in 76% yield (Scheme 2).



Scheme 54: Tuneable reactivity of heteroarylmagnesium reagent **3h** towards **4m** by the presence or absence of $Pd(PPh_3)_4$.

1.2.2 FURTHER FUNCTIONALIZATION OF MONOBROMOTHIOPHENES

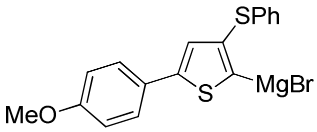
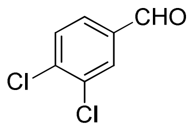
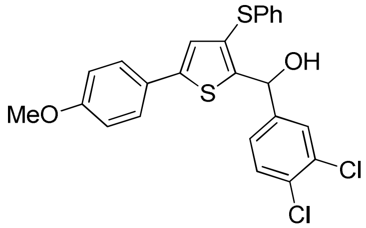
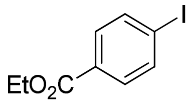
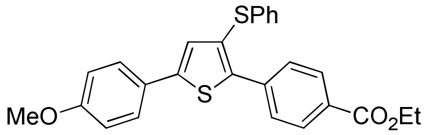
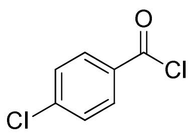
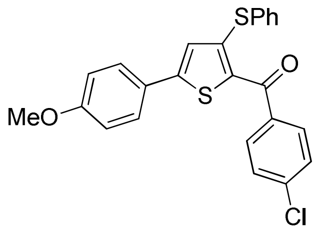
In order to exemplify the further functionalization of monobromo-thiophenes of type **5** obtained after the selective Br/Mg-exchange, the previously prepared monobromo-thiophene **5g** has been submitted to a second Br/Mg-exchange reaction using *i*PrMgCl·LiCl (**1a**; 1.1 equiv) at ambient temperature. The resulting magnesium reagent **6** was readily used in different types of functionalization reactions (Scheme 55 and Table 4).



Scheme 55: Further functionalization of cross-couling product **5g** *via* Br/Mg-exchange and subsequent reactions with different electrophiles.

Thus, thienylmagnesium reagent **6** easily adds to aldehyde **4n** providing the corresponding alcohol **7a** in 77% yield (Table 4, entry 1). After transmetalation with $ZnCl_2$ (1 equiv), a *Negishi* cross-coupling reaction with aryl iodide **4h** using 5% $Pd(PPh_3)_4$ as catalyst leads to the expected product **7b** in 73% yield (entry 2). Moreover, transmetalation with $ZnCl_2$ (1 equiv) followed by a Cu(I)-catalyzed acylation (10% CuCN·2LiCl) with the acyl chloride **4o** gives the functionalized ketone **7c** in 70% yield (entry 3).

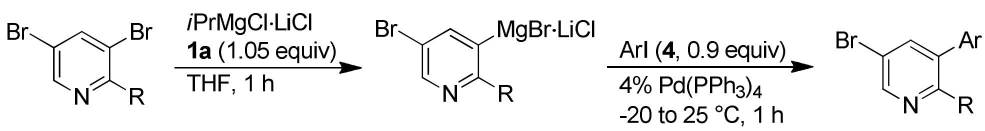
Table 4: Preparation of functionalized thiophenes of type **7** *via* regioselectively generated heteroarylmagnesium reagent **6**.

Entry	Mg-Reagent[a]	Electrophile	Product, Yield[b]
			
1	**6**	**4n**	**7a**: 77%
			
2	**6**	**4h**	**7b**: 73%[c]
			
3	**6**	**4o**	**7c**: 70%[d]

[a] Obtained after exchange reaction with *i*PrMgCl·LiCl (**1a**; 1.1 equiv) in THF at 25 °C in 1 h. [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after a *Negishi* cross-coupling ($ZnCl_2$ (1 equiv); then 5% $Pd(PPh_3)_4$) with ArI (0.9 equiv). [d] Obtained after acylation ($ZnCl_2$ (1 equiv); then 10% CuCN·2LiCl) with ArCOCl (0.9 equiv).

1.3 Regioselective Br/Mg-Exchange on Unsymmetrical 3,5-Dibromo-Pyridines Using iPrMgCl·LiCl

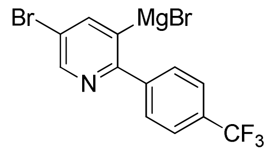
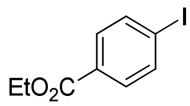
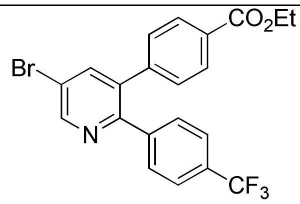
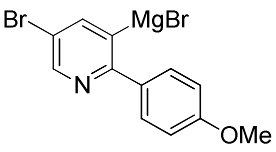
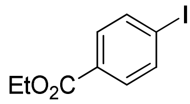
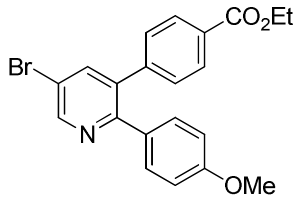
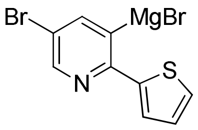
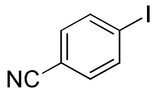
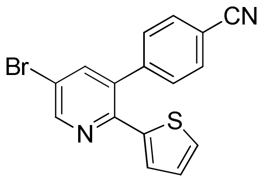
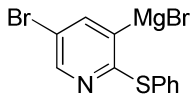
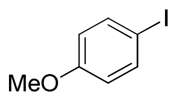
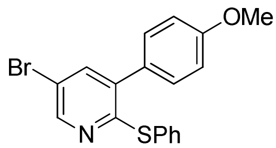
The regioselective Br/Mg-exchange has also been extended to various 3,5-dibromo-pyridine derivatives (Scheme 56). The corresponding magnesium-species **9a-d** have been obtained in satisfactory regioselectivities up to 28:1 (Table 5). Subsequent *Negishi* cross-coupling reactions after transmetalation with $ZnCl_2$ lead to trisubstituted pyridine derivatives **10a-d** in good yields (60-88%, entries 1-4). Both electron-poor and electron-rich aryl iodides have been used successfully. The cross-coupling reactions are usually completed within 1 h reaction time at 25 °C.



8 **9**: >95% (ratio regioisomers: up to 28:1) **10**: up to 88%

Scheme 56: Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromo pyridines of type **8** using *i*PrMgCl·LiCl (**1a**).

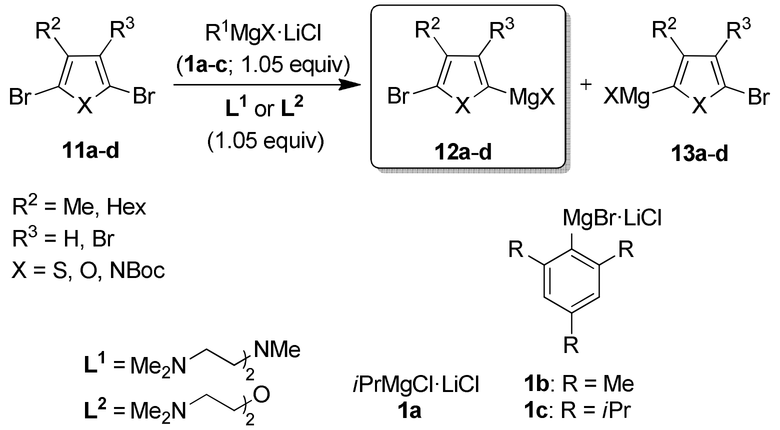
Table 5: Preparation of functionalized pyridines of type **10** *via* regioselectively generated heteroarylmagnesium reagents of type **9**.

Entry	Mg-Reagent (Conditions [T, t])[a]	Electrophile	Product, Yield[b]
1	 **9a** (-55 °C, 2 h): 27:1	 **4h**	 **10a**: 88%[c]
2	 **9b** (-78 °C, 2 h): 13:1	 **4h**	 **10b**: 64%[c]
3	 **9c** (0 °C, 1 h): 28:1	 **4k**	 **10c**: 74%[c]
4	 **9d** (-65 °C, 1 h):[d] 17:1	 **4g**	 **10d**: 60%[c]

[a] Obtained after exchange reaction with *i*PrMgCl·LiCl (**1a**; 1.05 equiv) in THF. Ratio of regioisomers determined by ^{1}H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after a *Negishi* cross-coupling ($ZnCl_2$ (1 equiv); then 4% $Pd(PPh_3)_4$) with ArI (0.9 equiv). [d] Exchange reaction was performed using *i*Pr_2Mg·LiCl (0.55 equiv).

1.4 REGIOSELECTIVE Br/Mg-EXCHANGE ON UNSYMMETRICAL DIBROMO-HETEROCYCLES USING IsitylMgBr·LiCl

Preliminary experiments showed that the regioselectivity of the Br/Mg-exchange reaction with *i*PrMgCl·LiCl (**1a**) on 2,5-dibromothiophenes with an alkyl substituent in position 3 resulted only in poor regioselectivities. Therefore, we envisioned that by increasing the steric hindrance of the *Grignard* reagent R^{1}MgX·LiCl of type **1** as well as its aggregation in solution by adding typical chelating amines as ligand (**L^1** or **L^2**) would allow to improve the regioselectivity of the Br/Mg-exchange reaction (Scheme 57).



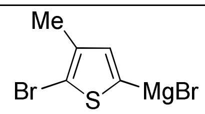
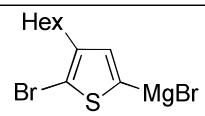
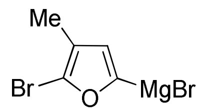
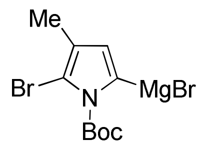
Scheme 57: Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromoheterocycles of type **11**.[149]

Thus, treatment of 2,5-dibromo-3-methylthiophene (**11a**) with *i*PrMgCl·LiCl (**1a**; 1.05 equiv) furnishes a regioisomeric mixture of the thienylmagnesium chlorides **12a** and **13a** in a ratio of 80:20 (Table 6, entry 1). However, the addition of tridentate ligands like *N*-[2-(dimethylamino)ethyl]-*N*,*N*',*N*'-trimethylethane-1,2-diamine (**L^1**; 1.05 equiv) or 2,2'-oxy-*bis*(*N*,*N*-dimethylethaneamine)[150] (**L^2**; 1.05 equiv) leading to the sterically more hindered complexes **1a·L^1** and **1a·L^2** significantly improves the regioisomeric ratio of the resulting magnesium reagents in favour of **12a** (85:15 and 87:13; entries 2-3). Moreover, lower temperatures (-60 °C, 1 h) further increase the regioisomeric ratio up to 90:10 favouring the formation of **12a** (entry 4). In comparison to secondary alkylmagnesium reagents like **1a**, arylmagnesium bromides, such as mesitylmagnesium bromide (**1b**) or isitylmagnesium bromide (**1c**), displayed lower exchange reaction rates, but lead to a regioselectivity increase from 84:16 to 96:4 (compare entry 1 with entries 5 and 7). Remarkably, the addition of 2,2'-oxy-*bis*(*N*,*N*-dimethylethan-amine) (**L^2**; 1.05 equiv) to LiCl-solubilized mesitylmagnesium bromide (**1b**; 1.05 equiv) convertes **11a** (-20 °C, 12 h) predominantly into the *Grignard* species **12a** with a regioisomeric ratio of 97:3 (entry 6). The even more sterically hindered exchange reagent isitylmagnesium bromide (**1c**) furnishes with 2,2'-oxy-*bis(N*,*N*-dimethylethanamine) (**L^2**, 1.05 equiv) at -10 °C in 16 h now a perfect regioselectivity ratio of >99:1 for **12a**:**13a** (entry 8).[151]

[149] a) S. Schröter, C. Stock, T. Bach *Tetrahedron* **2005**, *61*, 2245. b) Y. Garcia, F. Schoenebeck, C. Y. Legault, C. A. Merlic, K. N. Houk, *J. Am. Chem. Soc.* **2009**, *131*, 6632.
[150] a) X.-J. Wang, L. Zhang, X. Sun, Y. Xu, D. Krishnamurthy, C. Senanayake, *Org. Lett.* **2005**, *7*, 5593. b) C.-S. Da, J.-R. Wang, X.-G. Yin, X.-Y. Fan, Y. Liu, S.-L. Yu, *Org. Lett.* **2009**, *11*, 5578. c) Y. Liu, C.-S. Da, S.-L. Yu, X.-G. Yin, J.-R. Wang, X.-Y. Fan, W.-P. Li, R. Wang, *J. Org. Chem.* **2010**, *75*, 6869. d) X.-Y. Fan, Y.-X. Yang, F.-F. Zhuo, S.-L. Yu, X. Li, Q.-P. Guo, Z.-X. Du, Z.-S. Da, *Chem. Eur. J.* **2010**, *16*, 7988.
[151] The regioisomer **13a** was not observed in ^{1}H NMR measurements of the hydrolyzed crude reaction mixture (HOAc, 10 equiv, -20 to 25 °C).

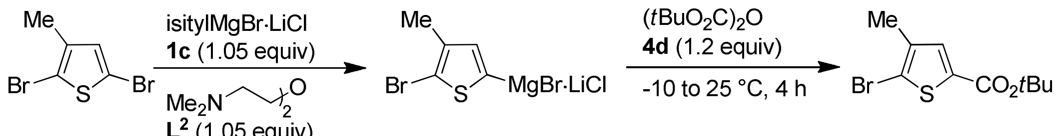
These results were extended to various 2,5-dibromo-heterocycles (**11b-d**; entries 9-14). In each case the use of the sterically hindered *Grignard* reagent **1c** in combination with $(Me_2NCH_2CH_2)_2O$ ($\mathbf{L^2}$; 1.05 equiv) gives the best results (compare entries 9, 11, 13 with 10, 12 and 14). However, the use of the bulky reagent $\mathbf{1c{\cdot}L^2}$ lead to significantly lower exchange rates and the Br/Mg-exchanges requires ca. 16 h compared to 1-6 h.

Table 6: Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromoheterocycles bearing alkyl substituents using various complexed and uncomplexed *Grignard* reagents of type **1**.

Entry	$\mathbf{R^1MgX{\cdot}LiCl}$	Ligand	Conditions [T, t][a]	Product of Type 10, Ratio Regioisomers[b]
				
1	**1a**	-	-20 °C, 20 min	**12a**: 80:20
2	**1a**	$\mathbf{L^1}$	-20 °C, 20 min	**12a**: 85:15
3	**1a**	$\mathbf{L^2}$	-20 °C, 20 min	**12a**: 87:13
4	**1a**	$\mathbf{L^2}$	-60 °C, 1 h	**12a**: 90:10
5	**1b**	-	-20 °C, 12 h	**12a**: 84:16
6	**1b**	$\mathbf{L^2}$	-20 °C, 12 h	**12a**: 97:3
7	**1c**	-	-10 °C, 12 h	**12a**: 96:4
8	**1c**	$\mathbf{L^2}$	-10 °C, 16 h	**12a**: >99:1[c]
				
9	**1a**	$\mathbf{L^2}$	-10 °C, 20 min	**12b**: 85:15
10	**1c**	$\mathbf{L^2}$	-10 °C, 16 h	**12b**: >99:1[c]
				
11	**1a**	$\mathbf{L^2}$	-10 °C, 6 h	**12c**: 80:20
12	**1c**	$\mathbf{L^2}$	-10 °C, 16 h	**12c**: >99:1
				
13	**1a**	$\mathbf{L^2}$	-10 °C, 6 h	**12d**: 75:25
14	**1c**	$\mathbf{L^2}$	-10 °C, 16 h	**12d**: 91:9

[a] Complete conversion as determined by GC analysis of an iodolyzed reaction aliquot. [b] Determined by ^{1}H NMR anaylsis of the quenched crude reaction mixture (HOAc, 10 equiv). [c] The regioisomer of type **13** was not observed in ^{1}H NMR analysis of the hydrolyzed crude reaction mixture (HOAc, 10 equiv, -20 to 25 °C).

With these conditions in hand (**1c·L²**, -10 °C, 16 h) various five-membered heterocyclic species have been selectively magnesiated with a regioselectivity of >99:1. Thus, 2,5-dibromo-3-methylthiophene (**11a**) undergoes readily the Br/Mg-exchange with isitylmagnesium bromide (**1c**, 1.05 equiv) in combination with 2,2'-oxy-*bis(N,N*-dimethylethanamine) (**L²**, 1.05 equiv) at -10 °C in 16 h in perfect regioselectivity of >99:1. The reaction of the corresponding organomagnesium reagent **12a** with di-*tert*-butyl dicarbonate (**4d**) leads to the ester-substituted thiophene derivative **14a** in 83% yield (Scheme 58).



11a **12a**: >95% (ratio regioisomers: >99:1) **14a**: 83%

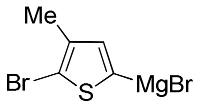
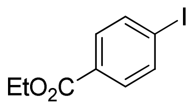
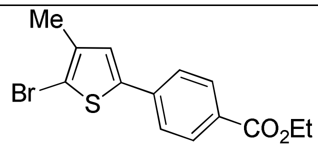
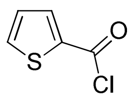
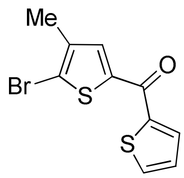
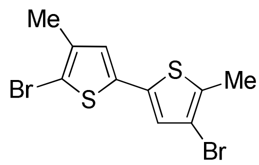
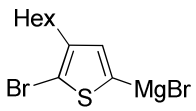
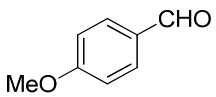
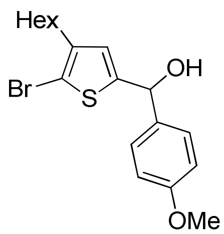
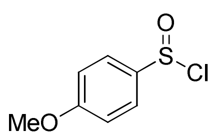
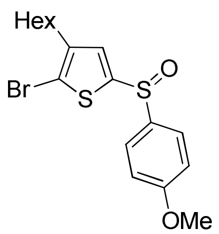
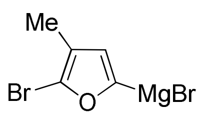
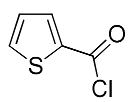
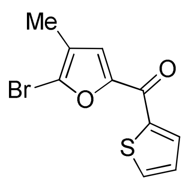
Scheme 58: Regioselective Br/Mg-exchange on unsymmetrical 2,5-dibromothiophene **11a** using isitylMgBr·LiCl (**1c**) in combination with ligand **L²**.

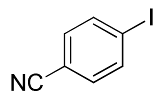
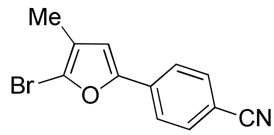
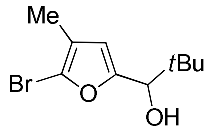
After transmetalation with $ZnCl_2$ (1 equiv), the *Negishi* cross-coupling reaction of magnesium species **12a** with ethyl 4-iodobenzoate (**4h**) using 4% $Pd(PPh_3)_4$ as catalyst furnishes the corresponding arylated thiophene **14b** in 86% yield (Table 7, entry 1). Moreover, transmetalation of **12a** with $ZnCl_2$ (1 equiv) followed by a Cu(I)-catalyzed acylation (10% CuCN·2LiCl) with thiophene-2-carbonyl chloride (**4p**) produces the functionalized ketone **14c** in 85% yield (entry 2). Similarly, the transmetalation of **12a** with $ZnCl_2$ (0.5 equiv) followed by CuCN·2LiCl (0.5 equiv) and the addition of chloranil (1.5 equiv) generates the substituted thiophenyl dimer **14d** in 87% yield (entry 3).[152] Furthermore, also the *n*-hexyl-substituted dibromothiophene **11b** can be converted to the corresponding magnesium reagent **12b** in perfect regioselectivity by applying this methodology. The addition of **12b** to anisaldehyde (**4e**) leads to the expected alcohol **14e** in 71% yield (entry 4). Moreover, the direct reaction of 4-methoxybenzenesulfinyl chloride (**4q**) with the heterocyclic magnesium-species **12b** furnishes sulfoxide **14f** in 70% yield (entry 5).[153] Besides alkyl-substituted dibromothiophenes, also the methyl-substituted furan **11c** has been regioselectively converted to its magnesium species **12c**. Through transmetalation of **12c** with $ZnCl_2$ (1 equiv) followed by a Cu(I)-catalyzed acylation (10% CuCN·2LiCl) with acyl chloride **4p** the functionalized ketone **14g** has been obtained in 79% yield (entry 6). The Pd-catalyzed cross-coupling of **12c** with

[152] A. Krasovskiy, A. Tishkov, V. Del Almo, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 5010.
[153] a) C. B. Rauhut, L. Melzig, P. Knochel, *Org. Lett.* **2008**, *10*, 3891. b) L. Melzig, C. B. Rauhut, P. Knochel, *Synthesis* **2009**, *6*, 1041. c) L. Melzig, C. B. Rauhut, N. Naredi-Rainer, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 5362.

4-iodobenzonitril (**4k**) furnishes after transmetalation with $ZnCl_2$ the desired product **14h** in 78% yield (entry 7). Finally, alcohol **14i** has been obtained in 73% yield by addition of magnesium species **12c** to pivalaldehyde (**4r**) (entry 8).

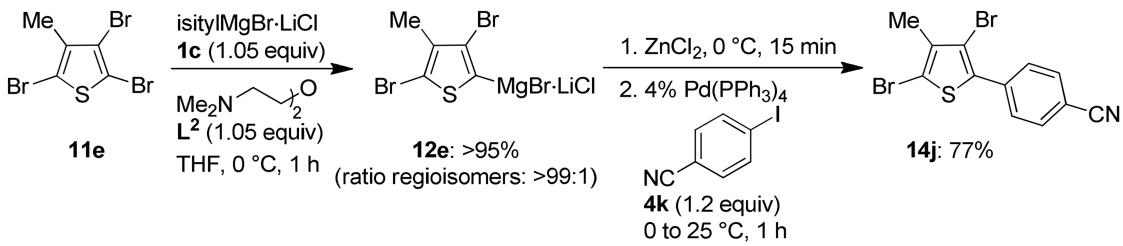
Table 7: Preparation of functionalized five-membered heterocycles of type **14** *via* regioselectively generated heteroarylmagnesium reagents of type **12**.

Entry	Mg-Reagent[a]	Electrophile	Product, Yield[b]
1	 **12a**: >99:1	 **4h**	 **14b**: 86%[c]
2	**12a**: >99:1	 **4p**	 **14c**: 85%[d]
3	**12a**: >99:1	-	 **14d**: 87%[e]
4	 **12b**: >99:1	 **4e**	 **14e**: 71%
5	**12b**: >99:1	 **4q**	 **14f**: 70%
6	 **12c**: >99:1	 **4p**	 **14g**:79%[d]

7	**12c**: >99:1	 **4k**	 **14h**: 78%[c]
8	**12c**: >99:1	*t*BuCHO **4r**	 **14i**: 73%

[a] Obtained after exchange reaction with **1c** (1.05 equiv) and **L^2** (1.05 equiv) in THF at -10 °C in 16 h. Ratio of regioisomers determined by ^{1}H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after a *Negishi* cross-coupling ($ZnCl_2$ (1 equiv); then 4% $Pd(PPh_3)_4$) with ArI (0.9 or 1.2 equiv). [d] Obtained after acylation ($ZnCl_2$ (1 equiv); then 10% CuCN·2LiCl) with ArCOCl (0.9 or 1.2 equiv). [e] Obtained after transmetalation with $ZnCl_2$ (0.5 equiv) and a copper-mediated oxidative dimerization (CuCN·2LiCl (0.5 equiv); then addition of chloranil (1.5 equiv)).

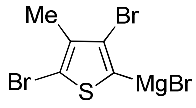
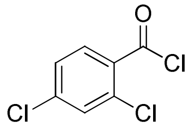
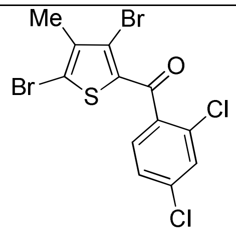
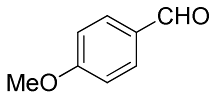
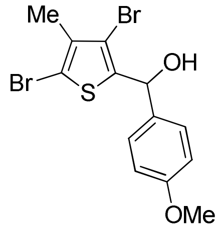
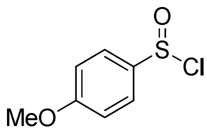
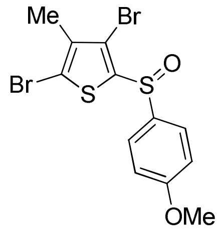
Remarkably, also the tribromothiophene **11e** undergoes a smooth Br/Mg-exchange with perfect regioselectivity. The reaction of **11e** with isitylmagnesium bromide (**1c**, 1.05 equiv) in combination with 2,2'-oxy-*bis(N,N*-dimethylethanamine) (**L^2**, 1.05 equiv) proceeds at 0 °C within 1 h furnishing the magnesium species **12e** in >99:1 regioselectity (Scheme 59). In this case, the exchange reaction is faster compared to the dibromo-analogon **11a** due to the inductive effect of the additional bromine atom in position 3 of the thiophene ring. After transmetalation of **12e** with $ZnCl_2$ a Pd-catalyzed cross-coupling with 4-iodobenzonitril (**4k**) furnishes the tetrasubstituted thiophene **14j** in 77% yield.



Scheme 59: Regioselective Br/Mg-exchange on unsymmetrical 2,3,5-tribromothiophene **11e** using isitylMgBr·LiCl (**1c**) in combination with ligand **L^2**.

Moreover, transmetalation of **12e** with $ZnCl_2$ (1 equiv) followed by a Cu(I)-catalyzed acylation (10% CuCN·2LiCl) with the acyl chloride **4s** gives the functionalized ketone **14k** in 86% yield (Table 8, entry 1). The addition reaction of **12e** and anisaldehyde (**4e**) produces the desired alcohol **14l** in 88% yield (entry 2). Finally, the direct reaction of 4-methoxybenzenesulfinyl chloride (**4q**) with the heterocyclic magnesium-species **12e** furnishes sulfoxide **14m** in 94% yield (entry 3).

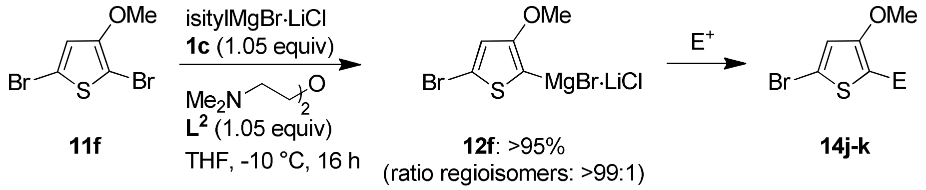
Table 8: Preparation of functionalized five-membered heterocycles of type **14** *via* regioselectively generated heteroarylmagnesium reagents of type **12**.

Entry	Mg-Reagent[a]	Electrophile	Product, Yield[b]
1	 **12e**: >99:1	 **4s**	 **14k**: 86%[c]
2	**12e**: >99:1	 **4e**	 **14l**: 88%
3	**12e**: >99:1	 **4q**	 **14m**: 94%

[a] Obtained after exchange reaction with **1c** (1.05 equiv) and $\mathbf{L^2}$ (1.05 equiv) in THF at 0 °C in 1 h. Ratio of regioisomers determined by ^{1}H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after acylation ($ZnCl_2$ (1 equiv); then 10% CuCN·2LiCl) with ArCOCl (0.9 or 1.2 equiv).

Interestingly, the Br/Mg-exchange reaction of 2,5-dibromo-3-methoxythiophene with isitylmagnesium bromide (**1c**) in combination with 2,2'-oxy-*bis(N*,*N*-imethylethan-amine) leads to the 2-magnesiated thiophene **12f** (Scheme 60) and not to the 5-magnesiated one (as for the other dibromo-thiophene derivatives **11a-c** and **11e**). It is assumed that this selectivity resulted from a preliminary coordination of the bulky magnesium reagent to the oxygen of the methoxy substituent. This complexation seems to be essential for the Br/Mg-exchange reaction to proceed. In contrast, by using *i*PrMgCl·LiCl (**1a**) in the exchange reaction, the opposite selectivity has been observed (4:1 ratio in favour of the 5-magnesiated thiophene).[154] This might be a result of the high reactivity of *i*PrMgCl·LiCl (**1a**) that allows the exchange reaction to proceed without prior chelation in an etheral solvent like THF.

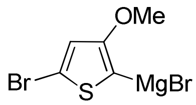
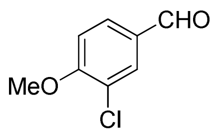
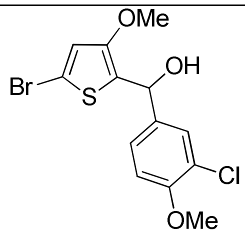
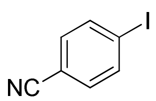
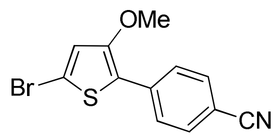
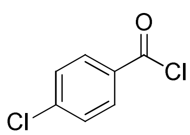
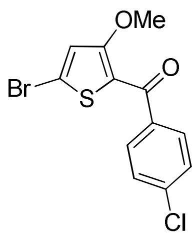
[154] The exchange reaction was carried out under the same conditions as described in Scheme 58 and Table 7 but at -78 °C. Higher temperatures deteriorated the ratio. At ambient temperature, the observed ratio was 2.4:1 in favour of the 5-magnesiated derivative.



Scheme 60: Regioselective Br/Mg-exchange on 2,5-dibromo-3-methoxythiophene **11f** using isitylMgBr·LiCl (**1c**) in combination with ligand $\mathbf{L^2}$.

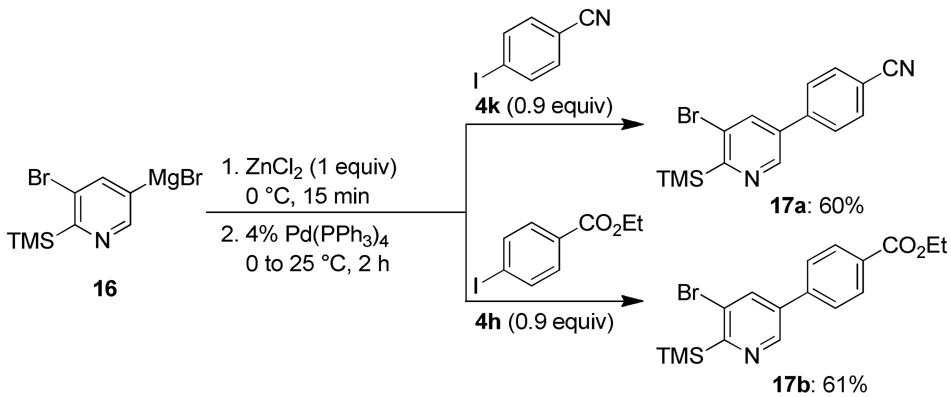
Thus, thienylmagnesium reagent **12f** easily adds to aldehyde **4a** providing the corresponding alcohol **14n** in 73% yield (Table 9, entry 1). After transmetalation with $ZnCl_2$ (1 equiv), a *Negishi* cross-coupling reaction with aryl iodide **4k** using 5% $Pd(PPh_3)_4$ as catalyst leads to the expected product **14o** in 69% yield (entry 2). Moreover, transmetalation with $ZnCl_2$ (1 equiv) followed by a Cu(I)-catalyzed acylation (10% CuCN·2LiCl) with the acyl chloride **4o** gives the functionalized ketone **14p** in 66% yield (entry 3).

Table 9: Preparation of functionalized five-membered heterocycles of type **14** *via* regioselectively generated heteroarylmagnesium reagents of type **12**.

Entry	Mg-Reagent[a]	Electrophile	Product, Yield[b]
			
1	**12f**: >99:1	**4a**	**14n**: 73%
			
2	**12f**: >99:1	**4k**	**14o**: 69%[c]
			
3	**12f**: >99:1	**4o**	**14p**: 66%[d]

[a] Obtained after exchange reaction with **1c** (1.05 equiv) and $\mathbf{L^2}$ (1.05 equiv) in THF at -10 °C in 16 h. Ratio of regioisomers determined by ^{1}H NMR analysis of the quenched crude reaction mixture (HOAc, 10 equiv). [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after a *Negishi* cross-coupling ($ZnCl_2$ (1 equiv); then 4% $Pd(PPh_3)_4$) with ArI (0.9 or 1.2 equiv). [d] Obtained after acylation ($ZnCl_2$ (1 equiv); then 10% CuCN·2LiCl) with ArCOCl (0.9 or 1.2 equiv).

The regioselective Br/Mg-exchange with **1c·L²** has also been extended to 3,5-dibromo-2-(trimethylsilyl)pyridine (**15**) leading to the corresponding magnesium reagent **16** at -25 °C within 2 h (Scheme 61). The subsequent *Negishi* cross-coupling reactions after transmetalation with $ZnCl_2$ led to trisubstituted pyridine derivatives **17a-b** in satisfactory yields (60-61%, Scheme 61).

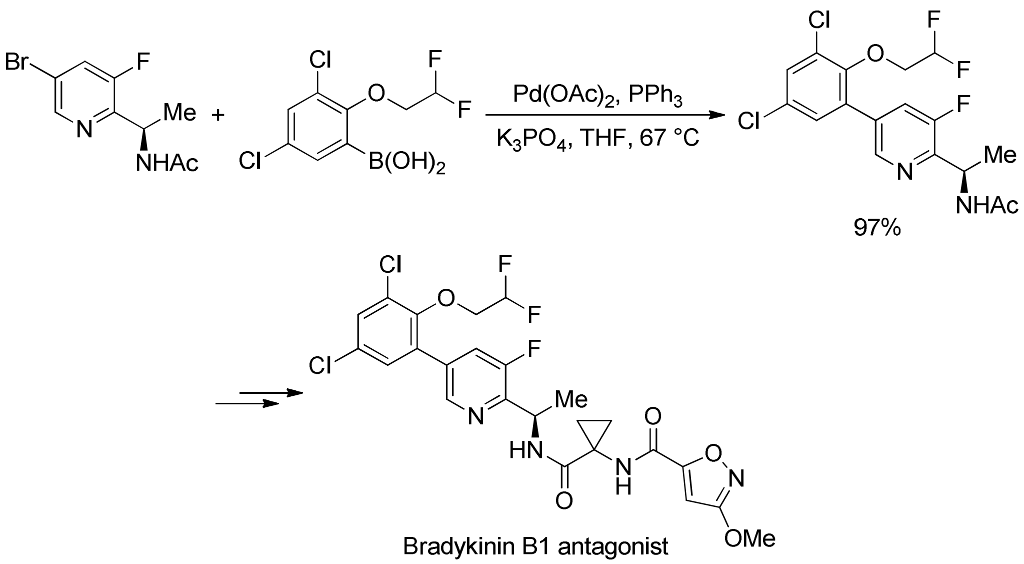


Scheme 61: Preparation of functionalized pyridines of type **17** *via* regioselectively generated heteroarylmagnesium reagent **16**.

2. ONE-POT PREPARATION OF MAGNESIUM DI(HETERO)ARYL- AND DIALKENYLBORONATES FOR *SUZUKI-MIYAURA* CROSS-COUPLINGS

2.1 INTRODUCTION

Organoboron derivatives have found broad applications for the performance of *Suzuki-Miyaura* cross-couplings.[7,49] In particular, various boronic acids,[52] esters[46-48] and their derivatives, such as trifluoroborates,[53,54] MIDA boronates[55] or DAN reagents[56] have been used very successfully as synthetic tools in the preparation of natural products and pharmaceutically active compounds. *Shultz et al.* for example described a convenient synthetic route for the preparation of a Bradykinin B1 antagonist including a *Suzuki-Miyaura* cross-coupling as key step (Scheme 62).[155] Bradykinin B1 is a kinin responsible for the mediation of physiological processes accompanying acute and chronic pain and inflammation.[156]

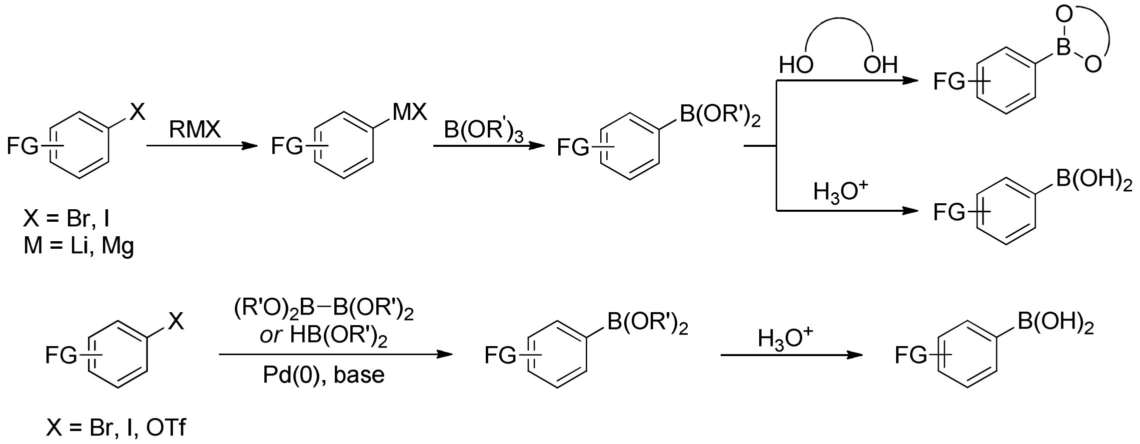


Scheme 62: *Suzuki-Miyaura* cross-coupling as key step in the synthesis of a Bradykinin B1 antagonist.

However, the known methods for preparation of the aforementioned organoboron reagents suffer from major drawbacks, such as multi-step syntheses, low atom-economy, expensive transition-metal catalysis or low tolerance towards functional groups. In general, most arylboronic compounds are prepared *via* Li- or Mg-organometallics in a

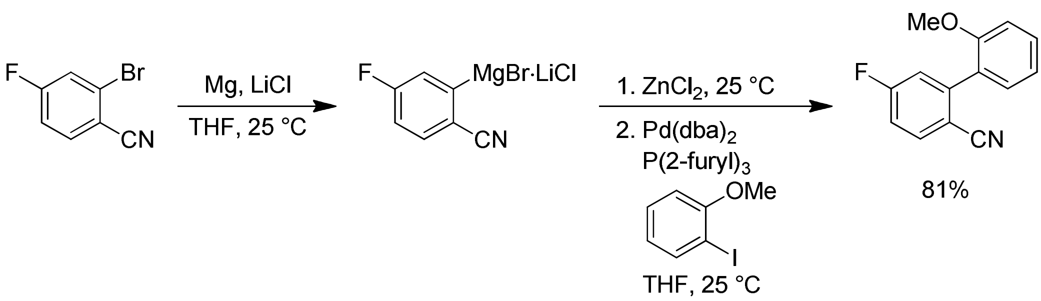
[155] P. D. O'Shea, D. Gauvreau, F. Gosselin, G. Hughes, C. Nadeau, A. Roy, C. S. Shultz, *J. Org. Chem.* **2009**, *74*, 4547.
[156] M. G. Bock, J. Longmore, *Curr. Opin. Chem. Biol.* **2000**, *4*, 401.

two-step process,[32a-c,35,36,157] although direct transition metal-catalyzed borylations can be realized (Scheme 63).[46-48,158]



Scheme 63: Common syntheses of arylboronate esters and acids.

In the search of a convenient, general and atom-economical4 method for the preparation of boronic derivatives suitable for cross-coupling reactions, we investigated a one-pot procedure using inexpensive aryl bromides, magnesium as a low-cost reducing agent with little toxicity and a trialkylborate as cheap boron source. Thus, we utilized the accelerating effect of LiCl as additive in direct metal insertions allowing the presence of a broad range of sensitive functional groups in organometallic reagents recently reported by *Knochel et al.*[21,64,159] 2-bromo-4-fluorobenzonitrile for instance undergoes smoothly a direct Mg-insertion in the presence of LiCl furnishing the corresponding organo-magnesium compound at room temperature tolerating the nitril-group (Scheme 64).



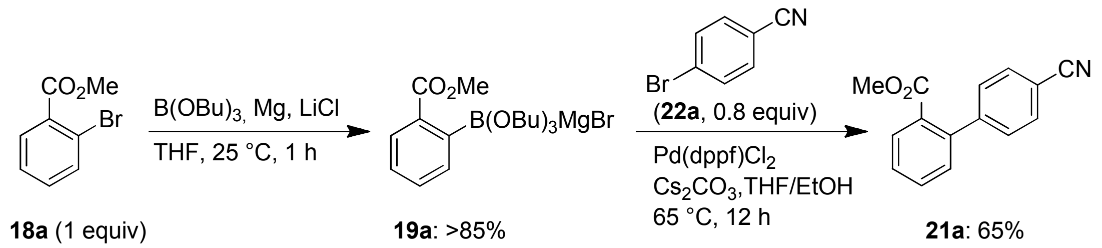
Scheme 64: LiCl-mediated preparation of (2-cyano-5-fluorophenyl)magnesium bromide and subsequent *Negishi* cross-coupling.

[157] a) D. D. Winkle, K. M. Schaab, *Org. Process Res. Dev.* **2001**, *5*, 450. b) M. Vaultier, B. Carboni, in *Comprehensive Organometallic Chemistry* (Eds.: G. Wilkinson, F. G. Stone, E. W. Abel), Pergamon, New York, **1995**, Vol. 11, 191. c) K. Smith, A. Pelter, in *Comprehensive Organic Synthesis*, (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1991**, Vol. 8, 703. d) M. Zaidlewicz, M. Krzeminski, *Science of Synthesis*, **2004**, *6*, 1097. e) M. M. Midland, *Chem. Rev.* **1989**, *89*, 1553. f) C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415. g) V. Darmency, P. Renaud, *Top. Curr. Chem.* **2006**, *263*, 71.

[158] a) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890. b) C. Kleeberg, L. Dang, Z. Lin, T. B. Marder, *Angew. Chem. Int. Ed.* **2009**, *48*, 5350. c) L. Dang, Z. Lin, T. B. Marder, *Chem. Commun.*, **2009**, 3987.

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

Based on this methodology, we explored various borate sources for the *in situ* trapping of the generated organomagnesium intermediate. The treatment of methyl 2-bromobenzoate (**18a**) with commercially available Mg turnings (1.6 equiv), $B(OBu)_3$ (1.0 equiv) and LiCl (1.1 equiv) furnishes within 1 h the magnesium arylboronate **19a** in full conversion at ambient temperature. Its cross-coupling with 4-bromobenzonitrile (**22a**) using 4% Pd(dppf)Cl[160] and Cs_2CO_3 (2 equiv) in a 1:1 THF/EtOH mixture provides the desired cross-coupling product **21a** in 65% yield (Scheme 65).



Scheme 65: Preparation of magnesium arylboronate **19a** and subsequent *Suzuki-Miyaura* cross-coupling.

Interestingly, the alternative conversion of **18a** to the corresponding zinc reagent using Mg turnings (1.6 equiv), $ZnCl_2$ (1.0 equiv) and LiCl (1.1 equiv) in THF[21] requires 3 h reaction time showing that the presence of $B(OBu)_3$ significantly accelerates the Mg-insertion. Besides $B(OBu)_3$ also other boron compounds such as $B(OMe)_3$, $B(OEt)_3$, $B(O\textit{i}Pr)_3$, $B(OAc)_3$, and even $NaB(OMe)_4$ or $LiB(OMe)_4$, proved to be feasible for *in situ* trapping of the magnesium reagent. However $B(OBu)_3$ was found to be the most promising boron source since no transesterification reactions with sensitive substrates like methyl 2-bromobenzoate (**18a**) were observed.

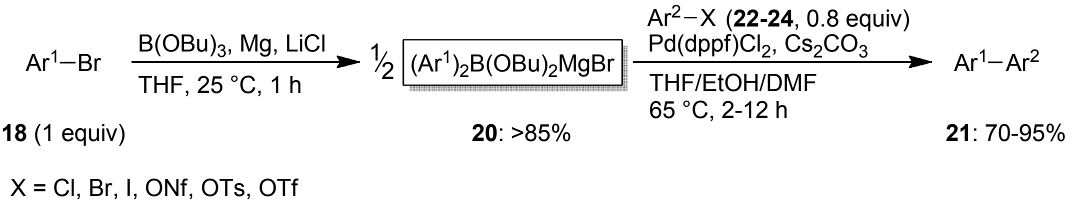
2.2 PREPARATION OF MAGNESIUM DIARYLBORONATES VIA MAGNESIUM-INSERTION FOR SUZUKI-MIYAURA CROSS-COUPLINGS

With these results in hands, the methodolody has been optimized considering both sufficiently fast reaction times while using only minimal amounts of the boron source. A better atom economy can be achieved without a loss of yield by using 0.5 equiv of $B(OBu)_3$ and forming therefore magnesium diarylboronates of type **20** (Scheme 66).[161] Remarkably, both aryl groups (Ar^1) are transferred under typical *Suzuki-Miyaura* cross-

[160] a) R.-S. *Gan*, T. S. Hor, in *Ferrocenes* (Eds.: A. Togni, T. Hayashi), Wiley-VCH, Weinheim, **1995**. b) G. A. Molander, M. R. Rivero, *Org. Lett.* **2002**, *4*, 107. c) G. A. Molander, C.-S. Yun, M. Ribagorda, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 5534.

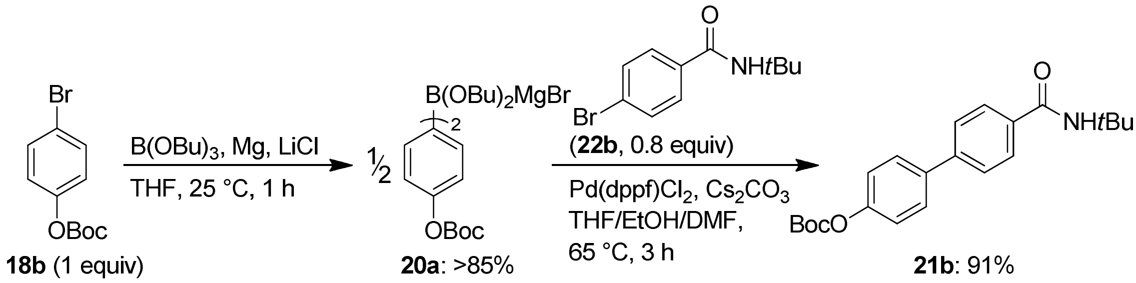
[161] NMR-experiments indicate that several arylboronates like $ArB(OBu)_3MgX$, $Ar_2B(OBu)_2MgX$ and $Ar_3B(OBu)MgX$ are in fact formed and that the formula $Ar_2B(OBu)_2MgX$ reflects only the stoichiometry used.

coupling conditions using various aryl halides or pseudo-halides of type Ar^2-X (**22-24**, X = Cl, Br, I, ONf,[162] OTs,[163] OTf[164]).



Scheme 66: General equation for the synthesis and cross-coupling of magnesium diarylboronates of type **20**.

Thus, under typical reaction conditions, the sensitive Boc-protected bromophenol **18b** reacted with $B(OBu)_3$ (0.5 equiv), Mg (1.6 equiv) and LiCl (1.1 equiv) in THF within 1 h at 25 °C providing the magnesium diarylboronate **20a** (>85% yield, Scheme 67). Its Pd-cross-coupling with the bromobenzamide **22b** proceeds within 3 h at 65 °C using 4% $Pd(dppf)Cl_2$ and Cs_2CO_3 (2 equiv) in a 4:4:1 THF/EtOH/DMF mixture and leads to the functionalized biphenyl **21b** in 91% yield clearly demonstrating that both aryl groups of **20a** are available for the cross-coupling.



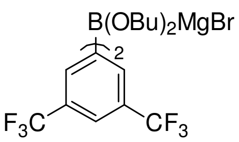
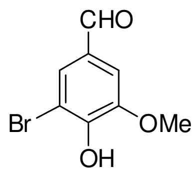
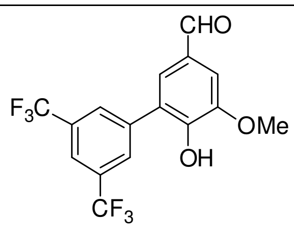
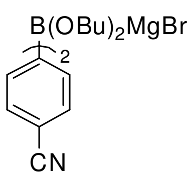
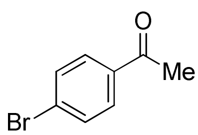
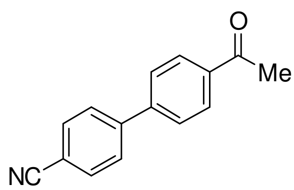
Scheme 67: Preparation and subsequent cross-coupling of magnesium diarylboronate **20a**.

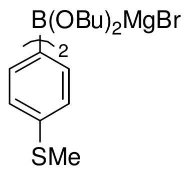
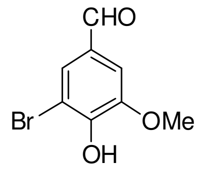
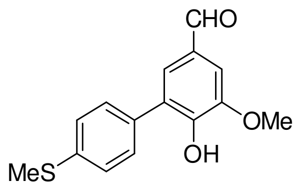
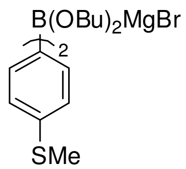
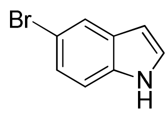
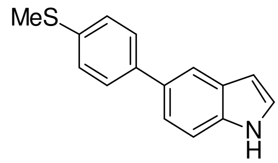
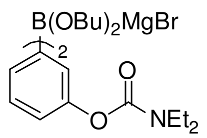
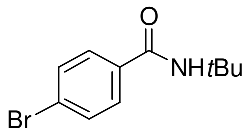
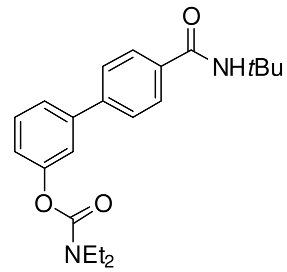
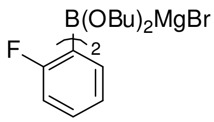
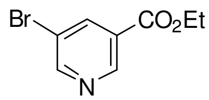
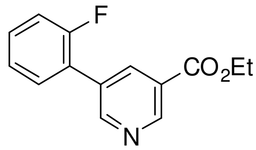
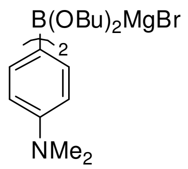
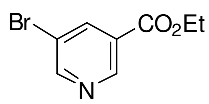
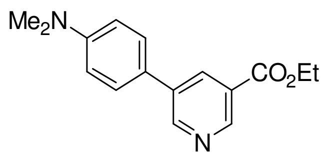
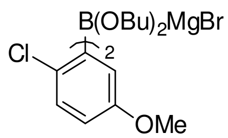
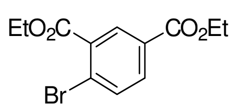
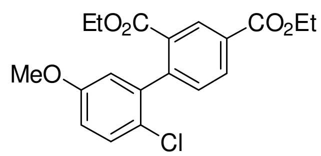
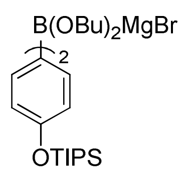
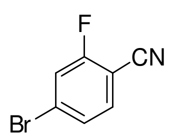
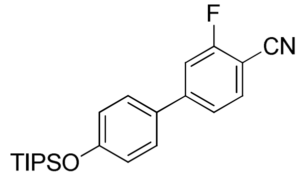
This behaviour was general and a wide range of diarylboronates of type **20** bearing various functional groups (ester, cyanid, Boc-, (thio)methoxy-, amino- or silyl-group) were prepared conveniently at 25 °C within 15 min to 1 h. The subsequent cross-coupling reactions of the magnesium diarylboronates **20b-i** with a broad variety of aryl and heteroaryl bromides as electrophiles produce under standard conditions the desired products **21c-k** in excellent yields (Table 10). In particular, 1-bromo-bis(trifluoromethyl)-benzene (**18c**) was efficiently converted into the corresponding diarylboronate **20b** *via* the direct magnesium insertion (Mg (1.6 equiv), LiCl (1.1 equiv))

[162] a) J. Hoegermeier, H.-U. Reissig, *Chem. Eur. J.* **2007**, *13*, 2410. b) J. Dash, T. Lechel, H.-U. Reissig, *Org. Lett.* **2007**, *9*, 5541. c) J. B. Grimm, K. J. Wilson, D. J. Witter, *J. Org. Chem.* **2009**, *74*, 6390.
[163] a) B. Bhayana, B. P. Fors, S. L. Buchwald, *Org. Lett.* **2009**, *11*, 3954. b) L . Zhang, T. Meng, J. Wu, *J. Org. Chem.* **2007**, *72*, 9346. c) D. Zim, V. R. Lando, J. Dupont, A. L. Monteiro, *Org. Lett.* **2001**, *3*, 3049.
[164] a) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020. b) G. A. Molander, C. R. Bernardi, *J. Org. Chem.* **2002**, *67*, 8424. c) G. A. Molander, C.-S. Yun, *Tetrahedron* **2002**, *58*, 1465.

in the presence of trisbutylborate ($B(OBu)_3$ (0.5 equiv)). Subsequent *Suzuki-Miyaura* cross-coupling with 5-bromovanillin (**22c**) bearing an aldehyde-, a methoxy- and a hydroxy-function furnishes successfully the substituted vanillin **21c** in 83% yield (entry 1). The diarylboronate **20c** bearing a nitril group has been prepared under standard conditions and undergoes smoothly the cross-coupling reaction with 4-bromo-acetophenone (**22d**) leading to the functionalized biphenyl **21d** in 82% yield (entry 2). Furthermore, using the same conditions, the dithioanisylboronate **20d** readily furnishes after the Pd-catalyzed cross-coupling the desired products **21e** and **21f** in 87-92% yield (entries 3 and 4). Noteworthy, the unprotected 5-bromoindole (**22e**) could be used as electrophile without hempering the cross-coupling. Moreover, also the corresponding diarylboronate **20e** of 3-bromophenyl diethylcarbamate (**18f**) has been successfully cross-coupled with the secondary amide **22b** bearing an acidic proton. The desired product **21g** has been obtained in 90% yield (entry 5). Also the ester-substituted bromopyridine **22f** could be successfully applied as electrophile. The fluoro- and amino-substituted diarylboronates **20f** and **20g** react readily in the cross-coupling reaction furnishing the corresponding products **21h** and **21i** in 79% and 90% yield respectively (entries 6 and 7). The cross-coupling reactions of the diarylboronates **20h** and **20i** with the electron-poor electrophiles **22g** and **22h** proceed well under standard conditions and the highly substituted biphenyls **21j** and **21k** have been optained in high yields (entries 8 and 9).

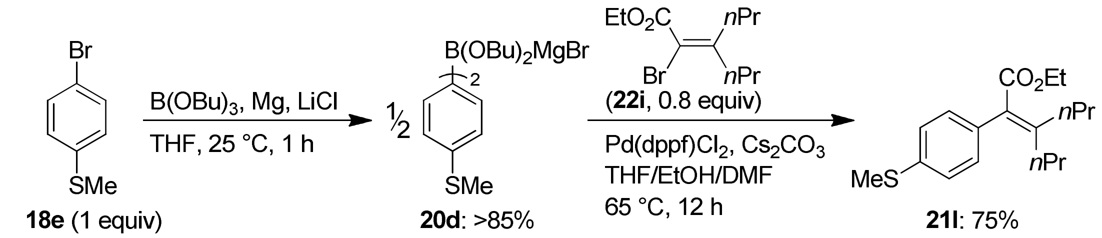
Table 10: *Suzuki-Miyaura* cross-couplings performed with magnesium diarylboronates of type **20** and aryl bromides of type **22** as electrophiles.

Entry	$Ar_2B(OBu)_2MgBr$ (conditions [T, t])	Electrophile	Product (t, Yield[a])
			
1	**20b** (25 °C, 15 min)	**22c**	**21c** (12 h, 83%)
			
2	**20c** (25 °C, 1 h)	**22d**	**21d** (12 h, 82%)

3	 **20d** (25 °C, 1 h)	 **22c**	 **21e** (6 h, 87%)
4	 **20d** (25 °C, 1 h)	 **22e**	 **21f** (6 h, 92%)
5	 **20e** (25 °C, 1 h)	 **22b**	 **21g** (7 h, 90%)
6	 **20f** (25 °C, 1 h)	 **22f**	 **21h** (3 h, 79%)
7	 **20g** (25 °C, 1 h)	 **22f**	 **21i** (2 h, 90%)
8	 **20h** (25 °C, 1 h)	 **22g**	 **21j** (6 h, 81%)
9	 **20i** (25 °C, 1 h)	 **22h**	 **21k** (3 h, 70%)

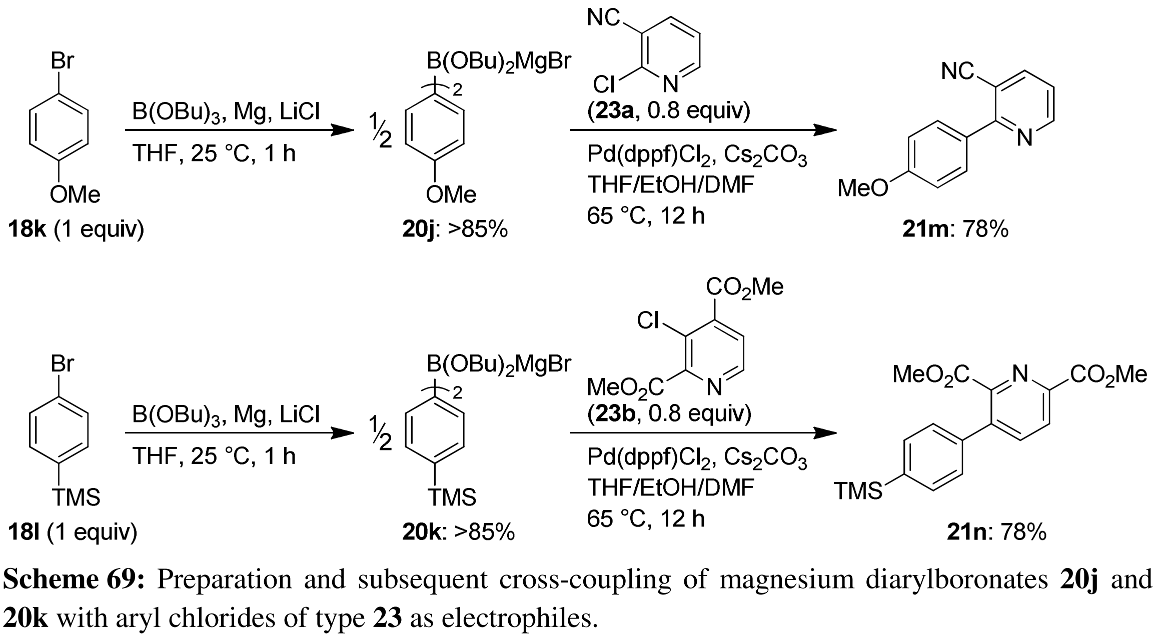
[a] Yield of isolated, analytically pure product.

As shown in Scheme 68, also alkenyl bromides can be used as electrophiles in the *Suzuki-Miyaura* cross-coupling. Thus, the highly functionalized styrene derivative **21l** has been obtained *via* the Pd-catalyzed cross-coupling of dithioanisylboronate **20d** and alkenyl bromide **22i** in 75% yield.



Scheme 68: Preparation and subsequent cross-coupling of magnesium diarylboronate **20d** with the alkenyl bromide **22i**.

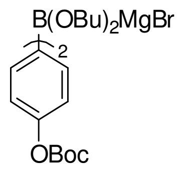
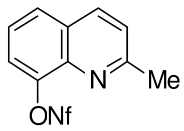
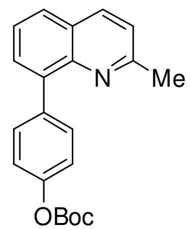
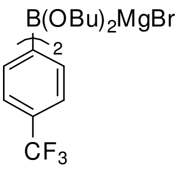
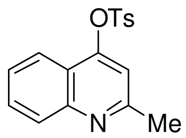
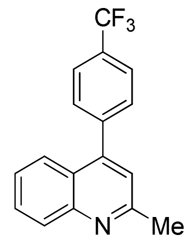
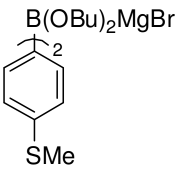
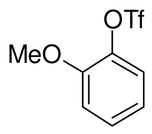
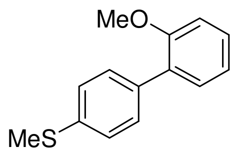
Although aryl bromides have been used mostly as electrophiles (Table 10), also heteroaryl chlorides readily undergo the *Suzuki-Miyaura* cross-coupling with diarylboronates of type **20** without any further optimization (Scheme 69). Thus, dianisylboronate **20j** readily furnishes after the Pd-catalyzed cross-coupling with 2-chloronicotinonitrile (**23a**) the desired product **21m** in 78% yield. Moreover, the highly functionalized pyridine derivative **21n** could be synthesized in high yield *via* the Pd-catalyzed reaction of the trimethylsilyl-substituted diarylboronate **20k** with the chloropyridine **23b**.



Scheme 69: Preparation and subsequent cross-coupling of magnesium diarylboronates **20j** and **20k** with aryl chlorides of type **23** as electrophiles.

Furthermore, also aryl pseudo-halides proved to be versatile electrophiles for the cross-coupling reaction with diarylboronates of type **20** (Table 11). The diarylboronate **20a** prepared from the corresponding Boc-protected bromophenol **18b** undergoes smoothly the Pd-catalyzed cross-coupling with nonaflate **24a** and furnishes the desired product **21o** in 78% yield (entry 1). Also the tosylate **24b** has been successfully employed in the cross-coupling reaction with the trifluoromethyl-substituted diarylboronate **20l** leading to the functionalized quinoline derivative **21p** in 70% yield (entry 2). Finally, dithioanisyl-boronate **20d** readily reacts in the Pd-catalyzed cross-coupling with the triflate **24c** to the functionalized biphenyl **21q** in 81% yield (entry 3).

Table 11: *Suzuki-Miyaura* cross-couplings performed with magnesium diarylboronates of type **20** and aryl pseudo-halides of type **24** as electrophiles.

Entry	$Ar_2B(OBu)_2MgBr$ (conditions [T, t])	Electrophile	Product (t, Yield[a])
			
1	**20a** (25 °C, 1 h)	**24a**	**21o** (3 h, 78%)
			
2	**20l** (25 °C, 1 h)	**24b**	**21p** (12 h, 70%)
			
3	**20d** (25 °C, 1 h)	**24c**	**21q** (12 h, 81%)

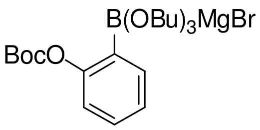
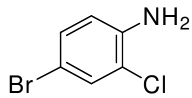
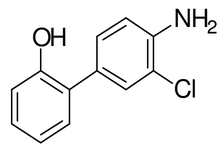
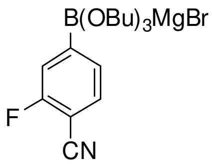
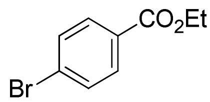
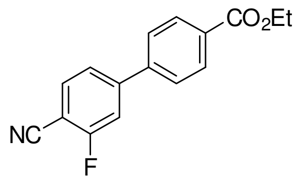
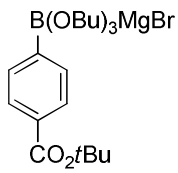
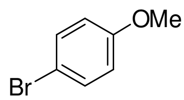
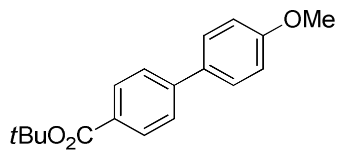
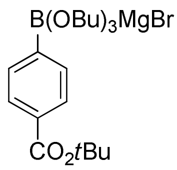
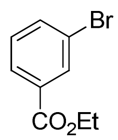
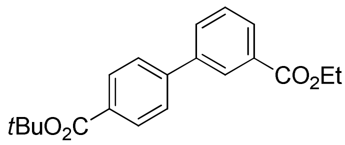
[a] Yield of isolated, analytically pure product.

In some cases, when the aryl bromide is sterically hindered (**18n**) or strongly electron-deficient (**18o** and **18p**), the preparation of the *mono*-arylboronate ($ArB(OBu)_3MgBr$) was preferable[165] leading to a significant yield improvement in the subsequent *Suzuki-Miyaura* cross-coupling (Table 12). Thus, *mono*-arylboronate **19b**, containing the sterically demanding Boc-protected alcohol in meta-position of the aryl, furnishes after the Pd-catalyzed cross-coupling with the unprotected bromoaniline **22j** the highly

[165] This proved to be necessary in less than 10% of all cases studied.

functionalized biphenyl **21r** in 86% yield (entry 1). Noteworthy, the alcohol group gets unprotected during the cross-coupling reaction leading to the free phenol derivative. The *mono*-arylboronate **19c** of the highly electron-deficient aryl bromide **18o** undergoes a smooth cross-coupling reaction with ethyl 4-bromobenzoate (**22k**) leading to the desired product **21s** in 72% yield (entry 2). Analogously, also for *tert*-butyl 4-bromobenzoate (**18p**) the *mono*-arylboronate **19d** reacts more efficiently than the corresponding diarylboronate with the electrophiles **22l** and **22m** in the cross-coupling reaction. For this reason, the resulting functionalized biphenyl derivates **21t** and **21u** could be obtained in excellent yields (entries 3 and 4).

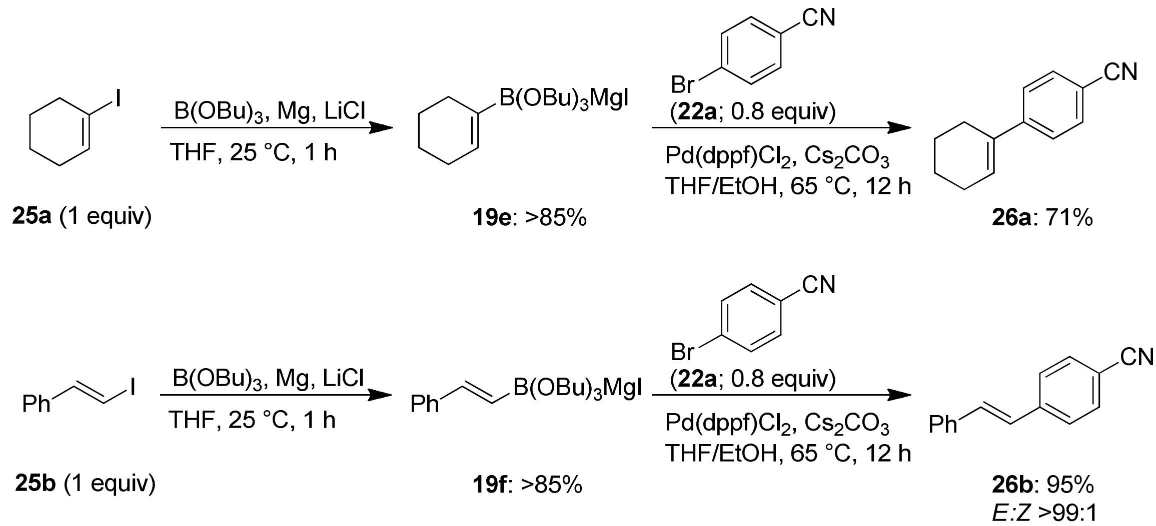
Table 12: *Suzuki-Miyaura* cross-couplings performed with magnesium *mono*-arylboronates of type **19** and aryl bromides of type **22** as electrophiles.

Entry	$ArB(OBu)_3MgBr$ (conditions [T, t])	Electrophile	Product (t, Yield[a])
1	 **19b** (25 °C, 1 h)[b]	 **22j**	 **21r** (6 h, 86%)
2	 **19c** (25 °C, 1 h)[b]	 **22k**	 **21s** (12 h, 72%)
3	 **19d** (25 °C, 1 h)[b]	 **22l**	 **21t** (12 h, 89%)
4	 **19d** (25 °C, 1 h)[b]	 **22m**	 **21u** (4 h, 78%)

[a] Yield of isolated, analytically pure product. [b] 1 equiv of $B(OBu)_3$ was used.

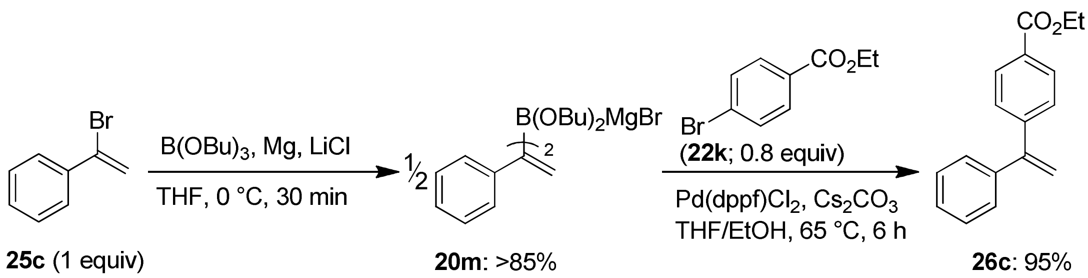
2.3 PREPARATION OF MAGNESIUM DIALKENYLBORONATES VIA MAGNESIUM-INSERTION FOR SUZUKI-MIYAURA CROSS-COUPLINGS

The method described above also proved to be suitable for alkenyl halides. *Suzuki-Miyaura* cross-coupling reactions with *mono*- and dialkenylboronic derivatives such as **19e-f** and **20m** proceed in high yields. Thus, the treatment of cyclohexenyl iodide (**25a**) with $B(OBu)_3$ (1 equiv), Mg (1.6 equiv) and LiCl (1.1 equiv) in THF at 25 °C produces within 1 h the corresponding magnesium alkenyl-boronate **19e** in >85% yield (Scheme 70). Similarly, the reaction of 2-iodostyrene (**25b**) furnishes under the same conditions the desired alkenylboronate **19f** (>85% yield). Cross-coupling of **6a-b** with 4-bromo-benzonitrile (**22a**) furnishes the functionalized alkenes **26a-b** in 71% and 95% yield respectively.



Scheme 70: Preparation and subsequent cross-coupling of magnesium alkenylboronates **19e** and **19f** with aryl bromide **22a** as electrophile.

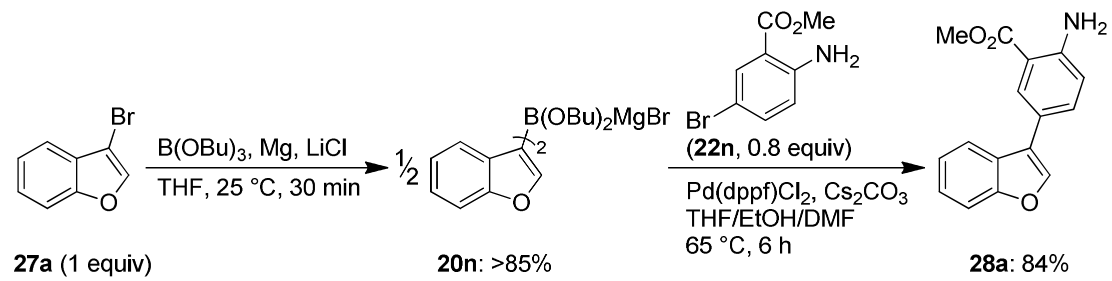
The magnesium dialkenylboronate **20m** was prepared from 1-bromostyrene (**25c**), $B(OBu)_3$ (0.5 equiv), Mg (1.6 equiv) and LiCl (1.1 equiv). Pd-catalyzed cross-coupling with ethyl 4-bromobenzoate (**22k**) under standard conditions gives the diaryl ethylene **26c** in 95% yield (Scheme 71).



Scheme 71: Preparation and subsequent cross-coupling of magnesium alkenylboronate **20m** with aryl bromide **22k** as electrophile.

2.4 PREPARATION OF MAGNESIUM DIHETEROARYLBORONATES VIA MAGNESIUM-INSERTION FOR SUZUKI-MIYAURA CROSS-COUPLINGS

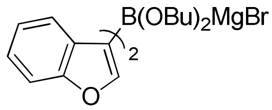
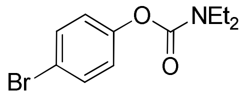
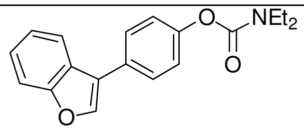
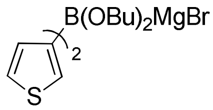
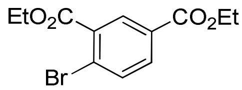
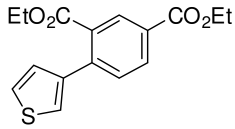
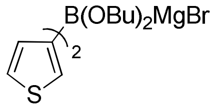
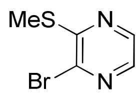
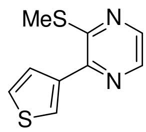
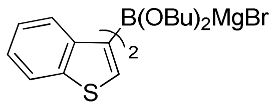
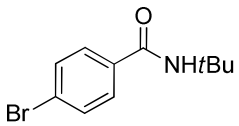
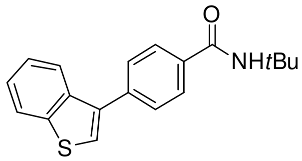
Remarkably, the aforementioned method could also be applied in the synthesis of functionalized diheteroarylboronates without any further optimization. Thus, 3-bromobenzofuran (**27a**) readily reacts with Mg (1.6 equiv) and LiCl (1.1 equiv) in the presence of $B(OBu)_3$ (0.5 equiv) in THF within 1 h at room temperature to the diheterocyclic magnesium boronate **20n** in >85% yield (Scheme 72). A subsequent *Suzuki-Miyaura* cross-coupling reaction with the aryl bromide **22n** furnishes the corresponding heterocyclic product **28a** in 84% yield. As expected, the unprotected amine did not hamper the cross-coupling reaction.



Scheme 72: Preparation and subsequent cross-coupling of diheterocyclic boronate **28a** with aryl bromide **22n** as electrophile.

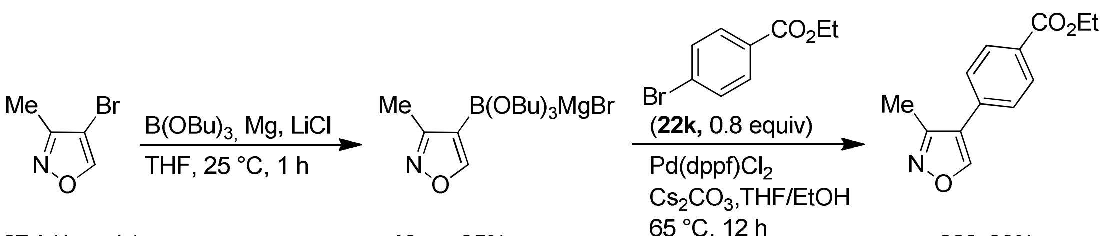
Furthermore, the reaction of diheteroarylboronate **20n** with aryl bromide **22o** leads to the desired substituted benzofuran **28bf** in 86% yield (Table 13, entry 1). The related diheterocyclic magnesium boronates **20o** and **20p** have been obtained in an analogous approach. 3-bromothiophene (**27b**) and 3-bromobenzothiophene (**27c**) provide after LiCl-mediated Mg-insertion with magnesium turnings (1.6 equiv) and *in situ* borylation with $B(OBu)_3$ (0.5 equiv) the corresponding diheteroarylboronates **20o** and **20p** in >85% yield. The *Suzuki-Miyaura* cross-coupling reaction of **20o** with the aryl bromides **22g** and **22p** furnish the highly functionalized heterocycles **28c** and **28d** in 72% and 79% yield, respectively (entries 2 and 3). Finally, also diheteroarylboronate **20p** undergoes readily a Pd-catalysed reaction with the aryl bromide **22b** and produces the substituted benzothiophene **28e** in 72% yield (entry 4).

Table 13: *Suzuki-Miyaura* cross-couplings performed with magnesium diheteroarylboronates of type **20** and aryl bromides of type **22** as electrophiles.

Entry	$Het_2B(OBu)_2MgBr$ (conditions [T, t])	Electrophile	Product (t, Yield[a])
			
1	**20n** (25 °C, 30 min)	**22o**	**28b** (3 h, 86%[b])
			
2	**20o** (0 °C, 30 min)	**22g**	**28c** (3 h, 72%[b])
			
3	**20o** (0 °C, 30 min)	**22p**	**28d** (12 h, 79%[b])
			
4	**20p** (0 °C, 1 h)	**22b**	**28e** (12 h, 77%[b])

[a] Yield of isolated, analytically pure product. [b] Obtained after Pd-catalyzed cross-coupling (4% $Pd(dppf)Cl_2$, Cs_2CO_3 (2 equiv), THF/EtOH/DMF (4:4:1), 65 °C).

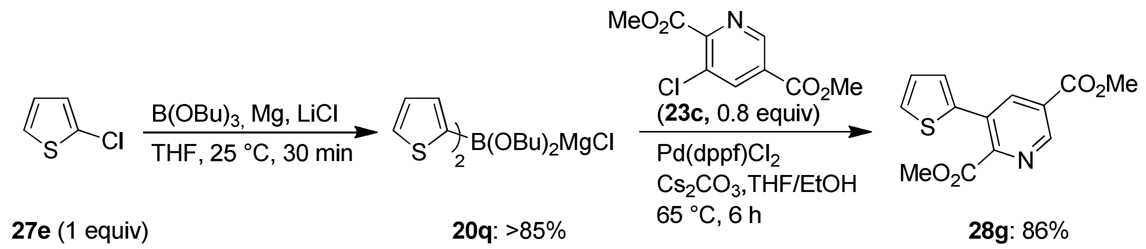
For 4-bromo-3-methylisoxazole (**27d**) the corresponding diheteroarylboronate showed only poor reactivity in the *Suzuki-Miyaura* cross-coupling. Therefore, the *mono*-heteroarylboronate **19g** has been synthesized using magnesium turnings (1.6 equiv), $B(OBu)_3$ (1.0 equiv) and LiCl (1.1 equiv) and has been submitted to the Pd-catalysed cross-coupling reaction. The functionalized heterocyclic derivate **28f** could then be obtained in a good yield (Scheme 73).



27d (1 equiv) **19g:** >85% **28f:** 60%

Scheme 73: Preparation and subsequent cross-coupling of magnesium *mono*-heteroarylboronate **19g** and subsequent cross-coupling with aryl bromide **22k** as electrophile.

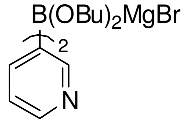
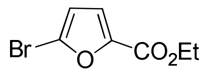
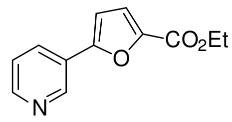
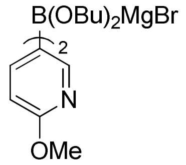
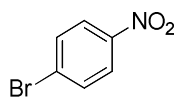
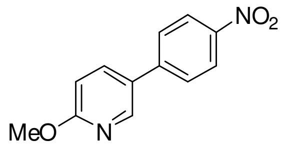
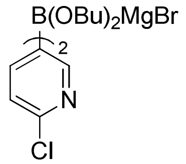
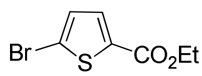
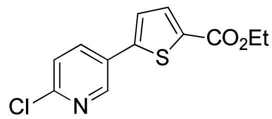
Remarkably, not only heterocyclic bromides can be converted to their corresponding diheteroarylboronates, also 2-chlorothiophene (**27e**) provides after LiCl-mediated Mg-insertion with magnesium turning (1.6 equiv) and *in situ* borylation with $B(OBu)_3$ (0.5 equiv) the corresponding dithienylboronate **20q** in >85% yield (Scheme 74). The subsequent *Suzuki-Miyaura* cross-coupling with the chloropyridine derivative **23c** furnishes the highly functionalized thiophene **28g** in 86% yield.



Scheme 74: Preparation and subsequent cross-coupling of magnesium dithienylboronate **20q** and subsequent cross-coupling with aryl chloride **23c** as electrophile.

Furthermore, under typical reaction conditions, also bromopyridine derivatives react effectively to the corresponding dipyridylboronates. Thus, 3-bromopyridine **27f** is converted to its dipyridylboronate **20r** in >85% yield within 1 h by using $B(OBu)_3$ (0.5 equiv), magnesium turnings (1.6 equiv) and LiCl (1.1 equiv) in THF at ambient temperature (Table 14, entry 1). The *Suzuki-Miyaura* cross-coupling employing the substituted 2-bromo-furan **22q** as electrophile leads to the corresponding cross-coupling product **28h** in 82% yield. The related dipyridyl magnesium boronates **20s** and **20t** have been obtained in an analogous approach. 5-bromo-2-methoxypyridine (**27g**) and 5-bromo-2-chloropyridine (**27h**) provided after LiCl-mediated Mg-insertion with magnesium turnings (1.6 equiv) and *in situ* borylation with $B(OBu)_3$ (0.5 equiv) the functionalzied dipyridylboronates **20s** and **20t** in >85% yield. The subsequent *Suzuki-Miyaura* cross-coupling reaction of **20s** with the aryl bromide **22r** furnishes the highly functionalized pyridine derivative **28i** 85% yield (entry 2). The dipyridylboronate **20t** undergoes readily a Pd-catalysed reaction with the heteroaryl bromide **22s** and produces the substituted pyridine **28j** in 72% yield (entry 3).

Table 14: *Suzuki-Miyaura* cross-couplings performed with magnesium dipyridylboronates of type **20** and aryl bromides of type **22** as electrophiles.

Entry	$Het_2B(OBu)_2MgBr$ (conditions [T, t])	Electrophile	Product (t, Yield[a])
1	 **20r** (25 °C, 1 h)	 **22q**[b]	 **28h** (24 h, 82%[c])
2	 **20s** (25 °C, 1 h)	 **22r**	 **28i** (12 h, 85%[d])
3	 **20t** (25 °C, 1 h)	 **22s**[b]	 **28j** (12 h, 72%[e])

[a] Yield of isolated, analytically pure product. [b] 0.7 equiv of electrophile were used. [c] Obtained after Pd-catalyzed cross-coupling (4% ($Pd(PPh_3)_4$, $Na_2CO_3 \cdot 10H_2O$ (1.3 equiv), THF/dioxane/H_2O (4:4:1), 110 °C). [d] Obtained after Pd-catalyzed cross-coupling (4% $Pd(dppf)Cl_2$, Cs_2CO_3 (2 equiv), THF/EtOH/DMF (4:4:1), 65 °C). [e] Obtained after Pd-catalyzed cross-coupling (4% $Pd(PPh_3)_4$, Cs_2CO_3 (2 equiv), THF/EtOH (1:1), 65 °C).

3. PREPARATION OF α-SUBSTITUTED β,γ-UNSATURATED KETONES AND ESTERS *VIA* THE DIRECT ADDITION OF SUBSTITUTED ALLYLIC ZINC REAGENTS

3.1 INTRODUCTION

The reaction of allylic organometallic reagents with carbonyl derivatives is of high importance in synthetic organic chemistry.[166] Since allylic moieties can be found in a plethora of natural occurring products, allylic organometallics play a significant role in their total synthesis (Figure 10).[167] Psymberin for example has been isolated from the sea sponge *Psammocinia sp*. and shows a high and selective cytotoxic activity against different human cancer cell lines.[168] In 2005 *De Brabander* and coworkers described its first total synthesis.[169]

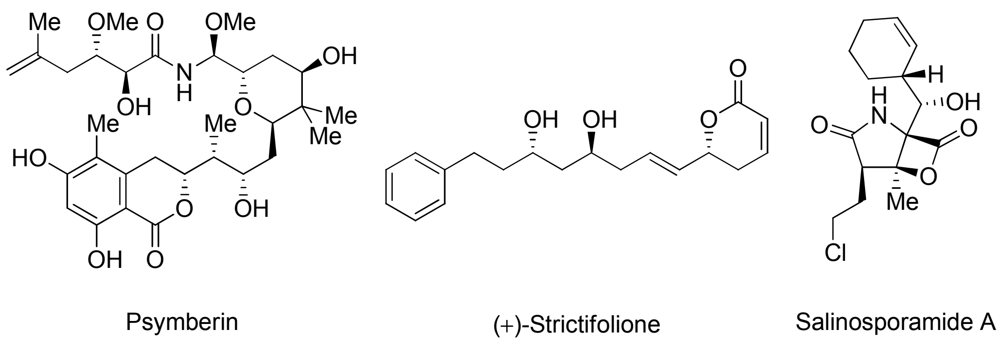


Figure 10: Naturally occurring substrates bearing allylic moieties.

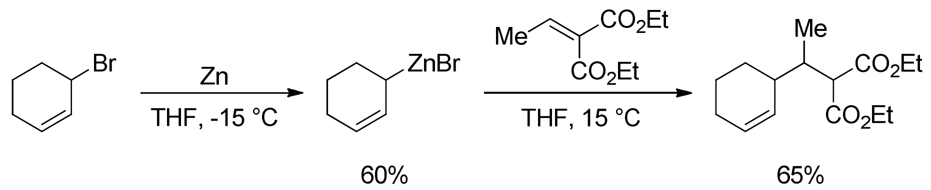
Cossy et al. used a stereoselective allyltitanation as key step in the synthesis of (+)-Strictifolione, which was isolated from the stem bark of *Cryptocaria strictifolia* growing in Indonesian tropical rainforests.[170,171] (+)-Strictifolione exhibits a potent antifungal activity. Salinosporamide A was found in the marine actinomycete

[166] For allylmetal additions, see: a) S. R. Chemler, W. R. Roush, in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**. b) S. E. Denmark, N. G. Almstead, in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**. c) *Stereoselective Synthesis, Methods of Organic Chemistry* (Eds.: G. Helmchen, R. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1996**. d) M. Yasuda, K. Hirata, M. Nishino, A. Yamamoto, A. Baba, *J. Am. Chem. Soc.* **2002**, *124*, 13442. e) A. N. Thadani, R. A. Batey, *Org. Lett.* **2002**, *4*, 3827. f) S. W. Li, R. A. Batey, *Chem. Commun.* **2004**, 1382. g) C. T. Buse, C. H. Heathcock, *Tetrahedron Lett.* **1978**, 1865. h) Y. Yamamoto, H. Yatagai, Y. Naruta, K. Maruyama, *J. Am. Chem. Soc.* **1980**, *102*, 7107. i) Y. Yatsumonji, T. Nishimura, A. Tsubouchi, K. Noguchi, T. Takeda, *Chem. Eur. J.* **2009**, *15*, 2680.
[167] M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2013**, *113*, 5595.
[168] R. H. Cichewicz, F. A. Valeriote, P. Crews, *Org. Lett.* **2004**, *6*, 1951.
[169] X. Jang, J. Garcia-Fortanet, J. K. De Brabander, *J. Am. Chem. Soc.* **2005**, *127*, 11254.
[170] S. Bouzbouz, J. Cossy, *Org. Lett.* **2003**, *5*, 1995.
[171] L. D. Juliawaty, M. Kitajima, H. Takayama, S. A. Achmad, N. Aimi, N. *Phytochemistry* **2000**, *54*, 989.

Salinospora tropica distributed in ocean sediments around the Bahamas.[172] It is a potent proteasome inhibitor and is currently being tested as an anticancer drug candidate to treat patients with multiple myeloma.[173] One of the key steps of its synthesis reported by *Corey* and coworkers was the reaction of 2-cyclohexenylzinc chloride with a chiral aldehyde bearing three stereogenic centers. In this process, two stereogenic centers were formed stereoselectively (20:1 dr) with the right configuration.[174]

Especially allylic zinc reagents are very versatile organometallic species since their behaviour is much more predictable than the behaviour of the corresponding allylic magnesium or lithium reagents.[175] Moreover, the magnesium and lithium compounds suffer from their instability as well as from their difficult and inconvenient preparation.[176]

Cyclohexenylzinc bromide for instance is readily prepared from zinc foil and the corresponding bromide at -15 °C in 60% yield (Scheme 75).[177] However, higher yields are prevented by accompanying side reactions such as homocoupling and hydrolysis.

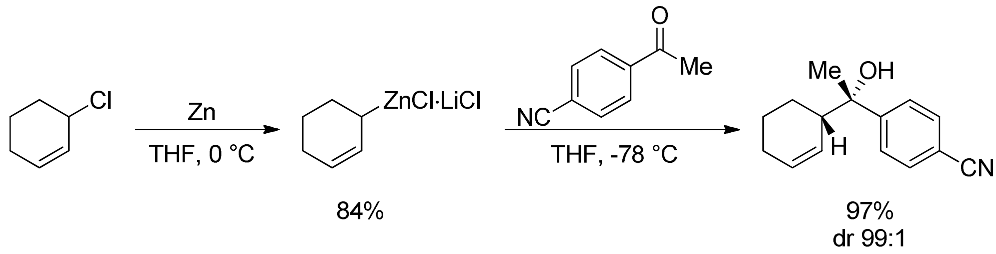


Scheme 75: Preparation of cyclohexenylzinc bromide from zinc and its corresponding bromide.

Recently *Knochel* and coworkers have reported the use of commercially available zinc powder in the presence of lithium chloride in THF as a cheap and convenient method for the synthesis of substituted allylic zinc reagents from allyl halides or phosphonates reducing unwanted side reactions on a minimum.[178] Thus, the LiCl-mediated zinc insertion provided cyclohexenylzinc chloride in 84% yield (Scheme 76).

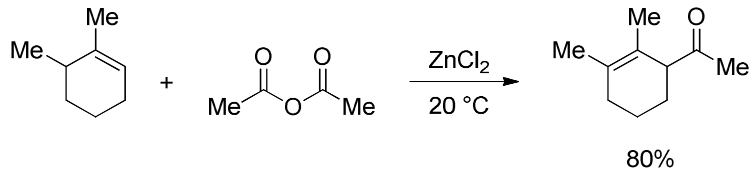
---

[172] R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem. Int. Ed.* **2003**, *42*, 355.
[173] D. Chauhan, L. Catley, G. Li, K. Podar, T. Hideshima, M. Velankar, C. Mitsiades, N. Mitsiades, H. Yasui, A. Letai, H. Ovaa, C. Berkers, B. Nicholson, T.-H. Chao, S. T. C. Neuteboom, P. Richardson, M. A. Palladino, K. C. Anderson, *Cancer Cell* **2005**, *8*, 407.
[174] L. R. Reddy, P. Saravanan, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 6230.
[175] a) S. Czernecki, C. Georgoulis, *Bull. Soc. Chim. Fr.* **1968**, 3713. b) G. Courtois, L. Miginiac, *J. Organomet. Chem.* **1974**, *69*, 1. c) Y. Yamamoto, *Acc. Chem. Rev.* **1987**, *20*, 243. d) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207. e) M. Schlosser, O. Desponds, R. Lehmann, E. Moret, G. Rauchschwalbe, *Tetrahedron* **1993**, *49*, 10175. f) J. A. Marshall, *Chem. Rev.* **2000**, *100*, 3163. g) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763. h) L. Chabaud, P. James,Y. Landais, *Eur. J. Org. Chem.* **2004**, 3173. i) A. Fürstner, D. Voigtländer, *Synthesis* **2000**, 975. j) W. R. Roush, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**. k) J. G. Kim, E. H. Camp, P. J. Walsh, *Org. Lett.* **2006**, *8*, 4413.
[176] M, Schlosser, O. Desponds, R. Lehmann, E. Moret, G. Rauchschwalbe, *Tetrahedron* **1993**, *49*, 10175.
[177] a) M. Gaudemar, *Bull. Soc. Chim. Fr.* **1962**, 974. b) H. Maeda, K. Shono, H. Ohmori, *Chem. Pharm. Bull.* **1994**, *42*, 1808. c) M. Bellassoued, Y. Frangin, M. Gaudemar, *Synthesis* **1977**, 205.
[178] a) H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 5376. b) M. D. Helm, P. Mayer, P. Knochel, *Chem. Commun.* **2008**, 1916.



Scheme 76: LiCl-medidated preparation of cyclohexenylzinc chloride.

β,γ-Unsaturated ketones and esters are versatile building blocks in organic chemistry.[179] Although a number of synthetic methods have been disclosed, only a few have been proven practical and useful. The acylation of olefins for example allows the synthesis of β,γ-unsaturated ketones, but generates α,β-unsaturated ketones as side-products and suffers from poor functional group tolerance (Scheme 77).[180]



Scheme 77: Praparation of β,γ-unsaturated ketones *via* acylation of olefines.

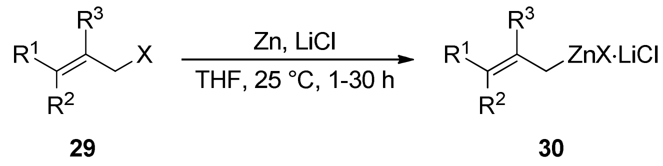
The reaction of various allylic organometallics with acyl halides has also been reported in literature. Silicon,[181] tin,[182] copper,[183] rhodium,[184] manganese,[185] titanium,[186] mercury,[187] cadmium,[188] and indium[189] are some of the metal powders used in the synthesis of β,γ-unsaturated ketones. But these protocols are mostly neither simple nor straightforward and are therefore of limited application. Since the reaction of allylic zinc reagents with acid chlorides[190] or nitriles[191] seemed to be a promising approach, our focus

[179] M. Demuth, G. Mikhail, *Synthesis* **1989,** 145.
[180] a) S. A. Monti, G. L. White, *J. Org. Chem.* **1975**, *40*, 215. b) H. M. R. Hoffman, T. Tsushima, *J. Am. Chem. Soc.* **1977***, 99*, 6008. c) P. Beak, K. R. Berger, *J. Am. Chem. Soc.* **1980**, *102*, 3848. d) C. Earnshaw, R. S. Torr, S. S. Warren, *J. Chem. Soc. Perkin Trans.* **1983***, 1***,** 2893.
[181] a) A. Hosomi, H. Hashimoto, H. Sakurai, *J. Org. Chem.* **1978**, *43*, 2551. b) M. Laguerre, J. Dunogues, R. Calas, *Tetrahedron Lett.* **1980**, *21*, 831. c) T. Hayashi, M. Konishi, H. Ito, M. Kumuda, *J. Am. Chem. Soc.* **1982**, *104*, 4962.
[182] J. W. Labadie, D. Tueting, J. K. Stille, *J. Org. Chem.* **1983**, *48*, 4634.
[183] T. Sato, T. Kawara, A. Nishizawa, T. Fujisawa, *Tetrahedron Lett.* **1980**, *21*, 3377.
[184] I. S. Hegedus, P. M. Kendall, S. M. Lo, J. R. Sheats, *J. Am. Chem. Soc.* **1975**, *97*, 5448.
[185] G. Cahiez, B. Laboue, *Tetrahedron Lett.* **1989**, *30*, 7369.
[186] A. N. Kasatkin, A. N. Kulak, G. A. Tolstikov, *J. Organomet. Chem.* **1988**, *346*, 23.
[187] R. C. Larock, Y. Lu, *J. Org. Chem.* **1993**, *58*, 2846.
[188] B. Bipul, B. Anima, P. Dipak, S. S. Jagir, *Tetrahedron Lett.* **1996**, *37*, 9087.
[189] J. S. Yadav, D. Srinivas, G. S. Reddy, K. Himabindu, *Tetrahedron Lett.***1997**, *36*, 8745.
[190] a) B. C. Ranu, A. Majee, A. R. Das, *Tetrahedron Lett.* **1995**, *36*, 4885. b) B. C. Ranu, A. Majee, A. R. Das, *Tetrahedron Lett.* **1996**, *37*, 1109.
[191] a) E. E. Blaise, *Compt. Rend.* **1901**, *132*, 478. b) H. S. P. Rao, S. Rafi, K. Padmavathy, *Tetrahedron* **2008**, *64*, 8037. c) J. Cason, K. L. Rinehart, Jr., S. D. Thorston, Jr., *J. Org. Chem.* **1953**, *18*, 1594. d) S. M. Hannick, Y. Kishi, *J. Org. Chem.* **1983**, *48*, 3833. e) D. Wang, J.-M. Yue, *Synlett* **2005**, 2077.

lay on the investigation of addition reactions using the now readily available substituted allylic zinc reagents. This led finally to the development of a simple and flexible method for the synthesis of α-substituted β,γ-unsaturated ketones and esters through the addition of substituted allylic zinc reagents to a broad range of acid chlorides and chloroformates.

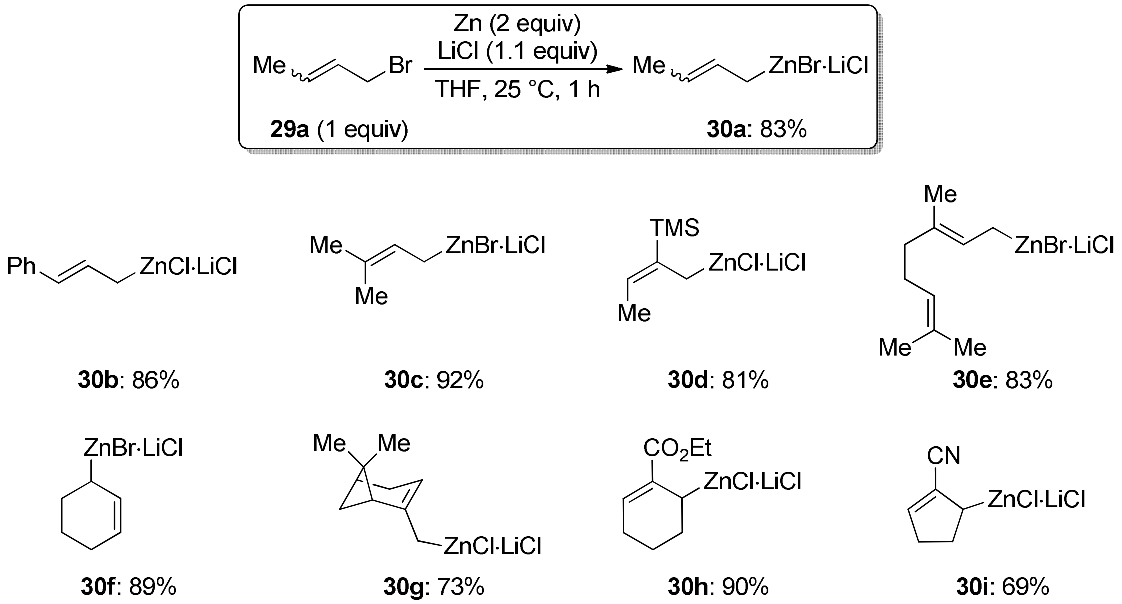
3.2 PREPARATION OF SUBSTITUTED ALLYLIC ZINC REAGENTS

As preliminary experiments had shown, the LiCl-mediated zinc insertion into allylic halides provided the corresponding allylic zinc reagents almost without formation of homocoupling products (Scheme 78).



Scheme 78: Preparation of allylic zinc reagents **30** from allylic halides **29** *via* LiCl-mediated zinc insertion.

Thus, under optimized conditions but-2-en-1-ylzinc bromide (**30a**) is formed within 1 h at 25 °C in 83% yield by dropwise addition of 1-bromobut-2-ene (**29a**, 1 equiv) to a suspension of commercially available zinc powder (2.0 equiv) and dry lithium chloride (1.1 equiv) in THF (Scheme 79).



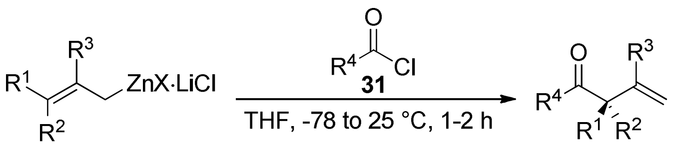
Scheme 79: LiCl-mediated preparation of the substituted allylic zinc organometallics **30** by direct insertion of zinc powder (yields determined by iodometric titration[192])

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

This procedure has been successfully extended to other allylic halides leading to cinnamylzinc chloride (**30b**, 86%), (3-methylbut-2-en-1-yl)zinc bromide (**30c**, 92%), (3,7-dimethylocta-2,6-dien-1-yl)zinc bromide (**30e**, 83%) and cyclohex-2-en-1-ylzinc bromide (**30f**, 89%). Especially the preparation of zinc reagent **30b** is remarkable, since cinnamyl chloride is known to readily undergo extensive homocoupling reaction during the synthesis of the corresponding zinc reagent. It is noteworthy, that also functional groups like an ester or a nitrile are tolerated in this insertion reaction. Hence, 2-enecarboxylic acid ethyl ester-6-cyclohexenylzinc chloride (**30h**) and 2-cyano-5-cyclopentenylzinc chloride (**30i**) have been obtained from their corresponding chlorides in 90% and 69% yield, respectively. Starting from 2-chloromethyl-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene (**29g**), also zinc reagent **30g** could be synthesized in 73% yield (25 °C, 30 h).[178a] (2-(Trimethylsilyl)but-2-en-1-yl)zinc chloride (**30d**) has been generated from its chloride in the presence of zinc powder (10 equiv) and lithium chloride (3 equiv) in 18 h at 25 °C in 81% yield.[178b]

3.3 Preparation of α-Substituted β,γ-Unsaturated Ketones

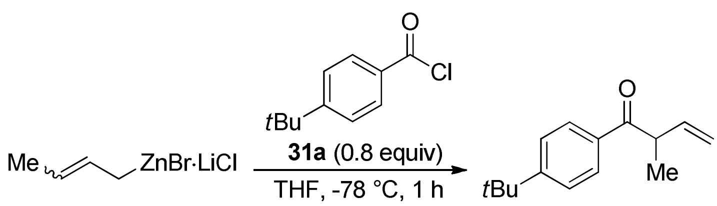
We then decided to concentrate our studies on the addition of these highly reactive allylic zinc reagents to a broad range of acid chlorides. It turned out that this reaction proceeds under exceedingly mild conditions (-78 °C, 1-2 h) and furnishes selectively β,γ-unsaturated ketones **32** without any traces of the α,β-unsaturated isomers (Scheme 80).



30 **32**

Scheme 80: Preparation of α-substituted β,γ-unsaturated ketones of type **32** *via* addition of allylic zinc reagents **30** to various acid chlorides of type **31**.

Thus, the addition of but-2-en-1-ylzinc bromide (**30a**) to 4-(*tert*-butyl)benzoyl chloride (**31a**) leads selectively to the corresponding α-substituted β,γ-unsaturated ketone **32a** in 85% yield (Scheme 81).

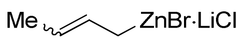
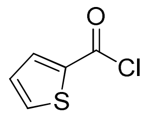
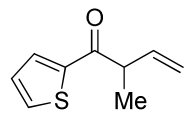
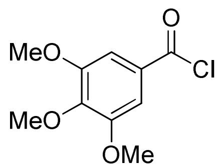
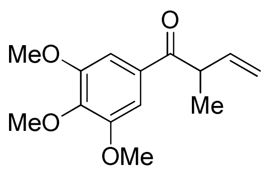
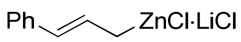
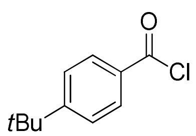
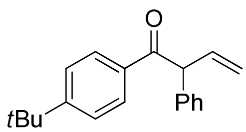
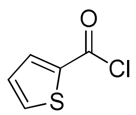
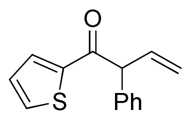
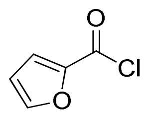
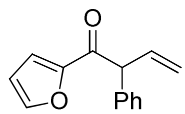
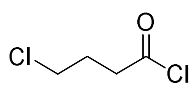
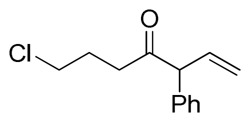


30a **32a**: 85%

Scheme 81: Preparation of α-substituted β,γ-unsaturated ketone **32a** from disubstituted allylic zinc reagent **30a**.

Moreover, also addition of organozinc reagent **30a** to the (hetero)aromatic acid chlorides **31b** and **31c** furnishes selectively the corresponding α-substituted β,γ-unsaturated ketones **32b-c** in high yields (Table 15, entries 1-2). Regardless of the substitution pattern of the (hetero)aromatic acid chloride, the reaction proceeds within 1 h at -78 °C. Noteworthy, the configuration of the double bond in the zinc reagent does not affect the reaction course, allowing the use of *E*- and *Z*-isomeric mixtures.

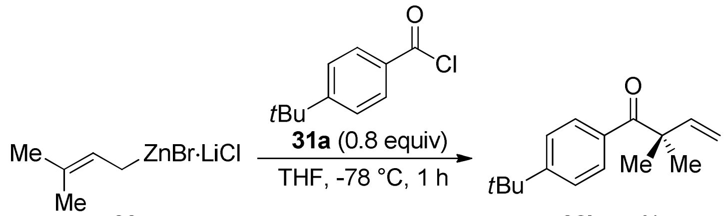
Table 15: Preparation of α-substituted β,γ-unsaturated ketones **32b**-**g** from disubstituted allylic zinc reagents **30a**-**b**.

Entry	Substrate	Acid Chloride	Product, Yield[a]	Conditions (T, t)
1	 **30a**	 **31b**	 **32b**: 71%	-78 °C, 1 h
2	**30a**	 **31c**	 **32c**: 65%	-78 °C, 1 h
3	 **30b**	 **31a**	 **32d**: 90%	-78 °C, 1 h
4	**30b**	 **31b**	 **32e**: 77%	-78 °C, 1 h
5	**30b**	 **31d**	 **32f**: 84%	-78 °C, 1 h
6	**30b**	 **31e**	 **32g**: 72%	-20 to 25 °C, 2 h

[a] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis.

Cinnamylzinc chloride (**30b**) reacts in a similar manner. The α-substituted β,γ-unsaturated ketones **32d-f** are obtained by addition to the corresponding (hetero)aromatic acid chlorides **31a, 31b** and **31d** in excellent yields (entries 3-5). Interestingly, also with aliphatic acid chloride **31e** the addition proceeds smoothly (-20 to 25 °C, 2 h) and leads to ketone **32g** in 72% yield (entry 6).

This procedure could also be successfully applied to trisubstituted allylic zinc derivatives. Thus, (3-methylbut-2-en-1-yl)zinc bromide (**30c**) reacted selectively in 1 h at -78 °C with 4-(*tert*-butyl)benzoyl chloride (**31a**) to afford the corresponding α,α-disubstituted β,γ-unsaturated ketone **32h** in 93% yield (Scheme 82).

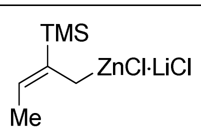
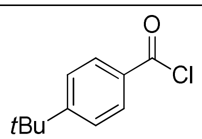
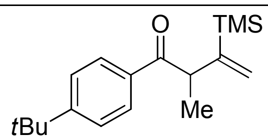
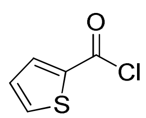
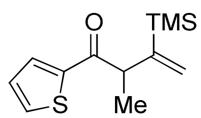


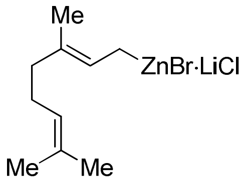
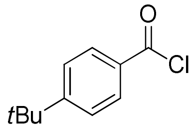
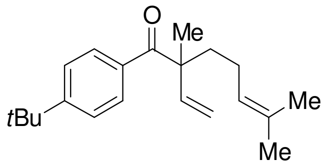
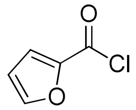
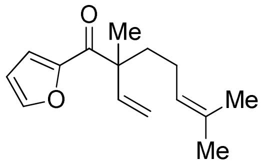
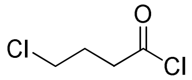
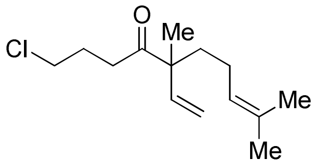
30c **32h**: 93%

Scheme 82: Preparation of α,α-substituted β,γ-unsaturated ketone **32h** from trisubstituted allylic zinc reagent **30c**.

Remarkably, the addition of (2-(trimethylsilyl)but-2-en-1-yl)zinc chloride (**30d**) to the acid chlorides **31a** and **31b** furnishes the corresponding ketones **32i** and **32j** in the almost quantitative yield of 98% and 99%, respectively (Table 16, entries 1 and 2). Also the trisubstituted allylic zinc reagent **30e**, containing another double bond besides the allylic one, could be employed in the addition reaction. (Hetero)aromatic acid chlorides (**31a** and **31d**) as well as an aliphatic one (**31e**) have been used to synthesize the corresponding ketones **32k-m** leaving the non-allylic double bond untouched (entries 3-5).

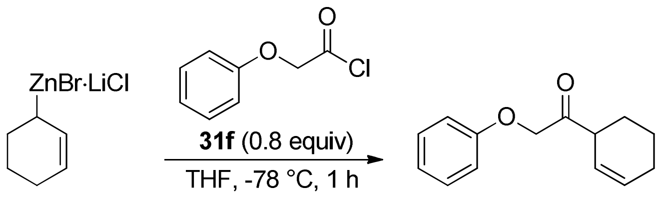
Table 16: Preparation of α- and α,α-substituted β,γ-unsaturated ketones **32i-m** from trisubstituted allylic zinc reagents **30d-e**.

Entry	Substrate	Acid Chloride	Product, Yield[a]	Conditions (T, t)
				
1	**30d**	**31a**	**32i**: 98%	25 °C, ovn
				
2	**30d**	**31b**	**32j**: 99%	-78 °C, 1 h

				
3	**30e**	**31a**	**32k**: 70%	-78 °C, 1 h
				
4	**30e**	**31d**	**32l**: 79%	-78 °C, 1 h
				
5	**30e**	**31e**	**32m**: 74%	-78 °C, 1 h

[a] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis.

The cyclic allylic zinc reagents **30f-i** show an analogous behaviour. The addition of cyclohey-2-en-1-ylzinc bromide (**30f**) to acid chloride **31f** affords selectively the corresponding α-substituted β,γ-unsaturated ketone **32n** in 75% yield (Scheme 83).

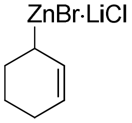
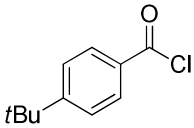
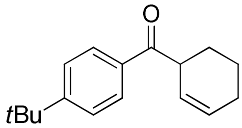
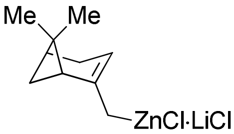
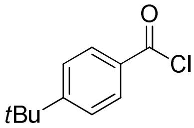
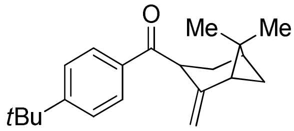
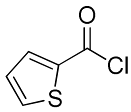
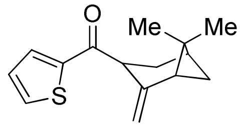
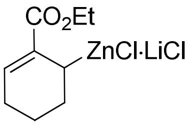
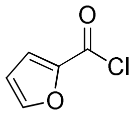
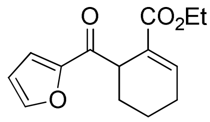
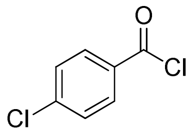
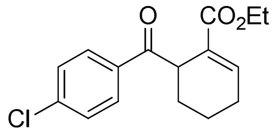
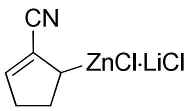
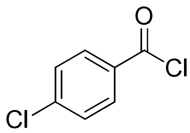
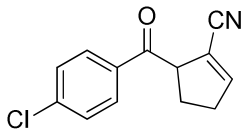


30f **32n**: 75%

Scheme 83: Preparation of α-substituted β,γ-unsaturated ketone **32n** from cyclic allylic zinc reagent **30f**.

Furthermore, the allylic zinc reagent **30f** smoothly adds to acid chloride **31a** affording selectively the corresponding α-substituted β,γ-unsaturated ketone **32o** in 83% yield (Table 17, entry 1). Moreover, the cyclic zinc reagent **30g** reacts readily with the (hetero)aromatic acid chlorides **31a** and **31b** to the ketones **32p** and **32q** in 67% and 89% yield, containing a terminal double bond (entries 2 and 3). Also, zinc reagent **30h** undergoes the addition reaction with the (hetero)aromatic acid chlorides **31d** and **32g** smoothly and furnishes the corresponding ketones **32r** and **32s** in high yields (90% and 80%, entries 4 and 5). The addition of 2-cyano-5-cyclopentenylzinc chloride (**30i**) to acid chloride **31g** leads to the α-substituted β,γ-unsaturated ketone **32t** (70% yield, entry 6).

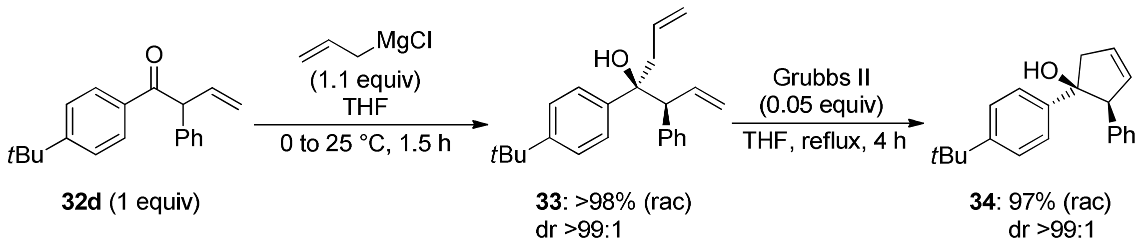
Table 17: Preparation of α-substituted β,γ-unsaturated ketones **32o**-**t** from cyclic allylic zinc reagents **30f**-**i**.

Entry	Substrate	Acid Chloride	Product, Yield[a]	Conditions (T, t)
1	 **30f**	 **31a**	 **32o**: 83%	-78 °C, 1 h
2	 **30g**	 **31a**	 **32p**: 67%	-78 °C, 1 h
3	**30g**	 **31b**	 **32q**: 89%	-78 to 25 °C, 2 h
4	 **30h**	 **31d**	 **32r**: 90%	-78 to 25 °C, ovn
5	**30h**	 **31g**	 **32s**: 80%	-78 to 25 °C, ovn
6	 **30i**	 **31g**	 **32t**: 70%	-78 to 25 °C, ovn

[a] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis.

3.3.1 FURTHER FUNCTIONALIZATION OF α-SUBSTITUTED β,γ-UNSATURATED KETONES

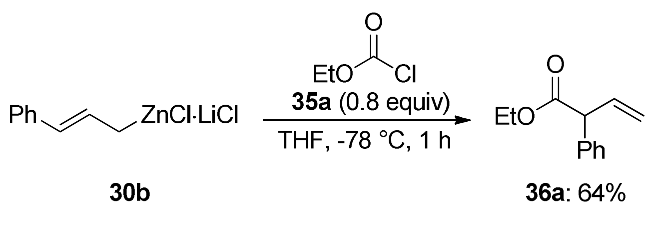
Ring-closing metathesis (RCM) represents one of the most powerful and versatile tools in organic synthesis for the formation of carbon-carbon double bonds[193] and has proven to be highly important for natural product synthesis.[194] With the α-substituted β,γ-unsaturated ketones in hands, the diene-precursor **33** for a RCM has readily been synthesized in only one step *via* the diastereoselective addition[166] of allyl magnesium chloride to the carbonyl moiety of **32d** in almost quantitative yield (Scheme 84). The subsequent RCM using the second generation of Grubbs' catalyst[195] furnishes diastereoselectively cyclopentene derivative **34** in 97% yield.



Scheme 84: Diastereoselective addition of allyl magnesium chloride to **32d** and subsequent ring-closing metathesis forming the cyclopentene derivative **34**.

3.4 PREPARATION OF α-SUBSTITUTED β,γ-UNSATURATED ESTERS

Due to the lack of a convenient and practical direct synthesis for α-substituted β,γ-unsaturated esters in the literature, we extended our method to this direction. As shown in Scheme 85, the allylic zinc reagent **30b** reacts readily under the optimized conditions with chloroformate **35a** and forms selectively the desired α-substituted β,γ-unsaturated ester **36a** in 64% yield.



Scheme 85: Preparation of α-substituted β,γ-unsaturated ester **36a** from disubstituted allylic zinc reagent **30b**.

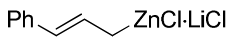
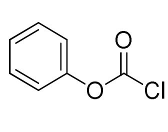
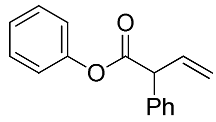
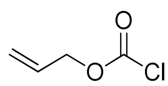
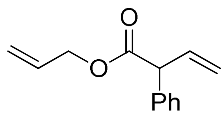
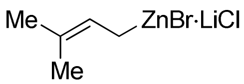
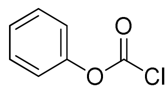
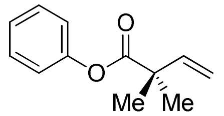
[193] For reviews, see: a) R. H. Grubbs, *Tetrahdron* **2004**, *60*, 7117. b) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446.

[194] For reviews, see: a) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, *19*, 3693. b) A. Gradillas, J. Perez-Castells, *Angew. Chem. Int. Ed.* **2006**, *45*, 6086. c) J. Prunet, *Angew. Chem. Int. Ed.* **2003**, *42*, 2826. d) M. Arisawa, A. Nishida, M. Nakagawa, *J. Organomet. Chem.* **2006**, *691*, 5109.

[195] a) J.-K. Huang, E. D. Stevens, S. P. Nolan, J. L. Petersen, *J. Am. Chem. Soc.* **1999**, *121*, 2674. b) M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 2247. c) L. Ackermann, A. Fürstner, T. Weskamp, F. J. Kohl, W. A. Herrmann, *Tetrahedron Lett.* **1999**, *40*, 4787.

Furthermore, cinnamylzinc chloride (**30b**) adds to aromatic (**35b**) as well as to allylic chloroformates (**35c**) affording the corresponding α-substituted β,γ-unsaturated esters **36b** and **36c** in 78% and 82% yield, respectively (Table 18, entries 1 and 2). The trisubstituted allylic zinc reagent **30c** shows a similar behaviour and furnishes ester **36d** in 70% yield (entry 3).

Table 18: Preparation of α-substituted β,γ-unsaturated esters of type **36**.

Entry	Substrate	Chloroformate	Product, Yield[a]	Conditions (T, t)
1	 **30b**	 **35b**	 **36b**: 78%	-78 to 25 °C, 2 h
2	**30b**	 **35c**	 **36c**: 82%	-78 to 25 °C, 2 h
3	 **30c**	 **35b**	 **36d**: 70%	-20 to 25 °C, 2 h

[a] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis.

4. PREPARATION OF FUNCTIONALIZED ALKENYLZINC REAGENTS BEARING CARBONYL GROUPS *VIA* DIRECT METAL INSERTION

4.1 INTRODUCTION

Functionalized alkenes bearing aldehyde, keto or ester functions are found in a plethora of naturally occurring products as well as in pharmaceutically active substances (Figure 11). Thuggacin A, for example, has been isolated from the myxobacterium *Sorangium cellulosum*[196] and shows strong antibiotic activity against *Mycobacterium tuberculosis* by targeting the bacterial respiratory chain.[197] Moreover, Rapamycin, found in *Streptomyces hygroscopicus*,[198] is a known immunosuppressant drug used to prevent rejection in organ transplantations (especially for kidney transplants). Its first total synthesis was reported by *Nicolaou et al.* in 1993.[199] Upenamide is a macrocyclic marine natural product from a branching sponge of the genus *Echinochalina*, containing an all-*trans* triene chain system.[200]

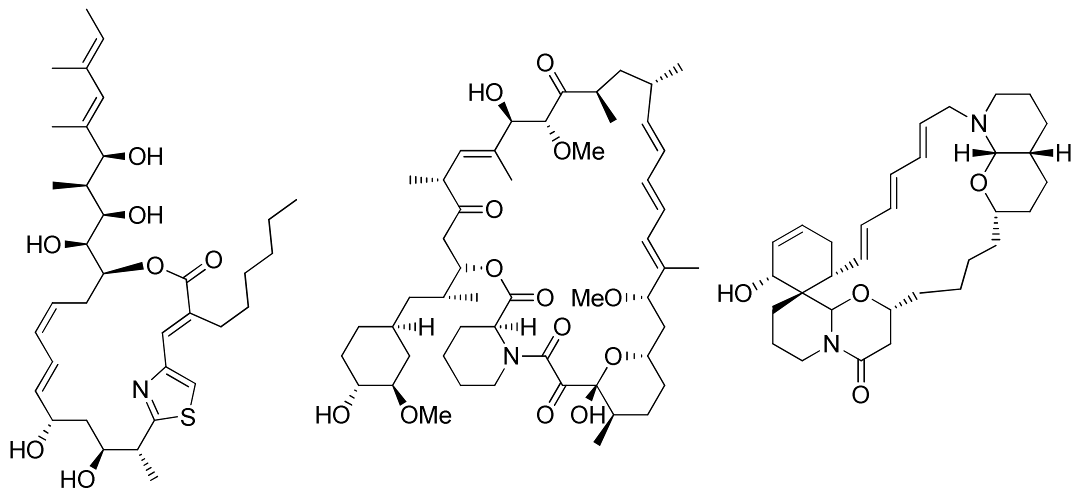
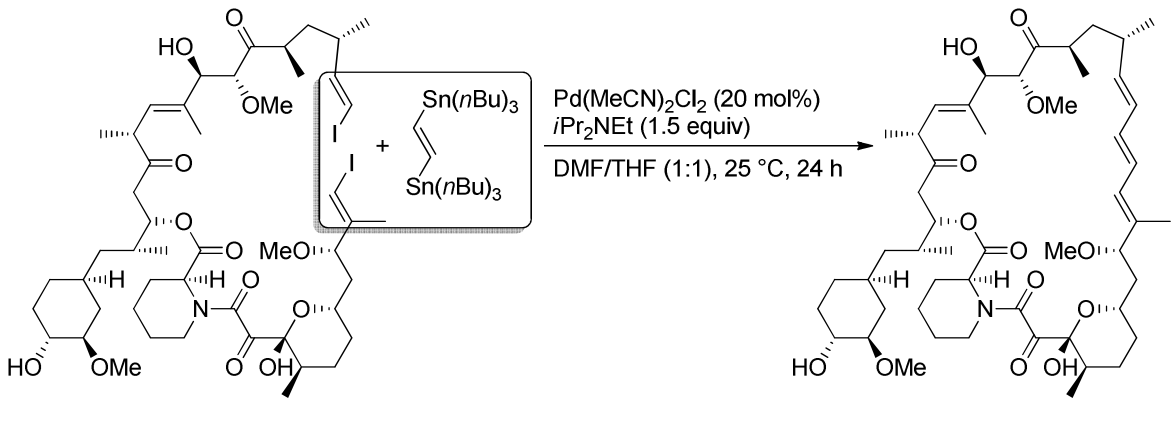


Figure 11: Naturally occurring substrates bearing funcionalized alkene moieties.

Olefin metathesis is one of the most important methods in organic synthesis for the formation of carbon-carbon double bonds and has proven to be highly useful for natural

[196] a) H. Steinmetz, H. Irschik, B. Kunze, H. Reichenbach, G. Höfle, R. Jansen, *Chem. Eur. J.* **2007**, *13*, 5822. b) M. Bock, R. Müller, K. Buntin, A. Kirschning, *Angew. Chem. Int. Ed.* **2008**, *47*, 2308.
[197] H. Irschik, H. Reichenbach, G. Höfle, R. Jansen, *J. Antibiot.* **2007**, *60*, 733.
[198] C. Vézina, A. Kudelski, S. N. Sehgal, *J. Antibiot.* **1975**, *28*, 721.
[199] K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, P. Bertinato, *J. Am. Chem. Soc.* **1993**, *115*, 4419.
[200] J. I. Jimenez, G. Goetz, C. M. S. Mau, W. Y. Yoshida, P. J. Scheuer, R. T. Williamson, M. Kelly, *J. Org. Chem.* **2000**, *65*, 8465.

product synthesis.[201] However, for the synthesis of highly functionalized double bonds an approach *via* cross-coupling reactions of alkenyl organometallics derived from the corresponding alkenyl halides seems to be more promising.[202] The synthesis of Rapamycin for instance contains as key step a *Stille*-coupling of two alkenyl iodides with vinylenedistannane for the stereoselective ring closure and the introduction of the conjugated double bond system (Scheme 86).[199]



Scheme 86: *Stille*-coupling as key step in the total synthesis of Rapamycin.

For this reason a simple and efficient method for the preparation of functionalized alkenyl organometallics bearing sensitive groups is highly desirable. Especially alkenylzinc halides are useful targets due to their high functional group tolerance and their excellent reactivity in the presence of an appropriate catalyst.5[,62,64c,203] In general, functionalized alkenyl organometallic compounds are mostly prepared *via* halogen-metal exchange reactions of the corresponding iodoalkenes. Thus, an iodine-lithium exchange with *n*-butyllithium at -80 °C on 5-chloro-1-iodopent-1-ene combinded with a subsequent transmetalation allows the synthesis of the corresponding alkenyl zinc reagent (Scheme 87).[204] Moreover, *Knochel et al.* described the use of *i*PrMgCl·LiCl as exchange reagent for the formation of alkenyl magnesium reagents. 6-(Ethoxymethoxy)-1-

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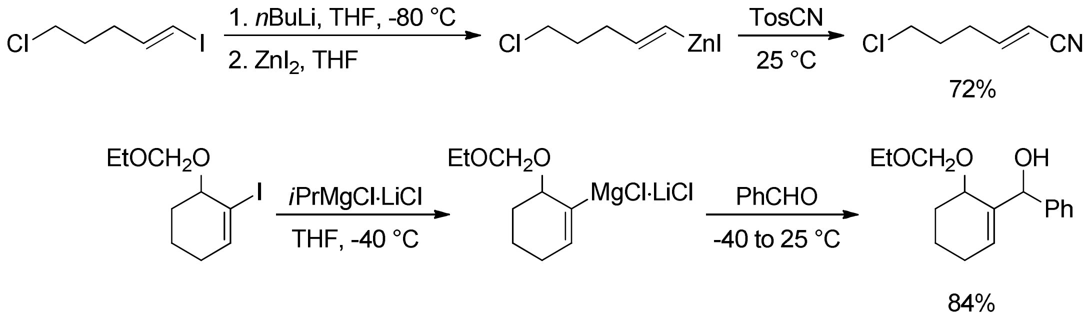
[201] a) *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts* (Eds.: J. Cossy, S. Arseniyadis, C. Meyer), Wiley-VCH, Weinheim, **2010**. b) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446. c) D. G. Gillingham, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2007**, *46*, 3860.
[202] K. Kiewel, Z. Luo, G. A. Sulikowski, *Org. Lett.* **2005**, *7*, 5163.
[203] a) A. Lemire, A. Côté, M. K. Janes, A. B. Charette, *Aldrichimica Acta* **2009**, *42*, 71. b) Z. Rappoport, in *The Chemistry of Organozinc Compounds* (Eds. Z. Rappoport, I. Marek), Wiley-VCH, Chichester, **2006**. c) M. Chen, X. Zheng, W. Li, J. He, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 4101. d) A. Rowley Kelly, A. E. Lurain, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 14668. e) A. Voituriez, L. E. Zimmer, A. B. Charette, *J. Org. Chem.* **2010**, *75*, 1244. f) W. S. Bechara, G. Pelletier, A. B. Charette, *Nature Chemistry* **2012**, *4*, 228.
[204] a) I. Klement, M. Rottländer, C. E. Tucker, T. N. Majid, P. Knochel, P. Venegas, G. Cahiez, *Tetrahedron* **1996**, *52*, 7201. b) L. Labaudinière, J.-F. Normant, *Tetrahedron Lett.* **1992**, *33*, 6139.

iodocyclo-hex-1-ene, for example, could readily be converted into its corresponding magnesium reagent (Scheme 87).[205]



Scheme 87: Preparation of alkenyl organometallics *via* iodine-metal exchange reactions.

The major drawbacks of this method are the low reaction temperatures required and the use of expensive and unstable alkenyl iodides as starting materials. To avoid these drawbacks, direct insertion reactions could be used. However, up to now, only unfunctionalized alkenyl organometallics could be employed in direct insertion reactions.[206] *Rieke et al.* for instance described the use of highly active zinc (Zn*) prepared *via* reduction of $ZnCl_2$ with lithium naphthalide for the synthesis of styrylzinc or (1-phenylvinyl)zinc bromide (Scheme 88).[63]

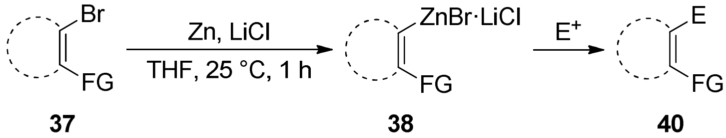
Scheme 88: Preparation of (1-phenylvinyl)zinc bromide from its corresponding bromide using *Rieke*-Zn (Zn*).

Recently, *Knochel* and coworkers have developed a practical and useful method for the synthesis of alkyl-,[64a,65b] aryl-,[21,64b] and benzylzinc[64b,65a,207] halides *via* LiCl-mediated metal-insertion into the corresponding chlorides and bromides. Based on these results, we searched for a convenient, mild and atom economical4 methodology for the preparation of highly functionalized alkenylzinc reagents starting from readily available alkenyl bromides bearing for the first time sensitive functional moieties.

[205] a) H. Ren, A. Krasovskiy, P. Knochel, *Org. Lett.* **2004**, *6*, 4215. b) H. Ren, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2005**, 543. e) E. M. E. Viseux, P. J. Parsons, J. B. J. Pavey, *Synlett* **2003**, 861.
[206] a) A. Wooten, P. J. Carroll, A. G. Maestri, P. J. Walsh, *J. Am. Chem. Soc.* **2006**, *128*, 4624. b) R. Anilkumar, D. J. Burton, *J. Fluorine Chem.* **2004**, *125*, 561. c) Q. Liu, D. J. Burton, *Tetrahedron Lett.* **2000**, *41*, 8045. d) Q. Liu, D. J. Burton, *J. Fluorine Chem.* **2011**, *132*, 78.
[207] A. Metzger, M. A. Schade, G. Manolikakes, P. Knochel, *Chem. Asian J.* **2008**, *3*, 1678.

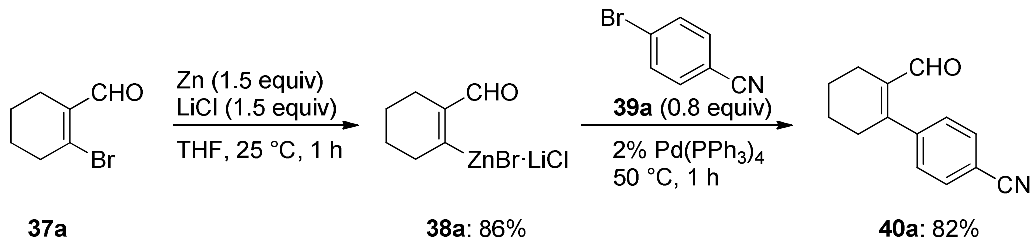
4.2 DIRECT INSERTION OF ZINC INTO ACTIVATED ALKENYL BROMIDES

Since the addition of LiCl enables a smooth zinc insertion into alkyl bromides, aromatic halides as well as benzylic chlorides, this method has been applied to activated alkenyl bromides for the effective preparation of functionalized alkenyl zinc reagents (Scheme 89).



Scheme 89: Preparation of alkenylzinc reagents **38** from activated alkenyl bromides **37** *via* dirct zinc insertion and subsequent functionalization.

Thus, 2-bromocyclohex-1-encarbaldehyde (**37a**) undergoes a smooth zinc insertion using commercially available zinc powder (1.5 equiv, 25 °C, 1 h) in the presence of LiCl (1.5 equiv) leading to the zinc reagent **38a** (86% yield, Scheme 90). A Pd-catalyzed *Negishi* cross-coupling reaction[145,208] with 4-bromobenzonitrile (**39a**) using 2% $Pd(PPh_3)_4$ affords the highly functionalized benzonitrile **40a** in 82% yield. The presence of the electron-withdrawing formyl group on the double bond accelerates the electron-transfer from the zinc to the organic halide through conjugation and therefore enables this exceptionally fast insertion reaction.



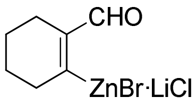
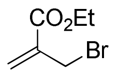
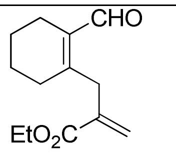
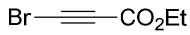
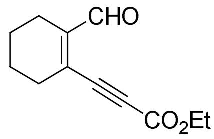
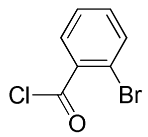
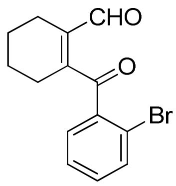
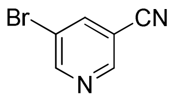
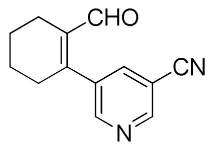
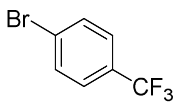
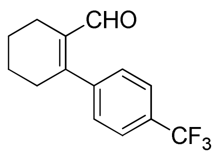
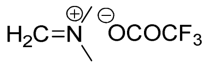
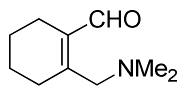
Scheme 90: LiCl-mediated zinc insertion in alkenyl bromide **37a** leading to zinc reagent **38a** and subsequent cross-coupling.

Moreover, a Cu(I)-catalyzed allylation reaction[146] with ethyl 2-(bromomethyl)acrylate (**39b**) leads to the desired product **40b** in 94% yield (Table 19, entry 1). The copper-catalyzed alkynylation reaction[11a,146] of **38a** with the bromoacetylene **39c**[209] affords the highly functionalized acetylene **40c** in 80% yield (entry 2). Furthermore, the acylation reaction[146] using 2-bromobenzoyl chloride (**39d**) affords ketone **40d** in 51% yield (entry 3). Additionally, Pd-catalyzed cross-coupling reactions with 5-bromo-3-cyanopyridine

[208] a) J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028. b) C. Han, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 7532. c) S. Çalimsiz, M. Sayah, D. Mallik, M. G. Organ, *Angew. Chem. Int. Ed.* **2010**, *49*, 2014. d) N. Hadei, G. T. Achonduh, C. Valente, C. J. O'Brien, M. G. Organ, *Angew. Chem. Int. Ed.* **2011**, *50*, 3896.
[209] M. C. P. Yeh, P. Knochel, *Tetrahedron Lett.* **1989**, *30*, 4799.

(**39e**) and 4-bromobenzotrifluoride (**39f**) produce the highly functionalized cyclohexenyl derivatives **40e** and **40f** in 65-73% yield (entries 4 and 5). Finally, the reaction of **38a** with the *Tietze* immonium reagent **39g**[210] leads to the aminoaldehyde **40g** (68% yield, entry 6).

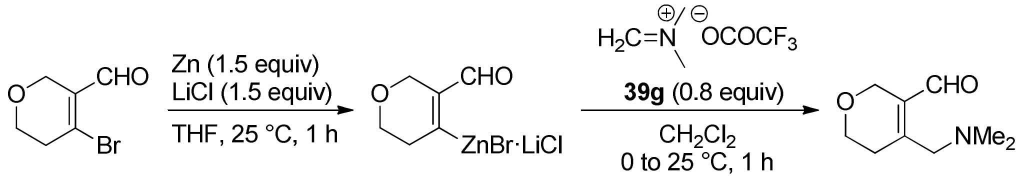
Table 19: Reactions of alkenylzinc reagent **38a** with electrophiles.

Entry	Zinc Reagent (Yield [%])[a]	Electrophile	Product	Yield [%][b]
1	 **38a** (86)	 **39b**	 **40b**	94[c]
2	**38a**	 **39c**	 **40c**	80[d]
3	**38a**	 **39d**	 **40d**	51[d]
4	**38a**	 **39e**	 **40e**	65[e]
5	**38a**	 **39f**	 **40f**	73[e]
6	**38a**	 **39g**	 **40g**	68

[a] Determined *via* titration with I_2. [b] Isolated yield of analytically pure product. [c] 3% CuCN·2LiCl was used. [d] 1 equiv CuCN·2LiCl was used. [e] 2% $Pd(PPh_3)_4$ was used and the reaction was performed at 50 °C.

[210] a) G. Kinast, L. F. Tietze, *Angew. Chem. Int. Ed.* **1976**, *15*, 239. b) M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed.* **1998**, *37*, 1044. c) N. Millot, C. Piazza, S. Avolio, P. Knochel, *Synthesis* **2000**, 941.

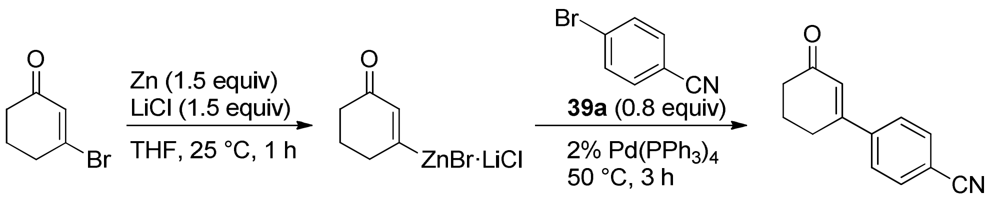
Analogous to aldehyde **38a**, the heterocyclic dihydropyranylzinc derivative **38b** has been prepared by a direct zinc insertion using zinc powder (1.5 equiv) in the presence of LiCl (1.5 equiv, 25 °C, 1 h, 77% yield). After reaction with immonium salt **39g**, the *N*,*N*-dimethyl-aminomethyl substituted dihydropyran derivative **40h** was isolated in 88% yield (Scheme 91).



37b **38b**: 77% **40h**: 88%

Scheme 91: LiCl-mediated zinc insertion in **37b** leading to **38b** and subsequent functionalization.

A direct insertion of zinc dust in 3-iodocyclohex-2-en-1-one and related structures is also possible.[211] However, the corresponding iodides are often unstable at room temperature which makes a synthesis starting from the corresponding bromide highly desireable. Hence, applying the method described above to 3-bromo-cyclohex-2-en-1-one (**37c**), a smooth insertion reaction occurs furnishing the 3-zincated cyclohexenone **38c** in 86% yield (Scheme 92). A Pd-catalyzed cross-coupling reaction with 4-bromo-benzonitrile (**39a**) affords the 3-substituted cyclohexenone derivative **40i** in 88% yield.



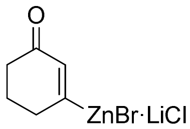
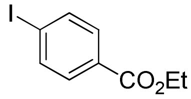
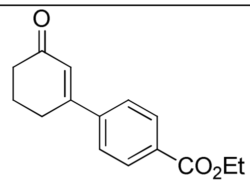
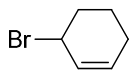
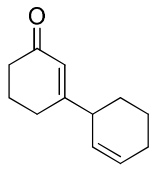
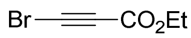
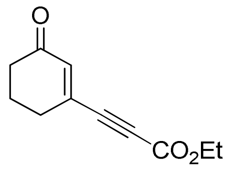
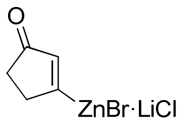
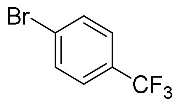
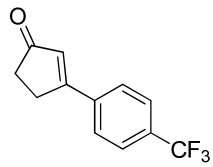
37c **38c**: 86% **40i**: 88%

Scheme 92: LiCl-mediated zinc insertion in **37c** leading to **38c** and subsequent cross-coupling.

The Pd-catalyzed cross-coupling of **38c** with ethyl 4-iodobenzoate (**39h**) affords the 3-substituted cyclohexenone derivative **40j** in 76% yield (Table 20, entry 1). Cu(I)-mediated reactions of **38c** with 3-bromocyclohexene (**39i**) or the bromoacetylene **39c** produce the unsaturated ketones **40k** and **40l** in 71-76% yield (entries 2 and 3). Analogously, 3-bromo-cyclopentenone (**37d**) is converted to the corresponding alkenylzinc reagent **38d** in 94% yield (25 °C, 5 h). Pd-catalyzed cross-coupling with 4-(trifluoromethyl)bromobenzene (**39f**) leads to the substituted cyclopentenone **40m** in 74% yield (entry 4).

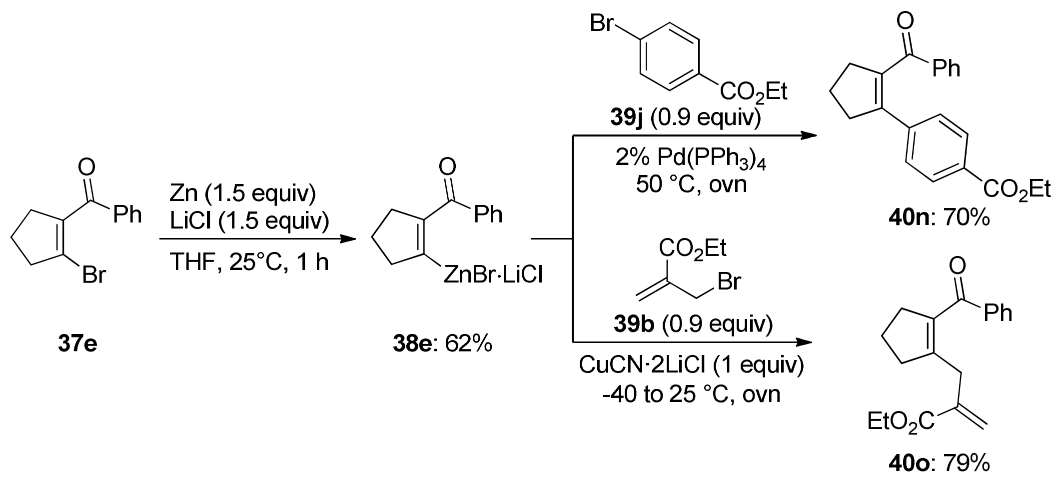
[211] a) P. Knochel, C. J. Rao, *Tetrahedron* **1993**, *49*, 29. b) A. S. Bhanu Prasad, P. Knochel, *Tetrahedron* **1997**, *53*, 16711. c) T. N. Majid, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 4413.

Table 20: Reactions of alkenylzinc reagents **38c** and **38d** with electrophiles.

Entry	Zinc Reagent (Yield [%])[a]	Electrophile	Product	Yield [%][b]
1	 **38c** (86)	 **39h**	 **40j**	76[c]
2	**38c**	 **39i**	 **40k**	76[e]
3	**38c**	 **39c**	 **40l**	71[e]
4	 **38d** (94)	 **39f**	 **40m**	74[c]

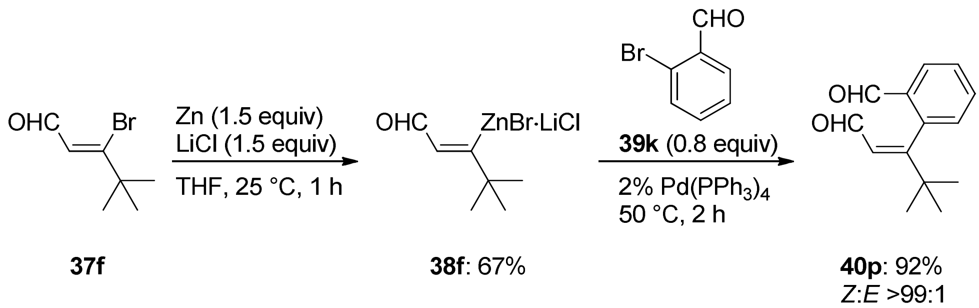
[a] Determined *via* titration with I_2. [b] Isolated yield of analytically pure product. [c] 2% $Pd(PPh_3)_4$ was used and the reaction was performed at 50 °C. [d] 3% CuCN·2LiCl was used. [e] 1 equiv CuCN·2LiCl was used.

Furthermore, also alkenyl bromides bearing a keto function can be directly converted into the corresponding zinc reagents *via* LiCl-mediated zinc insertion. Thus (2-bromocyclopent-1-en-1-yl)(phenyl)methan-one (**37e**) reacts readily with zinc powder (1.5 equiv) and LiCl (1.5 equiv) at 25 °C within 1 h to the corresponding organozinc compound **38e** in 62 % yield (Scheme 93). A Pd-catalyzed cross-coupling of **38e** with ethyl 4-bromobenzoate (39**3j**) leads to **40n** in 70% yield. A Cu(I)-catalyzed allylation reaction with ethyl 2-(bromomethyl)acrylate (**39b**) furnishes the desired product **40o** in 79% yield.



Scheme 93: LiCl-mediated Zn-insertion in **37e** leading to **38e** and subsequent functionalizations.

Due to chelation of the zinc center with the carbonyl group, acyclic alkenylzinc reagents bearing a vicinal aldehyde have been prepared without loosing the stereochemical information of the alkenyl precursors. In general, the formation of a five-membered ring chelate stabilizes the corresponding organometallic compound by several *kcal/mol*[212] and reduces the nucleophilicity of the carbonyl group. Thus, (*Z*)-3-bromo-4,4-dimethylpent-2-enal (**37f**) reacts with zinc powder (1.5 equiv) in the presence of LiCl (1.5 equiv) leading to the alkenylzinc reagent **38f** in 67% yield (Scheme 94). A Pd-catalyzed cross-coupling with 2-bromobenzaldehyde (**39k**) furnishes the unsaturated aldehyde **40p** in 92% yield and with a *Z:E*-selectivity of >99:1.

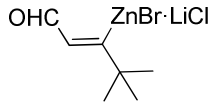
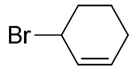
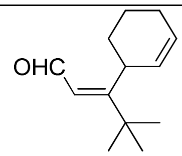
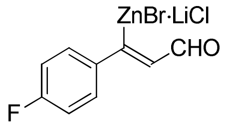
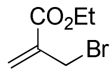
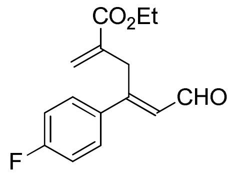
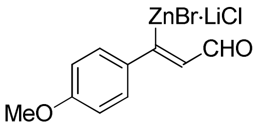
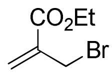
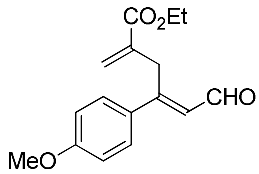


Scheme 94: LiCl-mediated Zn-insertion in **37f** leading to **38f** and subsequent cross-coupling.

A Cu(I)-catalyzed allylation of **38f** with 3-bromocyclohexene (**39i**) leads to the desired unsaturated product **40q** in 96% yield (Table 21, entry 1). Moreover, also the 4-fluoro and the 4-methoxy substituted derivatives **37g** and **37h** of (*Z*)-3-bromo-3-phenylprop-2-enal react to the corresponding zinc species **38g** and **38h** in 35-41% yield. The following Cu(I)-catalyzed allylation reaction with ethyl 2-(bromomethyl)-acrylate (**3b**) furnishes the cinnamyl-aldehydes **40r** and **40s** in 89-95% yield (*Z*:*E* >99:1, entries 2 and 3).

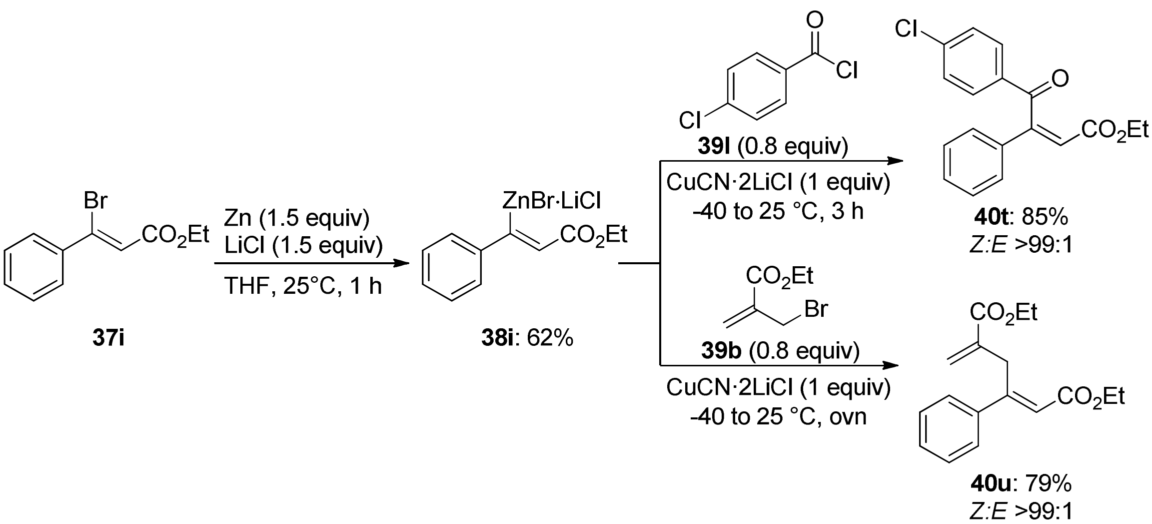
[212] G. W. Klumpp, *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1.

Table 21: Reactions of acyclic alkenylzinc reagents **38f-h** with electrophiles.

Entry	Zinc Reagent (Yield [%])[a]	Electrophile	Product	Yield [%][b]
1	 **38f** (67)	 **39i**	 **40q**	96[c],[e]
2	 **38g** (35)	 **39b**	 **40r**	95[d],[e]
3	 **38h** (41)	 **39b**	 **40s**	89[d],[e]

[a] Determined *via* titration with I_2. [b] Isolated yield of analytically pure product. [c] 3% CuCN·2LiCl was used. [d] 1 equiv CuCN·2LiCl was used. [e] Ratio of *Z*:*E* >99:1.

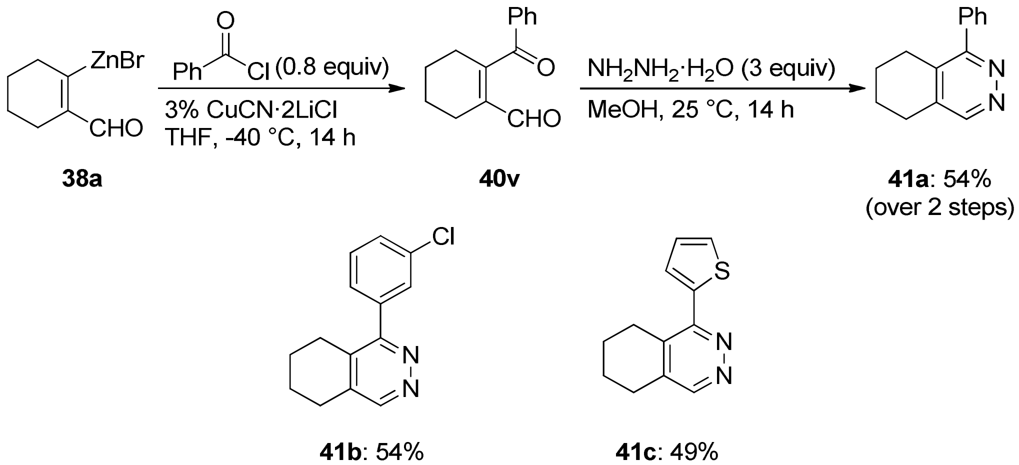
Noteworthy, the developed method has also been applied on an acyclic alkenyl bromide bearing an ester function. Hence, (*Z*)-ethyl 3-bromo-3-phenylacrylate (**37i**) has been converted into the corresponding zinc reagent **38i** with zinc powder (1.5 equiv) and LiCl (1.5 equiv; 25 °C, 1 h) in 62% yield (Scheme 95). The copper-mediated reaction of **38i** with 4-chlorobenzoyl chloride (**39l**) and ethyl 2-(bromomethyl)acrylate (**39b**) affords the highly functionalized cinnamyl esters **40t** and **40u** in 79-85% yield with a *Z*:*E*-selectivity of >99:1.



Scheme 95: LiCl-mediated zinc insertion in **37i** leading to **38i** and subsequent functionalizations.

4.2.1 PREPARATION OF 1-SUBSTITUTED TETRAHYDROPHTHALAZINES

Unsaturated 1,4-dicarbonyl compounds are highly reactive and undergo condensation reactions with hydrazine providing tetrahydrophthalazines.[213] Thus, zinc reagent **38a** was acylated with benzoyl chloride using 3% CuCN·2LiCl as catalyst affording the 1,4-dicarbonyl derivative **40v**. After aqueous workup, the crude **40v** undergoes without further purification a smooth condensation reaction with hydrazine hydrate ($NH_2NH_2 \cdot H_2O$) in methanol to afford the 1-substituted tetrahydrophthalazine **41a** in 54% yield (Scheme 96). Following this protocol, compounds **41b** and **41c**, bearing a 3-chlorophenyl- and a 2-thienyl-substituent, respectively, have been prepared (49-54% yield, Scheme 96).

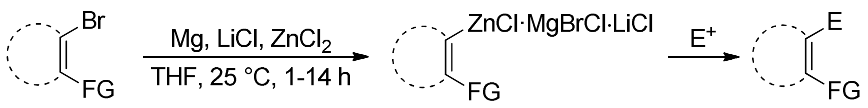


Scheme 96: Synthesis of substituted tetrahydrophthalazines of type **41**.

4.3 MAGNESIUM INSERTION IN THE PRESENCE OF $ZnCl_2$ INTO LESS ACTIVATED ALKENYL BROMIDES

The direct insertion of zinc into alkenyl bromides requires the presence of adjacent electron-withdrawing groups. Alkenyl bromides without such electronic activation either do not undergo an insertion reaction or react only at elevated temperatures and require long reaction times. To avoid these drawbacks, we have used the stronger reducing metal magnesium. The LiCl-mediated Mg insertion in the presence of $ZnCl_2$ allows an efficient synthesis of alkenylzinc halides starting from weakly activated alkenyl bromides (Scheme 97).

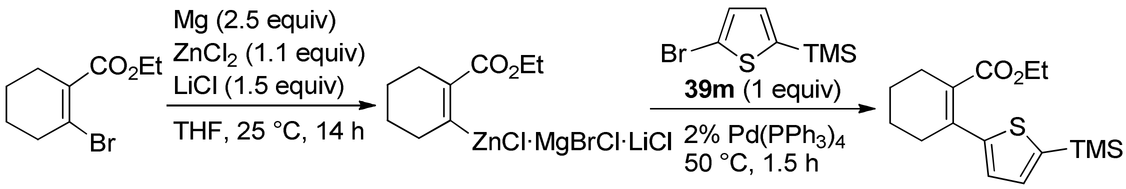
[213] G. Bold, K.-H. Altmann, J. Frei, M. Lang, P. W. Manley, P. Traxler, B. Wietfeld, J. Brüggen, E. Buchdunger, R. Cozens, S. Ferrari, P. Furet, F. Hofmann, G. Martiny-Baron, J. Mestan, J. Rösel, M. Sills, D. Stover, F. Acemoglu, E. Boss, R. Emmenegger, L. Lässer, E. Masso, R. Roth, C. Schlachter, W. Vetterli, D. Wyss, J. M. Wood, *J. Med. Chem.* **2000**, *43*, 2310.



42 **43** **44**

Scheme 97: Preparation of alkenylzinc reagents **43** from less activated alkenyl bromides **42** *via* magnesium insertion in presence of $ZnCl_2$ and subsequent functionalization.

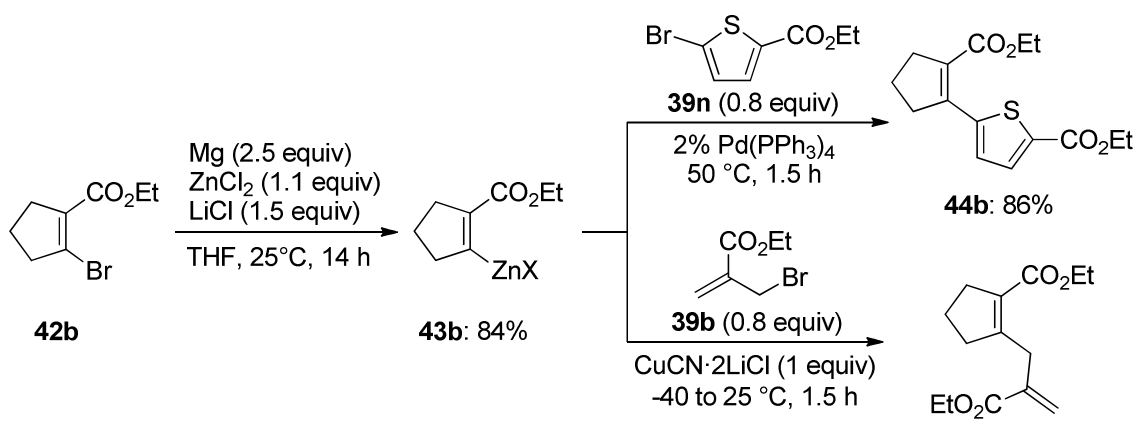
Whereas a vicinal ethyl ester does not sufficiently activate the alkenyl bromide **42a** for a LiCl-mediated zinc insertion, it undergoes a selective magnesium insertion in the presence of $ZnCl_2$ and LiCl furnishing the alkenylzinc reagent **43a** in 70% yield (Scheme 98). Its Pd-catalyzed cross-coupling with (5-bromothiophen-2-yl)trimethyl-silane (**39m**) leads to the substituted thiophene **44a** in 71% yield.



42a **43a**: 70% **44a**: 71%

Scheme 98: Selective insertion of Mg in the presence of $ZnCl_2$ and LiCl in the ester-substituted alkenyl bromides **42a** and subsequent cross-coupling.

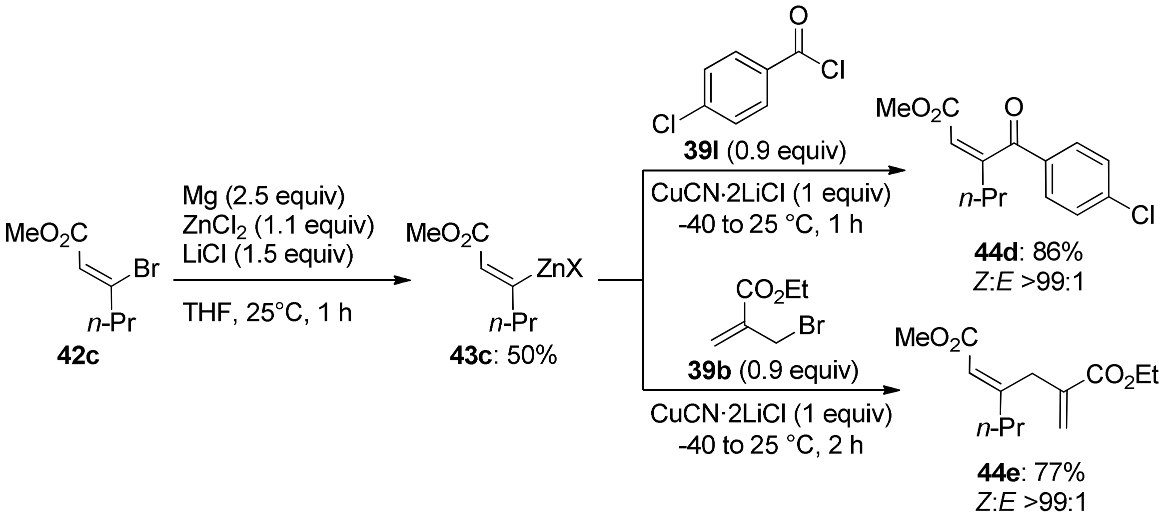
In an analogous way to **42a**, the ester-substituted cyclopentene derivative **42b** has been converted to its corresponding zinc reagent **43b** and submitted to a Pd-catalyzed cross-coupling with bromothiophene **39n** furnishing the substituted thiophene **44b** in 86% yield. The Cu(I)-mediated allylation with **39b** afforded the unsaturated product **44c** in 77% yield (Scheme 99).



42b **43b**: 84% **44b**: 86% **44c**: 77%

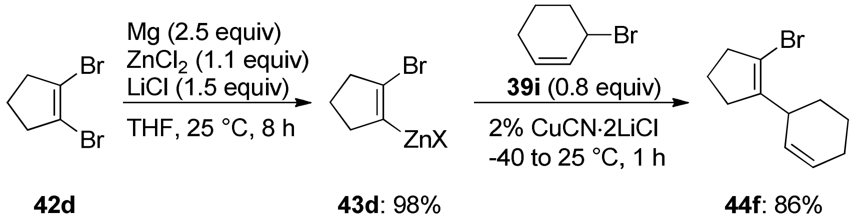
Scheme 99: Selective insertion of Mg in the presence of $ZnCl_2$ and LiCl in the ester-substituted alkenyl bromide **42b** and subsequent functionalizations (additional complexed salts are omitted for the sake of clarity).

Remarkably, the zinc insertion proceeds also well with the acyclic unsaturated bromoester **42c**. The LiCl-mediated Mg insertion in the presence of $ZnCl_2$ furnishes the corresponding zinc reagent **43c** in 50% yield without any loss of stereochemical information due to the chelation of the zinc center with the carbonyl group. The subsequent copper-catalyzed reaction of **43c** with 4-chlorobenzoyl chloride (**39l**) and ethyl 2-(bromomethyl)acrylate (**39b**) produces the functionalized acyclic compounds **44d** and **44e** in 77-86% yield (*Z*:*E* >99:1, Scheme 100).



Scheme 100: Selective insertion of Mg in the presence of $ZnCl_2$ and LiCl in the ester-substituted alkenyl bromide **42c** and subsequent functionalizations (additional complexed salts are omitted for the sake of clarity).

Although 1,2-dibromocyclopentene (**42d**) can be converted to the corresponding magnesium reagent by a Br/Mg-exchange with *i*PrMgCl·LiCl,[214] a more atom economical approach using $Mg/ZnCl_2/LiCl$ is possible. Thus, the treatment of **42d** with magnesium in the presence of $ZnCl_2$ and LiCl leads to the desired alkenylzinc reagent **43d** in quantitative yield (Scheme 101). Its Cu(I)-catalyzed reaction with 3-bromocyclohexene (**39i**) affords **44f** in 86% yield.

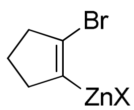
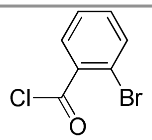
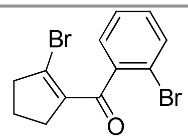
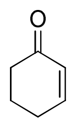
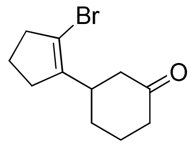
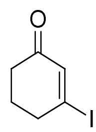
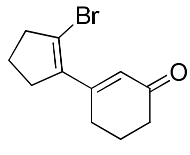
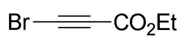
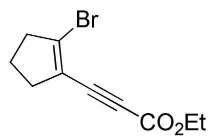
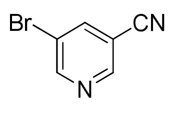
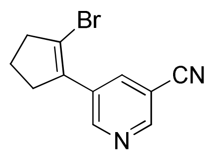


Scheme 101: Selective mono-insertion of Mg in the presence of $ZnCl_2$ and LiCl into alkenyl dibromide **42d** and subsequent allylation (additional complexed salts are omitted for the sake of clarity).

[214] C. Despotopoulou, A. Krasovskiy, P. Mayer, P. Knochel, R. C. Bauer, J. M. Stryker, *Chem. Eur. J.* **2008**, *14*, 2499.

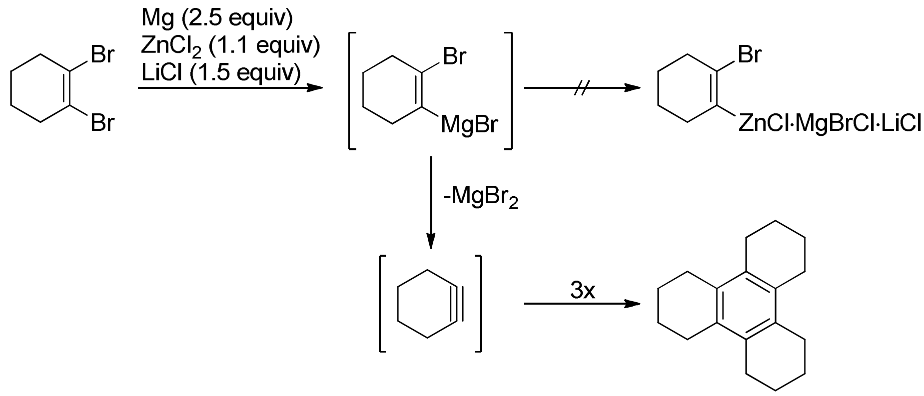
Furthermore, an acylation reaction of **43d** using 2-bromobenzoyl chloride (**39d**) affords the unsaturated ketone **44g** in 64% yield (Table 22, entry 1). Additional Cu(I)-mediated reactions with cyclohexenone (**39o**), 3-iodocyclo-hexenone (**39p**) and bromoacetylene **39c** lead to the expected products **44h-j** in 65-78% yield (entries 2-4). Finally, the Pd-catalyzed cross-coupling reaction of **43d** with 3-bromo-5-cyanopyridine (**3e**) furnishes the substituted pyridine **44k** in 54% yield (entry 5).

Table 22: Reactions of alkenylzinc reagent **43d** with electrophiles.

Entry	Zinc Reagent[a] (Yield [%])[b]	Electrophile	Product	Yield [%][c]
				
1	**43d** (98)	**39d**	**44g**	64[d]
				
2	**43d**	**39o**	**44h**	70[d]
				
3	**43d**	**39p**	**44i**	65[d]
				
4	**43d**	**39c**	**44j**	78[e]
				
5	**43d**	**39e**	**44k**	54[f]

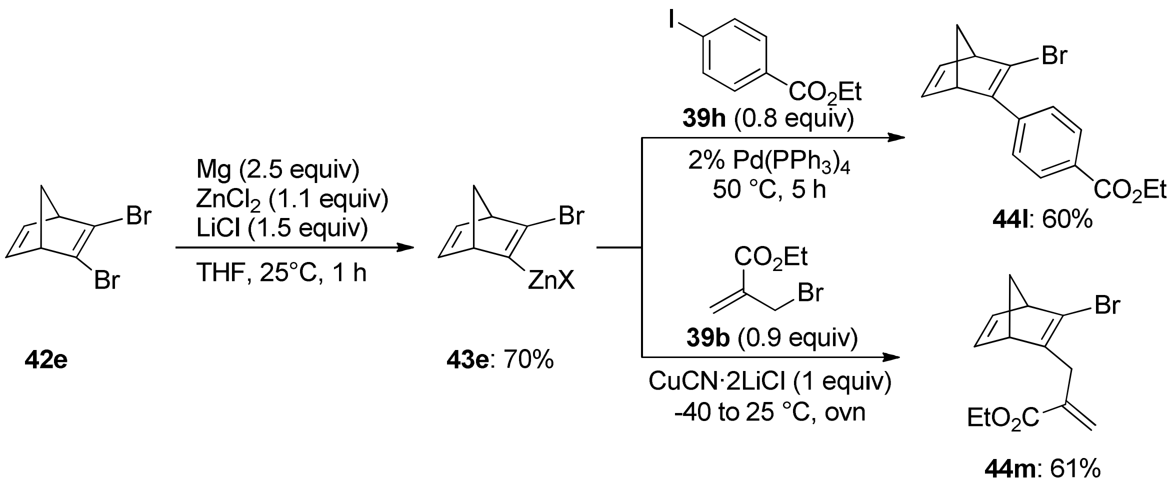
[a] Additional complexed salts are omitted for the sake of clarity. [b] Determined *via* titration with I_2. [c] Isolated yield of analytically pure product. [d] 1 equiv of CuCN·2LiCl was used. [e] 2% CuCN·2LiCl was used. [f] 2% $Pd(PPh_3)_4$ was used and the reaction was performed at 50 °C.

A functionalization of the related 1,2-dibromocyclohexene employing this method has not been possible. Since the 6-membered ring has a smaller ring strain, the initially formed organomagnesium reagent presumably eliminates $MgBr_2$ leading to cyclohexyne which undergoes fast side reactions such as trimerisation (Scheme 102).



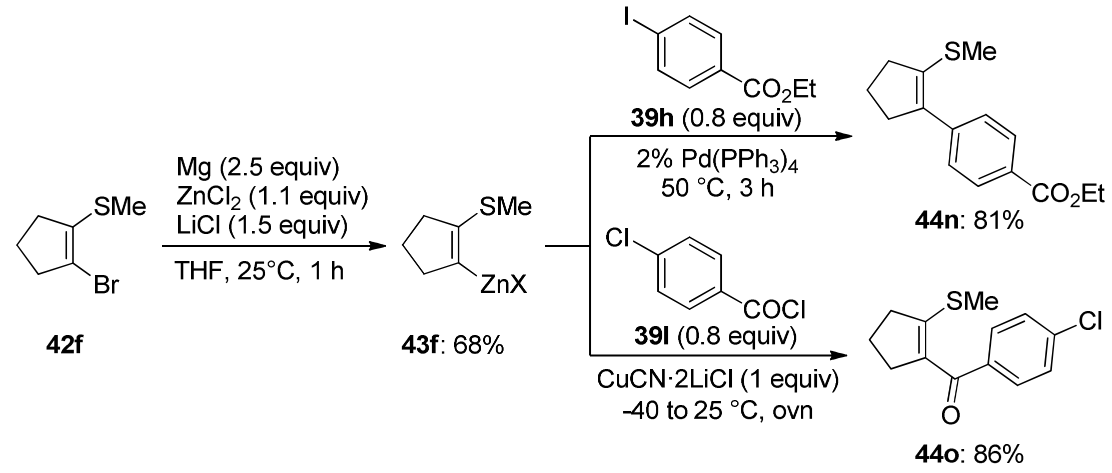
Scheme 102: Reaction of 1,2-dibromocyclohexene with Mg in the presence of $ZnCl_2$ and LiCl leading to elimination and subsequent trimerisation.

However, the increased ring strain in the dibromo-norbornadiene derivative **42e** prevents this elimination reaction and the corresponding zinc reagent **43e** is obtained within 1 h in 70% yield using Mg (2.5 equiv) in the presence of LiCl (1.5 equiv) and $ZnCl_2$ (1.1 equiv) (Scheme 103). A Pd-catalyzed cross-coupling of **43e** with ethyl 4-iodobenzoate (**39h**) produces the arylated norbornadiene **44l** in 60% yield. A Cu(I)-catalyzed allylation reaction with ethyl 2-(bromomethyl)acrylate (**39b**) leads to the desired product **44m** in 61% yield.



Scheme 103: Selective insertion of Mg in the presence of $ZnCl_2$ and LiCl in the alkenyl dibromide **42e** and subsequent functionalizations (additional complexed salts are omitted for the sake of clarity).

As expected, alkenyl bromides bearing an electron-donating substituent such as (2-bromocyclopent-1-en-1-yl)(phenyl)sulfane (**42f**) do not undergo a direct zinc insertion. However, using Mg (2.5 equiv) in the presence of LiCl (1.5 equiv) and $ZnCl_2$ (1.1 equiv) furnishes **43f** within 1 h in 69% yield (Scheme 104). A subsequent Pd-catalyzed cross-coupling reaction with ethyl 4-iodobenzoate (**39h**) leads to the arylated cyclopentene **44n** in 81% yield. A Cu(I)-mediated acylation of **43f** with 4-chlorobenzoyl chloride (**39l**) furnishes the unsaturated ketone **44o** in 86% yield.

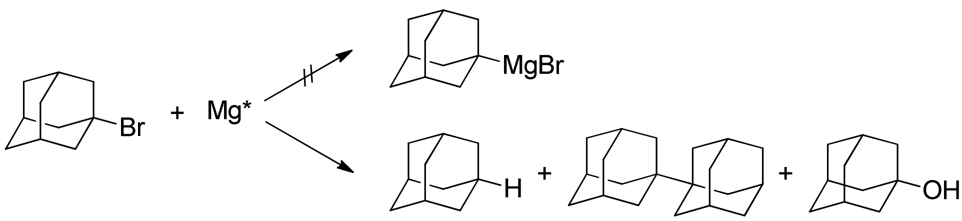


Scheme 104: Selective insertion of Mg in the presence of $ZnCl_2$ and LiCl in the alkenyl bromide **42f** and subsequent functionalizations (additional complexed salts are omitted for the sake of clarity).

5. SYNTHESIS OF FUNCTIONALIZED ADAMANTYLZINC REAGENTS USING A Br/Mg-INSERTION IN THE PRESENCE OF $ZnCl_2$

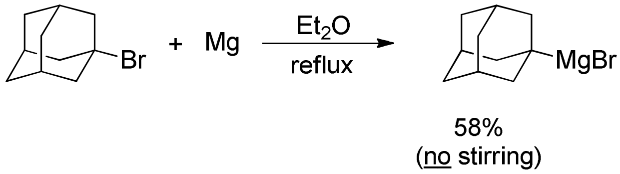
5.1 INTRODUCTION

Synthesis of organomagnesium reagents is known for many years.[16-21] Nevertheless, none of these many studies provides an explanation for the systematic failures encountered in attempts at synthesizing cage-structure organomagnesium compounds. Thus, at no time does 1- or 2-adamantyl bromide yield an organometallic compound, whereas secondary or tertiary halides such as isopropyl chloride, *tert*-butyl chloride, and 3-chloro-3-ethylpentane give excellent yields of organomagnesium compounds.[215] The reaction of 1-adamantylmagnesium bromide with highly reactive magnesium (Mg*) obtained *in situ* by the standard method of *Rieke* and coworkers[216] could not furnish any trace of organomagnesium compound. Instead, a 60% yield of hydrolysed adamantane and a 30% yield of homocoupling product can be isolated (Scheme 105).[215]



Scheme 105: Reaction of adamantyl bromide with *Rieke*-Mg (Mg*).

However, *Dubois et al.* develop a so-called "static" method whereby the entire reaction was conducted without any stirring of the reaction medium leading to 58% yield of 1-adamantylmagnesium bromide (Scheme 106).[217] When this process was extended to 2-AdBr, the yield of 2-adamantylmagnesium bromide lay at 60%.



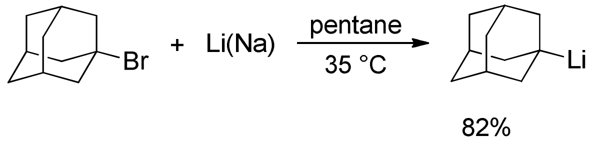
Scheme 106: Successful synthesis of adamantylmagnesium bromide.

It was shown, that the success of this "static" method lay in the preservation of the surface state of the magnesium. The formation of organomagnesium compounds is a typical surface reaction, whereas the side reactions occur in the medium. Competition

[215] G. Molle, P. Bauer, J. E. Dubois, *J. Org. Chem.* **1982**, *47*, 4120.
[216] R. D. Rieke, S. E. Bales, *J. Am. Chem. Soc*. **1974**, *96*, 1775.
[217] J. E. Dubois, P. Bauer, G. Molle, J. Daza, *C. R. Hebd. Seances Acad. Sci., Ser. C* **1977**, *284*,146.

between these two reaction pathways is depending on the degree of adsorption of the transient species at the metal surface. Since the volume of cage-structure adamantane has a steric effect on the degree of adsorption of the transient species, the reactions in the medium are favoured. This explains the failures to obtain an organometallic compound with stirring. In contrast, with less hindered molecules, surface reactions are favored, and the organometallic compounds are formed readily.[215]

Until 1983, all attempts for the direct synthesis of organolithium compounds[218] had failed, and only the halogene/lithium exchange reactions furnished a few cage-structure organolithium compounds.[219] The syntheses using secondary or tertiary adamantyl halides and methyl or *tert*-butyllithium, tertiary[220] and secondary[220d,221] adamantyl organolithium compounds could be obtained only when an excess of *tert*-butyllithium was used. Extension of the previously described method used for magnesium compounds[215] to organolithium compounds was unsuccessful since tertiary organolithium compounds are known to attack diethyl ether at a temperature above -30 °C. Moreover, in the absence of stirring, lithium chloride slowly coats the metal with a film rapidly inhibiting the attack by the halogenated derivative.[222] By using a 2% sodium lithium alloy in an apolar solvent, *Dubois* and coworker prevented scouring the metal surface during synthesis and limited solvent-attack side reactions. Under these conditions, 1-adamantyllithium could be obtained for the first time in a high yield (Scheme 107).[222]

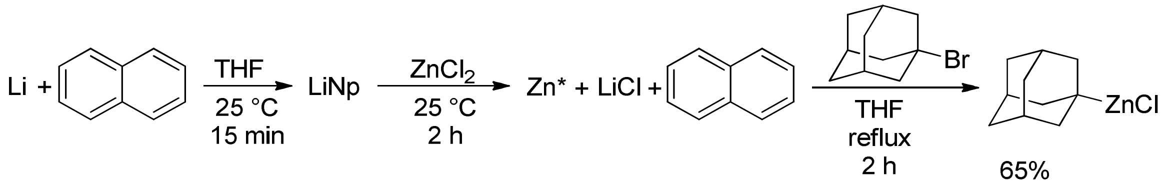


Scheme 107: Synthesis of adamantyllithium using a 2% sodium lithium alloy.

In 1973, *Rieke* and coworkers reported a general approach for the preparation of highly reactive zinc (Zn*) allowing for the first time the oxidative addition to primary alkyl bromides as well as to aryl iodides and bromides.[223] In 1991, they published an improved method which was not only safer but also furnished a more reactive zinc

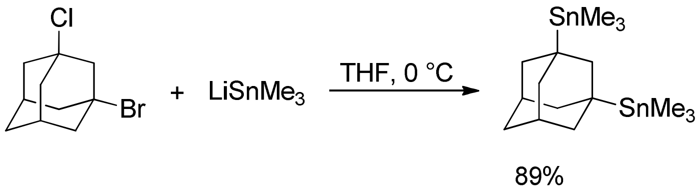
[218] a) F. N. Stepanov, V. F. Baklan, *J. Gen. Chem. USSR* **1964**, *34*, 580. b) W. Hoek, J. Strating, H. Wynberg, *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 1045.
[219] G. Wittig, U. Schöllkopf, *Tetrahedron* **1968**, *3*, 91.
[220] a) P. T. Lansbury, J. D. Sidler, *Chem. Commun.* **1966**, 273. b) P. T. Lansbury, V. A. Pattison, J. D. Sidler, J. B. Bicher, *J. Am. Chem. Soc.* **1966**, *88*, 78. c) J. H. Wieringa, J. Strating, H. Wynberg, *Synth. Commun.* **1972**, *4*, 191. d) J. H. Wieringa, H. Wynberg, J. Strating, *Tetrahedron Lett.* **1972**, *13*, 2071.
[221] J. H. Wieringa, H. Wynberg, J. Strating, *Synth. Commun.* **1971**, *1*, 7.
[222] G. Molle, P. Bauer, J. E. Dubois, *J. Org. Chem.* **1983**, *48*, 2975.
[223] R. D. Rieke, P. M. Hudnall, S. Uhm, *J. Chem. Soc.*, *Chem. Comm.* **1973**, 269.

enabling the synthesis of secondary and tertiary alkyl bromides to yield the corresponding organozinc reagents in good yields under mild conditions.[224] Thus, 1-adamantyl bromide reacts within 2 h under reflux with Zn* furnishing the corresponding organozinc species in 65% yield (Scheme 108).



Scheme 108: Synthesis of adamantylzinc chloride using *Rieke*-Zn (Zn*).

The trimethylstannylation of 1-bromo- and 1-iodoadamantanes as well as of 2-bromo-adamantane has been shown to occur by free radical intermediates in an $S_{RN}1$ like reaction.[225] Also 1,3-dihaloadamantane derivatives undergo the trimethylstannylation exclusively in a $S_{RN}1$ like manner (Scheme 109).[226]



Scheme 109: Trimethylstannylation of 1-bromo-3-chloroadamantane.

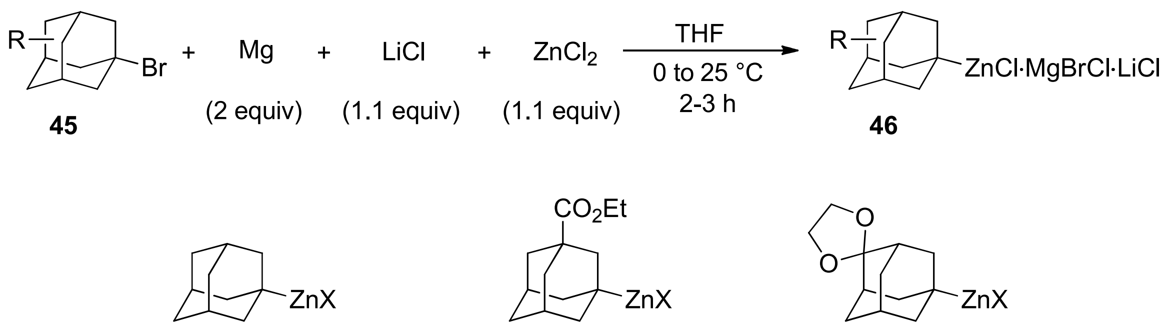
Noteworthy, the photostimulated reaction of Me_3Sn^- anions with 1-chloro- and 1-bromoadamantane in liquid ammonia afforded within a few minutes the corresponding stannylated products in good yields.[225b]

Recently, *Knochel* and coworkers have developed a practical and useful method for the synthesis of alkyl-,[64a,65b] aryl-,[21,64b] and benzylzinc[64b,65a,207] halides *via* LiCl-mediated metal-insertion into the corresponding chlorides and bromides. Based on these results, we searched for a convenient, mild and atom economical4 methodology for the preparation of functionalized adamantylzinc reagents starting from readily available adamantyl bromides bearing for the first time sensitive functional moieties.

[224] L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445.
[225] a) G. F. Smith, H. G. Kuivila, R. Simon, L. Sultan, *J. Am. Chem. Soc.* **1981**, *103*, 833. b) A. N. Santiago, A. E. Stahl, G. L. Rodriguez, R. A. Rossi, *J. Org. Chem.* **1997**, *62*, 4406. c) H. Duddeck, M. R. Islam, *Chem. Ber.* **1984**, *117*, 565.
[226] W. Adcock, C. I. Clark, *J. Org. Chem.* **1993**, *58*, 7341.

5.2 PREPARATION OF FUNCTIONALIZED ADAMANTYLZINC REAGENTS

Preliminary experiments have shown that only the use of the highly reactive *Rieke*-zinc (Zn*) provides a direct zinc insertion. Since we wanted to avoid the use of stochiometric amounts of lithium naphthalide, the main focus lay on the use of a stronger reducing metal than zinc. Thus, the LiCl-mediated Mg insertion in the presence of $ZnCl_2$ allowed an efficient synthesis of adamantylzinc reagents **46** starting from the corresponding tertiary bromides **45** (Scheme 110).



46a: 85% **46b**: 63% **46c**: 57%

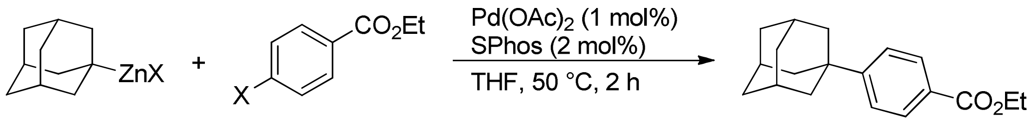
Scheme 110: Preparation of functionalized adamantylzinc reagents **46** *via* the LiCl-mediated Mg-insertion in the presence of $ZnCl_2$ (additional complexed salts are omitted for the sake of clarity).

As illustrated in Scheme 110, the zinc species **46a** was obtained from 1-bromo-adamantane **45a** within 2 h at ambient temperature in 85% yield using Mg (2 equiv) in the presence of LiCl (1.1 equiv) and $ZnCl_2$ (1.1 equiv). Remarkably, also the functionalized adamantylzinc reagents **46b** and **46c** have been obtained for the very first time in 63% and 57% yield, following this procedure. Noteworthy, the acetal protection of the keto-function of 5-bromoadamantan-2-one was compulsory since the preparation of the zinc reagent from the unprotected ketone caused the cleavage of the cage structure.

5.3 FUNCTIONALIZATION OF ADAMANTYLZINC REAGENTS

The obtained adamantylzinc reagents **46a-c** have proven to be highly reactive and readily undergo a broad variety of functionalization reactions in the presence of an appropriate catalyst. Thus, zinc reagent **46a** smoothly reacts in a Pd-catalyzed *Negishi* cross-coupling reaction[145,208] with aryl halides **47a-m**. Using 1% $Pd(OAc)_2$ and 2% SPhos[227] as catalytic system, zinc reagent **46a** reacts within 2 h at 50 °C with the ester substituted aryl iodide **47a**, aryl bromide **47b** and even the aryl chloride **47c** to the corresponding cross-coupling product **48a** in excellent yields (Scheme 111).

[227] J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028.

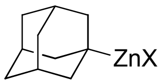
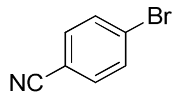
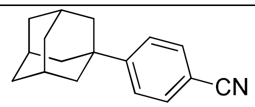
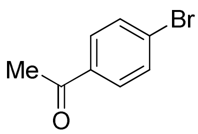
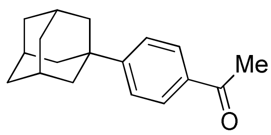
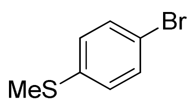
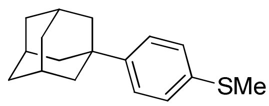
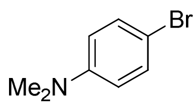
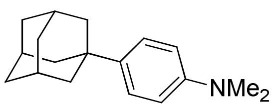
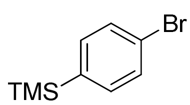
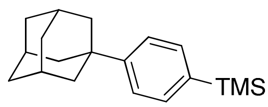
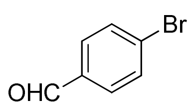
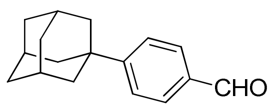


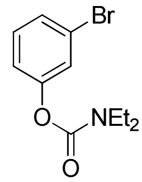
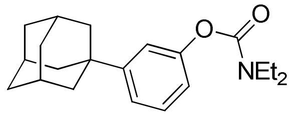
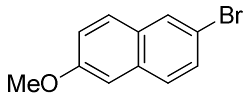
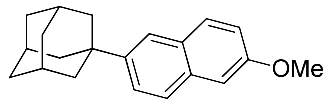
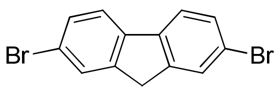
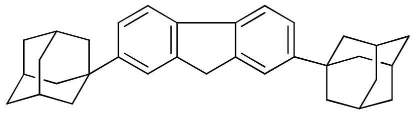
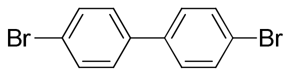
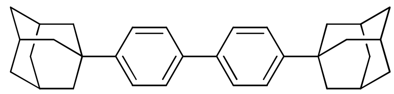
46a **47a-c** (0.9 equiv) **48a**: 87% (X = I) 83% (X = Br) 87% (X = Cl)

Scheme 111: *Negishi* cross-coupling reaction of adamantylzinc reagent **46a** with aryl halides of type **47** (additional complexed salts are omitted for the sake of clarity).

Various electron-rich and electron-poor electrophiles (0.9 equiv) are used in the cross-coupling reaction at 50 °C affording the corresponding arylated adamantyl derivatives **48b-i** in good to excellent yields, tolerating functional groups like nitril, aldehyde, ketone or carbamate (Table 23, entries 1-8). Noteworthy, also double cross-coupling could be achieved under these reaction conditions (entries 9 and 10), furnishing the corresponding products **48l** and **48m** in 82% and 55% yield, respectively.

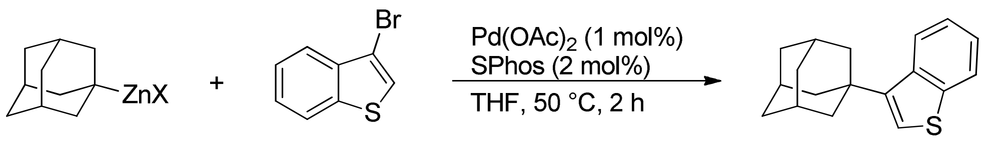
Table 23: *Negishi* cross-coupling reactions of adamantylzinc reagent **46a** with aryl bromides of type **47**.

Entry	Zn-Reagent	Electrophile	Product, Yield[a]
1	 **46a**	 **47d**	 **48b**: 88%[b]
2	**46a**	 **47e**	 **48c**: 84%[b]
3	**46a**	 **47f**	 **48d**: 94%[b]
4	**46a**	 **47g**	 **48e**: 62%[b]
5	**46a**	 **47h**	 **48f**: 80%[b]
6	**46a**	 **47i**	 **48g**: 88%[b]

7	**46a**	 **47j**	 **48h**: 70%[b]
8	**46a**	 **47k**	 **48i**: 95%[b]
9	**46a**	 **47l**	 **48j**: 82%[c]
10	**46a**	 **47m**	 **48k**: 55%[d]

[a] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [b] Obtained after a *Negishi* cross-coupling ($Pd(OAc)_2$ (1 mol%) and SPhos (2 mol%)) with ArBr (0.9 equiv). [c] Obtained after a *Negishi* cross-coupling ($Pd(OAc)_2$ (1 mol%) and SPhos (2 mol%)) with 2,7-dibromo-fluorene (0.45 equiv). [d] Obtained after a *Negishi* cross-coupling ($Pd(OAc)_2$ (2 mol%) and SPhos (4 mol%)) with 4,4'-dibromo-1,1'-biphenyl (0.4 equiv).

As illustrated in Scheme 112, also heteroaryl bromides have been employed in the *Negishi* cross-coupling reactions. Adamantyl zinc reagent **46a** reacts smoothly with 3-bromobenzothiophene (**49a**, 0.9 equiv) at 50 °C within 2 h to the corresponding substituted adamantane **48l** in 84% yield.

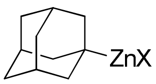
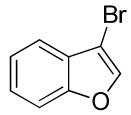
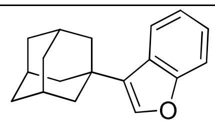
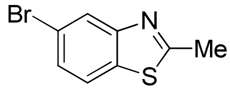
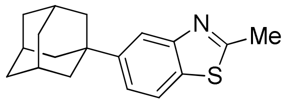
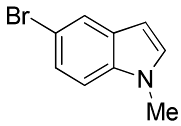
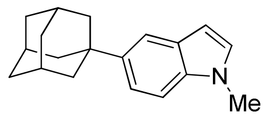
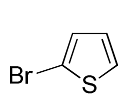
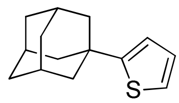
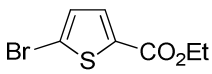
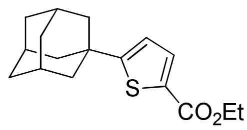
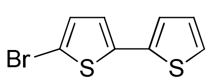
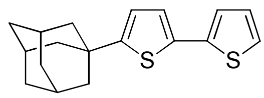


46a **49a** (0.9 equiv) **48l**: 84%

Scheme 112: *Negishi* cross-coupling reaction of adamantylzinc reagent **46a** with 3-bromobenzothiophene (**49a**) (additional complexed salts are omitted for the sake of clarity).

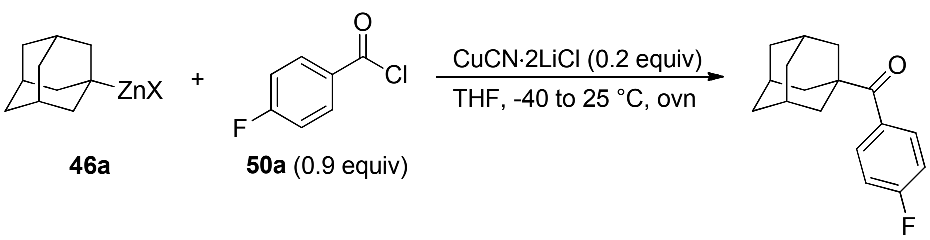
A broad variety of heteroaryl bromides as electrophiles produce under standard conditions the desired products **48m-r** in excellent yields (Table 24). In particular, benzofuran, benzothiazol, protected indol or different thiophene derivatives have successfully been employed in the cross-coupling reaction furnishing the corresponding heteroarylated adamantan compounds **48m-r** in good to excellent yields.

Table 24: *Negishi* cross-coupling reactions of adamantylzinc reagent **46a** with heteroaryl bromides of type **49**.

Entry	Zn-Reagent	Electrophile	Product, Yield[a]
1	 **46a**	 **49b**	 **48m**: 57%[b]
2	**46a**	 **49c**	 **48n**: 91%[b]
3	**46a**	 **49d**	 **48o**: 71%[b]
4	**46a**	 **49e**	 **48p**: 61%[b]
5	**46a**	 **49f**	 **48q**: 53%[b]
6	**46a**	 **49g**	 **48r**: 58%[b]

[a] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [b] Obtained after a *Negishi* cross-coupling ($Pd(OAc)_2$ (1 mol%) and SPhos (2 mol%)) with heteroaryl bromide (0.9 equiv).

Adamantylzinc reagent **46a** also undergoes Cu(I)-catalyzed acylation reactions leading to the desired ketone derivatives **51a-d** in good to excellent yields (Scheme 113 and Table 25). **46a** reacted with 4-fluorobenzoyl chloride (**50a**, 0.9 equiv) and 20% CuCN·2LiCl to the corresponding ketone **51a** in 89% yield (Scheme 113).



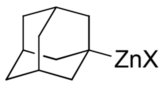
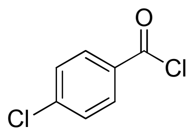
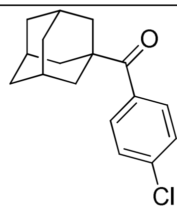
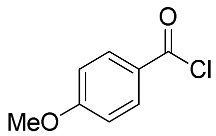
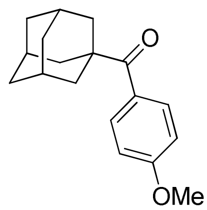
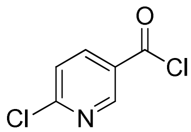
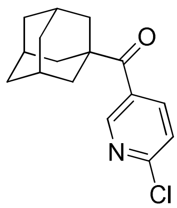
46a **50a** (0.9 equiv)

51a: 89%

Scheme 113: Cu(I)-catalyzed acylation reaction of adamantylzinc reagent **46a** with 4-fluorobenzoyl chloride (**50a**) (additional complexed salts are omitted for the sake of clarity).

Under the same reaction conditions, also other acid chlorides **50b-d** have been employed in the Cu(I)-catalyzed acylation reaction. Not only the substituted benzoyl chlorides **5b-c** undergo the acylation reaction with adamantylzinc species **46a** in good yields (Table 25, entries 1 and 2), also the heteroaromatic 6-chloronicotinoyl chloride (**50d**) furnished the corresponding ketone **51d** in the acceptable yield of 44% (entry 3).

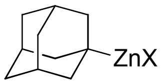
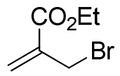
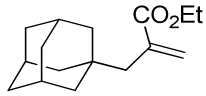
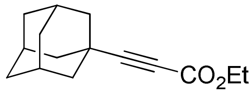
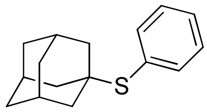
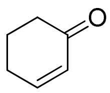
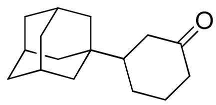
Table 25: Cu(I)-catalyzed acylation reactions of adamantylzinc reagent **46a** with acid chlorides of type **50**.

Entry	Zn-Reagent	Electrophile	Product, Yield[a]
			
1	**46a**	**50b**	**51b**: 70%[b]
			
2	**46a**	**50c**	**51c**: 80%[b]
			
3	**46a**	**50d**	**51d**: 44%[b]

[a] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [b] Obtained after a acylation reaction (CuCN·2LiCl (0.2 equiv)) with acid chloride (0.9 equiv).

Besides Pd-catalyzed *Negishi* cross-coupling reactions and Cu(I)-catalyzed acylation reactions the highly reactive adamantylzinc reagent **46a** also reacts in a a Cu(I)-catalyzed allylation reaction[146] with ethyl 2-(bromomethyl)acrylate (**52a**, 0.9 equiv) leading to the desired product **53a** in 91% yield (Table 26, entry 1). Moreover, the copper-catalyzed reaction[11a,146] of **46a** with the bromoacetylene **52b**[209] (0.9 equiv) affords the highly functionalized acetylene **53b** in 66% yield (entry 2). Furthermore, the adamantylzinc reagent **46a** also reacts smoothly with *S*-phenyl benzenesulfonothioate (**52c**, 0.9 equiv) affording thioether **9c** in almost quantitative yield (entry 3). Additionally, the Cu(I)-mediated reaction with cyclohex-2-enone (**52d**, 0.9 equiv) furnishes the desired 1,4-addition product **53d** in 91% yield (entry 4).

Table 26: Further functionalization reactions of adamantylzinc reagent **46a** with various electrophiles.

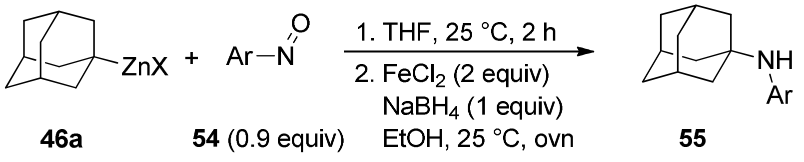
Entry	Zn-Reagent	Electrophile	Product, Yield[a]
1	 **46a**	 **52a**	 **53a**: 91%[b]
2	**46a**	$EtO_2C-C\equiv C-Br$ **52b**	 **53b**: 66%[c]
3	**46a**	$PhSSO_2Ph$ **52c**	 **53c**: 98%[d]
4	**46a**	 **52d**	 **53d**: 91%[e]

[a] Yield of analytically pure isolated product as determined by ^1H NMR analysis. [b] Obtained after allylation reaction (CuCN·2LiCl (0.2 equiv)) with ethyl 2-(bromomethyl)acrylate (0.9 equiv). [c] Obtained after alkynylation reaction (CuCN·2LiCl (0.2 equiv)) with ethyl 3-bromopropiolate (0.9 equiv). [d] Obtained after addition to *S*-aryl benzenethiosulfonate (0.9 equiv). [e] Obtained after 1,4-addition (CuCN·2LiCl (1.1 equiv) and TMSCl (2.0 equiv)) with cyclohex-2-enone (0.9 equiv).

Amination reactions are well known in literature.[228] Recently, several Pd(0)-[229] and Cu(I)-catalyzed[230] reactions between aromatic halides and various amines have been reported. Moreover, *Knochel* and coworkers found that this synthetic transformation can also be realized by reacting various arylmagnesium species with nitroarenes leading after a reductive workup to polyfunctional amines.[231] In order to avoid the use of 2 equivalents of arylmagnesium species, they employed nitrosoarenes for the amination reaction.[232]

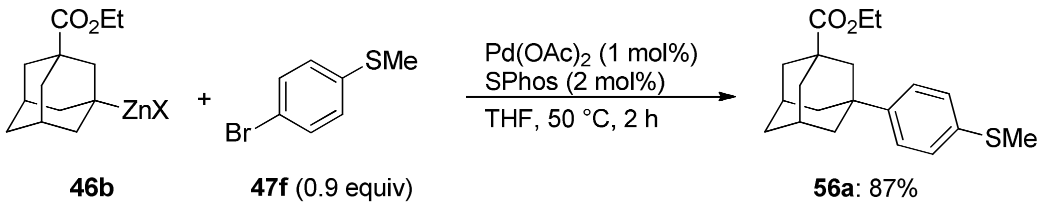
It turned out that also the adamantylzinc reagent **46a** readily reacts at ambient temperature within 2 h with nitroarenes of type **54**. After reductive workup, the substituted amino derivatives **55a** and **55b** could be obtained in 89% and 71% yield, respectively (Scheme 114).

[228] *Modern Amination Methods* (Ed.: A. Ricci) Wiley-VCH, Weinheim, **2000**.
[229] a) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125. b) J. P. Wolfe, S. Wagan, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805. c) J. F. Hartwig, *Angew. Chem. Int. Ed.* **1998**, *37*, 2046. d) L. M. Alcazar-Roman, J. F. Hartwig, A. L. Rheingold, L. M. Liable-Sands, I. A. Guzei, *J. Am. Chem. Soc.* **2000**, *122*, 4618.
[230] a) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727. b) M. Wolter, A. Klapars, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3803. c) R. Shen, J. A. Porco, *Org. Lett.* **2000**, *2*, 1333. d) A. V. Kalinin, J. F. Bower, P. Riebel, V. Snieckus, *J. Org. Chem.* **1999**, *64*, 2986.
[231] I. Sapountzis, P. Knochel, *J. Am. Chem. Soc.* **2002**, *124*, 9390.
[232] F. Kopp, I. Sapountzis, P. Knochel *Synlett* **2003**, *6*, 885.



Scheme 114: Addition of adamantylzinc reagent **46a** aryl nitroso compounds **54** and subsequent reduction to amines of type **55** (additional complexed salts are omitted for the sake of clarity).

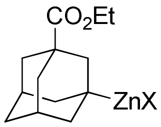
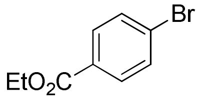
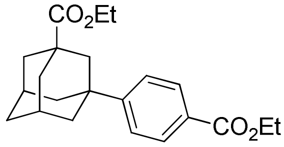
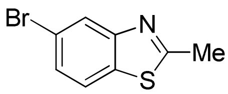
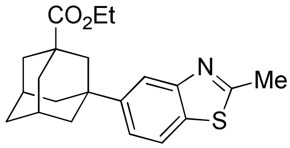
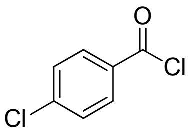
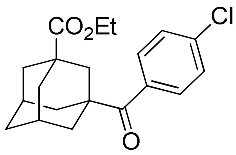
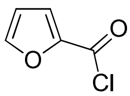
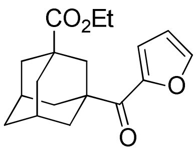
Analogous to the unfunctionalized adamantylzinc reagent **46a**, the ester-substituted adamantylzinc derivative **46b** readily reacts in a Pd-catalyzed *Negishi* cross-coupling with 4-bromothioanisole (**47f**, 0.9 equiv) at 50 °C within 2 h to the highly functionalized adamantyl derivate **56a** in 87% yield (Scheme 115).



Scheme 115: *Negishi* cross-coupling reaction of adamantylzinc reagent **46b** with 4-bromothioanisole (**47f**) (additional complexed salts are omitted for the sake of clarity).

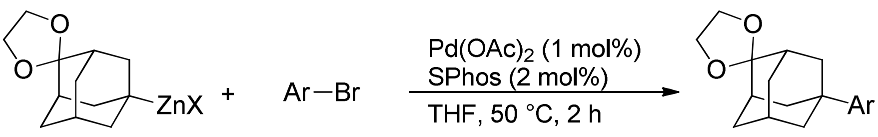
Under the same reaction conditions, also ethyl 4-bromobenzoate (**47b**, 0.9 equiv) and 5-bromo-2-methylbenzothiazole (**49c**, 0.9 equiv) have been employed in the Pd-catalyzed *Negishi* reaction with the ester-substituted adamantylzinc species **46b**. The corresponding cross-coupling products **56b** and **56c** have been obtained in 84% and 70%, respectively (Table 27, entries 1 and 2). Moreover, adamantylzinc reagent **46b** also undergoes smoothly Cu(I)-catalyzed acylation reactions with 4-chlorobenzoyl chloride (**50b**, 0.9 equiv) and 2-furoyl chloride (**50e**, 0.9 equiv) leading to the desired ketone derivatives **57a** and **57b** in good to excellent yields (entries 3 and 4).

Table 27: Functionalization reactions of adamantylzinc reagent **46b** with various electrophiles.

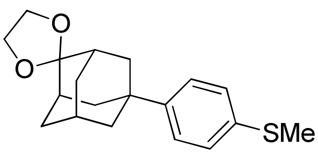
Entry	Zn-Reagent	Electrophile	Product, Yield[a]
1	 **46b**	 **47b**	 **56b**: 84%[b]
2	**46b**	 **49c**	 **56c**: 70%[b]
3	**46b**	 **50b**	 **57a**: 82%[c]
4	**46b**	 **50e**	 **57b**: 54%[c]

[a] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [b] Obtained after a *Negishi* cross-coupling ($Pd(OAc)_2$ (1 mol%) and SPhos (2 mol%)) with (hetero)aryl bromide (0.9 equiv). [c] Obtained after a acylation reaction (CuCN·2LiCl (0.2 equiv)) with acid chloride (0.9 equiv).

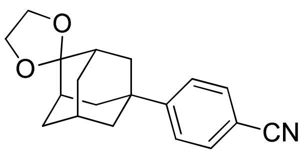
Also the adamantylzinc reagent **46c** could easily be functionalized by Pd-catalyzed *Negishi* cross-coupling reactions with both electron-poor and electron-rich aryl bromides. The highly functionalized cross-coupling products **58a-c** have been obtain in high yields (Scheme 116).



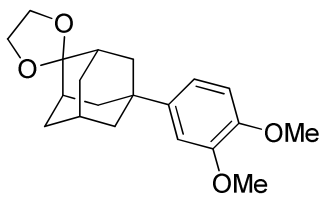
46c **47** (0.9 equiv) **58**



58a: 73%



58b: 77%



58c: 71%

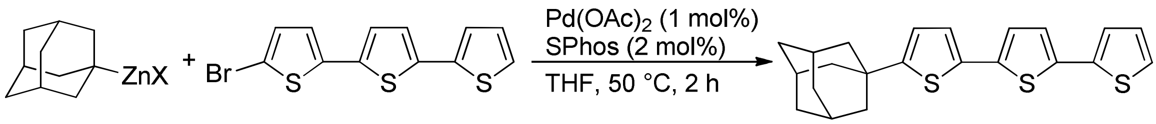
Scheme 116: *Negishi* cross-coupling reactions of adamantylzinc reagent **46c** with aryl bromides of type **47** (additional complexed salts are omitted for the sake of clarity).

5.4 APPLICATION OF ADAMANTYLZINC REAGENTS

The synthesis and investigation of well-defined model oligomers has recently become useful to gain insight into the structural and electronic properties of the corresponding polymers. Depending on their size and substitution pattern the oligothiophenes are usually more soluble than polymers allowing the precise characterization of the electronic and geometric structure both in solution and in solid state.[233]

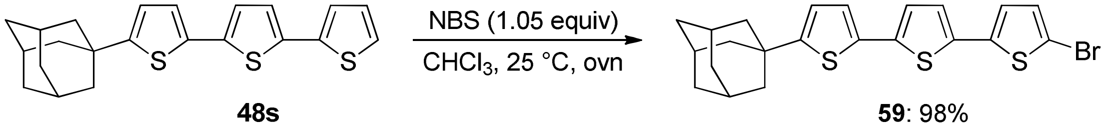
In analogy to the polymers, the solubility of oligothiophenes decreases dramatically with increasing chain length, which is due to the stiffness of the conjugated π-system and the strong interactions between the chains. The problem of low solubility can be solved by the synthesis of corresponding oligothiophenes bearing alkyl substituents.[234] Several α-alkyl and α,α'-dialkyl-substituted oligothiophenes were synthesized and characterized by different research groups. Especially, monosubstituted derivatives are attractive candidates since they offer the possibility of dimerizing them to the corresponding α,α'-disubstituted oligothiophenes with doubled conjugated chain length.[233]

Following this idea, adamantylzinc reagent **46a** has been submitted to a *Negishi* cross-coulpling reaction with the 5-bromo-terthiophene **49h** furnishing the corresponding α-substituted oligothiophene **48s** in 64% yield (Scheme 117).



Scheme 117: *Negishi* cross-coupling reactions of adamantylzinc reagent **46a** with 5-bromo-2,2':5',2''-terthiophene (**49h**) (additional complexed salts are omitted for the sake of clarity).

Subsequently, the adamantyl-substituted oligothiophene **48s** has been selectively brominated at the α-position of the oligothiophene with NBS leading to the corresponding product **59** in an almost quantitative manner (Scheme 118).



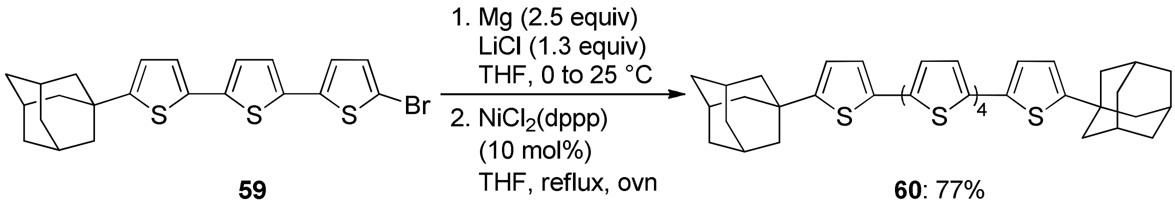
Scheme 118: Selective bromination of the adamantyl-substituted oligothiophene **4s** using *N*-bromosuccinimide.

The *Kumada* cross-coupling reaction together with the homocoupling of thienyl-*Grignard* reagents have become the most frequently used methods in the synthesis of

[233] P. Bäuerle, *The Synthesis of Oligothiophenes* in *Handbook of Oligo- and Polythiophenes* (Ed.: D. Fichou), Wiley-VCH, Weinheim, **1999**.
[234] D. Delabouglise, M. Hmyene, G. Horowitz, A. Yassar, F. Garnier, *Adv. Mater.* **1992**, *4*, 107.

various oligothiophenes.[235] From the large variety of catalysts examined for thiophene synthesis, Ni(dppp)Cl_2,[236] Ni(dppf)$C1_2$,[237] and Ni(dppe)$C1_2$[236] turned out to be the most effective.

Thus, the α,α'-diadamantyl-sexithiophene **60** could be synthesized in 77% yield by the reaction of the corresponding *Grignard* reagent of the brominated adamantyl-substituted oligiothiophene **59** by using Ni(dppp)Cl_2 as catalyst in the homocoupling (Scheme 119).



Scheme 119: Synthesis of α,α'-diadamantyl-sexithiophene **60** *via* Ni-catalyzed dimerisation of **59**.

Since the solubility of unsubstituted sexithiophene is lower than 50 mg/l chloroform[234] and even the α,α'-di-*n*-hexyl-substituted sexithiophene shows only a low solubility, it is noteworthy that the α,α'-diadamantyl-sexithiophene **60** is excellent soluble in all common organic solvents. The high solubility arises most probably from two reasons; on one hand, the apolar adamantyl-moiety is known to strongly increase the lipophilicity of molecules and on the other hand its bulkiness should prevent the *π*-stacking of the oligothiophenes.

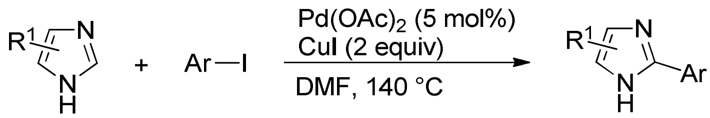
[235] a) K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S.-i. Kodama, I. Nakajima, A. Minato, M. Kumada *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958. b) M. Kumada, *Pure Appl. Chem.* **1980**, *52*, 669.
[236] a) G. R. van Hecke, W. de W. Horrocks, Jr., *Inorg. Chem.* **1966**, *5,* 1968. b) S. S. Sandhu, M. Gupta, *Chem. Ind. (London)*, **1967**, 1876.
[237] I. R. Butler, W. R. Cullen, T.-J. Kim, **S.** J. Rettig, J. Trotter, *Organometallics* **1985**, *4*, 972.

6. FULL FUNCTIONALIZATION OF THE IMIDAZOLE SCAFFOLD BY SELECTIVE METALATION AND SULFOXIDE/MAGNESIUM EXCHANGE

6.1 INTRODUCTION

Among functionalized imidazole derivatives a huge variety of compounds are known to possess a broad range of significant biological properties or are important templates in medicinal chemistry[238] (e.g. as antibacterial,[239] anticancer[240] or anti-inflammatory[241] pharmaceuticals). Due to their importance a number of methods has been described in the literature allowing the construction of the heteroaromatic core of these substances by cyclization protocols.[242] However, recently much more attention lay on the design and development of efficient protocols that are based on the selective functionalization of the imidazole ring *via* transition metal-catalyzed reactions. This enabled the synthesis of imidazole derivatives, including bioactive and/or naturally occurring compounds, which cannot be accessed by other means.[238]

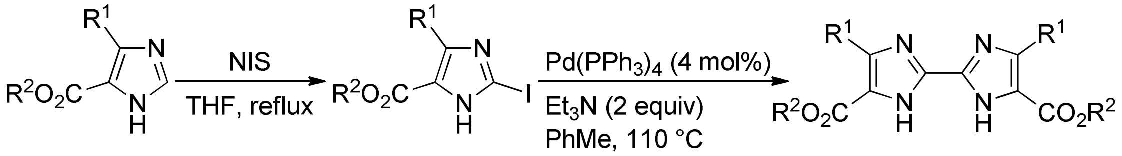
Rossi et al. described in 2007 a attractive, convenient and practical procedure[243] for the synthesis of free (NH)-2-arylimidazoles. Free (NH)-imidazoles were reacted with 2 equivalents of electron-deficient, electron-rich or electron-neutral aryl iodides in DMF in the presence of a catalytic amount of $Pd(OAc)_2$ and 2 equivalents of CuI under base-free and ligandless conditions to give the required 2-arylimidazoles in satisfactory yields and with excellent regioselectivity (Scheme 120).



Scheme 120: Pd-catalyzed Cu-mediated arylation at position 2 with aryl iodides.

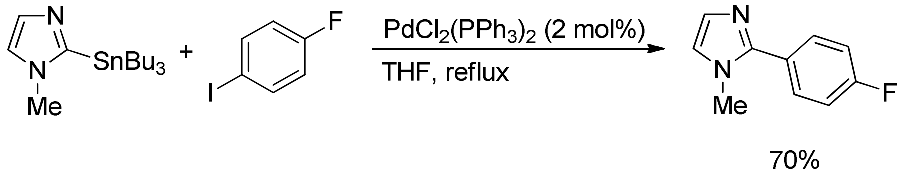
[238] For reviews, see: a) F. Bellina, R. Rossia, *Adv. Synth. Catal.* **2010**, *352*, 1223. b) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200. c) M. Schnürch, R. Flasik, A. F. Khan, M. Spina, M. D. Mihovilovic, P. Stanetty, *Eur. J. Org. Chem.* **2006**, 328. d) H. Du, Y. He, R. Sivappa, C. J. Lovely, *Synlett* **2006**, *7*, 965.
[239] M. Antolini, A. Bozzoli, C. Ghiron, G. Kennedy, T. Rossi, A. Ursini, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1023.
[240] L. Wang, K. W. Woods, Q. Li, K. J. Barr, R. W. McCroskey, S. M. Hannick, L. Gherke, R. B. Credo, Y.-H. Hui, K. Marsh, R. Warner, J. Y. Lee, N. Zielinski-Mozng, D. Frost, S. H. Rosenberg, H. L. Sham, *J. Med. Chem.* **2002**, *45*, 1697.
[241] J. C. Lee, J. T. Laydon, P. C. McDonnell, T. F. Gallagher, S. Kumar, D. Green, D. McNulty, M. J. Blumenthal, J. R. Heys, S. W. Landvatter, J. E. Strickler, M. M. McLaughlin, I. R. Siemens, S. M. Fisher, G. P. Livi, J. R. White, J. L. Adams, P. R. Young, *Nature* **1994**, *372*, 739.
[242] For review, see: B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104,* 1431.
[243] a) F. Bellina, C. Calandri, S. Cauteruccio, R. Rossi, *Tetrahedron* **2007**, *63*, 1970. b) F. Bellina, S. Cauteruccio, R. Rossi, *Eur. J. Org. Chem.* **2006**, 1379.

Sessler and coworkers reported a procedure for the synthesis of 2,2'-biimidazoles *via* a Pd-catalyzed homocoupling of 2-iodoimidazoles in toluene in the presence of Et_3N (Scheme 121).[244] These 2-iodo derivatives were synthesized by treatment of the corresponding 2-unsubstituted imidazoles with *N*-iodosuccinimide (NIS) in refluxing THF (Scheme 121).[244]



Scheme 121: Synthesis of free (NH)-2,2'-biimidazole derivatives.

Starting from 1987, *Stille*-type reactions have frequently been used to introduce organic groups at the 2-position of 1-methylimidazole derivatives.[245] 1-Methyl-2-tributylstannylimidazole, commercially available but also readily accessible in high yield by C-2 lithiation of 1-methylimidazole followed by treatment with tributyltin chloride, has been used in Pd-catalyzed reactions.[245] *Wasserscheid et al.* used catalytic amounts of $PdCl_2(PPh_3)_2$ in a *Stille*-type reaction of 1-methyl-2-tributylstannylimidazole with 4-fluoroiodobenzene in THF under reflux to synthesize 2-(4-fluorophenyl)-1-methylimidazole in 70% yield (Scheme 122).[245d]

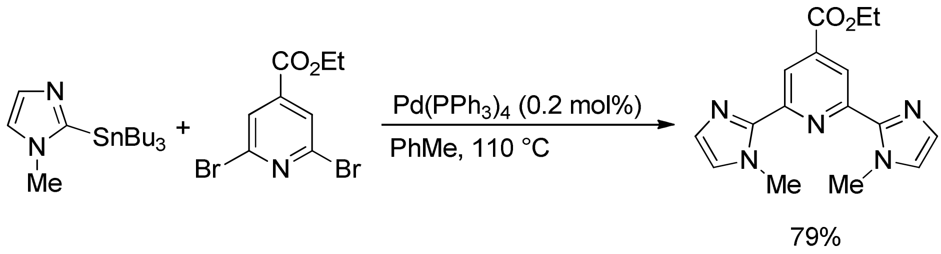


Scheme 122: *Stille*-type reaction of 1-methyl-2-tributylstannylimidazole.

In 2003, *Sudhçlter* and coworkers prepared a 2,6-diimidazol-2-ylpyridine derivative in 79% yield *via* $Pd(PPh_3)_4$-catalyzed double cross-coupling reaction of 1-methyl-2-tributylstannylimidazole with 2,6-dibromo-4-ethoxycarbonylpyridine in toluene under reflux (Scheme 123).[245e]

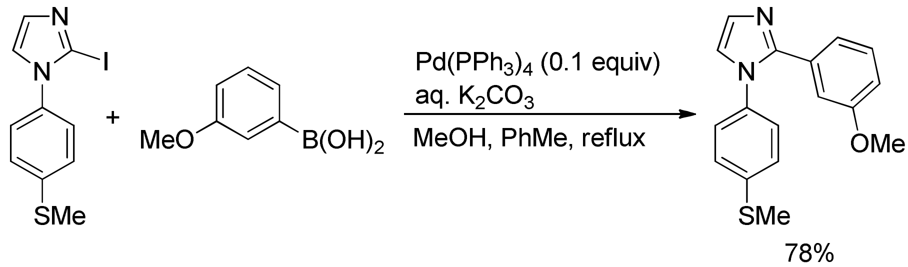
[244] W. E. Allen, C. J. Fowler, V. M. Lynch, J. L. Sessler, *Chem. Eur. J.* **2001**, *7*, 721.

[245] a) M. Kosugi, M. Koshiba, A. Atoh, H. Sano, T. Migita, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 677. b) K. Gaare, T. Repstad, T. Benneche, K. Undheim, *Acta Chem. Scand.* **1993**, *47*, 57. c) G. Kennedy, A. D. Perboni, *Tetrahedron Lett.* **1996**, *37*, 7611. d) D. J. Brauer, K. W. Kottsieper, C. Liek, O. Stelzer, H. Waffenschmidt, P. Wasserscheid, *J. Organomet. Chem.* **2001**, *630*, 177. e) T. Vermonden, D. Branowska, A. T. M. Marcelis, E. J. R. Sudhçlter, *Tetrahedron* **2003**, *59*, 5039. f) J. K. Stille, *Pure Appl. Chem.* **1985**, *57*, 1771. g) V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React.* **1997**, *50*, 1. h) J. Hassa, M. Svignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359. i) P. Espinet, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 4704.



Scheme 123: *Stille*-type reaction of 1-methyl-2-tributylstannylimidazole.

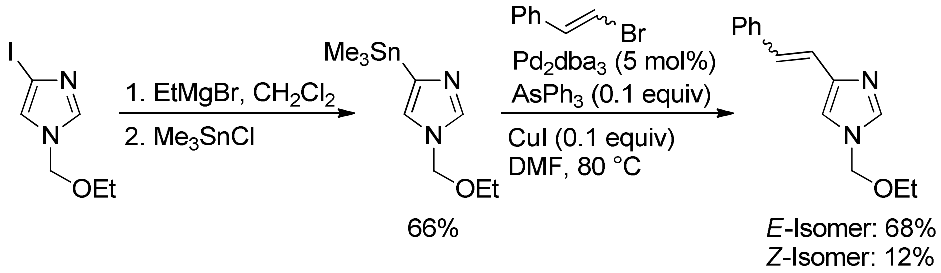
Also *Suzuki-Miyaura* cross-coupling reactions have been employed successfully to introduce aryl and alkenyl groups into the 2-position of imidazole derivatives. In 2005, *Langhammer* and *Erker* reported the $Pd(PPh_3)_4$-catalyzed reaction of 2-iodo-1-[(4-methylthio)phenyl]imidazole with 3-methoxyphenylboronic acid in the presence of K_2CO_3 as the base to give the arylated imidazole in 78% yield (Scheme 124). 2-iodo-1-[(4-methylthio)phenyl]imidazole, which was employed as the electrophile, was obtained by C-2 lithiation of 1-[(4-methylthio)phenyl)]-imidazole and subsequent quenching with iodine.[246]



Scheme 124: *Suzuki-Miyaura* cross-coupling reaction of 2-iodo-1-[(4-methylthio)phenyl]-imidazole.

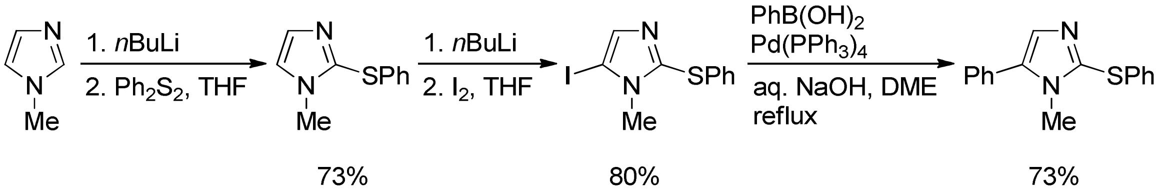
Stille-type cross-couplings have also frequently been used to efficiently introduce organic groups into the 4-position of 1-substituted imidazoles. In 1996, *Cliff* and *Pyne* described a $Pd_2(dba)_3/AsPh_3$/CuI-catalyzed reaction of 1-ethoxymethyl-4-trimethyl-stannylimidazole with β-bromostyrene (*E*/*Z*=10:1) furnishing (*E*)- and (*Z*)-1-ethoxy-methyl-4-(2-phenylethenyl)imidazole in 68% and 12% yield, respectively (Scheme 125). The 1-substituted 4-trialkylstannylimidazole was prepared by treatment of the corresponding iodo-imidazole derivative with EtMgBr in CH_2Cl_2 followed by quenching with Me_3SnCl (Scheme 125).[247]

[246] I. Langhammer, T. Erker, *Heterocycles* **2005**, *65*, 2721.
[247] M. D. Cliff, S. G. Pyne, *Tetrahedron* **1996**, *52*, 13703.



Scheme 125: Stille-type reaction for the functionalization of position 4 on the imidazole ring.

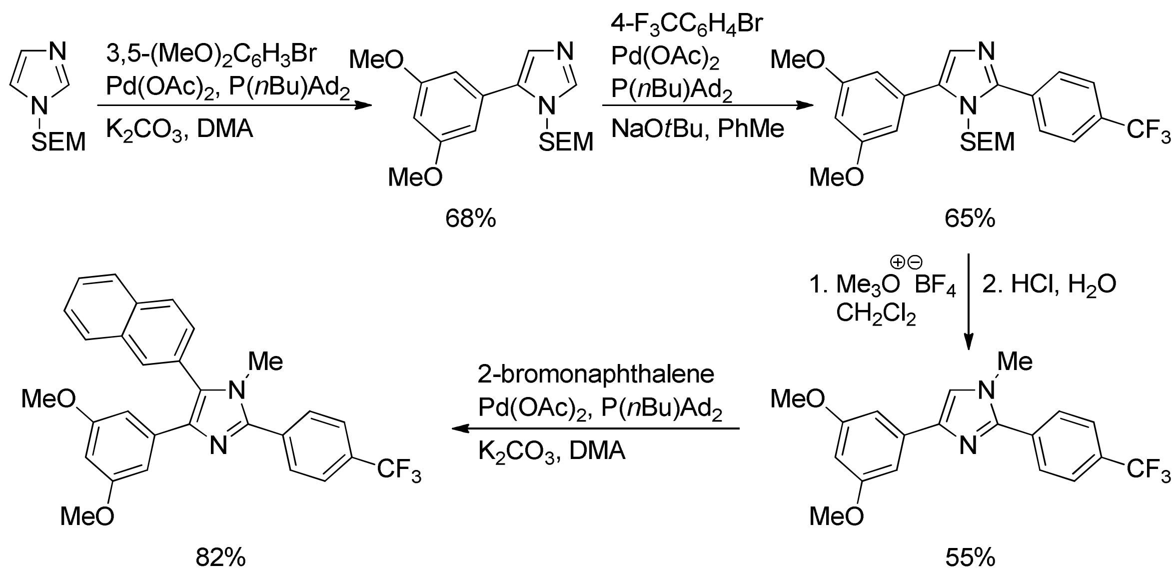
In 2000, *Wrobel et al.* developed a three-step synthesis for the selective arylation in position 5 of the imidazole ring. The iodoimidazole was prepared by C-2 lithiation of 1-methylimidazole followed by treatment with diphenyl disulfide. The resulting compound was then sequentially treated with *n*BuLi in THF at -78 °C and iodine to give 5-iodo-1-methyl-2-phenylsulfonylimidazole in 80% yield (Scheme 126).[248] Subsequently, a *Suzuki-Miyaura* reaction of 5-iodo-1-methyl-2-phenylsulfonylimidazole with phenylboronic acid furnished the arylated imidazole in 73% yield (Scheme 126). It should be mentioned that the $PdCl_2(PPh_3)_2$-catalyzed *Stille*-type reaction of the iodo-imidazole derivative with phenyltrimethylstannane in DMF led to the cross-coupling product in less yield (62%) than in the Suzuki-Miyaura reaction with phenylboronic acid under the conditions shown in Scheme 126.[249]



Scheme 126: Three-step synthesis for the selective functionalization of position 5 on the imidazole ring.

In 2010, *Sames* and coworkers reported a general and comprehensive approach for the synthesis of complex aryl imidazoles, in which all three C–H bonds of the imidazole core have been arylated in a regioselective and sequential manner.[250] To circumvent the low reactivity of the C-4 position, a transfer from the protecting group on N-1 to N-3 nitrogen was introduced. This enabled the preparation of 4-arylimidazoles and sequential C4-C5-arylation of the imidazole core (Scheme 127), providing rapid access to all regioisomers of mono-, di-, and triarylimidazoles.[250]

[248] M. A. Collins, V. Hudak, R. Bender, A. Fensome, P. Zhang, L. Miller, R. C. Winneker, Z. Zhang, Y. Zhu, J. Cohen, R. J. Unwalla, J. Wrobel, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2185.
[249] B. E. Blass, C. T. Huang, R. M. Kawamoto, M. Li, S. Liu, D. E. Portlock, W. M. Rennels, M. Simmons, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1543.
[250] J. M. Joo, B. B. Touré, D. Sames, *J. Org. Chem.* **2010**, *75*, 4911.



Scheme 127: Selective arylation of position 2, 4 and 5 on the imidazole ring *via* Heck-type cross-coupling reactions.

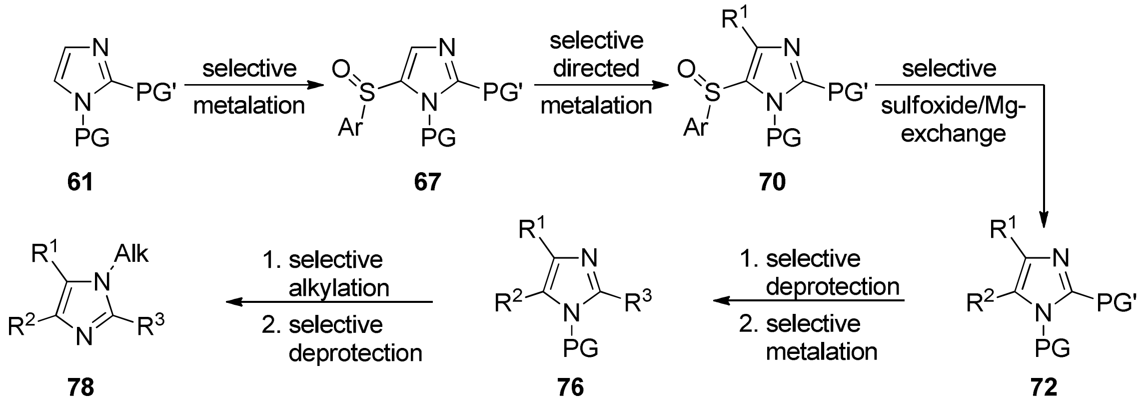
There are a number of established protocols for the synthesis of substituted imidazoles where the imidazole ring is constructed *via* cyclo-condensation as well as *via* direct arylation reactions. Although these approaches have been improved over the past decade, each method has its scope and efficiency limitations like generation of isomers or unselective functionalization reactions.[250,251] In contrast to conventional condensation and arylation methods, selective metalation reactions would enable the derivatization and elaboration of the imidazole ring in a regioselective manner and provide new possibilities for the synthesis of complex imidazole derivatives. Hence, we were looking for a mild and general metalation protocol allowing the flexible synthesis of individually substituted imidazole derivatives.

6.2 OVERVIEW

TMP-bases like TMPMgCl·LiCl or TMPZnCl·LiCl are known as mild and chemoselective metalating reagents for hydrogen-metal interconversion on sensitive substrates. A variety of sensitive aromatic and heteroaromatic compounds could be smoothly metalated and subsequently functionalized.[27,28,29,68] Hence, we decided in the search for a general, selective and flexible methodology for the full functionalization of the imidazole scaffold to focus on metalation reactions using these type of bases.

[251] a) J. A. Murry, *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 945. b) S. Kamijo, Y. Yamamoto, *Chem. Asian J.* **2007**, *2*, 568. c) C. Kanazawa, S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 10662. d) A. R. Siamaki, B. A. Arndtsen, *J. Am. Chem. Soc.* **2006**, *128*, 6050. e) D. E. Frantz, L. Morency, A. Soheili, J. A. Murry, E. J. J. Grabowski, R. D. Tillyer, *Org. Lett.* **2004**, *6*, 843. f) J. Sisko, A. J. Kassick, M. Mellinger, J. J. Filan, A. Allen, M. A. Olsen, *J. Org. Chem.* **2000**, *65*, 1516.

Scheme 128 illustrates a general overview for the fully functionalization of the imidazole scaffold starting from the double protected imidazole **61**.



Scheme 128: Selective fully functionalization of the imidazole ring in a regioselective manner.

The protected imidazole **61** was regioselective metalated in position 5 by using TMPMgCl·LiCl (**62**). The subsequent sulfinylation employing 4-methoxy-3,5-dimethylbenzenesulfinyl chloride[153c,252,253,254] (**68a**) led to imidazole **67**. The sulfoxide group on position 5 was found to be essential for the full functionalization procedure, since it allows both the direct metalation in *ortho* position and its replacement by a sulfoxide/magnesium exchange. Hence, the sulfoxide substituent enabled the subsequent metalation with TMPMgCl·LiCl (**62**) in position 4. After functionalization of the magnesium species **69** imidazoles of type **70** were obtained. The next functionalization step was performed in position 5 by means of a sulfoxide/magnesium exchange. Thus, treatment of imidazole derivatives **70** with *i*PrMgCl·LiCl (**63**) led to the corresponding magnesium intermediates **71** which could readily be functionalized leading to imidazoles of type **72**. The protecting group in position 2 was then selectively removed followed by metalation using either TMPMgCl·LiCl (**62**) or $TMP_2Zn\cdot 2MgCl\cdot 2LiCl$ (**65**). The metalated imidazole derivatives **74** and **75** were then functionalized to give imidazoles of type **76**. In the final step, the N-3 nitrogen was selectively alkylated by using *Meerwein's* reagent (**66**, triethyloxonium tetrafluoroborate) furnishing the corresponding imidazolium salts **77**. Afterwards, nitrogen N-1 was deprotected and the alkylated imidazoles of type **78** were obtained. Using this protocol, all positions of the imidazole scaffold could be functionalized in a selective manner.

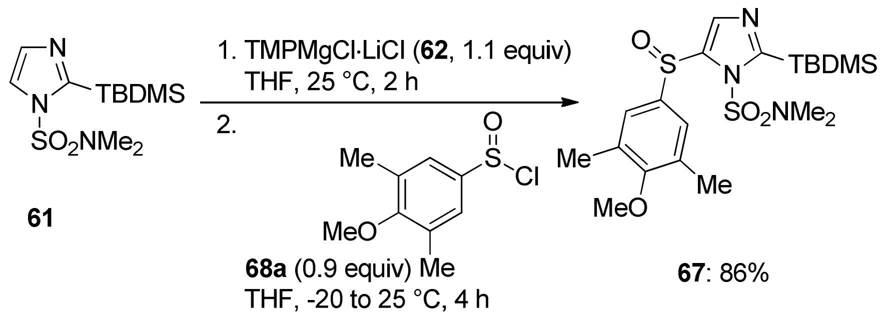
[252] a). L. Melzig, C. B. Rauhut, P. Knochel, *Chem. Commun.* **2009**, 3536. b) N. M. Barl, E. Sansiaume-Dagousset, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 10093.
[253] a) T. Satoh, D. Taguchi, C. Suzuki, S. Fujisawa, *Tetrahedron* **2001**, *57*, 493. b) T. Satoh, K. Takano, H. Someya, K. Matsuda, *Tetrahedron Lett.* **1995**, *36*, 7097. c) T. Satoh, K. Takano, H. Ota, H. Someya, K. Matsuda, K. Yamakawa, *Tetrahedron* **1998**, *54*, 5557. d) T. Satoh, *Chem. Soc. Rev.* **2007**, *36*, 1561. e) T. Satoh, K. Akita, *Chem. Pharm. Bull.* **2003**, *51*, 181. f) T. Satoh, M. Miura, K. Sakai, Y. Yokoyama, *Tetrahedron* **2006**, *62*, 4253. g) S. Sugiyama, H. Shimizu, T. Satoh, *Tetrahedron Lett.* **2006**, *47*, 8771.
[254] For the preparation of 4-methoxybenzenesulfinyl chloride, see: M. Peyronneau, N. Roques, S. Mazieres, C. Le Roux, *Synlett* **2003**, 631.

6.3 SELECTIVE FUNCTIONALIZATION ON POSITION 4 OF THE IMIDAZOLE RING

Preliminary experiments have shown that the best combination of protecting groups for the use of TMP-bases in the full functionalization of the imidazole scaffold is a TBDMS-group in position 2 and a *N*,*N*-dimethylsulfamoyl group at nitrogen N-1 (position 1). The TBDMS-group has proven to be stable under the metalation conditions but is also easily removeable by treatment with TBAF.[255]

Since the main challenge faced by the regioselective functionalization of imidazoles is the differentiation of positions 4 and 5 we envisioned an elegant way to solve this issue by introduction of a protecting group on the N-1 nitrogen directing the metalation to position 5.[256] When positioned on an aromatic ring, the *N*,*N*-dimethylsulfamoyl group is known to direct lithiation in the *ortho* position.[257] Moreover, if position 2 of the imidazole is already substituted, the presence of this sulfamoyl group on N-1 enables highly selective deprotonation in position 5.[256,258]

Thus, metalation of the protected imidazole **61**[259] with the highly chemoselective base TMPMgCl·LiCl (**62**, 1.1 equiv, 25 °C, 1 h) leads to magnesiation in position 5, directed by the sulfamoyl group on nitrogen N-1. Subsequent sulfinylation employing 4-methoxy-3,5-dimethyl-benzenesulfinyl chloride[254] (**68a**, 0.9 equiv, -20 to 25 °C, 4 h) furnishes imidazole **67** in 86% yield (Scheme 129).



Scheme 129: Selective metalation in position 5 of the imidazole ring with TMPMgCl·LiCl (**62**) and subsequent sulfoxide synthesis.

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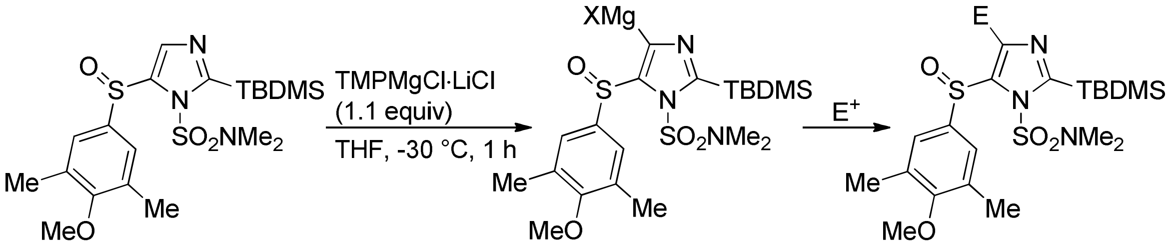
[255] M. Gianotti, C. Corti, S. Delle Fratte, R. Di Fabio, C. P. Leslie, F. Pavone, L. Piccoli, L. Stasi, M. J. Wigglesworth, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5069.
[256] B. Delest, P. Nshimyumukiza, O. Fasbender, B. Tinant, J. Marchand-Brynaert, F. Darro, R. Robiette, *J. Org. Chem.* **2008**, *73*, 6816.
[257] a) S. L. MacNeil, O. B. Familoni, V. Snieckus, *J. Org. Chem.* **2001**, *66*, 3662. b) H. Watanabe, R. A. Schwarz, C. R. Hauser, J. Lewis, D. W. Slocum, *Can. J. Chem.* **1969**, *47*, 1543.
[258] a) M. R. Grimmett, *Imidazole and Benzimidazole Synthesis*; Academic Press, San Diego, **1997**. b) K. S. Feldman, A. P. Skoumbourdis, *Org. Lett.* **2005**, *7*, 929. c) J. Winter, J. Rétey, *Synthesis* **1994**, 245. d) L. V. Kudzma, S. P. Turnbull, *Synthesis* **1991**, 1021. e) R. I. Ngochindo, *J. Chem. Soc., Perkin Trans. 1* **1990**, 1645. f) A. R. Katritzky, J. J. Slawinski, F. Brunner, *J. Chem. Soc., Perkin Trans. 1* **1989**, 1139. g) A. J. Carpenter, D. J. Chadwick, *Tetrahedron* **1986**, *42*, 2351.
[259] Compound **1** was synthesized in 72% yield over two steps from plain imidazole following literature known procedures: a) D. J. Chadwick, R. I. Ngochindo, *J. Chem. Soc., Perkin Trans. 1* **1984**, 481. b) Y. Lee, P. Martasek, L. J. Roman, B. S. Siler Masters R. B. Silverman, *Bioorg. Med. Chem.* **1999**, *7*, 1941.

As mentioned before, the sulfoxide group on position 5 was found to be essential for the full functionalization procedure, since it allows the direct metalation in *ortho* position (position 4). Hence, the sulfoxide substituent enables the selective metalation of imidazole **67** in position 4 with TMPMgCl·LiCl (**62**, 1.1 equiv, -30 °C, 1 h) in an almost quantitative manner. The resulting magnesium reagent **69** was readily used in different types of functionalization reactions furnishing the corresponding 4-substituted imidazoles of type **70** (Schemes 130-133 and Table 28).

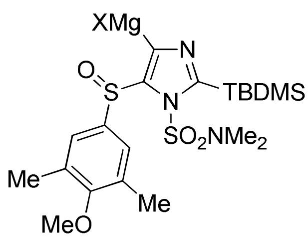
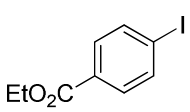
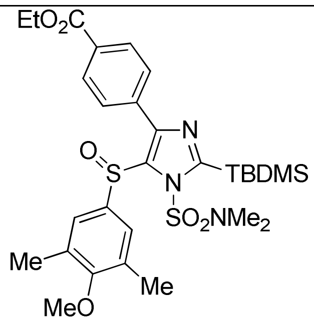


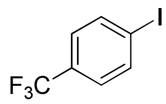
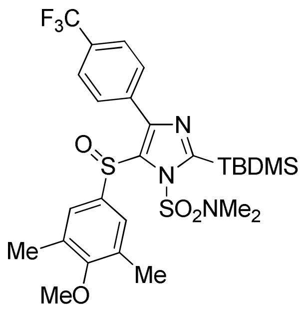
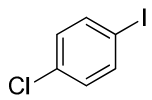
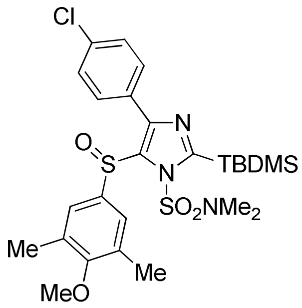
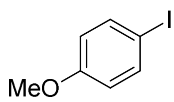
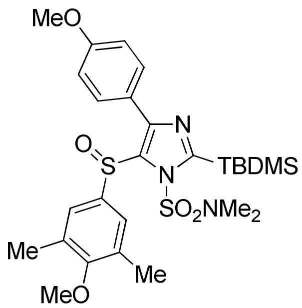
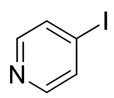
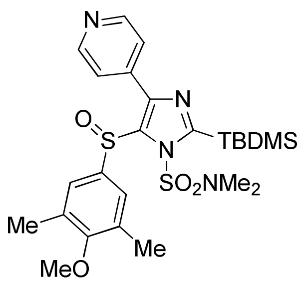
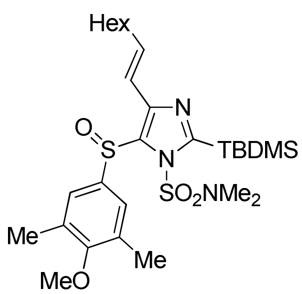
67 **69**: >95% **70**

Scheme 130: Selective metalation in position 4 of the imidazole ring with TMPMgCl·LiCl (**62**) and subsequent functionalization (additional complexed salts are omitted for the sake of clarity).

Thus, after transmetalation with $ZnCl_2$ (1.1 equiv, -30 °C, 15 min), the magnesium reagent **69** undergoes smooth Pd-catalyzed *Negishi* cross-coupling reactions.[145,208] Using 5% $Pd(PPh_3)_4$ as catalyst, various electron-rich and electron-poor electrophiles (0.9 equiv) are used in the cross-coupling at 50 °C affording the 4-substituted imidazole derivatives **70a-f** in good to excellent yields (Table 28, entries 1-6). Noteworthy, not only the simple aryl iodides **68b-e** could be used in the cross-coupling reactions (entries 1-4), also a pyridyl (**68f**, entry 5) and a vinylic iodide (**68g**, entry 6) lead to good results.

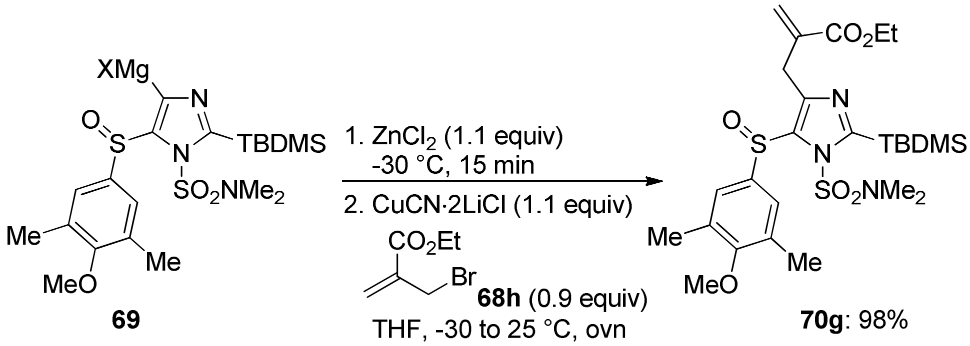
Table 28: Selective metalation in position 4 of the imidazole **67** with TMPMgCl·LiCl (**62**) and subsequent *Negishi* cross-coupling reactions.

Entry	Mg-Reagent[a]	Electrophile	Product, Yield[b]
			
1	**69**	**68b**	**70a**: 84%[c]

2	**69**	 **68c**	 **70b**: 72%[c]
3	**69**	 **68d**	 **70c**: 71%[c]
4	**69**	 **68e**	 **70d**: 60%[c]
5	**69**	 **68f**	 **70e**: 60%[c]
6	**69**	**68g**	 **70f**: 83%[c]

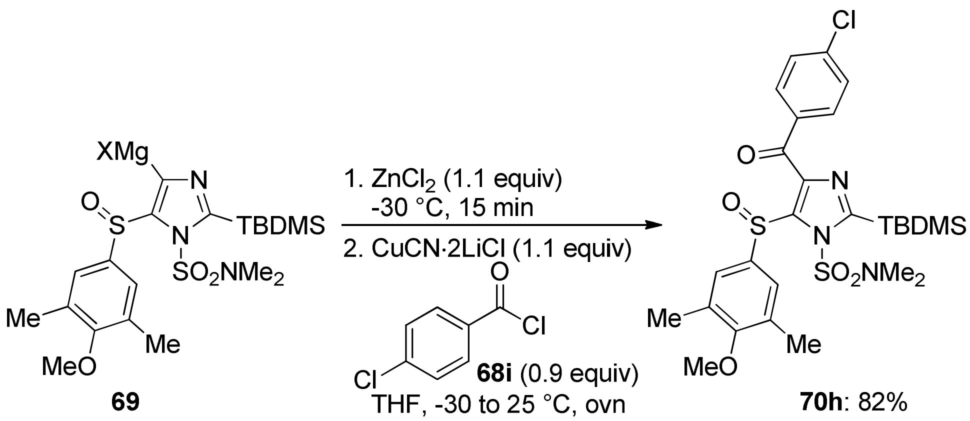
[a] Obtained after metalation with TMPMgCl·LiCl (1.1 equiv) in THF at -30 °C in 1 h. [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after a *Negishi* cross-coupling ($ZnCl_2$ (1.1 equiv); then 5% $Pd(PPh_3)_4$) with R–I (0.9 equiv).

Moreover, magnesium reagent **69** also undergoes after transmetalation with $ZnCl_2$ (1.1 equiv) a Cu(I)-catalyzed allylation reaction[146] with ethyl 2-(bromomethyl)acrylate (**68h**, 0.9 equiv) leading to the desired product **70g** in 98% yield (Scheme 131).



Scheme 131: Selective metalation in position 4 of the imidazole ring with TMPMgCl·LiCl (**62**) and subsequent Cu-catalyzed allylation (additional complexed salts are omitted for the sake of clarity).

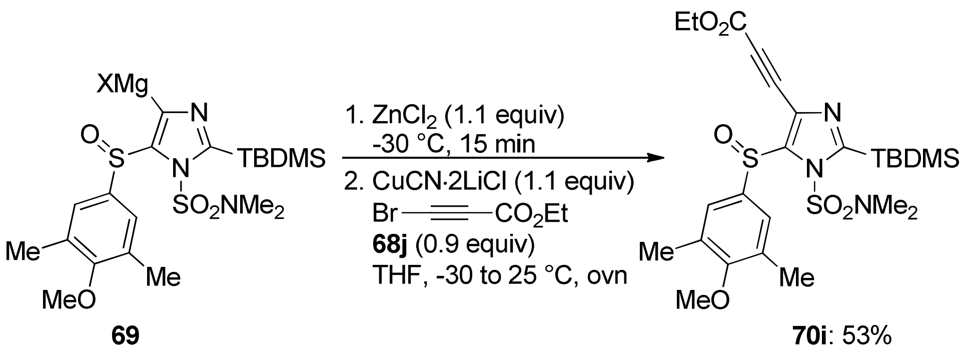
Furthermore, the Cu(I)-catalyzed acylation reaction[146] of magnesium reagent **69** using 4-chlorobenzoyl chloride (**68i**, 0.9 equiv) affords the corresponding ketone **70h** in 82% yield (Scheme 132).



Scheme 132: Selective metalation in position 4 of the imidazole ring with TMPMgCl·LiCl (**62**) and subsequent Cu-catalyzed acylation (additional complexed salts are omitted for the sake of clarity).

The Cu(I)-catalyzed reaction[11a,146] of magnesium reagent **69** with the bromoacetylene **68j**[260] (0.9 equiv) affords the highly functionalized acetylene **70i** in 53% yield (Scheme 133).

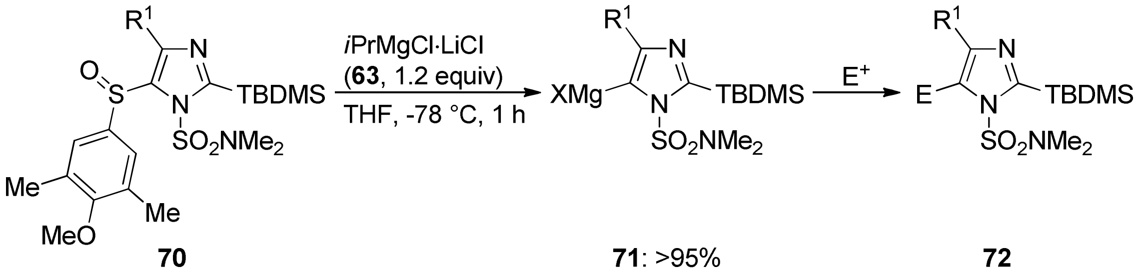
[260] M. C. P. Yeh, P. Knochel, *Tetrahedron Lett.* **1989**, *30*, 4799.



Scheme 133: Selective metalation in position 4 of the imidazole ring with TMPMgCl·LiCl (**62**) and subsequent Cu-catalyzed alkynylation (additional complexed salts are omitted for the sake of clarity).

6.4 Selective Functionalization on Position 5 of the Imidazole Ring

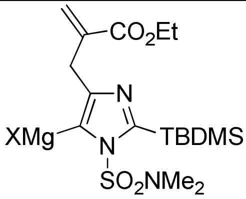
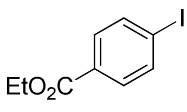
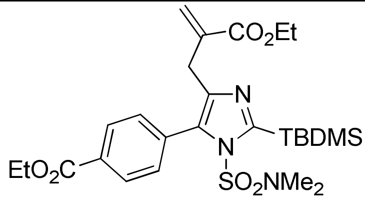
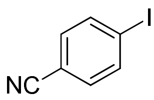
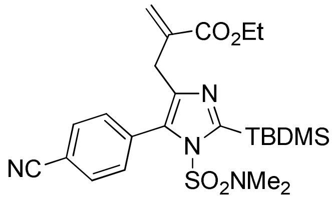
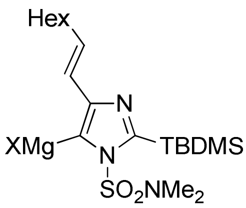
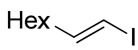
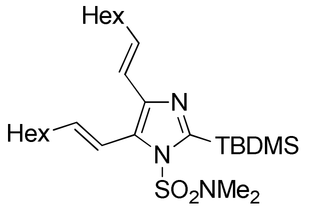
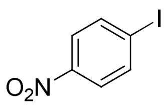
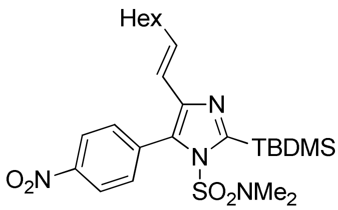
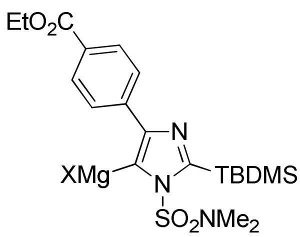
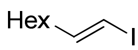
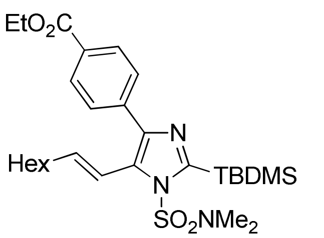
The next functionalization was performed in position 5 by means of a sulfoxide/magnesium exchange.[153c,252,253] Thus, treatment of imidazole derivatives of type **70** with *i*PrMgCl·LiCl (**63**, 1.2 equiv) at -78 °C leads within 1 h to the corresponding magnesium intermediates of type **71** in almost quantitative yield (Scheme 134). Subsequently, different types of functionalization reactions have been carried out furnishing the corresponding 4- and 5-substituted imidazoles of type **72** (Schemes 134-136 and Table 29).

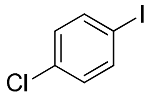
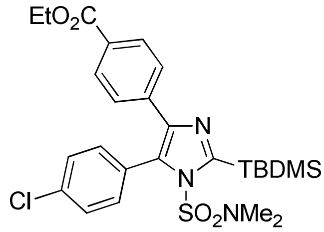
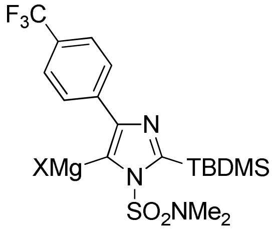
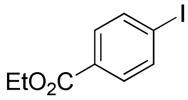
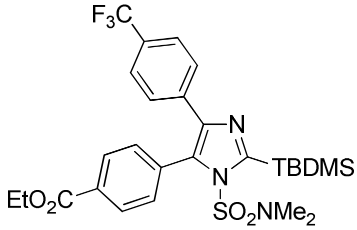
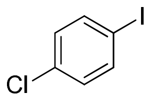
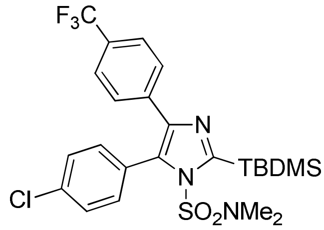
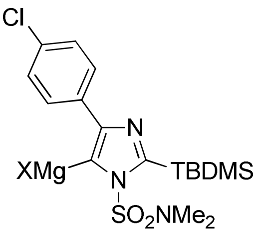
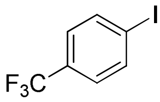
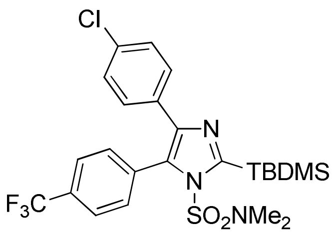


Scheme 134: Selective sulfoxide/Mg exchange in position 5 of the imidazole ring with *i*PrMgCl·LiCl (**63**) and subsequent functionalization (additional complexed salts are omitted for the sake of clarity).

After transmetalation with $ZnCl_2$ (1.2 equiv, -78 °C, 15 min), the magnesium reagents of type **71** readily undergo Pd-catalyzed *Negishi* cross-coupling reactions. Thus, the allyl-substituted imidazole derivative **71a** reacts with 5% of $Pd(PPh_3)_4$ as catalyst at 50 °C and ethyl 4-iodobenzoate (**68b**, 0.9 equiv) and 4-iodobenzonitrile (**68k**, 0.9 equiv) to the corresponding cross-coupling products **72a-b** in good to excellent yields (Table 29, entries 1and 2). Also the vinylic substituted imidazole derivative **70f** readily undergoes after the sulfoxide/magnesium exchange and transmetalation with $ZnCl_2$ (1.2 equiv, -78 °C, 15 min) Pd-catalyzed *Negishi* cross-coupling reactions (entries 3 and 4). Noteworthy, the double bond stays untouched and no isomerisation occurs. The magnesium species **71c-e** of the arylated imidazole derivatives have also been submitted to Pd-catalyzed *Negishi* reactions furnishing the corresponding cross-coupling products **72e-i** in high yields (entries 5-9).

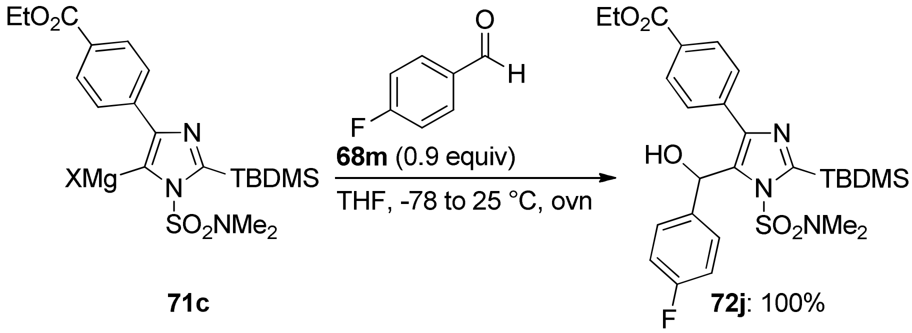
Table 29: Selective sulfoxide/Mg exchange in position 5 of imidazole derivatives of type **70** with *i*PrMgCl·LiCl (**63**) and subsequent *Negishi* cross-coupling reactions.

Entry	Mg-Reagent[a]	Electrophile	Product, Yield[b]
1	 **71a**	 **68b**	 **72a**: 71%[c]
2	**71a**	 **68k**	 **72b**: 90%[c]
3	 **71b**	 **68g**	 **72c**: 88%[c]
4	**71b**	 **68l**	 **72d**: 100%[c]
5	 **71c**	 **68g**	 **72e**: 60%[c]

			
6	**71c**	**68d**	**72f**: 70%[c]
			
7	**71d**	**68b**	**72g**: 85%[c]
			
8	**71d**	**68d**	**72h**: 80%[c]
			
9	**71e**	**68c**	**72i**: 68%[c]

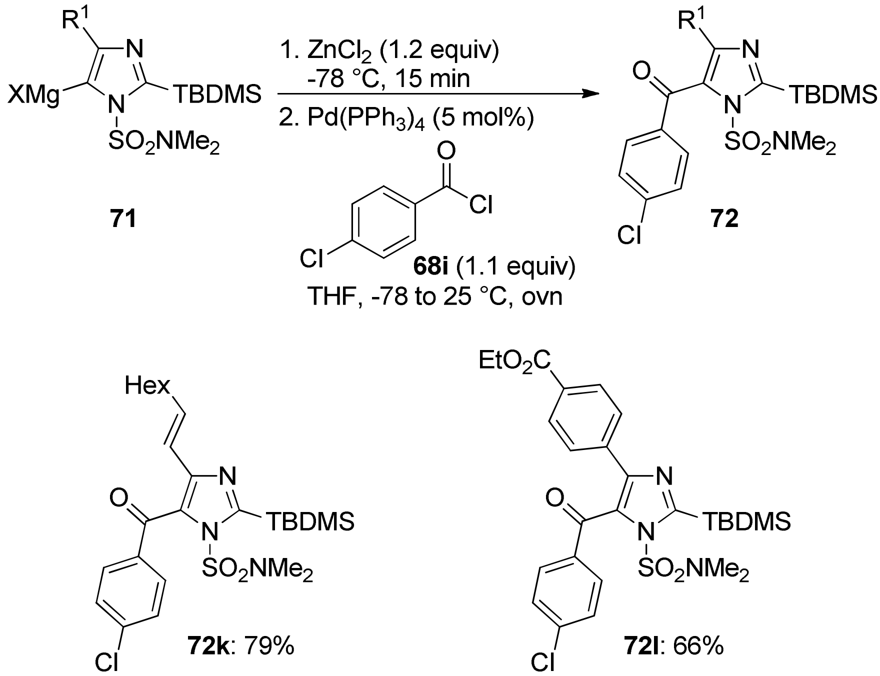
[a] Obtained after sulfoxide/Mg exchange with TMPMgCl·LiCl (1.2 equiv) in THF at -78 °C in 1 h. [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after a *Negishi* cross-coupling ($ZnCl_2$ (1.1 equiv); then 5% $Pd(PPh_3)_4$) with R–I (0.9 or 1.1 equiv).

In order to prove the existence of the magnesium species and to clarify whether the cross-coupling is a *Negishi* reaction and not a *Heck*-type reaction, the magnesium species **71c** of imidazole derivative **70a** has been submitted to a reaction with 4-fluorobenzaldehyde (**68m**, 0.9 equiv) after the sulfoxide/magnesium exchange. The obtained alcohol **72j** clearly demonstrated the availability of magnesium species **71c** (Scheme 135).



Scheme 135: Selective sulfoxide/Mg exchange in position 5 of the imidazole ring with *i*PrMgCl·LiCl (**63**) and subsequent addition to aldehyde **68m** (additional complexed salts are omitted for the sake of clarity).

Cu(I)-catalyzed acylation reactions of magnesium reagents of type **71** furnished only hydrolyzed species. Hence, a Pd-catalyzed acylation reaction[261] has been employed leading to the desired ketone derivatives in good to excellent yields (Scheme 136). The vinylic substituted imidazole **70f** reacted with 4-chlorobenzoyl chloride (**68i**, 0.9 equiv) and 5% $Pd(PPh_3)_4$ after sulfoxide/magnesium exchange and transmetalation with $ZnCl_2$ (1.2 equiv, -78 °C, 15 min) to the corresponding ketone **72k** in 79% yield. Also the arylated imidazole **70a** furnishes under the same reaction conditions the corresponding ketone **72l** in 66% yield (Scheme 136).



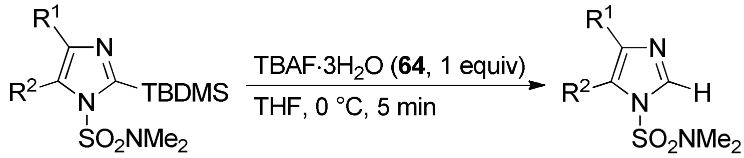
Scheme 136: Selective sulfoxide/Mg exchange in position 5 of the imidazole ring with *i*PrMgCl·LiCl (**63**) and subsequent Pd-catalyzed acylation (additional complexed salts are omitted for the sake of clarity).

[261] E.-i. Negishi, V. Bagheri, S. Chatterjee, F.-T. Luo, J. A. Miller, A. T. Stoll, *Tetrahedron Lett.* **1983**, *24*, 5181.

6.5 SELECTIVE FUNCTIONALIZATION ON POSITION 2 OF THE IMIDAZOLE RING

6.5.1 SELECTIVE DEPROTECTION ON POSITION 2

In order to be able to functionalize in position 2, the TBDMS-group had to be selectively removed from the imidazole ring. As illustrated in Scheme 137 imidazole derivatives of type **72** have been treated with tetra-*n*-butylammonium fluoride (**64**, 1 equiv) at 0 °C to cleave the C–Si-bond and furnish the unprotected imidazoles **73** in quantitative yield while leaving the *N*,*N*-dimethylsulfamoyl group at the N-1 untouched.

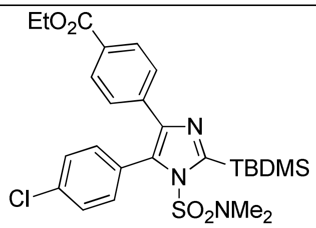
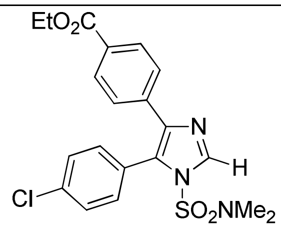
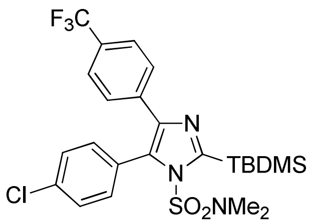
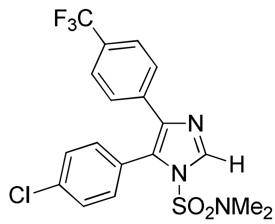
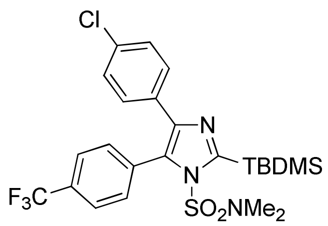
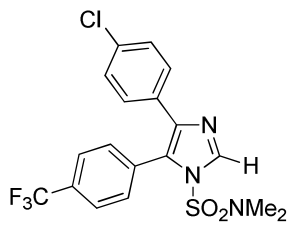


72 **73**

Scheme 137: Selective deprotection with TBAF·3H_2O (**64**) in position 2 of the imidazole ring.

Thus, the double functionalized imidazole derivatives **72f** and **72h-i** could selectively deprotected leading to the corresponding imidazoles **73a-c** in excellent yields (Table 30).

Table 30: Selective deprotection with TBAF·3H_2O (**64**) at position 2 of imidazoles of type **72**.

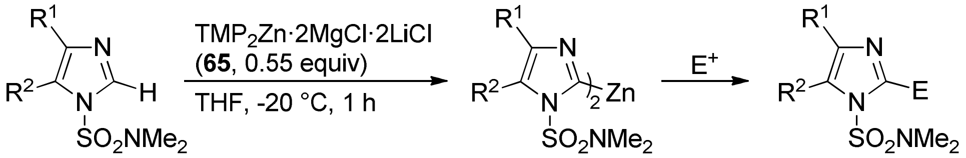
Entry	Imidazole Derivative	Deprotection Reagent	Product, Yield[a]
1	 **72f**	TBAF·3H_2O **64**	 **73a**: 93%[b]
2	 **72h**	TBAF·3H_2O **64**	 **73b**: 94%[b]
3	 **72i**	TBAF·3H_2O **64**	 **73c**: 100%[b]

[a] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [b] Obtained after addition of tetra-*n*-butylammonium fluoride (1 equiv).

6.5.2 SELECTIVE FUNCTIONALIZATION ON POSITION 2

For the metalation of position 2 of the imidazole scaffold two pathways were developed. Preliminary experiments have shown that either $TMP_2Zn·2MgCl·2LiCl$ (**65**) or TMPMgCl·LiCl (**65**) could be employed as metalating reagents.

Due to the mild and chemoselective properties of $TMP_2Zn·2MgCl·2LiCl$ (**65**), the metalating reaction of imidazoles derivatives of type **73** can be carried out at -20 °C furnishing the corresponding diimidazolylzinc derivatives **74** in almost quantitative yield within 1 h (Scheme 138). Subsequent functionalization reactions lead to the fully functionalized imidazole derivatives **76** (Table 31).

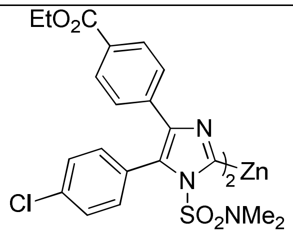
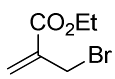
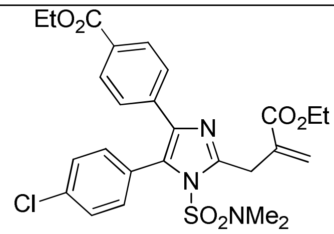


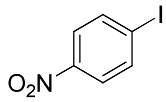
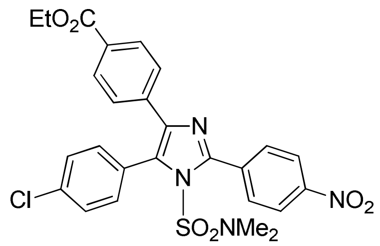
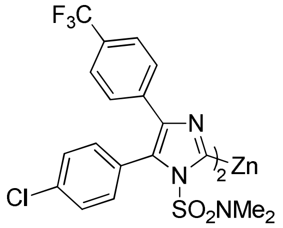
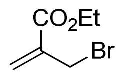
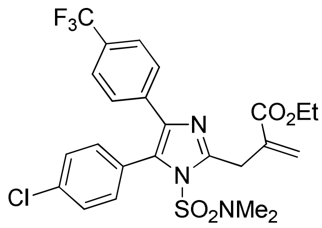
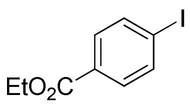
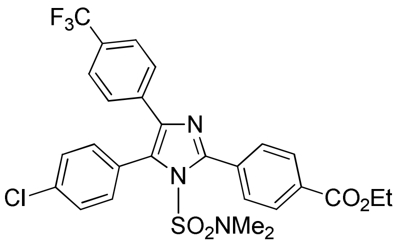
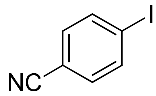
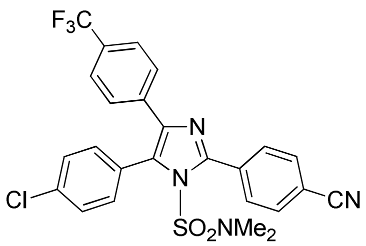
73 **74**: >95% **76**

Scheme 138: Selective metalation in position 2 of the imidazole ring $TMP_2Zn·2MgCl·2LiCl$ (**65**) and subsequent functionalization (additional complexed salts are omitted for the sake of clarity).

The Cu(I)-catalyzed allylation reaction of the imidazole zinc reagent **74a** with ethyl 2-(bromomethyl)acrylate (**68h**, 1.1 equiv) leads to the desired full functionalized imidazole **76a** in 81% yield (Table 31, entry 1). Additionally, a Pd-catalyzed *Negishi* cross-coupling reaction with 1-iodo-4-nitrobenzene (**68l**, 0.9 equiv) produces the highly functionalized imidazole derivative **76b** in 76% yield (entry 2). Furthermore, also the imidazole zinc reagent **74b** undergoes smoothly a Cu(I)-catalyzed allylation with ethyl 2-(bromomethyl)acrylate (**68h**, 0.9 equiv) furnishing imidazole **76c** in 86% yield (entry 3). The Pd-catalyzed *Negishi* cross-coupling reactions with ethyl 4-iodobenzoate (**68b**, 1.1 equiv) and 4-iodobenzonitrile (**68k**, 0.9 equiv) produces the highly functionalized imidazole derivatives **76d** and **76e** in 72% and 95% yield (entries 4 and 5).

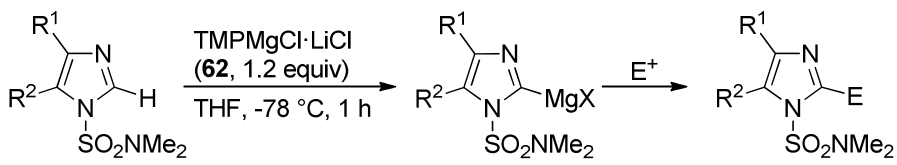
Table 31: Selective metalation in position 2 of imidazole derivatives of type **73** with $TMP_2Zn·2MgCl·2LiCl$ (**65**) and subsequent functionalization.

Entry	Zn-Reagent[a]	Electrophile	Product, Yield[b]
1	 **74a**	 **68h**	 **76a**: 81%[c]

			
2	**74a**	**68l**	**76b**: 76%[d]
			
3	**74b**	**68h**	**76c**: 86%[c]
			
4	**74b**	**68b**	**76d**: 72%[d]
			
5	**74b**	**68k**	**76e**: 95%[d]

[a] Obtained after metalation with $TMP_2Zn\cdot 2MgCl\cdot 2LiCl$ (0.55 equiv) in THF at -20 °C in 1 h. [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after allylation reaction (1 equiv. $CuCN\cdot 2LiCl$ with ethyl 2-(bromomethyl)acrylate (0.9 or 1.1 equiv)). [d] Obtained after a *Negishi* cross-coupling (5% $Pd(PPh_3)_4$) with Ar–I (0.9 or 1.1 equiv).

As illustrated in Scheme 139, position 2 of the imidazole scaffold could also be metalated using TMPMgCl·LiCl (**62**, 1.2 equiv) at -78 °C. Within 1 h, the reaction furnished the imidazol magnesium derivatives **75** in an almost quantitative manner. Functionalization reactions lead to the highly substituted imidazoles **76** (Table 32).

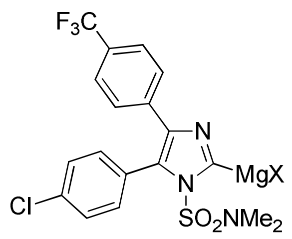
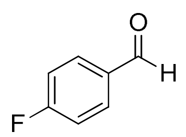
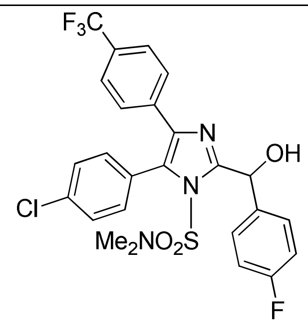
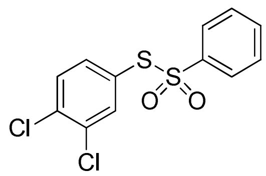
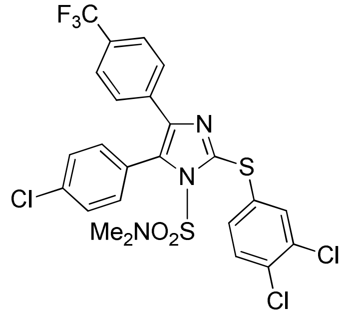


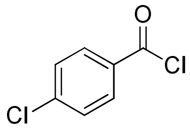
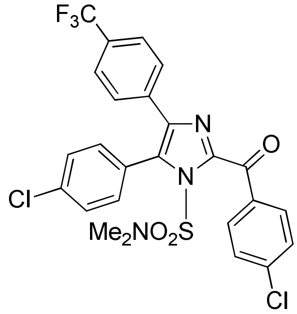
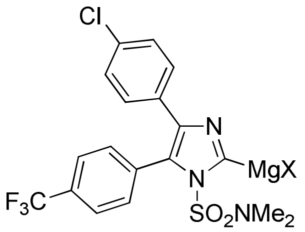
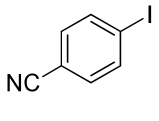
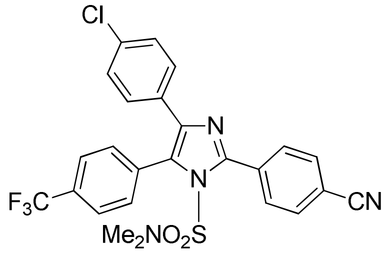
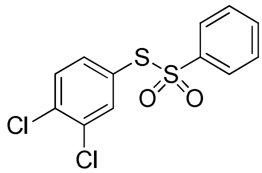
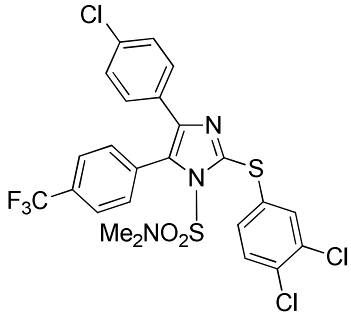
73 **75**: >95% **76**

Scheme 139: Selective metalation in position 2 of the imidazole ring with TMPMgCl·LiCl (**62**) and subsequent functionalization (additional complexed salts are omitted for the sake of clarity).

In order to demonstrate the higher reactivity of the magnesium reagents of type **75** compared to the diimidazolylzinc reagents of type **74**, imidazole derivative **75a** has been submitted to an addition reaction with 4-fluorobenzaldehyde (**68m**, 1.1 equiv) furnishing the corresponding alcohol **76f** in 92% yield (Table 32, entry 1). Moreover, the magnesium reagent **75a** also reacts smoothly with *S*-(3,4-dichlorophenyl) benzenesulfonothioate (**68n**, 0.9 equiv) affording thioether **76g** in 93% yield (entry 2). The corresponding diimidazolylzinc reagent **74b** could not undergo these two reactions and led only to the hydrolyzed species. Since Cu(I)-catalyzed acylation reaction does not proceed, a Pd-catalyzed acylation reaction has been employed leading to the desired ketone derivative in a good yield. The magnesium derivative **75a** reacts with 4-chlorobenzoyl chloride (**68i**, 1.1 equiv) and 5% $Pd(PPh_3)_4$ after transmetalation with $ZnCl_2$ (1.2 equiv, -78 °C, 15 min) to the corresponding ketone **76h** in 58% yield (entry 3). Furthermore, after transmetalation with $ZnCl_2$ (1.2 equiv, -78 °C, 15 min), the magnesium species **75b** successfully undergoes a Pd-catalyzed *Negishi* cross-coupling reaction furnishing imidazol **76i** in 75% yield (entry 4). Moreover, the magnesium reagent **75b** also reacts readily with *S*-(3,4-dichlorophenyl) benzenesulfonothioate (**68n**, 0.9 equiv) affording the corresponding thioether **76j** in 70% yield (entry 5).

Table 32: Selective metalation in position 2 of imidazole derivatives of type **73** with TMPMgCl·LiCl (**62**) and subsequent functionalization.

Entry	Mg-Reagent[a]	Electrophile	Product, Yield[b]
			
1	**75a**	**68m**	**76f**: 92%[c]
			
2	**75a**	**68n**	**76g**: 93%[e]

			
3	**75a**	**68i**	**76h**: 58%[d]
			
4	**75b**	**68k**	**76i**: 75%[f]
			
5	**75c**	**68n**	**76j**: 70%[e]

[a] Obtained after metalation with TMPMgCl·LiCl (1.2 equiv) in THF at -78 °C in 1 h. [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after addition to 4-fluorobenzaldehyde (1.1 equiv). [d] Obtained after a *Negishi* acylation ($ZnCl_2$ (1.1 equiv); then 5% $Pd(PPh_3)_4$ with 4-chlorobenzyol chloride (1.1 equiv)). [e] Obtained after addition to *S*-aryl benzenethio-sulfonate (0.9 equiv). [f] Obtained after a *Negishi* cross-coupling ($ZnCl_2$ (1.2 equiv); then 5% $Pd(PPh_3)_4$) with 4-iodobenzonitrile (0.9 equiv)).

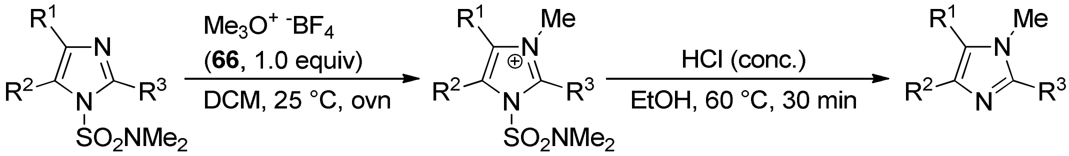
6.6 SELECTIVE N-3-ALKYLATION AND SUBSEQUENT N-1-DEPROTECTION

Depending on the substitution pattern, N-protected imidazoles have shown the tendency to tautomerize leading to mixtures of isomers after deprotection (due to steric factors).[262] *N*-sulfamoylimidazoles are known to react with alkylating reagents exclusively *via* their nonsubstituted nitrogen atom since alkylation on N-1 is hampered.[263] Moreover, the formation of an imidazolium salt by N-3-alkylation increases the lability of the dimethylsulfamoyl group allowing its removal *via* the addition of

[262] a) C. J. Lovely, H. Du, R. Sivappa, M. R. Bhandari, Y. He, H. V. R. Dias, *J. Org. Chem.* **2007**, *72*, 3741. b) Y. He, Y. Chen, H. Du, L. A. Schmid, C. J. Lovely, *Tetrahedron Lett.* **2004**, *45*, 5529.
[263] a) H. K. Lee, M. Bang, C. S. Pak, *Tetrahedron Lett.* **2005**, *46*, 7139. b) S. Beaudoin, K. E. Kinsey, J. F. Burns, *J. Org. Chem.* **2003**, *68*, 115.

concentrated HCl.[264] The outcome of this procedure is thus the *N*-alkylation of the imidazole ring selectively at the previously nonsubstituted nitrogen atom.[265]

Hence, the fully functionalized imidazole derivatives of type **76** have been treated with *Meerwein's* reagent (**66**, trimethyloxonium tetrafluoroborate, 1 equiv) generating the corresponding imidazolium salts **77**. The *N*,*N*-dimethylsulfamoyl group at the N-1 is then cleaved by addition of concentrated HCl furnishing the alkylated imidazoles of type **78** in good yields (Scheme 140).

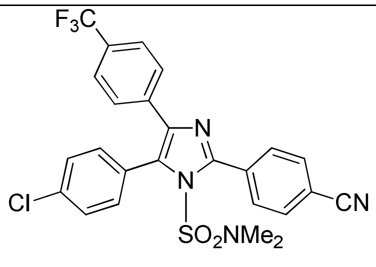
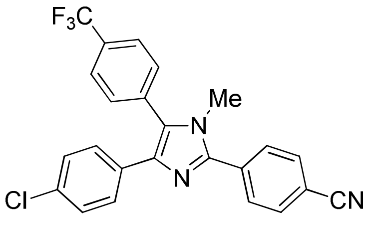


76 **77** **78**

Scheme 140: Selective methylation with *Meerwein's* reagent (**66**) at position N-3 of the imidazole ring and subsequent deprotection at position N-1.

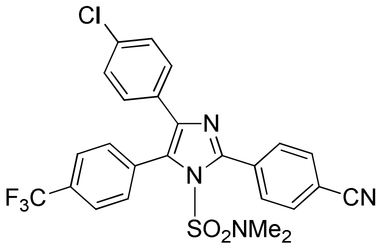
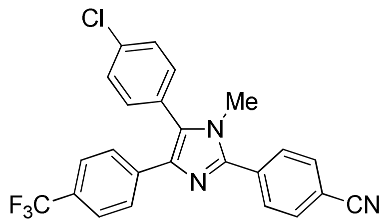
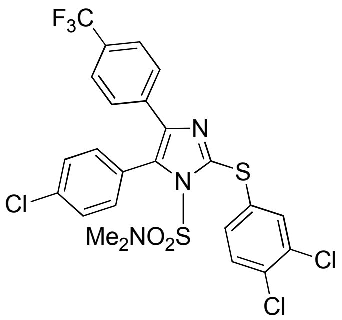
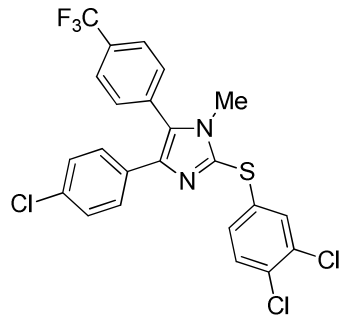
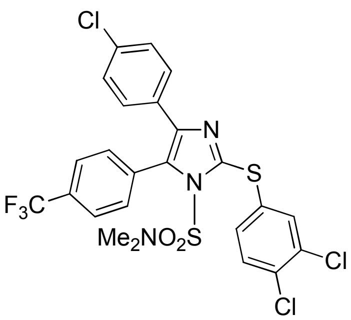
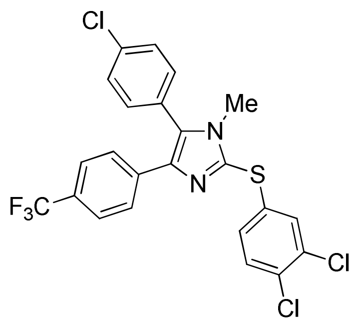
Thus, the fully functionalized imidazol **76e** undergoes smoothly the described alkylation/deprotection procedure leading to the methylated imidazole **78a** in 72% yield as the only isomer (Table 33, entry 1). By using regioisomer **76i** of imidazole **76e**, the corresponding alkylated isomer **78b** could be obtained (entry 2). Additionally, also the thioether-substituted isomeric imidazoles **76g** and **76j** have been alkylated successfully furnishing the regioisomeric imidazoles **78c** and **78d** in 65% and 72% yield, respectively (entries 3 and 4).

Table 33: Selective methylation with *Meerwein's* reagent (**66**) at position N-3 of imidazole derivatives of type 76 and subsequent deprotection at position N-1.

Entry	Imidazole Derivative	Methylating Reagent	Product, Yield[a]
		$Me_3O^+\ ^-BF_4$	
1	**76e**	**66**	**78a**: 72%[b]

[264] N. Jacobi, T. Lindel, *Eur. J. Org. Chem.* **2010**, 5415.

[265] a) P. Chandana, A. Nayyar, R. Jain, *Synth. Commun.* **2003**, *33*, 2925. b) F. B. Panosyan, I. W. J. Still, *Can. J. Chem.* **2001**, *79*, 1110. c) C. J. Chivikas, J. C. Hodges, *J. Org. Chem.* **1987**, *52*, 3591.

		$Me_3O^+\ ^-BF_4$	
2	**76i**	**66**	**78b**: 74%[b]
		$Me_3O^+\ ^-BF_4$	
3	**76g**	**66**	**78c**: 65%[b]
		$Me_3O^+\ ^-BF_4$	
4	**76j**	**66**	**78d**: 72%[b]

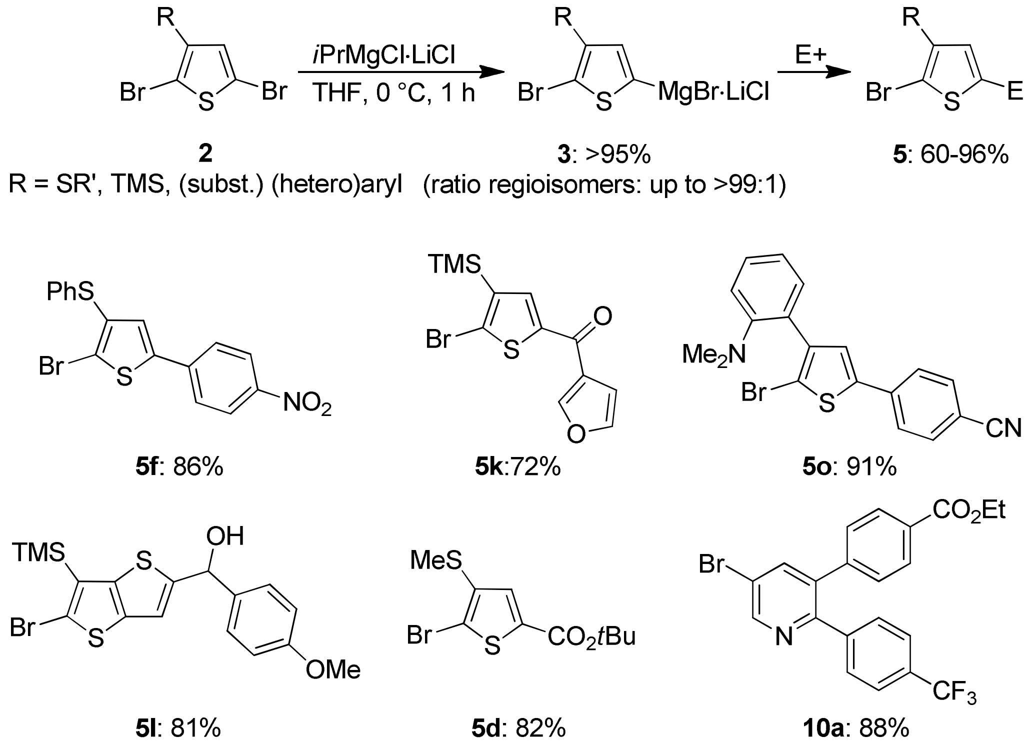
[a] Yield of analytically pure isolated product as determined by ^1H NMR analysis. [b] Obtained after addition of trimethyloxonium tetrafluoroborate (1 equiv) and subsequent treatment with HCl (excess).

7. SUMMARY AND OUTLOOK

This work focused on the development of a convenient and general regioselective Br/Mg-exchange reaction for unsymmetrically substituted dibromoheterocycles allowing the preparation of various thienyl-, furyl- and pyridyl-magnesium derivatives. Furthermore, in the search of a general and atom-economical method for preparing boronic derivatives suitable for cross-coupling reactions, a one-pot procedure using inexpensive aryl bromides, magnesium as a low-cost reducing agent with little toxicity and a trialkylborate as cheap boron source was established. In order to overcome the lack of a convenient and practical direct synthesis for α-substituted β,γ-unsaturated ketones and esters, their preparation *via* the addition of readily available substituted allylic zinc reagents to a broad range of acid chlorides and chloroformates was disclosed. Moreover, the LiCl-mediated metal insertion into alkyl bromides, aromatic halides as well as benzylic chlorides was extended to highly functionalized alkenyl bromides for the effective preparation of alkenyl zinc reagents bearing for the first time sensitive functional moieties. Due to the lack of a general methodology for the selective synthesis of adamantyl organometallic reagents, a mild and convenient procedure for the selective synthesis of adamantyl organometallics and their subsequent functionalization was developed. Furthermore, the adamantyl moiety was introduced as substituent in oligothiophenes, dramatically increasing their solubility. Finally, a methodology for the selective and predictable functionalization of all positions of the imidazole scaffold starting from simple imidazole by directed metalation and sulfoxide/magnesium exchange was developed.

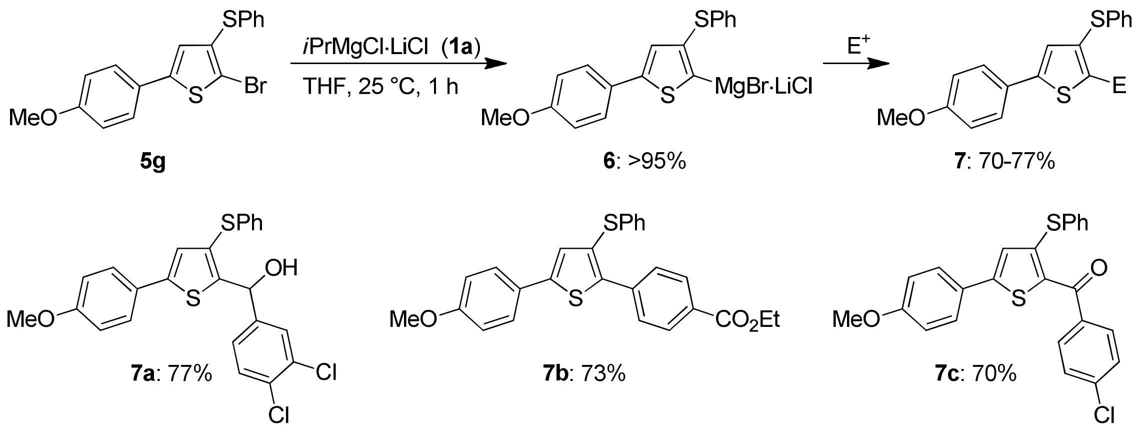
7.1 HIGHLY REGIOSELECTIVE PREPARATION OF HETEROARYL-MAGNESIUM REAGENTS USING A Br/Mg-EXCHANGE

A highly regioselective preparation of five- and six-membered heteroarylmagnesium derivatives was developed. The efficient Br/Mg-exchange reagents *i*PrMgCl·LiCl (**1a**) and isitylMgBr·LiCl (**1c**) proved to undergo highly regioselective Br/Mg-exchange reactions with unsymmetrically substituted dibromo-heterocycles **2** derived from thiophenes, benzo[*b*]thiophenes or pyridines. Ring-substituents such as thioether or trimethylsilyl groups, as well as pyridyl and thienyl groups or *ortho*-substituted aryl groups directed the Br/Mg-exchange in position 5 with a regioselectivity of up to >99:1 (Scheme 141). The corresponding magnesium reagents **3** were readily functionalized through e.g. *Negishi* cross-coupling reactions, acylations or addition to aldehydes.



Scheme 141: Regioselective Br/Mg-exchange on unsymmetrical dibromoheterocycles using *i*PrMgCl·LiCl (**1a**).

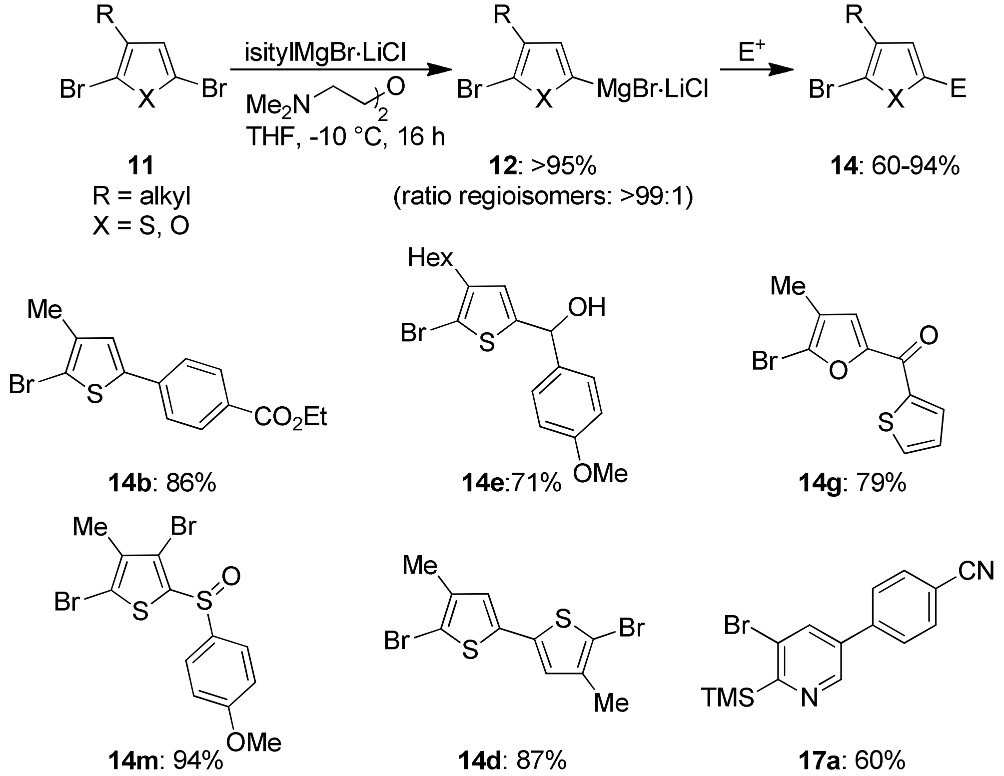
In order to exemplify the further functionalization of monobromo-thiophenes of type **5** obtained after the selective Br/Mg-exchange, the previously prepared monobromo-thiophene **5g** was submitted to a second Br/Mg-exchange reaction using *i*PrMgCl·LiCl (**1a**). The resulting magnesium reagent **6** was readily used in different types of functionalization reactions (Scheme 142).



Scheme 142: Further functionalization of cross-couling product **5g** *via* Br/Mg-exchange and subsequent reactions with different electrophiles.

In case of alkyl substituted dibromo-thiophene or -furan derivatives the sterically hindered *Grignard* reagent 2,4,6-triisopropylphenylmagnesium bromide (isitylMgBr·LiCl, **1c**) furnished in combination with the chelating diamine 2,2'-oxy-

bis(*N*,*N*-dimethylethanamine) (**L^2**) the best regioselectivities in the Br/Mg-exchange. The selectively magnesiated heterocyclic scaffolds **12** were subsequently funtionalized with a broad range of different electrophiles like aldehydes, aryl iodides, acyl chlorides or aryl sulfinyl chlorides (Scheme 143).



Scheme 143: Regioselective Br/Mg-exchange on unsymmetrical dibromoheterocycles of using isitylMgBr·LiCl (**1c**) and ligand **L^2**.

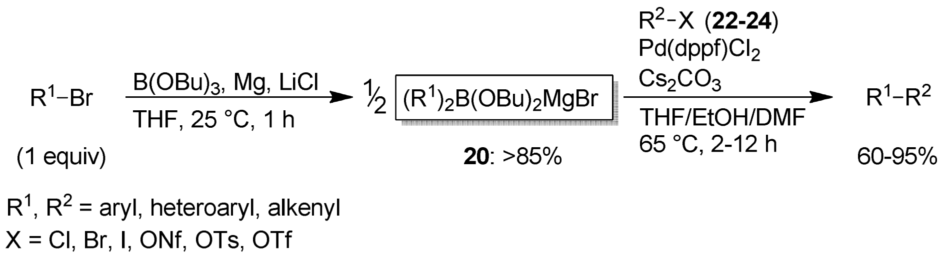
The disclosed method is very versatile and might find application e.g. for the synthesis of poly(3-hexylthiophene) (P3HT),[266] in which the regioregularity determines macroscopic physical properties of the polymers.[267]

[266] a) T.-A. Chen, R. D. Rieke, *J. Am. Chem. Soc.* **1992**, *114*, 10087. b) R. D. Lowe, R. D. McCullough, *J. Chem. Soc.,Chem. Commun.* **1992**, 70. c) R. Lowe, M. Jayaraman, D. L. Anderson, R. D. McCullough, *J. Org. Chem.* **1993**, *58*, 904. d) R. Lowe, M. Jayaraman, P. C. Ewbank, D. L. Anderson, S. Tristram-Nagle, R. D. McCullough, *Synth. Mat.* **1993**, *55*, 1198. e) S. Tristam-Nagle, S. P. Williams, R. D. Lowe, M. Jayaraman, R. D. McCullough, *J. Am. Chem. Soc.* **1993**, *115*, 4910. f) S. Williams, R. D. McCullough, *J. Am. Chem. Soc.* **1993**, *115*, 11608. g) T.-A. Chen, R. D. Rieke, *Synth. Met.* **1993**, *60*, 175. h) T.-A. Chen, R. A. O'Brien, R. D. Rieke, *Macromolecules* **1993**, *26*, 3462. i) S. P. Williams, S. Tristram-Nagle, M. Jayaraman, P. C. Ewbank, L. Miller, R. D. McCullough, *Synth. Met.* **1995**, *67*, 279. j) T.-A. Chen, X. Wu, R. D. Rieke, *J. Am. Chem. Soc.* **1995**, *117*, 233. k) R. S. Loewe, S. M. Khersonsky, R. D. McCullough, *Adv. Mater.* **1999**, *11*, 250. l) R. S. Loewe, P. C. Ewbank, J. Liu, L. Zhai, R. D. McCullough, *Macromolecules* **2001**, *34*, 4324. m) A. Yokoyama, R. Miyakoshi, T. Yokozawa, *Macromolecules* **2004**, *37*, 1169. n) R. Miyakoshi, A. Yokoyama, T. Yokozawa, *Macromol. Rapid. Commun.* **2004**, *25*, 1663. o) R. Miyakoshi, A. Yokoyama, T. Yokozawa, *J. Am. Chem. Soc.* **2005**, *127*, 17542. p) Y.-J. Cheng, S.-H. Yang, C.-S. Hsu, *Chem. Rev.* **2009**, *109*, 5868. q) A. Gadisa, W. D. Oosterbaan, K. Vandewal, J.-C. Bolsee, S. Bertho, J. D'Haen, L. Lutsen, D. Vanderzande, J. V. Manca, *Adv. Funct. Mater.* **2009**, *19*, 3300.

[267] a) M. Urien, L. Bailly, L. Vignau, E. Cloutet, A. de Cuendias, G. Wantz, H. Cramail, L Hirsch, J.-P. Parneix, *Polym. Int.* **2008**, *57*, 764. b) T. Yokozawa, A. Yokoyama, *Chem. Rev.* **2009**, *109*, 5595.

7.2 One-pot Preparation of Magnesium Di(hetero)aryl- and Dialkenyl-Boronates for Suzuki-Miyaura Cross-Couplings

Organoboronic derivatives are essential reagents for modern cross coupling chemistry. Since there is a continuous need for efficient synthetic routes for their preparation, a convenient, general and atom-economical method for preparing boronic derivatives in one step was investigated. The treatment of aryl and heteroaryl bromides as well as alkenyl halides with Mg turnings, $B(OBu)_3$ and LiCl in THF at ambient temperature leads within 1 h to the corresponding magnesium organoboronates tolerating a broad variety of functional groups. This atom-economical synthesis gives readily access to functionalized diaryl and diheteroaryl as well as to dialkenylboronates **20** from their corresponding organic bromides and might find its way into industrial syntheses. A good atom economy was achieved without loss of yield by using 0.5 equiv of $B(OBu)_3$ and forming therefore magnesium diorganoboronates of type **20** (Scheme 144).



Scheme 144: General equation for the synthesis and cross-coupling of magnesium diorganoboronates of type **20**.

Remarkably, both organo-groups (R^1) were transferred under typical *Suzuki-Miyaura* cross-coupling conditions with various aryl halides or pseudo-halides of type R^2-X (**22-24**) furnishing the corresponding products in excellent yields (Figure 12).

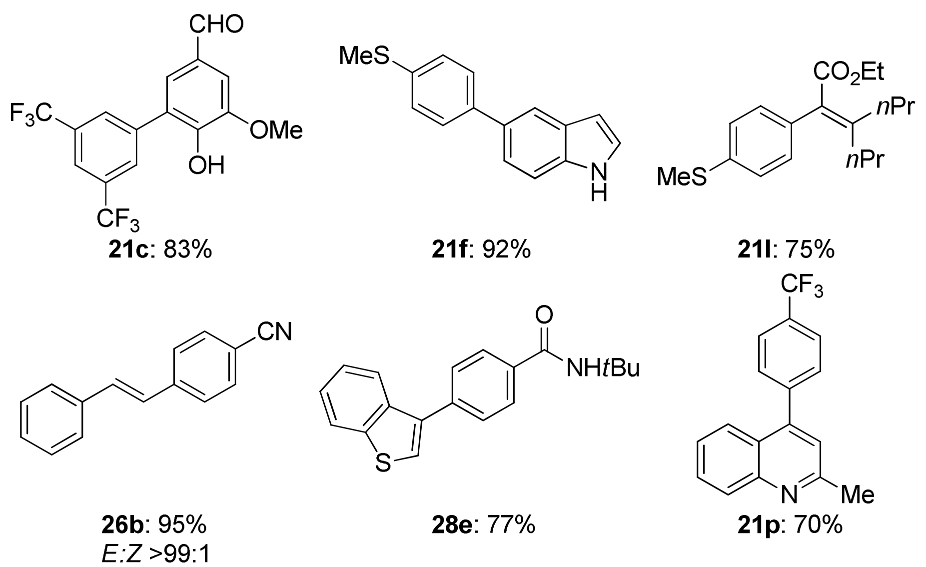
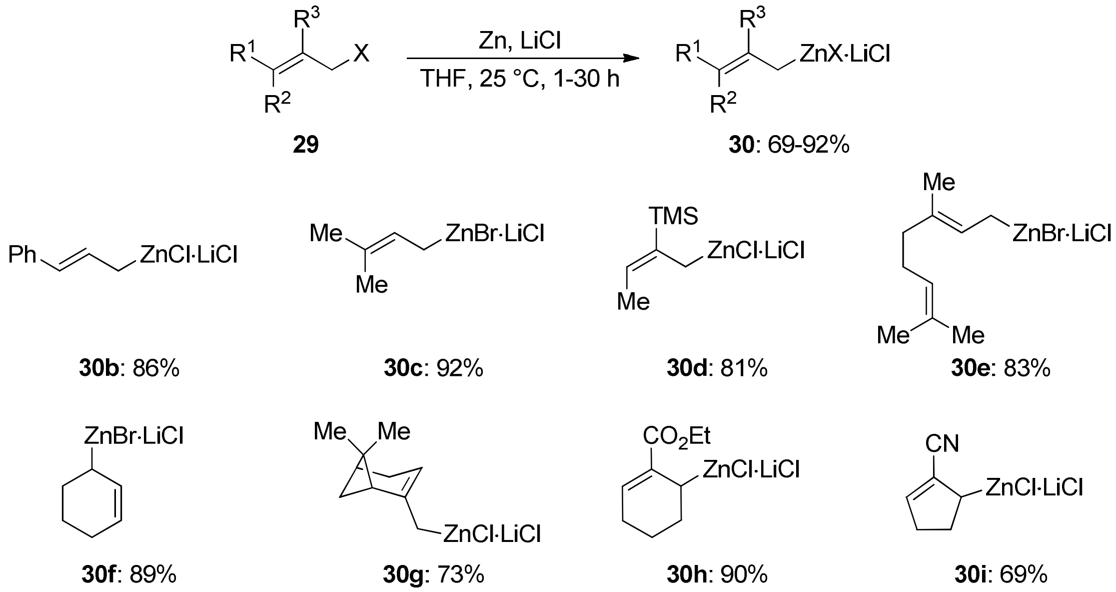


Figure 12: Cross-coupling products generated from diorganoboronates of type **20**.

7.3 PREPARATION OF α-SUBSTITUTED β,γ-UNSATURATED KETONES AND ESTERS VIA THE DIRECT ADDITION OF SUBSTITUTED ALLYLIC ZINC REAGENTS

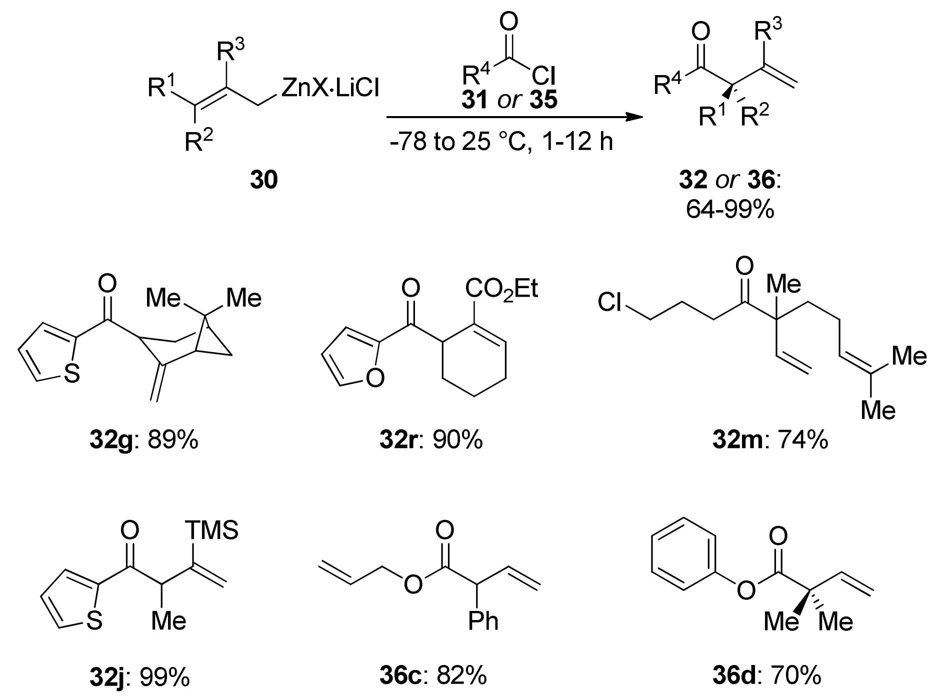
A practical and convenient procedure for the synthesis of α-substituted β,γ-unsaturated ketones and esters was developed. Substituted allylic zinc reagents, prepared *via* direct metal insertion in substituted allylic halides, react readily with a broad range of acid chlorides and chloroformates furnishing the corresponding α-substituted β,γ-unsaturated ketones and esters in high yield and perfect regioselectivity.

The recently by *Knochel et al.* developed method allowed the preparation of poly-substituted allyl zinc reagents starting from the corresponding allyl halides almost without formation of homocoupling products.[178] In order to expand this protocol, a broad variety of new allylic zinc organometallics was synthesized (Scheme 145).



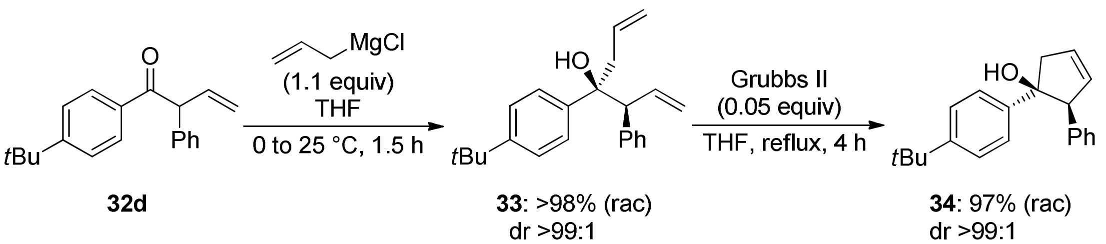
Scheme 145: LiCl-mediated preparation of substituted allylic zinc organometallics **30** *via* direct insertion of zinc powder.

The addition of these highly reactive allylic zinc reagents (**30a-i**) to a broad range of acid chlorides **31** and chloroformates **35** proceeded under exceedingly mild conditions (-78 °C, 1-2 h) and furnished selectively β,γ-unsaturated ketones **32** and esters **36** without any traces of the α,β-unsaturated isomers (Scheme 146).



Scheme 146: Preparation of α-substituted β,γ-unsaturated ketones (**32**) and esters (**36**) from allylic zinc reagents of type **30**.

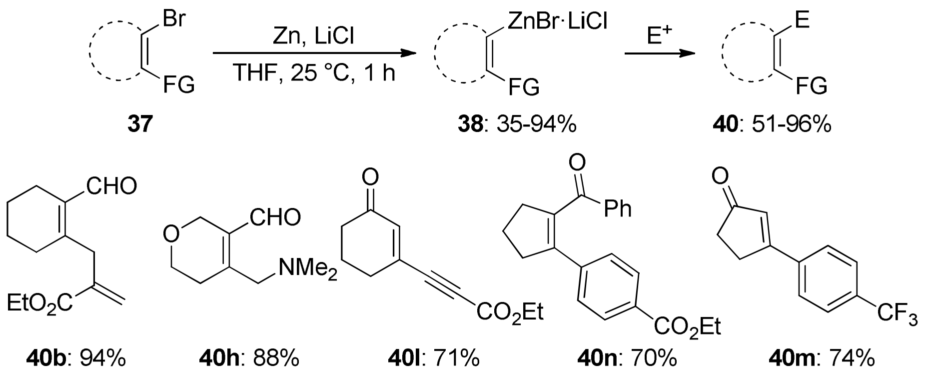
The diene-precursor **33** for a ring-closing metathesis (RCM) was readily synthesized from a α-substituted β,γ-unsaturated ketone **32d** in only one step *via* the diastereoselective addition of allyl magnesium chloride to the carbonyl moiety of **32d** in almost quantitative yield (Scheme 147). The subsequent RCM using the second generation of *Grubbs'* catalyst furnished diastereoselectively cyclopentene derivative **34** in 97% yield.



Scheme 147: Diastereoselective addition of allyl magnesium chloride to **32d** and subsequent ring-closing metathesis forming the cyclopentene derivative **34**.

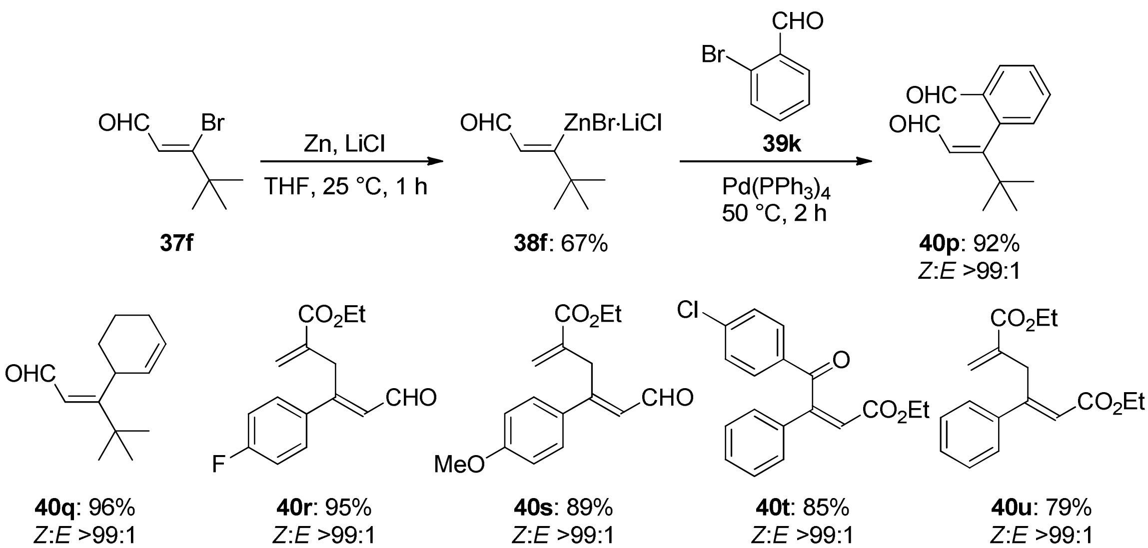
7.4 Preparation of Functionalized Alkenylzinc Reagents Bearing Carbonyl Groups via Direct Metal Insertion

A convenient, mild and atom-economical protocol for the synthesis of highly functionalized alkenylzinc reagents bearing sensitive carbonyl groups such as an aldehyde, a ketone or an ester was developed. Activated alkenyl bromides **37** underwent a direct insertion of zinc in the presence of LiCl furnishing the corresponding organozinc compounds **38**. Subsequent functionalization reactions like *Negishi* cross-couplings, acylations or allylations were performed readily leading to polyfunctional compounds **40** in excellent yields (Scheme 148).



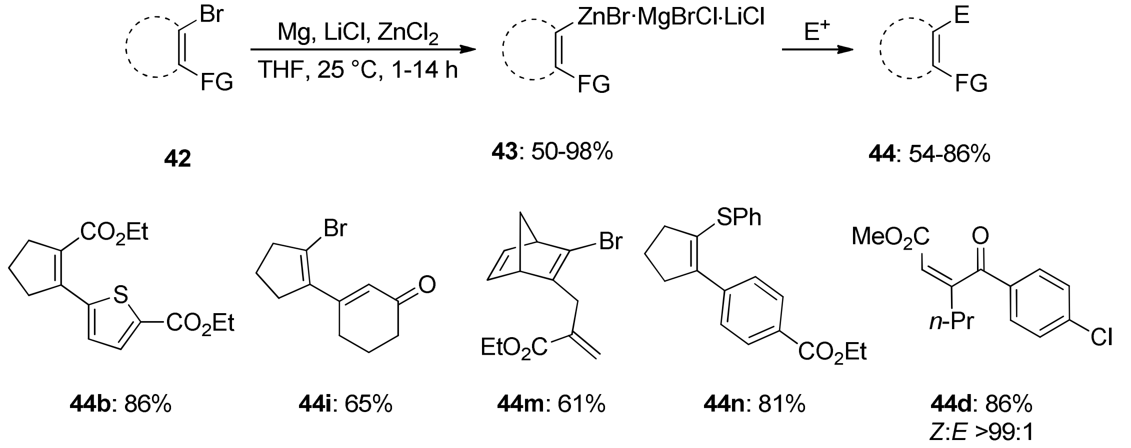
Scheme 148: Preparation of alkenylzinc reagents **38** from activated alkenyl bromides **37** *via* direct zinc insertion and subsequent functionalization.

Furthermore, acyclic alkenylzinc reagents **38f-i** could be prepared from the corresponding acyclic bromides **37f-i** without loosing their stereochemistry due to the chelating effect of the Zn-center with the vicinal carbonyl group and allowed therefore the synthesis of trisubstituted olefins with excellent *Z*-selectivity (Scheme 149).



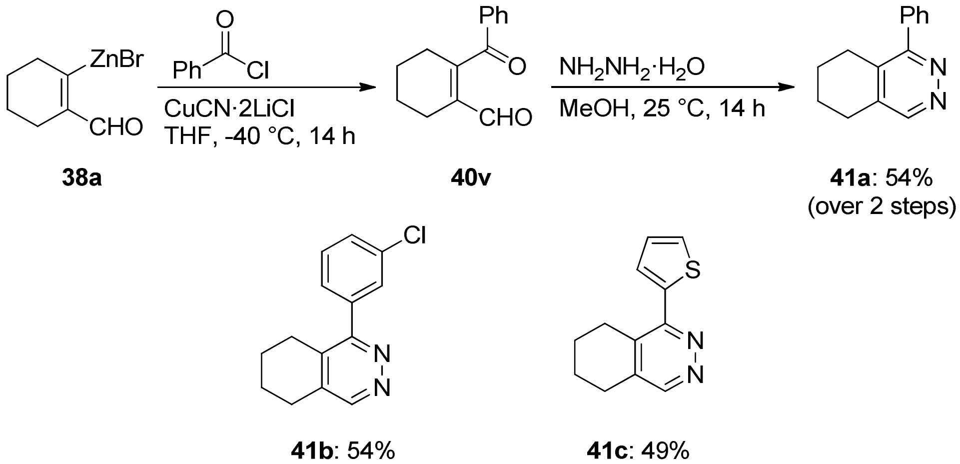
Scheme 149: LiCl-mediated zinc insertion into acyclic alkenyl bromides **37f-i** leading to zinc reagents **38f-i** and subsequent cross-coupling.

Electronically less activated alkenyl bromides **42** were converted to their corresponding zinc reagents **43** by using the stronger reducing metal magnesium in the presence of LiCl and $ZnCl_2$. Their subsequent functionalization with a broad variety of electrophiles furnished the substituted alkenyl derivatives **44** in high yields (Scheme 150).



Scheme 150: Preparation of alkenylzinc reagents **43** from less activated alkenyl bromides **42** *via* magnesium insertion in presence of $ZnCl_2$ and subsequent functionalization.

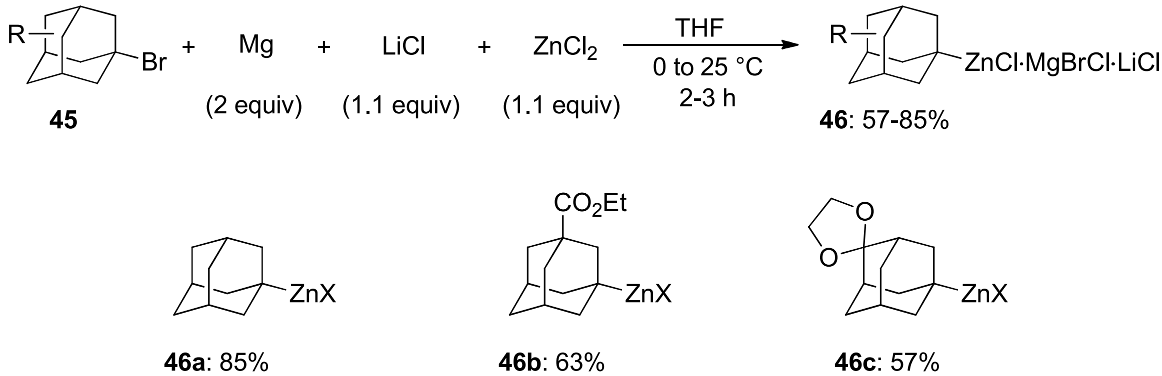
Due to their highly reactive nature, unsaturated 1,4-dicarbonyl compounds readily undergo condensation reactions with hydrazine providing tetrahydrophthalazines. Therefore, compound **40v** smoothly reacted with hydrazine hydrate ($NH_2NH_2 \cdot H_2O$) in methanol to the corresponding 1-substituted tetrahydrophthalazine **41a** in 54% yield (Scheme 151). Following this protocol, compounds **41b** and **41c**, bearing a 3-chlorophenyl- and a 2-thienyl-substituent respectively were prepared in 49-54% yield.



Scheme 151: Synthesis of substituted tetrahydrophthalazines of type **41**.

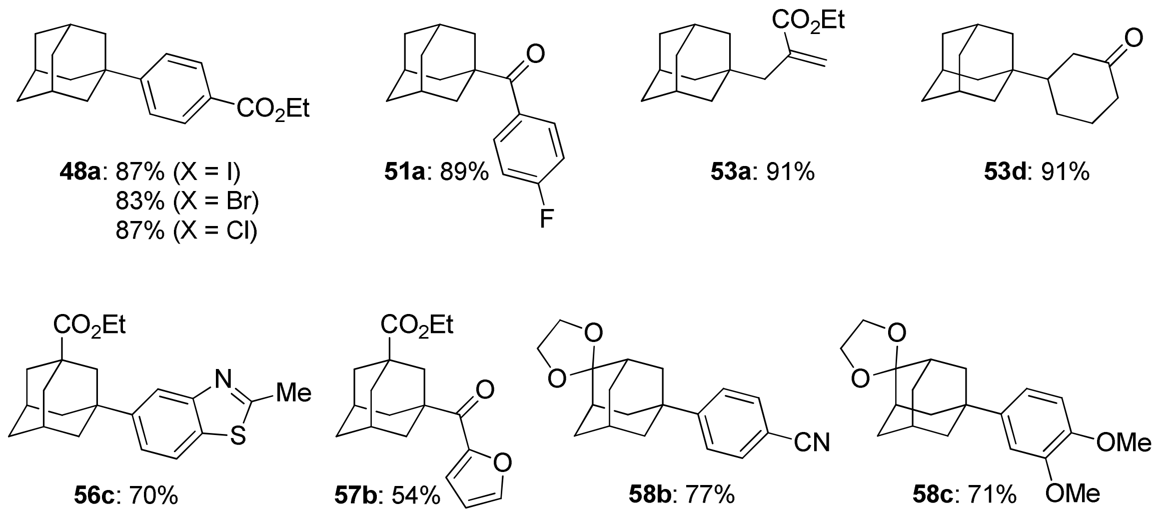
7.5 SYNTHESIS OF FUNCTIONALIZED ADAMANTYLZINC REAGENTS USING A Br/Mg-INSERTION IN THE PRESENCE OF $ZnCl_2$

A practical and convenient procedure for the synthesis of substituted adamantyl zinc reagents was developed. The LiCl-mediated Mg insertion in the presence of $ZnCl_2$ allowed an efficient synthesis of adamantylzinc reagents starting from the corresponding functionalized tertiary bromides (Scheme 152).



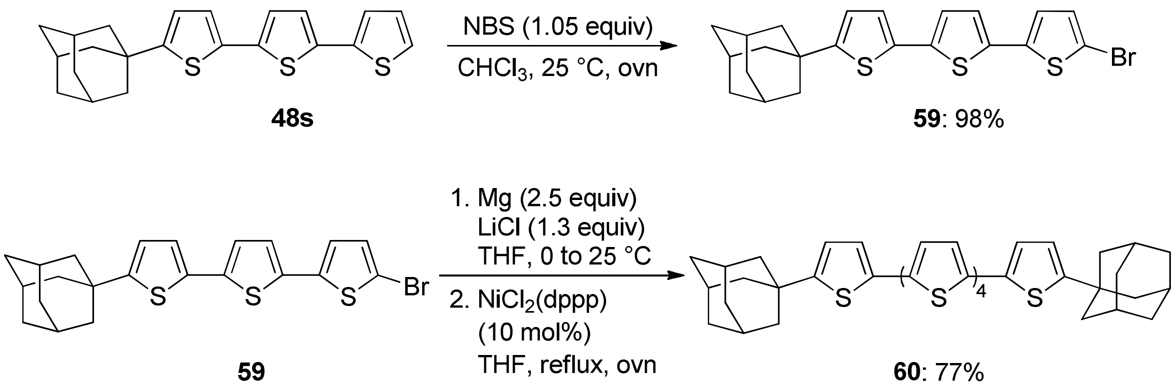
Scheme 152: Preparation of functionalized adamantylzinc reagents **46** *via* the LiCl-mediated Mg-insertion in the presence of $ZnCl_2$ (additional complexed salts are omitted for the sake of clarity).

The highly reactive adamantylzinc species **46a-c** readily undergo a broad variety of functionalization reactions in the presence of an appropriate catalyst. As illustrated in Scheme 153, *Negishi* cross-couplings, Cu(I)-catalyzed acylation and allylation as well as 1,4-addition reactions and many more could be successfully employed to generate highly functionalized adamantyl derivatives in high yields.



Scheme 153: Highly functionalized adamantyl derivatives synthesized *via* functionalization of the corresponding adamantylzinc species **46a-c**.

Furthermore, the adamantyl moiety could be introduced as substituent in oligothiophenes, dramatically increasing their solubility. Adamantylzinc reagent **46a** readily underwent a *Negishi* cross-coulpling reaction with the 5-bromo-terthiophene **49h** furnishing the corresponding α-substituted oligothiophene **48s**. Selective bromination of **48s** followed by a Ni-catalyzed homocoupling reaction of the corresponding *Grignard* reagent of the bromo-oligiothiophene **59** led to the α,α'-diadamantyl-sexithiophene **60** (Scheme 154).



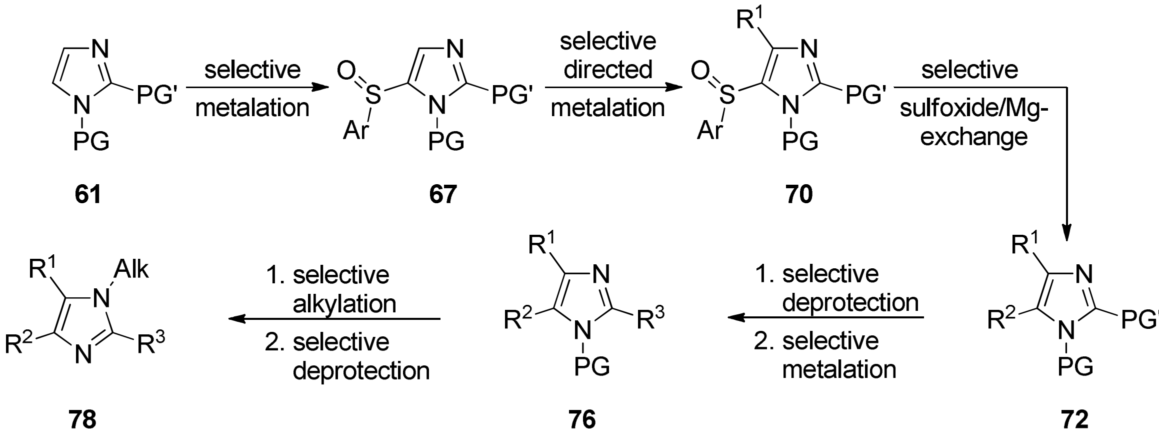
Scheme 154: Synthesis of α,α'-diadamantyl-sexithiophene **60**.

The presence of the apolar adamantyl-moiety strongly increases the lipophilicity of the sexithiophene. Combined with the bulkiness of the adamantine substituents preventing the *π*-stacking of the oligothiophenes, this explains the excellent solubility of compound **60** compared to the unsubstituted sexithiophene (solubility lower than 50 mg/l in chloroform[234]).

Recently *Garnier et al.* reported, that β-alkyl substituted oligothiophenes show an even higher solubility than the corresponding α-substituted ones.[234] Since the adamantyl-subtituents in α-position already proved to have an excellent impact on the solubility, it should be worth to investigate their effect as β-substituents. The increased solubility should provide the opportunity to synthesize much longer oligomers which would serve as desired models for the better understanding of polymeric systems.[233]

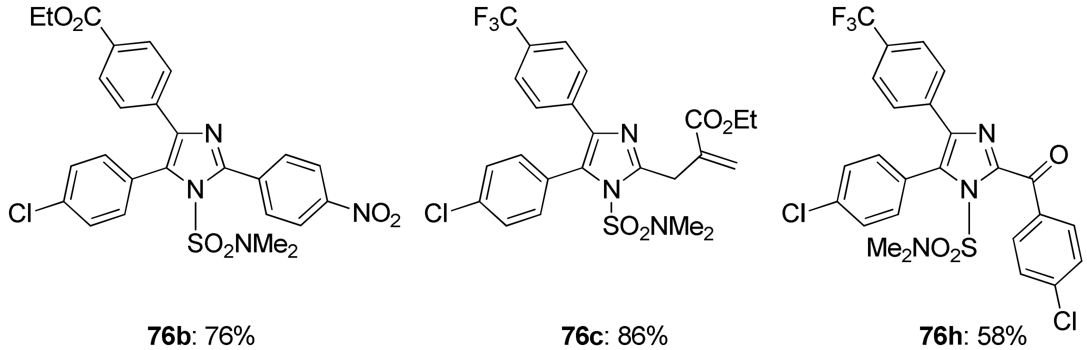
7.6 FULL FUNCTIONALIZATION OF THE IMIDAZOLE SCAFFOLD BY SELECTIVE METALATION AND SULFOXIDE/MAGNESIUM EXCHANGE

A general, selective and flexible approach for the synthesis of complex substituted imidazoles was developed. All three C–H bonds of the imidazole core could be functionalized in a regioselective and sequential manner by metalation using TMPMgCl·LiCl (**62**) and TMP_2Zn·2MgCl·2LiCl (**65**) as bases as well as by a selective sulfoxide/magnesium exchange triggered by *i*PrMgCl·LiCl (**63**) (Scheme 155).



Scheme 155: Selective fully functionalization of the imidazole ring in a regioselective manner.

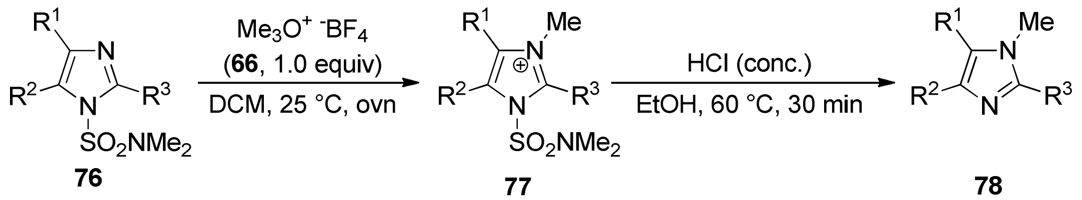
The *N*,*N*-dimethylsulfamoyl group at nitrogen N-1 directed the metalation of imidazole **61** with TMPMgCl·LiCl (**62**) regioselectively in position 5. The subsequent sulfinylation employing 4-methoxy-3,5-dimethyl-benzenesulfinyl chloride (**68a**) led to imidazole **67**. This substituent was found to be essential for the full functionalization procedure, since it allows both the direct metalation in *ortho* position and its replacement by a sulfoxide/magnesium exchange. Hence, the subsequent metalation with TMPMgCl·LiCl (**62**) occured in position 4 enabling the selective functionalization in this position. The next functionalization step was performed in position 5 by means of a sulfoxide/magnesium exchange. Treatment of imidazole derivatives **70** with *i*PrMgCl·LiCl (**63**) led to the corresponding magnesium intermediates **71** which could readily be functionalized leading to imidazoles of type **72**. After selective removal of the TBDMS-group in position 2 with TBAF·$3H_2O$ (**64**), metalation either using TMPMgCl·LiCl (**62**) or TMP_2Zn·2MgCl·2LiCl (**65**) furnished the corresponding organometallic reagents **74** and **75** that were subsequently functionalized to give the fully substituted imidazoles of type **76** (Scheme 156).

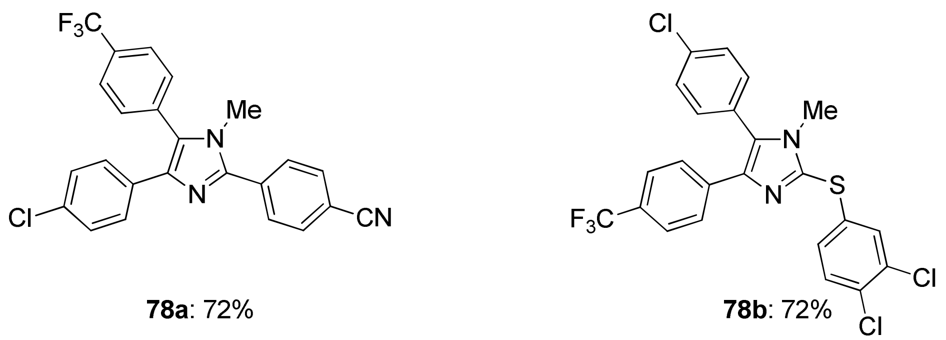


76b: 76% **76c**: 86% **76h**: 58%

Scheme 156: Fully functionalized imidazole derivatives of type **76**.

N-sulfamoylimidazoles are known to react with alkylating reagents exclusively *via* their nonsubstituted nitrogen atom since alkylation on N-1 is blocked. Moreover, the formation of an imidazolium salt by N-3-alkylation increases the lability of the dimethylsulfamoyl group allowing its removal *via* the addition of concentrated HCl. Hence, the fully functionalized imidazole derivatives of type **76** were treated with *Meerwein's* reagent (**66**, trimethyloxonium tetrafluoroborate) generating the corresponding imidazolium salts **77**. The *N*,*N*-dimethylsulfamoyl group at the N-1 was then cleaved by addition of concentrated HCl furnishing the alkylated imidazoles of type **78** (Scheme 157).





78a: 72% **78b**: 72%

Scheme 157: Selective methylation with *Meerwein's* reagent (**66**) at position N-3 of the imidazole ring and subsequent deprotection at position N-1.

C. EXPERIMENTAL SECTION

1. GENERAL CONSIDERATIONS

All reactions were carried out under argon or nitrogen atmosphere in glassware dried with a heat gun. Syringes which were used to transfer anhydrous solvents or reagents were purged thrice with argon or nitrogen prior to use. THF was freshly distilled from sodium benzophenone ketyl under nitrogen prior to use. Indicated yields are isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC. Column chromatography was performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck. Unless otherwise indicated, all reagents were obtained from commercial sources. Liquid starting materials were distilled prior to use. Magnesium turnings (> 99.5%), magnesium powder (> 99%) and zinc dust (> 90%) were obtained from Riedel-de Haën. CuCN, $ZnCl_2$ and LiCl were obtained from Fluka.

1.1 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.

$CHCl_3$ was predried over $CaCl_2$ and distilled from CaH_2.

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

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

Et_2O was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

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

Toluene was predried over $CaCl_2$ and distilled from CaH_2.

NEt_3 was dried over KOH and distilled.

Solvents for column chromatography were distilled on a rotary evaporator prior to use.

1.2 Reagents

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

***i*PrMgCl·LiCl** solution in THF was purchased from Chemetall.

***n*BuLi** solution in hexane was purchased from Chemetall.

TMPMgCl·LiCl was prepared according to a literature procedure.[28a]

$TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$ was prepared according to a literature procedure.[68a]

CuCN·2LiCl solution (1.00 M) was prepared by drying CuCN (80.0 mmol, 7.17 g) and LiCl (160 mmol, 6.77 g) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling, 80 mL dry THF were added and stirring was continued until the salts were dissolved.

$ZnCl_2$ solution (1.00 M) was prepared by drying $ZnCl_2$ (100 mmol, 136 g) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling, 100 mL dry THF were added and stirring was continued until the salt was dissolved.

1.3 Content Determination of Organometallic Reagents

Organozinc and organomagnesium reagents were titrated with I_2 in THF.[192]

Organolithium reagents were titrated with dry 2-propanol and 1,10-phenanthroline as indicator in THF.[268]

TMPMgCl·LiCl and **$TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$** were titrated with benzoic acid and 4-(phenylazo)diphenylamine as indicator in THF.[28a, 68]

1.4 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, by

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

incubating the plates in an iodine chamber and/or by staining of the TLC plate with one of the reagents given below followed by heating with a heat gun:

- $KMnO_4$ (3.0 g), 5 drops of conc. H_2SO_4 in water (300 mL).
- Phosphomolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12 mL) in water (230 mL).
- Ninhydrin (0.3 g) and AcOH (3.0 mL) in butanol (100 mL).

1.5 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 tetramethylsilane. The following abbreviations were used to characterize signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), spt (septet), m (multiplet) as well as br (broadened).

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%.

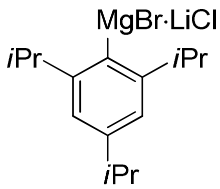
Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSampl*IR* II Diamond ATR sensor was used. Wavenumbers are reported in cm^{-1} starting at an absorption of 10%.

Melting points (m.p.) were determined on a BÜCHI B-540 melting point apparatus and are uncorrected. Compounds decomposing upon melting are indicated by (decomp.).

2. HIGHLY REGIOSELECTIVE PREPARATION OF HETEROARYL-MAGNESIUM REAGENTS USING A BR/MG-EXCHANGE

2.1 PREPARATION OF STARTING MATERIALS

Preparation of 2,4,6-triisopropylphenylmagnesium bromide (1c)



Magnesium turnings (3.64 g, 150 mmol, 1.5 equiv) and anhydrous LiCl (4.20 g, 100 mmol, 1.0 equiv) were placed in an Ar-flushed flask and dried with a heatgun at 450 °C for 10 min *in vacuo*. After cooling to 25 °C and purging with argon, THF (50 mL) was added. After addition of THF (60 mL), the magnesium was activated using 1,2-dibromoethane (2 mol %) and Me_3SiCl (5 mol %). Subsequently, a solution of 1-bromo-2,4,6-triisopropylbenzene (28.3 g, 100 mmol) in THF (40 mL) was slowly added at 25 °C. After addition, the reaction mixture was stirred for 12 h at 25 °C. Residual Mg was removed by cannulating the grey solution of 2,4,6-triisopropyl-magnesium bromide (**1c**) to a dry and argon-flushed flask. The reagent was titrated prior to use by the method of Paquette,[268] or the method developed in our laboratory.[192]

Dibromo-heteroaryl compounds 2a,[269] **2d**,[270] **2i**,[271] **11c**[272] and **11f**[273] were prepared according to literature procedures; compounds **11a**, **11b** and **11e** were commercially available.

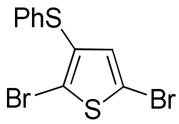
2,5-dibromo thiophenes 2b-c and **2e-h** and **2j** were prepared from 2,5-dibromo thiophene following a literature procedure.[269] For **2b** and **2c**, the (2,5-dibromothiophen-3-yl)lithium was quenched with the corresponding diorgano disulfide at -78 °C followed by a standard aqueous workup and column chromatography. For the compounds **2f-h** and **2j** (2,5-dibromothiophen-3-yl)lithium was transmetalated with $ZnCl_2$ at -40 °C followed by a *Negishi* cross-coupling reaction with 4% $Pd(PPh_3)_4$ and 0.9 equiv of the corresponding aryl iodide in THF at 50 °C over night. After a standard workup the crude was purified via column chromatography.

[269] E. C. Taylor, D. E. Vogel, *J. Org. Chem.* **1985**, *50*, 1002.
[270] P. Chiem Van, R. S. Macomber, H. B. Mark Jr., H. Zimmer, *J. Org. Chem.* **1984**, *49*, 5250.
[271] Y. Zhang, A.-B. Hörnfeldt, S. Gronowitz, *J. Heterocycl. Chem.* **1995**, *32*, 435.
[272] J. D. Prugha, A. L. Huitric, W. C. McCarthy, *J. Org. Chem.* **1964**, *29*, 1991.
[273] I. J. Turchi, J. B. Press, J. J. McNally, M. Pat Bonner, K. L. Sorgi, *J. Org. Chem.* **1993**, *58*, 4629.

2,5-dibromothieno[3,2-*b*]thiophene (2e) was prepared following a literature procedure[147c] replacing NCS by NBS. The NBS was used as purchased without recrystallization.

2,5-dibromo pyridines 8a-8d and 15 were prepared from 2,5-dibromo pyridine following a literature procedure.[28a] For **8a-8c**, the magnesiated 2,5-dibromo pyridine derivative was transmetalated with $ZnCl_2$ at -40 °C followed by a *Negishi* cross-coupling reaction with 4 mol % $Pd(PPh_3)_4$ and 0.9 equiv of the corresponding aryl iodide in THF at 50 °C over night. After a standard workup the crude was purified via column chromatography. For **8d** and **15**, the magnesiated 2,5-dibromo pyridine derivative was quenched either with *S*-phenyl benzenesulfonothioate or TMSCN at -78 °C followed by a standard aqueous workup and column chromatography.

2,5-dibromo-3-(phenylthio)thiophene (2b)



m.p.: 46.6-48.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.22-7.32 (m, 5H), 7.07 (s, 1H).

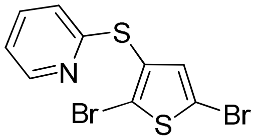
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 135.6, 133.4, 130.1, 129.3, 128.4, 127.1, 119.6, 116.2.

MS (70 eV, EI),, *m/z* (%) = 350 (M^+, 45), 348 (M^+, 21), 271 (24), 269 (22), 192 (10), 191 (14), 190 (100), 146 (13), 77 (9).

HRMS (EI), *m/z* calc. for $\mathbf{C_{10}H_6Br_2S_2}$ (349.8257): 349.8245 (M^+).

IR (ATR) υ (cm^{-1}) = 3092, 3043, 3017, 3007, 2360, 2338, 1966, 1947, 1883, 1865, 1805, 1733, 1646, 1578, 1489, 1476, 1437, 1390, 1302, 1138, 1078, 1009, 965, 824, 737, 686, 678.

2-((2,5-dibromothiophen-3-yl)thio)pyridine (2c)



m.p.: 45.8-47.5 °C.

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 8.42 (ddd, *J*=4.8Hz, 1.8Hz, 1.0Hz, 1H), 7.72 (td, *J*=7.8Hz, 1.9Hz, 1H), 7.21 (ddd, *J*=7.4Hz, 4.9Hz, 2.0Hz, 1H) 7.58 (s, 1H), 7.04 (d, *J*=8.2Hz, 1H).

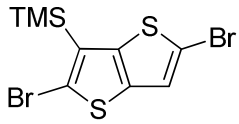
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 157.5, 150.2, 138.4, 134.4, 126.0, 121.8, 121.7, 120.7, 118.1.

MS (70 eV, EI), *m/z* (%) = 351 (M^{+}, 8), 349 (M^{+}, 4), 274 (10), 273 (13), 272 (100), 270 (88), 191 (25), 147 (5), 78 (7).

HRMS (EI), *m/z* calc. for **$C_9H_5Br_2S_2$** (348.8230): 348.8215 (M^{+}).

IR (ATR) υ (cm^{-1}) = 3085, 3045, 2996, 2971, 1739, 1570, 1557, 1485, 1451, 1444, 1414, 1391, 1377, 1366, 1299, 1229, 1217, 1117, 1012, 969, 830, 806, 756, 717, 679.

(2,5-dibromothieno[3,2-b]thiophen-3-yl)trimethylsilane (2e)



m.p.: 45.3-47.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.28 (s, 1 H), 0.43 (s, 9 H).

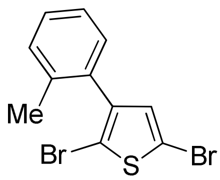
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 143.4, 141.0, 136.1, 122.7, 115.2, 107.7, -0.9.

MS (70 eV, EI), *m/z* (%) = 370 (M^{+}, 52), 368 (M^{+}, 24), 358 (10), 357 (62), 356 (16), 355 (100), 353 (54), 261 (12), 259 (11), 233 (44), 231 (46), 137 (11), 73 (22).

HRMS (EI), *m/z* calc. for **$C_9H_{10}Br_2S_2Si$** (369.8339) = 369.8331 (M^{+}).

IR (ATR) υ (cm^{-1}) = 3100, 2955, 2895, 1739, 1478, 1417, 1409, 1313, 1246, 1152, 1012, 970, 833, 799, 756, 712, 698.

2,5-dibromo-3-(*o*-tolyl)thiophene (2f)



^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.20-7.39 (m, 4H), 7.03 (s, 1H), 2.28 (s, 3H).

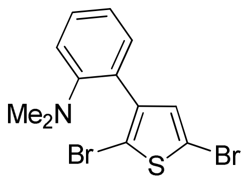
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 139.7, 138.1, 132.3, 131.3, 131.2, 130.3, 129.4, 125.7, 111.9, 109.2, 20.1.

MS (70 eV, EI), *m/z* (%) = 332 (M^+, 32), 330 (M^+, 17), 252 (10), 173 (14), 172 (100), 171 (37), 128 (14), 86 (16), 80 (9), 42 (12).

HRMS (EI), *m/z* calc. for $\mathbf{C_{11}H_8Br_2S}$ (329.8713): 329.8703 (M^+).

IR (ATR) υ (cm^{-1}) = 3094, 3062, 3045, 3020, 2970, 2952, 2921, 1531, 1482, 1451, 1379, 1301, 1128, 979, 816, 751, 721, 685.

2-(2,5-dibromothiophen-3-yl)-*N*,*N*-dimethylaniline (2g)



^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.37-7.42 (m, 1H), 7.28-7.35 (m, 1H), 6.99 (s, 3H), 2.63 (s, 6H).

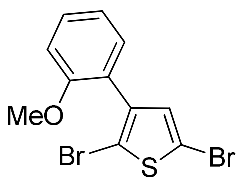
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 152.2, 139.3, 132.4, 132.0, 129.8, 124.6, 121.2, 118.2, 112.7, 108.0, 43.2.

MS (70 eV, EI), *m/z* (%) = 361 (M^+, 20), 359 (M^+, 10), 283 (12), 280 (14), 279 (80), 277 (12), 266 (48), 265 (10), 264 (53), 202 (12), 201 (44), 200 (100), 185 (14), 168 (30), 167 (10), 115 (16), 101 (27), 93 (10).

HRMS (EI), *m/z* calc. for $\mathbf{C_{12}H_{11}Br_2NS}$ (360.8958): 360.8971 (M^+).

IR (ATR) υ (cm^{-1}) = 3093, 3062, 2979, 2938, 2860, 2829, 2782, 1594, 1483, 1451, 1428, 1323, 1303, 1191, 1159, 1131, 1098, 1049, 979, 955, 942, 935, 811, 758, 741, 684.

2,5-dibromo-3-(2-methoxyphenyl)thiophene (2h)



m.p.: 65.0-67.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.33-7.48 (m, 2H), 6.93-7.10 (m, 3H), 3.85 (s, 3H).

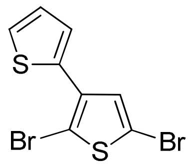
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 156.9, 136.3, 132.4, 132.0, 130.6, 120.7, 120.4, 112.2, 111.3, 109.0, 55.6.

MS (70 eV, EI), *m/z* (%) = 348 (M^+, 100), 346 (M^+, 53), 254 (83), 253 (12), 252 (88), 188 (40), 187 (40), 174 (17), 173 (12), 115 (13), 82 (12), 80 (12).

HRMS (EI), *m/z* calc. for $\mathbf{C_{11}H_8Br_2OS}$ (347.8642): 347.8659 (M^+).

IR (ATR) υ (cm^{-1}) = 3094, 3082, 3019, 2967, 2936, 2835, 1595, 1579, 1481, 1476, 1461, 1455, 1432, 1286, 1250, 1182, 1132, 1111, 1052, 1027, 980, 813, 805, 791, 744, 734.

2',5'-dibromo-2,3'-bithiophene (2j)



m.p.: 43.2-45.1 °C.

^{1}**H NMR** (300 MHz, $CDCl_3$) δ (ppm) = 7.35 (dd, *J*=5.7Hz, 4.3Hz, 2H), 7.07 (dd, *J*=5.1Hz, 3.7Hz, 1H), 6.99 (s, 1H).

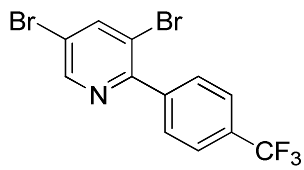
^{13}**C NMR** (75 MHz, $CDCl_3$) δ (ppm) = 134.0, 133.8, 133.4, 127.3, 127.1, 126.6, 111.1, 107.0.

MS (70 eV, EI), *m/z* (%) = 324 (M^+, 100), 322 (M^+, 51), 245 (10), 244 (10), 165 (9), 164 (77), 93 (7), 82 (15).

HRMS (EI), *m/z* calc. for $\mathbf{C_8H_4Br_2S_2}$ (323.8101): 323.8085 (M^+).

IR (ATR) υ (cm^{-1}) = 3096, 3064, 3027, 2956, 2924, 2851, 2238, 1606, 1536, 1505, 1436, 1397, 1107, 1015, 971, 909, 858, 841, 832, 823, 774, 704, 662.

3,5-dibromo-2-(4-(trifluoromethyl)phenyl)pyridine (8a)



m.p.: 73.8-75.2 °C.

^{1}**H NMR** (300 MHz, $CDCl_3$) δ (ppm) = 8.69 (d, *J*=1.9Hz, 1H), 8.18 (d, *J*=2.2Hz, 1H), 7.76-7.82 (m, 2H), 7.69-7.75 (m, 2H).

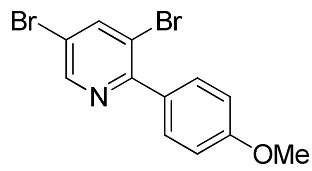
^{13}**C NMR** (75 MHz, $CDCl_3$) δ (ppm) = 155.2, 149.3, 143.3, 141.8, 131.0 (q, *J*=32.7Hz), 129.7, 125.1 (q, *J*=4.0Hz), 124.0 (q, *J*=272.4Hz), 119.7, 119.6.

MS (70 eV, EI), *m/z* (%) = 381 (M^+, 66), 379 (M^+, 32), 303 (14), 301 (14), 300 (100), 221 (61), 220 (15), 194 (13), 171 (10), 50 (11).

HRMS (EI), *m/z* calc. for $\mathbf{C_{12}H_6Br_2F_3N}$ (380.8799): 380.8778 (M^+).

IR (ATR) υ (cm^{-1}) = 3090, 3053, 2970, 1931, 1739, 1618, 1554, 1428, 1409, 1328, 1193, 1170, 1100, 1075, 1056, 1023, 1009, 888, 857, 842, 814, 762, 736, 690.

3,5-dibromo-2-(4-methoxyphenyl)pyridine (8b)



m.p.: 100.8-108.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.64 (d, J=1.9Hz, 1H), 8.12 (d, J=1.9Hz, 1H), 7.65 (d, J=9.1Hz, 2H), 6.82-7.07 (m, 2H), 3.86 (s, 3H).

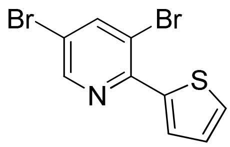
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 160.2, 156.2, 149.0, 143.1, 130.8, 130.7, 119.6, 118.1, 113.4, 55.3.

MS (70 eV, EI), m/z (%) = 343 (M^+, 100), 341 (M^+, 48), 300 (12), 264 (40), 249 (11), 247 (12), 221 (19), 183 (25), 140 (32), 113 (17).

HRMS (EI), m/z calc. for **$C_{12}H_6Br_2NO$** (342.9030): 342.9031 (M^+).

IR (ATR) υ (cm^{-1}) = 3085, 3034, 3010, 2971, 2937, 2912, 2836, 1739, 1607, 1578, 1508, 1434, 1366, 1250, 1218, 1173, 1104, 1060, 1026, 1013, 1000, 905, 844, 836, 770, 756.

3,5-dibromo-2-(thiophen-2-yl)pyridine (8c)



m.p.: 69.6-71.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.56 (d, J=2.2Hz, 1H), 8.13 (dd, J=3.9Hz, 1.1Hz, 1H), 8.09 (d, 1H), 7.49 (dd, J=5.0Hz, 1.11Hz, 1H), 7.13 (dd, J=5.3Hz, 3.9Hz, 1H).

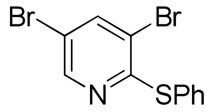
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 149.3, 148.6, 143.9, 142.0, 129.4, 129.2, 127.7, 117.4, 117.1.

MS (70 eV, EI), m/z (%) = 319 (M^+, 100), 317 (M^+, 43), 278 (18), 277 (43), 240 (16), 238 (17), 183 (10), 159 (38).

HRMS (EI), m/z calc. for **$C_9H_5Br_2NS$** (318.8489): 318.8527 (M^+).

IR (ATR) υ (cm^{-1}) = 3066, 3055, 3019, 3006, 1739, 1530, 1475, 1434, 1412, 1370, 1353, 1272, 1108, 1090, 1043, 1025, 966, 896, 852, 833, 775, 754, 740, 708, 692.

3,5-dibromo-2-(phenylthio)pyridine (8d)



m.p.: 67.5-69.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.29 (d, J=2.2Hz, 1H), 7.89 (d, J=2.2Hz, 1H), 7.51-7.59 (m, 2H), 7.41-7.48 (m, 3H).

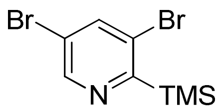
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 158.0, 148.8, 141.4, 135.5, 129.7, 129.3, 129.2, 118.2, 115.8.

MS (70 eV, EI), *m/z* (%) = 345 (M^+, 31), 344 (M^+, 100), 342 (M^+, 45), 185 (11), 133 (7), 109 (8), 65 (7).

HRMS (EI), *m/z* calc. for **$C_{11}H_7Br_2NS$** (344.8645): 344.8656 (M^+).

IR (ATR) υ (cm^{-1}) = 3076, 3050, 3037, 2985, 1575, 1544, 1476, 1438, 1414, 1396, 1347, 1228, 1213, 1138, 1097, 1018, 1000, 886, 786, 744, 713, 705, 687.

3,5-dibromo-2-(trimethylsilyl)pyridine (15)



^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.72 (d, J=2.2Hz, 1H), 7.93 (d, J=1.9Hz, 1H), 0.41 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.5, 148.9, 140.2, 126.5, 120.4, -1.1.

MS (70 eV, EI), *m/z* (%) = 308 (M^+, 21), 306 (M^+, 12), 296 (42), 295 (12), 294 (100), 292 (37), 230 (16), 228 (17), 215 (10).

HRMS (EI), *m/z* calc. for **$C_8H_{11}Br_2NSi$** (306.9028): 306.9008 (M^+).

IR (ATR) υ (cm^{-1}) = 3356, 2989, 2965, 2910, 2890, 1729, 1710, 1553, 1524, 1473, 1326, 1277, 1251, 1178, 1158, 1148, 1129, 1101, 1049, 1020, 1012, 905, 855, 788, 760, 725, 658.

2.2 TYPICAL PROCEDURES

Typical procedure 1 (TP1): Regioselective preparation of heteroarylmagnesium reagents using 1a

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with *i*PrMgCl·LiCl (**1a**; 1.05 equiv, 1.2 M in THF). The substituted dibromoheterocycle (1 equiv) was added as a solution in THF (1.0 M) at the given temperature and continuously stirred for the indicated time. Complete Br/Mg-exchange was monitored by GC-analysis of iodolyzed reaction aliquots using undecane as internal standard.

Typical procedure 2 (TP2): Regioselective preparation of heteroarylmagnesium reagents using 1c and L^2

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 2,4,6-triisopropylmagnesium bromide (**1c**; 1.05 equiv, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L^2**; 1.05 equiv). After stirring for 15 min at 25 °C, the substituted dibromoheterocycle (1 equiv) was added as a solution in THF (1.0 M) at the given temperature and continuously stirred for the indicated time. Complete Br/Mg-exchange was monitored by GC-analysis of iodolyzed reaction aliquots using undecane as internal standard.

Typical procedure 3 (TP3): Cross-coupling reactions of heteroarylmagnesium reagents

To the freshly prepared heteroarylmagnesium reagent was added $ZnCl_2$ (1.0 M in THF, 1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. $Pd(PPh_3)_4$ (4 mol %) and the aryl iodide (0.9 equiv) were added and the reaction mixture was warmed to 25 °C. After stirring for the indicated time, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted three times with EtOAc, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel.

Typical procedure 4 (TP4): Acylation reactions of heteroarylmagnesium reagents

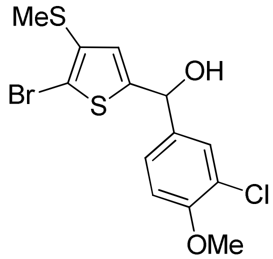
To the freshly prepared heteroarylmagnesium reagent was added $ZnCl_2$ (1.0 M in THF, 1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. CuCN·2LiCl (1.0 M in THF, 20 mol %) and the acyl chloride (0.9 equiv) were added and the reaction mixture was warmed to 25 °C. After stirring for the indicated time, the reaction mixture was quenched with saturated aqueous NH_4Cl/NH_3 solution (10:1), extracted three times with EtOAc, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel.

Typical procedure 5 (TP5): Preparation of sulfoxides using heteroarylmagnesium reagents

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 4-methoxybenzenesulfinyl chloride (0.9 equiv) and cooled to -20 °C. The freshly prepared heteroarylmagnesium reagent (1 equiv) in THF was added dropwise and the reaction mixture was warmed to 25 °C. After stirring for the indicated time, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted three times with EtOAc, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel.

2.3 PREPARATION OF FUNCTIONALIZED THIOPHENES AND THIENOTHIOPHENES OF TYPE 5

Preparation of (5-bromo-4-(methylthio)thiophen-2-yl)(3-chloro-4-methoxyphenyl)-methanol (5a)



Prepared according to **TP1** from 2,5-dibromo-3-(methylthio)thiophene (**2a**; 576 mg, 2 mmol) and *i*PrMgCl·LiCl (**1a**; 1.75 mL, 2.1 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to −20 °C and 3-chloro-4-methoxybenzaldehyde (**4a**; 307 mg, 1.8 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 1:1) furnished **5a** as a yellow oil (504 mg, 74%).

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 7.40 (d, *J*=2.1Hz, 1H), 7.29 (dd, *J*=8.5Hz, 2.1Hz, 1H), 7.08 (d, *J*=8.5Hz, 1H), 6.84 (s, 1H), 6.42 (d, *J*=4.4Hz, 1H), 5.81 (d, *J*=3.5Hz, 1H), 3.79 (s, 3H), 2.39 (s, 3H).

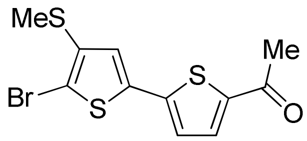
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 154.2, 152.8, 137.6, 131.5, 127.8, 127.1, 126.4, 121.2, 113.4, 113.1, 69.8, 56.5, 20.1.

MS (70 eV, EI), *m/z* (%) = 380 (M^+, 100), 378 (M^+, 78), 363 (42), 361 (27), 236 (21), 170 (38), 128 (15), 108 (14).

HRMS (EI), *m/z* calc. for **$C_{13}H_{12}BrClO_2S_2$** (377.9151): 377.9133 (M^+).

IR (ATR) υ (cm^{-1}) = 3083, 3002, 2965, 2921, 2868, 2837, 1602, 1499, 1460, 1438, 1414, 1283, 1256, 1196, 1183, 1149, 1116, 1061, 1021, 968, 884, 821, 813, 794, 688.

Preparation of 1-(5'-bromo-4'-(methylthio)-[2,2'-bithiophen]-5-yl)ethanone (5b)



Prepared according to **TP1** from 2,5-dibromo-3-(methylthio)thiophene (**2a**; 576 mg, 2 mmol) and *i*PrMgCl·LiCl (**1a**; 1.75 mL, 2.1 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (2.0 mL, 2.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) and 1-(5-iodothiophen-2-yl)ethanone (**4b**; 454 mg, 1.8 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 8:2) afforded **5b** as a red-brown yellow solid (491 mg, 82%).

m.p.: 73.8-75.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.58 (d, *J*=3.9Hz, 1H), 7.17 (s, 1H), 7.12 (d, *J*=3.9Hz, 1H), 2.55 (s, 3H), 2.52 (s, 3H).

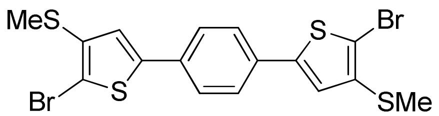
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 190.3, 143.7, 143.2, 137.2, 134.4, 133.2, 128.3, 124.4, 115.5, 26.6, 20.2.

MS (70 eV, EI), *m/z* (%) = 334 (M^+, 45), 332 (M^+, 40), 319 (36), 317 (31), 263 (21), 262 (100), 183 (70), 108 (26), 44 (36), 43 (33).

HRMS (EI), *m/z* calc. for **$C_{11}H_9BrOS_3$** (333.8999): 333.8992 (M^+).

IR (ATR) υ (cm^{-1}) = 3074, 3055, 2994, 2916, 1643, 1500, 1435, 1408, 1354, 1289, 1272, 1074, 1039, 1029, 966, 933, 882, 796, 744, 691, 662.

Preparation of 1,4-bis(5-bromo-4-(methylthio)thiophen-2-yl)benzene (5c)

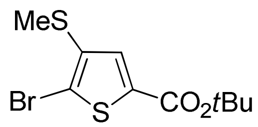


Prepared according to **TP1** from 2,5-dibromo-3-(methylthio)thiophene (**2a**; 576 mg, 2 mmol) and *i*PrMgCl·LiCl (**1a**; 1.75 mL, 2.1 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$

(2.0 mL, 2.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) and 1,4-diiodobenzene (**4c**; 314 mg, 0.95 mmol) in 1 h. Recristallisation from EtOAc afforded **5c** as a pale yellow solid (391 mg, 84%).

m.p.: 182.7-183.3 °C.
^{1}H NMR (400 MHz, CD_2Cl_2) δ (ppm) = 7.55 (s, 4H), 7.25 (s, 2H), 2.52 (s, 6H).
^{13}C NMR (100 MHz, CD_2Cl_2) δ (ppm) = 144.5, 132.8, 132.7, 126.5, 125.8, 115.8, 20.2.
MS (70 eV, EI), *m/z* (%) = 494 (M^+, 55), 492 (M^+, 100), 490 (M^+, 40), 479 (26), 477 (42), 475 (20), 383 (6), 246 (7), 242 (8), 236 (7).
HRMS (EI), *m/z* calc. for $\mathbf{C_{16}H_{12}Br_2S_4}$ (489.8189): 489.8171 (M^+).
IR (ATR) υ (cm^{-1}) = 3085, 3068, 3034, 2991, 2917, 2846, 2822, 1484, 1434, 1418, 1408, 1335, 1319, 1289, 1272, 1169, 1120, 1104, 1020, 1008, 967, 951, 808.

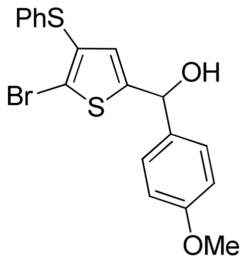
Preparation of *tert*-butyl 5-bromo-4-(methylthio)thiophene-2-carboxylate (5d)



Prepared according to **TP1** from 2,5-dibromo-3-(methylthio)thiophene (**2a**; 576 mg, 2 mmol) and *i*PrMgCl·LiCl (**1a**; 1.75 mL, 2.1 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to –40 °C and di-*tert*-butyl dicarbonate (**4d**; 524 mg, 2.4 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 3 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 50:1) furnished **5d** as a white solid (521 mg, 85%).

m.p.: 48.0-49.8 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.54 (s, 1H), 2.57 (s, 3H), 1.56 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.8, 142.1, 135.4, 134.3, 111.3, 82.5, 28.2, 19.0.
MS (70 eV, EI), *m/z* (%) = 310 (M^+, 32), 308 (M^+, 29), 256 (26), 255 (25), 254 (16), 253 (24), 252 (19), 239 (56), 237 (100), 235 (36), 127 (20).
HRMS (EI), *m/z* calc. for $\mathbf{C_{10}H_{13}BrO_2S_2}$ (307.9540): 307.9532 (M^+).
IR (ATR) υ (cm^{-1}) = 3098, 3008, 2979, 2931, 2920, 1691, 1514, 1391, 1368, 1330, 1266, 1252, 1166, 1152, 1134, 1076, 1031, 850, 835, 799, 746.

Preparation of (5-bromo-4-(phenylthio)thiophen-2-yl)(4-methoxyphenyl)methanol (5e)



Prepared according to **TP1** from 2,5-dibromo-3-(phenylthio)thiophene (**2b**; 350 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to −20 °C and 4-methoxybenzaldehyde (**4e**; 123 mg, 0.9 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 2 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 8.5:1.5) furnished **5e** as a white solid (334 mg, 91%).

m.p.: 94.0-95.7 °C.

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 7.27-7.33 (m, 3H), 7.20 (t, *J*=7.3Hz, 1H), 7.12 (d, *J*=7.2Hz, 2H), 6.81-6.98 (m, 3H), 6.39 (d, *J*=4.5Hz, 1H), 5.83 (d, J=4.5Hz, 1H), 3.70 (s, 3H).

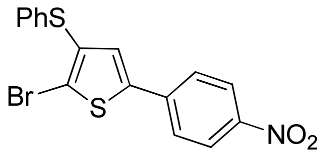
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 159.1, 157.5, 136.2, 136.1, 129.9, 127.8, 127.7, 127.5, 127.2, 125.3, 119.7, 114.2, 70.6, 55.5.

MS (70 eV, EI), *m/z* (%) = 408 (M^+, 58), 406 (M^+, 60), 388 (21), 386 (18), 298 (12), 218 (19), 217 (30), 190 (13), 137 (11), 125 (100), 109 (15), 77 (31).

HRMS (EI), *m/z* calc. for $\mathbf{C_{18}H_{15}BrO_2S_2}$ (405.9697): 405.9680 (M^+).

IR (ATR) υ (cm^{-1}) = 3436, 3070, 3046, 3006, 2957, 2836, 2362, 2339, 1610, 1581, 1515, 1476, 1454, 1439, 1313, 1251, 1173, 1144, 1104, 1033, 1022, 996, 844, 820, 816, 741, 684.

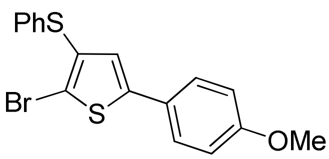
Preparation of 2-bromo-5-(4-nitrophenyl)-3-(phenylthio)thiophene (5f)



Prepared according to **TP1** from 2,5-dibromo-3-(phenylthio)thiophene (**2b**; 350 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 1-iodo-4-nitrobenzene (**4f**; 224 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 100:3) afforded **5f** as a yellow solid (302 mg, 86%).

m.p.: 129.0-130.9 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.21-8.29 (m, 2H), 7.62-7.69 (m, 2H), 7.42 (s, 1H), 7.25-7.39 (m, 5H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 147.3, 144.5, 138.7, 135.2, 132.1, 129.4, 129.3, 128.9, 127.5, 125.9, 124.5, 119.9.
MS (70 eV, EI), *m/z* (%) = 395 (M^+, 10), 393 (M^+, 100), 391 (95), 312 (13), 267 (15), 266 (72), 265 (24), 234 (14), 221 (36), 189 (13), 121 (11), 113 (15), 77 (14), 43 (14).
HRMS (EI), *m/z* calc. for $\mathbf{C_{16}H_{10}BrNO_2S_2}$ (390.9336): 390.9333 (M^+).
IR (ATR) υ (cm^{-1}) = 3092, 3076, 3061, 2932, 2842, 1591, 1578, 1516, 1506, 1477, 1341, 1332, 1108, 1022, 851, 819, 740, 726, 687.

Preparation of 2-bromo-5-(4-methoxyphenyl)-3-(phenylthio)thiophene (5g)



Prepared according to **TP1** from 2,5-dibromo-3-(phenylthio)thiophene (**2b**; 5.25 g, 15 mmol) and *i*PrMgCl·LiCl (**1a**; 13.13 mL, 15.75 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (15 mL, 15.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (867 mg, 0.75 mmol) and 1-iodo-4-methoxybenzene (**4g**; 3.16 g, 13.5 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 50:1) afforded **5g** as a pale yellow solid (4.9 g, 96%).

m.p.: 96.0-98.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.40-7.51 (m, 2H), 7.13-7.34 (m, 6H), 6.85-6.98 (m, 2H), 3.78-3.89 (m, 3H).

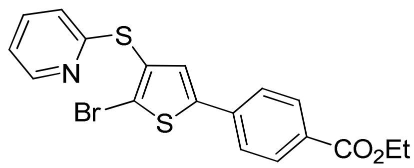
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 160.1, 148.8, 136.7, 129.1, 127.7, 127.0, 126.5, 125.7, 125.6, 125.5, 121.1, 114.5, 55.4

MS (70 eV, EI), *m/z* (%) = 378 (M^+, 100), 376 (M^+, 100), 297 (47), 253 (23), 221 (30), 177 (19), 151 (19), 108 (19), 77 (45), 43 (24).

HRMS (EI), *m/z* calc. for $\mathbf{C_{17}H_{13}BrOS_2}$ (377.9571): 377.9569 (M^+).

IR (ATR) υ (cm^{-1}) = 3071, 3052, 2998, 2962, 2936, 2907, 2831, 1604, 1572, 1527, 1492, 1476, 1436, 1412, 1283, 1247, 1178, 1112, 1023, 813, 800, 738, 688.

Preparation of ethyl 4-(5-bromo-4-(pyridin-2-ylthio)thiophen-2-yl)benzoate (5h)



Prepared according to **TP1** from 2-((2,5-dibromothiophen-3-yl)thio)pyridine (**2c**; 351 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and ethyl 4-iodobenzoate (**4h**; 249 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 8.5:1.5 + 1% NEt_3) afforded **5h** as a pale yellow solid (347 mg, 92%).

m.p.: 102.6-104.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.46 (dd, *J*=3.9Hz, 2.0Hz, 1H), 8.04-8.13 (m, 2H), 7.59-7.68 (m, 2H), 7.55 (td, *J*=7.7Hz, 2.0Hz, 1H), 7.45 (s, 1 H), 7.06 (ddd, *J*=7.5Hz, 5.0Hz, 1.1Hz, 1H), 6.92-7.02 (m, 1H), 4.40 (q, *J*=7.2Hz, 2H), 1.42 (t, *J*=7.1Hz, 3H).

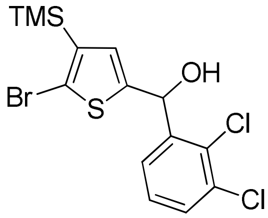
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.9, 159.2, 149.7, 148.2, 137.1, 136.6, 130.5, 130.4, 128.0, 125.8, 125.4, 122.5, 120.5, 120.4, 61.2, 14.3.

MS (70 eV, EI), *m/z* (%) = 421 (M^+, 5), 419 (M^+, 5), 342 (12), 341 (25), 340 (100), 313 (12), 312 (64), 267 (11), 266 (10).

HRMS (EI), *m/z* calc. for $\mathbf{C_{18}H_{14}BrNO_2S_2}$ (418.9649): 418.9617 (M^+).

IR (ATR) υ (cm^{-1}) = 3087, 3068, 3046, 2982, 2957, 2935, 2896, 1704, 1605, 1569, 1562, 1444, 1418, 1276, 1180, 1117, 1107, 1088, 1019, 851, 834, 822, 815, 765, 719, 692.

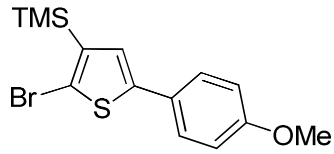
Preparation of (5-bromo-4-(trimethylsilyl)thiophen-2-yl)(2,3-dichlorophenyl)-methanol (5i)



Prepared according to **TP1** from (2,5-dibromothiophen-3-yl)trimethylsilane (**2d**; 628 mg, 2 mmol) and *i*PrMgCl·LiCl (**1a**; 1.75 mL, 2.1 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to −20 °C and 2,3-dichlorobenzaldehyde (**4i**; 315 mg, 1.8 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 2 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 8.5:1.5) furnished **5i** as a colorless oil (635 mg, 86%).

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 7.65-7.69 (m, 1H), 7.59 (dd, *J*=8.0Hz, 1.8Hz, 1H), 7.44 (t, *J*=7.8Hz, 1H), 6.98 (d, *J*=0.8Hz, 1H), 6.65 (d, *J*=4.7Hz, 1H), 6.22 (d, *J*=4.3Hz, 1H), 0.32 (s, 9H).
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 153.6, 144.3, 133.5, 132.1, 130.1, 130.0, 129.3, 129.0, 126.7, 116.1, 67.5, -0.5.
MS (70 eV, EI), *m/z* (%) = 410 (M^+, 35), 408 (M^+, 40), 399 (11), 398 (12), 397 (56), 396 (22), 395 (100), 394 (15), 393 (64), 337 (16), 335 (18), 237 (25), 235 (25), 175 (25), 139 (46), 137 (39), 73 (100).
HRMS (EI), *m/z* calc. for **$C_{14}H_{15}BrCl_2OSSi$** (407.9173): 407.9172 (M^+).
IR (ATR) υ (cm^{-1}) = 3332, 2957, 2897, 2873, 2361, 2349, 1515, 1450, 1419, 1330, 1298, 1264, 1249, 1179, 1154, 1102, 1052, 1027, 993, 837, 816, 788, 773, 754, 742, 731, 697, 655.

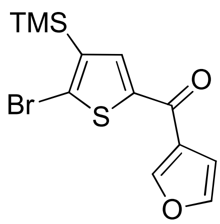
Preparation of (2-bromo-5-(4-methoxyphenyl)thiophen-3-yl)trimethylsilane (5j)



Prepared according to **TP1** from (2,5-dibromothiophen-3-yl)trimethylsilane (**2d**; 3.14 g, 10 mmol) and *i*PrMgCl·LiCl (**1a**; 8.75 mL, 10.5 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (10 mL, 10 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (462 mg, 0.4 mmol) and 1-iodo-4-methoxybenzene (**4g**; 2.57 g, 11 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 100:1) afforded **5j** as a pale yellow solid (3.0 g, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.45-7.55 (m, 2H), 7.19 (s, 1H), 6.88-6.95 (m, 2H), 3.85 (s, 3H), 0.43 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.6, 149.1, 132.7, 127.3, 127.1, 126.1, 117.6, 114.3, 55.4, -0.7.
MS (70 eV, EI), *m/z* (%) = 342 (M^+, 70), 340 (M^+, 42), 327 (35), 325 (21), 203 (52), 173 (27), 139 (31), 137 (28), 74 (22), 73 (30), 45 (68), 44 (100), 43 (32).
HRMS (EI), *m/z* calc. for **$C_{14}H_{17}BrOSSi$** (339.9953): 339.9939 (M^+).
IR (ATR) υ (cm^{-1}) = 3090, 3054, 2997, 2955, 2935, 2899, 2831, 1878, 1606, 1532, 1490, 1456, 1422, 1308, 1288, 1249, 1179, 1108, 1035, 1001, 948, 835, 818, 808, 753, 698.

Preparation of (5-bromo-4-(trimethylsilyl)thiophen-2-yl)(furan-3-yl)methanone (5k)



(2,5-dibromothiophen-3-yl)trimethylsilane (**2d**; 628 mg, 2 mmol) and *i*PrMgCl·LiCl (**1a**; 1.75 mL, 2.1 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the acylation reaction was accomplished according to **TP4** with $ZnCl_2$ (2 mL, 2 mmol, 1.0 M in THF), CuCN·2LiCl (0.2 mL, 0.2 mmol, 1.0M in THF) and furan-2-carbonyl chloride (**4j**; 235 mg, 1.8 mmol) in 8 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 50:1) afforded **5k** as a pale yellow solid (423 mg, 72%).

m.p.: 108.6-110.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.10 (s, 1H), 7.70 (dd, *J*=1.8Hz, 0.7Hz, 1H), 7.42 (dd, *J*=3.6Hz, 0.8Hz, 1H), 6.62 (dd, *J*=3.6Hz, 1.7Hz, 1H), 0.45 (s, 9H).

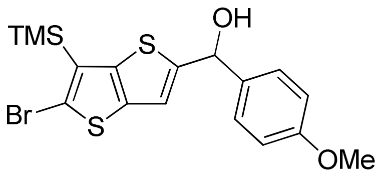
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 172.0, 152.1, 146.7, 145.5, 145.0, 137.6, 119.3, 117.6, 112.6, -1.0.

MS (70 eV, EI), *m/z* (%) = 330 (M^+, 33), 328 (M^+, 31), 316 (12), 315 (72), 313 (68), 163 (28), 139 (17), 99 (16), 95 (100), 73 (16).

HRMS (EI), *m/z* calc. for **$C_{12}H_{13}BrO_2SSi$** (327.9589): 327.9588 (M^+).

IR (ATR) υ (cm^{-1}) = 3137, 3110, 2959, 2362, 2349, 1623, 1566, 1491, 1462, 1396, 1296, 1247, 1226, 1174, 1143, 1124, 1076, 998, 941, 844, 828, 788, 766, 742, 720.

Preparation of (5-bromo-6-(trimethylsilyl)thieno[3,2-*b*]thiophen-2-yl)(4-methoxy-phenyl)methanol (5l)



Prepared according to **TP1** from (2,5-dibromothieno[3,2-*b*]thiophen-3-yl)trimethylsilane (**2e**; 370 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to −20 °C and 4-methoxy-benzaldehyde (**4e**; 123 mg, 0.9 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 2 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 8:2) furnished **5l** as a colorless oil (311 mg, 81%).

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 7.30-7.36 (m, 2H), 7.24 (d, *J*=1.0Hz, 1H), 6.87-6.90 (m, 2H), 6.38 (d, *J*=4.3 Hz, 1H), 5.92 (d, *J*=4.3 Hz, 1H), 3.71 (s, 3H), 0.36 (s, 9H).

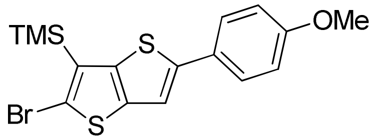
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 159.0, 155.9, 141.9, 141.7, 136.8, 135.5, 127.9, 117.5, 114.0, 108.8, 71.0, 55.5, -0.5.

MS (70 eV, EI), *m/z* (%) = 426 (M^+, 44), 424 (M^+, 22), 412 (60), 411 (74), 409 (51), 397 (19), 395 (22), 332 (11), 331 (14), 139 (12), 137 (13), 136 (12), 135 (100), 121 (14), 77 (21), 75 (24), 73 (39).

HRMS (EI), *m/z* calc. for **$C_{17}H_{17}BrO_2S_2Si$** (423.9623): 423.9619 (M^+).

IR (ATR) υ (cm^{-1}) = 3393, 3075, 3034, 2999, 2954, 2896, 2865, 2835, 2060, 1610, 1586, 1510, 1328, 1304, 1246, 1171, 1110, 1032, 1002, 829, 757, 699, 664.

Preparation of (2-bromo-5-(4-methoxyphenyl)thieno[3,2-*b*]thiophen-3-yl)trimethyl-silane (5m)



Prepared according to **TP1** from (2,5-dibromothieno[3,2-*b*]thiophen-3-yl)trimethylsilane (**2e**; 370 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 1-iodo-4-methoxybenzene (**4g**; 258 mg, 1.1 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 100:1) afforded **5m** as white solid (381 mg, 96%).

m.p.: 133.7-135.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.53-7.60 (m, 2H), 7.37 (s, 1H), 6.92-6.98 (m, 2H), 3.86 (s, 3H), 0.41-0.53 (m, 9H).

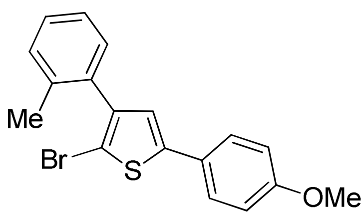
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.7, 147.6, 143.0, 141.8, 135.7, 127.3, 127.2, 114.7, 114.4, 108.8, 55.4, -0.8.

MS (70 eV, EI), *m/z* (%) = 398 (M^+, 100), 396 (M^+, 86), 383 (40), 381 (36), 326 (33), 324 (32), 311 (16), 309 (17), 260 (12), 259 (66), 216 (12), 75 (16), 73 (19), 43 (19).

HRMS (EI), *m/z* calc. for **$C_{16}H_{17}BrOS_2Si$** (395.9673): 395.9662 (M^+).

IR (ATR) υ (cm^{-1}) = 3080, 3000, 2955, 2940, 2895, 2834, 1603, 1523, 1488, 1438, 1425, 1291, 1247, 1185, 1030, 1007, 965, 874, 837, 828, 813, 802, 789, 756, 698, 681.

Preparation of 2-bromo-5-(4-methoxyphenyl)-3-(o-tolyl)thiophene (5n)



Prepared according to **TP1** from 2,5-dibromo-3-(*o*-tolyl)thiophene (**2f**; 332 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 1-iodo-4-methoxybenzene (**4g**; 211 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 100:1) afforded **5n** as a pale yellow oil (310 mg, 96%).

m.p.: 56.9-58.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.48-7.54 (m, 2H), 7.24-7.38 (m, 4H), 6.88-6.98 (m, 2H) 7.15 (s, 1H), 3.85 (s, 3H), 2.33 (s, 3H).

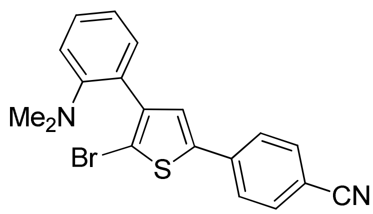
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.7, 143.8, 138.1, 136.1, 132.3, 131.2, 130.2, 129.0, 126.8, 126.1, 125.6, 124.8, 114.4, 110.2, 55.4, 20.2.

MS (70 eV, EI), *m/z* (%) = 360 (M^+, 100), 358 (M^+, 95), 345 (12), 338 (11), 279 (15), 277 (10), 263 (9), 235 (12), 203 (15), 171 (8), 115 (9).

HRMS (EI), *m/z* calc. for **$C_{18}H_{15}BrOS$** (358.0027): 358.0024 (M^+).

IR (ATR) υ (cm^{-1}) = 3092, 3058, 3012, 2955, 2933, 2904, 2834, 1605, 1515, 1486, 1460, 1450, 1439, 1289, 1250, 1178, 1111, 1024, 972, 819, 808, 798, 756, 750, 720, 694, 663.

Preparation of 4-(5-bromo-4-(2-(dimethylamino)phenyl)thiophen-2-yl)benzonitrile (5o)



Prepared according to **TP1** from 2-(2,5-dibromothiophen-3-yl)-*N*,*N*-dimethylaniline (**2g**; 361 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 4-iodobenzonitrile (**4k**; 206 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 50:1 + 1% NEt_3) afforded **5o** as a pale yellow solid (312 mg, 91%).

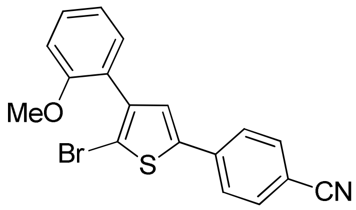
m.p.: 111.8-113.1 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.68 (s, 4H), 7.43 (dd, *J*=7.7Hz, 1.7Hz, 1H), 7.31-7.40 (m, 2H), 7.08 (dd, *J*=8.2Hz, 1.1Hz, 1H), 7.03 (td, *J*=7.4Hz, 1.1Hz, 1H), 2.67 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 152.3, 141.1, 139.5, 137.7, 132.8, 132.5, 129.9, 127.9, 125.6, 124.4, 121.1, 118.7, 118.1, 111.0, 110.2, 43.2.

MS (70 eV, EI), *m/z* (%) = 384 (M^+, 20), 382 (M^+, 19), 304 (23), 303 (100), 301 (29), 289 (13), 288 (60), 287 (11), 269 (10), 146 (13), 43 (26).
HRMS (EI), *m/z* calc. for **$C_{19}H_{15}BrN_2S$** (382.0139): 382.0132 (M^+).
IR (ATR) υ (cm^{-1}) = 3063, 3044, 2969, 2934, 2858, 2830, 2784, 2223, 1602, 1594, 1484, 1451, 1440, 1330, 1316, 1176, 1159, 1049, 974, 946, 935, 837, 827, 817, 763, 742, 696.

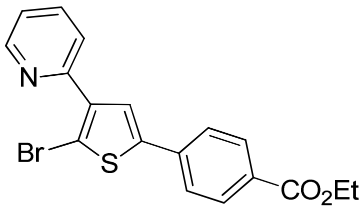
Preparation of 4-(5-bromo-4-(2-methoxyphenyl)thiophen-2-yl)benzonitrile (5p)



Prepared according to **TP1** from 2,5-dibromo-3-(2-methoxyphenyl)thiophene (**2h**; 348 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 4-iodobenzonitrile (**4k**; 206 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 9:1) afforded **5p** as a pale yellow solid (300 mg, 90%).

m.p.: 128.6-130.5 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.67 (s, 4H), 7.40-7.50 (m, 2H), 7.38 (s, 1H), 7.01-7.09 (m, 2H), 3.88 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 157.0, 141.2, 137.6, 136.3, 132.8, 132.0, 130.7, 128.2, 125.7, 120.9, 120.5, 118.6, 111.4, 111.1, 111.1, 55.7.
MS (70 eV, EI), *m/z* (%) = 371 (M^+, 100), 369 (M^+, 95), 276 (19), 275 (99), 246 (16), 146 (9).
HRMS (EI), *m/z* calc. for **$C_{18}H_{12}BrNOS$** (368.9823): 368.9790 (M^+).
IR (ATR) υ (cm^{-1}) = 3086, 3059, 3016, 2979, 2949, 2845, 2224, 1597, 1485, 1464, 1438, 1330, 1251, 1178, 1166, 1112, 1011, 971, 844, 828, 817, 790, 757, 738, 721, 701, 660.

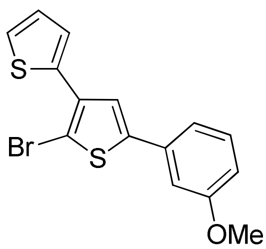
Preparation of ethyl 4-(5-bromo-4-(pyridin-2-yl)thiophen-2-yl)benzoate (5q)



Prepared according to **TP1** from 2-(2,5-dibromothiophen-3-yl)pyridine (**2i**; 319 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and ethyl 4-iodobenzoate (**4h**; 249 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 8.5:1.5 + 1% NEt_3) afforded **5q** as a white solid (310 mg, 89%).

m.p.: 104.6-106.2 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.63 (dd, *J*=5.8Hz, 2.0Hz, 1H), 8.36 (dt, *J*=8.2Hz, 0.9Hz, 1H), 8.36 (dt, *J*=8.2Hz, 0.9Hz, 1H), 7.99-8.13 (m, 2H), 7.77 (td, *J*=7.8Hz, 1.8Hz, 1H), 7.63-7.72 (m, 2H), 7.37 (s, 1H), 7.24 (ddd, *J*=7.6Hz, 4.8Hz, 1.1Hz, 1H), 4.40 (q, *J*=7.2Hz, 2H), 1.41 (t, *J*=7.2 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.0, 151.0, 149.6, 143.6, 139.3, 137.0, 136.5, 130.3, 130.0, 129.5, 125.2, 122.7, 120.6, 108.2, 61.1, 14.3.
MS (70 eV, EI), *m/z* (%) = 389 (M^+, 100), 387 (M^+, 96), 359 (21), 342 (24), 235 (25), 234 (12), 190 (5).
HRMS (EI), *m/z* calc. for **$C_{18}H_{14}BrNO_2S$** (386.9929): 386.9951 (M^+).
IR (ATR) υ (cm^{-1}) = 3069, 2990, 2979, 2931, 2902, 2871, 1706, 1603, 1579, 1505, 1469, 1434, 1409, 1365, 1266, 1180, 1109, 1100, 1015, 855, 832, 781, 767, 742, 714, 694.

Preparation of 2'-bromo-5'-(3-methoxyphenyl)-2,3'-bithiophene (5r)

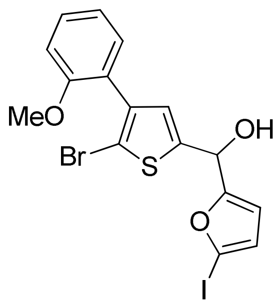


Prepared according to **TP1** from 2',5'-dibromo-2,3'-bithiophene (**2j**; 324 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at -20 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 1-iodo-3-

methoxybenzene (**4l**; 211 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 40:1) afforded **5r** as a yellow oil (261 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.43-7.49 (m, 1H), 7.34-7.38 (m, 1H), 7.31 (t, *J*=7.9 Hz, 1H), 7.22 (bs, 1H), 7.13-7.18 (m, 1H), 7.06-7.12 (m, 2H), 6.88 (dd, *J*=8.0Hz, 2.5Hz, 1H), 3.86 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 160.1, 142.2, 134.4, 134.1, 131.5, 130.1, 127.6, 127.3, 126.6, 126.1, 118.0, 113.9, 111.1, 108.1, 55.4.
MS (70 eV, EI), *m/z* (%) = 352 (M^+, 100), 350 (M^+, 93), 309 (16), 307 (15), 240 (3), 228 (4), 176 (4), 175 (3), 108 (3).
HRMS (EI), *m/z* calc. for $\mathbf{C_{15}H_{11}BrOS_2}$ (275.9820): 275.9817 (M^+).
IR (ATR) υ (cm^{-1}) = 3101, 3068, 2999, 2955, 2934, 2832, 1597, 1578, 1480, 1462, 1429, 1288, 1272, 1260, 1201, 1166, 1045, 837, 824, 809, 770, 682.

Preparation of (5-bromo-4-(2-methoxyphenyl)thiophen-2-yl)(5-iodofuran-2-yl)-methanol (5s)



Prepared according to **TP1** from 2,5-dibromo-3-(2-methoxyphenyl)thiophene (**2h**; 348 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to 0 °C and $ZnCl_2$ (0.5 mL, 0.5 mmol, 1.0 M in THF) was added. The reaction mixture was allowed to warm to 25 °C in 30 min. Then, 5-iodofuran-2-carbaldehyde (**4m**; 200 mg, 0.9 mmol) in THF was added and the reaction mixture was continuously stirred for 2 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 8:2) furnished **5s** as a brown oil (266 mg, 60%).

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 7.40 (ddd, *J*=15.6Hz, 7.4Hz, 1.8Hz, 1H), 7.31 (dd, *J*=7.6Hz, 1.8 Hz, 1H), 7.11 (dd, *J*=8.4Hz, 1.0Hz, 1H), 7.00 (dt, *J*=7.5Hz, 1.2Hz, 1H), 6.93 (d, *J*=1.0Hz, 1H), 6.64 (d, *J*=3.1Hz, 1H), 6.56 (d, *J*=5.3Hz, 1H), 6.30 (dd, *J*=3.2Hz, 0.7Hz, 1H), 5.94 (d, *J*=5.3Hz, 1H), 3.76 (s, 3H).

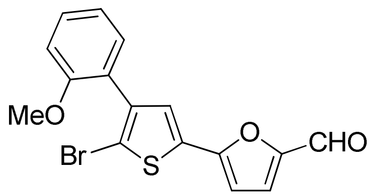
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 161.1, 157.1, 146.9, 133.9, 132.1, 131.0, 127.4, 121.0, 121.0, 120.8, 112.2, 110.4, 108.6, 91.8, 64.6, 56.0.

MS (70 eV, EI), *m/z* (%) = 492 (M^+, 88), 490 (M^+, 100), 488 (17), 475 (40), 473 (37), 411 (17), 364 (14), 362 (12), 224 (16), 221 (25), 190 (27), 128 (15), 127 (12), 115 (10).

HRMS (EI), *m/z* calc. for **$C_{16}H_{12}BrIO_3S$** (489.8735): 489.8737 (M^+).

IR (ATR) υ (cm^{-1}) = 3070, 3051, 2960, 2930, 2894, 2362, 2337, 1775, 1699, 1641, 1596, 1458, 1430, 1394, 1328, 1248, 1174, 1148, 1119, 1045, 1019, 956, 927, 748.

Preparation of 5-(5-bromo-4-(2-methoxyphenyl)thiophen-2-yl)furan-2-carbaldehyde (5t)



Prepared according to **TP1** from 2,5-dibromo-3-(2-methoxyphenyl)thiophene (**2h**; 348 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 5-iodofuran-2-carbaldehyde (**4m**; 200 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 100:1) afforded **5t** as a light brown solid (249 mg, 76%).

m.p.: 114.8-116.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.63 (s, 1H), 7.38-7.52 (m, 3H), 7.30 (d, *J*=3.6Hz, 1H), 6.99-7.08 (m, 2H), 6.69 (d, *J*=3.9Hz, 1H), 3.87 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 176.9, 156.9, 153.5, 151.7, 136.6, 132.0, 131.1, 130.7, 128.9, 120.6, 120.5, 111.4, 110.9, 107.9, 55.6.

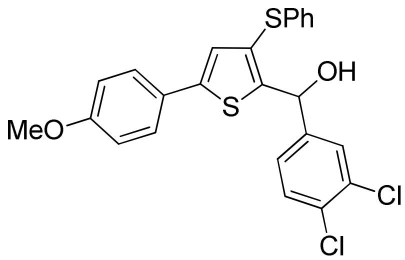
MS (70 eV, EI), *m/z* (%) = 364 (M^+, 100), 362 (M^+, 99), 269 (12), 268 (74), 211 (33), 139 (11).

HRMS (EI), *m/z* calc. for **$C_{16}H_{11}BrO_3S$** (361.9612): 361.9604 (M^+).

IR (ATR) υ (cm^{-1}) = 3125, 3107, 3096, 2998, 2982, 2950, 2925, 2843, 1664, 1484, 1470, 1461, 1393, 1280, 1251, 1238, 1034, 1016, 961, 893, 794, 762.

*2.3.1 FURTHER FUNCTIONALIZATION OF MONOBROMOTHIOPHENE **5g***

Preparation of (3,4-dichlorophenyl)(5-(4-methoxyphenyl)-3-(phenylthio)thiophen-2-yl)methanol (7a)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with *i*PrMgCl·LiCl (**1a**; 0.92 ml, 1.1 mmol, 1.2 M in THF). 2-bromo-5-(4-methoxy-phenyl)-3-(phenylthio)thiophene (**5g**; 377 mg, 1.0 mmol) was added as a solution in THF (1.0 M) at 25 °C and continuously stirred for 1 h. Complete Br/Mg-exchange was monitored by GC-analysis of iodolyzed reaction aliquots using undecane as internal standard. Subsequently, the reaction mixture was cooled to −20 °C and 3,4-dichlorobenzaldehyde (**4n**; 158 mg, 0.9 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 6:4) furnished **7a** as a white solid (328 mg, 77%).

m.p.: 108.6-110.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.44-7.51 (m, 2H), 7.42 (dd, *J*=1.4 Hz, 0.8 Hz,1H), 7.22-7.31 (m, 3H), 7.10-7.21 (m, 5H), 6.85-6.92 (m, 2H), 6.10 (d, *J*=3.0 Hz, 1H), 3.82 (s, 3H), 2.45 (d, *J*=3.6 Hz, 1H).

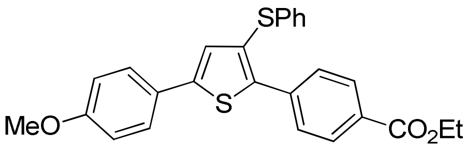
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.9, 150.5, 149.3, 142.8, 137.8, 132.5, 131.3, 130.3, 129.2, 128.1, 127.1, 126.8, 126.3, 126.2, 125.4, 124.4, 121.4, 114.4, 69.4, 55.4.

MS (70 eV, EI), *m/z* (%) = 472 (M^+, 100), 456 (11), 217 (13), 190 (15), 175 (36), 173 (42), 151 (15), 145 (20), 121 (11), 111 (19), 77 (30).

HRMS (EI), *m/z* calc. for $\mathbf{C_{24}H_{18}Cl_2O_2S_2}$ (472.0125): 472.0114 (M^+).

IR (ATR) υ (cm^{-1}) = 3533, 3466, 3070, 3049, 3003, 2955, 2928, 2897, 2836, 1603, 1581, 1571, 1505, 1478, 1463, 1417, 1291, 1251, 1177, 1031, 1024, 828, 822, 772, 739, 733, 687.

Preparation of ethyl 4-(5-(4-methoxyphenyl)-3-(phenylthio)thiophen-2-yl)benzoate (7b)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with *i*PrMgCl·LiCl (**1a**; 0.92 ml, 1.1 mmol, 1.2 M in THF). 2-bromo-5-(4-methoxy-phenyl)-3-(phenylthio)thiophene (**5g;** 377 mg, 1.0 mmol) was added as a solution in THF (1.0 M) at 25 °C and continuously stirred for 1 h. Complete Br/Mg-exchange was monitored by GC-analysis of iodolyzed reaction aliquots using undecane as internal standard. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and ethyl 4-iodobenzoate (**4h**; 249 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 9:1) afforded **7b** as a pale yellow solid (293 mg, 73%).

m.p.: 129.4-132.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.06 (d, *J*=8.6Hz, 2H), 7.50-7.69 (m, 4H), 7.36 (s, 1H), 7.12-7.28 (m, 5H), 6.94 (d, *J*=8.9 Hz, 2H), 4.39 (q, *J*=7.1 Hz, 2H), 3.84 (s, 3H), 1.40 (t, *J*=7.2 Hz, 3H)

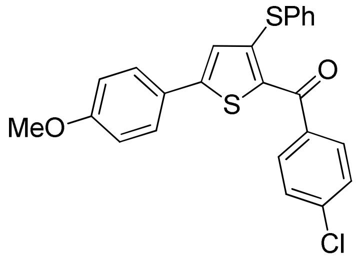
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.4, 159.9, 148.2, 147.6, 139.8, 138.6, 129.5, 129.1, 128.7, 127.1, 126.9, 126.2, 126.1, 126.1, 124.5, 124.2, 114.5, 61.0, 55.4, 14.3.

MS (70 eV, EI), *m/z* (%) = 446 (M^+, 100), 403 (7), 296 (6), 281 (9), 221 (12), 200 (8), 77 (12).

HRMS (EI), *m/z* calc. for $\mathbf{C_{26}H_{22}O_3S_2}$ (446.1010): 446.1004 (M^+).

IR (ATR) υ (cm^{-1}) = 3071, 3050, 3000, 2983, 2928, 2904, 2852, 2830, 1709, 1607, 1581, 1517, 1499, 1428, 1269, 1250, 1183, 1176, 1101, 1024, 851, 824, 798, 773, 738, 702, 690.

Preparation of (4-chlorophenyl)(5-(4-methoxyphenyl)-3-(phenylthio)thiophen-2-yl)methanone (7c)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with *i*PrMgCl·LiCl (**1a**; 0.92 ml, 1.1 mmol, 1.2 M in THF). 2-bromo-5-(4-methoxy-phenyl)-3-(phenylthio)thiophene (**5g;** 377 mg, 1.0 mmol) was added as a solution in THF (1.0 M) at 25 °C and continuously stirred for 1 h. Complete Br/Mg-exchange was monitored by GC-analysis of iodolyzed reaction aliquots using undecane as internal standard. Subsequently, the acylation reaction was accomplished according to **TP4** with $ZnCl_2$ (1 mL, 1 mmol, 1.0 M in THF), CuCN·2LiCl (0.1 mL, 0.1 mmol, 1.0 M in THF) and 4-chlorobenzoyl chloride (**4o**; 158 mg, 0.9 mmol) in 8 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 9:1) afforded **7c** as a pale yellow oil (274 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.74-7.85 (m, 2H), 7.50-7.65 (m, 2H), 7.28-7.50 (m, 7H), 7.23-7.27 (m, 1H), 6.78-6.91 (m, 2H),3.80 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 189.1, 159.7, 147.6, 142.9, 138.7, 137.4, 137.0, 134.2, 133.1, 130.7, 129.6, 129.2, 128.7, 126.9, 125.8, 123.6, 114.4, 55.4.

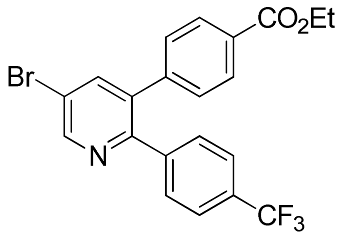
MS (70 eV, EI), *m/z* (%) = 436 (M^+, 100), 421 (12), 325 (5), 281 (5), 253 (5), 221 (8), 141 (14), 139 (42).

HRMS (EI), *m/z* calc. for $\mathbf{C_{24}H_{17}ClO_2S_2}$ (436.0358): 436.0359 (M^+).

IR (ATR) υ (cm^{-1}) = 3054, 2998, 2953, 2926, 2869, 2845, 2834, 1630, 1607, 1585, 1536, 1500, 1421, 1407, 1292, 1248, 1172, 1087, 1031, 1007, 998, 823, 806, 788, 760, 746, 688.

2.4 Preparation of Functionalized Pyridines of Type ***10***

Preparation of ethyl 4-(5-bromo-2-(4-(trifluoromethyl)phenyl)pyridin-3-yl)benzoate (10a)



Prepared according to **TP1** from 3,5-dibromo-2-(4-(trifluoromethyl)phenyl)pyridine (**8a**; 381 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at -55 °C in 2 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and ethyl 4-iodobenzoate (**4h**; 249 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 9:1 + 1% NEt_3) afforded **10a** as a white solid (354 mg, 88%).

m.p.: 97.5-99.1 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.80 (d, *J*=2.2Hz, 1H), 7.99-8.02 (m, 2H), 7.92 (d, *J*=2.2Hz, 1H), 7.51 (d, *J*=8.2Hz, 2H), 7.44 (d, *J*=8.2Hz, 2H), 7.23-7.26 (m, 2H), 4.39 (q, *J*=7.4Hz, 2H), 1.41 (t, *J*=7.4Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 166.0, 154.0, 150.0, 142.4, 142.2 (q, *J*=1.1Hz), 140.7, 136.8, 130.3 (q, *J*=32.8Hz), 130.2, 130.0, 129.9, 129.4, 125.1 (q, *J*=3.7Hz), 123.9 (q, *J*=272.4Hz), 119.9, 61.2, 14.3.

MS (70 eV, EI), *m/z* (%) = 451 (M^+, 97), 450 (M^+, 100), 449 (M^+, 95), 448 (M^+, 85), 421 (32), 419 (35), 406 (21), 404 (21), 378 (15), 376 (17), 297 (31), 296 (15), 228 (11), 227 (11).

HRMS (EI), *m/z* calc. for $\mathbf{C_{21}H_{15}BrF_3NO_2}$ (449.0238): 449.0231 (M^+).

IR (ATR) υ (cm^{-1}) = 3055, 2982, 2940, 2904, 1705, 1608, 1426, 1368, 1323, 1310, 1288, 1273, 1166, 1120, 1111, 1101, 1068, 1024, 1009, 854, 783, 769, 715, 706

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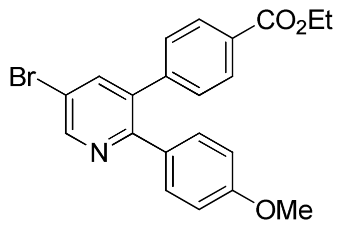
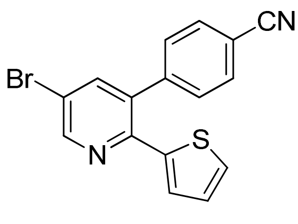
Preparation of ethyl 4-(5-bromo-2-(4-methoxyphenyl)pyridin-3-yl)benzoate (10b)



Prepared according to **TP1** from 3,5-dibromo-2-(4-methoxyphenyl)pyridine (**8b**; 343 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at -78 °C in 2 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and ethyl 4-iodobenzoate (**4h**; 249 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 8.5:1.5 + 1% NEt_3) afforded **10b** as a white solid (236 mg, 64%).

m.p.: 157.5-160.1 °C.
^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.71 (d, *J*=2.2Hz, 1H), 7.91-8.02 (m, 2H), 7.82 (d, *J*=2.2Hz, 1H), 7.14-7.32 (m, 4H), 6.68-6.79 (m, 2H), 4.36 (q, *J*=7.1Hz, 2H), 3.76 (s, 3H), 1.38 (t, *J*=7.1Hz, 3H).
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 166.2, 159.7, 155.3, 149.6, 143.4, 140.4, 136.1, 131.1, 131.0, 129.7, 129.7, 129.3, 118.4, 113.6, 61.1, 55.2, 14.3.
MS (70 eV, EI), *m/z* (%) = 413 (M^+, 91), 411 (M^+, 100), 410 (M^+, 61), 384 (27), 382 (26), 340 (11), 339 (11), 338 (10).
HRMS (EI), *m/z* calc. for $\mathbf{C_{21}H_{18}BrNO_3}$ (411.0470): 411.0473 (M^+).
IR (ATR) υ (cm^{-1}) = 3062, 3003, 2979, 2961, 2936, 2843, 1708, 1604, 1511, 1424, 1402, 1368, 1308, 1283, 1271, 1252, 1175, 1115, 1098, 1043, 1026, 1022, 1010, 1004, 909, 860, 841, 793, 782, 772, 706.

Preparation of 4-(5-bromo-2-(thiophen-2-yl)pyridin-3-yl)benzonitrile (10c)



Prepared according to **TP1** from 3,5-dibromo-2-(thiophen-2-yl)pyridine (**8c**; 343 mg, 1 mmol) and *i*PrMgCl·LiCl (**1a**; 0.88 mL, 1.05 mmol, 1.2 M in THF) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 4-iodobenzonitrile

(**4k**; 206 mg, 0.9 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 8.5:1.5 + 1% NEt_3) afforded **10c** as a white solid (228 mg, 74%).

m.p.: 192.0-193.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.68 (d, *J*=2.2Hz, 1H), 7.66-7.81 (m, 3H), 7.39-7.51 (m, 2H), 7.34 (dd, *J*=5.3Hz, 1.1Hz, 1H), 6.84 (dd, *J*=5.1Hz, 3.7Hz, 1H), 6.54 (dd, *J*=3.9Hz, 1.1Hz, 1H) .

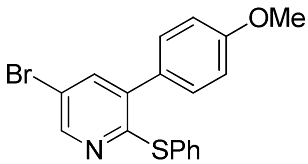
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 150.0, 148.7, 143.3, 142.3, 140.4, 134.0, 132.7, 130.0, 128.5, 128.5, 127.7, 118.3, 118.1, 112.5.

MS (70 eV, EI), *m/z* (%) = 342 (M^+, 100), 341 (M^+, 79), 340 (M^+, 100), 339 (M^+, 60), 261 (13), 260 (36).

HRMS (EI), *m/z* calc. for **$C_{16}H_9BrN_2S$** (339.9670): 339.9667 (M^+).

IR (ATR) υ (cm^{-1}) = 3096, 3092, 3064, 3027, 2956, 2924, 2851, 2238, 1606, 1536, 1505, 1436, 1397, 1268, 1188, 1180, 1107, 1015, 971, 909, 858, 841, 832, 823, 774, 704, 662.

Preparation of 5-bromo-3-(4-methoxyphenyl)-2-(phenylthio)pyridine (10d)



Prepared according to **TP1** from 3,5-dibromo-2-(phenylthio)pyridine (**8d**; 343 mg, 1 mmol) and *i*$Pr_2Mg{\cdot}LiCl$ (**1a**; 0.5 mL, 0.55 mmol, 1.1 M in THF) at -65 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 1-iodo-4-methoxybenzene (**4g**; 211 mg, 0.9 mmol) in 12 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 100:3 + 1% NEt_3) afforded **10d** as a white solid (199 mg, 60%).

m.p.: 107.8-109.8 °C.

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 8.36 (d, *J*=2.4Hz, 1H), 7.78 (d, *J*=2.4Hz, 1H), 7.35-7.44 (m, 7H), 7.01-7.05 (m, 2H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 160.0, 156.0, 148.8, 139.6, 137.3, 135.2, 130.9, 130.7, 129.6, 129.1, 128.8, 117.2, 114.5, 55.7.

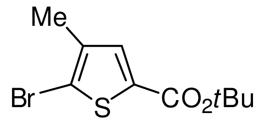
MS (70 eV, EI), *m/z* (%) = 374 (M^+, 23), 373 (M^+, 100), 371 (M^+, 88), 328 (12), 140 (29), 88 (10), 61 (12), 44 (29), 43 (58).

HRMS (EI), *m/z* calc. for **$C_{18}H_{14}BrNOS$** (370.9979): 370.9971 (M^+).

IR (ATR) ʋ (cm^{-1}) = 3039, 3009, 2963, 2940, 2837, 2361, 2339, 1610, 1513, 1440, 1395, 1383, 1290, 1283, 1245, 1176, 1126, 1084, 1032, 1020, 1003, 903, 833, 815, 747, 683, 664.

*2.5 PREPARATION OF FUNCTIONALIZED HETEROCYCLES OF TYPE **14** AND **17***

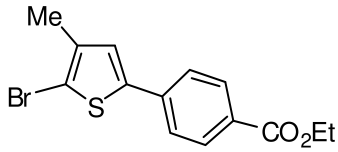
Preparation of *tert*-butyl 5-bromo-4-methylthiophene-2-carboxylate (14a)



Prepared according to **TP2** from 2,5-dibromo-3-(methylthio)thiophene (**11a**; 512 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L**$^{\mathbf{2}}$; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the reaction mixture was cooled to −40 °C and di-*tert*-butyl dicarbonate (**4d**; 524 mg, 2.4 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 4 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 100:1) furnished **14a** as a yellow oil (460 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.39 (s, 1H), 2.19 (s, 3H), 1.56 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 160.6, 138.2, 134.5, 134.1, 116.7, 82.1, 28.2, 15.2.
MS (70 eV, EI), *m/z* (%) = 278 (M^+, 14), 276 (M^+, 15), 223 (10), 222 (100), 221 (12), 220 (100), 205 (43), 203 (44), 186 (26), 141 (60), 96 (24), 69 (10), 57 (60), 55 (21).
HRMS (EI), *m/z* calc. for **$C_{10}H_{13}BrO_2S$** (275.9820): 275.9817 (M^+).
IR (ATR) ʋ (cm^{-1}) = 2978, 2932, 1702, 1426, 1368, 1296, 1254, 1156, 1074, 848, 818, 798, 748, 718.

Preparation of ethyl 4-(5-bromo-4-methylthiophen-2-yl)benzoate (14b)



Prepared according to **TP2** from 2,5-dibromo-3-(methylthio)thiophene (**11a**; 512 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L^2**; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (2.0 mL, 2.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (92 mg, 0.04 mmol) and ethyl 4-iodobenzoate (**4h**; 498 mg, 1.8 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 95:5) afforded **14b** as a pale yellow solid (556 mg, 83%).

m.p.: 89.2-90.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.03 (d, *J*=8.8Hz, 2H), 7.54 (d, *J*=8.6Hz, 2H), 7.09 (s, 1H), 4.39 (q, *J*=7.1Hz, 2H), 2.22 (s, 3H), 1.4 (t, *J*=7.1Hz, 3H).

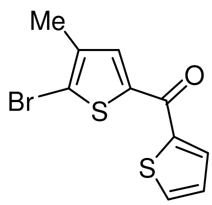
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.1, 142.1, 138.6, 137.8, 130.3, 129.4, 126.2, 124.9, 110.4, 61.0, 15.3, 14.4.

MS (70 eV, EI), *m/z* (%) =327 (14), 326 (M^+, 100), 325 (14), 324 (M^+, 93), 298 (33), 296 (30), 281 (57), 279 (56), 217 (11), 172 (32), 171 (31).

HRMS (EI), *m/z* calc. for **$C_{14}H_{13}BrO_2S$** (323.9820): 323.9807 (M^+).

IR (ATR) υ (cm^{-1}) = 3076, 2984, 2906, 1704, 1604, 1510, 1472, 1438, 1364, 1272, 1232, 1186, 1128, 1110, 1020, 850, 764, 690.

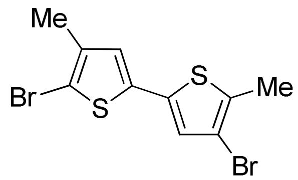
Preparation of (5-bromo-4-methylthiophen-2-yl)(thiophen-2-yl)methanone (14c)



Prepared according to **TP2** from 2,5-dibromo-3-methylthiophene (**11a**; 512 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L^2**; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the acylation reaction was accomplished according to **TP4** with $ZnCl_2$ (2 mL, 2 mmol, 1.0 M in THF), CuCN·2LiCl (0.2 mL, 0.2 mmol, 1.0 M in THF) and thiophene-2-carbonyl chloride (**4p**; 352 mg, 2.4 mmol) in 4 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 95:5) afforded **14c** an off-white solid (488 mg, 85%).

m.p.: 100.2-101.4 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.85 (dd, *J*=3.8Hz, 1.1Hz, 1H), 7.69 (dd, *J*=4.9Hz, 1.1Hz, 1H), 7.57 (s, 1H), 7.17 (dd, *J*=5.0Hz, 3.8Hz, 1H), 2.25 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 177.6, 142.2, 141.8, 138.7, 134.6, 133.6, 133.0, 128.0, 120.0, 15.4.
MS (70 eV, EI), *m/z* (%) =289 (11), 288 (M^+, 100), 287 (11), 286 (M^+, 93), 207 (13), 205 (37), 203 (36), 111 (77), 96 (11).
HRMS (EI), *m/z* calc. for **$C_{10}H_7BrOS_2$** (285.9122): 285.9117 (M^+).
IR (ATR) υ (cm^{-1}) = 3004, 2362, 2340, 1740, 1658, 1582, 1522, 1432, 1366, 1228, 1222, 1204, 1098, 1056, 780, 706.

Preparation of 5,5'-dibromo-4,4'-dimethyl-2,2'-bithiophene (14d)



Prepared according to **TP2** from 2,5-dibromo-3-methylthiophene (**11a**; 1.02 g, 4 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 6.0 mL, 4.2 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L^2**; 672 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, at -40 °C, $ZnCl_2$ (2 mL, 2 mmol, 1 M in THF) and CuCN·2LiCl (2 mL, 2 mmol, 1 M in THF) were successively added and continuously stirred for 10 min. The reaction mixture was added dropwise to a solution of chloranil (1.47 g, 6 mmol) in THF (15 mL) at 0 °C. Then, the solution was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (5x 10 mL). The combined organic phases were washed with aq. NH_3 (2 M, 2x 30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **14d** as a pale yellow solid (612 mg, 87%).

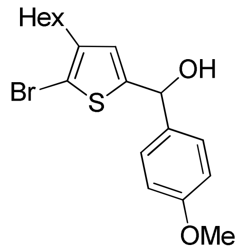
m.p.: 106.2-107.8 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.77 (s, 2H), 2.17 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 138.1, 135.9, 125.5, 108.4, 15.2.

MS (70 eV, EI), *m/z* (%) = 354 (M^+, 51), 353 (10), 352 (M^+, 100), 350 (M^+, 43), 229 (10), 192 (19), 191 (11).

HRMS (EI), *m/z* calc. for $\mathbf{C_{10}H_8{}^{79}Br_2S_2}$ (349.8434): 349.8422 (M^+).

IR (ATR) υ (cm^{-1}) = 3054, 2916, 1740, 1634, 1544, 1410, 1374, 1318, 1186, 1022, 994, 942, 834, 812, 734.

Preparation of (5-bromo-4-hexylthiophen-2-yl)(4-methoxyphenyl)methanol (14e)



Prepared according to **TP2** from 2,5-dibromo-3-hexylthiophene (**11b**; 652 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) ($\mathbf{L^2}$; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the reaction mixture was cooled to −20 °C and 4-methoxybenzaldehyde (**4e**; 245 mg, 1.8 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 2 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 8.5:1.5) furnished **14e** as a pale yellow oil (487 mg, 71%).

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 7.27 (d, *J*=8.8Hz, 2H), 6.81-6.93 (m, 2H), 6.59 (d, *J*=0.8Hz, 1H), 6.19 (d, *J*=4.4Hz, 1H), 5.75 (d, *J*=4.4Hz, 1H), 3.71 (s, 3H), 2.33-2.43 (m, 2H), 1.35-1.49 (m, 2H), 1.13-1.28 (m, 6H), 0.72-0.90 (m, 3H).

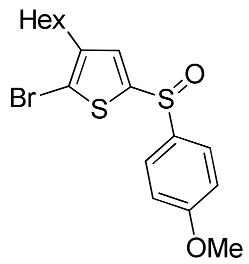
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 158.9, 151.2, 141.4, 136.8, 127.8, 125.0, 114.0, 107.0, 70.7, 55.5, 31.4, 29.6, 29.3, 28.6, 22.5, 14.4.

MS (70 eV, EI), *m/z* (%) = 384 (M^+, 25), 382 (M^+, 26), 367 (28), 365 (27), 304 (19), 303 (100), 287 (17), 233 (20), 137 (20), 135 (94), 109 (25), 77 (11).

HRMS (EI), *m/z* calc. for $\mathbf{C_{18}H_{23}BrO_2S}$ (382.0602): 382.0593 (M^+).

IR (ATR) υ (cm^{-1}) = 3063, 3035, 3000, 2954, 2926, 2855, 1610, 1510, 1457, 1441, 1303, 1245, 1170, 1135, 1109, 1032, 1008, 996, 833.

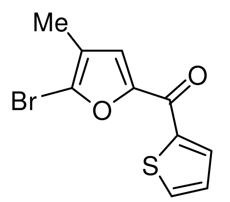
Preparation of 2-bromo-3-hexyl-5-((4-methoxyphenyl)sulfinyl)thiophene (14f)



Prepared according to **TP2** from 2,5-dibromo-3-hexylthiophene (**11b,** 652 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c;** 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L²**; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the sulfoxide was prepared according to **TP5** with 4-methoxybenzenesulfinyl chloride (**4q**; 343 mg, 1.8 mmol) in 4 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded **14f** as colorless oil (503 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.56-7.69 (m, 2H), 7.25 (s, 1H), 6.97-7.09 (m, 2H), 3.86 (s, 3H), 2.47-2.58 (m, 2H), 1.47-1.64 (m, 2H), 1.20-1.38 (m, 6H), 0.72-0.98 (m, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 162.3, 147.4, 142.8, 135.5, 131.6, 126.4, 116.6, 114.8, 55.5, 31.5, 29.5, 29.4, 28.8, 22.5, 14.0.
MS (70 eV, EI), *m/z* (%) = 400 (M^+, 2), 354 (46), 352 (43), 204 (23), 203 (100), 139 (31), 123 (10), 77 (7), 41 (8).
HRMS (EI), *m/z* calc. for **$C_{17}H_{21}BrO_2S_2$** (400.0166): 400.0166 (M^+).
IR (ATR) υ (cm^{-1}) = 3069, 3043, 3005, 2954, 2926, 2856, 1592, 1577, 1494, 1460, 1441, 1406, 1304, 1249, 1180, 1170, 1085, 1049, 1026, 989, 827, 796.

Preparation of (5-bromo-4-methylfuran-2-yl)(thiophen-2-yl)methanone (14g)



Prepared according to **TP2** from 2,5-dibromo-3-methylfuran (**11c**; 480 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L²**; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the acylation reaction was accomplished according to **TP4** with $ZnCl_2$ (2 mL, 2 mmol, 1.0 M in THF), CuCN·2LiCl (0.2 mL, 0.2 mmol, 1.0 M in THF) and thiophene-2-carbonyl chloride (**4p**; 352 mg, 2.4 mmol) in 4 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 95:5) afforded **14g** as a pale yellow solid (428 mg, 79%).

m.p.: 80.6-81.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.14 (dd, *J*=3.8Hz, 1.1Hz, 1H), 7.70 (dd, *J*=5.0Hz, 1.2Hz, 1H), 7.24 (s, 1H), 7.19 (t, *J*=4.4Hz, 1H), 2.07 (s, 3H).

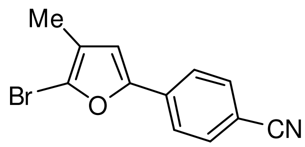
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 172.1, 152.9, 141.9, 134.1, 133.8, 128.3, 126.6, 123.0, 122.0, 10.5.

MS (70 eV, EI), *m/z* (%) =272 (M^+, 31), 270 (M^+, 31), 190 (11), 135 (26), 111 (100).

HRMS (EI), *m/z* calc. for **$C_{10}H_7BrO_2S$** (269.9350): 269.9347 (M^+).

IR (ATR) υ (cm^{-1}) = 3118, 3112, 2962, 2926, 2360, 2342, 1714, 1608, 1596, 1490, 1410, 1356, 1306, 1294, 1240, 1208, 1168, 1074, 1060, 964, 812, 744, 734, 616.

Preparation of 4-(5-bromo-4-methylfuran-2-yl)benzonitrile (14h)



Prepared according to **TP2** from 2,5-dibromo-3-methylfuran (**11c**; 480 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L^2**; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (2.0 mL, 2.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) and 4-iodobenzonitrile (**4k**; 550 mg, 2.4 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 95:5) afforded **14h** as a yellow solid (409 mg, 78%).

m.p.: 99.5-101.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.6-7.7 (m, 4H), 6.68 (s, 1H), 2.03 (s, 3H).

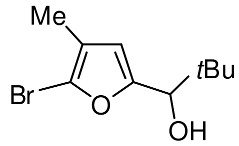
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 152.7, 133.7, 132.6, 124.9, 123.5, 122.3, 118.8, 112.0, 110.5, 10.6.

MS (70 eV, EI), *m/z* (%) = 264 (9), 263 (M^+, 72), 262 (10), 261 (M^+, 73), 182 (22), 155 (13), 154 (100), 153 (24), 130 (19), 127 (45), 126 (11), 102 (13), 77 (11), 63 (13).

HRMS (EI), *m/z* calc. for **$C_{12}H_8BrNO$** (260.9789): 260.9780 (M^+).

IR (ATR) υ (cm^{-1}) = 3108, 2962, 2926, 2870, 2222, 1918, 1766, 1606, 1532, 1516, 1484, 1446, 1386, 1348, 1266, 1178, 1078, 924, 834, 814, 684, 660.

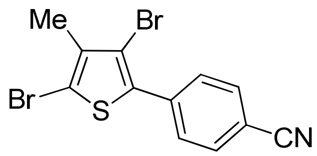
Preparation of 1-(5-bromo-4-methylfuran-2-yl)-2,2-dimethylpropan-1-ol (14i)



Prepared according to **TP2** from 2,5-dibromo-3-methylfuran (**11c**; 480 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) ($\mathbf{L^2}$; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the reaction mixture was cooled to –20 °C and pivaldehyde (**4r**; 206 mg, 2.4 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 1 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/EtOAc, 95:5) furnished **14i** as a yellow oil (361 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.11 (s, 1H), 4.21 (s, 1H), 1.94-2.01 (m, 4H), 0.96 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 156.7, 119.6, 118.6, 111.5, 76.4, 35.6, 25.7, 10.5.
MS (70 eV, EI), *m/z* (%) = 248 (M^+, 6), 246 (M^+, 8), 231 (19), 229 (19), 192 (8), 191 (94), 190 (11), 189 (100), 57 (32), 55 (17), 53 (18).
HRMS (EI), *m/z* calc. for $\mathbf{C_{10}H_{15}BrO_2}$ (246.0255): 246.0242 (M^+).
IR (ATR) υ (cm^{-1}) = 3426, 2956, 2870, 1542, 1396, 1366, 1206, 1158, 1074, 1048, 1008, 934, 902, 814, 794, 734, 612.

Preparation of 4-(3,5-dibromo-4-methylthiophen-2-yl)benzonitrile (14j)



Prepared according to **TP2** from 2,3,5-tribromo-4-methylthiophene (**11e**; 670 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) ($\mathbf{L^2}$; 336 mg, 2.1 mmol) at 0 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (2.0 mL, 2.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) and 4-iodobenzonitrile (**4k**; 550 mg, 2.4 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 50:1) afforded **14j** as a white solid (545 mg, 77%).

m.p.: 160.8-162.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.72 (s, 4H), 2.29 (s, 3H).

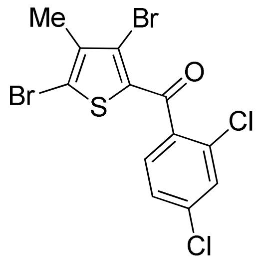
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 138.3, 137.2, 135.8, 132.4, 129.4, 118.4, 112.0, 111.2, 110.0, 16.4.

MS (70 eV, EI), *m/z* (%) = 357 (M^+, 87), 355 (M^+, 49), 278 (21), 276 (21), 197 (22), 196 (17), 152 (11), 70 (18), 61 (13), 45 (18), 44 (57), 43 (100).

HRMS (EI), *m/z* calc. for **$C_{12}H_7Br_2NS$** (354.8666): 354.8657 (M^+).

IR (ATR) υ (cm^{-1}) = 3085, 3070, 3056, 3035, 2957, 2919, 2852, 2359, 2228, 1920, 1605, 1504, 1454, 1407, 1393, 1386, 1380, 1334, 1328, 1308, 1180, 1110, 1044, 1019, 924, 842, 832, 807, 800, 755.

Preparation of (3,5-dibromo-4-methylthiophen-2-yl)(2,4-dichlorophenyl)methanone (14k)



Prepared according to **TP2** from 2,3,5-tribromo-4-methylthiophene (**11e**; 670 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L^2**; 336 mg, 2.1 mmol) at 0 °C in 1 h. Subsequently, the acylation reaction was accomplished according to **TP4** with $ZnCl_2$ (2 mL, 2 mmol, 1.0 M in THF), CuCN·2LiCl (0.2 mL, 0.2 mmol, 1.0 M in THF) and 2,4-dichlorobenzoyl chloride (**4s**; 377 mg, 1.8 mmol) in 8 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 50:1) afforded **14k** as a pale yellow solid (662 mg, 86%).

m.p.: 133.6-134.8 °C.

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 7.74-7.83 (m, 1H), 7.55-7.61 (m, 2H), 2.16 (s, 3H).

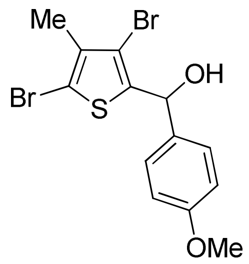
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 184.6, 140.8, 137.3, 137.2, 136.6, 131.4, 130.7, 130.0, 128.5, 121.1, 119.7, 16.3.

MS (70 eV, EI), *m/z* (%) = 429 (M^+, 79), 427 (M^+, 31), 177 (11), 175 (61), 173 (100), 147 (19), 145 (32), 44 (22).

HRMS (EI), *m/z* calc. for **$C_{12}H_6Br_2Cl_2OS$** (427.7863): 427.7931 (M^+).

IR (ATR) υ (cm^{-1}) = 3066, 2915, 2362, 2339, 1614, 1587, 1418, 1379, 1323, 1289, 1241, 1138, 1102, 1053, 1020, 865, 844, 818, 776, 753, 706, 670.

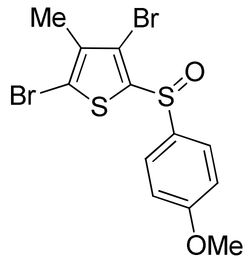
Preparation of (3,5-dibromo-4-methylthiophen-2-yl)(4-methoxyphenyl)methanol (14l)



Prepared according to **TP2** from 2,3,5-tribromo-4-methylthiophene (**11e**; 670 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L^2**; 336 mg, 2.1 mmol) at 0 °C in 1 h. Subsequently, the reaction mixture was cooled to −20 °C and 4-methoxybenzaldehyde (**4e**; 245 mg, 1.8 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 2 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 8:2) furnished **14l** as a colorless oil (618 mg, 88%).

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 7.21-7.29 (m, 2H), 6.82-6.89 (m, 2H), 6.41 (d, *J*=4.1Hz, 1H), 5.79 (d, *J*=4.1Hz, 1H), 3.69 (s, 3H), 2.05 (s, 3H).
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 159.1, 146.0, 136.1, 135.1, 128.1, 114.1, 108.3, 107.4, 70.8, 55.5, 15.8.
MS (70 eV, EI), *m/z* (%) = 392 (M^+, 57), 390 (M^+, 27), 377 (16), 375 (33), 311 (15), 283 (18), 136 (16), 135 (42), 109 (100), 108 (20), 92 (11), 77 (25).
HRMS (EI), *m/z* calc. for **$C_{13}H_{12}Br_2O_2S$** (389.8925): 389.8917 (M^+).
IR (ATR) υ (cm^{-1}) = 3334, 2999, 2953, 2922, 2834, 1609, 1586, 1510, 1462, 1440, 1379, 1328, 1304, 1246, 1173, 1148, 1110, 1030, 952, 831, 797, 760, 740, 685.

Preparation of 2,4-dibromo-5-((4-methoxyphenyl)sulfinyl)-3-methylthiophene (14m)



Prepared according to **TP2** from 2,3,5-tribromo-4-methylthiophene (**11e**; 670 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L²**; 336 mg, 2.1 mmol) at 0 °C in 1 h. Subsequently, the sulfoxide was prepared according to **TP5** with 4-methoxybenzene-sulfinyl chloride (**4q**; 496 mg, 2.6 mmol) in 4 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 6:4) afforded **14m** as white solid (770 mg, 94%).

m.p.: 110.8-112.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.64-7.77 (m, 2H), 6.98-7.04 (m, 2H), 3.85 (s, 3H), 2.17 (s, 3H).

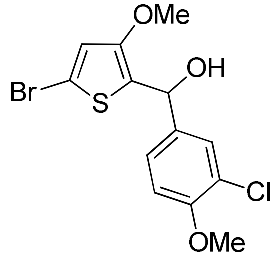
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 162.5, 144.1, 138.2, 134.6, 126.8, 115.6, 115.2, 114.8, 55.6, 15.5.

MS (70 eV, EI), *m/z* (%) = 412 (M^+, 14), 410 (M^+, 15), 364 (49), 361 (100), 360 (47), 347 (23), 345 (11), 155 (32), 139 (38), 123 (14), 92 (12), 77 (12).

HRMS (EI), *m/z* calc. for **$C_{12}H_{10}Br_2O_2S_2$** (409.8468): 409.8503 (M^+).

IR (ATR) υ (cm^{-1}) = 3088, 3067, 3002, 2963, 2933, 2904, 2842, 2361, 2339, 1590, 1574, 1494, 1452, 1446, 1388, 1324, 1301, 1255, 1184, 1176, 1081, 1062, 1045, 1024, 993, 932, 834, 822, 794, 780.

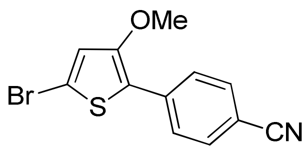
Preparation of (5-bromo-3-methoxythiophen-2-yl)(3-chloro-4-methoxyphenyl)-methanol (14n)



Prepared according to **TP2** from 2,5-dibromo-3-methoxythiophene (**11f**; 544 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L^2**; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the reaction mixture was cooled to –20 °C and 3-chloro-4-methoxybenzaldehyde (**4a**; 307 mg, 1.8 mmol) in THF was added. The reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 2 h. Subsequently, sat. aq. NH_4Cl (10 mL) was added. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (pentane/Et_2O, 6:4) furnished **14n** as a yellow oil (478 mg, 73%).

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 7.29 (d, *J*=2.2Hz, 1H), 7.20 (dd, *J*=8.8Hz, 2.1Hz, 1H), 7.11 (s, 1H), 7.04 (d, *J*=8.6Hz, 1H), 6.17 (bs, 1H), 5.82 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H).
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 153.9, 151.8, 138.0, 127.9, 127.5, 126.1, 121.2, 121.0, 112.9, 109.2, 66.4, 59.4, 56.5.
MS (70 eV, EI), *m/z* (%) = 364 (M^+, 49), 362 (M^+, 32), 347 (58), 345 (38), 285 (37), 283 (100), 223 (28), 219 (33), 171 (32), 155 (26), 111 (30), 108 (36), 85 (46), 77 (52), 63 (48), 42 (54).
HRMS (EI), *m/z* calc. for **$C_{13}H_{12}BrClO_3S$** (361.9379): 361.9371 (M^+).
IR (ATR) υ (cm^{-1}) = 3094, 3004, 2962, 2935, 2905, 2840, 1697, 1595, 1580, 1558, 1498, 1459, 1438, 1366, 1309, 1282, 1255, 1207, 1196, 1183, 1150, 1090, 1061, 1020, 981, 914, 884, 809, 726, 692, 685.

Preparation of 4-(5-bromo-3-methoxythiophen-2-yl)benzonitrile (14o)



Prepared according to **TP2** from 2,5-dibromo-3-methoxythiophene (**11f**; 544 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L^2**; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (2.0 mL, 2.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) and 4-iodobenzonitrile (**4k** 412 mg, 1.8 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 9:1) afforded **14o** as a yellow solid (361 mg, 69%).

m.p.: 162.1-164.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.67-7.80 (m, 2H), 7.54-7.64 (m, 2H), 6.95 (s, 1H), 3.93 (s, 3H).

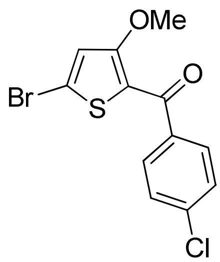
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 154.5, 137.2, 132.4, 126.4, 120.6, 119.3, 119.1, 112.5, 109.2, 59.0.

MS (70 eV, EI), *m/z* (%) = 295 (M^+, 84), 293 (M^+, 80), 201 (16), 200 (39), 147 (10), 146 (100), 139 (12), 127 (32), 125 (10), 114 (14), 102 (38), 75 (15), 63 (16), 62 (14), 45 (16), 43 (17).

HRMS (EI), *m/z* calc. for **$C_{12}H_8BrNOS$** (292.9510): 292.9511 (M^+).

IR (ATR) υ (cm^{-1}) = 3099, 3082, 2980, 2940, 2852, 2223, 1601, 1556, 1543, 1508, 1433, 1369, 1313, 1204, 1181, 1165, 1079, 988, 911, 826, 800, 705, 660, 653.

Preparation of 2(5-bromo-3-methoxythiophen-2-yl)(4-chlorophenyl)methanone (14p)



Prepared according to **TP2** from 2,5-dibromo-3-methoxythiophene (**11f**; 544 mg, 2 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 3.0 mL, 2.1 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L^2**; 336 mg, 2.1 mmol) at -10 °C in 16 h. Subsequently, the acylation reaction was accomplished according to **TP4** with $ZnCl_2$ (2 mL, 2 mmol, 1.0 M in THF), CuCN·2LiCl (0.2 mL, 0.2 mmol, 1.0 M in THF) and 4-chlorobenzoyl chloride (**4o**; 315 mg, 1.8 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 8.5:1.5) afforded **14p** as a pale yellow solid (389 mg, 66%).

m.p.: 137.0-138.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.65-7.75 (m, 2H), 7.36-7.46 (m, 2H), 6.91 (s, 1H), 3.81 (s, 3H).

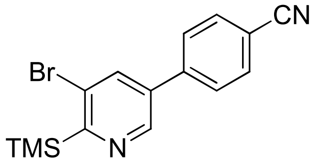
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 185.5, 159.0, 138.2, 137.1, 130.3, 128.1, 122.9, 122.4, 119.8, 59.0.

MS (70 eV, EI), *m/z* (%) = 332 (M^+, 63), 330 (M^+, 44), 315 (20), 297 (23), 295 (24), 221 (59), 219 (58), 216 (20), 139 (100), 111 (97), 75 (37).

HRMS (EI), *m/z* calc. for $\mathbf{C_{12}H_8BrClO_2S}$ (329.9117): 329.9115 (M^+).

IR (ATR) υ (cm^{-1}) = 3108, 3098, 2980, 2945, 2862, 1604, 1532, 1422, 1380, 1290, 1277, 1211, 1088, 1014, 986, 871, 827, 805, 748, 701, 693.

Preparation of 4-(5-bromo-6-(trimethylsilyl)pyridin-3-yl)benzonitrile (17a)



Prepared according to **TP2** from 3,5-dibromo-2-(trimethylsilyl)pyridine (**15**; 309 mg, 1 mmol), 2,4,6-triisopropylmagnesium bromide (**1c**; 1.5 mL, 1.05 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L**$^{\mathbf{2}}$; 168 mg, 2.1 mmol) at 25 °C in 2 h. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 4-iodobenzonitrile (**4k**; 206 mg, 0.9 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 9:1 + 1% NEt_3) afforded **17a** as a pale yellow solid (179 mg, 60%).

m.p.: 126.5-128.4 °C.

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 9.04 (d, *J*=2.0Hz, 1H), 8.29 (d, *J*=2.1Hz, 1H), 7.90-7.97 (m, 4H), 0.37 (s, 9H).

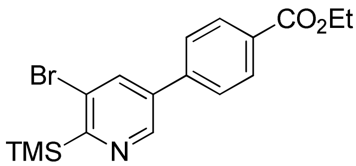
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 166.2, 146.7, 140.5, 136.7, 135.2, 133.4, 129.3, 128.5, 119.0, 111.8, -0.5.

MS (70 eV, EI), *m/z* (%) = 332 (M^+, 15), 330 (M^+, 16), 318 (18), 317 (100), 316 (20), 315 (92), 271 (10), 251 (38), 194 (12), 139 (11), 137 (11), 73 (10), 72 (14).

HRMS (EI), *m/z* calc. for $\mathbf{C_{15}H_{15}BrN_2Si}$ (330.0188): 330.0136 (M^+).

IR (ATR) υ (cm^{-1}) = 3095, 3049, 2966, 2949, 2896, 2227, 1609, 1577, 1505, 1430, 1358, 1348, 1247, 1147, 1047, 1024, 1012, 856, 836, 769, 757, 722.

Preparation of ethyl 4-(5-bromo-6-(trimethylsilyl)pyridin-3-yl)benzoate (17b)



Prepared according to **TP2** from 3,5-dibromo-2-(trimethylsilyl)pyridine (**15**; 309 mg, 1 mmol), 2,4,6-triisopropylmagnesium bromide (**1d**; 1.5 mL, 1.05 mmol, 0.7 M in THF) and 2,2'-oxy-*bis*(*N*,*N*-diethylethanamine) (**L**$^{\mathbf{2}}$; 168 mg, 2.1 mmol) at 25 °C in 2 h.

Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and ethyl 4-iodobenzoate (**4h**; 249 mg, 0.9 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/Et_2O, 95:5) afforded **17b** as a pale yellow solid (208 mg, 61%).

m.p.: 88.2-89.8 °C.
^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 9.02 (d, *J*=2.0Hz, 1H), 8.25 (d, *J*=2.0Hz, 1H), 7.95-8.03 (m, 2H), 7.84-7.90 (m, 2H), 4.29 (q, *J*=7.1Hz, 2H), 1.29 (t, *J*=7.2Hz, 3H), 0.37 (s, 9H).
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 165.8, 165.7, 146.7, 140.4, 136.5, 135.8, 130.3, 130.2, 129.3, 127.9, 61.3, 14.6, -0.5.
MS (70 eV, EI), *m/z* (%) = 379 (M^+, 44), 377 (M^+, 44), 365 (22), 364 (100), 363 (20), 362 (94), 334 (31), 332 (17), 299 (47), 298 (79), 284 (30), 270 (12), 139 (11), 137 (11), 44 (32), 43 (30).
HRMS (EI), *m/z* calc. for **$C_{17}H_{20}BrNO_2Si$** (379.0426): 379.0417 (M^+).
IR (ATR) υ (cm^{-1}) = 3045, 3041, 2976, 2953, 2899, 1701, 1608, 1573, 1479, 1410, 1365, 1355, 1288, 1274, 1244, 1226, 1184, 1115, 1103, 1046, 1022, 1012, 855, 838, 807, 724, 699.

3. ONE-POT PREPARATION OF MAGNESIUM DI(HETERO)ARYL- AND DIALKENYLBORONATES FOR *SUZUKI-MIYAURA* CROSS-COUPLINGS

3.1 TYPICAL PROCEDURES

Typical procedure 1 (TP1): Preparation of magnesium diorganoboronates $R_2B(OBu)_2MgX$ *via* direct Mg insertion in the presence of $B(OBu)_3$

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with Mg turnings (78 mg, 3.2 mmol) and LiCl (93 mg, 2.2 mmol). LiCl was dried *in vacuo* using a heatgun (450 °C, 5 min). After addition of THF (2 mL), the Mg was activated with 1,2-dibromoethane (2 mol%) and Me_3SiCl (5 mol%). Then $B(OBu)_3$ (230 mg, 1 mmol) was added at 25 °C followed by a solution of the organic halide (2 mmol) in THF (2 mL) and stirred for the given time leading to a THF-solution of the magnesium diorganoboronate.

Typical procedure 2 (TP2): Preparation of magnesium organoboronates $RB(OBu)_3MgX$ *via* direct Mg insertion in the presence of $B(OBu)_3$

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with Mg turnings (78 mg, 3.2 mmol) and LiCl (93 mg, 2.2 mmol). LiCl was dried *in vacuo* using a heatgun (450 °C, 5 min). After addition of THF (2 mL), the Mg was activated with 1,2-dibromoethane (2 mol%) and Me_3SiCl (5 mol%). Then $B(OBu)_3$ (460 mg, 2 mmol) was added at 25 °C followed by a solution of the organic halide (2 mmol) in THF (2 mL) and stirred for the given time leading to a THF-solution of the magnesium organoboronate.

Typical procedure 3 (TP3): Suzuki-Miyaura cross-coupling reactions

A dry, argon-flushed Schlenk flask was charged with the electrophile E–X (1.6 mmol), $PdCl_2$ (44 mg, 4 mol%), dppf (14 mg, 4 mol%) and Cs_2CO_3 (1.3 g, 4 mmol) and suspended in EtOH (4 mL) and DMF (1 mL). Afterwards the magnesium (di-)organoboronate solution (2 mmol) was transferred to this mixture via cannula. The resulting suspension was stirred at 65 °C for the given time. Subsequently, the reaction mixture was diluted with EtOAc (5 mL) and quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography to give the analytically pure product.

Typical procedure 4 (TP4): Suzuki-Miyaura cross-coupling reactions

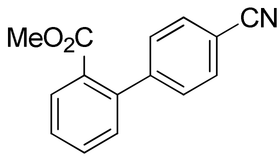
A dry, argon-flushed Schlenk flask was charged with the electrophile E–X (1.6 mmol), $Pd(PPh_3)_4$ (93 mg, 4 mol%) and Cs_2CO_3 (1.3 g, 4 mmol) and suspended in EtOH (4 mL). Afterwards the magnesium (di-)organoboronate solution (2 mmol) was transferred to this mixture via cannula. The resulting suspension was stirred at 65 °C for the given time. Subsequently, the reaction mixture was diluted with EtOAc (5 mL) and quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography to give the analytically pure product.

Typical procedure 5 (TP5): Suzuki-Miyaura cross-coupling reactions

A dry, argon-flushed Schlenk flask was charged with the electrophile E–X (1.4 mmol), $Pd(PPh_3)_4$ (93 mg, 4 mol%) and $Na_2CO_3 \cdot 10H_2O$ (0.76 g, 2.66 mmol) and suspended in 1,4-dioxane (4 mL) and H_2O (1.5 mL). Afterwards the magnesium (di-)organo-boronate solution (2 mmol) was transferred to this mixture via cannula. The resulting suspension was stirred at 110 °C for the given time. Subsequently, the reaction mixture was diluted with EtOAc (5 mL) and quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography to give the analytically pure product.

3.2 Preparation of Functionalized Magnesium (Di)arylboronates and Subsequent Suzuki-Miyaura Cross-Couplings

Preparation of methyl 4'-cyanobiphenyl-2-carboxylate (21a)



The magnesium organoboronate **19a** was prepared according to **TP2** from methyl 2-bromobenzoate (**18a**, 430 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 4-bromobenzonitrile (**22a**, 291 mg, 1.6 mmol) in 12 h. Flash column chromatographical purifitacion (pentane/Et_2O = 7:3) furnished **21a** as a brown oil (243 mg, 65%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.95 (dd, *J*=7.7Hz, 1.1Hz, 1H), 7.70 (d, *J*=8.3Hz, 2H), 7.55-7.63 (m, 1H), 7.46-7.53 (m, 1H), 7.41 (d, *J*=8.3Hz, 2H), 7.32 (dd, *J*=7.5Hz, 0.8Hz, 1H), 3.68 (s, 3H).

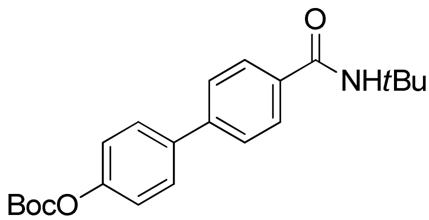
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 167.9, 146.3, 141.0, 131.7, 131.7, 130.5, 130.4, 130.0, 129.1, 128.2, 118.8, 111.0, 52.0.

MS (70 eV, EI), *m/z* (%) = 237 (M^+, 43), 207 (15), 206 (100), 178 (22), 177 (18), 151 (17).

HRMS (EI), *m/z* calc. for **$C_{15}H_{11}NO_2$** (237.0790): 237.0780 (M^+).

IR (ATR) υ (cm^{-1}) = 3062, 3000, 2951, 2855, 2227, 1720, 1608, 1598, 1482, 1446, 1432, 1288, 1276, 1254, 1190, 1126, 1089, 1028, 1006, 959, 842, 762, 734, 704.

Preparation of *tert*-butyl (4'-(*tert*-butylcarbamoyl)-biphenyl-4-yl) carbonate (21b)



The magnesium diorganoboronate **20a** was prepared according to **TP1** from 4-bromophenyl *tert*-butyl carbonate (**18b**, 546 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 4-bromo-*N*-(*tert*-butyl)benzamide (**22b**, 410 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 5.5:4.5) furnished **21b** as a white solid (539 mg, 91%).

m.p.: 166.0-168.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.79 (d, *J*=8.0Hz, 2H), 7.59 (d, *J*=8.8Hz, 4H), 7.26 (d, *J*=8.6Hz, 2H), 6.02 (br s, 1H), 1.58 (s, 9H), 1.50 (s, 9H).

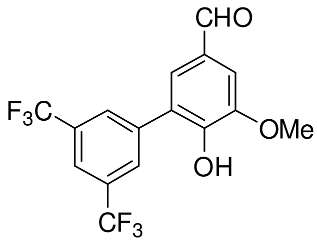
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 151.7, 150.9, 142.9, 137.7, 134.7, 128.1, 127.2, 127.0, 121.7, 83.7, 51.6, 28.9, 27.7.

MS (70 eV, EI), *m/z* (%) = 369 (M^+, 1), 269 (37), 213 (56), 198 (11), 197 (100), 57 (20), 42 (27), 41 (10).

HRMS (EI), *m/z* calc. for **$C_{22}H_{27}NO_4$** (369.1940): 369.1943 (M^+).

IR (ATR) υ (cm^{-1}) = 3253, 2973, 2925, 1750, 1630, 1609, 1544, 1487, 1455, 1368, 1273, 1256, 1218, 1143, 1006, 895, 881, 838, 824, 794, 777, 683.

Preparation of 6-hydroxy-5-methoxy-3',5'-bis(trifluoromethyl)-biphenyl-3-carbaldehyde (21c)



The magnesium diorganoboronate **20b** was prepared according to **TP1** from 3,5-di(trifluoromethyl)bromobenzene (**18c**, 586 mg, 2 mmol) in 15 min at 25 °C. A cross-coupling reaction was performed according to **TP3** with 5-bromovanillin (**22c**, 368 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/EtOAc = 8:2) furnished **21c** as a pale yellow solid (483 mg, 87%).

m.p.: >275 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.9 (s, 1H), 8.1 (s, 2H), 7.9 (s, 1H), 7.6 (s, 1H), 7.5 (s, 1H), 4.1 (s, 3H).

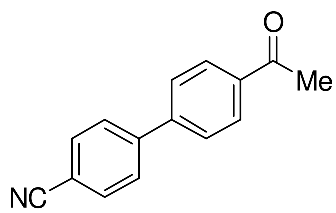
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 190.5, 157.5, 148.7, 147.6, 138.3, 131.7 (q, *J*=33.4Hz), 129.7, 129.1, 128.4, 127.5 (m), 121.5 (m), 108.8, 56.6.

MS (70 eV, EI), *m/z* (%) = 364 (M^+, 5), 228 (8), 88 (4), 61 (12), 45 (13), 43 (100).

HRMS (EI), *m/z* calc. for $\mathbf{C_{16}H_{10}F_6O_3}$ (364.0534): 364.0522 (M^+).

IR (ATR) υ (cm^{-1}) = 3294, 2970, 2360, 1740, 1672, 1500, 1468, 1382, 1362, 1294, 1272, 1180, 1152, 1118, 898, 864, 844, 750, 710, 682.

Preparation of 4'-acetyl-biphenyl-4-carbonitrile (21d)



The magnesium diorganoboronate **20c** was prepared according to **TP1** from 4-bromobenzonitrile (**18d**, 364 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 4-bromoacetophenone (**22d**, 318 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/EtOAc = 9:1) furnished **21d** as a white solid (290 mg, 82%).

m.p.: 106.2-107.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.08 (d, J=8.7Hz, 2H), 7.67-7.81 (m, 6H), 2.66 (s, 3H).

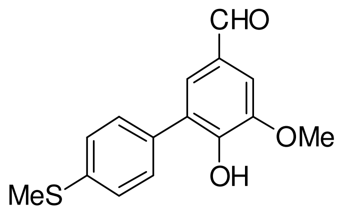
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 197.4, 144.3, 143.5, 136.9, 132.9, 129.1, 127.9, 27.4, 118.6, 111.9, 26.7.

MS (70 eV, EI), m/z (%) = 222 (5), 221 (M^+, 19), 207 (14), 206 (100), 178 (30), 177 (18), 151(24).

HRMS (EI), m/z calc. for $\mathbf{C_{15}H_{11}NO}$ (221.0841): 221.0826 (M^+).

IR (ATR) υ (cm^{-1}) = 3050, 2226, 1682, 1602, 1396, 1358, 1266, 1178, 1116, 1004, 956, 862, 814, 742, 714, 622.

Preparation of 6-hydroxy-5-methoxy-4'-(methylthio)-biphenyl-3-carbaldehyde (21e)



The magnesium diorganoboronate **20d** was prepared according to **TP1** from 4-bromothioanisole (**18e**, 406 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 5-bromovanillin (**22c**, 370 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/EtOAc = 3:1) furnished **21e** as a white solid (382 mg, 87%).

m.p.: 124.9-125.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.88 (s, 1H), 7.57 (d, J=8.2Hz, 2H), 7.52 (d, J=1.9Hz, 1H), 7.42 (d, J=1.9Hz, 1H), 7.35 (d, J=8.5Hz, 2H), 6.46 (br s, 1H), 4.03 (s, 3H), 2.54 (s, 3H).

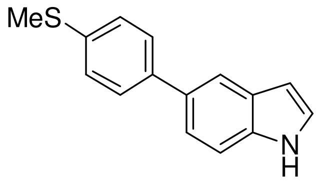
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 190.9, 148.6, 147.5, 138.3, 132.9, 129.4, 128.3, 127.1, 126.4, 108.7, 107.4, 56.5, 15.7.

MS (70 eV, EI), m/z (%) = 276 (5), 275 (14), 274 (M^+, 100), 212 (5), 184 (6).

HRMS (EI), m/z calc. for $\mathbf{C_{15}H_{14}O_3S}$ (274.0664): 274.0655 (M^+).

IR (ATR) υ (cm^{-1}) = 3198, 2978, 2922, 2848, 2362, 1732, 1666, 1588, 1498, 1454, 1428, 1388, 1366, 1304, 1246, 1150, 1124, 1090, 1044, 1014, 854, 822, 732, 706, 680.

Preparatin of 5-(4-(methylthio)phenyl)-1H-indole (21f)



The magnesium diorganoboronate **20d** was prepared according to **TP1** from 4-bromothio-anisole (**18e**, 406 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 5-bromo-1*H*-indole (**22e**, 314 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/EtOAc = 8.5:1.5) furnished **21f** as a pale yellow solid (352 mg, 92%).

m.p.: 82.6-83.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.16 (br s, 1H), 7.87 (s, 1H), 7.61 (d, *J*=8.6Hz, 2H), 7.43-7.48 (m, 2H), 7.37 (d, *J*=8.4Hz, 2H), 7.24 (t, *J*=2.4Hz, 1H), 6.59-6.65 (m, 1H), 2.55 (s, 3H).

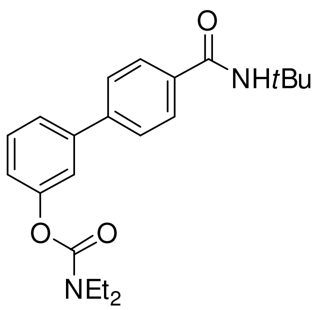
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 139.6, 136.1, 135.2, 132.7, 128.4, 127.7, 127.2, 124.9, 121.6, 118.9, 111.2, 103.0, 16.2.

MS (70 eV, EI), *m/z* (%) = 240 (15), 239 (M^+, 100), 224 (54), 57 (12).

HRMS (EI), *m/z* calc. for **$C_{15}H_{13}NS$** (239.0769): 239.0764 (M^+).

IR (ATR) υ (cm^{-1}) = 3402, 3022, 2920, 1738, 1594, 1578, 1464, 1412, 1342, 1230, 1210, 1096, 1066, 1008, 970, 954, 886, 800, 722.

Preparation of 4'-(*tert*-butylcarbamoyl)-biphenyl-3-yl diethylcarbamate (21g)



The magnesium diorganoboronate **20e** was prepared according to **TP1** from 3-bromophenyl diethylcarbamate (**18f**, 544 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 4-bromo-*N*-(*tert*-butyl)benzamide (**22b**, 410 mg, 1.6 mmol) in 7 h. Flash column chromatographical purification (pentane/Et_2O = 4:6) furnished **21g** as a pale yellow solid (525 mg, 90%).

m.p.: 140.1-143.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.78 (d, *J*=8.0Hz, 2H), 7.62 (d, *J*=8.0Hz, 2H), 7.39-7.44 (m, 2H), 7.35-7.38 (m, 1H), 7.12-7.17 (m, 1H), 6.02 (br s, 1H), 3.44 (q, *J*=6.9Hz, 4H), 1.49 (s, 9H), 1.25 (t, *J*=8.0Hz, 6H).

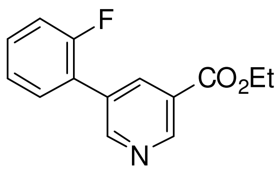
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.5, 154.1, 151.9, 143.0, 141.4, 134.7, 129.6, 127.2, 127.1, 123.8, 121.2, 120.5, 51.6, 42.1 (d, *J*=24.8Hz), 28.9, 13.8 (d, *J*=66.0Hz).

MS (70 eV, EI), *m/z* (%) = 368 (M^+, 6), 100 (100), 72 (30).

HRMS (EI), *m/z* calc. for **$C_{22}H_{28}N_2O_3$** (368.2100): 368.2092 (M^+).

IR (ATR) υ (cm^{-1}) = 3486, 3393, 3035, 2972, 2946, 2894, 2876, 1707, 1621, 1595, 1516, 1485, 1442, 1333, 1247, 1164, 1116, 1096, 1073, 1040, 877, 820, 796, 735, 692.

Preparation of ethyl 5-(2-fluorophenyl)nicotinate (21h)



The magnesium diorganoboronate **20f** was prepared according to **TP1** from 1-bromo-2-fluorobenzene (**18g**, 350 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with ethyl 5-bromonicotinate (**22f**, 368 mg, 1.6 mmol) in 3 h. Flash column chromatographical purification (pentane/EtOAc = 8:2) furnished **21h** as a brown powder (307 mg, 79%).

m.p.: 80.2-81.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.18 (br s, 1H), 8.91 (br s, 1H), 8.42 (s, 1H), 7.32-7.45 (m, 2H), 7.12-7.24 (m, 2H), 4.39 (q, *J*=7.1Hz, 2H), 1.38 (t, *J*=7.1Hz, 3H).

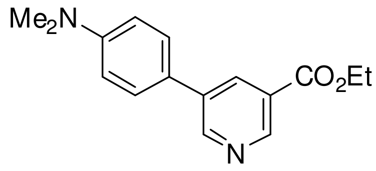
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.2, 159.8 (d, *J*=249.0Hz), 153.1, 149.8, 137.1 (d, *J*=3.1Hz), 131.6, 130.6 (d, *J*=1.7Hz), 130.5 (d, *J*=3.9 Hz), 126.3, 124.9 (d, *J*=3.9Hz), 124.7, 116.5 (d, *J*=22.1Hz), 61.6, 14.4.

MS (70 eV, EI), *m/z* (%) = 246 (14), 245 (M^+, 100), 217 (71), 200 (94), 172 (93), 145 (26), 125 (23), 100 (7), 75 (7).

HRMS (EI), *m/z* calc. for **$C_{14}H_{12}FNO_2$** (245.0852): 245.0848 (M^+).

IR (ATR) υ (cm^{-1}) = 3059, 2986, 1724, 1496, 1438, 1367, 1314, 1275, 1250, 1232, 1211, 1109, 1053, 1026, 916, 865, 819, 755, 728, 704, 662.

Preparation of ethyl 5-(4-(dimethylamino)phenyl)nicotinate (21i)



The magnesium diorganoboronate **20g** was prepared according to **TP1** from 4-bromo-*N*,*N*-dimethylaniline (**18h**, 400 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with ethyl 5-bromonicotinate (**22f**, 368 mg, 1.6 mmol) in 2 h. Flash column chromatographical purification (pentane/EtOAc = 7:3) furnished **21i** as a brown solid (390 mg, 90%).

m.p.: 100.8-102.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.05 (d, *J*=1.9Hz, 1H), 8.94 (d, *J*=2.3Hz, 1H), 8.41 (t, *J*=2.1Hz, 1H), 7.50-7.53 (m, 2H), 6.78-6.81 (m, 2H), 4.41 (q, *J*=7.1Hz, 2H), 2.99 (s, 6H), 1.41 (t, *J*=6.9Hz, 3H).

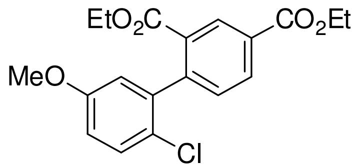
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.8, 151.0, 150.8, 148.0, 136.5, 134.1, 127.9, 126.3, 124.2, 112.9, 61.5, 40.5, 14.5.

MS (70 eV, EI), *m/z* (%) = 271 (16), 270 (M^+, 100), 242 (46), 225 (7), 154 (7), 98 (10).

HRMS (EI), *m/z* calc. for $\mathbf{C_{16}H_{18}N_2O_2}$ (270.1368): 270.1363 (M^+).

IR (ATR) υ (cm^{-1}) = 3788, 2980, 2900, 2814, 2361, 2341, 1716, 1607, 1529, 1434, 1362, 1306, 1290, 1255, 1230, 1119, 1006, 815, 768.

Preparation of diethyl 2'-chloro-5'-methoxy-biphenyl-2,4-dicarboxylate (21j)



The magnesium diorganoboronate **20h** was prepared according to **TP1** from 2-bromo-1-chloro-4-methoxybenzene (**18i**, 443 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with diethyl 4-bromoisophthalate (**22g**, 482 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/Et_2O = 8:2) furnished **21j** as yellow oil (467 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.67 (dd, *J*=1.9Hz, 0.4Hz, 1H), 8.23 (dd, *J*=7.9Hz, 1.8Hz, 1H), 7.37 (dd, *J*=7.9Hz, 0.5Hz, 1H), 7.32 (dd, *J*=8.8Hz, 0.4Hz, 1H), 6.87 (dd, J=8.8Hz, 3.0Hz, 1H), 6.79 (d, J=3.0Hz, 1H), 4.44 (q, J=7.1Hz, 2H), 4.17 (q, J=7.1Hz, 2H), 3.81 (s, 3H), 1.43 (t, J=7.2Hz, 3H), 1.10 (t, J=7.2Hz, 3H).

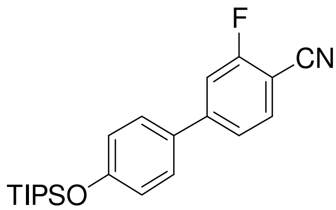
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.3, 165.5, 158.0, 144.3, 140.7, 132.4, 131.3, 131.2, 131.2, 130.3, 129.7, 124.0, 115.4, 114.4, 61.4, 61.2, 55.6, 14.3, 13.7.

MS (70 eV, EI), *m/z* (%) = 362 (M^+, 2), 328 (21), 327 (100), 317 (13), 300 (18), 299 (99), 271 (40), 253 (10).

HRMS (EI), *m/z* calc. for $\mathbf{C_{19}H_{19}ClO_5}$ (362.0921): 362.0916 (M^+).

IR (ATR) υ (cm^{-1}) = 3487, 3392, 3018, 2964, 2953, 2924, 2885, 2861, 1699, 1621, 1485, 1442, 1333, 1260, 1191, 1161, 1118, 1040, 990, 879, 796, 692.

Preparation of 3-fluoro-4'-((triisopropylsilyl)oxy)-biphenyl-4-carbonitrile (21k)



The magnesium diorganoboronate **20i** was prepared according to **TP1** from (4-bromo-phenoxy)-triisopropylsilane (**18j**, 659 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 4-bromo-2-fluorobenzonitrile (**22h**, 320 mg, 1.6 mmol) in 4 h. Flash column chromatographical purification (pentane/Et_2O = 9.5:0.5) furnished **21k** as a pale brown solid (411 mg, 70%).

m.p.: 56.2-57.9 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.64 (dd, J=8.1Hz, 6.8Hz, 1H), 7.46-7.49 (m, 2H), 7.44 (dd, J=8.1Hz, 1.7Hz, 1H), 7.39 (dd, J=10.5Hz, 1.7Hz, 1H), 6.96-7.01 (m, 2H), 1.31 (spt, J=7.5Hz, 3H), 1.13 (d, J=7.5Hz, 18H).

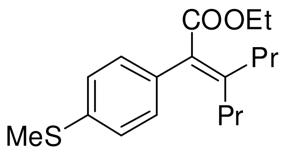
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 163.5 (d, J=256.5Hz), 157.5, 148.2 (d, J=8.3Hz), 133.5, 130.5 (d, J=2.3Hz), 128.3, 122.7 (d, J=3.0Hz), 120.6, 114.2, 114.0 (d, J=19.5Hz), 98.9 (d, J=15.8Hz), 17.9, 12.7.

MS (70 eV, EI), *m/z* (%) = 269 (M^+, 20), 327 (19), 326 (66), 298 (36), 271 (20), 270 (100), 257 (11), 256 (54), 240 (13), 196 (11), 135 (31), 43(16).

HRMS (EI), *m/z* calc. for $\mathbf{C_{22}H_{28}FNOSi}$ (369.1924): 369.1921 (M^+).

IR (ATR) υ (cm^{-1}) = 3488, 3392, 3048, 3036, 2958, 2935, 2878, 2857, 2243, 2222, 1623, 1514, 1484, 1442, 1333, 1310, 1253, 1160, 1115, 1096, 1073, 1041, 868, 796, 692.

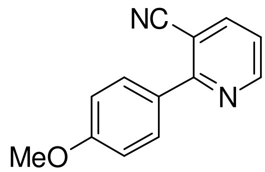
Preparation of ethyl 2-(4-(methylthio)phenyl)-3-propylhex-2-enoate (21l)



The magnesium diorganoboronate **20d** was prepared according to **TP1** from 4-bromothioanisole (**18e**, 406 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with ethyl 2-bromo-3-propylhex-2-enoate (**22i**, 421 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 9.5:0.5) furnished **21l** as a colorless oil (365 mg, 75%).

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.22 (dt, J=8.5Hz, 1.9Hz, 2H), 7.11 (dt, J=8.5Hz, 2.2Hz, 2H), 4.15 (q, J=7.0Hz, 2H), 2.50 (s, 3H), 2.35-2.40 (m, 2H), 1.93-1.97 (m, 2H), 1.54-1.58 (m, 2H), 1.36-1.41 (m, 2H), 1.22 (t, J=7.1Hz, 3H), 0.98 (t, J=7.4Hz, 3H), 0.78 (t, J=7.4Hz, 3H).
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 168.9, 150.6, 136.9, 134.8, 130.3, 129.9, 126.1, 60.4, 34.9, 34.9, 22.1, 21.4, 15.7, 14.3, 14.2.
MS (70 eV, EI), m/z (%) = 307 (26), 306 (M^+, 100), 260 (62), 245 (50), 231 (55), 203 (37), 189 (48), 143 (62), 129 (58), 128 (40), 115 (43).
HRMS (EI), m/z calc. for **$C_{18}H_{26}O_2S$** (306.1654): 306.1645 (M^+).
IR (ATR) υ (cm^{-1}) = 3487, 3392, 3072, 2981, 2946, 2887, 2845, 1735, 1695, 1621, 1515, 1485, 1444, 1333, 1260, 1215, 1161, 1120, 1097, 1073, 1046, 878, 796, 692.

Preparation of 2-(4-methoxyphenyl)nicotinonitrile (21m)



The magnesium diorganoboronate **20j** was prepared according to **TP1** from 4-bromo-anisole (**18k**, 374 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 2-chloronicotinonitrile (**23a**, 222 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/EtOAc = 7:3) furnished **21m** as a yellow powder (260 mg, 78%).

m.p.: 138.0-139.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.79-8.81 (m, 1H), 7.99-8.01 (m, 1H), 7.89-7.93 (m, 2H), 7.26-7.29 (m, 1H), 6.99-7.03 (m, 2H), 3.85 (s, 3H).

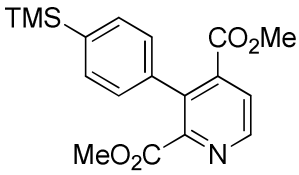
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.7, 158.9, 150.9, 140.3, 128.8, 128.0, 119.3, 116.4, 112.5, 105.1, 53.8.

MS (70 eV, EI), *m/z* (%) = 211 (17), 210 (M^+, 100), 195 (26), 167 (39), 140 (19).

HRMS (EI), *m/z* calc. for **$C_{13}H_{10}N_2O$** (210.0793): 210.0776 (M^+).

IR (ATR) υ (cm^{-1}) = 3070, 3010, 2967, 2838, 2224, 1882, 1607, 1582, 1574, 1553, 1516, 1458, 1431, 1416, 1308, 1247, 1183, 1108, 1040, 1021, 830, 804, 787, 772.

Preparation of dimethyl 3-(4-(trimethylsilyl)phenyl)pyridine-2,4-dicarboxylate (21n)



The magnesium diorganoboronate **20k** was prepared according to **TP1** from (4-bromo-phenyl)trimethylsilane (**18l**, 458 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with dimethyl 3-chloropyridine-2,4-dicarboxylate (**23b**, 368 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 4:6) furnished **21n** as a pale yellow oil (429 mg, 78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.21 (d, *J*=1.7Hz, 1H), 8.38 (d, *J*=1.7Hz, 1H), 7.61 (d, *J*=8.0Hz, 2H), 7.36 (d, *J*=8.3Hz, 2H), 3.99 (s, 3H), 3.82 (s, 3H), 0.31 (s, 9H).

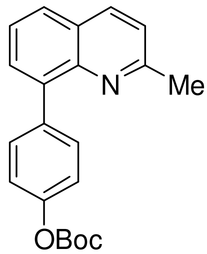
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.6, 164.8, 151.6, 148.7, 141.0, 139.6, 137.2, 137.0, 133.6, 127.4, 127.2, 52.8, 52.7, -1.2.

MS (70 eV, EI), *m/z* (%) = 343 (M^+, 26), 329 (26), 328 (100), 208 (10), 180 (27), 106 (19), 89 (90), 59 (11).

HRMS (EI), *m/z* calc. for **$C_{18}H_{21}NO_4Si$** (343.1240): 343.1232 (M^+).

IR (ATR) υ (cm^{-1}) = 3488, 3392, 3062, 3040, 3012, 2981, 2925, 2868, 1713, 1621, 1515, 1485, 1441, 1333, 1274, 1162, 1113, 1095, 1073, 902, 877, 796, 692.

Preparation of *tert*-butyl (4-(2-methylquinolin-8-yl)phenyl) carbonate (21o)



The magnesium diorganoboronate **20a** was prepared according to **TP1** from 4-bromophenyl *tert*-butyl carbonate (**18b**, 546 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 2-methyl-8-(perfluorobutoxy)quinoline (**24a**, 706 mg, 1.6 mmol) in 3 h. Flash column chromatographical purification (pentane/EtOAc = 8.5:1.5) furnished **21o** as a white solid (415 mg, 78%).

m.p.: 98.2-100.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.07 (d, *J*=8.4Hz, 1H), 7.63-7.91 (m, 4H), 7.53 (t, *J*=7.6Hz, 1H), 7.29 (dd, *J*=8.2Hz, 2.1Hz, 3H), 2.70 (s, 3H), 1.62 (s, 9H).

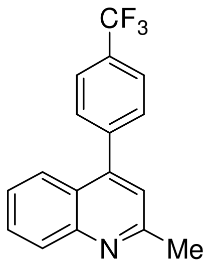
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 158.7, 152.0, 150.3, 145.3, 138.9, 137.1, 136.2, 131.9, 130.2, 127.3, 126.9, 125.3, 121.8, 120.4, 83.4, 27.7, 25.6.

MS (70 eV, EI), *m/z* (%) = 335 (M^+, 73), 235 (59), 234 (100), 218 (10), 57 (12), 43 (11).

HRMS (EI), *m/z* calc. for **$C_{21}H_{21}NO_3$** (335.1521): 335.1524 (M^+).

IR (ATR) υ (cm^{-1}) = 3005, 2982, 2933, 2359, 2333, 1749, 1601, 1500, 1370, 1274, 1258, 1218, 1145, 892, 831, 813, 783, 756.

Preparation of 2-methyl-4-(4-(trifluoromethyl)phenyl)quinoline (21p)



The magnesium diorganoboronate **20l** was prepared according to **TP1** from 1-bromo-4-(trifluoromethyl)benzene (**18m**, 450 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 2-methylquinolin-4-yl 4-methylbenzenesulfonate (**24b**, 502 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 6:4) furnished **21p** as a pale yellow solid (314 mg, 70%).

m.p.: 111.2-112.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.13 (d, *J*=8.3Hz, 1H), 7.67-7.85 (m, 4H), 7.62 (d, *J*=8.0Hz, 2H), 7.41-7.50 (m, 1H), 7.23 (s, 1H), 2.80 (s, 3H).

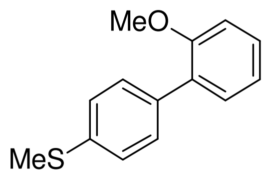
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 158.5, 148.3, 147.0, 141.8, 130.5 (q, *J*=32.3Hz), 129.8, 129.6, 129.1, 126.1, 125.5 (q, *J*=3.8Hz), 125.1, 124.6, 124.1 (q, *J*=270.8Hz), 122.1, 25.3.

MS (70 eV, EI), *m/z* (%) = 288 (12), 287 (M^+, 73), 286 (15), 218 (11), 70 (11), 61 (14), 45 (12), 43 (100).

HRMS (EI), *m/z* calc. for $\mathbf{C_{17}H_{12}F_3N}$ (287.0922): 287.0921 (M^+).

IR (ATR) υ (cm^{-1}) = 3069, 2970, 2923, 1737, 1619, 1597, 1557, 1504, 1414, 1403, 1377, 1322, 1154, 1113, 1065, 1018, 852, 837, 766, 757.

Preparation of (2'-methoxy-biphenyl-4-yl)(methyl)sulfane (21q)



The magnesium diorganoboronate **20d** was prepared according to **TP1** from 4-bromothioanisole (**18e**, 406 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 2-methoxyphenyl trifluoromethanesulfonate (**24c**, 410 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 9.5:0.5) furnished **21q** as a pale yellow solid (298 mg, 81%).

m.p.: 78.0-81.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.50 (d, *J*=8.3Hz, 2H), 7.29-7.40 (m, 4H), 7.04 (dd, *J*=15.5Hz, 7.2Hz, 2H), 3.84 (s, 3H), 2.54 (s, 3H).

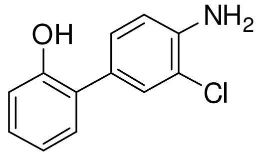
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 156.4, 137.0, 135.3, 130.6, 129.9, 128.6, 127.0, 126.3, 120.8, 111.2, 55.5, 15.9.

MS (70 eV, EI), *m/z* (%) = 230 (M^+, 100), 168 (100).

HRMS (EI), *m/z* calc. for $\mathbf{C_{14}H_{14}OS}$ (230.0765): 230.0749 (M^+).

IR (ATR) υ (cm^{-1}) = 3052, 3024, 3000, 2964, 2937, 2919, 2836, 2361, 2337, 1739, 1593, 1576, 1478, 1465, 1434, 1256, 1228, 1182, 1089, 1050, 1025, 1002, 815, 803, 753, 719.

Preparation of 4'-amino-3'-chloro-biphenyl-2-ol (21r)



The magnesium organoboronate **19b** was prepared according to **TP2** from 2-bromophenyl *tert*-butyl carbonate (**18n**, 546 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 4-bromo-2-chloroaniline (**22j**, 330 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/Et_2O = 4:6) furnished **21r** as a brown solid (301 mg, 86%) (Note: under the reaction conditions, the protecting group is cleaved and the free phenol is obtained).

m.p.: 119.9-122.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.41 (d, *J*=1.9Hz, 1H), 7.14-7.31 (m, 3H), 6.91-7.10 (m, 2H), 6.88 (d, *J*=8.3Hz, 1H), 4.28 (bs, 3H).

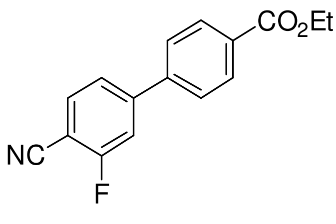
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 152.5, 142.5, 130.1, 130.0, 128.8, 128.4, 127.7, 127.1, 120.8, 119.8, 116.2, 115.7.

MS (70 eV, EI), *m/z* (%) = 221 (29), 220 (12), 219 (M^+, 100), 184 (45), 183 (27), 156 (35), 109 (10), 78 (16), 77 (17).

HRMS (EI), *m/z* calc. for **$C_{12}H_{10}ClNO$** (219.0451): 219.0447 (M^+).

IR (ATR) υ (cm^{-1}) = 3365, 3275, 2957, 2923, 2853, 1745, 1605, 1589, 1495, 1486, 1448, 1369, 1293, 1272, 1203, 1158, 1112, 1050, 880, 857, 833, 803, 754, 717, 679.

Preparation of ethyl 4'-cyano-3'-fluoro-biphenyl-4-carboxylate (21s)



The magnesium organoboronate **19c** was prepared according to **TP2** from 4-bromo-2-fluorobenzonitrile (**18o**, 400 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with ethyl 4-bromobenzoate (**22k**, 367 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 8:2) furnished **21s** as a white solid (270 mg, 72%).

m.p.: 131.5-133.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.16 (dt, *J*=8.4Hz, *J*=2.1Hz, 2H), 7.72 (dd, *J*=8.1Hz, 6.6Hz. 1H), 7.65 (dt, *J*=8.6Hz, 1.9Hz, 2H), 7.49 (ddd, *J*=15.0Hz, 8.0Hz, 1.7Hz, 2H), 4.42 (q, *J*=7.1Hz, 2H), 1.43 (t, *J*=7.2Hz, 3H).

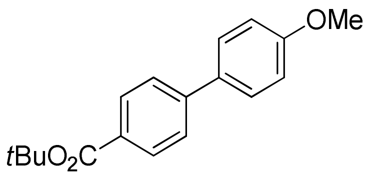
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.9, 163.4 (d, *J*=258.0Hz), 147.3 (d, *J*=7.5Hz), 142.0 (d, *J*=1.5Hz), 133.9, 131.1, 130.4, 127.1, 123.6 (d, *J*=3.8Hz), 115.1 (d, *J*=20.3Hz), 113.8, 100.7 (d, *J*=15.8Hz), 61.3, 14.3.

MS (70 eV, EI), *m/z* (%) =269 (M^+, 23), 241 (36), 225 (20), 224 (100), 196 (35), 195 (30), 176 (18), 169 (34), 168 (13), 112 (17), 98 (27), 85 (11), 84 (24), 45 (12).

HRMS (EI), *m/z* calc. for $\mathbf{C_{16}H_{12}FNO_2}$ (269.0852): 269.0845 (M^+).

IR (ATR) υ (cm^{-1}) = 3392, 3208, 3065, 3034, 2924, 2234, 1703, 1622, 1515, 1485, 1443, 1333, 1161, 1117, 1096, 1073, 876.

Preparation of *tert*-butyl 4'-methoxy-biphenyl-4-carboxylate (21t)



The magnesium organoboronate **19d** was prepared according to **TP2** from *tert*-butyl 4-bromo-benzoate (**18p**, 514 mg, 1 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 4-bromoanisole (**22l**, 300 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 9.5:0.5) furnished **21t** as a white solid (402 mg, 89%).

m.p.: 101.3-103.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.05 (d, *J*=8.3Hz, 2H), 7.59 (t, *J*=8.8Hz, 4H), 7.01 (d, *J*=8.6Hz, 2H), 3.87 (s, 3H), 1.63 (s, 9H).

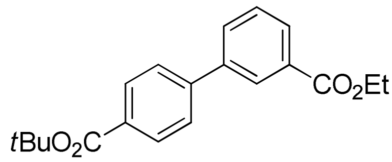
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.7, 159.7, 144.7, 132.6, 129.9, 128.3, 127.0, 126.3, 114.3, 80.9, 55.3, 28.2.

MS (70 eV, EI), *m/z* (%) = 284 (M^+, 20), 241 (14), 228 (13), 227 (100), 212 (22), 210 (12), 184 (11), 43 (44).

HRMS (EI), *m/z* calc. for $\mathbf{C_{18}H_{20}O_3}$ (284.1412): 284.1408 (M^+).

IR (ATR) υ (cm^{-1}) = 2990, 2976, 2932, 2852, 2835, 1706, 1598, 1529, 1488, 1456, 1366, 1292, 1250, 1181, 1162, 1106, 1035, 1007, 848, 829, 772, 760, 698.

Preparation of 4'-*tert*-butyl 3-ethyl biphenyl-3,4'-dicarboxylate (21u)

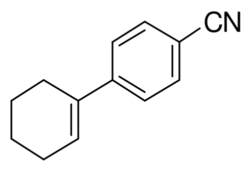


The magnesium organoboronate **19d** was prepared according to **TP2** from *tert*-butyl 4-bromo-benzoate (**18p**, 514 mg, 1 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with ethyl 4-bromobenzoate (**22m**, 386 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 9:1) furnished **21u** as a colorless oil (402 mg, 78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.31 (s, 1H), 7.99- 8.15 (m, 3H), 7.80 (d, *J*=7.7Hz, 1H), 7.67 (d, *J*=8.3Hz, 2H), 7.53 (t, *J*=7.7Hz, 1H), 4.43 (q, *J*=7.2Hz, 2H), 1.63 (s, 9H), 1.43 (t, *J*=7.2Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.3, 165.5, 144.0, 140.4, 131.4, 131.2, 131.2, 130.0, 129.0, 128.9, 128.3, 126.9, 81.1, 61.1, 28.2, 14.3.
MS (70 eV, EI), *m/z* (%) = 326 (M^+, 2), 270 (10), 225 (12), 70 (13), 61 (15).
HRMS (EI), *m/z* calc. for **$C_{18}H_{22}O_4$** (326.1518): 326.1519 (M^+).
IR (ATR) υ (cm^{-1}) = 2977, 2932, 2906, 1708, 1608, 1477, 1439, 1392, 1366, 1291, 1237, 1162, 1103, 1083, 1042, 1015, 858, 848, 746, 691.

3.3 PREPARATION OF FUNCTIONALIZED MAGNESIUM DIALKENYLBORONATES AND SUBSEQUENT SUZUKI-MIYAURA CROSS-COUPLINGS

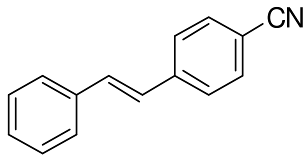
Preparation of 2',3',4',5'-tetrahydro-biphenyl-4-carbonitrile (26a)



The magnesium organoboronate **19e** was prepared according to **TP2** from 1-iodo-cyclohex-1-ene (**25a**, 416 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 4-bromo-benzonitrile (**22a**, 291 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 9.5:0.5) furnished **26a** as a pale yellow oil (206 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.58 (d, J=8.3Hz, 2H), 7.45 (d, J=8.3Hz, 2H), 6.21-6.32 (m, 1H), 2.34-2.47 (m, 2H), 2.19-2.33 (m, 2H), 1.74-1.86 (m, 2H), 1.61-1.74 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 147.0, 135.3, 132.0, 128.3, 125.3, 119.2, 109.8, 27.0, 25.9, 22.7, 21.8.
MS (70 eV, EI), *m/z* (%) = 184 (16), 183 (M^+, 100), 182 (28), 169 (13), 168 (74), 167 (11), 155 (55), 154 (56), 153 (16), 142 (17), 141 (10), 140 (35), 129 (23), 128 (14), 127 (19), 116 (18), 115 (35).
HRMS (EI), *m/z* calc. for $\mathbf{C_{13}H_{13}N}$ (183.1048): 183.1038 (M^+).
IR (ATR) υ (cm^{-1}) = 3057, 2928, 2863, 2833, 2226, 1727, 1692, 1602, 1503, 1432, 1413, 1350, 1181, 1137, 1080, 918, 862, 821, 799, 712.

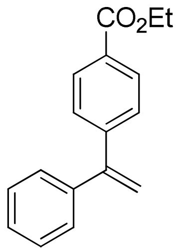
Preparation of (*E*)-4-styrylbenzonitrile (26b)



The magnesium organoboronate **19f** was prepared according to **TP2** from (*E*)-(2-iodovinyl)benzene (**25b**, 460 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 4-bromo-benzonitrile (**22a**, 291 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 8:2) furnished **26b** as a pale yellow solid (310 mg, 95%).

m.p.: 118.0-119.2 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.48-7.73 (m, 6H), 7.30-7.44 (m, 3H), 7.23 (d, J=16.3Hz, 1H), 7.10 (d, J=16.3Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 141.8, 136.3, 132.4, 132.4, 128.8, 128.6, 126.9, 126.8, 126.7, 119.0, 110.5.
MS (70 eV, EI), *m/z* (%) = 206 (15), 205 (M^+, 100), 204 (98), 203 (34), 190 (44), 178 (12), 177 (24), 176 (19), 165 (21), 102 (22), 89 (43), 88 (47).
HRMS (EI), *m/z* calc. for $\mathbf{C_{15}H_{11}N}$ (205.0891): 205.0883 (M^+).
IR (ATR) υ (cm^{-1}) = 3082, 3023, 3001, 2954, 2921, 2224, 1739, 1600, 1575, 1502, 1449, 1412, 1174, 972, 956, 872, 823, 757, 718, 690.

Preparation of ethyl 4-(1-phenylvinyl)benzoate (26c)

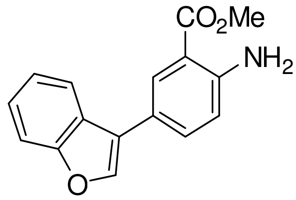


The magnesium diorganoboronate **20m** was prepared according to **TP1** from (1-bromovinyl)-benzene (**25c**, 366 mg, 2 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to **TP3** with ethyl 4-bromobenzoate (**22k**, 367 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/Et_2O = 9.5:0.5) furnished **26c** as a colorless oil (383 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.01 (d, *J*=8.7Hz, 2H), 7.40 (d, *J*=8.7Hz, 2H), 7.28-7.37 (m, 5H), 5.55 (d, *J*=1.0Hz, 1H), 5.53 (d, *J*=1.0Hz, 1H), 4.39 (q, *J*=7.1Hz, 2H), 1.40 (t, *J*=7.1Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.4, 149.3, 145.9, 140.8, 129.7, 129.5, 128.3, 128.2, 128.0, 127.8, 115.8, 60.9, 14.3.
MS (70 eV, EI), *m/z* (%) = 252 (M^+, 34), 207 (39), 179 (24), 178 (30), 155 (11), 141 (12), 127 (16), 113 (20), 111 (14), 99 (25), 96 (25), 85 (60), 84 (11), 83 (24), 71 (79), 70 (16), 69 (23), 57 (100), 56 (17), 55 (27), 43 (100), 41 (21).
HRMS (EI), *m/z* calc. for **$C_{17}H_{16}O_2$** (252.1150): 252.1150 (M^+).
IR (ATR) υ (cm^{-1}) = 2982, 1714, 1608, 1494, 1446, 1404, 1366, 1268, 1176, 1102, 1018, 904, 864, 774, 700.

3.4 PREPARATION OF FUNCTIONALIZED MAGNESIUM DIHETEROARYLBORONATES AND SUBSEQUENT SUZUKI-MIYAURA CROSS-COUPLINGS

Preparation of methyl 2-amino-5-(benzofuran-3-yl)benzoate (28a)



The magnesium diorganoboronate **20n** was prepared according to **TP1** from 3-bromo-1-benzofuran (**27a**, 394 mg, 2 mmol) in 30 min at 25 °C. A cross-coupling reaction was performed according to **TP3** with methyl 2-amino-5-bromobenzoate (**22n**, 368 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/EtOAc = 8:2 with 0.5% NEt_3) furnished **28a** as a white solid (359 mg, 84%).

m.p.: 86.3-87.4 °C.

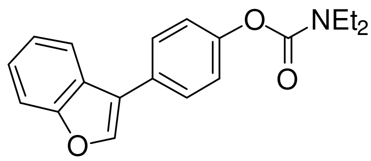
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.17 (d, *J*=2.2Hz, 1H), 7.81 (dd, *J*=4.7Hz, 2.2Hz, 1H), 7.74 (s, 1H), 7.51-7.59 (m, 2H), 7.28-7.40 (m, 2H), 6.81 (d, *J*=8.4Hz, 1H), 3.93 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 168.4, 155.7, 149.5, 140.5, 133.4, 130.0, 126.6, 124.4, 122.8, 121.5, 120.2, 120.2, 117.4, 111.7, 111.2, 51.7.

HRMS (ESI) = *m/z* calc. for **$C_{16}H_{14}NO_3$** (268.0974): 268.0967 ($[M+H]^+$).

IR (ATR) υ (cm^{-1}) = 3492, 3378, 2954, 1684, 1628, 1578, 1556, 1450, 1438, 1360, 1306, 1292, 1230, 1102, 1084, 826, 790, 746, 710.

Preparation of 4-(benzofuran-3-yl)phenyl diethylcarbamate (28b)



The magnesium diorganoboronate **20n** was prepared according to **TP1** from 3-bromo-1-benzofuran (**27a**, 394 mg, 2 mmol) in 30 min at 25 °C. A cross-coupling reaction was performed according to **TP3** with 3-bromophenyl diethylcarbamate (**22o**, 436 mg, 1.6 mmol) in 3 h. Flash column chromatographical purification (pentane/Et_2O = 7.5:2.5) furnished **28b** as a orange oil (428 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.84-7.91 (m, 1H), 7.82 (s, 1H), 7.45-7.61 (m, 3H), 7.41-7.45 (m, 1H), 7.28-7.41 (m, 2H), 7.16 (dt, *J*=6.7Hz, 2.5Hz, 1H), 3.20-3.64 (m, 4H), 1.10-1.37 (m, 6H).

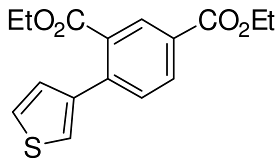
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 155.7, 154.1, 152.0, 141.5, 133.2, 129.6, 126.3, 124.5, 124.1, 123.0, 121.7, 120.8, 120.8, 120.3, 111.7, 42.1 (d, *J*=25.5Hz), 13.8 (d, *J*=65.3Hz).

MS (70 eV, EI), *m/z* (%) = 310 (12), 309 (M^+, 65), 181 (14), 152 (19), 100 (47), 72 (100), 44 (15).

HRMS (EI), *m/z* calc. for **$C_{19}H_{19}NO_3$** (309.1365): 309.1368 (M^+).

IR (ATR) υ (cm^{-1}) = 3487, 3392, 3009, 2955, 2915, 2859, 1740, 1691, 1622, 1485, 1440, 1398, 1332, 1246, 1167, 1119, 1073, 975, 872, 796, 734.

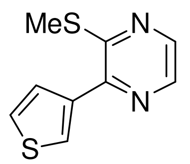
Preparation of diethyl 4-(thiophen-3-yl)isophthalate (28c)



The magnesium diorganoboronate **20o** was prepared according to **TP1** from 3-bromothiophene (**27b**, 406 mg, 2 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to **TP3** with diethyl 4-bromoisophthalate (**22g**, 482 mg, 1.6 mmol) in 4 h. Flash column chromatographical purification (pentane/Et_2O = 8.5:1.5) furnished **28c** as a pale brown solid (346 mg, 72%).

m.p.: 48.8-50.5 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.42 (d, *J*=1.9Hz, 1H), 8.15 (dd, *J*=8.2Hz, 1.8Hz, 1H), 7.50 (d, *J*=8.0Hz, 1H), 7.34-7.40 (m, 1H), 7.32 (dd, *J*=3.0Hz, 1.4Hz, 1H), 7.12 (dd, *J*=5.0Hz, 1.4Hz, 1H), 4.42 (q, *J*=7.1Hz, 2H), 4.21 (q, *J*=7.2Hz, 2H), 1.42 (t, *J*=7.0Hz, 3H), 1.16 (t, *J*=7.2Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 168.1, 165.6, 140.7, 140.5, 131.8, 131.7, 130.7, 130.5, 129.4, 128.2, 125.4, 123.1, 61.4, 61.3, 14.3, 13.8.
MS (70 eV, EI), *m/z* (%) = 305 (16), 304 (M^+, 90), 259 (100), 232 (17).
HRMS (EI), *m/z* calc. for **$C_{16}H_{16}O_4S$** (304.0769): 304.0739 (M^+).
IR (ATR) υ (cm^{-1}) = 3487, 3392, 3117, 3075, 3034, 2951, 2918, 2884, 1737, 1694, 1621, 1485, 1442, 1333, 1261, 1216, 1160, 1117, 1073, 981, 873, 795, 774, 751, 692.

Preparation of 2-(methylthio)-3-(thiophen-3-yl)pyrazine (28d)



The magnesium diorganoboronate **20o** was prepared according to **TP1** from 3-bromothiophene (**27b**, 406 mg, 2 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to **TP3** with 2-bromo-3-(methylthio)pyrazine (**22p**, 328 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 9:1) furnished **28d** as a brown oil (262 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.31 (d, J=2.4Hz, 1H), 8.26 (d, J=2.6Hz, 1H), 8.03 (dd, J=2.8Hz, 1.3Hz, 1H) 7.68 (dd, J=5.0Hz, 1.3Hz, 1H), 7.41 (dd, J=5.0Hz, 2.8Hz, 1H), 2.57 (s, 3H).

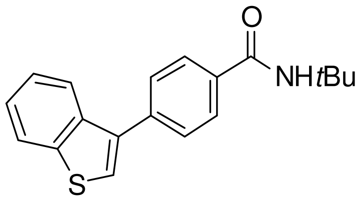
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 155.0, 147.9, 141.2, 138.3, 138.0, 128.4, 126.8, 125.4, 13.6.

MS (70 eV, EI), *m/z* (%) = 209 (11), 208 (M^+, 100), 207 (17), 193 (32), 175 (72), 134(10), 110 (16).

HRMS (EI), *m/z* calc. for **$C_9H_8N_2S_2$** (208.0129): 208.0128 (M^+).

IR (ATR) υ (cm^{-1}) = 3486, 3392, 3142, 3059, 2940, 2895, 1621, 1485, 1333, 1260, 1162, 1124, 1096, 1072, 1041, 880, 794, 736, 692.

Preparation of 4-(benzothiophen-3-yl)-N-(*tert*-butyl)benzamide (28e)



The magnesium diorganoboronate **20p** was prepared according to **TP1** from 3-bromo-benzothiophene (**27c**, 426 mg, 2 mmol) in 1 h at 0 °C. A cross-coupling reaction was performed according to **TP3** with 4-bromo-*N*-(*tert*-butyl)benzamide (**22b**, 410 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 7:3) furnished **28e** as a white solid (380 mg, 77%).

m.p.: 114.9-116.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.91-7.96 (m, 1H), 7.82-7.91 (m, 3H), 7.64 (d, J=8.0Hz, 2H), 7.45 (s, 1H), 7.38-7.41 (m, 2H), 6.07 (br s, 1H), 1.52 (s, 9H).

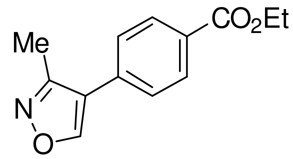
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 166.5, 140.7, 138.7, 137.5, 137.0, 134.8, 128.6, 127.2, 124.5, 124.5, 124.2, 122.9, 122.6, 51.7, 28.9.

MS (70 eV, EI), *m/z* (%) = 309 (M^+, 38), 253 (60), 238 (15), 237 (100), 209 (17), 208 (30), 165 (19), 104 (10).

HRMS (EI), *m/z* calc. for **$C_{19}H_{19}NOS$** (309.1187): 309.1192 (M^+).

IR (ATR) υ (cm^{-1}) = 3485, 3392, 3209, 3074, 3037, 1621, 1485, 1333, 1260, 1161, 1116, 1096, 1073, 1045, 879, 796, 692.

Preparation of ethyl 4-(3-methylisoxazol-4-yl)benzoate (28f)



The magnesium organoboronate **19g** was prepared according to **TP2** from 4-bromo-3,5-dimethylisoxazole (**27d**, 352 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with ethyl 4-bromobenzoate (**22k**, 367 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/Et_2O = 7.5:2.5) furnished **28f** as a pale brown solid (232 mg, 60%).

m.p.: 71.1-72.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.12 (dt, *J*=8.6Hz, 1.7Hz, 2H), 7.34 (dt, *J*=8.6Hz, 1.7Hz, 2H), 4.41 (q, *J*=7.1Hz, 2H), 2.43 (s, 3H), 2.29 (s, 3H), 1.41 (t, *J*=7.2Hz, 3H).

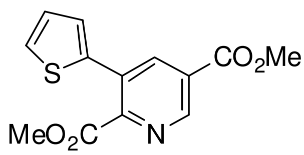
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.1, 165.7, 158.3, 135.1, 130.0, 129.5, 128.8, 116.0, 61.1, 14.3, 11.6, 10.8.

MS (70 eV, EI), *m/z* (%) = 246 (10), 245 (M^+, 75), 217 (15), 202 (10), 201 (13), 200 (100), 172 (12), 131 (39), 103 (13), 77 (10).

HRMS (EI), *m/z* calc. for $\mathbf{C_{14}H_{15}NO_3}$ (245.1052): 245.1046 (M^+).

IR (ATR) υ (cm^{-1}) = 3486, 3392, 3062, 3035, 2986, 2942, 1710, 1621, 1515, 1485, 1443, 1333, 1259, 1161, 1116, 1096, 1073, 1041, 878, 796, 692.

Preparation of dimethyl 3-(thiophen-2-yl)pyridine-2,5-dicarboxylate (28g)



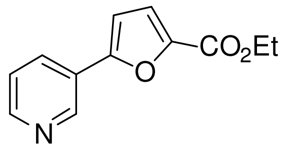
The magnesium diorganoboronate **20q** was prepared according to **TP1** from 2-chloro-thiophene (**27e**, 237 mg, 2 mmol) in 30 min at 25 °C. A cross-coupling reaction was performed according to **TP3** with dimethyl 3-chloropyridine-2,5-dicarboxylate (**23c**, 367 mg, 1.6 mmol) in 6 h. Flash column chromatographical purification (pentane/EtOAc = 9:1) furnished **28g** as a pale yellow solid (381 mg, 86%).

m.p.: 110.9-111.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.17 (d, *J*=1.9Hz, 1H), 8.46 (d, *J*= 1.9Hz, 1H), 7.48 (dd, *J*=5.1Hz, 1.2Hz, 1H), 7.21 (dd, *J*=3.6Hz, 1.2Hz, 1H), 7.13 (dd, *J*=5.0Hz, 3.6Hz, 1H), 4.01 (s, 3H), 3.90 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.7, 164.7, 152.0, 148.8, 139.3, 137.3, 129.3, 128.0, 127.8, 127.7, 127.1, 53.0, 52.8.
MS (70 eV, EI), *m/z* (%) = 277 (M^+, 57), 246 (11), 219 (56), 218 (25), 171 (21), 161 (65), 70 (15), 61 (21), 45 (15), 43 (100).
HRMS (EI), *m/z* calc. for $\mathbf{C_{13}H_{11}NO_4S}$ (277.0409): 277.0405 (M^+).
IR (ATR) υ (cm^{-1}) = 3074, 2956, 1736, 1724, 1594, 1556, 1450, 1424, 1300, 1256, 1198, 1130, 1106, 1012, 766, 734.

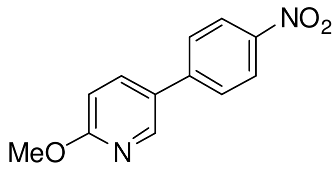
Preparation of ethyl 5-(pyridin-3-yl)furan-2-carboxylate (28h)



The magnesium diorganoboronate **20r** was prepared according to **TP1** from 3-bromo-pyridine (**27f**, 316 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP5** with ethyl 5-bromofuran-2-carboxylate (**22q**, 307 mg, 1.4 mmol) in 24 h. Flash column chromatographical purification (pentane/EtOAc = 7:3 with 0.5% NEt_3) furnished **28h** as a white solid (248 mg, 82%).

m.p.: 44.5-45.7 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.95 (d, *J*=1.5Hz, 1H), 8.51 (dd, *J*=4.8Hz, 1.6Hz, 1H), 7.99-8.02 (m, 1H), 7.29 (dd, *J*=8.0Hz, 4.8Hz, 1H), 7.19 (d, *J*=3.6Hz, 1H), 6.77 (d, *J*=3.6Hz, 1H), 4.33 (q, *J*=7.1Hz, 2H), 1.34 (t, *J*=7.1Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 158.6, 154.4, 149.6, 146.3, 144.9, 131.9, 125.8, 123.7, 119.6, 108.1, 61.2, 14.4.
MS (70 eV, EI), *m/z* (%) = 218 (11), 217 (M^+, 100), 189 (72), 172 (54), 145 (35), 116 (43), 89 (14), 44 (10).
HRMS (EI), *m/z* calc. for $\mathbf{C_{12}H_{11}NO_3}$ (217.0739): 217.0728 (M^+).
IR (ATR) υ (cm^{-1}) = 3120, 3085, 3049, 2982, 2928, 2904, 1716, 1566, 1524, 1516, 1470, 1415, 1371, 1334, 1301, 1279, 1226, 1149, 1113, 1017, 964, 920, 867, 821, 806, 758, 712, 675.

Preparation of 2-methoxy-5-(4-nitrophenyl)pyridine (28i)



The magnesium diorganoboronate **9h** was prepared according to **TP1** from 5-bromo-2-methoxypyridine (**27g**, 376 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP3** with 1-bromo-4-nitrobenzene (**22r**, 323 mg, 1.6 mmol) in 12 h. Flash column chromatographical purification (pentane/EtOAc = 8.5:1.5) furnished **28i** as a pale yellow solid (311 mg, 85%).

m.p.: 162.9-164.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.42 (d, J=2.6Hz, 1H), 8.26-8.30 (m, 2H), 7.81 (dd, J=8.6Hz, 2.6Hz, 1H), 7.64-7.68 (m, 2H), 6.85 (dd, J=8.6Hz, 0.6Hz, 1H), 3.98 (s, 3H).

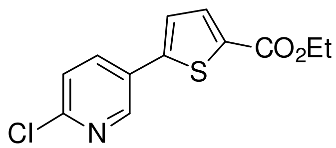
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 164.8, 147.2, 145.8, 144.6, 137.5, 127.9, 127.3, 124.6, 111.5, 53.9.

MS (70 eV, EI), *m/z* (%) = 231 (16), 230 (M^+, 100), 201 (56), 183 (29), 154 (52), 141 (34), 127 (31), 114 (24), 42 (17).

HRMS (EI), *m/z* calc. for $\mathbf{C_{12}H_{10}N_20_3}$ (230.0691): 230.0669 (M^+).

IR (ATR) υ (cm^{-1}) = 3075, 2949, 2440, 1596, 1564, 1505, 1477, 1442, 1415, 1395, 1375, 1341, 1309, 1297, 1257, 1179, 1139, 1106, 1042, 1019, 999, 923, 855, 834, 733. 695.

Preparation of ethyl 5-(6-chloropyridin-3-yl)thiophene-2-carboxylate (28j)



The magnesium diorganoboronate **20t** was prepared according to **TP1** from 5-bromo-2-chloropyridine (**27h**, 385 mg, 2 mmol) in 1 h at 25 °C. A cross-coupling reaction was performed according to **TP4** with 5-bromothiophene-2-carboxylate (**22s**, 329 mg, 1.4 mmol) in 12 h. Flash column chromatographical purification (pentane/EtOAc = 9:1) furnished **28j** as a white solid (270 mg, 72%).

m.p.: 81.8-83.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.64 (dd, *J*=2.6Hz, 0.7Hz, 1H), 7.83 (dd, *J*=8.3Hz, 2.6Hz, 1H), 7.75-7.77 (m, 1H), 7.30 (d, *J*=3.9Hz, 1H), 4.36 (q, *J*=7.1Hz, 1H), 1.38 (t, *J*=7.1Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 162.0, 151.5, 145.4, 136.1, 134.6, 134.4, 128.8, 125.2, 124.7, 61.7, 14.5.

MS (70 eV, EI), *m/z* (%) = 268 (10), 267 (M^+, 64), 240 (20), 221 (100), 152 (17), 102 (6), 61 (10).

HRMS (EI), *m/z* calc. for $\mathbf{C_{12}H_{10}ClNO_2S}$ (267.0121): 267.0119 (M^+).

IR (ATR) υ (cm^{-1}) = 3394, 2993, 2340, 1710, 1532, 1443, 1363, 1288, 1275, 1098, 1008, 834, 814, 745.

4. PREPARATION OF α-SUBSTITUTED β,γ-UNSATURATED KETONES AND ESTERS *VIA* THE DIRECT ADDITION OF SUBSTITUTED ALLYLIC ZINC REAGENTS

4.1 PREPARATION OF STARTING MATERIALS

All reagents were obtained from commercial sources. Compounds **29f**[176a], **29g**[178b] as well as **29h**[274] and **29i**[274] were prepared according to literature known procedures.

4.2 TYPICAL PROCEDURES

Typical procedure 1 (TP1): Preparation of allylic zinc reagents RZnX·LiCl *via* direct zinc insertion in the presence of lithium chloride

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol). LiCl was dried *in vacuo* using a heatgun (450 °C, 5 min). After addition of THF (10 mL), the Zn powder was activated with 1,2-dibromoethane (2 mol%) and Me_3SiCl (5 mol%). Then a solution of the allyl halide (10 mmol) in THF (10 mL) was added at 25 °C and stirred for 1 h until GC-analysis of hydrolyzed reaction aliquot showed full consumption of the starting material. Then, the remaining Zn powder was allowed to settle down or centrifuged (10 min, 2000 rpm). The yield of the insertion reaction was determined by iodometric titration.[192]

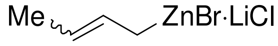
Typical procedure 2 (TP2): Preparation of α-substituted β,γ-unsaturated ketones and esters *via* direct addition of allylic zinc reagents to acid chlorides and chloroformates

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding acid chloride or chloroformate (0.8 equiv) in THF (1.0 M) and cooled down to the indicated temperature. Subsequently, the freshly prepared allylic zinc reagent in THF (1 equiv) was added dropwise and the reaction mixture was stirred at the indicated temperature for the given time. The reaction mixture was quenched at room temperature with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

[274] P. Zhihua, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 8516.

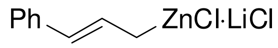
4.3 PREPARATION OF SUBSTITUTED ALLYLIC ZINC REAGENTS

Preparation of but-2-en-1-ylzinc bromide (30a)



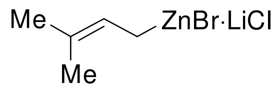
According to **TP1**, the allyic zinc reagent **30a** was prepared from 1-bromobut-2-ene (**29a**, 1.35 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.42 M (83%).

Preparation of cinnamylzinc chloride (30b)



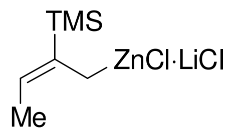
According to **TP1**, the allyic zinc reagent **30b** was prepared from cinnamyl chloride (**29b**, 1.53 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.43 M (86%).

Preparation of (3-methylbut-2-en-1-yl)zinc bromide (30c)



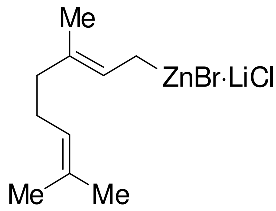
According to **TP1**, the allyic zinc reagent **30c** was prepared from 1-bromo-3-methylbut-2-ene (**29c**, 1.49 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.46 M (92%).

Preparation of (2-(trimethylsilyl)but-2-en-1-yl)zinc chloride (30d)



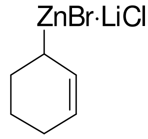
According to **TP1**, the allyic zinc reagent **30d** was prepared according a literature-known procedure[2] from (1-chlorobut-2-en-2-yl)trimethylsilane (**29d**, 1.63 g, 10.0 mmol) using Zn powder (6.54 g, 100 mmol) and LiCl (1.27 g, 30 mmol) at 25 °C in 18 h. Titration with iodine indicates a concentration of 0.41 M (81%).

Preparation of (3,7-dimethylocta-2,6-dien-1-yl)zinc bromide (30e)



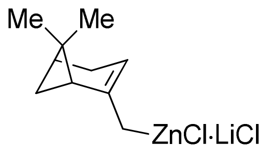
According to **TP1**, the allyic zinc reagent **30e** was prepared from 1-bromo-3,7-dimethylocta-2,6-diene (**29e**, 2.17 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.42 M (83%).

Preparation of cyclohex-2-en-1-ylzinc bromide (30f)



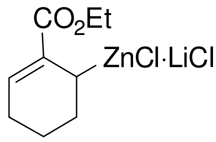
According to **TP1**, the allyic zinc reagent **30f** was prepared from 3-bromocyclohex-1-ene (**29f**, 1.61 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.45 M (89%).

Preparation of 2-methyl-6,6-dimethyl-bicyclo[3.1.1]hept-2-enylzinc chloride (30g)



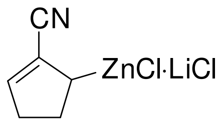
Zinc powder (1.60 g, 25.0 mmol) and dry LiCl (500 mg, 12.0 mmol) were covered with dry THF (10 mL) and activated by the addition of 1,2-dibromoethane (2 mol%) and Me_3SiCl (5 mol%). Subsequently, a solution of 2-chloromethyl-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene (**29g**, 1.71 g, 10.0 mmol) in THF (10 mL) was added in with a syringe pump at 25 °C within 2 h. The resulting mixture was stirred under nitrogen at 25 °C for 30 h. The remaining zinc powder was allowed to settle down. Titration with iodine indicates a concentration of 0.37 M (73%).

Preparation of 2-enecarboxylic acid ethyl ester-6-cyclohexenylzinc chloride (30h)



According to **TP1**, the allyic zinc reagent **30h** was prepared from 6-chloro cyclohex-1-enecarboxylic acid ethyl ester (**29h**, 1.89 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.45 M (90%).

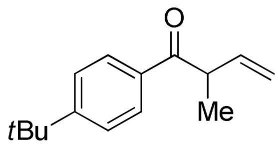
Preparation of 2-cyano-5-cyclopentenylzinc chloride (30i)



According to **TP1**, the allyic zinc reagent **30i** was prepared from 5-chloro-cyclopent-1-enecarbonitrile (**29i**, 1.28 g, 10.0 mmol) using Zn powder (1.31 g, 20 mmol) and LiCl (466 mg, 11 mmol) at 25 °C in 1 h. Titration with iodine indicates a concentration of 0.35 M (69%).

4.4 PREPARATION OF α-SUBSTITUTED β,γ-UNSATURATED KETONES

Preparation of 1-(4-(*tert*-butyl)phenyl)-2-methylbut-3-en-1-one (32a)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32a** was prepared from **30a** (4.75 mL, 2.00 mmol, 0.42 M in THF) and 4-(*tert*-butyl)benzoyl chloride (**31a**, 315 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 50:1) furnished **4a** as a colorless oil (294 mg, 85 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.96 (d, *J*=8.6Hz, 2H), 7.50 (d, *J*=8.9Hz, 2H), 5.95-6.11 (m, 1H), 5.08-5.27 (m, 2H), 4.10-4.25 (m, 1H), 1.28-1.48 (m, 12H).

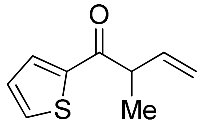
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.8, 156.7, 138.4, 133.7, 128.5, 125.5, 116.3, 45.4, 35.1, 31.1, 17.1.

MS (70 eV, EI), *m/z* (%) = 216 (M^+, 1), 162 (27), 161 (100), 160 (6), 146 (23), 118 (24), 115 (8), 91 (14).

HRMS (EI), *m/z* calc. for **$C_{15}H_{20}O$** (216.1514): 216.1501 (M^+).

IR (ATR) υ (cm^{-1}) = 3080, 3055, 3039, 2964, 2933, 2905, 2870, 1678, 1634, 1604, 1455, 1408, 1364, 1268, 1220, 1191, 1109, 993, 974, 963, 916, 847, 790, 719.

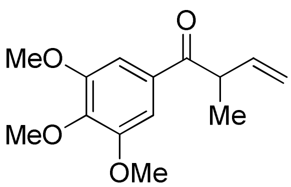
Preparation of 2-methyl-1-(thiophen-2-yl)but-3-en-1-one (32b)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32b** was prepared from **30a** (4.75 mL, 2.00 mmol, 0.42 M in THF) and thiophene-2-carbonyl chloride (**31b**, 235 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 30:1) furnished **32b** as a colorless oil (226 mg, 85 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.79 (dd, *J*=3.9Hz, 1.1Hz, 1H), 7.66 (dd, *J*=5.0Hz, 1.1Hz, 1H), 7.15 (dd, *J*=5.0Hz, 3.9Hz, 1 H), 6.01 (ddd, *J*=17.5Hz, 10.0Hz, 7.9Hz, 1H), 5.11-5.30 (m, 2H), 3.93-4.07 (m, 1H), 1.37 (d, *J*=6.9Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 194.0, 143.6, 138.0, 133.8, 132.1, 128.1, 116.6, 47.4, 17.2.
MS (70 eV, EI), *m/z* (%) = 166 (M^+, 21), 112 (39), 111 (100), 83 (37), 55 (13), 45 (7).
HRMS (EI), *m/z* calc. **$C_9H_{10}OS$** (166.0452): 166.0447 (M^+).
IR (ATR) υ (cm^{-1}) = 3081, 2976, 2932, 2873, 1655, 1632, 1517, 1412, 1354, 1234, 1212, 1056, 991, 918, 862, 830, 772, 719.

Preparation of 2-methyl-1-(3,4,5-trimethoxyphenyl)but-3-en-1-one (32c)

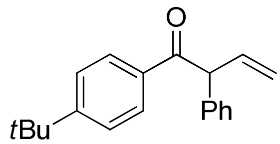


According to **TP2**, the α-substituted β,γ-unsaturated ketone **32c** was prepared from **30a** (4.75 mL, 2.00 mmol, 0.42 M in THF) and 3,4,5-trimethoxybenzoyl chloride (**31c**, 369 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 7:3) furnished **32c** as a white solid (260 mg, 65 %).

m.p.: 60.4-61.3 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.27 (s, 2H), 5.92-6.09 (m, 1H), 5.15-5.23 (m, 2H), 4.07-4.21 (m, 1H), 3.78-4.03 (m, 9H), 1.35 (d, *J*=6.9Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 199.9, 153.0, 142.6, 138.4, 131.5, 116.4, 106.2, 60.9, 56.3, 45.5, 17.2.
MS (70 eV, EI), *m/z* (%) = 250 (M^+, 55), 235 (13), 219 (28), 196 (62), 195 (100), 167 (19), 139 (16), 124 (15), 122 (27), 92 (12), 77 (26), 66 (17), 55 (20), 53 (16).
HRMS (EI), *m/z* calc. for $\mathbf{C_{14}H_{18}O_4}$ (250.1205): 250.1198 (M^+).
IR (ATR) υ (cm^{-1}) = 3080, 3009, 2971, 2953, 2933, 2873, 2839, 1670, 1580, 1507, 1464, 1453, 1411, 1339, 1310, 1230, 1166, 1154, 1149, 1125, 990, 918, 867, 781, 771, 742.

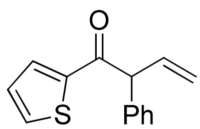
Preparation of 1-(4-(*tert*-butyl)phenyl)-2-phenylbut-3-en-1-one (32d)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32d** was prepared from **30b** (4.65 mL, 2.00 mmol, 0.43 M in THF) and 4-(*tert*-butyl)benzoyl chloride (**31a**, 315 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 30:1) furnished **32d** as a yellow oil (401 mg, 90 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.96 (d, *J*=8.9Hz, 2H), 7.45 (d, *J*=8.9Hz, 2H), 7.24-7.40 (m, 5 H), 6.32-6.47 (m, 1H), 5.20-5.34 (m, 2H), 5.07-5.17 (m, 1H), 1.32 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 198.1, 156.8, 138.6, 137.4, 133.8, 129.0, 128.9, 128.4, 127.1, 125.5, 117.0, 57.9, 35.1, 31.0.
MS (70 eV, EI), *m/z* (%) = 278 (M^+, 6), 222 (21), 221 (24), 162 (11), 161 (100), 146 (10), 118 (17), 117 (15), 115 (15), 91 (17).
HRMS (EI), *m/z* calc. for $\mathbf{C_{20}H_{22}O}$ (278.1671): 278.1669 (M^+).
IR (ATR) υ (cm^{-1}) = 3060, 3028, 2962, 2904, 2867, 1720, 1676, 1602, 1452, 1408, 1363, 1268, 1223, 1187, 1108, 844, 760, 698.

Preparation of 2-phenyl-1-(thiophen-2-yl)but-3-en-1-one (32e)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32e** was prepared from **30b** (4.65 mL, 2.00 mmol, 0.43 M in THF) and thiophene-2-carbonyl chloride (**31b**, 235 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 30:1) furnished **32e** as a yellow oil (281 mg, 77 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.75 (dd, J=3.9Hz, 1.1Hz, 1H), 7.62 (dd, J=5.0Hz, 1.1Hz, 1H), 7.17-7.49 (m, 5H), 7.10 (dd, J=5.0Hz, 3.9Hz, 1H), 6.39 (ddd, J=17.0Hz, 10.1Hz, 8.0Hz, 1H), 5.02-5.43 (m, 3H).

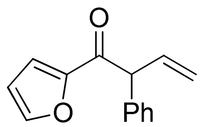
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.3, 143.5, 138.4, 136.6, 134.0, 132.7, 129.0, 128.3, 128.1, 127.4, 117.5, 59.4.

MS (70 eV, EI), *m/z* (%) = 228 (M^+, 37), 195 (14), 117 (21), 115 (32), 111 (100), 91 (14), 44 (16).

HRMS (EI), *m/z* calc. for **$C_{14}H_{12}OS$** (228.0609): 228.0601 (M^+).

IR (ATR) υ (cm^{-1}) = 3104, 3087, 3060, 3025, 2977, 1643, 1634, 1515, 1454, 1410, 1357, 1316, 1249, 1204, 1069, 991, 921, 801, 752, 720, 696, 669, 652.

Preparation of 1-(furan-2-yl)-2-phenylbut-3-en-1-one (32f)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32f** was prepared from **30b** (4.65 mL, 2.00 mmol, 0.43 M in THF) and furan-2-carbonyl chloride (**31d**, 209 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 30:1) furnished **32f** as an off-white solid (285 mg, 84 %).

m.p.: 42.0-43.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.57 (dd, J=1.7Hz, 0.8Hz, 1H), 7.14-7.46 (m, 6H), 6.50 (dd, J=3.6Hz, 1.7Hz, 1H), 6.38 (ddd, J=17.1Hz, 10.1Hz, 8.0Hz, 1H), 5.08-5.31 (m, 3 H).

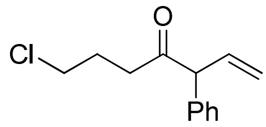
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 187.3, 152.0, 146.6, 138.1, 136.2, 128.8, 128.4, 127.3, 118.2, 117.7, 112.4, 58.0.

MS (70 eV, EI), *m/z* (%) = 212 (M^+, 24), 170 (17), 118 (12), 117 (100), 116 (16), 115 (60), 91 (29).

HRMS (EI), *m/z* calc. for **$C_{14}H_{12}O_2$** (212.0837): 212.0836 (M^+).

IR (ATR) υ (cm^{-1}) = 3144, 3119, 3096, 3083, 3060, 3029, 3021, 1665, 1650, 1463, 1453, 1390, 1327, 1256, 1165, 1041, 1001, 993, 943, 928, 917, 905, 824, 770, 762, 751, 728, 695, 668.

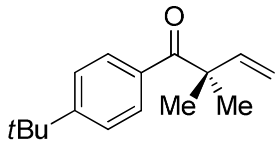
Preparation of 7-chloro-3-phenylhept-1-en-4-one (32g)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32g** was prepared from **30b** (4.65 mL, 2.00 mmol, 0.43 M in THF) and 4-chlorobutanoyl chloride (**31e**, 226 mg, 1.6 mmol) at -20 °C → 25 °C in 2 h. Flash column chromatography (silica, pentane:Et_2O 9.5:0.5) furnished **32g** as a yellow oil (257 mg, 72 %).

^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) = 7.18-7.36 (m, 5H), 6.13-6.35 (m, 1H), 5.03-5.26 (m, 2H), 4.39 (d, *J*=8.2Hz, 1H), 3.24-3.69 (m, 2H), 2.51-2.75 (m, 2H), 1.59-2.26 (m, 2H).
^{13}C-NMR (150 MHz, $CDCl_3$) δ(ppm) = 207.7, 137.7, 135.6, 129.0, 128.2, 127.5, 117.8, 63.2, 44.2, 38.1, 26.4.
MS (70 eV, EI), *m/z* (%) = 222 (M^+, 5), 186 (10), 129 (5), 116 (18), 115 (63), 107 (28), 105 (100), 91 (22), 77 (16), 41 (28).
HRMS (EI), *m/z* calc. for **$C_{13}H_{15}ClO$** (222.0811): 222.0804 (M^+).
IR (ATR) υ (cm^{-1}) = 3080, 3056, 3025, 2961, 2925, 1711, 1687, 1671, 1620, 1598, 1494, 1441, 1311, 1296, 1241, 1216, 1124, 1072, 1030, 974, 942, 917, 762, 700.

Preparation of 1-(4-(*tert*-butyl)phenyl)-2,2-dimethylbut-3-en-1-one (32h)



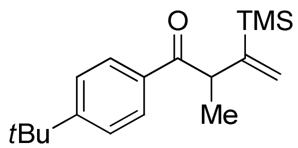
According to **TP2**, the α-substituted β,γ-unsaturated ketone **32h** was prepared from **30c** (4.35 mL, 2.00 mmol, 0.46 M in THF) and 4-(*tert*-butyl)benzoyl chloride (**31a**, 315 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 30:1) furnished **32h** as a colorless oil (343 mg, 93 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm) = 7.89 (d, *J*=8.3Hz, 2H), 7.41 (d, *J*=8.6Hz, 2H), 6.16-6.29 (m, 1H), 5.17-5.31 (m, 2H), 1.42 (s, 6H), 1.34 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm) = 203.8, 155.3, 144.2, 134.0, 129.5, 124.9, 113.8, 50.0, 34.9, 31.1, 26.2.
MS (70 eV, EI), *m/z* (%) = 230 (M^+, 5), 162 (100), 161 (52), 146 (61), 145 (11), 118 (60), 117 (23), 115 (21), 105 (14), 91 (33), 77 (15), 41 (30).

HRMS (EI), *m/z* calc. for $\mathbf{C_{16}H_{12}O}$ (230.1671): 230.1663 (M^+).

IR (ATR) υ (cm^{-1}) = 3084, 2964, 2905, 2868, 1674, 1632, 1604, 1463, 1411, 1363, 1260, 1173, 1109, 973, 917, 846, 773, 668.

Preparation of 1-(4-(*tert*-butyl)phenyl)-2-methyl-3-(trimethyl-silyl)but-3-en-1-one (32i)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32i** was prepared from **30d** (4.90 mL, 2.00 mmol, 0.41 M in THF) and 4-(*tert*-butyl)benzoyl chloride (**31a**, 315 mg, 1.6 mmol) at 25 °C over night. Flash column chromatography (silica, pentane:Et_2O 9.5:0.5) furnished **32i** as a colorless oil (415 mg, 98 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.87 (d, *J*=8.6Hz, 2H), 7.45 (d, *J*=8.6Hz, 2H), 5.57-5.74 (m, 1H), 5.50 (d, *J*=1.9Hz, 1H), 4.16-4.32 (m, 1H), 1.35 (s, 9H), 1.31 (d, *J*=6.6Hz, 3H), 0.18 (s, 9H).

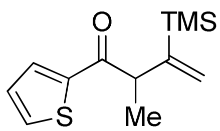
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 201.0, 156.2, 151.9, 134.2, 128.5, 126.9, 125.3, 46.5, 35.0, 31.1, 18.1, -0.7.

MS (70 eV, EI), *m/z* (%) = 288 (M^+, 1), 274 (25), 162 (100), 161 (69), 146 (31), 118 (26), 115 (12), 91 (17), 73 (57), 57 (20).

HRMS (EI), *m/z* calc. for $\mathbf{C_{18}H_{28}OSi}$ (288.1909): 288.1906 (M^+).

IR (ATR) υ (cm^{-1}) = 3081, 3074, 2965, 2940, 2871, 1667, 1517, 1419, 1369, 1358, 1254, 1232, 1059, 939, 856, 837, 729, 671.

Preparation of 2-methyl-1-(thiophen-2-yl)-3-(trimethylsilyl)-but-3-en-1-one (32j)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32j** was prepared from **30d** (4.90 mL, 2.00 mmol, 0.41 M in THF) and thiophene-2-carbonyl chloride (**31b**, 235 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 25:1) furnished **32j** as a colorless oil (378 mg, 99 %).

^{1}H-NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.65-7.73 (m, 1H), 7.55-7.63 (m, 1H), 7.03-7.17 (m, 1H), 5.70-5.79 (m, 1H), 5.53 (d, J=1.7Hz, 1H), 4.03-4.19 (m, 1H), 1.33 (d, J=6.4Hz, 3H), 0.16 (s, 9H).

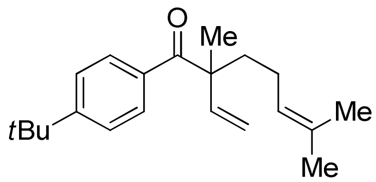
^{13}C-NMR (75 MHz, CDCl$_3$) δ (ppm) = 194.2, 151.6, 144.2, 133.1, 131.8, 127.9, 127.1, 48.5, 18.1, -0.7.

MS (70 eV, EI), *m/z* (%) = 238 (M$^+$, 5), 224 (18), 223 (80), 149 (9), 111 (100), 75 (17), 73 (40), 45 (9).

HRMS (EI), *m/z* calc. for **$C_{12}H_{18}OSSi$** (238.0848): 238.0853 (M$^+$).

IR (ATR) υ (cm^{-1}) = 3104, 3084, 3054, 2954, 2933, 2896, 2874, 1656, 1512, 1452, 1414, 1369, 1354, 1247, 1233, 1222, 1053, 931, 872, 832, 756, 716, 690.

Preparation of 1-(4-(*tert*-butyl)phenyl)-6-methyl-2-vinylhept-5-en-1-one (32k)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32k** was prepared from **30e** (4.75 mL, 2.00 mmol, 0.42 M in THF) and 4-(*tert*-butyl)benzoyl chloride (**31a**, 315 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et$_2$O 50:1) furnished **32k** as a colorless oil (319 mg,70 %).

^{1}H-NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.86 (d, J=8.9Hz, 2H), 7.41 (d, J=8.9Hz, 2H), 6.13-6.28 (m, 1H), 5.16-5.31 (m, 2H), 5.00-5.10 (m, 1H), 1.91-2.04 (m, 2H), 1.74-1.85 (m, 2H), 1.65 (s, 3H), 1.26-1.53 (m, 15H).

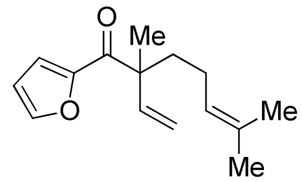
^{13}C-NMR (75 MHz, CDCl$_3$) δ (ppm) = 203.9, 155.1, 143.5, 134.7, 131.9, 129.2, 124.8, 124.1, 114.5, 53.5, 39.1, 34.9, 31.1, 25.6, 23.1, 23.0, 17.4.

MS (70 eV, EI), *m/z* (%) = 298 (M$^+$, 17), 230 (44), 217 (16), 216 (100), 147 (11), 146 (88), 145 (18), 122 (16), 117 (34), 115 (19), 103 (12), 91 (44), 90 (11), 77 (16), 41 (31).

HRMS (EI), *m/z* calc. for **$C_{21}H_{30}O$** (298.2297): 298.2283 (M$^+$).

IR (ATR) υ (cm^{-1}) = 3081, 3043, 2964, 2906, 2868, 1715, 1674, 1605, 1461, 1364, 1268, 1188, 1110, 1070, 1016, 972, 914, 843, 835, 775, 707.

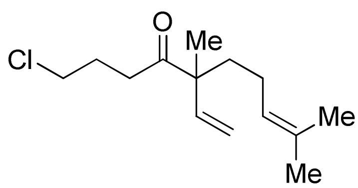
Preparation of 1-(furan-2-yl)-6-methyl-2-vinylhept-5-en-1-one (32l)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32l** was prepared from **30e** (4.75 mL, 2.00 mmol, 0.42 M in THF) and furan-2-carbonyl chloride (**31d**, 209 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 50:1) furnished **32l** as a yellow oil (276 mg, 79 %).

^{1}**H-NMR** (300 MHz, $CDCl_3$) δ (ppm) = 7.55 (dd, *J*=1.7Hz, 0.8Hz, 1H), 7.23 (dd, *J*=3.6Hz, 0.8Hz, 1H), 6.49 (dd, *J*=3.6Hz, 1.7Hz, 1H), 6.23 (dd, *J*=17.4Hz, 10.8Hz, 1H), 5.13-5.26 (m, 2H), 5.00-5.13 (m, 1H), 1.78-2.08 (m, 4H), 1.65 (s, 3H), 1.52 (s, 3H), 1.41 (s, 3H).
^{13}**C-NMR** (75 MHz, $CDCl_3$) δ (ppm) = 191.5, 152.1, 145.3, 142.1, 132.0, 124.0, 118.6, 114.7, 111.6, 52.7, 38.2, 25.6, 23.0, 21.2, 17.5.
MS (70 eV, EI), *m/z* (%) = 232 (M^+, 1), 150 (100), 122 (22), 121 (37), 81 (14), 73 (11), 70 (20), 69 (57), 67 (12), 61 (34), 55 (10), 43 (10), 42 (13), 41 (45).
HRMS (EI), *m/z* calc. for $\mathbf{C_{15}H_{20}O_2}$ (232.1483): 232.1472 (M^+).
IR (ATR) υ (cm^{-1}) = 3130, 3084, 2971, 2935, 2875, 1720, 1663, 1560, 1461, 1384, 1278, 1225, 1161, 1078, 1068, 1012, 979, 910, 884, 824, 762.

Preparation of 1-chloro-9-methyl-5-vinyldec-8-en-4-one (32m)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32m** was prepared from **30e** (4.75 mL, 2.00 mmol, 0.42 M in THF) and 4-chlorobutanoyl chloride (**31e**, 226 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 50:1) furnished **32m** as a colorless oil (271 mg, 74 %).

^{1}**H-NMR** (300 MHz, $CDCl_3$) δ (ppm) = 5.94 (dd, *J*=17.6Hz, 10.6Hz, 1H), 4.97-5.36 (m, 3H), 3.57 (t, *J*=6.2Hz, 2H), 2.66 (dt, *J*=7.0Hz, 3.5Hz, 2H), 1.40-2.33 (m, 12H), 1.14-1.36 (m, 3H).

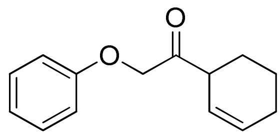
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 211.7, 141.4, 132.0, 123.9, 115.2, 54.2, 44.6, 37.6, 34.6, 26.7, 25.7, 23.0, 19.6, 17.6.

MS (70 eV, EI), *m/z* (%) = 242 (M^+, 1), 162 (13), 160 (41), 107 (18), 105 (57), 88 (29), 83 (34), 81 (24), 77 (14), 73 (35), 70 (70), 69 (96), 67 (17), 61 (100), 45 (94), 43 (67), 42 (41), 41 (68).

HRMS (EI), *m/z* calc. for $\mathbf{C_{14}H_{23}ClO}$ (242.1437): 242.1432 (M^+).

IR (ATR) υ (cm^{-1}) = 3085, 3050, 2967, 2925, 2856, 1705, 1632, 1447, 1410, 1374, 1358, 1296, 1101, 1076, 1002, 919, 731.

Preparation of 1-(cyclohex-2-en-1-yl)-2-phenoxyethanone (32n)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32n** was prepared from **30f** (4.45 mL, 2.00 mmol, 0.45 M in THF) and 2-phenoxyacetyl chloride (**31f**, 273 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 9.5:0.5) furnished **32n** as a yellow oil (260 mg, 75 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.24-7.41 (m, 2H), 6.82-7.07 (m, 3H), 5.89-6.01 (m, 1H), 5.81 (ddd, *J*=10.2Hz, 5.3Hz, 2.2Hz, 1H), 4.61-4.81 (m, 2H), 3.50 (ddd, *J*=9.1Hz, 6.1Hz, 3.3Hz, 1H), 2.00-2.13 (m, 1H), 1.51-1.98 (m, 5H).

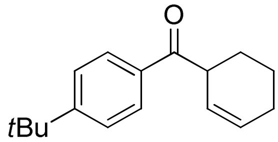
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 207.9, 157.9, 131.0, 129.7, 122.9, 121.7, 114.6, 71.7, 45.5, 24.7, 24.3, 20.6.

MS (70 eV, EI), *m/z* (%) = 216 (M^+, 29), 188 (11), 123 (25), 122 (11), 109 (46), 108 (16), 107 (58), 95 (28), 81 (100), 80 (14), 79 (50), 77 (64), 66 (10), 65 (13), 53 (11), 41 (10).

HRMS (EI), *m/z* calc. for $\mathbf{C_{14}H_{16}O_2}$ (216.1150): 216.1149 (M^+).

IR (ATR) υ (cm^{-1}) = 3097, 3060, 3041, 2936, 2867, 1707, 1681, 1598, 1588, 1494, 1432, 1198, 1173, 1085, 1072, 1049, 963, 885, 833, 751, 690.

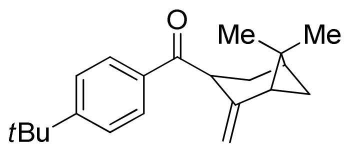
Preparation of (4-(*tert*-butyl)phenyl)(cyclohex-2-en-1-yl)-methanone (32o)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32o** was prepared from **30f** (4.45 mL, 2.00 mmol, 0.45 M in THF) and 4-(*tert*-butyl)benzoyl chloride (**31a**, 315 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 30:1) furnished **32o** as a yellow oil (322 mg, 83 %).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.91 (d, J=8.8Hz, 2H), 7.47 (d, J=8.8Hz, 2H), 5.85-6.01 (m, 1H), 5.65-5.79 (m, 1H), 4.01-4.11 (m, 1H), 1.81-2.12 (m, 5H), 1.62-1.73 (m, 1H), 1.25-1.39 (m, 9H).
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm) = 201.5, 156.5, 133.6, 129.9, 128.5, 125.5, 124.9, 43.8, 35.1, 31.1, 25.9, 24.8, 20.9.
MS (70 eV, EI), *m/z* (%) = 242 (M^+, 1), 238 (3), 227 (2), 223 (6), 185 (6), 162 (13), 161 (100), 146 (7), 117 (3), 115 (2), 91 (3), 77 (2).
HRMS (EI), *m/z* calc. for **$C_{17}H_{22}O$** (242.1671): 242.1662 (M^+).
IR (ATR) υ (cm^{-1}) = 3087, 3062, 3032, 2958, 2905, 2867, 1675, 1650, 1603, 1461, 1407, 1363, 1267, 1233, 1187, 1116, 1110, 1102, 1015, 963, 845, 718, 700.

Preparation of (4-(*tert*-butyl)phenyl)((1S,5S)-6,6-dimethyl-2-methylenebicyclo-[3.1.1]heptan-3-yl)methanone (32p)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32p** was prepared from **30g** (5.41 mL, 2.00 mmol, 0.37 M in THF) and 4-(*tert*-butyl)benzoyl chloride (**31a**, 315 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 50:1) furnished **32p** as a white solid (318 mg, 67 %).

m.p.: 122.8-124.8 °C.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.92 (d, J=8.6Hz, 2H), 7.48 (d, J=8.6Hz, 2H), 4.76-4.87 (m, 1H), 4.59 (s, 1H), 4.43-4.55 (m, 1H), 2.46-2.59 (m, 1H), 2.30-2.42 (m, 1H), 2.19-2.30 (m, 1H), 1.98-2.10 (m, 2H), 1.66 (d, J=10.2Hz, 1H), 1.34 (s, 9H), 1.28 (s, 3H), 0.85 (s, 3H).

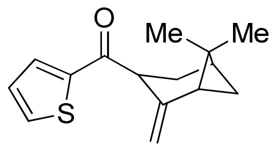
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 202.2, 156.4, 149.3, 134.7, 128.9, 125.5, 111.0, 51.7, 42.1, 40.3, 40.2, 35.0, 31.1, 28.6, 27.3, 25.8, 21.6.

MS (70 eV, EI), *m/z* (%) = 296 (M^+, 3), 255 (11), 162 (26), 161 (100), 146 (12), 134 (16), 119 (12), 118 (17), 93 (11), 91 (15), 57 (11), 41 (10).

HRMS (EI), *m/z* calc. for **$C_{21}H_{28}O$** (296.2140): 296.2144 (M^+).

IR (ATR) υ (cm^{-1}) = 3076, 3063, 2960, 2944, 2915, 2864, 1669, 1629, 1602, 1464, 1363, 1333, 1268, 1237, 1220, 1195, 1106, 1050, 1006, 938, 886, 861, 846, 838, 824, 800, 752, 711, 683.

Preparation of ((1S,5S)-6,6-dimethyl-2-methylenebicyclo-[3.1.1]heptan-3-yl)-(thiophen-2-yl)methanone (32q)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32q** was prepared from **30g** (5.41 mL, 2.00 mmol, 0.37 M in THF) and thiophene-2-carbonyl chloride (**31b**, 235 mg, 1.6 mmol) at -78 °C → 25 °C in 2 h. Flash column chromatography (silica, pentane:Et_2O 30:1) furnished **32q** as a yellow oil (351 mg, 89 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.75 (dd, *J*=3.8Hz, 1.1Hz, 1H), 7.66 (dd, *J*=4.9Hz, 1.2Hz, 1H), 7.16 (dd, *J*=5.0Hz, 3.8Hz, 1H), 4.83 (s, 1H), 4.64-4.74 (m, 1H), 4.28-4.40 (m, 1H), 2.52 (t, *J*=5. Hz, 1H), 2.32-2.44 (m, 1H), 2.20-2.30 (m, 1H), 1.99-2.15 (m, 2H), 1.75 (d, *J*=9.9Hz, 1H), 1.28 (s, 3H), 0.84 (s, 3H).

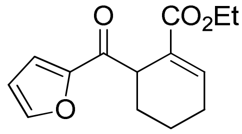
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 195.5, 149.0, 145.3, 134.0, 132.3, 128.1, 111.2, 51.5, 43.6, 40.3, 39.9, 28.8, 27.3, 25.8, 21.6.

MS (70 eV, EI), *m/z* (%) = 246 (M^+, 1), 177 (7), 135 (19), 134 (11), 119 (10), 111 (100), 93 (37), 91 (12), 69 (7), 43 (26), 41 (28).

HRMS (EI), *m/z* calc. for **$C_{15}H_{18}OS$** (246.1078): 246.1073 (M^+).

IR (ATR) υ (cm^{-1}) = 3098, 3083, 2974, 2918, 2866, 1660, 1632, 1517, 1412, 1353, 1235, 1212, 1196, 1064, 1050, 938, 885, 833, 761, 718.

Preparation of ethyl 6-(furan-2-carbonyl)cyclohex-1-ene-carboxylate (32r)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32r** was prepared from **30h** (4.45 mL, 2.00 mmol, 0.45 M in THF) and furan-2-carbonyl chloride (**31d**, 209 mg, 1.6 mmol) at -78 °C → 25 °C over night. Flash column chromatography (silica, pentane:Et_2O 1:1) furnished **32r** as a white solid (223 mg, 90 %).

m.p.: 56.6-57.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.56-7.61 (m, 1H), 7.29 (dt, *J*=4.0Hz, 1.4Hz, 1H), 7.24 (dt, *J*=3.6Hz, 0. Hz, 1H), 6.53 (dd, *J*=3.6Hz, 1.7Hz, 1H), 4.23-4.33 (m, 1H), 4.02-4.16 (m, 2H), 2.18-2.40 (m, 2H), 1.81-2.01 (m, 2H), 1.56-1.71 (m, 2H), 1.14 (t, *J*=7.3Hz, 3H).

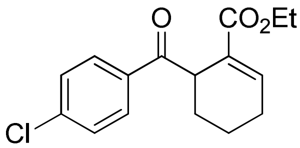
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 190.2, 166.4, 152.1, 146.2, 142.9, 128.6, 117.2, 112.2, 60.4, 42.7, 26.3, 25.4, 18.6, 14.0.

MS (70 eV, EI), *m/z* (%) = 248 (M^+, 10), 203 (23), 202 (100), 174 (17), 95 (45), 79 (16).

HRMS (EI), *m/z* calc. for **$C_{14}H_{16}O_4$** (248.1049): 248.1046 (M^+).

IR (ATR) υ (cm^{-1}) = 3139, 3123, 3096, 2984, 2968, 2957, 2907, 2869, 2827, 1696, 1657, 1646, 1470, 1395, 1374, 1285, 1267, 1253, 1233, 1201, 1171, 1142, 1094, 1080, 1071, 1055, 1034, 1020, 1007, 957, 943, 923, 789, 753, 730, 707.

Preparation of ethyl 6-(4-chlorobenzoyl)cyclohex-1-ene-carboxylate (32s)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32s** was prepared from **30h** (4.45 mL, 2.00 mmol, 0.45 M in THF) and 4-chlorobenzoyl chloride (**31g**, 280 mg, 1.6 mmol) at -78 °C → 25 °C over night. Flash column chromatography (silica, pentane:Et_2O 8:2) furnished **32s** as a white solid (234 mg, 80 %).

m.p.: 59.4-60.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.89-8.01 (m, 2H), 7.37-7.50 (m, 2H), 7.26-7.37 (m, 1H), 4.39-4.51 (m, 1H), 4.09 (dq, *J*=7.1Hz, 1.7Hz, 2H), 2.15-2.40 (m, 2H), 1.89-2.02 (m, 1H), 1.74-1.87 (m, 1H), 1.50-1.71 (m, 2H), 1.15 (t, *J*=7.1Hz, 3H).

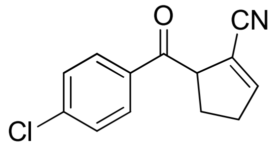
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.2, 166.5, 142.6, 139.2, 134.6, 129.9, 129.2, 128.9, 60.5, 42.0, 26.1, 25.4, 18.5, 14.1.

MS (70 eV, EI), *m/z* (%) = 292 (M^+, 2), 247 (4), 246 (8), 140 (7), 139 (100), 111 (11), 79 (4).

HRMS (EI), *m/z* calc. for $\mathbf{C_{16}H_{17}ClO_3}$ (292.0866): 292.0860 (M^+).

IR (ATR) υ (cm^{-1}) = 3097, 3069, 2990, 2938, 2863, 2824, 1699, 1677, 1586, 1481, 1446, 1397, 1281, 1245, 1214, 1101, 1091, 1082, 1065, 1043, 1005, 947, 916, 834, 751, 737, 674.

Preparation of 5-(4-chlorobenzoyl)cyclopent-1-enecarbonitrile (32t)



According to **TP2**, the α-substituted β,γ-unsaturated ketone **32t** was prepared from **30i** (5.70 mL, 2.00 mmol, 0.35 M in THF) and 4-chlorobenzoyl chloride (**31g**, 280 mg, 1.6 mmol) at -78 °C → 25 °C over night. Flash column chromatography (silica, pentane:Et_2O 1:1) furnished **32t** as a white solid (162 mg, 70 %).

m.p.: 77.3-79.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.86-7.97 (m, 2H), 7.42-7.53 (m, 2H), 6.88 (q, *J*=2.5Hz, 1H), 4.59-4.73 (m, 1H), 2.58-2.74 (m, 2H), 2.38-2.55 (m, 1H), 2.09-2.23 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 196.7, 152.0, 140.4, 133.6, 130.1, 129.2, 115.7, 113.7, 53.9, 33.1, 28.2.

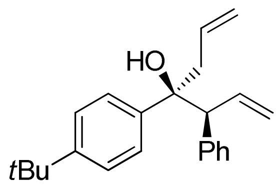
MS (70 eV, EI), *m/z* (%) = 231 (M^+, 1), 142 (2), 140 (6), 139 (100), 111 (21), 92 (2), 76 (3), 75 (7), 65 (2).

HRMS (EI), *m/z* calc. for $\mathbf{C_{13}H_{10}ClNO}$ (231.0451): 231.0443 (M^+).

IR (ATR) υ (cm^{-1}) = 3091, 3066, 2976, 2921, 2848, 2220, 1675, 1587, 1573, 1486, 1434, 1399, 1345, 1319, 1282, 1222, 1209, 1086, 1006, 859, 844, 832, 818, 732, 720, 670.

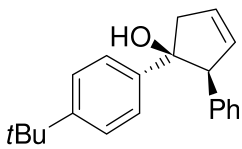
4.4.1 FURTHER FUNCTIONALIZATION OF β,γ-UNSATURATED KETONE ***32d***

Preparation of (3S,4S)-4-(4-(*tert*-butyl)phenyl)-3-phenylhepta-1,6-dien-4-ol (rac)(33)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 1-(4-(*tert*-butyl)phenyl)-2-phenylbut-3-en-1-one (**32d**, 557 mg, 2.0 mmol) and cooled to 0 °C. Then, allyl Grignard reagent (1.80 mL, 2.2 mmol, 1.22 M in THF) was added dropwise and the reaction mixture was warmed to 25 °C. After stirring for 1.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with EtOAc (3x10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The compound was used directly for the metathesis reaction without further purification since GC-analysis indicated >98 % purity.

Preparation of (1S,2S)-1-(4-(*tert*-butyl)phenyl)-2-phenylcyclo-pent-3-enol (rac)(34)



The synthesis of **34** is following a literature-known procedure.[275] A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with Grubbs II catalyst (85 mg, 0.10 mmol) and dissolved in dichloromethane (15 mL). The crude of **7** (641 mg, 2.0 mmol) was dissolved in dichloromethane (5 mL) and added dropwise to the reaction mixture. After heating to 40 °C for 4 h, the solvent was removed *in vacuo* and the crude residue obtained was purified by flash column chromatography (silica, pentane:Et_2O 9:1) to give the analytically pure product **34** as an off-white solid (567 mg, 97 %).

m.p.: 67.9-69.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.37-7.48 (m, 4H), 7.26-7.36 (m, 3H), 7.02-7.15 (m, 2H), 6.04-6.16 (m, 1H), 5.82-5.98 (m, 1H), 4.37-4.50 (m, 1H), 3.01-3.13 (m, 1H), 2.82-2.96 (m, 1H), 1.53-1.65 (m, 1H), 1.40 (s, 9H).

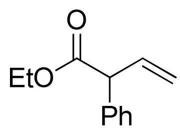
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 149.4, 144.0, 137.2, 131.4, 130.3, 129.0, 128.5, 127.5, 124.9, 124.9, 83.0, 63.7, 50.6, 34.4, 31.4.

[275] A. K. Chatterjee, J. P. Morgan, M. Scholl, R. H. Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.

MS (70 eV, EI) *m/z* (%) = 292 (M^+, 52), 275 (21), 274 (94), 260 (24), 259 (100), 215 (15), 146 (10), 129 (14), 128 (10), 118 (16), 117 (25), 116 (11), 115 (25), 91 (33), 57 (16), 41 (14).
HRMS (EI), *m/z* calc. for $\mathbf{C_{21}H_{24}O}$ (292.1827): 292.1821 (M^+).
IR (ATR) υ (cm^{-1}) = 3530, 3502, 3076, 3053, 3023, 2957, 2925, 2911, 2866, 1491, 1452, 1363, 1273, 1109, 1067, 1031, 1026, 1021, 959, 904, 897, 827, 822, 770, 752, 740, 709, 694, 687.

4.5 Preparation of α-Substituted β,γ-Unsaturated Esters

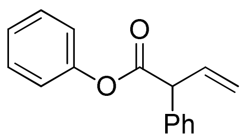
Preparation of ethyl 2-phenylbut-3-enoate (36a)



According to **TP2**, the α-substituted β,γ-unsaturated ester **36a** was prepared from **30b** (4.65 mL, 2.00 mmol, 0.43 M in THF) and ethyl carbonochloridate (**35a**, 174 mg, 1.6 mmol) at -78 °C in 1 h. Flash column chromatography (silica, pentane:Et_2O 30:1) furnished **36a** as a colorless oil (195 mg, 64 %).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.22-7.41 (m, 5H), 6.16-6.28 (m, 1H), 5.09-5.25 (m, 2H), 4.31 (d, *J*=8.1Hz, 1H), 4.09-4.26 (m, 2H), 1.24 (t, *J*=7.2Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm) = 172.3, 138.1, 135.9, 128.7, 128.0, 127.3, 117.4, 61.0, 55.8, 14.1.
MS (70 eV, EI), *m/z* (%) = 190 (M^+, 7), 117 (100), 116 (8), 115 (31), 91 (10).
HRMS (EI), *m/z* calc. for $C_{12}H_{14}O_2$ (190.0994): 190.0985 (M^+).
IR (ATR) υ (cm^{-1}) = 3084, 3063, 3029, 2981, 2936, 2905, 2872, 1729, 1495, 1454, 1367, 1306, 1225, 1191, 1151, 1027, 990, 922, 728, 697.

Preparation of phenyl 2-phenylbut-3-enoate (36b)



According to **TP2**, the α-substituted β,γ-unsaturated ester **36b** was prepared from **30b** (4.65 mL, 2.00 mmol, 0.43 M in THF) and phenyl carbonochloridate (**35b**, 251 mg, 1.6 mmol) at -78 °C → 25 °C in 2 h. Flash column chromatography (silica, pentane:Et_2O 30:1) furnished **36b** as a colorless oil (297 mg, 78 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm) = 7.12-7.55 (m, 8H), 6.94-7.11 (m, 2H), 6.33 (ddd, J=17.1Hz, 10.2Hz, 7.9Hz, 1H), 5.21-5.36 (m, 2H), 4.56 (d, J=7.8Hz, 1H).

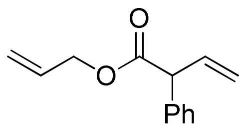
^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm) = 170.7, 150.7, 137.6, 135.2, 129.4, 128.9, 128.0, 127.6, 125.9, 121.3, 118.1, 55.7.

MS (70 eV, EI), *m/z* (%) = 238 (M^+, 1), 145 (22), 144 (100), 116 (26), 115 (65), 91 (20), 65 (10).

HRMS (EI), *m/z* calc. for **$C_{16}H_{14}O_2$** (238.0994): 238.0993 (M^+).

IR (ATR) υ (cm^{-1}) = 3081, 3067, 3025, 2983, 2925, 1743, 1590, 1490, 1453, 1304, 1290, 1186, 1161, 1144, 1119, 1069, 984, 979, 941, 821, 756, 729, 696, 687.

Preparation of allyl 2-phenylbut-3-enoate (36c)



According to **TP2**, the α-substituted β,γ-unsaturated ester **36c** was prepared from **30b** (4.65 mL, 2.00 mmol, 0.43 M in THF) and allyl carbonochloridate (**35c**, 193 mg, 1.6 mmol) at -78 °C → 25 °C in 2 h. Flash column chromatography (silica, pentane:Et_2O 30:1) furnished **36c** as a colorless oil (265 mg, 82 %).

^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) = 7.21-7.41 (m, 5H), 6.19-6.28 (m, 1H), 5.82-5.93 (m, 1H), 5.10-5.32 (m, 4H), 4.55-4.67 (m, 2H), 4.35 (d, J=8.2Hz, 1H).

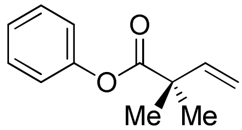
^{13}C-NMR (150 MHz, $CDCl_3$) δ(ppm) = 172.0, 138.0, 135.7, 131.9, 128.7, 128.0, 127.4, 118.3, 117.6, 65.5, 55.8.

MS (70 eV, EI), *m/z* (%) = 202 (M^+, 1), 118 (13), 117 (100), 116 (11), 115 (42), 91 (13), 41 (11).

HRMS (EI), *m/z* calc. for **$C_{13}H_{14}O_2$** (202.0994): 202.0985 (M^+).

IR (ATR) υ (cm^{-1}) = 3084, 3063, 3029, 2983, 2941, 2882, 1732, 1495, 1453, 1306, 1220, 1190, 1149, 989, 921, 729, 697.

Preparation of phenyl 2,2-dimethylbut-3-enoate (36d)



According to **TP2**, the α-substituted β,γ-unsaturated ester **36d** was prepared from **30c** (4.35 mL, 2.00 mmol, 0.46 M in THF) and phenyl carbonochloridate (**35b**, 251 mg, 1.6 mmol) at -20 °C → 25 °C in 2 h. Flash column chromatography (silica, pentane:Et_2O 30:1) furnished **36d** as a colorless oil (213 mg, 70 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.31-7.47 (m, 2H), 7.18-7.29 (m, 1H), 7.00-7.15 (m, 2H), 6.20 (dd, *J*=17.4Hz, 10.8Hz, 1H), 5.14-5.34 (m, 2H), 1.49 (s, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 174.8, 151.0, 142.0, 129.4, 125.7, 121.4, 113.6, 45.1, 24.6.
MS (70 eV, EI), *m/z* (%) = 190 (M^+, 7), 97 (10), 95 (11), 94 (100), 69 (89), 41 (36).
HRMS (EI), *m/z* calc. for $\mathbf{C_{12}H_{14}O_2}$ (190.0994): 190.0996 (M^+).
IR (ATR) υ (cm^{-1}) = 3088, 3067, 3043, 2979, 2935, 2873, 1747, 1638, 1593, 1493, 1470, 1192, 1161, 1106, 1070, 1001, 915, 832, 738, 688, 670.

5. PREPARATION OF FUNCTIONALIZED ALKENYLZINC REAGENTS BEARING CARBONYL GROUPS *VIA* DIRECT METAL INSERTION

5.1 PREPARATION OF STARTING MATERIALS

All reagents were obtained from commercial sources. Compounds **37a**,[276] **37b**,[277] **37c**,[278] **37d**,[279] **37e** and **42d**[280], **37f**,[281] **37g** and **37h,**[282] **37i**,[283] **42a** and **42b**,[284] **42c**[285] as well as **42e**[286] were prepared according to literature-known procedures. Compound **42f** was synthesized analogous a literature-known procedure[280] employing $PhSSO_2Ph$ as electrophile.

5.2 TYPICAL PROCEDURES

Typical procedure 1 (TP1): LiCl-mediated zinc insertion into activated alkenyl bromides

A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (1.5-2 equiv) and heated with a heat gun under high vacuum (5 min). After cooling to room temperature, zinc powder (1.5-2 equiv) was added, followed by THF (1 mL/mmol). The zinc powder then was activated using 1,2-dibromoethane (5 mol%) and TMSCl (5 mol%). Then, the substrate (1 equiv) was added neat at 25 °C. In the case of very exothermic reactions, the reaction mixture was kept at 25 °C using a water bath and stirred for the given time until GC-analysis of hydrolyzed reaction aliquot showed full consumption of the starting material. Then, the remaining zinc powder was allowed to settle down or centrifuged (10 min, 2000 rpm). The yield of the insertion rection was determined by iodometric titration[192] and the supernatant solution was then used in the reaction with electrophiles.

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Typical procedure 2 (TP2): LiCl-mediated magnesium insertion in the presence of zinc chloride into less activated alkenyl bromides

A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (1.5 equiv) and heated with a heat gun under high vacuum (5 min). After cooling to room temperature, magnesium turnings (2.5 equiv) were added, followed by THF (1 mL/mmol). The magnesium was activated using 1,2-dibromoethane (5 mol%) and TMSCl (5 mol%). Then, $ZnCl_2$-solution (1.1 equiv, 1 M in THF) was added followed by the substrate (1 equiv). The reaction mixture was stirred at 25 °C until GC-analysis of hydrolyzed reaction aliquot showed full consumption of the starting material. Then, solids were allowed to settle or the reation mixture was centrifuged (10 min, 2000 rpm). The yield of the insertion rection was determined by iodometric titration[192] of the supernatant solution.

Typical procedure 3 (TP3): Allylation or Acylation of alkenyl zinc reagents

The freshly prepared zinc reagent was cooled to -40 °C and the corresponding allyl bromide (0.8–0.9 equiv) was added, followed by CuCN·2LiCl (1 M in THF). The reaction mixture was allowed to warm to 0 °C. After stirring for the given time, the reaction mixture was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL), washed with sat. NH_4Cl/NH_3 solution (9:1, 2x10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

Typical procedure 4 (TP4): Cross-coupling reactions of alkenyl zinc reagents

The desired aryl bromide or iodide (0.8 equiv) was added to the freshly prepared zinc reagent followed by $Pd(PPh_3)_4$ (2 mol%) and the mixture was stirred for the given time at 50 °C. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

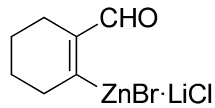
Typical procedure 5 (TP5): Preparation of tetrahydrophthalazines of type 5

The freshly prepared zinc reagent was cooled to -40 °C and CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF) was added followed by the corresponding acid chloride (0.6-

0.8 equiv). After stirring for the given time at -40 °C, the reaction mixture was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL), washed with sat. NH_4Cl/NH_3 solution (9:1, 2x10 mL) and extracted with Et_2O (3x10 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was dissolved in MeOH (20 mL) and hydrazine hydrate (3 equiv) was added at room temperature. After stirring for 14 h, the reaction mixture was concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

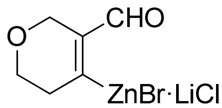
5.3 PREPARATION OF ALKENYL ZINC REAGENTS FROM ACTIVATED ALKENYL BROMIDES

Preparation of (2-formylcyclohex-1-en-1-yl)zinc bromide (38a)



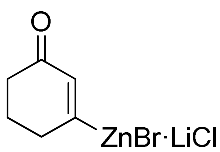
According to **TP1**, the zinc reagent **38a** was prepared from 2-bromocyclohex-1-ene-1-carbaldehyde (**37a**, 1.89 g, 10.0 mmol) using Zn powder (1.31 g, 20.0 mmol) and LiCl (848 mg, 20.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.77 M (86%).

Preparation of (5-formyl-3,6-dihydro-*2H*-pyran-4-yl)zinc bromide (38b)



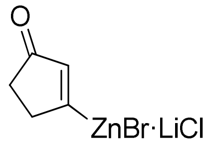
According to **TP1**, the zinc reagent **38b** was prepared from 4-bromo-5,6-dihydro-2H-pyran-3-carbaldehyde (**37b**, 955 mg, 5.00 mmol) using Zn powder (490 mg, 7.50 mmol) and LiCl (318 mg, 7.5 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.72 M (77%).

Preparation of (3-oxocyclohex-1-en-1-yl)zinc bromide (38c)



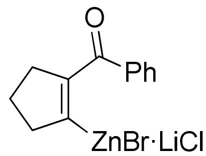
According to **TP1**, the zinc reagent **38c** was prepared from 3-bromocyclohex-2-enone (**37c**, 1.75 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.77 M (86%).

Preparation of (3-oxocyclohex-1-en-1-yl)zinc bromide (38d)



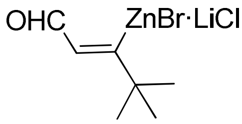
According to **TP1**, the zinc reagent **38d** was prepared from 3-bromocyclopent-2-enone (**37d**, 1.50 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.99 M (94%).

Preparation of (2-benzoylcyclopent-1-en-1-yl)zinc bromide (38e)



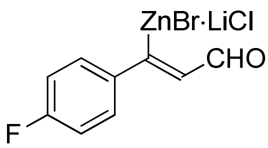
According to **TP1**, the zinc reagent **38e** was prepared from (2-bromocyclopent-1-en-1-yl)(phenyl)methanone (**37e**, 2.51 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.56 M (62%).

Preparation of (*Z*)-(4,4-dimethyl-1-oxopent-2-en-3-yl)zinc bromide (38f)



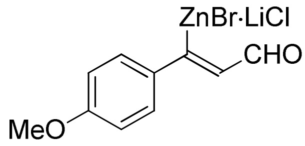
According to **TP1**, the zinc reagent **38f** was prepared from (*Z*)-3-bromo-4,4-dimethylpent-2-enal (**37f**, 1.91 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.61 M (67%).

Preparation of (*Z*)-(1-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)zinc bromide (38g)



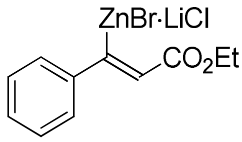
According to **TP1**, the zinc reagent **38g** was prepared from (*Z*)-3-bromo-3-(4-fluorophenyl)acrylaldehyde (**37g**, 2.29 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.32 M (35%).

Preparation of (*Z*)-(1-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)zinc bromide (38h)



According to **TP1**, the zinc reagent **38h** was prepared from (*Z*)-3-bromo-3-(4-methoxyphenyl)acrylaldehyde (**37h**, 2.41 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.37 M (41%).

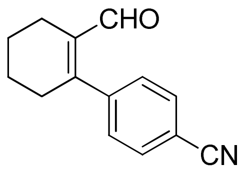
Preparation of (*Z*)-(3-ethoxy-3-oxo-1-phenylprop-1-en-1-yl)zinc bromide (38i)



According to **TP1**, the zinc reagent **38i** was prepared from (*Z*)-ethyl 3-bromo-3-phenylacrylate (**37i**, 2.55 g, 10.0 mmol) using Zn powder (981 mg, 15.0 mmol) and LiCl (636 mg, 15.0 mmol) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.56 M (62%).

*5.4 REACTIONS OF ALKENYL ZINC REAGENTS OF TYPE **38** WITH ELECTROPHILES*

Preparation of 4-(2-formylcyclohex-1-en-1-yl)benzonitrile (40a)



The cross-coupling reaction of **38a** (2.60 mL, 2.00 mmol, 0.77 M in THF) with 4-bromobenzonitrile (**39a**, 291 mg, 1.60 mmol) was performed according to **TP4** in 1.5 h. Flash column chromatography (silica, pentane:Et_2O 8.5:1.5) furnished **40a** as a yellow solid (276 mg, 82 %).

m.p.: 78.0-79.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.42 (s, 1 H), 7.68 (d, *J*=8.6Hz, 2H), 7.35 (d, *J*=8.6Hz, 2H), 2.57-2.47 (m, 2H), 2.43-2.11 (m, 2H), 1.89-1.65 (m, 4H).

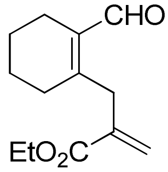
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 192.2, 156.7, 144.3, 136.9, 132.0, 129.3, 118.3, 112.1, 33.6, 22.2, 22.2, 21.2.

MS (70 eV, EI), *m/z* (%) = 211 (M^+, 100), 210 (84), 182 (28), 154 (29), 140 (24), 116 (32).

HRMS *m/z* calc. for $\mathbf{C_{14}H_{13}NO}$ (211.0997): 211.0992.

IR (ATR) (cm^{-1}) υ = 2928, 2856, 2227, 1709, 1663, 1621, 1604, 1500, 1408, 1361, 1275, 1211, 1193, 1171, 984, 856, 826, 711.

Preparation of ethyl 2-[(2-formylcyclohex-1-en-1-yl)methyl]prop-2-enoate (40b)



The allylation reaction of **38a** (2.60 mL, 2.00 mmol, 0.77 M in THF) with CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (**39b**, 347 mg, 1.80 mmol) was performed according to **TP3** in 1 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **40b** as a colorless oil (377 mg, 94 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.07 (s, 1H), 6.27 (d, *J*=1.1Hz, 1H), 5.51 (d, *J*=1.1Hz, 1H), 4.21 (d, *J*=7.1Hz, 2H), 3.54 (s, 2H), 2.28-2.14 (m, 4H), 1.16 (dt, *J*=6.4Hz, 3.2Hz, 4H), 1.37 (t, *J*=7.1Hz, 3H).

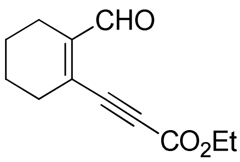
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.2, 166.5, 154.8, 138.0, 135.5, 126.2, 61.0, 33.7, 31.6, 22.4, 22.0, 21.6, 14.1.

MS (70 eV, EI), *m/z* (%) = 222 (M^+, 3), 149 (100), 148 (49), 147 (28), 119 (25), 91 (37), 79 (25).

HRMS *m/z* calc. for $\mathbf{C_{13}H_{18}O_3}$ (222.1256): 222.1258.

IR (ATR) υ (cm^{-1}) = 2956, 2257, 1781, 1678, 1629, 1588, 1505, 1377, 1255, 1169, 1144, 1112, 1035, 934, 814, 762.

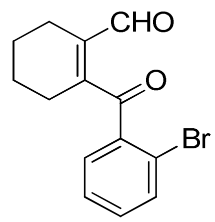
Preparation of ethyl 3-(2-formylcyclohex-1-en-1-yl)prop-2-ynoate (40c)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the alkenyl zinc reagent **38a** (2.80 mL, 2.40 mmol, 0.85 M in THF) and cooled to -78 °C. CuCN·2LiCl (0.24 mL, 0.24 mmol, 1.0 M in THF) was added, followed by ethyl 3-bromoprop-2-ynoate (**39c**, 354 mg, 2.00 mmol) and the reaction mixture was stirred for 3 h at -78 °C. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et_2O 4:1) to give **40c** as a colorless oil (331 mg, 80 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.15 (s, 1H), 4.28 (q, *J*=6.0Hz, 2H), 2.50-2.40 (m, 2H), 2.35-2.25 (m, 2H), 1.75-1.60 (m, 4H), 1.33 (t, *J*=6.0Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.5, 153.3, 147.6, 135.8, 88.3, 81.8, 62.4, 31.2, 22.3, 21.5, 20.6, 14.0.
MS (70 eV, EI), *m/z* (%) = 296 (M^+, 9), 162 (75), 105 (36), 91 (40), 77 (49), 43 (100).
HRMS *m/z* calc. for **$C_{12}H_{14}O_3$** (206.0943): 206.0946.
IR (ATR) υ (cm^{-1}) = 2939, 2210, 1708, 1678, 1366, 1255, 1217, 1140, 1017, 747.

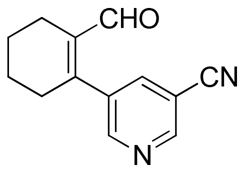
Preparation of 2-[(2-bromophenyl)carbonyl]cyclohex-1-ene-1-carbaldehyde (40d)



The acylation reaction of **38a** (2.80 mL, 2.40 mmol, 0.85 M in THF) with CuCN·2LiCl (2.40 mL, 2.40 mmol, 1 M in THF) and 2-bromobenzoyl chloride (**39d**, 439 mg, 2.00 mmol) was performed according to **TP3** in 4 h. Flash column chromatography (silica, pentane:Et_2O 10:1 then 4:1) furnished **40d** as a colorless oil (297 mg, 51 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.74 (s, 1H). 7.70-7.55 (m, 2H), 7.45-7.35 (m, 2H), 2.50-2.35 (m, 4H), 1.80-1.70 (m, 4H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 197.3, 191.2, 154.6, 141.7, 139.0, 134.3, 133.2, 131.2, 127.9, 120.7, 28.7, 22.5, 21.8, 20.8.
MS (70 eV, EI), *m/z* (%) =213 (M^+, 100), 185 (77), 183 (77), 109 (72), 43 (80).
HRMS *m/z* calc. for **$C_{14}H_{13}BrO_2$** (292.0099): 292.0092.
IR (ATR) υ (cm^{-1}) = 2937, 1751, 1434, 1172, 1065, 1026, 1008, 911, 755, 734.

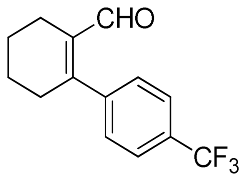
Preparation of 5-(2-formylcyclohex-1-en-1-yl)pyridine-3-carbonitrile (40e)



The cross-coupling reaction of **38a** (2.80 mL, 2.40 mmol, 0.85 M in THF) with 5-bromopyridine-3-carbonitrile (**39e**, 366 mg, 2.00 mmol) was performed according to **TP4** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 1:1) furnished **40e** as a yellow oil (276 mg, 65 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.42 (s, 1H), 8.88-8.87 (m, 1H), 8.69-8.68 (m, 1H), 7.88-7.87(m, 1H), 2.55-2.45 (m, 2H), 2.43-2.35 (m, 2H), 1.85-1.70 (m, 4H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.0, 152.2, 151.9, 151.7, 138.8, 138.6, 135.5, 115.9, 109.9, 33.8, 22.3, 22.1, 21.0.
MS (70 eV, EI), *m/z* (%) = 212 (M^+, 73), 211 (73), 183 (100), 169 (29), 155 (63).
HRMS *m/z* calc. for **$C_{13}H_{12}N_2O$** (212.0950): 212.0939.
IR (ATR) υ (cm^{-1}) = 2934, 2860, 2234, 1667, 1625, 1418, 1223, 1024, 905, 707, 652.

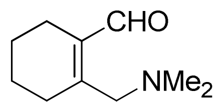
Preparation of 2-[4-(trifluoromethyl)phenyl]cyclohex-1-ene-1-carbaldehyde (40f)



The cross-coupling reaction of **38a** (2.80 mL, 2.40 mmol, 0.85 M in THF) with 4-bromobenzotrifluoride (**39f**, 450 mg, 2.00 mmol) was performed according to **TP4** in 4 h. Flash column chromatography (silica, hexanes:Et_2O 10:1 then 4:1) furnished **40f** as a yellow oil (369 mg, 73 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.45 (s, 1H). 7.66 (q, *J*=9.0Hz, 2H), 7.37 (q, *J*=9.0Hz, 2H), 2.60-2.50 (m, 2H), 2.40-2.30 (m, 2H), 1.85-1.60 (m, 4H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 192.1, 157.4, 143.2, 136.7, 130.4 (q, *J*=33Hz), 128.9, 125.3 (q, *J*=4Hz), 123.9 (q, *J*=272Hz), 33.9, 22.3, 22.2, 21.3.
MS (70 eV, EI), *m/z* (%) = 254 (M^+, 25), 253 (22), 185 (50), 159 (19), 43 (100).
HRMS *m/z* calc. for **$C_{14}H_{13}F_3O$** (254.0918): 254.0907.
IR (ATR) $\widetilde{\nu}$ (cm^{-1}) = 2937, 1671, 1614, 1322, 1211, 1163, 1121, 1109, 1067, 1017, 840.

Preparation of 2-[(dimethylamino)methyl]cyclohex-1-ene-1-carbaldehyde (40g)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with CH_2Cl_2 (2 mL) and *N*,*N*,*N*',*N*'-tetramethyldiaminomethane (204 mg, 2.00 mmol) and was cooled to 0 °C. Then, trifluoroacetic anhydride (420 mg, 2 mmol) was added dropwise at 0 °C and the resulting clear solution was stirred for 15 min. Then, the alkenyl zinc reagent **38a** (2.82 mL, 2.00 mmol, 0.71 M in THF) was added and the reaction mixture was stirred for 30 min. The reaction was quenched with sat. NaCl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was dissolved in EtOAc (30 mL) and washed with HCl (2x20 mL, 2 M). The aqueous solution was neutralized with $NaHCO_3$, NaOH (2 M, 10 mL) was added and subsequently extracted with EtOAc (3x10 mL). After drying over Na_2SO_4 and evaporation of solvents **40g** was isolated as a yellow liquid (226 mg, 68 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.13 (s, 1H), 3.27 (s, 2H), 2.36-2.27 (m, 2H), 2.24 (s, 6H), 2.24-2.19 (m, 2H), 1.68-1.54 (m, 4H).

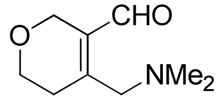
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 188.4, 155.1, 136.5, 59.7, 45.4, 30.8, 22.4, 22.0, 21.6.

MS (70 eV, EI), *m/z* (%) = 167 (M^+, 20), 138 (100), 122 (22), 110 (22), 79 (23), 58 (34), 42 (57).

HRMS *m/z* calc. for **$C_{10}H_{17}NO$** (167.1310): 167.1307.

IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2945, 1675, 1604, 1454, 1319, 1277, 1256, 1169, 1104, 1033, 1012, 951, 843, 832, 762, 675.

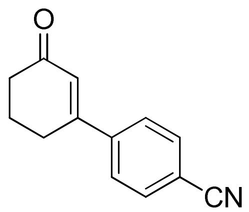
Preparation of 4-[(dimethylamino)methyl]-5,6-dihydro-*2H*-pyran-3-carbaldehyde (40h)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with CH_2Cl_2 (2 mL) and *N*,*N*,*N*`,*N*'-tetramethyldiaminomethane (163 mg, 1.6 mmol) and was cooled to 0 °C. Then, trifluoroacetic anhydride (336 mg, 1.6 mmol) was added dropwise at 0 °C and the resulting clear solution was stirred for 15 min. Then, the alkenylzinc reagent **38b** (3.1 mL, 2.00 mmol, 0.65 M in THF) was added and the reaction mixture was stirred for 30 min. The reaction was quenched with sat. NaCl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was dissolved in EtOAc (30 mL) and washed with HCl (2x 20 mL, 2 M). The aqueous solution was neutralized with $NaHCO_3$, NaOH (2 M, 10 mL) was added and subsequently extracted with EtOAc (3x10 mL). After drying over Na_2SO_4 and evaporation of solvents **40h** was isolated as a yellow liquid (237 mg, 88 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.08 (s, 1H), 4.49-4.45 (m, 2H), 3.39 (t, J=5.5Hz, 2H), 2.67 (s, 2H), 2.01-1.95 (m, 2H), 1.83 (s, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 188.1, 152.7, 136.1, 64.3, 64.0, 58.9, 45.4, 29.7.
MS (70 eV, EI), m/z (%) = 169 (M^+, 19), 124 (100), 123 (16), 94 (25), 58 (87), 44 (15), 42 (16).
HRMS m/z calc. for **$C_9H_{15}NO_2$** (169.1103): 161.1108.
IR (ATR) υ (cm^{-1}) = 2944, 2822, 2768, 1663, 1461, 1387, 1290, 1252, 1165, 1115, 1041, 1016, 1002, 950, 855, 839, 758, 694, 675.

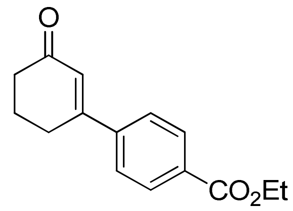
Preparation of 3-(4-Cyanophenyl)-2-cyclohexen-1-one (40i)



The cross-coupling reaction of **38c** (4.80 mL, 2.40 mmol, 0.50 M in THF) with 4-iodobenzonitrile (**39a**, 458 mg, 2.00 mmol) was performed according to **TP4** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 1:1 then 1:2) furnished **40i** as a colorless solid (349 mg, 88 %).

m.p.: 95.8-97.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.70 (d, J=8.3Hz, 2 H), 7.61 (d, J=8.5Hz, 2 H), 6.41 (s, 1H), 2.75 (dt, J=6.0Hz, 1.2Hz, 2H), 2.50 (d, J=7.1Hz, 2H), 2.18 (quint, J=6.4Hz, 2H),
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 199.1, 157.2, 143.3, 132.5, 127.3, 126.6, 118.2, 113.2, 37.1, 27.9, 22.6,
MS (70 eV, EI), m/z (%) = 197 (M^+, 44), 169 (100), 141 (69), 140 (90), 113 (24).
HRMS m/z calc. for **$C_{13}H_{11}NO$** (197.0841): 197.0838.
IR (ATR) υ (cm^{-1}) = 2951, 2223, 1662, 1603, 1343, 1259, 1183, 1130, 889, 830, 816.

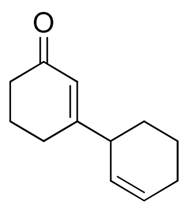
Preparation of 3-[4-(ethoxycarbonyl)phenyl]-2-cyclohexen-1-one (40j)



The cross-coupling reaction of **38c** (4.80 mL, 2.40 mmol, 0.50 M in THF) with ethyl 4-iodobenzoate (**39h**, 552 mg, 2.00 mmol) was performed according to **TP4** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 2:1 then 1:1) furnished **40j** as a colorless solid (373 mg, 76 %).

m.p.: 62.2-64.3 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.07 (d, *J* = 8.8 Hz, 2 H), 7.58 (d, *J* = 8.8 Hz, 2 H), 6.44 (t, *J* = 1.5 Hz, 1 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 2.78 (dt, *J* = 6.1, 1.5 Hz, 2 H), 2.53-2.47 (m, 2 H), 2.17 (quint, *J* = 6.4 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 199.5, 165.9, 158.4, 143.0, 131.5, 129.8, 126.7, 125.9, 61.2, 37.2, 28.0, 22.7, 14.3.
MS (70 eV, EI), *m/z* (%) = 244 (M^+, 100), 216 (41), 199 (48), 171 (99), 144 (94).
HRMS *m/z* : calc. for $C_{15}H_{16}O_3$ 244.1099, found 244.1099.
IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2944, 1704, 1665, 1602, 1287, 1269, 1184, 1110, 1021, 766, 698.

Preparation of ethyl 1,1'-bi(cyclohexane)-1,2'-dien-3-one (40k)

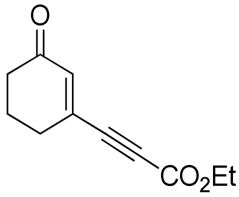


The allylation reaction of **38c** (4.80 mL, 2.40 mmol, 0.50 M in THF) with CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF) and 3-bromocyclohexene (**39i**, 322 mg, 2.00 mmol) was performed according to **TP3** in 1 h. Flash column chromatography (silica, pentane:Et_2O 4:5) furnished **40k** as a colorless oil (269 mg, 76 %).

^{1}H-NMR (300 MHz, $CDCl_3$) *δ* (ppm) = 5.90-5.80 (m, 2H), 5.55-5.48 (m, 1H), 2.95-2.85 (m, 1H), 2.40-2.20 (m, 4H), 2.15-1.80 (m, 5H), 1.75-1.40 (m, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) *δ* (ppm) = 200.1, 169.4, 129.7, 126.9, 125.8, 43.22, 37.5, 28.3, 27.6, 24.9, 23.0, 20.6.
MS (70 eV, EI), *m/z* (%) = 176 (M^+, 45), 120 (100), 105 (72), 92 (74), 91 (92).

HRMS *m/z* calc. for **$C_{12}H_{16}O$** (176.1201): 176.1201.
IR (ATR) υ (cm^{-1}) = 2930, 1662, 1619, 1257, 1241, 1187, 1133, 965, 884, 725.

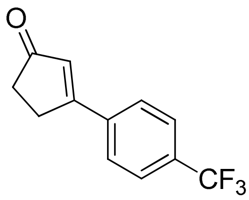
Preparation of 3-[2-(Ethoxycarbonyl)ethynyl]-2-cyclohexen-1-one (40l)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the alkenyl zinc reagent **38c** (4.80 mL, 2.40 mmol, 0.50 M in THF) and cooled to -78 °C. CuCN·2LiCl (0.24 mL, 0.24 mmol, 1.0 M in THF) was added, followed by ethyl 3-bromoprop-2-ynoate (**39c**, 354 mg, 2.00 mmol) and the reaction mixture was stirred for 3 h at -78 °C. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et_2O 2:1) to give **40l** as a colorless oil (273 mg, 71 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.35 (t, *J*=1.9Hz, 1H), 4.27 (q, *J*=7.1Hz, 2H), 2.50-2.40 (m, 4H), 2.11-2.01 (m, 2H), 1.33 (t, *J*=7.2Hz, 3H),
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 197.6, 153.1, 139.4, 135.7, 88.2, 83.1, 62.5, 37.2, 29.3, 22.3, 13.9.
MS (70 eV, EI), *m/z* (%) = 192 (M^+, 41), 164 (85), 147 (85), 120 (99), 92 (100).
HRMS *m/z* calc. for **$C_{11}H_{12}O_3$** (192.0786): 192.0780.
IR (ATR) υ (cm^{-1}) = 2942, 2218, 1707, 1676, 1261, 1245, 1187, 1145, 1135, 1015, 747.

Preparation of 3-[4-(trifluoromethyl)phenyl]-2-cyclopenten-1-one (40m)



The cross-coupling reaction of **38d** (3.43 mL, 2.40 mmol, 0.70 M in THF) with 4-iodobenzotrifluoride (**39f**, 544 mg, 2.00 mmol) was performed according to **TP4** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 1:1 then 1:2) furnished **40m** as a colorless solid (333 mg, 74 %).

m.p.: 106.5-108.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.78-7.70 (m, 4H), 6.64 (t, J=1.5Hz, 1H), 3.09-3.06 (m, 2H), 2.65-2.62 (m, 2H).

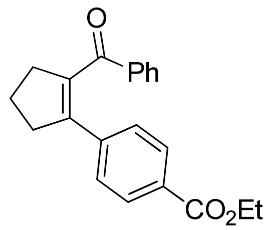
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 208.7, 171.7, 137.4, 132.6 (q, J=32Hz), 129.4, 127.0, 125.9 (q, J=4Hz), 123.7 (q, J=272Hz), 35.3, 28.7.

MS (70 eV, EI), *m/z* (%) = 226 (M^+, 95), 225 (33), 170 (28), 157 (100), 129 (38).

HRMS *m/z* calc. for **$C_{12}H_9F_3O$** (226.0605): 226.0597.

IR (ATR) υ (cm^{-1}) = 2925, 1689, 1677, 1601, 1319, 1163, 1132, 1110, 1064, 1014, 829.

Preparation of ethyl 4-(2-benzoylcyclopent-1-en-1-yl)benzoate (40n)



The cross-coupling reaction of **38e** (3.60 mL, 2.00 mmol, 0.56 M in THF) with ethyl 4-bromobenzoate (**39j**, 367 mg, 1.60 mmol) was performed according to **TP4** over night. Flash column chromatography (silica, hexanes:Et_2O 9:1) furnished **40n** as a white solid (359 mg, 70 %).

m.p.: 70.5-71.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.62-7.87 (m, 4H), 7.33-7.48 (m, 1H), 7.16-7.33 (m, 4H), 4.29 (q, J=7.2Hz, 2H), 2.84-3.14 (m, 4H), 2.15 (quin, J=7.6Hz, 2H), 1.32 (t, J=7.1Hz, 3H).

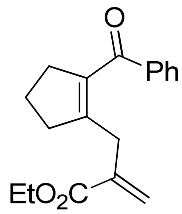
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 198.1, 166.1, 144.2, 140.4, 139.7, 136.2, 133.1, 129.3, 129.3, 129.2, 128.4, 127.6, 60.9, 38.0, 37.7, 22.7, 14.2.

MS (70 eV, EI), *m/z* (%) = 320 (M^+, 42), 319 (29), 292 (27), 291 (100), 275 (12), 247 (42), 141 (13), 105 (54), 77 (23).

HRMS *m/z* calc. for **$C_{21}H_{20}O_3$** (320.1412): 320.1407.

IR (ATR) υ (cm^{-1}) = 3061, 2981, 2961, 2930, 2901, 2868, 2836, 1709, 1645, 1606, 1592, 1578, 1447, 1406, 1365, 1342, 1309, 1266, 1176, 1172, 1104, 1022, 862, 844, 772, 715, 703, 692, 674.

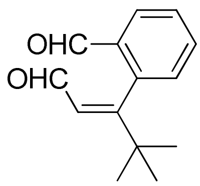
Preparation of ethyl 2-((2-benzoylcyclopent-1-en-1-yl)methyl)acrylate (4o)



The allylation reaction of **38e** (3.60 mL, 2.00 mmol, 0.56 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (**39b**, 347 mg, 1.80 mmol) was performed according to **TP3** over night. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **40o** as a colorless oil (404 mg, 79 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.70-7.85 (m, 2H), 7.47-7.56 (m, 1H), 7.35-7.47 (m, 2H), 6.16 (d, *J*=1.1Hz, 1H), 5.48 (q, *J*=1.4Hz, 1H), 4.11 (q, *J*=7.0Hz, 2H), 3.14 (s, 2H), 2.63-2.84 (m, 2H), 2.49 (t, *J*=7.6Hz, 2H), 1.77-2.05 (m, 2H), 1.21 (t, *J*=7.1Hz, 3 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 197.0, 166.7, 148.5, 138.5, 138.2, 137.6, 132.5, 128.8, 128.4, 126.2, 60.7, 37.2, 36.2, 32.2, 22.4, 14.1.
MS (70 eV, EI), *m/z* (%) = 284 (M^+, 18), 211 (10), 184 (15), 105 (100), 77 (20).
HRMS *m/z* calc. for $\mathbf{C_8H_{20}O_3}$ (284.1412): 284.1402.
IR (ATR) υ (cm^{-1}) = 3075, 3061, 3027, 2977, 2954, 2937, 2905, 2852, 1712, 1643, 1596, 1578, 1447, 1298, 1267, 1235, 1174, 1141, 1124, 1023, 947, 865, 817, 795, 712, 695.

Preparation of 2-[1-tert-butyl-3-oxoprop-1-en-1-yl]benzaldehyde (40p)



The cross-coupling reaction of **38f** (3.80 mL, 2.00 mmol, 0.53 M in THF) with 2-bromobenzaldehyde (**39k**, 296 mg, 1.60 mmol) was performed according to **TP4** in 2 h. Flash column chromatography (silica, hexanes:Et_2O 1:1) furnished **40p** as a yellow wax (319 mg, 92 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.04 (s, 1H). 9.10 (d, *J*=8.0Hz, 1H), 8.02 (dd, *J* =8.0Hz, 1.4Hz, 1H), 7.65 (td, *J* =7.5Hz, 1.7Hz, 1H), 7.56 (dt, *J*=7.5Hz, 1.4Hz, 1H), 7.22 (dd, *J*=7.6Hz, 1.0Hz, 1H), 6.39 (d, *J*=8.0Hz, 1H), 1.18 (s, 9H).

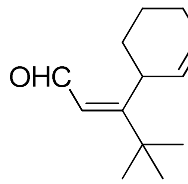
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 193.0, 190.9, 171.3, 139.3, 134.6, 133.3, 130.2, 129.3, 128.7, 128.7, 38.0, 29.3.

MS (70 eV, EI), *m/z* (%) = 216 (M^+, >1), 187 (100), 160 (17), 131 (23), 103 (11), 77 (13), 57 (17), 41 (11).

HRMS *m/z* calc. for $\mathbf{C_{14}H_{16}O_2}$ (216.1150): 216.1158.

IR (ATR) υ (cm^{-1}) = 2970, 2850, 2758 (vw), 1684, 1671, 1591, 1480, 1396, 1366, 1264, 1198, 1176, 1132, 878, 826, 803, 781, 754, 713, 702.

Preparation of ethyl 2-[(2-formylcyclohex-1-en-1-yl)methyl]prop-2-enoate (40q)



The allylation reaction of **38f** (3.85 mL, 2.00 mmol, 0.52 M in THF) with 3-bromocyclohexene (**39i**, 258 mg, 1.60 mmol) was performed according to **TP3** in 30 min. Flash column chromatography (silica, pentane:Et_2O 95:5) furnished **40q** as a colorless oil (294 mg, 96 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.36 (d, *J*=8.3Hz, 1H), 5.84 (dd, *J*=8.2Hz, 1.2Hz, 1H), 5.77-5.58 (m, 2H), 3.35-3.14 (m, 1H), 2.23-2.09 (m, 3H), 2.00-1.81 (m, 1H), 1.79-1.51 (m, 2H), 1.14 (s, 9H).

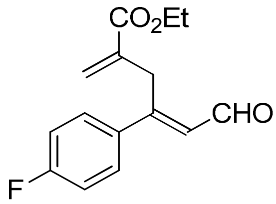
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.2, 188.1, 152.7, 145.9, 136.1, 64.3, 64.0, 58.9, 45.4, 29.7, 26.5.

MS (70 eV, EI), *m/z* (%) = 192 (M^+, 23), 163 (85), 135 (100), 108 (75), 79 (86), 57 (81), 41 (89).

HRMS *m/z* calc. for $\mathbf{C_{13}H_{20}O}$ (192.1514): 192.1508.

IR (ATR) υ (cm^{-1}) = 2938, 2868, 1668, 1614, 1449, 1394, 1366, 1208, 1152, 1134, 1030, 890, 855, 722, 664.

Preparation of (*E*)-ethyl 4-(4-fluorophenyl)-2-methylene-6-oxohex-4-enoate (40r)



The allylation reaction of **38g** (6.30 mL, 2.00 mmol, 0.32 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (**39b**, 347 mg, 1.80 mmol) was performed according to **TP3** in 1 h. Flash column chromatography (silica, pentane:Et_2O 7.5:2.5) furnished **40r** as a yellow oil (466 mg, 95 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.05 (d, *J*=7.7Hz, 1H), 7.39-7.54 (m, 2H), 6.96-7.15 (m, 2H), 6.43 (d, *J*=7.7Hz, 1H), 6.27 (s, 1H), 5.49 (t, *J*=1.8Hz, 1H), 4.23 (q, *J*=7.0Hz, 2H), 4.02 (s, 2H) 1.30 (t, *J*=7.0Hz, 3H).

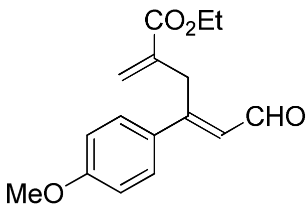
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.0, 166.1, 163.8 (d, *J*=251.3Hz), 156.2, 137.3, 135.0 (d, *J*=3.4Hz), 128.8, 128.7 (d, *J*=8.4Hz), 127.0, 116.0 (d, *J*=21.6Hz), 61.3, 31.6, 14.1.

MS (70 eV, EI), *m/z* (%) = 262 (M^+, 9), 233 (22), 205 (20), 190 (12), 189 (100), 159 (13), 146 (22), 133 (9).

HRMS *m/z* calc. for **$C_{15}H_{15}FO_3$** (262.1005): 262.1003.

IR (ATR) υ (cm^{-1}) = 3116, 3062, 2982, 2937, 2910, 2857, 2762, 2724, 1712, 1662, 1600, 1506, 1225, 1197, 1178, 1159, 1110, 1096, 1027, 1017, 855, 834, 769, 717, 654.

Preparation of (*E*)-ethyl 4-(4-methoxyphenyl)-2-methylene-6-oxohex-4-enoate (40s)



The allylation reaction of **38h** (5.40 mL, 2.00 mmol, 0.37 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (**39b**, 347 mg, 1.80 mmol) was performed according to **TP3** in 1 h. Flash column chromatography (silica, pentane:Et_2O 6:4) furnished **40s** as a yellow oil (439 mg, 89 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.02 (d, *J*=7.7 Hz, 1H), 7.35-7.59 (m, 2H), 6.80-7.00 (m, 2H), 6.47 (d, *J*=7.7Hz, 1H), 6.26 (s, 1H), 5.49 (s, 1H), 4.24 (q, *J*=7.2Hz, 2H), 4.01 (s, 2H), 3.82 (s, 3H), 1.30 (t, *J*=7.2Hz, 3H).

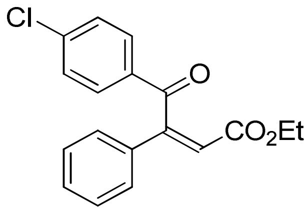
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.2, 166.3, 161.4, 156.9, 137.7, 130.8, 128.3, 127.2, 126.8, 114.2, 61.2, 55.3, 31.2, 14.1.

MS (70 eV, EI), *m/z* (%) = 274 (M^+, 9), 246 (11), 245 (19), 228 (20), 217 (15), 202 (14), 201 (100), 199 (18), 173 (19), 171 (13), 161 (27), 158 (15), 133 (11), 128 (11).

HRMS *m/z* calc. for $\mathbf{C_{16}H_{18}O_4}$ (274.1205): 274.1198.

IR (ATR) υ (cm^{-1}) = 3093, 3037, 2978, 2961, 2936, 2905, 2839, 1710, 1661, 1600, 1567, 1510, 1462, 1442, 1291, 1246, 1177, 1140, 1115, 1027, 961, 828, 752.

Preparation of (*Z*)-ethyl 4-(4-chlorophenyl)-4-oxo-3-phenylbut-2-enoate (40t)



The acylation reaction of **38i** (3.60 mL, 2.00 mmol, 0.56 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and 4-chlorobenzoyl chloride (**39l**, 280 mg, 1.60 mmol) was performed according to **TP3** in 3 h. Flash column chromatography (silica, pentane:Et_2O 8.5:1.5) furnished **40t** as a white solid (427 mg, 85 %).

m.p.: 126.6-129.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.82-7.95 (m, 2H), 7.29-7.54 (m, 7H), 6.50 (s, 1H), 4.09 (q, *J*=7.2Hz, 2H), 1.15 (t, *J*=7.1Hz, 3H).

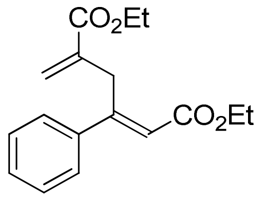
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 195.2, 165.0, 155.0, 139.9, 134.5, 133.9, 130.6, 130.2, 129.2, 129.1, 126.9, 118.0, 61.0, 13.9.

MS (70 eV, EI), *m/z* (%) = 314 (M^+, 36), 286 (14), 269 (10), 141 (25), 139 (100), 111 (12).

HRMS *m/z* calc. for $\mathbf{C_{18}H_{15}ClO_3}$ (314.0710): 314.0702.

IR (ATR) υ (cm^{-1}) = 3089, 3066, 3030, 2991, 2980, 2903, 1703, 1671, 1615, 1585, 1571, 1367, 1349, 1340, 1288, 1280, 1219, 1194, 1185, 1175, 1156, 1093, 1021, 1009, 971, 966, 914, 869, 845, 838, 776, 762, 736, 688.

Preparation of (*E*)-diethyl 5-methylene-3-phenylhex-2-enedioate (40u)

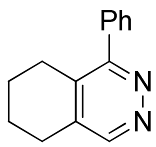


The allylation reaction of **38i** (3.60 mL, 2.00 mmol, 0.56 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (**39b**, 307 mg, 1.60 mmol) was performed according to **TP3** over night. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **40u** as a yellow oil (364 mg, 79 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.28-7.52 (m, 5H), 6.31 (s, 1H), 6.17 (t, *J*=1.4Hz, 1H), 5.43 (t, *J*=1.5Hz, 1H), 4.07-4.31 (m, 6H), 1.18-1.40 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.8, 166.0, 155.3, 140.3, 137.7, 129.1, 128.5, 126.7, 125.2, 119.5, 60.8, 60.1, 32.4, 14.2, 14.1.
MS (70 eV, EI), *m/z* (%) = 288 (M^+, 6), 243 (34), 242 (100), 214 (19), 213 (12), 185 (17), 170 (29), 169 (68), 142 (22), 141 (91), 115 (21).
HRMS *m/z* calc. for **$C_{17}H_{20}O_4$** (288.1362): 288.1358.
IR (ATR) υ (cm^{-1}) = 3104, 3083, 3058, 2980, 2937, 2904, 2872, 1708, 1624, 1446, 1367, 1268, 1251, 1197, 1164, 1157, 1131, 1095, 1050, 1022, 941, 877, 816, 767, 696.

5.4.1 PREPARATION OF 1-SUBSTITUTED TETRAHYDOPHTHALAZINES

Preparation of 1-phenyl-5,6,7,8-tetrahydrophthalazine (41a)



The acylation reaction of **38a** (3.10 mL, 2.00 mmol, 0.65 M in THF) with benzoyl chloride (225 mg, 1.60 mmol) was performed in 14 h followed by the reaction hydrazine hydrate (300 mg, 6.00 mmol) according to **TP5**. Flash column chromatography (silica, CH_2Cl_2:EtOAc 9:1) furnished **41a** as a colorless solid (166 mg, 54 %).

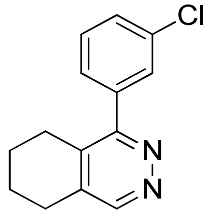
m.p.: 80.0-84.2 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.86 (s, 1H), 7.30-7.64 (m, 5H), 2.83 (t, *J*=6.3Hz, 2H), 2.65 (t, *J*=6.2Hz, 2 H), 1.73-1.94 (m, 4H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 160.2, 151.5, 138.7, 137.7, 135.8, 134.3, 129.6, 127.3, 26.4, 26.1, 22.0, 21.3.

MS (70 eV, EI), *m/z* (%) = 210 (M^+, 67), 209 (100), 195 (11), 165 (11), 152 (11), 77 (14).

HRMS (EI) *m/z* calc. for $\mathbf{C_{14}H_{14}N_2}$ (209.1073): 209.1079.

IR (ATR) υ (cm^{-1}) = 2922, 2859, 1663, 1565, 1444, 1427, 1407, 1339, 1234, 1070, 1027, 1017, 1001, 951, 928, 777, 756, 708.

Preparation of 1-(3-chlorophenyl)-5,6,7,8-tetrahydrophthalazine (41b)



The acylation reaction of **38a** (3.77 mL, 2.00 mmol, 0.53 M in THF) with 3-chlorobenzoyl chloride (210 mg, 1.20 mmol) was performed in 14 h followed by the reaction hydrazine hydrate (300 mg, 6.00 mmol) according to **TP5**. Flash column chromatography (silica, CH_2Cl_2:EtOAc 1:1) furnished **41b** as a brown solid (160 mg, 54 %).

m.p.: 110.3-112.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.85 (s, 1H), 7.56-7.51 (m, 1H), 7.46-7.36 (m, 3H), 2.81 (t, *J*=6.3Hz, 2H), 2.64 (t, *J*=6.2Hz, 2H), 1.93-1.72 (m, 4H).

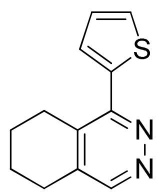
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 160.1, 151.5, 138.7, 137.6, 135.7, 134.3, 129.6, 129.2, 128.9, 127.2, 26.4, 26.0, 22.0, 21.3.

MS (70 eV, EI), *m/z* (%): 244 (M^+, 61), 243 (100), 229 (14), 109 (7), 165 (8), 153 (8), 152 (16).

HRMS (EI) *m/z* calc. for $\mathbf{C_{14}H_{13}ClN_2}$ (245.0846 [M^++H]): 245.0839.

IR (ATR) υ (cm^{-1}) = 2944, 2855, 1562, 1425, 1398, 1331, 1231, 1076, 1022, 1006, 956, 885, 860, 828, 800, 768, 728, 700.

Preparation of 1-thiophen-2-yl-5,6,7,8-tetrahydrophthalazine (41c)



The acylation reaction of **38a** (4.00 mL, 3.00 mmol, 0.75 M in THF) with 2-thiophenecarbonyl chloride (264 mg, 1.80 mmol) was performed in 14 h followed by the reaction hydrazine hydrate (450 mg, 9.00 mmol) according to **TP5**. Flash column chromatography (silica, CH_2Cl_2:EtOAc 9:1) furnished **41c** as a yellow solid (164 mg, 49 %).

m.p.: 120.6-123.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.72 (s, 1H), 7.52 (dd, *J*=3.7Hz, 1.1Hz, 1H), 7.49 (dd, *J*=5.0Hz, 1.1Hz, 1H), 7.15 (dd, *J*=5.2Hz, 3.7Hz, 1H), 2.99-2.86 (m, 2H), 2.84-2.71 (m, 2H), 1.96-1.76 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 154.8, 150.6, 140.5, 137.2, 134.1, 128.6, 128.5, 127.4, 26.9, 26.3, 22.2, 21.1.

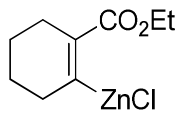
MS (70 eV, EI), *m/z* (%): 216 (M^+, 100), 215 (68), 160 (50), 91 (49), 77 (54), 44 (67), 41 (66).

HRMS (EI) *m/z* calc. for **$C_{12}H_{12}N_2S$** (216.0721): 216.0719.

IR (ATR): υ (cm^{-1}) = 2940, 2860, 1559, 1542, 1437, 1414, 1365, 1300, 1114, 1053, 940, 928, 858, 836, 798, 708.

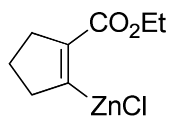
5.5 Preparation of Alkenyl Zinc Reagents of from Less Activated Alkenyl Bromides

Preparation of (2-(ethoxycarbonyl)cyclohex-1-en-1-yl)zinc chloride (43a)



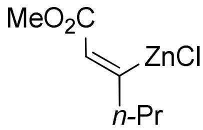
According to **TP2**, the zinc reagent **43a** was prepared from ethyl 2-bromocyclohex-1-ene-1-carboxylate (**42a**, 2.33 g, 10.0 mmol) using Mg turnings (608 mg, 25.0 mmol), LiCl (636 mg, 15.0 mmol) and $ZnCl_2$ (11.0 mL, 1 M in THF) in 14 h at 25 °C. Titration with iodine indicates a concentration of 0.33 M (70 %).

Preparation of (2-(ethoxycarbonyl)cyclopent-1-en-1-yl)zinc chloride (43b)



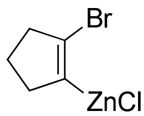
According to **TP2**, the zinc reagent **7c** was prepared from ethyl 2-bromocyclopent-1-ene-1-carboxylate (**42b**, 438 mg, 2.00 mmol) using Mg turnings (122 mg, 5.00 mmol), LiCl (127 mg, 3.00 mmol) and $ZnCl_2$ (2.2 mL, 1 M in THF) in 14 h at 25 °C. Titration with iodine indicates a concentration of 0.42 M (84 %).

Preparation of (*Z*)-(1-methoxy-1-oxohex-2-en-3-yl)zinc chloride (43c)



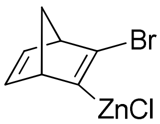
According to **TP2**, the zinc reagent **43c** was prepared from (*Z*)-methyl 3-bromohex-2-enoate (**42c**, 2.07 g, 10.0 mmol) using Mg turnings (608 mg, 25.0 mmol), LiCl (636 mg, 15.0 mmol) and $ZnCl_2$ (11.0 mL, 1 M in THF) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.26 M (50 %).

Preparation of 2-bromocyclopentenzinc chloride (43d)



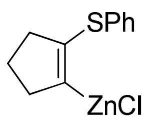
According to **TP2**, the zinc reagent **43d** was prepared from 1,2-dibromocyclopentene (**42d**, 2.26 g, 10.0 mmol) using Mg turnings (608 mg, 25.0 mmol), LiCl (636 mg, 15.0 mmol) and $ZnCl_2$ (11.0 mL, 1 M in THF) in 8 h at 25 °C. Titration with iodine indicates a concentration of 0.51 M (98 %).

Preparation of ((1*S*,4*R*)-3-bromobicyclo[2.2.1]hepta-2,5-dien-2-yl)zinc chloride (43e)



According to **TP2**, the zinc reagent **43e** was prepared from 2,3-dibromobicyclo-[2.2.1]hepta-2,5-diene (**43e**, 2.50 g, 10.0 mmol) using Mg turnings (608 mg, 25.0 mmol), LiCl (636 mg, 15.0 mmol) and $ZnCl_2$ (11.0 mL, 1 M in THF) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.39 M (70 %).

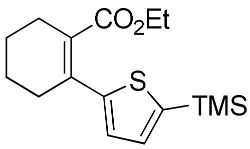
Preparation of (2-(phenylthio)cyclopent-1-en-1-yl)zinc chloride (43f)



According to **TP2**, the zinc reagent **43f** was prepared from (2-bromocyclopent-1-en-1-yl)(phenyl)sulfane (**42f**, 2.55 g, 10.0 mmol) using Mg turnings (608 mg, 25.0 mmol), LiCl (636 mg, 15.0 mmol) and $ZnCl_2$ (11.0 mL, 1 M in THF) in 1 h at 25 °C. Titration with iodine indicates a concentration of 0.35 M (68 %).

*5.6 REACTIONS OF ALKENYL ZINC REAGENTS OF TYPE **43** WITH ELECTROPHILES*

Preparation of ethyl 2-(5-(trimethylsilyl)thiophen-2-yl)cyclohex-1-enecarboxylate (44a)



The cross-coupling reaction of **43a** (4.00 mL, 2.00 mmol, 0.50 M in THF) with 2-bromo-5-trimethylsilylthiophene (**39m**, 470 mg, 2.00 mmol) was performed according to **TP4** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 1:1 then 9:1) furnished **44a** as a colorless solid (436 mg, 71 %).

m.p.: 106.5-108.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.07 (d, *J*=3.5Hz, 1H), 6.98 (d, *J*=3.3Hz, 1H), 4.03 (q, *J*=7.2Hz, 2H), 2.46-2.38 (m, 4H), 1.75-1.68 (m, 4H), 1.01 (t, *J*=7.2Hz, 3H), 0.28 (s, 9H).

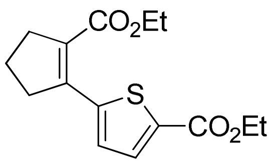
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 170.8, 149.3, 139.7, 134.9, 133.6, 129.7, 126.0, 60.5, 32.4, 27.2, 22.4, 21.6, 13.6, -0.1.

MS (70 eV, EI), *m/z* (%) = 308 (M^+, 100), 293 (41), 262 (18), 235 (43), 234 (30), 103 (20).

HRMS *m/z* calc. for **$C_{16}H_{24}O_2SSi$** (308.1266): 308.1246.

IR (ATR) υ (cm^{-1}) = 2936, 1709, 1277, 1247, 1218, 1046, 990, 836, 804, 755.

Preparation of ethyl 5-[2-(ethoxycarbonyl)cyclopent-1-en-1-yl]thiophene-2-carboxylate (44b)



The cross-coupling reaction of **43b** (6.25 mL, 2.00 mmol, 0.32 M in THF) with ethyl 5-bromothiophene-2-carboxylate (**39n**, 376 mg, 1.60 mmol) was performed according to **TP4** in 1.5 h. Flash column chromatography (silica, hexanes:Et_2O 9:1) furnished **44b** as a colorless solid (373 mg, 79 %).

m.p.: 64.2-65.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.70 (d, J=3.9Hz, 1H), 7.46 (d, J=3.9Hz, 1H), 4.35 (q, J=7.1 Hz, 2H), 4.27 (q, J=7.1Hz, 2H), 3.00 (tt, J=7.7Hz, 2.3Hz, 2H), 2.91-2.83 (m, 2H), 1.98 (quint, J=7.7Hz, 2H), 1.38 (t, J=7.2Hz, 3H), 1.32 (t, J=7.2Hz, 3H).

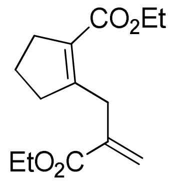
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.9, 162.4, 143.8, 143.0, 134.7, 132.6, 129.9, 129.7, 61.1, 60.5, 39.7, 35.9, 21.5, 14.3, 14.2.

MS (70 eV, EI), m/z (%) = 294 (M^+, 100), 265 (30), 251 (45), 223 (16), 222 (58), 221 (36), 193 (11), 147 (12).

HRMS m/z calc. for $\mathbf{C_{15}H_{18}O_4S}$ (294.0926): 294.0920.

IR (ATR) υ (cm^{-1}) = 2982, 2961, 1695, 1599, 1519, 1474, 1440, 1366, 1328, 1216, 1098, 1040, 1022, 824, 752.

Preparation of ethyl 2-[2-(ethoxycarbonyl)prop-2-en-1-yl]cyclopent-1-ene-1-carboxylate (44c)



The allylation reaction of **43b** (6.25 mL, 2.00 mmol, 0.32 M in THF) with CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (**39b**, 309 mg, 1.60 mmol) was performed according to **TP3** in 1.5 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **44c** as a colorless oil (348 mg, 86 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.23-6.18 (m, 1H), 5.54-5.49 (m, 1H), 4.26-4.12 (m, 4H), 3.66-3.61 (m, 2H), 2.69-2.60 (m, 2H), 2.49-2.39 (m, 2H), 1.81 (quint, J=7.7 Hz, 2H), 1.33-1.21 (m, 6H).

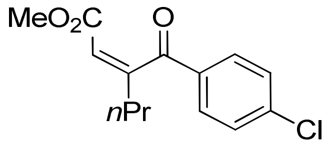
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 167.0, 165.9, 155.1, 137.8, 129.4, 125.5, 60.7, 59.7, 37.9, 33.6, 31.9, 21.5, 14.3, 14.1.

MS (70 eV, EI), m/z (%) = 252 (M^+, 2), 206 (100), 149 (56), 134 (35), 133 (75), 105 (68), 79 (31).

HRMS m/z calc. for $\mathbf{C_{14}H_{20}O_4}$ (252.1362): 252.1353.

IR (ATR) υ (cm^{-1}) = 2980, 1706, 1631, 1446, 1368, 1255, 1174, 1144, 1107, 1026, 946, 771.

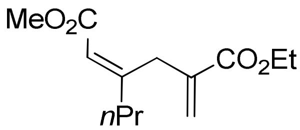
Preparation of (*Z*)-methyl 3-(4-chlorobenzoyl)hex-2-enoate (44d)



The acylation reaction of **43c** (7.70 mL, 2.00 mmol, 0.26 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and 4-chlorobenzoyl chloride (**39l**, 315 mg, 1.80 mmol) was performed according to **TP3** in 1 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **44d** as a yellow oil (412 mg, 86 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.75-7.90 (m, 2H), 7.35-7.51 (m, 2H), 5.99 (t, *J*=1.6Hz, 1H), 3.55 (s, 3H), 2.36 (dt, *J*=7.8Hz, 1.6Hz, 2H), 1.46-1.61 (m, 2H), 0.96 (t, *J*=7.4Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 196.9, 165.4, 159.0, 139.9, 133.5, 129.9, 129.1, 118.3, 51.7, 37.1, 20.3, 13.6.
MS (70 eV, EI), *m/z* (%) = 266 (M^+, 3), 236 (10), 235 (16), 234 (23), 199 (23), 172 (10), 171 (30), 139 (100), 111 (36), 75 (14).
HRMS *m/z* calc. for **$C_{14}H_{15}ClO_3$** (266.0710): 266.0712.
IR (ATR) υ (cm^{-1}) = 3095, 3071, 3033, 2991, 2962, 2950, 2927, 2904, 2875, 1718, 1671, 1635, 1586, 1571, 1436, 1398, 1338, 1286, 1251, 1232, 1195, 1167, 1122, 1107, 1085, 1023, 1012, 960, 930, 894, 840, 829, 755, 742, 729, 680, 653.

Preparation of (*Z*)-6-ethyl 1-methyl 5-methylene-3-propylhex-2-enedioate (44e)

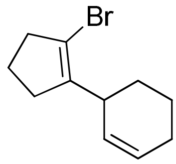


The allylation reaction of **43c** (7.70 mL, 2.00 mmol, 0.26 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (**39b**, 348 mg, 1.80 mmol) was performed according to **TP3** in 2 h. Flash column chromatography (silica, pentane:Et_2O 9.5:0.5) furnished **44e** as a colorless oil (368 mg, 77 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.21 (q, *J*=1.1Hz, 1H), 5.81 (s, 1H), 5.48 (q, *J*=1.7Hz, 1H), 4.20 (q, *J*=7.0Hz, 2H), 3.52-3.83 (m, 5H), 1.97-2.18 (m, 2H), 1.39-1.55 (m, 2H), 1.28 (t, *J*=7.1Hz, 3H), 0.89 (t, *J*=7.5 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.9, 166.6, 159.9, 137.5, 125.3, 117.2, 60.8, 50.9, 39.9, 33.2, 20.8, 14.1, 13.7.

MS (70 eV, EI), *m/z* (%) = 240 (M^+, 3), 208 (53), 195 (32), 194 (52), 180 (30), 167 (28), 162 (63), 151 (28), 135 (90), 134 (85), 107 (100), 106 (43), 105 (22), 93 (23), 91 (58), 79 (54), 77 (30).
HRMS *m/z* calc. for $\mathbf{C_{13}H_{20}O_4}$ (240.1362): 240.1344.
IR (ATR) υ (cm^{-1}) = 2959, 2934, 2907, 2874, 1713, 1645, 1629, 1433, 1368, 1325, 1272, 1245, 1191, 1176, 1131, 1093, 1022, 940, 928, 876, 817.

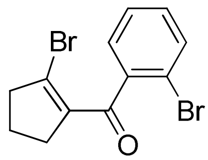
Preparation of 1-bromo-2-(3-cyclohexen-1-yl)cyclopentene (44f)



The allylation reaction of **43d** (4.30 mL, 2.40 mmol, 0.56 M in THF) with CuCN·2LiCl (ca. 0.03 mL, 0.03 mmol, 1 M in THF) and 3-bromocyclohexene (**39i**, 322 mg, 2.00 mmol) was performed according to **TP3** in 1 h. Flash column chromatography (silica, hexanes) furnished **44f** as a colorless oil (392 mg, 86 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.85-5.70 (m, 1H), 5.45-5.35 (m, 1H), 3.40-3.30 (m, 1H), 2.70-2.55 (m, 2H), 2.35-2.20 (m, 2H), 2.20-1.40 (m, 8H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 143.9, 128.8, 128.2, 115.2, 39.8, 36.7, 31.1, 26.7, 24.7, 21.8, 21.7.
MS (70 eV, EI), *m/z* (%) = 226 (M^+, 7), 147 (100), 119 (37), 91 (57), 91 (57).
HRMS *m/z* calc. for $\mathbf{C_{11}H_{15}Br}$ (226.0357): 226.0335.
IR (ATR) υ (cm^{-1}) = 2930, 2855, 1708, 1652, 1445, 1316, 1044, 917, 881, 722.

Preparation of (2-bromocyclopent-1-en-1-yl)(2-bromophenyl)methanone (44g)



The acylation reaction of **44d** (3.51 mL, 2.00 mmol, 0.57 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1.0 M in THF) and 2-bromobenzoyl chloride (**39d**, 527 mg, 2.40 mmol) was performed according to **TP3** in 4 h. Flash column chromatography (silica, hexanes:CH_2Cl_2 4:1) furnished **44g** as a colorless oil (421 mg, 64 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.67-7.52 (m, 1H), 7.49-7.19 (m, 3H), 2.90 (tt, *J*=7.8Hz, 2.3Hz, 2H), 2.84-2.74 (m, 2H), 2.04 (quint, *J*=7.7Hz, 2H).

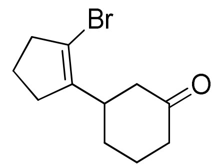
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 193.4, 141.2, 139.5, 133.1, 133.0, 131.3, 128.9, 127.5, 119.5, 43.9, 33.4, 21.5.

MS (70 eV, EI), *m/z* (%) = 330 (M^+, 14), 250 (96), 249 (100), 185 (51), 183 (51), 170 (50).

HRMS *m/z* calc. for **$C_{12}H_{10}Br_2O$** (329.9255): 329.9074.

IR (ATR) υ (cm^{-1}) = 2925, 1647, 1588, 1431, 1330, 1298, 1250, 1025, 744, 683.

Preparation of 3-(2-bromocyclopent-1-en-1-yl)cyclohexanone (44h)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the alkenyl zinc reagent **43d** (4.3 mL, 2.40 mmol, 0.56 M in THF) and cooled to -40 °C. CuCN·2LiCl (2.40 mL, 2.40 mmol, 1.0 M in THF) was added, followed by a solution of cyclohexenone (**39o**, 192 mg, 2.00 mmol) and chlorotrimethylsilane (0.8 mL, 5 mmol) in THF (1 mL) and the reaction mixture was stirred for 0.5 h at -40 °C and then 2 h at room temperature. The reaction was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et_2O 9:1) to give **44h** as a colorless oil (338 mg, 70 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 3.04-2.91 (m, 1H), 2.68-2.58 (m, 2H), 2.47-2.20 (m, 5H), 2.19-2.05 (m, 1H), 2.01-1.88 (m, 2H), 1.85-1.53 (m, 4H).

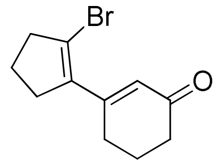
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 210.5, 141.6, 116.0, 45.1, 41.1, 39.8, 39.5, 30.3, 29.0, 25.4, 21.5.

MS (70 eV, EI), *m/z* (%) = 242 (M^+, >1), 163 (35), 91 (16), 70 (16), 61 (16), 43 (100).

HRMS *m/z* calc. for **$C_{11}H_{15}BrO$** (242.0306): 242.0288.

IR (ATR) υ (cm^{-1}) = 2935, 1699, 1652, 1446, 1319, 1261, 1221, 1061, 926, 755.

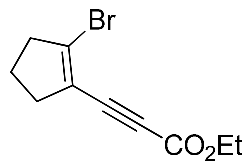
Preparation of 3-(2-bromocyclopent-1-en-1-yl)cyclohex-3-enone (44i)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the alkenylzinc reagent **43d** (4.3 mL, 2.40 mmol, 0.56 M in THF) and cooled to -40 °C. CuCN·2LiCl (2.40 mL, 2.40 mmol, 1.0 M in THF) was added, followed by 3-iodocyclohexenone (**39p**, 444 mg, 2.00 mmol) and the reaction mixture was stirred for 0.5 h at -40 °C and then 2 h at 0 °C. The reaction was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et_2O 9:1) to give **44i** as a colorless oil (314 mg, 65 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.10 (s, 1H). 2.85-2.70 (m, 4H), 2.65-2.50 (m, 2H), 2.45-2.35 (m, 2H), 2.20-1.90 (m, 4H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 200.1, 155.9, 137.9, 127.2, 123.7, 43.7, 37.4, 34.9, 28.3, 22.9, 21.7.
MS (70 eV, EI), *m/z* (%) = 242 (31), 240 (M^+, 32), 161 (38), 133 (100), 105 (44).
HRMS *m/z* calc. for **$C_{11}H_{13}BrO$** (240.0150): 240.0146.
IR (ATR) υ (cm^{-1}) = 2945, 1658, 1589, 1325, 1254, 1188, 1133, 956, 884, 732.

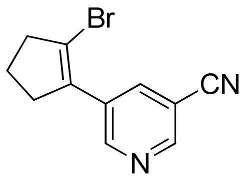
Preparation of 1-bromo-2-(2-ethoxycarbonylethynyl)cyclopentene (44j)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the alkenylzinc reagent **43d** (3.80 mL, 2.00 mmol, 0.53 M in THF) and cooled to -78 °C. CuCN·2LiCl (0.20 mL, 0.20 mmol, 1.0 M in THF) was added, followed by a solution of ethyl 3-bromoprop-2-ynoate (**39c**, 425 mg, 2.40 mmol) in THF (2 mL) and the reaction mixture was stirred for 3 h at -78 °C. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x20 mL). The combined organic phases were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, hexanes:Et_2O 10:1) to give **44j** as a colorless oil (377 mg, 78 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 4.27 (q, *J*=7.1Hz, 2H), 2.78 (tt, *J*=7.7Hz, 2.6Hz, 2H), 2.61-2.51 (m, 2H), 2.11-1.97 (m, 2H), 1.33 (t, *J*=7.1Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 153.9, 134.8, 121.9, 85.9, 81.4, 62.1, 40.9, 35.5, 22.6, 14.1.
MS (70 eV, EI), *m/z* (%) = 242 (M^+, 4), 91 (100), 90 (53), 89 (57), 63 (62), 62 (53).
HRMS *m/z* calc. for **$C_{10}H_{11}BrO_2$** (241.9942): 241.9936.
IR (ATR) υ (cm^{-1}) = 2981, 2204, 1704, 1366, 1268, 1207, 1162, 1092, 1020, 746.

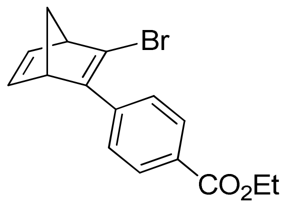
Preparation of 5-(2-bromocyclopent-1-en-1-yl)pyridine-3-carbonitrile (44k)



The cross-coupling reaction of **43d** (3.92 mL, 2.00 mmol, 0.51 M in THF) with 5-bromo-3-cyanopyridine (**39e**, 403 mg, 2.20 mmol) was performed according to **TP4** in 3 h. Flash column chromatography (silica, hexanes:Et_2O 3:1) furnished **44k** as a brown solid (271 mg, 54 %).

m.p.: 74.8-76.7 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.01 (d, *J*=2.2Hz, 1H), 8.77 (d, *J*=1.9 Hz, 1H), 8.25 (t, *J*=2.1Hz, 1H), 2.97-2.86 (m, 2H), 2.86-2.75 (m, 2H), 2.18-2.04 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 151.5, 150.4, 137.5, 133.3, 132.2, 122.2, 116.4, 109.5, 42.5, 35.4, 21.8.
MS (70 eV, EI), *m/z* (%) = 248 (M^+, 34), 169 (100), 168 (23), 142 (12), 115 (12), 63 (11).
HRMS *m/z* calc. for **$C_{11}H_9BrN_2$** (247.9949): 247.9930.
IR (ATR) υ (cm^{-1}) = 2943, 2844, 2231, 1620, 1559, 1431, 1423, 1308, 1289, 1186, 1158, 1092, 1026, 932, 904, 787, 701, 666.

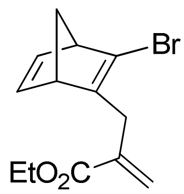
Preparation of ethyl 4-((1*S*,4*R*)-3-bromobicyclo[2.2.1]hepta-2,5-dien-2-yl)benzoate (44l)



The cross-coupling reaction of **43e** (5.15 mL, 2.00 mmol, 0.39 M in THF) with ethyl 4-iodobenzoate (**39h**, 442 mg, 1.60 mmol) was performed according to **TP4** in 5 h. Flash column chromatography (silica, pentane:Et_2O 50:1) furnished **44l** as a yellow oil (306 mg, 60 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.96-8.08 (m, 2H), 7.51-7.76 (m, 2H), 6.77-7.09 (m, 2H), 4.37 (q, *J*=7.0Hz, 2H), 3.86-4.02 (m, 1H), 3.60-3.78 (m, 1H), 2.36 (dt, *J*=6.4Hz, 1.7Hz, 1H), 2.16 (dt, *J*=6.4Hz, 1.8Hz, 1H), 1.39 (t, *J*=7.1Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.3, 147.6, 141.7, 141.4, 139.3, 132.7, 129.4, 128.9, 125.7, 70.3, 60.9, 60.8, 54.8, 14.3.
MS (70 eV, EI), *m/z* (%) = 320 (M^+, 70), 318 (M^+, 70), 240 (14), 239 (63), 213 (13), 211 (19), 168 (10), 167 (63), 166 (86), 165 (100), 152 (14), 66 (35).
HRMS *m/z* calc. for **$C_{16}H_{15}BrO_2$** (318.0255): 318.0253.
IR (ATR) υ (cm^{-1}) = 3119, 3066, 2979, 2938, 2904, 2869, 1756, 1710, 1605, 1407, 1366, 1269, 1251, 1181, 1101, 1018, 854, 771, 761, 718, 701.

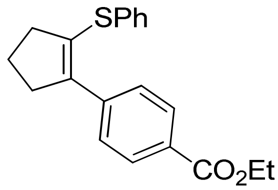
Preparation of ethyl 2-(((1*S*,4*R*)-3-bromobicyclo[2.2.1]hepta-2,5-dien-2-yl)methyl)-acrylate (44m)



The allylation reaction of **43e** (5.15 mL, 2.00 mmol, 0.39 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (**39b**, 348 mg, 1.80 mmol) was performed according to **TP3** overnight. Flash column chromatography (silica, pentane:Et_2O 50:1) furnished **44m** as a yellow oil (310 mg, 61 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.60-6.96 (m, 2H), 6.19 (d, J=1.1Hz, 1H), 4.20 (q, J=6.8Hz, 2H), 3.51 (bs, 1H), 3.40 (bs, 1H), 3.04-3.29 (m, 2H), 2.21 (dt, J=6.1Hz, 1.5Hz, 1H), 2.03 (dt, J=6.1Hz, 1.8Hz, 1H), 1.30 (t, J=7.2Hz, 3H), 0.03-0.22 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.9, 147.9, 142.0, 141.5, 136.5, 131.6, 126.0, 71.7, 60.8, 58.2, 53.7, 31.8, 14.2.
MS (70 eV, EI), *m/z* (%) = 284 (M^+, 16), 282 (M^+, 16), 218 (17), 216 (18), 203 (59), 175 (29), 157 (34), 131 (19), 130 (28), 129 (100), 128 (41), 127 (15), 115 (20), 103 (19), 91 (20), 66 (23), 43 (13).
HRMS *m/z* calc. for **$C_{13}H_{15}BrO_2$** (282.0255): 282.0250.
IR (ATR) υ (cm^{-1}) = 3067, 2977, 2938, 2905, 2869, 1713, 1629, 1368, 1295, 1250, 1219, 1175, 1140, 1114, 1026, 945, 842, 812, 705.

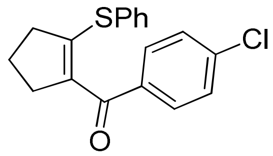
Preparation of ethyl 4-(2-(phenylthio)cyclopent-1-en-1-yl)benzoate (44n)



The cross-coupling reaction of **43f** (5.70 mL, 2.00 mmol, 0.35 M in THF) with ethyl 4-iodobenzoate (**39h**, 442 mg, 1.60 mmol) was performed according to **TP4** in 3 h. Flash column chromatography (silica, pentane:Et_2O 9,5:0,5) furnished **44n** as a colorless oil (420 mg, 81 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.94-8.12 (m, 2H), 7.55-7.71 (m, 2H), 7.15-7.47 (m, 5H), 4.38 (q, J=7.2Hz, 2H), 2.84-2.99 (m, 2H), 2.46-2.62 (m, 2H), 1.96 (quin, J=7.3Hz, 2H), 1.39 (t, J=7.1Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.4, 141.3, 139.8, 133.7, 132.9, 131.7, 129.3, 128.9, 128.7, 127.5, 127.3, 60.8, 38.8, 37.4, 22.0, 14.3.
MS (70 eV, EI), *m/z* (%) = 324 (M^+, 100), 279 (6), 218 (5), 173 (4), 141 (9), 128 (5), 115 (8).
HRMS *m/z* calc. for **$C_{20}H_{20}O_2S$** (324.1184): 324.1166.
IR (ATR) υ (cm^{-1}) = 3070, 3056, 2976, 2952, 2934, 2903, 2843, 1709, 1605, 1575, 1474, 1439, 1405, 1365, 1269, 1181, 1105, 1097, 1022, 850, 771, 741, 700, 690.

Preparation of (4-chlorophenyl)(2-(phenylthio)cyclopent-1-en-1-yl)methanone (44o)



The acylation reaction of **43f** (5.70 mL, 2.00 mmol, 0.35 M in THF) with CuCN·2LiCl (2.00 mL, 2.00 mmol, 1 M in THF) and 4-chlorobenzoyl chloride (**39l**, 280 mg, 1.60 mmol) was performed according to **TP3** overnight. Flash column chromatography (silica, pentane:Et_2O 9.5:0.5) furnished **44o** as a white solid (432 mg, 86 %).

m.p.: 74.7-76.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.63-7.75 (m, 2H), 7.46-7.57 (m, 2H), 7.28-7.46 (m, 5H), 2.80-2.93 (m, 2H), 2.33-2.46 (m, 2H), 1.80-1.97 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 191.2, 159.0, 137.9, 137.7, 134.5, 132.3, 129.6, 129.0, 129.0, 128.5, 128.5, 38.7, 35.7, 23.6.

MS (70 eV, EI), *m/z* (%) = 314 (M^+, 61), 236 (18), 203 (22), 175 (15), 147 (13), 142 (12), 141 (14), 139 (100), 111 (54), 110 (35), 109 (10), 77 (16), 75 (12), 65 (15).

HRMS *m/z* calc. for **$C_{18}H_{15}ClOS$** (314.0532): 314.0527.

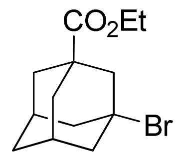
IR (ATR) υ (cm^{-1}) = 3083, 3063, 3045, 2993, 2984, 2913, 1706, 1675, 1615, 1585, 1574, 1366, 1349, 1340, 1288, 1280, 1219, 1194, 1185, 1175, 1156, 1093, 1021, 1009, 971, 966, 914, 869, 846, 773, 764, 736, 688.

6. SYNTHESIS OF FUNCTIONALIZED ADAMANTYLZINC REAGENTS USING A Br/Mg-INSERTION IN THE PRESENCE OF $ZnCl_2$

6.1 PREPARATION OF STARTING MATERIALS

All reagents were obtained from commercial sources. Compound **45c**[287] was prepared according to a literature-known procedure.

Preparation of ethyl 3-bromoadamantane-1-carboxylate (45b)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with 3-bromoadamantane-1-carboxylic acid[288] (5.2 g, 20 mmol) and dissolved in 100 mL EtOH. After cooling to 0 °C, $SOCl_2$ (3,57 g, 30 mmol) was added dropwise and the reaction mixture was stirred over night while slowly warming up to room temperature. The reaction was quenched with water (100 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The pure product was obtained without further purification as a colorless oil (5.69 g, 99 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 4.11 (q, *J*=7.2Hz, 2H), 2.47 (s, 2H), 2.23-2.39 (m, 4H), 2.14-2.24 (m, 2H), 1.88 (d, *J*=3.0Hz, 4H), 1.69 (d, *J*=1.4Hz, 2H), 1.24 (t, *J*=7.0Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 175.4, 63.9, 60.5, 49.7, 48.1, 44.9, 37.1, 34.5, 31.7, 14.1.
MS (70 eV, EI), *m/z* (%) = 285 ($[M-H]^+$, 2), 208 (13), 207 (100), 161 (16), 133 (45), 91 (14), 79 (13), 43 (18).
HRMS (EI), *m/z* calc. for $\mathbf{C_{13}H_{18}BrO_2}$ (285.0490 ([M-H])): 285.0490 ([M-H]).
IR (ATR) υ (cm^{-1}) = 2979, 2935, 2911, 2859, 1724, 1476, 1453, 1365, 1332, 1310, 1244, 1219, 1171, 1149, 1103, 1075, 1020, 1004, 968, 945, 909, 863, 825, 744, 697, 672.

[287] M. Xie, W. J. le Noble, *J. Org. Chem.* **1989**, *54*, 3836.
[288] K. H. Min, E. K. Kim, E. S. Kim, D. K. Kim, Y. Xia, Y. Jin, N. Kaur, K. Lee, K. Lee, H. Y. Jung, Y. Choi, M.-K. Park, Y. K. Min, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5376.

6.2 TYPICAL PROCEDURES

Typical procedure 1 (TP1): LiCl-mediated magnesium insertion in the presence of zinc chloride in adamantyl bromides

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (1.1 equiv) and heated with a heat gun under high vacuum (5 min). After cooling to room temperature, magnesium turnings (2 equiv) were added, followed by THF (1 mL/mmol). The magnesium was activated using 1,2-dibromoethane (5 mol%) and TMSCl (5 mol%). Then, $ZnCl_2$-solution (1.1 equiv, 1 M in THF) was added followed by the substrate (1 equiv). The reaction mixture was stirred at 25 °C until GC-analysis of hydrolyzed reaction aliquot showed full consumption of the starting material. Then, solids were allowed to settle or the reation mixture was centrifuged (10 min, 2000 rpm). The yield of the insertion rection was determined by iodometric titration[192] of the supernatant solution.

Typical procedure 2 (TP2): Cross-coupling reactions of adamantyl zinc reagents

The desired aryl halide (0.9 equiv) was added to the freshly prepared zinc reagent followed by $Pd(OAc)_2$ (1 mol%) and SPhos (2 mol%) and the mixture was stirred for the given time at 50 °C. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

Typical procedure 3 (TP3): Acylation of adamantly zinc reagents

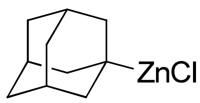
The freshly prepared zinc reagent was cooled to -40 °C and the corresponding acyl chloride (0.9 equiv) was added, followed by CuCN·2LiCl (1 M in THF). The reaction mixture was allowed to warm to room temperature. After stirring for the given time, the reaction mixture was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL), washed with sat. NH_4Cl/NH_3 solution (9:1, 2x10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

Typical procedure 4 (TP4): Addition of adamantly zinc reagents to nitroso derivatives

To the freshly prepared adamantyl zinc reagent was added the nitroso derivative (0.9 equiv, 1.0M in THF and the reaction mixture was stirred for the indicated time at room temperature. EtOH (1 ml/mmol), $FeCl_2$ (2 equiv) and $NaBH_4$ (1.1 equiv) were added and the reaction mixture was stirred at room temperature over night. After stirring for the given time, the reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

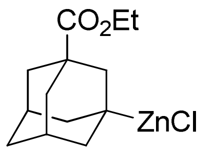
6.3 PREPARATION OF FUNCTIONALIZED ADAMANTYLZINC REAGENTS

Preparation of adamantan-1-ylzinc chloride (46a)



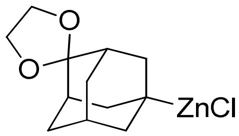
According to **TP1**, the zinc reagent **46a** was prepared from 1-bromoadamantane (**45a**, 1.08 g, 5.0 mmol) using Mg turnings (241 mg, 10.0 mmol), LiCl (233 mg, 5.5 mmol) and $ZnCl_2$ (5.5 mL, 1 M in THF) in 2 h at 25 °C. Titration against iodine indicates a concentration of 0.32 M (85 %).

Preparation of 3-(ethoxycarbonyl)adamantan-1-yl)zinc chloride (46b)



According to **TP1**, the zinc reagent **46b** was prepared from ethyl 3-bromoadamantane-1-carboxylate (**45b**, 1.44 g, 5.0 mmol) using Mg turnings (241 mg, 10.0 mmol), LiCl (233 mg, 5.5 mmol) and $ZnCl_2$ (5.5 mL, 1 M in THF) in 2 h at 25 °C. Titration against iodine indicates a concentration of 0.24 M (63 %).

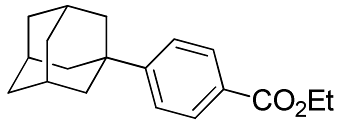
Preparation of spiro[adamantane-2,2'-[1,3]dioxolan]-5-ylzinc chloride (46c)



According to **TP1**, the zinc reagent **46c** was prepared from 5-bromospiro[adamantane-2,2'-[1,3]dioxolane] (**45c**, 1.37 g, 5.0 mmol) using Mg turnings (241 mg, 10.0 mmol), LiCl (233 mg, 5.5 mmol) and $ZnCl_2$ (5.5 mL, 1 M in THF) in 3 h at 25 °C. Titration against iodine indicates a concentration of 0.22 M (57 %).

6.4 FUNCTIONALIZATION OF ADAMANTYLZINC REAGENTS

Preparation of ethyl 4-(adamantan-1-yl)benzoate (48a)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and ethyl 4-chlorobenzoate (**47c**, 166 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 50:1) furnished **48a** as a white solid (222 mg, 87 %).

m.p.: 119.8-120.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.90-8.05 (m, 2H), 7.35-7.49 (m, 2H), 4.36 (q, J=7.2Hz, 2H), 2.11 (bs, 3H), 1.92 (d, J=2.8Hz, 6H), 1.70-1.86 (m, 6H), 1.38 (t, J=7.2Hz, 3H).

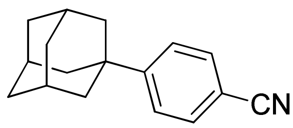
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.7, 156.5, 129.4, 127.7, 124.9, 60.7, 42.9, 36.7, 36.6, 28.8, 14.4.

MS (70 eV, EI), m/z (%) = 284 (M^+, 2), 88 (5), 73 (6), 70 (11), 61 (16), 45 (15), 44 (6), 43 (100), 42 (6).

HRMS (EI), m/z calc. for $\mathbf{C_{19}H_{24}O_2}$ (284.1776): 284.1771.

IR (ATR) υ (cm^{-1}) = 2908, 2849, 1712, 1609, 1447, 1408, 1368, 1309, 1275, 1188, 1179, 1102, 1042, 1015, 977, 960, 874, 860, 851, 814, 768, 714, 704.

Preparation of 4-(adamantan-1-yl)benzonitrile (48b)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 4-bromobenzonitrile (**47d**, 164 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 20:1) furnished **48b** as a white solid (187 mg, 88 %).

m.p.: 125.3-127.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.53-7.66 (m, 2H), 7.37-7.51 (m, 2H), 2.12 (bs, 3H), 1.89 (d, *J*=2.8Hz, 6H), 1.67-1.85 (m, 6H).

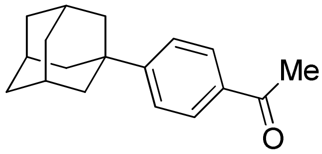
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 156.7, 132.0, 125.8, 119.2, 109.3, 42.7, 36.8, 36.5, 28.7.

MS (70 eV, EI), *m/z* (%) = 237 (M^+, 56), 181 (27), 180 (75), 135 (20), 94 (25), 61 (17), 45 (15), 43 (100).

HRMS (EI), *m/z* calc. for $\mathbf{C_{17}H_{19}N}$ (237.1517): 237.1503.

IR (ATR) υ (cm^{-1}) = 3069, 3045, 3041, 2915, 2897, 2847, 2233, 1607, 1505, 1448, 1408, 1398, 1343, 1318, 1289, 1260, 1175, 1100, 1067, 1040, 1031, 1019, 974, 850, 834, 805.

Preparation of 1-(adamantan-1-yl)phenyl)ethanone (48c)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 1-(4-bromophenyl)ethanone (**47e**, 179 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 20:1) furnished **48e** as a white solid (192 mg, 84 %).

m.p.: 115.6-116.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.91 (d, *J*=8.6Hz, 2H), 7.45 (d, *J*=8.8Hz, 2H), 2.58 (s, 3H), 2.11 (bs, 3H), 1.93 (d, *J*=2.8Hz, 6H), 1.67-1.88 (m, 6H).

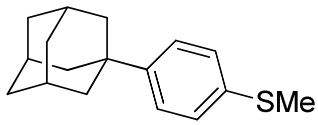
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 197.9, 156.9, 134.6, 128.3, 125.1, 42.9, 36.7, 36.7, 28.8, 26.5.

MS (70 eV, EI), *m/z* (%) = 254 (M^+, 2), 239 (8), 88 (5), 70 (10), 61 (16), 45 (14), 43 (100), 42 (6).

HRMS (EI), *m/z* calc. for $\mathbf{C_{18}H_{22}O}$ (254.1671): 254.1665.

IR (ATR) υ (cm^{-1}) = 2908, 2848, 1714, 1679, 1602, 1562, 1406, 1359, 1345, 1269, 1244, 1191, 1177, 1104, 1077, 1058, 1041, 1032, 1012, 976, 963, 951, 847, 832, 804, 768, 678.

Preparation of (4-(adamantan-1-yl)phenyl)(methyl)sulfane (48d)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and (4-bromophenyl)-(methyl)sulfane (**47f**, 183 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **48d** as a white solid (218 mg, 94 %).

m.p.: 78.2-80.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.19-7.41 (m, 4H), 2.49 (s, 3H), 2.12 (bs, 3H), 1.91 (d, *J*=2.8Hz, 6H), 1.69-1.86 (m, 6H).

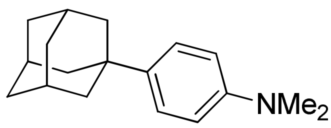
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 148.6, 134.8, 126.9, 125.5, 43.2, 36.8, 35.9, 28.9, 16.3.

MS (70 eV, EI), *m/z* (%) = 258 (M^+, 100), 201 (47), 164 (13), 154 (28), 57 (14), 43 (11), 41 (10).

HRMS (EI), *m/z* calc. for $\mathbf{C_{17}H_{22}S}$ (258.1442): 258.1448.

IR (ATR) υ (cm^{-1}) = 3074, 3055, 3024, 2906, 2897, 2846, 1495, 1446, 1433, 1398, 1342, 1246, 1175, 1101, 1092, 1033, 1010, 963, 824, 804, 796, 737, 718.

Preparation of 4-(adamantan-1-yl)-N,N-dimethylaniline (48e)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 4-bromo-*N*,*N*-dimethylaniline (**47g**, 180 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **48e** as a white solid (142 mg, 62 %).

m.p.: 118.2-119.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.23-7.35 (m, 2H), 6.72-6.86 (m, 2H), 2.86-3.07 (m, 6H), 2.12 (bs, 3H), 1.89-2.00 (m, 6H), 1.72-1.87 (m, 6H).

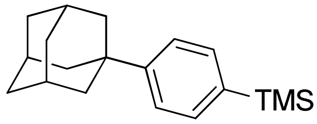
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 148.6, 140.0, 125.4, 112.8, 43.4, 40.9, 36.9, 35.3, 29.1.

MS (70 eV, EI), *m/z* (%) = 255 (M^+, 100), 199 (16), 198 (87), 184 (8), 161 (10), 135 (8), 134 (21), 43 (16).

HRMS (EI), *m/z* calc. for **$C_{18}H_{25}N$** (255.1987): 255.1977.

IR (ATR) υ (cm^{-1}) = 3090, 3032, 2983, 2896, 2844, 1615, 1518, 1491, 1446, 1442, 1356, 1350, 1341, 1232, 1205, 1165, 1099, 1063, 975, 949, 822, 797.

Preparation of (4-(adamantan-1-yl)phenyl)trimethylsilane (48f)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and (4-bromophenyl)trimethylsilane (**47h**, 206 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane pur) furnished **48f** as a white solid (205 mg, 80 %).

m.p.: 126.2-127.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.46-7.57 (m, 2H), 7.35-7.44 (m, 2H), 2.13 (bs, 3H), 1.96 (d, *J*=2.8Hz, 6H), 1.69-1.89 (m, 6H), 0.29 (s, 9H).

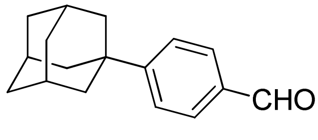
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 151.9, 137.0, 133.3, 124.3, 43.1, 36.8, 36.2, 29.0, -1.0.

MS (70 eV, EI), *m/z* (%) = 284 (M^+, 9), 271 (8), 270 (23), 269 (100), 135 (4), 73 (8), 43 (11).

HRMS (EI), *m/z* calc. for **$C_{19}H_{28}Si$** (284.1960): 284.1958.

IR (ATR) υ (cm^{-1}) = 3070, 3015, 2954, 2905, 2847, 1596, 1448, 1396, 1342, 1250, 1244, 1115, 1102, 1031, 1017, 859, 835, 826, 798, 757, 722, 691, 668.

Preparation of 4-(adamantan-1-yl)benzaldehyde (48g)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 4-bromobenzaldehyde (**47i**, 167 mg, 0.9 mmol) was performed according to **TP2** in 1 h. Flash column chromatography (silica, pentane:Et_2O 50:1) furnished **48g** as a white solid (190 mg, 88 %).

m.p.: 97.0-98.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.98 (s, 1H), 7.75-7.89 (m, 2H), 7.45-7.62 (m, 2H), 2.13 (bs, 3H), 1.94 (d, *J*=2.8Hz, 6H), 1.66-1.88 (m, 6H).

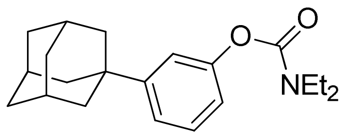
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 192.1, 158.5, 134.1, 129.7, 125.6, 42.9, 36.9, 36.6, 28.8.

MS (70 eV, EI), *m/z* (%) = 240 (M^+, 100), 184 (18), 183 (39), 155 (54), 94 (16), 91 (12), 79 (9).

HRMS (EI), *m/z* calc. for $\mathbf{C_{17}H_{20}O}$ (240.1514): 240.1500.

IR (ATR) υ (cm^{-1}) = 3090, 3055, 2901, 2846, 1695, 1685, 1602, 1569, 1446, 1412, 1368, 1344, 1304, 1222, 1205, 1165, 1112, 1102, 1079, 1030, 1012, 977, 860, 825, 801, 654.

Preparation of 3-(adamantan-1-yl)phenyl diethylcarbamate (48h)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 3-bromophenyl diethylcarbamate (**47j**, 245 mg, 0.9 mmol) was performed according to **TP2** in 1 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **48h** as a white solid (206 mg, 70 %).

m.p.: 66.1-67.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.30 (t, *J*=7.9Hz, 3H), 7.16-7.22 (m, 2H), 7.10 (t, *J*=2.1Hz, 1H), 6.95 (ddd, *J*=7.9Hz, 2.3Hz, 1.1Hz, 1H), 3.23-3.57 (m, 4H), 2.10 (bs, 3H), 1.93 (d, *J*=3.0Hz, 6H), 1.68-1.86 (m, 6H), 1.09-1.36 (m, 6H).

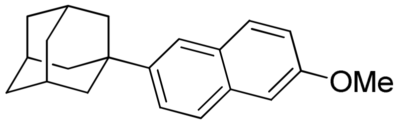
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 154.4, 152.9, 151.5, 128.6, 121.6, 118.8, 118.4, 43.1, 42.2, 41.9, 36.8, 36.2, 28.9, 14.3, 13.4.

MS (70 eV, EI), *m/z* (%) = 327 (M^+, 7), 228 (2), 171 (3), 101 (5), 100 (100), 91 (2), 79 (2), 72 (18), 43 (2).

HRMS (EI), *m/z* calc. for $\mathbf{C_{21}H_{29}NO_2}$ (327.2198): 327.2186.

IR (ATR) υ (cm^{-1}) = 3035, 2977, 2900, 2846, 1709, 1603, 1585, 1489, 1470, 1453, 1412, 1378, 1345, 1316, 1271, 1237, 1222, 1183, 1165, 1151, 1097, 1088, 1049, 980, 966, 876, 786, 774, 754, 695.

Preparation of 1-(6-methoxynaphthalen-2-yl)adamantane (48i)



The cross-coupling reaction of **48a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 2-bromo-6-methoxynaphthalene (**47k**, 213 mg, 0.9 mmol) was performed according to **TP2** in 3 h. Flash column chromatography (silica, pentane:Et_2O 7:3) furnished **48i** as a white solid (250 mg, 95 %).

m.p.: 150.5-152.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.64-7.80 (m, 3H), 7.50-7.61 (m, 1H), 7.07-7.19 (m, 2H), 3.93 (s, 3H), 2.16 (bs, 3H), 2.04 (s, 6H), 1.73-1.96 (m, 6H).

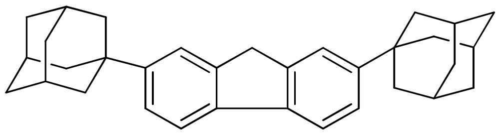
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 157.3, 146.6, 132.7, 129.4, 129.0, 126.4, 124.6, 122.7, 118.4, 105.4, 55.3, 43.2, 36.9, 36.2, 29.0.

MS (70 eV, EI), *m/z* (%) = 292 (M^+, 100), 236 (13), 235 (52), 220 (12), 203 (6), 198 (14), 171 (14), 165 (6).

HRMS (EI), *m/z* calc. for **$C_{21}H_{24}O$** (292.1827): 292.1829.

IR (ATR) υ (cm^{-1}) = 3049, 3014, 2946, 2899, 2843, 1632, 1605, 1503, 1484, 1460, 1451, 1391, 1337, 1265, 1223, 1196, 1186, 1179, 1163, 1154, 1122, 1036, 1031, 923, 885, 849, 822, 814, 797, 726, 672.

Preparation of 2,7-di(adamantan-1-yl)-fluorene (48j)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 2,7-dibromo-fluorene (**47l**, 146 mg, 0.45 mmol) was performed according to **TP2** in 3 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **48j** as a white solid (206 mg, 70 %).

m.p.: 308.9-311.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.70 (d, *J*=8.0Hz, 2H), 7.57 (s, 2H), 7.39 (dd, *J*=8.0Hz, 1.7Hz, 2H), 3.88 (s, 2H), 2.16 (bs, 6H), 2.02 (d, *J*=3.0Hz, 12H), 1.74-1.95 (m, 12H).

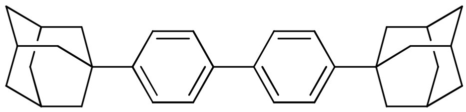
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 149.8, 143.3, 139.3, 123.3, 121.4, 119.1, 43.5, 37.2, 36.9, 36.4, 29.1.

MS (70 eV, EI), *m/z* (%) = 434 (M^+, 100), 313 (3), 135 (33), 107 (3), 93 (7), 79 (6), 67 (3).

HRMS (EI), *m/z* calc. for $\mathbf{C_{33}H_{38}}$ (434.2974): 434.2961.

IR (ATR) υ (cm^{-1}) = 2898, 2846, 1649, 1604, 1474, 1446, 1414, 1344, 1314, 1262, 1247, 1176, 1100, 1079, 1068, 1060, 1038, 976, 875, 861, 827, 800, 742, 714, 694, 673.

Preparation of 4,4'-di(adamantan-1-yl)-1,1'-biphenyl (48k)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (4 mg, 0.02 mmol), SPhos (16 mg, 0.04 mmol) and 4,4'-dibromo-1,1'-biphenyl (**47m**, 125 mg, 0.4 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 98:2) furnished **48k** as a white solid (206 mg, 70 %).

m.p.: >250 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.51-7.68 (m, 4H), 7.36-7.50 (m, 4H), 2.15 (bs, 6H), 1.99 (d, *J*=2.8Hz, 12H), 1.66-1.93 (m, 12H).

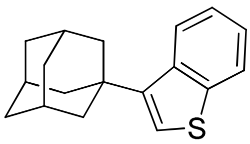
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 150.1, 138.3, 126.7, 125.2, 43.2, 36.9, 36.1, 29.0.

MS (70 eV, EI), *m/z* (%) = 422 (M^+, 100), 365 (4), 328 (5), 301 (9), 136 (4), 135 (31), 93 (8), 79 (9).

HRMS (EI), *m/z* calc. for $\mathbf{C_{32}H_{38}}$ (422.2974): 422.2967.

IR (ATR) υ (cm^{-1}) = 3083, 3056, 3023, 2898, 2846, 1499, 1448, 1366, 1355, 1342, 1315, 1243, 1214, 1178, 1101, 1020, 1003, 977, 828, 810, 799, 761, 727, 703.

Preparation of 3-(adamantan-1-yl)benzothiophene (48l)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 3-bromobenzothiophene (**49a**, 192 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane pur) furnished **48l** as a white solid (188 mg, 84 %).

m.p.: 150.3-151.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.11-8.31 (m, 1H), 7.78-7.97 (m, 1H), 7.19-7.44 (m, 2H), 7.08 (s, 1H), 1.99-2.45 (m, 9H), 1.62-1.99 (m, 6H).

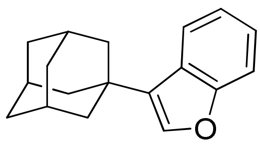
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 146.1, 141.7, 137.5, 124.7, 123.4, 123.0, 119.8, 42.0, 37.1, 37.0, 28.8.

MS (70 eV, EI), *m/z* (%) = 268 (M^+, 100), 225 (6), 212 (14), 211 (84), 185 (5), 184 (6), 174 (14), 147 (10), 115 (6).

HRMS (EI), *m/z* calc. for $\mathbf{C_{18}H_{20}S}$ (268.1286): 268.1279.

IR (ATR) υ (cm^{-1}) = 3104, 3072, 2935, 2910, 2900, 2884, 2848, 1452, 1446, 1423, 1344, 1308, 1258, 1175, 1163, 1100, 1062, 1028, 994, 974, 932, 871, 846, 790, 757, 705, 652.

Preparation of 3-(adamantan-1-yl)benzofuran (48m)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 3-bromobenzofuran (**49b**, 177 mg, 0.9 mmol) was performed according to **TP2** in 3 h. Flash column chromatography (silica, pentane:Et_2O 100:1) furnished **48m** as a white solid (129 mg, 57 %).

m.p.: 69.7-71.5 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.83 (d, *J*=8.0Hz, 1H), 7.49 (d, *J*=8.2Hz, 1H), 7.32 (s, 1H), 7.27 (d, *J*=8.2Hz, 1H), 7.22 (t, *J*=7.4Hz, 1H), 2.05-2.20 (m, 9H), 1.78-1.92 (m, 6H).

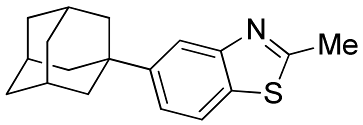
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 156.0, 139.4, 130.5, 126.5, 123.6, 121.9, 121.7, 111.7, 42.2, 37.0, 33.3, 28.5.

MS (70 eV, EI), *m/z* (%) = 252 (M^+, 100), 196 (9), 195 (46), 167 (22), 158 (12), 131 (6).

HRMS (EI), *m/z* calc. for $\mathbf{C_{18}H_{20}O}$ (252.1514): 252.1511.

IR (ATR) υ (cm^{-1}) = 3085, 3063, 3032, 2901, 2847, 1582, 1451, 1344, 1284, 1255, 1203, 1183, 1157, 1104, 1083, 1030, 1004, 976, 929, 867, 793, 766, 744, 684.

Preparation of 5-(adamantan-1-yl)-2-methylbenzothiazole (48n)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 5-bromo-2-methylbenzothiazole (**49c**, 205 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, EtOAc pur) furnished **48n** as a brown solid (232 mg, 91 %).

m.p.: 147.4-149.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.89-8.00 (m, H), 7.73 (d, *J*=8.6Hz, 1H), 7.40 (dd, *J*=8.6Hz, 1.9Hz, 1H), 2.82 (s, 3H), 2.12 (bs, 3H), 1.93-2.03 (m, 6H), 1.68-1.87 (m, 6H).

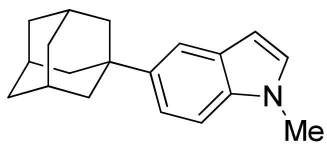
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.8, 153.7, 149.9, 132.5, 122.3, 120.7, 118.6, 43.4, 36.8, 36.3, 29.0, 20.1.

MS (70 eV, EI), *m/z* (%) = 283 (M^+, 83), 240 (10), 227 (19), 226 (100), 189 (18), 184 (5), 162 (10).

HRMS (EI), *m/z* calc. for **$C_{18}H_{21}NS$** (283.1395): 283.1351.

IR (ATR) υ (cm^{-1}) = 3054, 3028, 2954, 2925, 2916, 2901, 2843, 1739, 1526, 1458, 1448, 1415, 1342, 1308, 1260, 1241, 1168, 1160, 1101, 1067, 980, 974, 923, 795, 728, 656.

Preparation of 5-(adamantan-1-yl)-1-methyl-indole (48o)



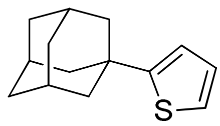
The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 5-bromo-1-methyl-indole (**49d**, 189 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 8:2) furnished **48o** as a white solid (170 mg, 71 %).

m.p.: 171.7-173.5 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.64 (d, *J*=1.9Hz, 1H), 7.34-7.38 (m, 1H), 7.29-7.33 (m, 1H), 7.04 (d, *J*=3.0Hz, 1H), 6.49 (d, *J*=3.0Hz, 1H), 3.79 (s, 3H), 2.16 (bs, 3H), 2.05 (d, *J*=3.0Hz, 6H), 1.75-1.91 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 142.6, 135.0, 128.7, 128.4, 119.2, 116.5, 108.7, 100.9, 43.9, 37.0, 36.0, 32.8, 29.2.
MS (70 eV, EI), *m/z* (%) = 265 (M^+, 100), 222 (6), 209 (17), 208 (90), 194 (5), 193 (11), 171 (16), 144 (15), 131 (5), 43 (24).
HRMS (EI), *m/z* calc. for $\mathbf{C_{19}H_{23}N}$ (265.1830): 265.1823.
IR (ATR) υ (cm^{-1}) = 3112, 3061, 3037, 2925, 2901, 2843, 2818, 1514, 1489, 1448, 1421, 1368, 1342, 1333, 1287, 1244, 1167, 1104, 1081, 1030, 1008, 981, 974, 924, 875, 847, 791, 760, 724, 676.

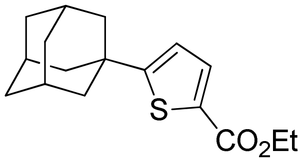
Preparation of 2-(adamantan-1-yl)thiophene (48p)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 2-bromothiophene (**49e**, 147 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 100:1) furnished **48p** as a white solid (120 mg, 61 %).

m.p.: 66.1-67.2 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.14 (dd, *J*=5.0Hz, 1.1Hz, 1H), 6.89-7.01 (m, 1H), 6.83 (dd, *J*=3.5Hz, 1.2Hz, 1H), 2.10 (bs, 3H), 2.00 (d, *J*=2.8Hz, 6H), 1.71-1.88 (m, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 158.3, 126.3, 121.9, 120.1, 45.0, 36.7, 36.2, 28.9.
MS (70 eV, EI), *m/z* (%) = 218 (M^+, 71), 175 (7), 163 (5), 162 (13), 161 (100), 128 (6), 124 (15), 97 (6).
HRMS (EI), *m/z* calc. for $\mathbf{C_{14}H_{18}S}$ (218.1129): 218.1144.
IR (ATR) υ (cm^{-1}) = 3098, 3070, 2898, 2846, 1526, 1446, 1342, 1314, 1261, 1228, 1100, 1077, 1052, 1004, 966, 850, 823, 808, 703, 694, 686.

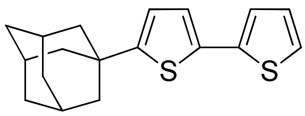
Preparation of ethyl 5-(adamantan-1-yl)thiophene-2-carboxylate (48q)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and ethyl 5-bromothiophene-2-carboxylate (**49f**, 212 mg, 0.9 mmol) was performed according to **TP2** in 3 h. Flash column chromatography (silica, pentane:Et_2O 9.5:0.5) furnished **48q** as a white solid (139 mg, 53 %).

m.p.: 85.9-88.2 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.65 (d, *J*=3.9Hz, 1H), 6.83 (d, *J*=3.9Hz, 1H), 4.33 (q, *J*=7.2Hz, 2H), 2.09 (bs, 3H), 1.97 (d, *J*=2.8Hz, 6H), 1.65-1.86 (m, 6H), 1.36 (t, *J*=7.2Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.9, 162.6, 133.2, 130.0, 121.4, 60.8, 44.6, 36.8, 36.4, 28.7, 14.4.
MS (70 eV, EI), *m/z* (%) = 290 (M^+, 100), 257 (23), 245 (26), 234 (12), 233 (51), 196 (15), 161 (31), 135 (45), 94 (10), 93 (13), 91 (10), 79 (16).
HRMS (EI), *m/z* calc. for **$C_{175}H_{22}O_2S$** (290.1341): 290.1336.
IR (ATR) υ (cm^{-1}) = 3077, 2983, 2960, 2918, 2851, 2842, 1707, 1536, 1455, 1366, 1335, 1317, 1254, 1212, 1192, 1086, 1048, 1036, 1010, 999, 976, 867, 820, 814, 805, 762, 747.

Preparation of 5-(adamantan-1-yl)-2,2'-bithiophene (48r)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 5-bromo-2,2'-bithiophene (**49g**, 221 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane pur) furnished **48r** as a white solid (157 mg, 58 %).

m.p.: 69.9-70.7 °C.
^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.17 (dd, *J*=5.1Hz, 1.2Hz, 1H), 7.11 (dd, *J*=3.6Hz, 1.1Hz, 1H), 6.96-7.05 (m, 2H), 6.72 (d, *J*=3.6Hz, 1H), 2.10 (bs, 3H), 1.93-2.06 (m, 6H), 1.71-1.87 (m, 6H).

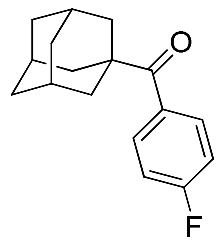
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 157.6, 138.1, 133.9, 127.6, 123.7, 123.1, 122.9, 121.0, 44.8, 36.6, 36.6, 36.4, 28.9, 28.9.

MS (70 eV, EI), *m/z* (%) = 300 (M^+, 100), 257 (4), 245 (6), 244 (13), 243 (63), 210 (11), 209 (4), 206 (12), 121 (5), 61 (4), 45 (4), 43 (26).

HRMS (EI), *m/z* calc. for **$C_{18}H_{20}S_2$** (300.1006): 300.0996.

IR (ATR) υ (cm^{-1}) = 3119, 3069, 2910, 2898, 2846, 1512, 1460, 1445, 1428, 1342, 1318, 1204, 1184, 1100, 1060, 1003, 976, 887, 876, 840, 823, 810, 797, 688, 684.

Preparation of adamantan-1-yl(4-fluorophenyl)methanone (51a)



The acylation reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) and 4-fluorobenzoyl chloride (**50a**, 143 mg, 0.9 mmol) was performed according to **TP3** over night. Flash column chromatography (silica, pentane:Et_2O 50:1) furnished **51a** as a white solid (207 mg, 89 %).

m.p.: 78.8-80.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.53-7.73 (m, 2H), 6.96-7.14 (m, 2H), 2.09 (bs, 3H), 2.01 (d, *J*=2.8Hz, 6H), 1.67-1.85 (m, 6H).

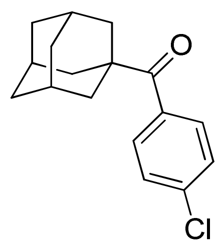
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 208.1, 163.9 (d, *J*=251.1Hz), 135.3 (d, *J*=3.4Hz), 129.9 (d, *J*=8.5Hz), 115.0 (d, *J*=21.4Hz), 46.9, 39.2, 36.5, 28.1.

MS (70 eV, EI), *m/z* (%) = 258 (M^+, 3), 136 (8), 135 (100), 123 (6), 107 (5), 93 (9), 81 (3), 79 (10), 77 (3), 67 (4).

HRMS (EI), *m/z* calc. for **$C_{17}H_{19}FO$** (258.1420): 258.1416.

IR (ATR) υ (cm^{-1}) = 3085, 2957, 2922, 2905, 2890, 2884, 2854, 1665, 1591, 1501, 1452, 1404, 1346, 1266, 1231, 1208, 1178, 1156, 1112, 1102, 1096, 1039, 1010, 986, 973, 956, 952, 929, 846, 815, 794, 746, 687, 678.

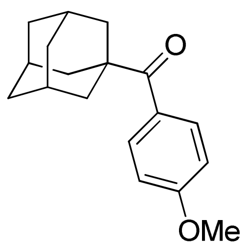
Preparation of adamantan-1-yl(4-chlorophenyl)methanone (51b)



The acylation reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) and 4-chlorobenzoyl chloride (**50b**, 158 mg, 0.9 mmol) was performed according to **TP3** over night. Flash column chromatography (silica, pentane:Et_2O 92:8) furnished **51b** as a pale yellow solid (173 mg, 70 %).

m.p.: 92.4-95.7 °C.
^{1}H NMR (100 MHz, $CDCl_3$) δ (ppm) = 7.43-7.61 (m, 2H), 7.26-7.40 (m, 2H), 2.07 (bs, 3H), 1.98 (d, J=2.8Hz, 6H), 1.63-1.81 (m, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 208.6, 137.6, 136.4, 128.8, 128.2, 47.0, 39.1, 36.5, 28.1.
MS (70 eV, EI), *m/z* (%) = 274 (M^+, 4), 139 (6), 136 (12), 135 (100), 111 (5), 107 (5), 93 (11), 79 (13), 67 (5), 42 (17).
HRMS (EI), *m/z* calc. for **$C_{17}H_{19}ClO$** (274.1124): 274.1111.
IR (ATR) υ (cm^{-1}) = 2911, 2849, 1724, 1659, 1586, 1484, 1450, 1394, 1343, 1268, 1232, 1184, 1172, 1115, 1089, 1046, 1010, 989, 972, 957, 950, 927, 840, 816, 808, 768, 760, 742, 728, 686, 668.

Preparation of adamantan-1-yl(4-methoxyphenyl)methanone (51c)



The acylation reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) and 4-methoxybenzoyl chloride (**50c**, 154 mg, 0.9 mmol) was performed according to **TP3** over night. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **51c** as a white solid (195 mg, 80 %).

m.p.: 61.5-63.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.61-7.85 (m, 2H), 6.56-7.03 (m, 2H), 3.84 (s, 3H), 1.88-2.21 (m, 9H), 1.57-1.91 (m, 6H).

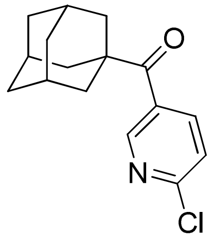
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 207.1, 161.6, 131.1, 130.3, 113.1, 55.3, 46.8, 39.5, 36.7, 28.3.

MS (70 eV, EI), *m/z* (%) = 270 (M^+, 20), 136 (9), 135 (100), 107 (6), 93 (13).

HRMS (EI), *m/z* calc. for $\mathbf{C_{18}H_{22}O_2}$ (270.1620): 270.1617.

IR (ATR) υ (cm^{-1}) = 3079, 3054, 3020, 3002, 2944, 2902, 2890, 2848, 1656, 1596, 1510, 1453, 1439, 1319, 1303, 1264, 1233, 1186, 1170, 1113, 1104, 1029, 1010, 986, 974, 952, 930, 835, 820, 809, 788, 766, 750, 697, 680.

Preparation of adamantan-1-yl(6-chloropyridin-3-yl)methanone (51d)



The acylation reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) and 6-chloronicotinoyl chloride (**50d**, 159 mg, 0.9 mmol) was performed according to **TP3** over night. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **51d** as a yellow oil (109 mg, 44 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.66 (d, *J*=2.5Hz, 1H), 7.86 (dd, *J*=8.3Hz, 2.5Hz, 1H), 7.36 (d, *J*=8.3Hz, 1H), 2.09 (bs, 3H), 1.97 (d, *J*=2.8Hz, 6H), 1.64-1.84 (m, 6H).

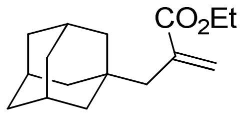
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 206.4, 153.0, 148.4, 138.0, 133.4, 123.9, 47.2, 38.8, 36.3, 27.9.

MS (70 eV, EI), *m/z* (%) = 275 (M^+, 1), 136 (14), 135 (100), 107 (8), 93 (16), 81 (5), 79 (13).

HRMS (EI), *m/z* calc. for $\mathbf{C_{16}H_{18}ClNO}$ (275.1077): 275.1071.

IR (ATR) υ (cm^{-1}) = 2953, 2917, 2849, 1727, 1633, 1570, 1459, 1377, 1261, 1211, 1194, 1173, 1119, 1093, 1036, 1007, 972, 961, 950, 926, 832, 815, 809, 762, 751, 723, 687.

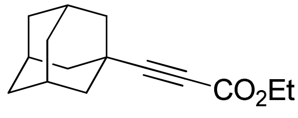
Preparation of ethyl 2-(adamantan-1-ylmethyl)acrylate (53a)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the adamantyl zinc reagent **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) and cooled to -40 °C. Ethyl 2-(bromomethyl)acrylate (**52a**, 174 mg, 0.9 mmol) was added, followed by CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF). The reaction mixture was allowed to warm to room temperature. After stirring over night, the reaction mixture was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL), washed with sat. NH_4Cl/NH_3 solution (9:1, 2x10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane:Et_2O 100:1) to give the analytically pure product **53a** as a colorless oil (203 mg, 91 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.18 (d, *J*=1.9Hz, 1H), 5.40 (d, *J*=1.9Hz, 1H), 4.20 (q, *J*=7.2Hz, 2H), 2.16 (s, 2H), 1.93 (bs, 3H), 1.57-1.67 (m, 6H), 1.39-1.51 (m, 6H), 1.30 (t, *J*=7.0Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 168.2, 137.6, 126.8, 60.6, 45.5, 42.1, 36.9, 33.2, 28.7, 14.2.
MS (70 eV, EI), *m/z* (%) = 248 (M^+, 2), 177 (3), 149 (3), 136 (11), 135 (100), 107 (4), 93 (8), 81 (3), 79 (8), 67 (3).
HRMS (EI), *m/z* calc. for $\mathbf{C_{16}H_{24}O_2}$ (248.1776): 248.1755.
IR (ATR) υ (cm^{-1}) = 2980, 2899, 2847, 1717, 1625, 1448, 1406, 1366, 1312, 1297, 1291, 1278, 1208, 1176, 1131, 1101, 1027, 982, 941, 875, 856, 819, 735, 690.

Preparation of ethyl 3-(adamantan-1-yl)propiolate (53b)

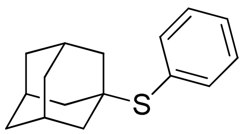


A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the adamantyl zinc reagent **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) and cooled to -40 °C. CuCN·2LiCl (0.2 mL, 0.2 mmol, 1.0 M in THF) was added, followed by ethyl 3-bromoprop-2-ynoate (**52b**, 159 mg, 0.9 mmol) and the reaction mixture was stirred over night slowling warming up to room temperature. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAcdried over

Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane:Et_2O 100:1) to give **53b** as a a white solid (138 mg, 66 %).

m.p.: 55.2-56.2 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 4.20 (q, *J*=7.2Hz, 2H), 1.97 (bs, 3H), 1.92 (d, *J*=2.8Hz, 6H), 1.58-1.78 (m, 6H), 1.29 (t, *J*=7.2Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 154.2, 95.9, 72.1, 61.7, 41.5, 36.1, 29.6, 27.5, 14.1.
MS (70 eV, EI), *m/z* (%) = 232 (M^+, 5), 205 (82), 204 (77), 187 (84), 148 (48), 135 (31), 119 (100), 93 (30), 91 (52), 79 (48), 77 (36), 43 (47).
HRMS (EI), *m/z* calc. for **$C_{15}H_{20}O_2$** (232.1463): 232.1457.
IR (ATR) υ (cm^{-1}) = 2983, 2906, 2853, 2226, 1702, 1665, 1474, 1453, 1366, 1317, 1300, 1248, 1184, 1144, 1114, 1100, 1025, 989, 856, 812, 791, 752.

Preparation of adamantan-1-yl(phenyl)sulfane (53c)

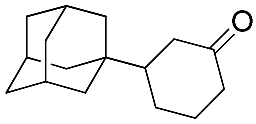


A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the adamantyl zinc reagent **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) and cooled to 0 °C. *S*-phenyl benzenesulfonothioate (**52c**, 225 mg, 0.9 mmol) was added and the reaction mixture was stirred for 2 h at at room temperature. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane pur) to give **53c** as a pale brown solid (216 mg, 98 %).

m.p.: 73.9-74.9 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.48-7.57 (m, 2H), 7.40-7.55 (m, 2H), 7.26-7.42 (m, 3H), 2.01 (bs, 3H), 1.82 (d, *J*=2.8Hz, 6H), 1.50-1.71 (m, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 137.6, 130.5, 128.5, 128.2, 47.8, 43.6, 36.2, 30.0.
MS (70 eV, EI), *m/z* (%) = 244 (M^+, 9), 136 (13), 135 (100), 107 (7), 93 (14), 79 (15), 61 (9), 43 (49).
HRMS (EI), *m/z* calc. for **$C_{16}H_{20}S$** (244.1286): 244.1292.

IR (ATR) υ (cm^{-1}) = 3059, 2901, 2848, 1583, 1574, 1474, 1450, 1442, 1400, 1340, 1296, 1252, 1207, 1140, 1084, 1068, 1050, 1036, 976, 959, 920, 885, 826, 810, 752, 693, 684.

Preparation of 3-(adamantan-1-yl)cyclohexanone (53d)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the adamanyl zinc reagent **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) and cooled to -40 °C. CuCN·2LiCl (1.0 mL, 1.0 mmol, 1.0 M in THF) was added, followed by a solution of cyclohexenone (**52d**, 87 mg, 0.9 mmol) and chlorotrimethylsilane (0.4 mL, 2.5 mmol) in THF (1 mL) and the reaction mixture was stirred over night slowly warming up to room temperature. The reaction was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane:Et_2O 8:2) to give **53d** as a white solid (190 mg, 91 %).

m.p.: 67.0-67.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.27-2.48 (m, 2H), 2.02-2.27 (m, 3H), 1.87-2.01 (m, 4H), 1.65-1.75 (m, 3H), 1.55-1.65 (m, 3H), 1.39-1.54 (m, 7H), 1.23-1.37 (m, 2H).

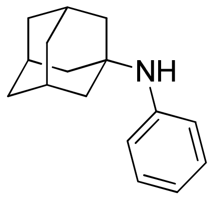
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 213.4, 49.7, 42.1, 41.5, 39.4, 37.2, 34.4, 28.6, 25.7, 24.6.

MS (70 eV, EI), *m/z* (%) = 232 (M^+, 3), 136 (10), 135 (100), 96 (6), 93 (9), 79 (10), 42 (32), 41 (6).

HRMS (EI), *m/z* calc. for **$C_{16}H_{24}O$** (232.1827): 232.1821.

IR (ATR) υ (cm^{-1}) = 2965, 2942, 2896, 2862, 2844, 1709, 1449, 1424, 1418, 1360, 1347, 1322, 1316, 1304, 1277, 1268, 1238, 1228, 1216, 1168, 1102, 1058, 1034, 998, 967, 927, 899, 862, 814, 760, 722, 661.

Preparation of *N*-phenyladamantan-1-amine (55a)



The amine synthesis was performed according to **TP4** in 2 h with **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF), nitrosobenzene (**54a**, 96 mg, 0.9 mmol), $FeCl_2$ (254 mg, 2 mmol) and $NaBH_4$ (42 mg, 1.1 mmol). Flash column chromatography (silica, pentane:EtOAc 7:1) furnished **55a** as a pale yellow solid (182 mg, 89 %).

m.p.: 73.3-75.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.07-7.25 (m, 2H), 6.59-6.93 (m, 3H), 3.40 (bs, 1H), 2.12 (bs, 3H), 1.89 (d, *J*=2.8Hz, 6H), 1.58-1.82 (m, 6H).

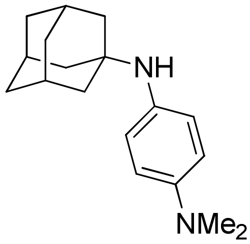
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 145.9, 128.7, 119.3, 119.2, 52.3, 43.5, 36.5, 29.7.

MS (70 eV, EI), *m/z* (%) = 227 (M^+, 33), 170 (50), 136 (10), 135 (100), 93 (24), 91 (9), 79 (21), 43 (39).

HRMS (EI), *m/z* calc. for **$C_{16}H_{21}N$** (227.1674): 227.1664.

IR (ATR) υ (cm^{-1}) = 3414, 3089, 3050, 3014, 2902, 2847, 1597, 1503, 1494, 1472, 1448, 1432, 1356, 1344, 1324, 1306, 1286, 1270, 1236, 1181, 1131, 1096, 1081, 992, 978, 861, 818, 741, 690.

Preparation of N^1-(adamantan-1-yl)-N^4,N^4-dimethylbenzene-1,4-diamine (55b)



The amine synthesis was performed according to **TP4** in 2 h with **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF), *N*,*N*-dimethyl-4-nitrosoaniline (**54b**, 135 mg, 0.9 mmol), $FeCl_2$ (254 mg, 2 mmol) and $NaBH_4$ (42 mg, 1.1 mmol). Flash column chromatography (silica, pentane:EtOAc 1:1) furnished **55b** as a brown solid (172 mg, 71 %).

m.p.: 105.2-107.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.83 (d, *J*=8.3Hz, 2H), 6.66 (d, *J*=8.3Hz, 2H), 2.64-3.11 (m, 7H), 1.95-2.22 (m, 3H), 1.46-1.88 (m, 12H).

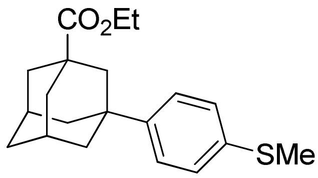
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 146.6, 135.1, 125.0, 113.5, 52.6, 43.8, 41.3, 36.5, 29.8.

MS (70 eV, EI), *m/z* (%) = 270 (M^+, 100), 213 (14), 136 (13), 135 (34), 121 (12), 93 (7), 79 (6).

HRMS (EI), *m/z* calc. for **$C_{18}H_{26}N_2$** (270.2096): 270.2090.

IR (ATR) υ (cm^{-1}) = 3296, 3036, 2985, 2901, 2842, 2790, 1616, 1511, 1479, 1443, 1354, 1340, 1326, 1309, 1282, 1243, 1212, 1177, 1163, 1124, 1107, 1101, 1094, 1054, 944, 934, 922, 818, 806, 788, 773, 722, 689.

Preparation of ethyl 3-(4-(methylthio)phenyl)adamantane-1-carboxylate (56a)



The cross-coupling reaction of **46b** (4.2 mL, 1.0 mmol, 0.24 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and (4-bromophenyl)(methyl)-sulfane (**47f**, 183 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 7:3) furnished **56a** as a colorless oil (259 mg, 87 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.17-7.35 (m, 4H), 4.12 (q, *J*=7.2Hz, 2H), 2.47 (s, 3H), 2.22 (bs, 2H), 2.00 (s, 2H), 1.83-1.97 (m, 8H), 1.73 (bs, 2H), 1.24 (t, *J*=7.0Hz, 3H).

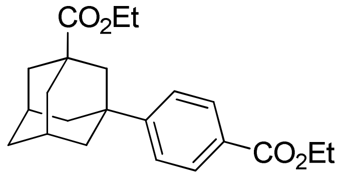
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 177.3, 147.2, 135.4, 126.9, 125.4, 60.2, 44.2, 42.1, 41.7, 38.1, 36.2, 35.6, 28.7, 16.2, 14.2.

MS (70 eV, EI), *m/z* (%) = 330 (M^+, 100), 257 (16), 201 (16), 164 (9), 137 (12).

HRMS (EI), *m/z* calc. for **$C_{20}H_{26}O_2S$** (330.1654): 330.1653.

IR (ATR) υ (cm^{-1}) = 3079, 3024, 2979, 2904, 2853, 1720, 1569, 1497, 1448, 1400, 1364, 1343, 1320, 1242, 1200, 1173, 1149, 1104, 1097, 1067, 1022, 1013, 970, 958, 915, 824, 808, 736, 720, 690.

Preparation of ethyl 3-(4-(ethoxycarbonyl)phenyl)adamantane-1-carboxylate (56b)



The cross-coupling reaction of **46b** (4.2 mL, 1.0 mmol, 0.24 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and ethyl 4-bromobenzoate (**47b**, 206 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 7:3) furnished **56b** as a colorless solid (269 mg, 84 %).

m.p.: 27.1-28.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.84-8.11 (m, 2H), 7.33-7.58 (m, 2H), 4.36 (q, *J*=7.2Hz, 2H), 4.12 (q, *J*=7.1Hz, 2H), 2.15-2.34 (m, 2H), 2.03 (s, 2H), 1.83-1.97 (m, 7H), 1.74 (bs, 3H), 1.37 (t, *J*=7.2Hz, 3H), 1.24 (t, *J*=7.2Hz, 3H).

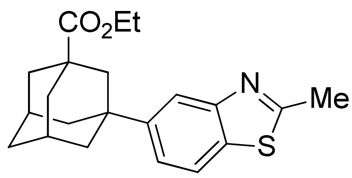
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 177.1, 166.6, 155.1, 129.5, 128.1, 124.9, 60.7, 60.3, 43.8, 41.9, 41.6, 38.0, 36.9, 35.5, 28.6, 14.3, 14.2.

MS (70 eV, EI), *m/z* (%) = 356 (M^+, 37), 311 (13), 284 (20), 283 (100), 255 (6), 227 (8), 163 (6), 155 (12), 93 (10), 91 (6).

HRMS (EI), *m/z* calc. for **$C_{22}H_{28}O_4$** (356.1988): 356.1981.

IR (ATR) υ (cm^{-1}) = 3092, 3053, 2986, 2927, 2903, 2855, 1710, 1608, 1447, 1409, 1389, 1365, 1271, 1250, 1241, 1197, 1172, 1103, 1067, 1017, 978, 912, 859, 842, 775, 766, 749, 730, 707.

Preparation of ethyl 3-(2-methylbenzothiazol-5-yl)adamantane-1-carboxylate (56c)



The cross-coupling reaction of **46b** (4.2 mL, 1.0 mmol, 0.24 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 5-bromo-2-methylbenzothiazole (**49c**, 205 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 6.5:3.5) furnished **56c** as a white solid (224 mg, 70 %).

m.p.: 83.6-84.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.95 (d, *J*=1.9Hz, 1H), 7.75 (d, *J*=8.6Hz, 1H), 7.40 (dd, *J*=8.6Hz, 1.9Hz, 1H), 4.11 (q, *J*=7.2Hz, 2H), 2.82 (s, 3H), 2.16-2.35 (m, 2H), 2.08 (s, 2H), 1.95 (d, *J*=3.3Hz, 8H), 1.65-1.81 (m, 2H), 1.24 (t, *J*=7.0Hz, 3H).

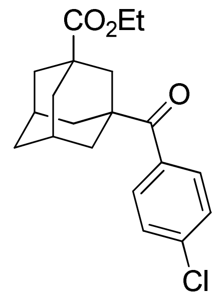
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 177.2, 167.1, 153.5, 148.7, 132.8, 122.3, 120.9, 118.6, 60.2, 44.4, 42.3, 41.7, 38.1, 36.6, 35.6, 28.7, 20.0, 14.2.

MS (70 eV, EI), *m/z* (%) = 355 (M^+, 100), 283 (16), 282 (76), 240 (11), 227 (11), 226 (51), 190 (13), 189 (16), 162 (25), 93 (14), 61 (11), 45 (12), 44 (16), 43 (95).

HRMS (EI), *m/z* calc. for $\mathbf{C_{21}H_{25}NO_2S}$ (355.1606): 355.1609.

IR (ATR) υ (cm^{-1}) = 3053, 3032, 2981, 2930, 2918, 2905, 2853, 1716, 1548, 1530, 1458, 1450, 1417, 1389, 1367, 1341, 1266, 1256, 1248, 1230, 1170, 1164, 1149, 1101, 1074, 1057, 1022, 1002, 974, 954, 935, 901, 878, 863, 815, 775, 734, 699, 681.

Preparation of ethyl 3-(4-chlorobenzoyl)adamantane-1-carboxylate (57a)



The acylation reaction of **46b** (4.2 mL, 1.0 mmol, 0.24 M in THF) with CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) and 4-chlorobenzoyl chloride (**50b**, 158 mg, 0.9 mmol) was performed according to **TP3** over night. Flash column chromatography (silica, pentane:Et_2O 8:2) furnished **57a** as a colorless oil (256 mg, 82 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.46-7.61 (m, 2H), 7.30-7.42 (m, 2H), 4.02-4.19 (m, 2H), 2.16-2.25 (m, 2H), 2.10 (s, 2H), 1.85-2.04 (m, 8H), 1.64-1.84 (m, 4H), 1.18-1.29 (m, 3H).

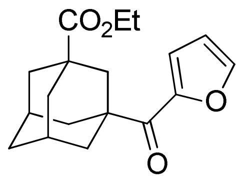
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 207.4, 176.7, 137.1, 136.8, 128.9, 128.3, 60.4, 47.1, 41.0, 40.0, 38.3, 37.9, 35.4, 28.0, 14.2.

MS (70 eV, EI), *m/z* (%) = 346 (M^+, 4), 273 (5), 208 (12), 207 (100), 161 (15), 139 (9), 134 (5), 133 (33), 91 (6), 79 (6).

HRMS (EI), *m/z* calc. for $\mathbf{C_{20}H_{23}ClO_3}$ (346.1336): 346.1326.

IR (ATR) υ (cm^{-1}) = 3069, 2978, 2907, 2857, 1720, 1670, 1591, 1487, 1450, 1393, 1366, 1344, 1324, 1263, 1243, 1227, 1208, 1175, 1117, 1103, 1091, 1076, 1038, 1011, 952, 905, 839, 828, 740, 684, 670.

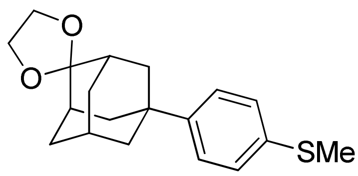
Preparation of ethyl 3-(furan-2-carbonyl)adamantane-1-carboxylate (57b)



The acylation reaction of **46b** (4.2 mL, 1.0 mmol, 0.24 M in THF) with CuCN·2LiCl (0.2 mL, 0.2 mmol, 1 M in THF) and furan-2-carbonyl chloride (**50e**, 118 mg, 0.9 mmol) was performed according to **TP3** over night Flash column chromatography (silica, pentane:Et_2O 7:3) furnished **57b** as a colorless oil (147 mg, 54 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.53 (d, *J*=1.1Hz, 1H), 7.21 (d, *J*=3.6Hz, 1H), 6.48 (dd, *J*=3.6Hz, 1.7Hz, 1H), 4.10 (q, *J*=7.2Hz, 2H), 2.14-2.28 (m, 4H), 2.03 (bs, 4H), 1.91 (d, *J*=3.0Hz, 4H), 1.74 (bs, 2H), 1.23 (t, *J*=7.0Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 193.4, 176.9, 152.7, 145.0, 118.3, 111.7, 60.3, 45.9, 41.0, 39.1, 38.1, 37.3, 35.6, 28.0, 14.2.
MS (70 eV, EI), *m/z* (%) = 302 (M^+, 37), 229 (12), 208 (13), 207 (100), 161 (22), 133 (52), 91 (11), 91 (11), 79 (10).
HRMS (EI), *m/z* calc. for **$C_{18}H_{22}O_4$** (302.1518): 302.1513.
IR (ATR) υ (cm^{-1}) = 3125, 2975, 2908, 2857, 1721, 1658, 1560, 1462, 1386, 1366, 1297, 1278, 1235, 1162, 1123, 1104, 1078, 1053, 1040, 1014, 956, 921, 883, 864, 815, 760, 732, 696, 673.

Preparation of 5-(4-(methylthio)phenyl)spiro[adamantane-2,2'-[1,3]dioxolane] (58a)



The cross-coupling reaction of **46c** (4.5 mL, 1.0 mmol, 0.22 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and (4-bromophenyl)(methyl)-sulfane (**47f**, 183 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 9:1) furnished **58a** as a white solid (208 mg, 73 %).

m.p.: 89.1-89.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.15-7.36 (m, 4H), 3.97 (s, 4H), 2.47 (s, 3H), 1.98-2.33 (m, 6H), 1.95 (bs, 2H), 1.88 (bs, 2H), 1.62-1.81 (m, 4H).

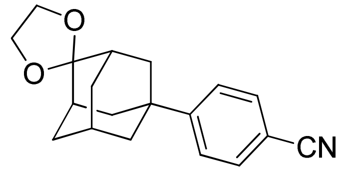
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 147.3, 135.0, 126.8, 125.5, 110.8, 64.3, 64.2, 42.4, 40.5, 36.9, 35.1, 34.0, 27.5, 16.2.

MS (70 eV, EI), *m/z* (%) = 316 (M^+, 100), 201 (7), 137 (7), 113 (17), 99 (15), 73 (8), 55 (8).

HRMS (EI), *m/z* calc. for $\mathbf{C_{19}H_{24}O_2S}$ (316.1497): 316.1483.

IR (ATR) υ (cm^{-1}) = 3075, 3017, 2991, 2921, 2906, 2856, 1718, 1594, 1495, 1443, 1393, 1384, 1245, 1223, 1181, 1123, 1096, 1063, 1036, 1006, 966, 952, 924, 904, 883, 816, 808, 796, 761, 738, 719, 677.

Preparation of 4-(spiro[adamantane-2,2'-[1,3]dioxolan]-5-yl)benzonitrile (58b)



The cross-coupling reaction of **46c** (4.5 mL, 1.0 mmol, 0.22 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 4-bromobenzonitrile (**47d**, 164 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 6.5:3.5) furnished **58b** as a white solid (204 mg, 77 %).

m.p.: 85.3-87.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.53-7.63 (m, 2H), 7.40-7.49 (m, 2H), 3.91-4.05 (m, 4H), 2.16-2.28 (m, 2H), 1.66-2.15 (m, 12H).

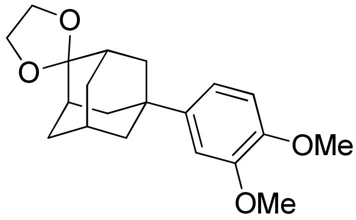
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 155.5, 132.0, 125.9, 119.1, 110.4, 109.5, 64.4, 64.3, 42.0, 40.2, 36.7, 36.0, 33.8, 27.3.

MS (70 eV, EI), *m/z* (%) = 295 (M^+, 100), 252 (27), 193 (44), 180 (15), 113 (46), 99 (61), 73 (24), 55 (18), 45 (11), 43 (50).

HRMS (EI), *m/z* calc. for $\mathbf{C_{19}H_{21}NO_2}$ (295.1572): 295.1569.

IR (ATR) υ (cm^{-1}) = 3066, 3042, 2975, 2928, 2907, 2857, 2223, 1726, 1503, 1469, 1446, 1385, 1252, 1228, 1188, 1137, 1123, 1097, 1091, 1064, 1038, 1018, 1004, 945, 924, 905, 832, 824, 797, 731, 682.

Preparation of 5-(3,4-dimethoxyphenyl)spiro[adamantane-2,2'-[1,3]dioxolane] (58c)



The cross-coupling reaction of **46c** (4.5 mL, 1.0 mmol, 0.22 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 4-bromo-1,2-dimethoxybenzene (**47n**, 195 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 4:6) furnished **58c** as a white solid (211 mg, 71 %).

m.p.: 94.6-96.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.84-6.94 (m, 2H), 6.75-6.84 (m, 1H), 3.97 (d, J=1.1Hz, 4H), 3.88 (s, 3H), 3.85 (s, 3H), 2.24-2.20 (m, 2H), 1.99-2.08 (m, 3H), 1.95 (bs, 2H), 1.88 (bs, 2H), 1.58-1.83 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 148.5, 147.0, 143.0, 116.9, 110.8, 108.8, 64.3, 64.2, 55.9, 55.8, 42.7, 40.8, 36.9, 35.1, 34.0, 27.6.

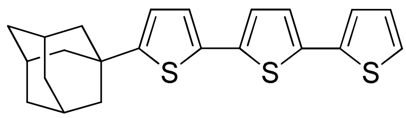
MS (70 eV, EI), m/z (%) = 330 (M^+, 100), 215 (6), 193 (5), 151 (4), 113 (13), 99 (9), 55 (4), 43 (8).

HRMS (EI), m/z calc. for $\mathbf{C_{20}H_{26}O_4}$ (330.1831): 330.1831.

IR (ATR) υ (cm^{-1}) = 3074, 3002, 2992, 2932, 2906, 2852, 2838, 1602, 1585, 1517, 1462, 1444, 1408, 1385, 1364, 1323, 1255, 1238, 1224, 1186, 1163, 1155, 1135, 1123, 1095, 1053, 1027, 1005, 955, 932, 902, 843, 797, 767, 754.

6.5 PREPARATION OF α,α'-DIADAMANTYL-SEXITHIOPHENE

Preparation of 5-(adamantan-1-yl)-2,2':5',2''-terthiophene (48s)



The cross-coupling reaction of **46a** (3.2 mL, 1.0 mmol, 0.32 M in THF) with $Pd(OAc)_2$ (2 mg, 0.01 mmol), SPhos (8 mg, 0.02 mmol) and 5-bromo-2,2':5',2''-terthiophene (**49h**, 295 mg, 0.9 mmol) was performed according to **TP2** in 2 h. Flash column chromatography (silica, pentane:Et_2O 100:1) furnished **48s** as a yellow solid (220 mg, 64 %).

m.p.: 171.0-173.0 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.13-7.25 (m, 2H), 6.96-7.10 (m, 4H), 6.67-6.76 (m, 1H), 2.10 (bs, 3H), 1.99 (d, *J*=2.7Hz, 6H), 1.70-1.84 (m, 6H).

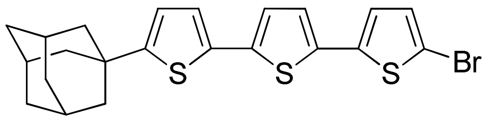
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 157.9, 137.4, 137.0, 135.5, 133.6, 127.8, 124.3, 124.2, 123.4, 123.4, 123.1, 121.1, 44.8, 36.6, 36.5, 28.8.

MS (70 eV, EI), *m/z* (%) = 382 (M^+, 100), 327 (5), 326 (6), 325 (27), 292 (5), 288 (6), 261 (5), 248 (22), 42 (5), 41 (6).

HRMS (EI), *m/z* calc. for **$C_{22}H_{22}S_3$** (382.0884): 382.0870.

IR (ATR) υ (cm^{-1}) = 3072, 3063, 2954, 2902, 2847, 1514, 1495, 1460, 1447, 1423, 1377, 1364, 1342, 1315, 1232, 1207, 1193, 1159, 1099, 1058, 1004, 965, 912, 831, 790, 675.

Preparation of 5-(adamantan-1-yl)-5''-bromo-2,2':5',2''-terthiophene (59)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with **48s** (180 mg, 0.4 mmol) and dissolved in 2 mL $CHCl_3$. Then, *N*-bromo-succinimide (75 mg, 0.42 mmol) was added and the reaction mixture was stirred over night at room temperature. The reaction was quenched with water (5 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The pure product **59** was obtained without further purification as a colorless solid (181 mg, 98 %).

m.p.: 154.6-157.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.81-7.14 (m, 5H), 6.72 (d, *J*=3.6Hz, 1H), 2.09 (bs, 3H), 1.89-2.04 (m, 6H), 1.67-1.89 (m, 6H).

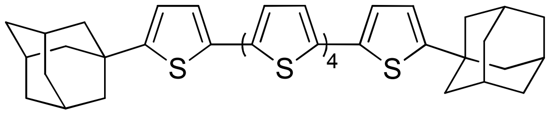
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 192.4, 158.2, 138.8, 137.5, 134.3, 133.3, 130.6, 124.5, 123.4, 123.4, 121.2, 110.7, 44.8, 36.6, 36.5, 28.8.

MS (70 eV, EI), *m/z* (%) = 461 (M^+, 100), 459 (M^+, 90), 406 (7), 405 (25), 404 (8), 403 (23), 368 (5), 366 (6), 203 (6).

HRMS (EI), *m/z* calc. for **$C_{22}H_{21}BrS_3$** (461.9968): 461.9951.

IR (ATR) υ (cm^{-1}) = 3079, 3063, 2900, 2846, 1506, 1445, 1426, 1343, 1315, 1248, 1225, 1194, 1101, 1064, 1052, 1003, 969, 892, 853, 788, 692, 684, 654.

Preparation of 5,5'''''-diadamantan-1-yl)-2,2':5',2'':5'',2''':5''',2'''':5'''',2'''''-sexithiophene (60)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with magnesium turnings (24 mg, 1 mmol), LiCl (22 mg, 0.5 mmol) and **59** (153 mg, 0.39 mmol) and dissolved in 2 mL THF. Then, the reaction mixture was cold to 0 °C and the reaction was initiated by adding a catalytic amount of iodine. The reaction mixture was stirred for 1 h slowly warming up to room temperature. After addition of Ni(dppp)Cl_2 (22 mg, 0.04 mmol) in 1 mL THF, the reaction mixture was refluxed over night. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane:Et_2O 97:3) to give **60** as a yellow solid (229 mg, 77 %).

m.p.: 115.3-117.0 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.15-7.22 (m, 2H), 6.92-7.12 (m, 8H), 6.64-6.77 (m, 2H), 2.09 (bs, 6H), 1.98 (d, *J*=2.7Hz, 12H), 1.72-1.85 (m, 12H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 157.9, 137.3, 137.0, 135.4, 133.6, 127.8, 124.3, 124.2, 123.4, 123.4, 123.1, 121.1, 44.8, 36.6, 36.5, 28.8.

MS (70 eV, EI), *m/z* (%) = 762 (M^+, 1), 518 (12), 517 (22), 516 (51), 384 (17), 383 (26), 382 (100), 326 (7), 325 (28), 292 (5), 288 (6).

HRMS (EI), *m/z* calc. for $\mathbf{C_{44}H_{42}S_6}$ (762.1611): 762.1599.

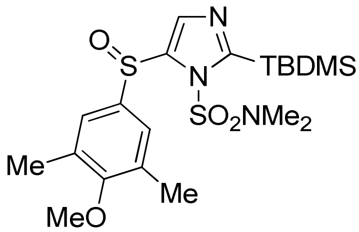
IR (ATR) υ (cm^{-1}) = 3064, 2901, 2846, 1738, 1714, 1506, 1446, 1425, 1343, 1315, 1256, 1225, 1195, 1100, 1063, 1051, 1003, 969, 892, 868, 837, 790, 689, 683, 654.

7. FULL FUNCTIONALIZATION OF THE IMIDAZOLE SCAFFOLD BY SELECTIVE METALATION AND SULFOXIDE/MAGNESIUM EXCHANGE

7.1 PREPARATION OF STARTING MATERIALS

All reagents were obtained from commercial sources. Compounds **61**[259] and **68a**[254] were prepared according to literature-known procedures.

Preparation of 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)-sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (67)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with **61** (5.79 g, 20 mmol) and dissolved in 20 mL THF. TMPMgCl·LiCl (**62**, 20 mL, 22 mmol, 1.1 M in THF) was added and the resulting mixture was stirred for 2 h at room temperature. After cooling to -20 °C, a solution of **68a** (3,94 g, 18 mmol) in 20 mL THF was added dropwise and stirred for 4 h while slowly warming up to room temperature. The reaction was quenched with sat. NH_4Cl solution (50 mL) and extracted with EtOAc (3x50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane:EtOAc 6.5:3.5) to give **67** as a white solid (7.30 g, 86 %).

m.p.: 116.3-117.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.37 (s, 2H), 7.02 (s, 1H), 3.74 (s, 3H), 3.04 (s, 6H), 2.31 (s, 6H), 0.97 (s, 9H), 0.38 (d, *J*=1.11Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.9, 159.5, 138.2, 136.1, 135.9, 132.5, 125.6, 59.8, 37.9, 27.0, 18.3, 16.3, -4.0, -4.0.

MS (70 eV, EI), *m/z* (%) = 456 ($[M-CH_3]^+$, 3), 416 (14), 415 (24), 414 (100), 168 (11), 167 (26), 166 (87), 102 (21), 73 (20).

HRMS (EI), *m/z* calc. for **$C_{19}H_{30}N_3O_4S_2Si$** (456.1447 ($[M-CH_3]$)): 456.1442 ($[M-CH_3]$).

IR (ATR) υ (cm^{-1}) = 3124, 2981, 2953, 2930, 2885, 2853, 1472, 1457, 1364, 1250, 1178, 1146, 1138, 1095, 1058, 1005, 976, 930, 834, 823, 814, 775, 736, 667.

7.2 TYPICAL PROCEDURES

Typical procedure 1 (TP1): Deprotonation at position 4 with TMPMgCl·LiCl

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with **67** and dissolved in THF (1 mL/mmol). After cooling to -30 °C, TMPMgCl·LiCl (**62**, 1.1 equiv) was added dropwise and the reaction mixture was stirred for 1 h at -30 °C until GC-analysis of iodolyzed reaction aliquot showed full consumption of the starting material.

Typical procedure 2 (TP2): Sulfoxide-Magnesium Exchange at position 5

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the sulfoxide and dissolved in THF (1 mL/mmol). After cooling to -78 °C, *i*PrMgCl·LiCl (**63**, 1.2 equiv) was added dropwise and the reaction mixture was stirred for 1 h at -78 °C until GC-analysis of iodolyzed reaction aliquot showed full consumption of the starting material.

Typical procedure 3 (TP3): Deprotonation at position 2 with $TMP_2Zn{\cdot}2MgCl{\cdot}2LiCl$

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the imidazol derivative and dissolved in THF (1 mL/mmol). After cooling to -20 °C, $TMP_2Zn{\cdot}2MgCl{\cdot}2LiCl$ (**65**, 1.2 equiv) was added dropwise and the reaction mixture was stirred for 1 h at -20 °C until GC-analysis of iodolyzed reaction aliquot showed full consumption of the starting material.

Typical procedure 4 (TP4): Deprotonation at position 2 with TMPMgCl·LiCl

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the imidazol derivative and dissolved in THF (1 mL/mmol). After cooling to -78 °C, TMPMgCl·LiCl (**62**, 1.2 equiv) was added dropwise and the reaction mixture was stirred for 1 h at -78 °C until GC-analysis of iodolyzed reaction aliquot showed full consumption of the starting material.

Typical procedure 5 (TP5): Deprotection at position 2 with TBAF

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the protected imidazol derivative and dissolved in THF (10 mL/mmol).

After cooling down to 0 °C, TBAF·$3H_2O$ (**64**, 1 equiv, 0.1 M in THF) was added dropwise and the reaction mixture was stirred for 5 min. The reaction mixture was quenched with sat. NH_4Cl solution and extracted with EtOAc (3x). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

Typical procedure 6 (TP6): Cross-coupling reactions of imidazol zinc reagents

To the freshly prepared imidazol magnesium reagent was added $ZnCl_2$ (1.0M in THF, 1.1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. $Pd(PPh_3)_4$ (5 mol %) and the aryl iodide (0.9 or 1.1 equiv) were added and the reaction mixture was stirred for the given time at 50 °C. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

Typical procedure 7 (TP7): Allylation of imidazol zinc reagents

To the freshly prepared imidazol magnesium reagent was added $ZnCl_2$ (1.0M in THF, 1.1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. CuCN·2LiCl (1.0M in THF, 1.1 equiv) and the allyl bromide (0.9 or 1.1 equiv) were added and the reaction mixture was warmed to 25 °C. After stirring for the given time, the reaction mixture was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

Typical procedure 8 (TP8): Acylation of imidazol zinc reagents

To the freshly prepared imidazol magnesium reagent was added $ZnCl_2$ (1.0M in THF, 1.1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. CuCN·2LiCl (1.0M in THF, 1.1 equiv) and the acyl chloride (0.9 or 1.1 equiv) were added and the reaction mixture was warmed to 25 °C. After stirring for the given time, the reaction mixture was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

Typical procedure 9 (TP9): Pd-catalyzed acylation of imidazol zinc reagents

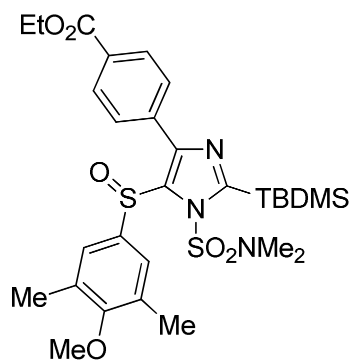
To the freshly prepared imidazol magnesium reagent was added $ZnCl_2$ (1.0M in THF, 1.1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. $Pd(PPh_3)_4$ (5 mol %) and the acyl chloride (0.9 or 1.1 equiv) were added and the reaction mixture was stirred for the given time at room temperature. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

Typical procedure 10 (TP10): Deprotection/Reprotection

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the protected imidazol derivative and dissolved in DCM (2 mL/mmol). Trimethyloxonium tetrafluoroborate (1 equiv) was added at room temperature and the reaction mixture was stirred over night. After removing the solvent in high vacuum, the remaining solid was dissolved in EtOH (10 mL/mmol), conc. HCl (5 ml/mmol) was added and the reaction mixture was stirred at 60 °C for 30 min. The reaction was quenched with sat. $NaHCO_3$ solution and extracted with EtOAc (3x). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

7.3 SELECTIVE FUNCTIONALIZATION ON POSITION 4 OF THE IMIDAZOLE RING

Preparation of ethyl 4-(2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)imidazol-4-yl)benzoate (70a)

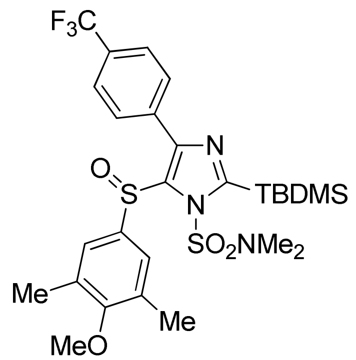


Prepared according to **TP1** from 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (**67**, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (**62**, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h.

Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and ethyl 4-iodobenzoate (**68b**, 124 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded **70a** as a orange solid (234 mg, 84%).

m.p.: 132.7-133.9 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.84 (d, J=8.0Hz, 2H), 7.66 (d, J=8.0 Hz, 2H), 6.92 (s, 2H), 4.27-4.43 (m, 2H), 3.49 (s, 3H), 3.13 (s, 6H), 2.03-2.11 (m, 6H), 1.37 (t, J=7.2Hz, 3 H), 1.08 (s, 9H), 0.46 (d, J=11.9Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.2, 158.4, 157.7, 147.8, 136.4, 133.7, 132.9, 131.2, 130.2, 130.0, 128.3, 125.4, 60.9, 59.4, 37.9, 27.1, 18.7, 15.8, 14.3, -4.1, -4.2.
MS (70 eV, EI), m/z (%) = 604 ($[M-CH_3]^+$, 3), 564 (22), 563 (40), 562 (100), 328 (18), 183 (15), 167 (25), 166 (20), 102 (17), 92 (11), 73 (49).
HRMS (EI), m/z calc. for **$C_{28}H_{38}N_3O_6S_2Si$** (604.1971 ($[M-CH_3]$)): 604.1961 ($[M-CH_3]$).
IR (ATR) υ (cm^{-1}) = 3056, 2980, 2936, 2853, 1716, 1474, 1376, 1282, 1272, 1171, 1130, 1109, 1097, 1050, 1012, 964, 843, 822, 779, 726, 669.

Preparation of 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)-sulfinyl)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (70b)



Prepared according to **TP1** from 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (**67**, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (**62**, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.55 mL, 0.55 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and 1-iodo-4-(trifluoromethyl)benzene (**68c**, 122 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded **70b** as a pale orange solid (201 mg, 72%).

m.p.: 149.5-151.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.72 (d, *J*=8.6Hz, 2H), 7.43 (d, *J*=8.9Hz, 2H), 6.91 (s, 2H), 3.50 (s, 3H), 3.15 (s, 6H), 2.08 (s, 6H), 1.08 (s, 9H), 0.48 (s, 3H), 0.45 (s, 3H).

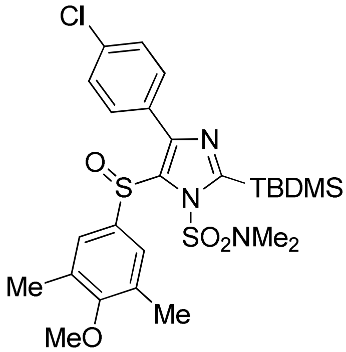
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 158.5, 157.7, 147.4, 135.6, 133.6, 133.1, 131.2, 130.4, 130.3 (q, *J*=32.3Hz), 125.4, 124.0 (q, *J*=3,7Hz), 124.0 (q, *J*=272.1Hz), 59.4, 37.9, 27.0, 18.6, 15.8, -4.1, -4.1.

MS (70 eV, EI), *m/z* (%) = 614 ($[M-H]^+$, 3), 560 (17), 559 (31), 558 (100), 167 (10), 73 (11).

HRMS (EI), *m/z* calc. for **$C_{27}H_{35}F_3N_3O_4S_2Si$** (614.1790 ([M-H])): 614.1781 ([M-H]).

IR (ATR) υ (cm^{-1}) = 3061, 2954, 2926, 2888, 2853, 1737, 1620, 1474, 1380, 1322, 1224, 1172, 1159, 1118, 1093, 1072, 1054, 1011, 959, 857, 841, 823, 817, 780, 722, 716, 668.

Preparation of 2-(*tert*-butyldimethylsilyl)-4-(4-chlorophenyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (70c)



Prepared according to **TP1** from 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (**67**, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (**62**, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.55 mL, 0.55 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and 1-chloro-4-iodobenzene (**68d**, 107 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8.5:1.5) afforded **70c** as a pale yellow solid (186 mg, 71%).

m.p.: 144.8-146.1 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.51 (d, *J*=8.5Hz, 2H), 7.12 (d, *J*=8.5Hz, 2H), 6.90 (s, 2H), 3.55 (s, 3H), 3.12 (s, 6H), 2.10 (s, 6H), 1.06 (s, 9H), 0.46 (s, 3H), 0.42 (s, 3H).

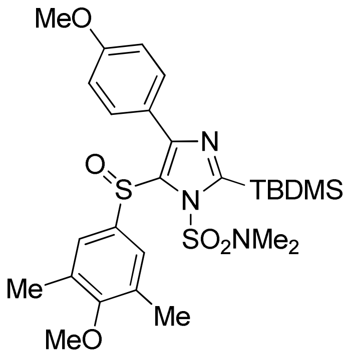
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 158.4, 157.6, 147.8, 134.5, 133.7, 132.1, 131.4, 131.2, 130.6, 127.3, 125.4, 59.5, 37.9, 27.1, 18.6, 15.9, -4.1, -4.2.

MS (70 eV, EI), *m/z* (%) = 566 ($[M-CH_3]^+$, 3), 527 (14), 526 (49), 525 (31), 524 (100), 290 (18), 232 (12), 193 (10), 183 (13), 167 (25), 166 (20), 102 (19), 92 (11), 73 (44).

HRMS (EI), *m/z* calc. for **$C_{25}H_{33}ClN_3O_4S_2Si$** (566.1370 ($[M-CH_3]$)): 566.1368 ($[M-CH_3]$).

IR (ATR) υ (cm^{-1}) = 3074, 3052, 2956, 2932, 2888, 2856, 1740, 1603, 1533, 1473, 1417, 1380, 1290, 1254, 1218, 1193, 1170, 1131, 1097, 1088, 1053, 1012, 976, 965, 934, 854, 838, 822, 813, 779, 738, 726, 710, 668.

Preparation of 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)-sulfinyl)-4-(4-methoxyphenyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (70d)



Prepared according to **TP1** from 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (**67**, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (**62**, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.55 mL, 0.55 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and 1-iodo-4-methoxybenzene (**68e**, 105 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7:3) afforded **70d** as a orange solid (157 mg, 60%).

m.p.: 124.4-126.3 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.57 (d, *J*=8.78Hz, 2H), 6.94 (s, 2H), 6.71 (d, *J*=8.78Hz, 2H), 3.76 (s, 3H), 3.55 (s, 3H), 3.11 (s, 6H), 2.10 (s, 6H), 1.08 (s, 9H), 0.47 (s, 3H), 0.43 (s, 3H).

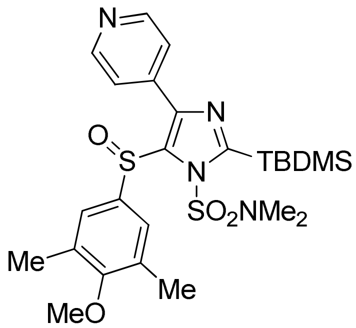
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 160.0, 158.3, 157.5, 149.1, 134.1, 131.4, 131.0, 130.5, 125.4, 124.7, 112.6, 59.5, 55.1, 37.9, 27.1, 18.7, 15.9, -4.1, -4.1.

MS (70 eV, EI), *m/z* (%) = 577 (M^+, 2), 522 (15), 521 (26), 520 (77), 383 (18), 382 (63), 287 (26), 286 (100), 189 (20), 183 (11), 167 (34), 166 (19), 145 (18), 102 (12), 73 (44).

HRMS (EI), *m/z* calc. for $\mathbf{C_{27}H_{39}N_3O_5S_2Si}$ (577.2100): 577.2093.

IR (ATR) υ (cm^{-1}) = 3117, 2981, 2952, 2936, 2910, 2857, 1707, 1634, 1616, 1474, 1373, 1292, 1271, 1249, 1182, 1171, 1154, 1128, 1110, 1097, 1022, 975, 951, 864, 838, 820, 813, 775, 734, 725, 710, 696, 673.

Preparation of 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)-sulfinyl)-*N*,*N*-dimethyl-4-(pyridin-4-yl)imidazole-1-sulfonamide (70e)



Prepared according to **TP1** from 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (**67**, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (**62**, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.55 mL, 0.55 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and 4-iodopyridine (**68f**, 92 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 3:7) afforded **70e** as a yellow oil (147 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.34-8.50 (m, 2H), 7.52-7.67 (m, 2H), 6.97 (s, 2H), 3.55 (s, 3H), 3.13 (s, 6H), 2.12 (s, 6H), 1.08 (s, 9H), 0.47 (s, 3H), 0.44 (s, 3H).

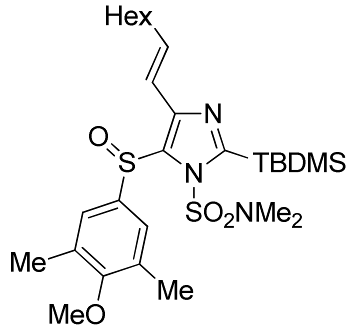
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 158.7, 157.9, 149.6, 148.8, 146.0, 133.9, 133.7, 128.5, 128.4, 124.1, 59.6, 38.0, 27.0, 18.7, 16.0, -4.2, -4.2.

MS (70 eV, EI), *m/z* (%) = 548 (M^+, 1), 493 (15), 492 (25), 491 (100), 311 (10), 310 (19), 309 (94), 278 (21), 277 (47), 201 (11), 183 (17), 167 (13), 166 (11), 102 (11), 92 (16), 43 (27).

HRMS (EI), *m/z* calc. for $\mathbf{C_{25}H_{36}N_4O_4S_2Si}$ (548.1947): 548.1927.

IR (ATR) υ (cm^{-1}) = 3053, 3035, 2953, 2931, 2892, 2857, 1736, 1604, 1474, 1413, 1378, 1274, 1251, 1219, 1190, 1171, 1133, 1119, 1097, 1053, 1007, 969, 823, 781, 725, 712, 696.

Preparation of (*E*)-2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)-sulfinyl)-*N*,*N*-dimethyl-4-(oct-1-en-1-yl)-imidazole-1-sulfonamide (70f)



Prepared according to **TP1** from 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (**67**, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (**62**, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.55 mL, 0.55 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and (*E*)-1-iodooct-1-ene (**68g**, 107 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded **70f** as a brown solid (216 mg, 83%).

m.p.: 98.9-101.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.31 (s, 2H), 6.57-6.77 (m, 1H), 6.26-6.39 (m, 1H), 3.72 (s, 3H), 3.01 (s, 6H), 2.31 (s, 6H), 2.00-2.15 (m, 2H), 1.21-1.32 (m, 8H), 1.05 (s, 9H), 0.82-0.93 (m, 3H), 0.40 (s, 3H), 0.39 (s, 3H).

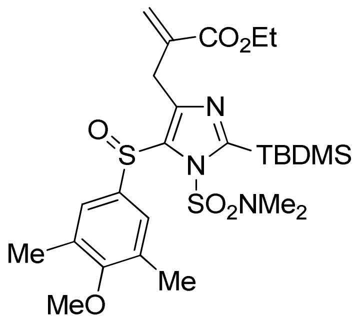
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.2, 158.4, 157.7, 147.8, 136.4, 133.7, 132.9, 131.2, 130.2, 130.0, 128.3, 125.4, 60.9, 59.4, 37.9, 27.1, 18.7, 15.8, 14.3, -4.1, -4.2.

MS (70 eV, EI), *m/z* (%) = 581 (M^+, 2), 547 (10), 526 (18), 525 (31), 524 (96), 474 (15), 473 (38), 398 (17), 291 (27), 290 (100), 257 (10), 193 (28), 183 (11), 167 (43), 166 (18).

HRMS (EI), *m/z* calc. for **$C_{28}H_{47}N_3O_4S_2Si$** (581.2777): 581.2766.

IR (ATR) υ (cm^{-1}) = 3062, 2992, 2959, 2923, 2902, 2858, 1741, 1654, 1458, 1372, 1359, 1248, 1220, 1178, 1157, 1091, 1049, 1010, 944, 841, 824, 779, 725, 673, 660.

Preparation of ethyl 2-((2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)methyl)acrylate (70g)



Prepared according to **TP1** from 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (**67**, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (**62**, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, the allylation reaction was accomplished according to **TP7** with $ZnCl_2$ (0.55 mL, 0.55 mmol, 1.0M in THF), CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.0M in THF) and ethyl 2-(bromomethyl)acrylate (**68h**, 235 mg, 0.45 mmol) over night. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7:3) afforded **70g** as a colorless solid (256 mg, 98%).

m.p.: 97.7-99.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.24 (s, 2H), 5.88 (d, *J*=1.1Hz, 1H), 4.85 (d, *J*=1.4Hz, 1H), 4.08-4.16 (m, 2H), 3.71 (s, 3H), 3.04 (s, 6H), 2.26 (s, 6H), 1.22-1.26 (m, 3H), 0.98 (s, 9H), 0.27-0.47 (m, 6H).

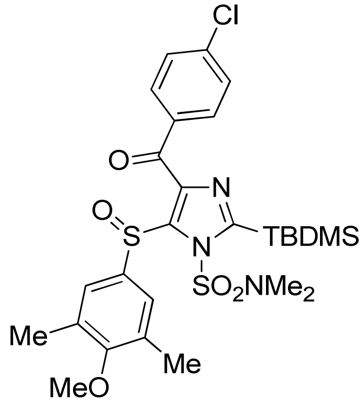
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.4, 158.9, 156.9, 146.4, 136.7, 136.1, 132.3, 131.0, 124.9, 124.8, 60.6, 59.7, 37.9, 29.5, 26.9, 18.5, 16.2, 14.1, -4.1, -4.2.

MS (70 eV, EI), *m/z* (%) = 583 (M^+, 1), 528 (16), 527 (29), 526 (100), 345 (16), 344 (11), 183 (21), 168 (10), 167 (30), 166 (33), 102 (14), 73 (29).

HRMS (EI), *m/z* calc. for $\mathbf{C_{26}H_{41}N_6O_6S_2Si}$ (583.2206): 583.2212.

IR (ATR) υ (cm^{-1}) = 3112, 2983, 2950, 2928, 2911, 2888, 2855, 1717, 1636, 1474, 1376, 1272, 1244, 1220, 1180, 1152, 1119, 1094, 1054, 1040, 1020, 1006, 960, 842, 823, 780, 726.

Preparation of 2-(*tert*-butyldimethylsilyl)-4-(4-chlorobenzoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (70h)



Prepared according to **TP1** from 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (**67**, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (**62**, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, the acylation reaction was accomplished according to **TP8** with $ZnCl_2$ (0.55 mL, 0.55 mmol, 1.0M in THF), CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.0M in THF) and 4-chlorobenzoyl chloride (**68i**, 79 mg, 0.45 mmol) over night. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7:3) afforded **70h** as a pale yellow solid (225 mg, 82%).

m.p.: 139.0-140.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.68 (d, *J*=8.9Hz, 2H), 7.30 (d, *J*=8.9Hz, 2H), 7.16 (s, 2H), 3.53 (s, 3H), 3.07 (s, 6H), 2.14 (s, 6H), 1.00 (s, 9H), 0.38-0.47 (m, 6H).

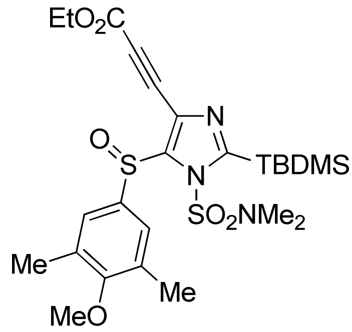
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 186.7, 159.0, 157.5, 144.2, 139.7, 137.9, 134.8, 134.3, 131.8, 131.4, 128.2, 125.9, 59.6, 38.1, 26.9, 18.6, 16.1, -4.0, -4.1.

MS (70 eV, EI), *m/z* (%) = 594 ([M-CH_3]$^+$, 4), 555 (20), 554 (66), 553 (43), 552 (100), 454 (21), 183 (46), 168 (28), 167 (100), 166 (78), 139 (78), 111 (25), 108 (37), 102 (46), 75 (35), 73 (74), 43 (29).

HRMS (EI), *m/z* calc. for **$C_{26}H_{33}ClN_3O_5S_2Si$** (594.1319 ([M-$CH_3$])): 594.1329 ([M-$CH_3$]).

IR (ATR) υ (cm^{-1}) = 3125, 2952, 2931, 2900, 2857, 1730, 1676, 1586, 1473, 1417, 1381, 1274, 1250, 1217, 1176, 1156, 1091, 1065, 1022, 1011, 971, 902, 844, 822, 814, 781, 762, 726, 686, 670.

Preparation of ethyl 3-(2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)propiolate (70i)

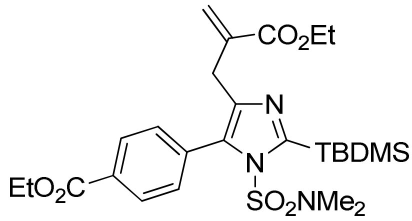


Prepared according to **TP1** from 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (**67**, 236 mg, 0.5 mmol) and TMPMgCl·LiCl (**62**, 0.5 mL, 0.55 mmol, 1.1M in THF) at -30 °C in 1 h. Subsequently, $ZnCl_2$ (0.55 mL, 0.55 mmol, 1.0M in THF) was added and stirred for 15 min at -30 °C. CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.0M in THF) and ethyl 3-bromopropiolate (**68j**, 80 mg, 0.45 mmol) were added and the reaction mixture was stirred over night while warming up to room temperature. The reaction was quenched with sat. NH_4Cl/NH_3 (9:1) solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane:EtOAc 7:3) to give **70i** as a yellow oil (133 mg, 53 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.42 (s, 2H), 4.24 (q, *J*=6.8Hz, 2H), 3.73 (s, 3H), 3.09 (s, 6H), 2.32 (s, 6H), 1.31 (t, *J*=6.8Hz, 3H), 1.00 (s, 9H), 0.33-0.45 (m, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.6, 158.2, 153.0, 141.6, 134.3, 132.4, 125.4, 125.0, 86.7, 76.3, 62.1, 59.7, 38.1, 27.0, 18.4, 16.3, 14.1, -4.0, -4.0.
MS (70 eV, EI), *m/z* (%) = 552 ($[M-CH_3]^+$, 1), 412 (38), 356 (32), 334 (36), 298 (57), 269 (58), 189 (27), 183 (44), 182 (65), 167 (91), 147 (71), 102 (87), 75 (37), 73 (100).
HRMS (EI), *m/z* calc. for **$C_{24}H_{34}N_3O_6S_2Si$** (552.1658 ($[M-CH_3]$)): 552.1654 ($[M-CH_3]$).
IR (ATR) υ (cm^{-1}) = 3114, 2954, 2931, 2906, 2858, 2232, 1710, 1472, 1418, 1383, 1288, 1275, 1245, 1217, 1176, 1165, 1096, 1066, 1033, 1010, 971, 844, 822, 813, 781, 748, 725.

7.4 Selective Functionalization on Position 5 of the Imidazole Ring

Preparation of ethyl 4-(2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-4-(2-(ethoxycarbonyl)allyl)- imidazol-5-yl)benzoate (72a)



Prepared according to **TP2** from ethyl 2-((2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)methyl)-acrylate (**70g**, 292 mg, 0.5 mmol) and *i*PrMgCl·LiCl (**63**, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and ethyl 4-iodobenzoate (**68b**, 124 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8.5:1.5) afforded **72a** as a pale yellow solid (173 mg, 71%).

m.p.: 83.8-85.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.10 (d, *J*=8.0Hz, 2 H), 7.47 (d, *J*=8.0Hz, 2H), 6.18 (s, 1H), 5.41 (s, 1H), 4.39 (q, *J*=7.2Hz, 2H), 4.13 (q, *J*=7.0Hz, 2H), 3.37 (s, 2H), 2.28 (s, 6H), 1.40 (t, *J*=6.9Hz, 3H), 1.23 (t, *J*=7.1Hz, 3H), 1.06 (s, 6H), 0.39 (s, 6H).

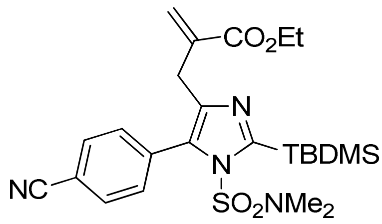
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.8, 166.0, 155.0, 140.1, 138.4, 134.0, 131.0, 130.7, 129.2, 128.4, 125.8, 61.2, 60.6, 36.6, 29.1, 27.0, 18.6, 14.3, 14.1, -4.0.

MS (70 eV, EI), *m/z* (%) = 548 ($[M-H]^+$, 1), 534 (4), 504 (5), 494 (15), 493 (30), 492 (100), 344 (6), 103 (8).

HRMS (EI), *m/z* calc. for **$C_{26}H_{38}N_3O_6SSi$** (548.2251 ([M-H])): 548.2239 ([M-H]).

IR (ATR) υ (cm^{-1}) = 3118, 2981, 2947, 2937, 2910, 2857, 1708, 1634, 1617, 1474, 1373, 1293, 1271, 1254, 1249, 1183, 1153, 1128, 1111, 1099, 1022, 976, 951, 864, 826, 821, 776, 735, 724, 710, 697, 673.

Preparation of ethyl 2-((2-(*tert*-butyldimethylsilyl)-5-(4-cyanophenyl)-1-(*N*,*N*-dimethyl-sulfamoyl)- imidazol-4-yl)methyl)acrylate (72b)



Prepared according to **TP2** from ethyl 2-((2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)methyl)-acrylate (**70g**, 292 mg, 0.5 mmol) and *i*PrMgCl·LiCl (**63**, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and 4-iodobenzonitrile (**68k**, 103 mg, 0.45 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded **72b** as a brown solid (202 mg, 90%).

m.p.: 98.3-99.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.72 (d, *J*=8.6Hz, 2H), 7.54 (d, *J*=8.6Hz, 2H), 6.21 (d, *J*=1.1Hz, 1H), 5.46 (d, *J*=1.4Hz, 1H), 4.14 (q, *J*=7.0Hz, 2H), 3.36 (s, 2H), 2.31 (s, 6H), 1.24 (t, *J*=7.2Hz, 3H), 1.05 (s, 9H), 0.39 (s, 6H).

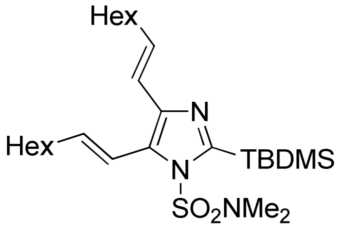
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.6, 155.7, 140.6, 138.1, 134.4, 131.7, 131.7, 127.5, 126.1, 118.3, 112.6, 60.7, 36.7, 29.2, 27.0, 18.6, 14.1, -4.1.

MS (70 eV, EI), *m/z* (%) = 501 ($[M-H]^+$, 1), 447 (11), 446 (28), 445 (100), 103 (17), 92 (19), 76 (10), 75 (28), 73 (14).

HRMS (EI), *m/z* calc. for **$C_{24}H_{33}N_4O_4SSi$** (501.1992 ([M-H])): 501.1992 ([M-H]).

IR (ATR) υ (cm^{-1}) = 3060, 2978, 2956, 2929, 2908, 2854, 2229, 1715, 1640, 1612, 1466, 1372, 1302, 1250, 1190, 1179, 1152, 1135, 1108, 1096, 1043, 1020, 972, 848, 838, 823, 813, 776, 729, 694, 665.

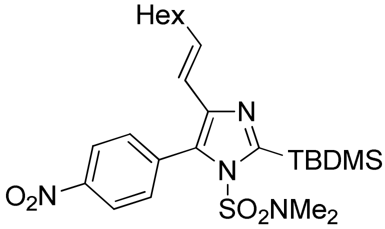
Preparation of 2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-4,5-di((*E*)-oct-1-en-1-yl)-imidazole-1-sulfonamide (72c)



Prepared according to **TP2** from (*E*)-2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)-sulfinyl)-*N*,*N*-dimethyl-4-(oct-1-en-1-yl)-imidazole-1-sulfonamide (**70f**, 291 mg, 0.5 mmol) and *i*PrMgCl·LiCl (**63**, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and (*E*)-1-iodooct-1-ene (**68g**, 107 mg, 0.45 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 75:1) afforded **72c** as a colorless oil (202 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.56-6.71 (m, 1H), 6.21-6.46 (m, 2H), 5.85-5.98 (m, 1H), 2.79 (s, 6H), 2.13-2.31 (m, 4H), 1.23-1.40 (m, 16H), 1.08 (s, 9H), 0.82-0.96 (m, 6H), 0.37 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 153.6, 139.2, 138.1, 132.8, 126.9, 120.1, 117.5, 37.8, 33.4, 33.0, 31.7, 31.7, 29.2, 29.2, 29.0, 28.9, 27.1, 22.6, 22.6, 18.6, 14.1, 14.0, -4.2.
MS (70 eV, EI), *m/z* (%) = 509 (M^+, 1), 454 (15), 453 (36), 452 (100), 389 (12), 388 (31), 377 (33), 287 (22), 262 (33), 76 (12), 73 (25), 57 (14), 43 (20), 41 (11).
HRMS (EI), *m/z* calc. for **$C_{27}H_{51}N_3O_2SSi$** (509.3471): 509.3456.
IR (ATR) υ (cm^{-1}) = 3037, 2955, 2926, 2855, 1646, 1463, 1376, 1286, 1248, 1183, 1162, 1143, 1123, 1022, 962, 840, 823, 813, 777, 763, 749, 722, 668.

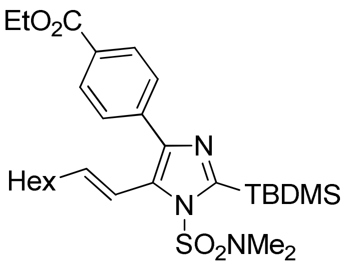
Preparation of (*E*)-2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-5-(4-nitrophenyl)-4-(oct-1-en-1-yl)- imidazole-1-sulfonamide (72d)



Prepared according to **TP2** from (*E*)-2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)-sulfinyl)-*N*,*N*-dimethyl-4-(oct-1-en-1-yl)-imidazole-1-sulfonamide (**70f**, 291 mg, 0.5 mmol) and *i*PrMgCl·LiCl (**63**, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and 1-iodo-4-nitrobenzene (**68l**, 112 mg, 0.45 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded **72d** as a yellow solid (232 mg, 100%).

m.p.: 120.2-123.1 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.31 (d, *J*=8.8Hz, 2H), 7.61 (d, *J*=8.8Hz, 2H), 6.60-6.73 (m, 1H), 5.82-5.95 (m, 1H), 2.33 (s, 6H), 2.04-2.18 (m, 2H), 1.22-1.40 (m, 8H), 1.13 (s, 9H), 0.81-0.92 (m, 3H), 0.42 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 156.4, 147.7, 141.2, 136.3, 135.1, 132.2, 125.2, 123.1, 118.4, 36.7, 33.0, 31.6, 29.1, 28.9, 27.1, 22.6, 18.7, 14.0, -4.3.
MS (70 eV, EI), *m/z* (%) = 505 ($[M-CH_3]^+$, 3), 465 (14), 464 (31), 463 (100), 420 (7), 399 (9), 388 (19), 298 (8), 277 (13), 274 (9).
HRMS (EI), *m/z* calc. for **$C_{24}H_{37}N_4O_4SSi$** (505.2305 ($[M-CH_3]$)): 505.2305 ($[M-CH_3]$).
IR (ATR) υ (cm^{-1}) = 3106, 2953, 2928, 2857, 1700, 1662, 1602, 1515, 1468, 1377, 1341, 1249, 1156, 1103, 1045, 1014, 969, 862, 854, 836, 822, 812, 776, 731, 713, 668.

Preparation of (*E*)-ethyl 4-(2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-5-(oct-1-en-1-yl)-imidazol-4-yl)benzoate (72e)



Prepared according to **TP2** from ethyl 4-(2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)benzoate (**70a**, 310 mg, 0.5 mmol) and *i*PrMgCl·LiCl (**63**, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and (*E*)-1-iodooct-1-ene (**68g**; 107 mg, 0.45 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded **72e** as a pale yellow solid (147 mg, 60%).

m.p.: 68.9-70.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.01 (d, J=8.7Hz, 2H), 7.90 (d, J=8.7Hz, 2H), 6.38-6.50 (m, 1H), 5.89-6.03 (m, 1H), 4.37 (q, J=7.1Hz, 2H), 2.85 (s, 6H), 2.14-2.23 (m, 2H), 1.19-1.48 (m, 11H), 1.09 (s, 6H), 0.84-0.94 (m, 3H), 0.40 (s, 6H).

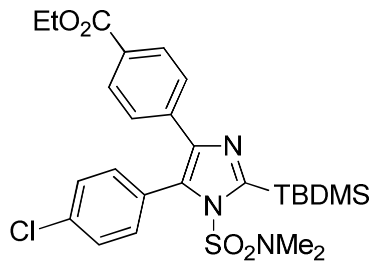
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 166.6, 154.0, 140.5, 139.1, 139.0, 129.4, 128.7, 128.5, 127.6, 117.0, 60.8, 37.8, 33.4, 31.7, 29.0, 28.5, 27.1, 22.6, 18.7, 14.3, 14.1, -4.2.

MS (70 eV, EI), *m/z* (%) = 546 ([M-H]$^+$, 1), 504 (11), 492 (14), 491 (33), 490 (100), 426 (7), 416 (5), 415 (16), 330 (5).

HRMS (EI), *m/z* calc. for **$C_{28}H_{44}N_3O_4SSi$** (546.2822 ([M-H])): 546.2835 ([M-H]).

IR (ATR) υ (cm^{-1}) = 3084, 3058, 2981, 2950, 2929, 2856, 1715, 1608, 1470, 1455, 1375, 1270, 1246, 1222, 1176, 1146, 1121, 1106, 1072, 998, 977, 862, 822, 776, 731, 713, 694, 666.

Preparation of ethyl 4-(2-(*tert*-butyldimethylsilyl)-5-(4-chlorophenyl)-1-(*N*,*N*-dimethyl-sulfamoyl)-imidazol-4-yl)benzoate (72f)



Prepared according to **TP2** from ethyl 4-(2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)benzoate (**70a**, 310 mg, 0.5 mmol) and *i*PrMgCl·LiCl (**63**, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and 1-chloro-4-iodobenzene (**68d**, 131 mg, 0.55 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded **72f** as a white solid (191 mg, 70%).

m.p.: 197.7-199.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.88 (d, J=8.3Hz, 2H), 7.33-7.52 (m, 6H), 4.33 (q, J=7.2Hz, 2H), 2.38 (s, 6H), 1.35 (t, J=7.2Hz, 3H), 1.17 (s, 9H), 0.45 (s, 6H).

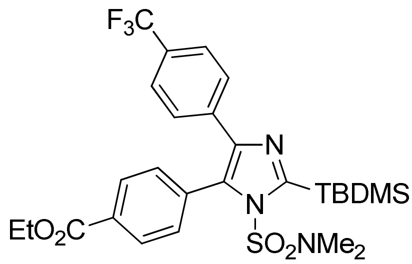
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.4, 155.0, 139.9, 137.6, 135.7, 132.8, 129.4, 129.1, 128.8, 128.4, 127.9, 126.6, 60.8, 36.5, 27.1, 18.8, 14.3, -4.2.

MS (70 eV, EI), *m/z* (%) = 546 ([M-H]$^+$, 1), 504 (7), 493 (13), 492 (42), 491 (30), 490 (100), 398 (11), 372 (7), 107 (9), 102 (8), 76 (17).

HRMS (EI), *m/z* calc. for **$C_{26}H_{33}ClN_3O_4SSi$** (546.1650 ([M-H])): 546.1634 ([M-H]).

IR (ATR) υ (cm^{-1}) = 3092, 2991, 2976, 2956, 2934, 2904, 2886, 2854, 1707, 1612, 1472, 1384, 1272, 1246, 1162, 1108, 1084, 1044, 1015, 981, 844, 823, 816, 779, 731, 724, 669.

Preparation of ethyl 4-(2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-4-(4-(trifluoromethyl)phenyl)-imidazol-5-yl)benzoate (72g)



Prepared according to **TP2** from 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (**70b**, 308 mg, 0.5 mmol) and *i*PrMgCl·LiCl (**63**, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and ethyl 4-iodobenzoate (**68b**, 124 mg, 0.45 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded **72g** as a brown solid (223 mg, 80%).

m.p.: 110.8-112.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.17 (d, *J*=8.0Hz, 2H), 7.53 (d, *J*=8.0Hz, 2H), 7.37-7.49 (m, 4H), 4.43 (q, *J*=7.2Hz, 2H), 2.33 (s, 6H), 1.44 (t, *J*=7.2Hz, 3H), 1.17 (s, 9H), 0.45 (s, 6H).

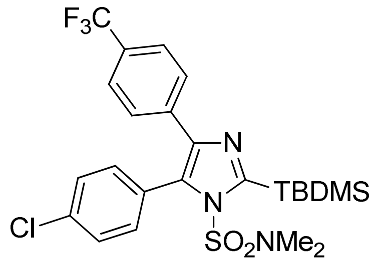
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.9, 155.1, 139.6, 136.7, 134.6, 131.5, 131.4, 129.9 (q, *J*=32.3Hz), 128.8, 128.0, 127.0, 125.1 (q, *J*=3.7Hz), 124.2 (q, *J*=271.8Hz), 61.4, 36.5, 27.1, 18.8, 14.3, -4.2.

MS (70 eV, EI), *m/z* (%) = 580 ([M-H]$^+$, 2), 538 (9), 526 (11), 525 (31), 524 (100), 107 (13), 92 (20), 76 (20).

HRMS (EI), *m/z* calc. for **$C_{28}H_{38}N_3O_6S_2Si$** (580.1913 ([M-H])): 580.1905 ([M-H]).

IR (ATR) υ (cm^{-1}) = 2954, 2935, 2901, 2857, 1718, 1619, 1475, 1464, 1378, 1323, 1284, 1273, 1250, 1160, 1119, 1107, 1086, 1064, 1043, 1017, 973, 847, 823, 814, 782, 776, 733, 725, 712, 697, 669.

Preparation of 2-(*tert*-butyldimethylsilyl)-5-(4-chlorophenyl)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (72h)



Prepared according to **TP2** from 2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (**70b**, 308 mg, 0.5 mmol) and *i*PrMgCl·LiCl (**63**, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and 1-chloro-4-iodobenzene (**68d**, 131 mg, 0.55 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded **72h** as a white solid (217 mg, 80%).

m.p.: 175.5-177.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.42-7.55 (m, 6H), 7.34-7.41 (m, 2H), 2.39 (s, 6H), 1.17 (s, 9H), 0.45 (s, 6H).

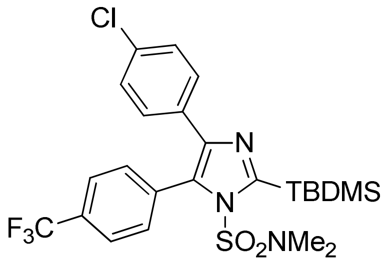
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 155.0, 139.5, 136.8, 135.8, 132.8, 129.2, 128.9 (q, *J*=32.3Hz), 128.3, 127.8, 126.9, 125.1 (q, *J*=3.9Hz), 124.2 (q, *J*=272.1Hz), 36.5, 27.1, 18.8, -4.2.

MS (70 eV, EI), *m/z* (%) = 543 (M^+, 1), 489 (11), 488 (40), 487 (26), 486 (100), 379 (6), 107 (10), 92 (14), 76 (12).

HRMS (EI), *m/z* calc. for **$C_{24}H_{29}ClF_3N_3O_2SSi$** (543.1390): 543.1399.

IR (ATR) υ (cm^{-1}) = 3060, 2978, 2959, 2937, 2890, 2855, 1620, 1486, 1377, 1325, 1248, 1159, 1126, 1108, 1086, 1065, 1043, 1016, 977, 844, 837, 822, 815, 779, 746, 728, 719.

Preparation of 2-(*tert*-butyldimethylsilyl)-4-(4-chlorophenyl)-*N*,*N*-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (72i)



Prepared according to **TP2** from 2-(*tert*-butyldimethylsilyl)-4-(4-chlorophenyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-*N*,*N*-dimethyl-imidazole-1-sulfonamide (**70c**, 291 mg, 0.5 mmol) and *i*PrMgCl·LiCl (**63**, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and 1-iodo-4-(trifluoromethyl)benzene (**68c**, 123 mg, 0.45 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded **72i** as a white solid (166 mg, 68%).

m.p.: 199.3-200.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.75 (d, *J*=8.1Hz, 2H), 7.58 (d, *J*=8.2Hz, 2H), 7.23-7.33 (m, 2H), 7.09-7.21 (m, 2H), 2.33 (s, 6H), 1.17 (s, 9H), 0.45 (s, 6H).

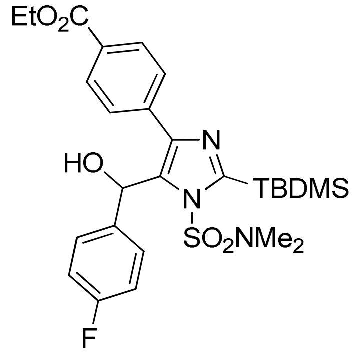
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 155.1, 140.1, 134.1, 133.1, 132.0, 131.5, 131.4 (q, *J*=33.0Hz), 128.4, 128.2, 126.5, 125.6 (q, *J*=3.8Hz), 123.8 (q, *J*=272.6Hz), 36.4, 27.1, 18.8, -4.2.

MS (70 eV, EI), *m/z* (%) = 528 ($[M-CH_3]^+$, 4), 489 (12), 488 (51), 487 (33), 486 (100), 394 (11), 107 (15), 102 (11), 92 (21), 43 (12).

HRMS (EI), *m/z* calc. for **$C_{23}H_{26}ClF_3N_3O_2SSi$** (528.1156 ($[M-CH_3]$)): 528.1155 ($[M-CH_3]$).

IR (ATR) υ (cm^{-1}) = 3087, 3056, 2982, 2958, 2937, 2910, 2895, 2858, 1621, 1516, 1486, 1408, 1374, 1327, 1295, 1263, 1249, 1204, 1190, 1156, 1120, 1107, 1092, 1080, 1068, 1041, 1016, 976, 956, 935, 854, 847, 837, 828, 819, 778, 732, 698, 674.

Preparation of ethyl 4-(2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-5-((4-fluorophenyl)(hydroxy)methyl)-imidazol-4-yl)benzoate (72j)



Prepared according to **TP2** from ethyl 4-(2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)benzoate (**70a**, 310 mg, 0.5 mmol) and *i*PrMgCl·LiCl (**63**, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, 4-fluorobenzaldehyde (**68m**, 56 mg, 0.45 mmol) was added and the reaction mixture was allowed to slowly warm to 25 °C and continuously stirred over night. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane:EtOAc 7:3) to give **72j** as a yellow solid (250 mg, 100 %).

m.p.: 143.4-146.0 °C.

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm) = 7.79-7.91 (m, 2H), 7.74 (d, *J*=8.5Hz, 2H), 7.08-7.21 (m, 2H), 6.87-7.04 (m, 2H), 6.57 (d, *J*=4.4Hz, 1H), 6.34 (d, *J*=4.4Hz, 1H), 4.23 (q, *J*=7.1Hz, 2H), 2.80 (s, 6H), 1.26 (t, *J*=7.1Hz, 3H), 1.05 (s, 9H), 0.23-0.50 (m, 6H).

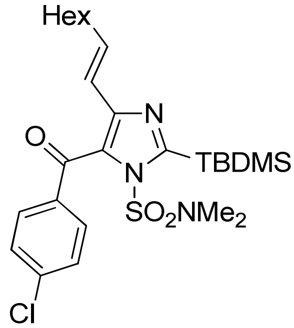
^{13}C NMR (100 MHz, d6-DMSO) δ (ppm) = 165.9, 161.4 (d, *J*=242.7Hz), 153.6, 141.2, 138.3, 138.1 (d, *J*=2.9Hz), 133.5, 129.0, 128.7, 128.6, 128.1 (d, *J*=8.2Hz), 114.9 (d, *J*=21.4Hz), 63.7, 61.0, 37.6, 27.6, 18.9, 14.5, -3.5, -3.6.

MS (70 eV, EI), *m/z* (%) = 561 (M^+, 1), 506 (15), 505 (32), 504 (100), 123 (11), 102 (12), 92 (35), 75 (24), 73 (20).

HRMS (EI), *m/z* calc. for **$C_{27}H_{36}FN_3O_5SSi$** (561.2129): 561.2122.

IR (ATR) υ (cm^{-1}) = 3408, 3068, 2987, 2951, 2933, 2909, 2856, 1683, 1609, 1510, 1474, 1417, 1380, 1366, 1278, 1256, 1250, 1220, 1178, 1164, 1148, 1133, 1110, 1069, 1032, 1019, 968, 858, 835, 821, 812, 794, 778, 721, 696, 670.

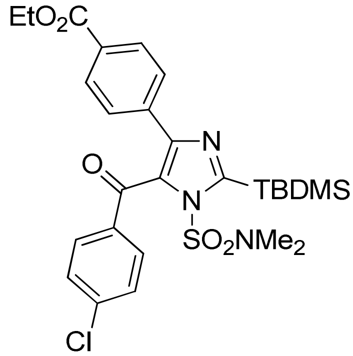
Preparation of (*E*)-2-(*tert*-butyldimethylsilyl)-5-(4-chlorobenzoyl)-*N*,*N*-dimethyl-4-(oct-1-en-1-yl)- imidazole-1-sulfonamide (72k)



Prepared according to **TP2** from (*E*)-2-(*tert*-butyldimethylsilyl)-5-((4-methoxy-3,5-dimethylphenyl)-sulfinyl)-*N*,*N*-dimethyl-4-(oct-1-en-1-yl)-imidazole-1-sulfonamide (**70f**, 291 mg, 0.5 mmol) and *i*PrMgCl·LiCl (**63**, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the Pd-catalyzed acylation was accomplished according to **TP9** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and 4-chlorobenzoyl chloride (**68i**, 96 mg, 0.55 mmol) over night at room temperature. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded **72k** as a yellow oil (212 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.76 (d, *J*=8.3Hz, 2H), 7.45 (d, *J*=8.6Hz, 2H), 6.56-6.74 (m, 1H), 5.77-5.92 (m, 1H), 2.72 (s, 6H), 1.94-2.14 (m, 2H), 1.18-1.37 (m, 8H), 1.10 (s, 9H), 0.81-0.93 (m, 3H), 0.44 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 186.4, 157.7, 143.8, 140.4, 136.8, 136.2, 131.2, 129.0, 125.5, 118.9, 37.9, 32.8, 31.6, 28.8, 28.7, 27.1, 22.5, 18.6, 14.0, -4.2.
MS (70 eV, EI), *m/z* (%) = 522 ($[M-CH_3]^+$, 3), 483 (12), 482 (46), 481 (28), 480 (100), 389 (17), 287 (11), 140 (13), 139 (35), 92 (43), 76 (16), 75 (13), 73 (45), 56 (10), 41 (11).
HRMS (EI), *m/z* calc. for **$C_{25}H_{37}ClN_3O_3SSi$** 522.2013 ($[M-CH_3]$)): 522.2131 ($[M-CH_3]$).
IR (ATR) υ (cm^{-1}) = 3031, 2955, 2928, 2856, 1659, 1587, 1464, 1373, 1250, 1218, 1169, 1157, 1090, 1014, 967, 924, 842, 823, 814, 780, 762, 736, 724, 683, 670.

Preparation of ethyl 4-(2-(*tert*-butyldimethylsilyl)-5-(4-chlorobenzoyl)-1-(*N*,*N*-dimethyl-sulfamoyl)- imidazol-4-yl)benzoate (72l)



Prepared according to **TP2** from ethyl 4-(2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-imidazol-4-yl)benzoate (**70a**, 310 mg, 0.5 mmol) and *i*PrMgCl·LiCl (**63**, 0.5 mL, 0.6 mmol, 1.2M in THF) at -78 °C in 1 h. Subsequently, the Pd-catalyzed acylation was accomplished according to **TP9** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and 4-chlorobenzoyl chloride (**68i**, 96 mg, 0.55 mmol) over night at room temperature. Flash column chromatographical purification on silica gel (pentane/EtOAc, 9:1) afforded **72l** as a white solid (190 mg, 66%).

m.p.: 143.4-146.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.90 (d, *J*=8.8Hz, 2H), 7.71 (d, *J*=9.0Hz, 2H), 7.62 (d, *J*=8.8Hz, 2H), 7.36 (d, *J*=8.8Hz, 2H), 4.32 (q, *J*=7.0Hz, 2H), 2.73 (s, 6H), 1.34 (t, *J*=7.1Hz, 3H), 1.13 (s, 9H), 0.47 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 188.3, 166.2, 155.8, 141.5, 141.1, 136.3, 135.1, 131.0, 129.8, 129.7, 129.3, 127.1, 126.2, 61.0, 37.9, 27.1, 18.6, 14.3, -4.1.

MS (70 eV, EI), *m/z* (%) = 560 ([M-CH_3]$^+$, 1), 463 (20), 461 (51), 354 (43), 325 (18), 309 (33), 138 (62), 111 (28), 108 (100), 44 (28), 43 (31).

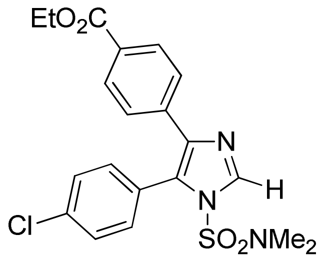
HRMS (EI), *m/z* calc. for **$C_{26}H_{31}ClN_3O_5SSi$** (560.1442 ([M-CH_3])): 560.1459 ([M-CH_3]).

IR (ATR) υ (cm^{-1}) = 3085, 3066, 2978, 2954, 2928, 2852, 1784, 1720, 1659, 1586, 1379, 1355, 1273, 1245, 1231, 1183, 1167, 1140, 1100, 1092, 1073, 1019, 995, 976, 902, 841, 822, 780, 771, 743, 733, 726, 698, 671.

7.5 SELECTIVE FUNCTIONALIZATION ON POSITION 2 OF THE IMIDAZOLE RING

7.5.1 SELECTIVE DEPROTECTION ON POSITION 2

Preparation of ethyl 4-(5-(4-chlorophenyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazol-4-yl)-benzoate (73a)



Prepared according to **TP5** from ethyl 4-(2-(*tert*-butyldimethylsilyl)-5-(4-chlorophenyl)-1-(*N*,*N*-dimethyl-sulfamoyl)-imidazol-4-yl)benzoate (**72f**, 619 mg, 1.13 mmol) and TBAF·$3H_2O$ (**64**, 357 mg, 1.13 mmol, 0.1M in THF) at 0 °C in 5 min. Flash column chromatographical purification on silica gel (pentane/EtOAc, 1:1) afforded **73a** as a pale yellow solid (456 mg, 93%).

m.p.: 165.4-167.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.13 (s, 1H), 7.90 (d, *J*=8.3Hz, 2H), 7.35-7.50 (m, 6H), 4.33 (q, *J*=7.2Hz, 2H), 2.52 (s, 6H), 1.36 (t, *J*=7.0Hz, 3H).

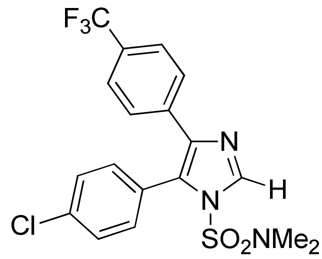
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.3, 140.0, 139.1, 137.0, 136.2, 133.2, 129.6, 129.3, 129.2, 127.1, 126.8, 126.0, 60.9, 37.2, 14.3.

MS (70 eV, EI), *m/z* (%) = 433 (M^+, 100), 325 (42), 253 (18), 252 (26), 218 (22), 133 (17), 123 (40), 108 (28), 57 (19).

HRMS (EI), *m/z* calc. for **$C_{20}H_{20}ClN_3O_4S$** (433.0863): 433.0856.

IR (ATR) υ (cm^{-1}) = 3147, 3088, 3071, 2957, 2923, 2866, 2854, 1707, 1612, 1484, 1474, 1382, 1364, 1268, 1254, 1246, 1185, 1169, 1135, 1100, 1092, 1081, 1018, 1005, 977, 966, 938, 863, 835, 780, 742, 722, 696.

Preparation of 5-(4-chlorophenyl)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (73b)



Prepared according to **TP5** from 2-(*tert*-butyldimethylsilyl)-5-(4-chlorophenyl)-*N*,*N*-dimethyl-4-(4-(tri-fluoromethyl)phenyl)-imidazole-1-sulfonamide (**72h**, 1.43 g, 2.63 mmol) and TBAF·3H_2O (**64**, 829 mg, 2.63 mmol, 0.1M in THF) at 0 °C in 5 min. Flash column chromatographical purification on silica gel (pentane/EtOAc, 6.5:3.5) afforded **73b** as a white solid (1.06 g, 94%).

m.p.: 157.7-159.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.13 (s, 1H), 7.43-7.52 (m, 6H), 7.36-7.43 (m, 2H), 2.53 (s, 6H).

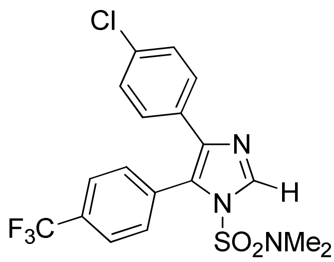
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 139.6, 139.1, 136.3, 136.2, 133.1, 129.3 (q, *J*=32.5Hz), 129.2, 127.2, 127.0, 126.0, 125.3 (q, *J*=3.7Hz), 124.1 (q, *J*=272.1Hz), 37.2.

MS (70 eV, EI), *m/z* (%) = 429 (M^+, 100), 323 (28), 322 (21), 321 (75), 286 (46), 157 (27), 152 (12), 150 (27), 137 (11), 123 (57), 108 (72), 57 (19), 44 (12).

HRMS (EI), *m/z* calc. for **$C_{18}H_{15}ClF_3N_3O_2S$** (429.0526): 429.0522.

IR (ATR) υ (cm^{-1}) = 3138, 3122, 2956, 2930, 2856, 1618, 1479, 1390, 1325, 1240, 1206, 1166, 1141, 1117, 1106, 1084, 1062, 1022, 1014, 1003, 960, 940, 846, 832, 742, 725, 715.

Preparation of 4-(4-chlorophenyl)-*N*,*N*-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (73c)



Prepared according to **TP5** from 2-(*tert*-butyldimethylsilyl)-4-(4-chlorophenyl)-*N*,*N*-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (**72i**, 544 mg, 1.0 mmol) and TBAF·3H_2O (**64**, 316 mg, 1.0 mmol, 0.1M in THF) at 0 °C in 5 min.

Flash column chromatographical purification on silica gel (pentane/EtOAc, 6.5:3.5) afforded **73c** as a white solid (430 mg, 100%).

m.p.: 201.7-203.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.13 (s, 1H), 7.72 (d, *J*=8.0Hz, 2H), 7.59 (d, *J*=8.0Hz, 2H), 7.23-7.32 (m, 2H), 7.16-7.23 (m, 2H), 2.50 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 140.3, 139.2, 133.6, 132.7, 132.4, 131.8 (q, *J*=33.0Hz), 130.9, 128.6, 128.5, 125.6 (q, *J*=3.5Hz), 124.7, 123.7 (q, *J*=272.6Hz), 37.2.

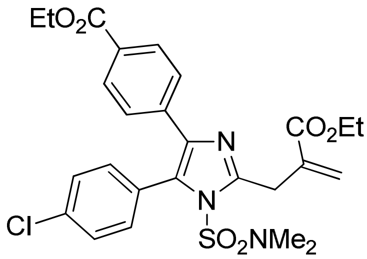
MS (70 eV, EI), *m/z* (%) = 429 (M^+, 100), 323 (25), 322 (19), 321 (67), 286 (41), 122 (59), 108 (73), 57 (17), 44 (13), 43 (19).

HRMS (EI), *m/z* calc. for $\mathbf{C_{18}H_{15}ClF_3N_3O_2S}$ (429.0526): 429.0520.

IR (ATR) υ (cm^{-1}) = 3150, 3127, 3066, 2976, 2937, 1701, 1622, 1493, 1461, 1412, 1392, 1330, 1270, 1240, 1207, 1171, 1161, 1140, 1118, 1106, 1094, 1081, 1070, 1052, 1024, 1014, 1004, 959, 940, 859, 844, 836, 827, 754, 737, 726, 696, 656.

7.5.2 Selective Functionalization on Position 2

Preparation of ethyl 4-(5-(4-chlorophenyl)-1-(*N*,*N*-dimethylsulfamoyl)-2-(2-(ethoxy-carbonyl)allyl)- imidazol-4-yl)benzoate (76a)

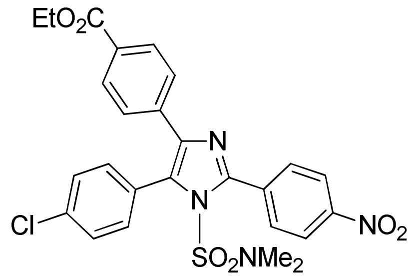


Prepared according to **TP3** from ethyl 4-(5-(4-chlorophenyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazol-4-yl)-benzoate (**73a**, 109 mg, 0.25 mmol) and $TMP_2Zn\cdot 2MgCl\cdot 2LiCl$ (**65**, 0.28 mL, 0.14 mmol, 0.5M in THF) at -20 °C in 1 h. Subsequently, the allylation reaction was accomplished according to **TP7** with $CuCN\cdot 2LiCl$ (0.25 mL, 0.25 mmol, 1.0M in THF) and ethyl 2-(bromomethyl)acrylate (**68h**, 53 mg, 0.275 mmol) in 1.5 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7.5:2.5) afforded **76a** as a yellow oil (121 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.84 (d, *J*=8.8Hz, 2H), 7.38-7.51 (m, 2H), 7.29-7.38 (m, 4H), 6.33 (s, 1H), 5.60 (s, 1H), 4.19-4.37 (m, 4H), 4.11 (s, 2H), 2.49 (s, 6H), 1.27-1.37 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.7, 166.4, 148.8, 137.4, 137.2, 137.1, 135.8, 133.3, 129.4, 129.4, 129.0, 128.9, 128.2, 127.0, 126.9, 126.0, 60.9, 60.9, 37.0, 14.3, 14.3.
MS (70 eV, EI), *m/z* (%) = 545 (M^+, 9), 440 (18), 439 (45), 438 (51), 437 (100), 409 (14), 366 (17), 365 (14), 364 (19), 43 (42).
HRMS (EI), *m/z* calc. for $\mathbf{C_{26}H_{28}ClN_3O_6S}$ (545.1387): 545.1374.
IR (ATR) υ (cm^{-1}) = 2979, 2935, 2912, 2873, 1712, 1611, 1482, 1450, 1380, 1273, 1168, 1124, 1092, 1079, 1017, 975, 838, 825, 780, 722.

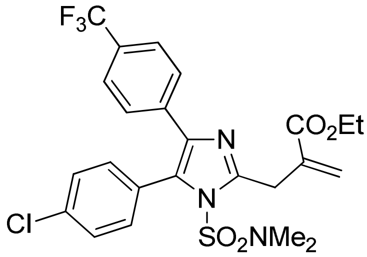
Preparation of ethyl 4-(5-(4-chlorophenyl)-1-(*N*,*N*-dimethylsulfamoyl)-2-(4-nitrophenyl)imidazol-4-yl)benzoate (76b)



Prepared according to **TP3** from ethyl 4-(5-(4-chlorophenyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazol-4-yl)-benzoate (**73a**, 109 mg, 0.25 mmol) and $TMP_2Zn\cdot 2MgCl\cdot 2LiCl$ (**65**, 0.28 mL, 0.14 mmol, 0.5M in THF) at -20 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol) and 1-iodo-4-nitrobenzene (**68l**, 56 mg, 0.225 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7.5:2.5) afforded **76b** as a yellow solid (91 mg, 76%).

m.p.: 131.0-133.6 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.27-8.37 (m, 2H), 7.84-7.98 (m, 4H), 7.37-7.56 (m, 6H), 4.34 (q, *J*=7.2Hz, 2H), 2.39 (s, 6H), 1.36 (t, *J*=7.2Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.2, 148.5, 148.3, 138.7, 137.8, 136.6, 136.1, 132.6, 130.9, 129.6, 129.6, 129.3, 129.1, 127.6, 127.2, 123.0, 61.0, 37.1, 14.3.
MS (70 eV, EI), *m/z* (%) = 554 (M^+, 2), 449 (44), 448 (33), 447 (100), 419 (17), 417 (25), 402 (15), 373 (11), 340 (22), 177 (18), 150 (11), 139 (16).
HRMS (EI), *m/z* calc. for $\mathbf{C_{26}H_{23}ClN_4O_6S}$ (554.1027): 554.1015.
IR (ATR) υ (cm^{-1}) = 3095, 2983, 2947, 2924, 2911, 2860, 1719, 1604, 1519, 1483, 1383, 1351, 1267, 1240, 1168, 1134, 1125, 1107, 1098, 1091, 1078, 1018, 1006, 974, 953, 856, 832, 780, 760, 737, 728, 718, 696.

Preparation of ethyl 2-((5-(4-chlorophenyl)-1-(*N*,*N*-dimethylsulfamoyl)-4-(4-(tri-fluoromethyl)phenyl)-imidazol-2-yl)methyl)acrylate (76c)



Prepared according to **TP3** from 5-(4-chlorophenyl)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (**73b**, 109 mg, 0.25 mmol) and $TMP_2Zn \cdot 2MgCl \cdot 2LiCl$ (**65**, 0.28 mL, 0.14 mmol, 0.5M in THF) at -20 °C in 1 h. Subsequently, the allylation reaction was accomplished according to **TP7** with CuCN·2LiCl (0.25 mL, 0.25 mmol, 1.0M in THF) and ethyl 2-(bromomethyl)acrylate (**68h**, 44 mg, 0.225 mmol) over night. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded **76c** as a white solid (105 mg, 86%).

m.p.: 86.3-89.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.28-7.55 (m, 8H), 6.34 (s, 1H), 5.61 (s, 1H), 4.26 (q, *J*=7.2 Hz, 2H), 4.11 (s, 2H), 2.51 (s, 6H), 1.31 (t, *J*=7.0Hz, 3H).

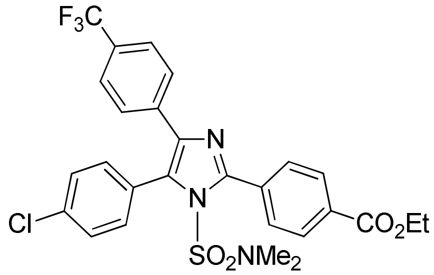
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.7, 148.8, 137.1, 137.0, 136.3, 135.9, 133.3, 129.0 (q, *J*=32.5Hz), 129.0, 128.1, 127.1, 126.9, 126.0, 125.0 (q, *J*=3.7Hz), 124.1 (q, *J*=272.1Hz), 60.9, 37.0, 33.4, 14.2.

MS (70 eV, EI), *m/z* (%) = 541 (M^+, 5), 436 (13), 435 (40), 434 (38), 433 (100), 405 (15), 389 (14), 388 (14), 387 (19), 362 (20), 361 (22), 360 (24), 359 (20), 108 (14), 43 (27).

HRMS (EI), *m/z* calc. for **$C_{24}H_{23}ClF_3N_3O_4S$** (541.1050): 541.1043.

IR (ATR) υ (cm^{-1}) = 3096, 3003, 2984, 2928, 2882, 2855, 1724, 1618, 1423, 1391, 1324, 1306, 1204, 1169, 1155, 1118, 1108, 1091, 1079, 1064, 1017, 969, 960, 948, 850, 832, 822, 808, 744, 724, 714.

Preparation of ethyl 4-(5-(4-chlorophenyl)-1-(*N*,*N*-dimethylsulfamoyl)-4-(4-(trifluoromethyl)phenyl)-imidazol-2-yl)benzoate (76d)



Prepared according to **TP3** from 5-(4-chlorophenyl)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (**73b**, 109 mg, 0.25 mmol) and $TMP_2Zn\cdot 2MgCl\cdot 2LiCl$ (**65**, 0.28 mL, 0.14 mmol, 0.5M in THF) at -20 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol) and ethyl 4-iodobenzoate (**68b**, 76 mg, 0.275 mmol) in 1 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded **76d** as a pale yellow solid (104 mg, 72%).

m.p.: 157.8-159.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.10-8.22 (m, 2H), 7.77-7.88 (m, 2H), 7.40-7.54 (m, 8H), 4.41 (q, *J*=7.2Hz, 2H), 2.38 (s, 6H), 1.42 (t, *J*=7.0Hz, 3H).

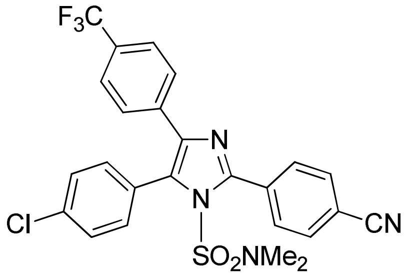
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.0, 149.4, 137.8, 136.1, 136.1, 135.8, 135.6, 132.6, 131.5, 129.9, 129.4 (q, *J*=32.5Hz), 129.2, 129.1, 128.1, 127.5, 125.2 (q, *J*=3.9Hz), 124.1 (q, *J*=271.8Hz), 61.3, 37.1, 14.3.

MS (70 eV, EI), *m/z* (%) = 577 (M^+, 5), 472 (29), 471 (52), 470 (92), 469 (100), 161 (13), 157 (12), 133 (12), 122 (12).

HRMS (EI), *m/z* calc. for $\mathbf{C_{27}H_{23}ClF_3N_3O_4S}$ (577.1050): 577.1043.

IR (ATR) υ (cm^{-1}) = 3087, 3062, 2984, 2972, 2956, 2934, 2904, 2872, 2855, 1721, 1618, 1489, 1389, 1326, 1288, 1277, 1167, 1125, 1106, 1090, 1081, 1064, 1018, 1005, 971, 850, 833, 778, 740, 729, 718.

Preparation of 5-(4-chlorophenyl)-2-(4-cyanophenyl)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)- imidazole-1-sulfonamide (76e)



Prepared according to **TP3** from 5-(4-chlorophenyl)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (**73b**, 109 mg, 0.25 mmol) and $TMP_2Zn{\cdot}2MgCl{\cdot}2LiCl$ (**65**, 0.28 mL, 0.14 mmol, 0.5M in THF) at -20 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol) and 4-iodobenzonitrile (**68k**, 52 mg, 0.225 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7:3) afforded **76e** as a pale brown solid (113 mg, 95%).

m.p.: 142.4-144.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.82-7.91 (m, 2H), 7.71-7.81 (m, 2H), 7.45-7.52 (m, 8H), 2.38 (s, 6H).

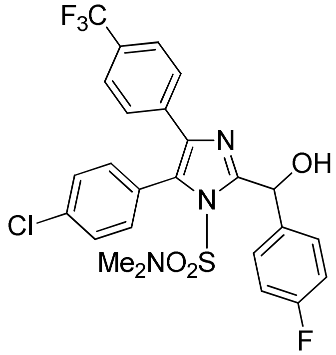
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 148.7, 138.2, 136.2, 136.0, 135.9, 132.6, 131.6, 130.6, 129.8 (q, *J*=32.3Hz), 129.4, 128.9, 127.6, 127.5, 125.2 (q, *J*=3.9Hz), 124.0 (q, *J*=271.8Hz), 118.4, 113.3, 37.1.

MS (70 eV, EI), *m/z* (%) = 530 (M^+, 8), 425 (33), 424 (58), 423 (86), 422 (100), 267 (15), 157 (17), 123 (22), 114 (42), 108 (16), 43 (12).

HRMS (EI), *m/z* calc. for $\mathbf{C_{25}H_{18}ClF_3N_4O_2S}$ (530.0791): 530.0785.

IR (ATR) υ (cm^{-1}) = 3094, 3056, 2983, 2955, 2929, 2858, 2229, 1926, 1720, 1612, 1605, 1520, 1384, 1351, 1324, 1312, 1297, 1270, 1203, 1169, 1135, 1118, 1109, 1096, 1082, 1063, 1017, 1008, 974, 956, 853, 848, 832, 748, 729, 722, 696.

Preparation of 5-(4-chlorophenyl)-2-((4-fluorophenyl)(hydroxy)methyl)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76f)



Prepared according to **TP4** from 5-(4-chlorophenyl)-*N*,*N*-dimethyl-4-(4-(trifluoro-methyl)phenyl)-imidazole-1-sulfonamide (**73b**, 109 mg, 0.25 mmol) and TMPMgCl·LiCl (**62**, 0.27 mL, 0.3 mmol, 1.1M in THF) at -78 °C in 1 h. Subsequently, 4-fluorobenzaldehyde (**68m**, 34 mg, 0.275 mmol) was added and the reaction mixture was allowed to slowly warm to 25 °C and continuously stirred for 6 h. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane:EtOAc 7:3) to give **76f** as a white solid (127 mg, 92 %).

m.p.: 155.1-157.8 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.44-7.52 (m, 6H), 7.33-7.44 (m, 4H), 7.06 (t, *J*=8.6Hz, 2H), 6.28 (d, *J*=6.7Hz, 1H), 4.47 (d, *J*=7.9Hz, 1H), 2.23 (s, 6H).

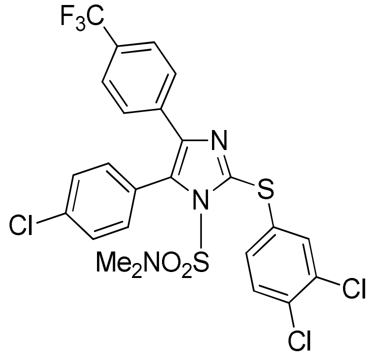
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 162.5 (d, *J*=246.8Hz), 152.4, 137.3 (d, *J*=3.1Hz), 136.7, 136.4, 135.7, 133.3, 133.3, 129.5 (d, *J*=8.1Hz), 129.4 (q, *J*=32.5Hz), 129.2, 127.6, 127.1, 125.2 (q, *J*=3.9Hz), 124.0 (q, *J*=271.5Hz), 115.4 (d, *J*=21.3Hz), 70.1, 36.6.

MS (70 eV, EI), *m/z* (%) = 553 (M^+, 12), 431 (35), 430 (48), 429 (100), 428 (71), 417 (21), 323 (17), 321 (41), 286 (24), 156 (17), 123 (64), 120 (24), 108 (56), 61 (15), 57 (21), 44 (18), 43 (31).

HRMS (EI), *m/z* calc. for **$C_{25}H_{20}ClF_4N_3O_3S$** (553.0850): 553.0841.

IR (ATR) υ (cm^{-1}) = 3387, 3003, 2960, 2929, 2857, 1619, 1604, 1508, 1382, 1327, 1222, 1170, 1120, 1111, 1086, 1064, 1016, 977, 962, 854, 838, 747, 724.

Preparation of 5-(4-chlorophenyl)-2-((3,4-dichlorophenyl)thio)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76g)



Prepared according to **TP4** from 5-(4-chlorophenyl)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (**73b**, 109 mg, 0.25 mmol) and TMPMgCl·LiCl (**62**, 0.27 mL, 0.3 mmol, 1.1M in THF) at -78 °C in 1 h. Subsequently, *S*-(3,4-dichlorophenyl) benzenesulfonothioate (**68n**, 72 mg, 0.225 mmol) was added and the reaction mixture was allowed to slowly warm to 25 °C and continuously stirred over night. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane:EtOAc 8.5:1.5) to give **76g** as a white solid (127 mg, 93 %).

m.p.: 131.1-133.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.83 (d, *J*=1.7Hz, 1H), 7.32-7.53 (m, 8H), 7.23-7.31 (m, 2H), 2.65 (s, 6H).

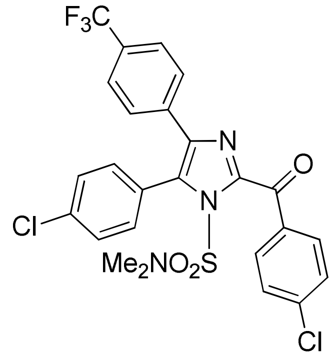
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 145.5, 138.4, 136.2, 136.0, 135.8, 133.8, 133.7, 133.3, 132.9, 130.8, 129.9, 129.4 (q, *J*=32.5Hz), 129.1, 128.6, 127.6, 126.9, 125.1 (q, *J*=3.7Hz), 124.0 (q, *J*=272.1Hz), 37.5.

MS (70 eV, EI), *m/z* (%) = 605 (M^+, 23), 502 (21), 501 (47), 500 (67), 498 (57), 497 (100), 465 (17), 464 (61), 462 (82), 461 (23), 439 (46), 191 (17), 189 (24), 154 (17), 43 (49).

HRMS (EI), *m/z* calc. for $\mathbf{C_{24}H_{17}Cl_3F_3N_3O_2S_2}$ (604.9780): 604.9778.

IR (ATR) υ (cm^{-1}) = 3092, 2994, 2956, 2920, 2851, 1618, 1487, 1455, 1410, 1379, 1322, 1250, 1223, 1190, 1165, 1122, 1108, 1094, 1082, 1062, 1045, 1033, 1016, 972, 951, 851, 834, 815, 747, 728, 710.

Preparation of 2-(4-chlorobenzoyl)-5-(4-chlorophenyl)-*N*,*N*-dimethyl-4-(4-(tri-fluoromethyl)phenyl)-imidazole-1-sulfonamide (76h)



Prepared according to **TP4** from 5-(4-chlorophenyl)-*N*,*N*-dimethyl-4-(4-(trifluoro-methyl)phenyl)-imidazole-1-sulfonamide (**73b**, 109 mg, 0.25 mmol) and TMPMgCl·LiCl (**62**, 0.27 mL, 0.3 mmol, 1.1M in THF) at -78 °C in 1 h. Subsequently, the Pd-catalyzed acylation was accomplished according to **TP9** with $ZnCl_2$ (0.3 mL, 0.3 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol) and 4-chlorobenzoyl chloride (**68i**, 48 mg, 0.275 mmol) over night at room temperature. Flash column chromatographical purification on silica gel (pentane/EtOAc, 8.5:1.5) afforded **76h** as a pale yellow solid (83 mg, 58%).

m.p.: 245.4-246.2 °C.

^{1}H NMR (400 MHz, d8-THF) δ (ppm) = 8.03 (d, *J*=8.4Hz, 2H), 7.51-7.60 (m, 10H), 2.65 (s, 6H).

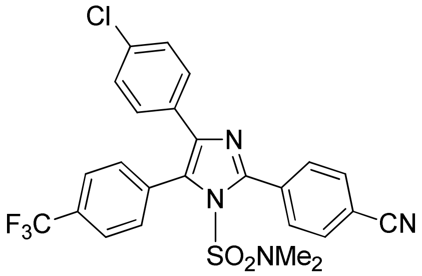
^{13}C NMR (100 MHz, d8-THF) δ (ppm) = 185.5, 146.9, 141.2, 138.6, 137.6, 137.1, 135.6, 134.9, 132.6, 130.1 (q, *J*=32.1Hz), 130.0, 129.8, 129.5, 128.6, 128.2, 126.0 (q, *J*=3.9Hz), 125.4 (q, *J*=271.7Hz).

MS (70 eV, EI), *m/z* (%) = 567 (M^+, 39), 460 (15), 433 (20), 431 (32), 146 (22), 139 (60), 122 (36), 111 (45), 108 (100), 44 (18), 42 (16).

HRMS (EI), *m/z* calc. for **$C_{25}H_{18}Cl_2F_3N_3O_3S$** (567.0398): 567.0384.

IR (ATR) υ (cm^{-1}) = 3088, 2961, 2920, 2852, 1678, 1617, 1583, 1482, 1380, 1324, 1211, 1204, 1164, 1126, 1109, 1096, 1083, 1063, 1014, 981, 962, 912, 856, 846, 836, 764, 734, 720.

Preparation of 4-(4-chlorophenyl)-2-(4-cyanophenyl)-*N*,*N*-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76i)



Prepared according to **TP4** from 4-(4-chlorophenyl)-*N*,*N*-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (**73c**, 109 mg, 0.25 mmol) and TMPMgCl·LiCl (**62**, 0.27 mL, 0.3 mmol, 1.1M in THF) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP6** with $ZnCl_2$ (0.3 mL, 0.3 mmol, 1.0M in THF), $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol) and 4-iodobenzonitrile (**68k**, 52 mg, 0.225 mmol) in 2 h. Flash column chromatographical purification on silica gel (pentane/EtOAc, 7:3) afforded **76i** as a white solid (90 mg, 75%).

m.p.: 208.3-209.5 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.82-7.91 (m, 2H), 7.71-7.79 (m, 4H), 7.63 (d, *J*=8.0Hz, 2H), 7.23-7.29 (m, 2H), 7.16-7.23 (m, 2H), 2.34 (s, 6H).

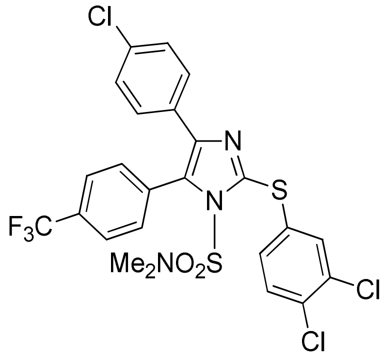
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 148.8, 138.9, 135.8, 133.9, 133.2, 131.7, 131.6, 131.6 (q, *J*=32.8Hz), 130.6, 130.5, 128.7, 128.6, 127.9, 125.7 (q, *J*=3.7Hz), 124.6 (q, *J*=272.4Hz), 118.3, 113.3, 37.0.

MS (70 eV, EI), *m/z* (%) = 530 (M^+, 6), 425 (37), 424 (49), 423 (100), 422 (81), 267 (13), 123 (13), 114 (28), 108 (10), 43 (11).

HRMS (EI), *m/z* calc. for $\mathbf{C_{25}H_{18}ClF_3N_4O_2S}$ (530.0791): 530.0790.

IR (ATR) υ (cm^{-1}) = 3098, 3071, 2982, 2948, 2238, 1620, 1544, 1490, 1403, 1383, 1330, 1315, 1294, 1240, 1200, 1172, 1161, 1136, 1122, 1106, 1091, 1078, 1068, 1022, 1008, 977, 852, 838, 733, 696, 658.

Preparation of 4-(4-chlorophenyl)-2-((3,4-dichlorophenyl)thio)-*N*,*N*-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (76j)



Prepared according to **TP4** from 4-(4-chlorophenyl)-*N*,*N*-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (**73c**, 109 mg, 0.25 mmol) and TMPMgCl·LiCl (**62**, 0.27 mL, 0.3 mmol, 1.1M in THF) at -78 °C in 1 h. Subsequently, *S*-(3,4-dichlorophenyl) benzenesulfonothioate (**68n**, 72 mg, 0.225 mmol) was added and the reaction mixture was allowed to slowly warm to 25 °C and continuously stirred over night. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica, pentane:EtOAc 8.5:1.5) to give **76j** as a white solid (96 mg, 70 %).

m.p.: 155.4-156.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.82 (d, *J*=1.9Hz, 1H), 7.73 (d, *J*=8.1Hz, 2H), 7.49-7.57 (m, 4H), 7.09-7.14 (m, 2H), 7.02-7.08 (m, 2H), 2.64 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 145.4, 139.1, 135.8, 133.7, 133.6, 133.6, 133.4, 132.9, 132.5, 131.7 (q, *J*=32.6Hz), 130.8, 130.5, 129.9, 128.5, 128.2, 127.4, 125.5 (q, *J*=3.8Hz), 123.7 (q, *J*=272.9Hz), 37.5.

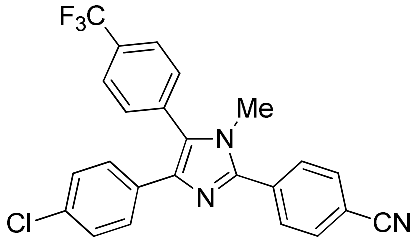
MS (70 eV, EI), *m/z* (%) = 605 (M^+, 23), 502 (22), 501 (51), 500 (54), 497 (100), 466 (14), 465 (20), 464 (56), 463 (34), 462 (78), 461 (19), 440 (11), 439 (43), 191 (11), 189 (15), 154 (11), 108 (10), 43 (10).

HRMS (EI), *m/z* calc. for $\mathbf{C_{24}H_{17}Cl_3F_3N_3O_2S_2}$ (604.9780): 604.9767.

IR (ATR) υ (cm^{-1}) = 3099, 3068, 2986, 2927, 2859, 1487, 1452, 1421, 1394, 1363, 1330, 1283, 1244, 1225, 1185, 1173, 1161, 1124, 1106, 1091, 1080, 1067, 1035, 1014, 969, 952, 858, 844, 832, 810, 725, 698, 676.

7.6 SELECTIVE N-3-ALKYLATION AND SUBSEQUEBT N-1 DEPROTECTION

Preparation of 4-(4-(4-chlorophenyl)-1-methyl-5-(4-(trifluoromethyl)phenyl)-imidazol-2-yl)benzonitrile (78a)



The reaction was performed according to **TP10** with 5-(4-chlorophenyl)-2-(4-cyanophenyl)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (**76e**, 265 mg, 0.5 mmol), trimethyloxonium tetrafluoroborate (**66**, 74 mg, 0.5 mmol) and conc. HCl (2.5 mL). Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded **78a** as a white solid (158 mg, 72%).

m.p.: 204.4-207.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.88 (d, *J*=7.8Hz, 2H), 7.76 (dd, *J*=11.1Hz, 8.1Hz, 4H), 7.51 (d, *J*=7.8Hz, 2H), 7.39 (d, *J*=7.8Hz, 2H), 7.20 (d, *J*=7.8Hz, 2H), 3.55 (s, 3H).

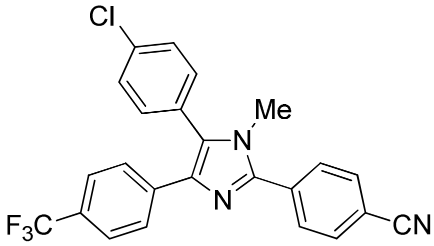
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 146.5, 138.3, 134.4, 133.8, 133.0, 132.4, 132.0, 131.1 (q, *J*=32.9Hz), 131.0, 130.2, 129.3, 128.6, 128.3, 126.2 (q, *J*=3.7Hz), 123.8 (q, *J*=272.3Hz), 118.3, 112.6, 33.6.

MS (70 eV, EI), *m/z* (%) = 437 (M^+, 100), 436 (35), 421 (6), 401 (3), 267 (3), 190 (4), 186 (3), 123 (3).

HRMS (EI), *m/z* calc. for **$C_{24}H_{15}ClF_3N_3$** (437.0907): 437.0902.

IR (ATR) υ (cm^{-1}) = 3097, 3072, 2956, 2925, 2872, 2856, 2226, 1730, 1608, 1513, 1486, 1465, 1407, 1381, 1326, 1294, 1284, 1275, 1244, 1167, 1130, 1106, 1092, 1069, 1032, 1018, 1010, 959, 848, 837, 825, 792, 739, 716, 705, 690, 652.

Preparation of 4-(5-(4-chlorophenyl)-1-methyl-4-(4-(trifluoromethyl)phenyl)-imidazol-2-yl)benzonitrile (78b)



The reaction was performed according to **TP10** with 4-(4-chlorophenyl)-2-(4-cyanophenyl)-*N*,*N*-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfonamide (**76i**, 265 mg, 0.5 mmol), trimethyloxonium tetrafluoroborate (**66**, 74 mg, 0.5 mmol) and conc. HCl (2.5 mL). Flash column chromatographical purification on silica gel (pentane/EtOAc, 8:2) afforded **78b** as a white solid (162 mg, 72%).

m.p.: 176.1-178.0 °C.

^{1}H NMR (600 MHz, $CDCl_3$) = 7.88 (d, *J*=8.5Hz, 2H), 7.74-7.82 (m, 2H), 7.60 (d, *J*=8.0Hz, 2H), 7.42-7.53 (m, 4H), 7.29-7.38 (m, 2H), 3.54 (s, 3H).

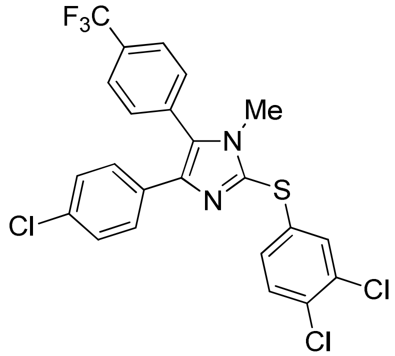
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 146.3, 137.5, 137.2, 135.7, 134.5, 132.5, 132.0, 131.4, 129.8, 129.3, 128.7 (q, *J*=32.3Hz), 128.4, 126.9, 125.2 (q, *J*=3.9Hz), 123.3 (q, *J*=271.8Hz), 118.4, 112.6, 33.4.

MS (70 eV, EI), *m/z* (%) = 437 (M^+, 100), 436 (36), 425 (5), 424 (5), 423 (16), 422 (5), 421 (7), 267 (5), 190 (6).

HRMS (EI), *m/z* calc. for $\mathbf{C_{24}H_{15}ClF_3N_3}$ (437.0907): 437.0903.

IR (ATR) υ (cm^{-1}) = 3067, 2959, 2928, 2871, 2228, 1739, 1608, 1515, 1484, 1412, 1378, 1321, 1246, 1162, 1132, 1108, 1090, 1064, 1035, 1014, 960, 852, 837, 737, 716, 699, 676.

Preparation of 4-(4-chlorophenyl)-2-((3,4-dichlorophenyl)thio)-1-methyl-5-(4-(trifluoro-methyl)phenyl)- imidazole (78c)



The reaction was performed according to **TP10** with 5-(4-chlorophenyl)-2-((3,4-dichloro-phenyl)thio)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfon-amide (**76g**, 303 mg, 0.5 mmol), trimethyloxonium tetrafluoroborate (**66**, 74 mg, 0.5 mmol) and conc. HCl (2.5 mL). Flash column chromatographical purification on silica gel (pentane/EtOAc, 8.5:1.5) afforded **78c** as a white solid (167 mg, 65%).

m.p.: 158.4-160.9 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.73 (d, *J*=8.3Hz, 6H), 7.41-7.47 (m, 3H), 7.33-7.39 (m, 3H), 7.18-7.22 (m, 2H), 7.15 (dd, *J*=8.5Hz, 2.1Hz, 1H), 3.48 (s, 3H).

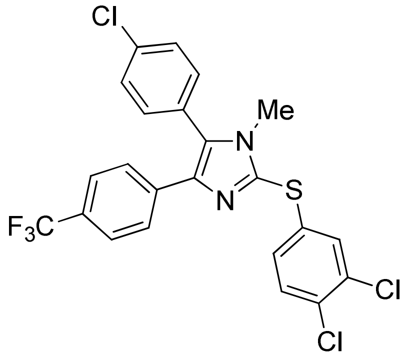
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 139.3, 137.8, 134.0, 133.8, 133.5, 133.1, 131.6, 131.5, 131.3 (q, *J*=32.8Hz), 131.1, 131.0, 130.9, 129.9, 128.6, 128.3, 127.7, 126.3 (q, *J*=3.7Hz), 124.6 (q, *J*=272.4Hz), 32.6.

MS (70 eV, EI), *m/z* (%) = 512 (M^+, 100), 511 (41), 479 (11), 295 (14), 246 (11), 186 (29), 145 (10), 43 (32).

HRMS (EI), *m/z* calc. for $\mathbf{C_{23}H_{14}Cl_3F_3N_2S}$ (511.9895): 511.9890.

IR (ATR) υ (cm^{-1}) = 3080, 3060, 2925, 2852, 1738, 1617, 1569, 1513, 1484, 1458, 1406, 1367, 1322, 1297, 1263, 1164, 1121, 1107, 1090, 1068, 1030, 1014, 960, 875, 851, 836, 816, 807, 776, 735, 713, 692, 674.

Preparation of 5-(4-chlorophenyl)-2-((3,4-dichlorophenyl)thio)-1-methyl-4-(4-(trifluoro-methyl)phenyl)-imidazole (78d)



The reaction was performed according to **TP10** with 4-(4-chlorophenyl)-2-((3,4-dichlorophenyl)thio)-*N*,*N*-dimethyl-5-(4-(trifluoromethyl)phenyl)-imidazole-1-sulfon-amide (**76j**, 303 mg, 0.5 mmol), trimethyloxonium tetrafluoroborate (**66**, 74 mg, 0.5 mmol) and conc. HCl (2.5 mL). Flash column chromatographical purification on silica gel (pentane/EtOAc, 9.5:0.5) afforded **78d** as a white solid (185 mg, 72%).

m.p.: 168.3-169.6 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.58 (d, *J*=8.2Hz, 2H), 7.47 (d, *J*=8.5Hz, 4H), 7.42 (d, *J*=2.2Hz, 1H), 7.36 (d, *J*=8.5Hz, 1H), 7.26 (d, *J*=8.5Hz, 2H), 7.14 (dd, *J*=8.2Hz, 2.2Hz, 1H), 3.46 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 138.5, 137.6, 136.9, 135.8, 134.1, 133.4, 132.3, 131.7, 131.4, 131.1, 129.8, 129.8, 128.8 (q, *J*=32.5Hz), 128.3, 127.6, 126.8, 125.2 (q, *J*=3.9Hz), 124.2 (q, *J*=271.8Hz), 32.4.

MS (70 eV, EI), *m/z* (%) = 512 (M^+, 98), 511 (51), 479 (12), 295 (13), 152 (29), 61 (11), 45 (11), 44 (15), 43 (51).

HRMS (EI), *m/z* calc. for $\mathbf{C_{23}H_{14}Cl_3F_3N_2S}$ (511.9895): 511.9904.

IR (ATR) υ (cm^{-1}) = 3078, 3056, 2956, 2925, 2854, 1617, 1515, 1482, 1450, 1366, 1325, 1305, 1246, 1166, 1134, 1112, 1104, 1093, 1066, 1032, 1015, 961, 881, 847, 835, 821, 808, 753, 746, 700, 675.

D. APPENDIX

1. LIST OF ABBREVIATIONS

Ac	acetyl
Ad	adamanyl
Alk	alkyl
aq.	aqueous
Ar	aryl
ATR	attenuated total reflection (IR)
9-BBN	9-borabicyclo[3.3.1]nonane
Boc	*tert*-butyloxycarbonyl
br	broad (NMR)
Bu	butyl
cal.	calculated
Cbz	carboxybenzyl
conc.	concentrated
d	doublet (NMR) / day
dba	*trans,trans*-dibenzylideneacetone
dist.	distilled
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,2-bis(diphenylphosphino)propane
equiv	equivalent
E	electrophile
EI	electron ionization
Et	ethyl
EWG	electron-withdrawing group
FG	functional group
GC	gas chromatography
h	hour
Hal	halogene
Het	hetero

Hex	hexyl
HRMS	high resolution mass spectroscopy
Hz	Hertz
*i*Pr	*iso*-propyl
IR	infrared
isityl	2,4,6-triisopropylphenyl
J	coupling constant (NMR)
L	ligand
LDA	lithium *N*,*N*-diisopropylamide
M	mol/L
m	*meta*
Me	methyl
min	minute
mp.	melting point
MS	mass spectroscopy
MHz	Megahertz
*n*Bu	*n*-butyl
*n*Pr	*n*-propyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
Nf	nonaflate
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidin-2-one
NP	naphthalide
o	*ortho*
p	*para*
PEPPSI-IPr	[1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
PG	protecting group
Ph	phenyl
Piv	pivalyl
ppm	parts per million
Py	pyridyl

R	organic substituent
rpm	revolutions per minute
sat.	saturated
SEM	2-(Ttrimethylsilyl)ethoxymethyl
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
*t*Bu	*tert*-butyl
T	temperature
t	reaction time
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TLC	thin layer chromatography
Tf	triflate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
Tol	tolyl
Ts	4-toluenesulfonyl
TP	typical procedure