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LiCl-Mediated Direct Insertion of Magnesium Into Aryl, Heteroaryl and Benzylic Halides. Regio- and Chemoselective Synthesis of 5-Membered Ring Heterocycles.

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Paris, Frankreich

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Erklärung

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

Ehrenwörtliche Versicherung

Diese Dissertation wurde selbstständig, ohne unerlaubte Hilfe erarbeitet.

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Fabian Michel Piller

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Parts of this Ph.D. Thesis have been published

1) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, **Convenient Preparation of Polyfunctional Arylmagnesium Reagents Using a Direct Magnesium Insertion in the Presence of LiCl**, *Angew. Chem. Int. Ed*. **2008**, *47*, 6802-6806; *Angew. Chem.* **2008**, *120*, 6907-6911.
2) A. Metzger, F. M. Piller, P. Knochel, **Polyfunctional Benzylic Zinc Chlorides by the Direct Insertion of Magnesium in the Presence of LiCl and $ZnCl_2$**, *Chem. Commun.* **2008**, 5824-5826.
3) P. Knochel, P. Appukkuttan, A. Gavryushin, G. Manolikakes, A. Metzger, M. Mosrin, F. M. Piller, C. J. Rohbogner, M. A. Schade, S. H. Wunderlich, **Functionalization of Heterocyclic Compounds using Polyfunctional Magnesium and Zinc Reagents**, *Pfizer In-House Journal Synthon,* **2008**.
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5) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, **Preparation of Polyfunctional Arylmagnesium, Arylzinc and Benzylic Zinc Reagents Using Magnesium in the Presence of LiCl**, *Chem. Eur. J.* **2009**, *15*, 7192-7202.
6) T. D. Blümke, F. M. Piller, P. Knochel, **Preparation of Highly Functionalized Alkylzinc Halides from Alkyl Bromides using Mg, $ZnCl_2$ and LiCl,** *Chem. Commun*. **2010**, DOI: 10.1039/c001845g.
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8) F. M. Piller, P. Knochel, **Functionalization of Furan, Thiophene, Pyrrole and Indole Derivatives via *Ortho*-Magnesiation Reactions,** *manuscript in preparation.*

Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
Boc	*tert*-butoxycarbonyl
Bu	butyl
conc.	concentrated
dba	*trans,trans*-dibenzylideneacetone
DCE	dichloroethane
dest.	distilled
DMAP	dimethylaminopyridine
DMF	*N,N*-dimethylformamide
equiv	equivalent
E	electrophile
EI	electron ionization
EN	electronegativity
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectroscopy
*i*Pr	*iso*-propyl
IR	infra-red
J	coupling constant (NMR)
LDA	lithium diisopropylamide
M	molar
m	*meta*
Me	methyl
min	minute
M.p.	melting point
MS	mass spectroscopy

NMR	nuclear magnetic resonance
NMP	*N*-methyl-2-pyrrolidine
o	*ortho*
p	*para*
PG	protecting group
Ph	phenyl
R	organic substituent
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
*t*Bu	*tert*-butyl
TLC	thin layer chromatography
THF	tetrahydrofuran
tfp	tris-(2-furyl)phosphine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
Ts	4-toluenesulfonyl
TP	typical procedure

A. INTRODUCTION

1. Overview

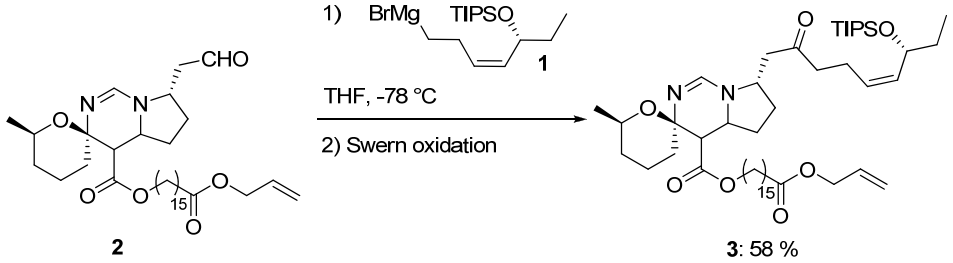
Chemistry's future will rely on the development of new environmentally benign and inexpensive methods for the synthesis of complex structures. Since *Frankland's* revolutionary discovery of Et_2Zn over 150 years ago,[1] organometallic chemistry has constantly been developed to a versatile toolbox for synthetic, medicinal and industrial chemists. A plethora of reactions have been designed for the formation of carbon-carbon and carbon-heteroatom bonds.

Due to the fact that organometallic reagents are known for many different main group and transition metals they offer a wide range of different applications. Transition metals such as Pd, Ni, Ru or Fe are often used as catalysts for cross-coupling or metathesis reactions.[2] Main-group organometallic reagents containing metals such as Li, Mg, Zn[3] or B on the other hand are mostly used as nucleophiles.[4] The reactivity of these nucleophiles greatly depends on the polarity of the carbon-metal bond and therefore on the electronegativity of the metal.[5] Organolithium reagents for example (electronegativity of Li: 1.0) display a very high reactivity towards electrophiles but therefore have a low tolerance towards many functional groups. In contrast, organoboron reagents (electronegativity of B: 2.0) show a very low reactivity towards electrophiles but tolerate a wide range of functional groups. Organomagnesium reagents (electronegativity of Mg: 1.2) play a special role in this series because they react easily with electrophiles but also are indifferent towards many important functional groups. Their convenient method of preparation and their low toxicity make organomagnesium reagents widely used reagents for organic synthesis and industrial applications.

In 1995 *Overman* and coworkers published an enantioselective total synthesis of (–)-Ptilomycalin A which is a guanidine alkaloid isolated from the Caribbean sponge *Ptilocaulis*

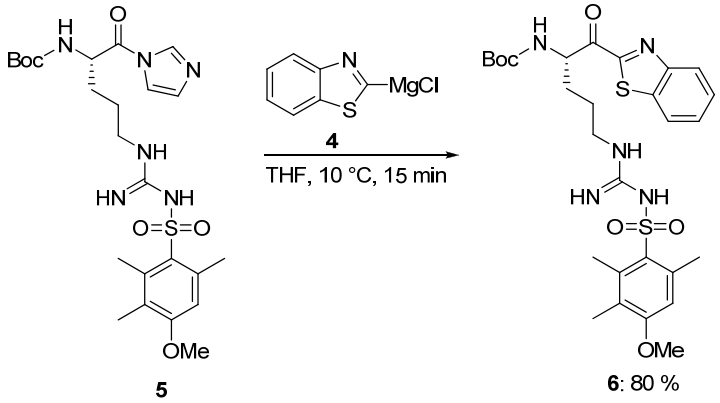
[1] E. Frankland, *Liebigs Ann. Chem.* **1849**, *71*, 171.
[2] a) *Transition Metals for Organic Synthesis*, (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**; b) J. Tsuji, *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, **1995**.
[3] In chemistry text books, zinc can be found classified both as a transition-element and as a main-group element. The IUPAC defines a transition-element as "*an element whose atom has an incomplete d sub-shell, or which can give rise to cations with an incomplete d sub-shell.*" (A. D. McNaught, A. Wilkinson (Eds.), *Compendium of Chemical Terminology*, Blackwell Scientific Publications, Oxford, **1997**). According to this rule, zinc has to be classified as a main-group element since both elemental zinc ($[Ar]3d^{10}\ 4s^2$) and the Zn^{2+} ion ($[Ar]3d^{10}$) have a complete d-shell. For a thorough investigation, see: W. B. Jensen, *J. Chem. Educ.* **2003**, *80*, 952.
[4] *Handbook of Functionalized Organometallics*, (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.
[5] A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4415.

spiculifer and the Red Sea sponge *Hemimycale sp*.[6] In a key step of the synthesis, the alkylmagnesium reagent **1** is added to the highly functionalized aldehyde **2** and the resulting alcohol is directly oxidized to the ketone **3** in 58 % yield (Scheme 1).



Scheme 1: Use of an alkylmagnesium reagent in the total synthesis of (–)-Ptilomycalin A according to *Overman*

More recently, in 2007 process chemists at *Johnson & Johnson* have developed an improved multi-kilogram synthesis of the tryptase inhibitor RWJ-56423[7] which has potential for the treatment of allergic and inflammatory disorders.[8] In this case, benzothiazol-2-yl magnesium chloride (**4**) was added to the imidazolide **5** to produce the ketone **6** in 80 % yield on a 10 kg scale (Scheme 2).



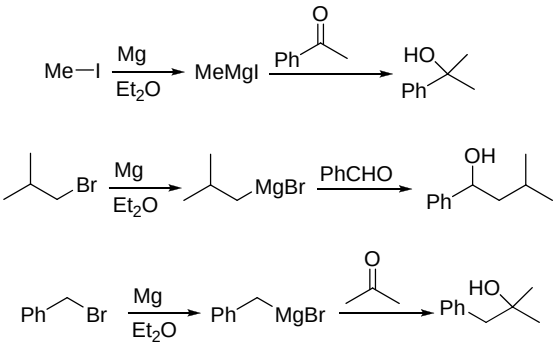
Scheme 2: *Johnson & Johnson's* synthesis of an intermediate towards RWJ-56423 on a 10 kg scale

[6] L. E. Overman, M. H. Rabinowitz, P. A. Renhowe, *J. Am. Chem. Soc*. **1995**, *116*, 549.
[7] M. Costanzo, B. Maryanoff, L. Hecker, L. Schott, S. Yabut, H. Zhang, P. Andrade-Gordon, J. Kauffman, J. Lewis, R. Krishnan, A. Tulinsky, *J. Med. Chem.* **1996**, *39*, 3039.
[8] B. D. Kenney, M. Breslav, R. Chang, R. Glaser, B. D. Harris, C. A. Maryanoff, J. Mills, A. Roessler, B. Segmuller, F. J. Villani Jr., *J. Org. Chem.* **2007**, *72*, 9798.

2. Preparation of Magnesium Reagents

2.1. Magnesium Insertion Into Carbon-Halogen Bonds

The first preparation of an organomagnesium reagent was performed in the year 1900 when *Victor Grignard* made the observation that methyl iodide reacted with magnesium turnings to yield a clear and colorless solution in the presence of diethyl ether.[9] He could show that this solution and similar reagents were able to attack aldehydes and ketones to give the corresponding alcohols in approximately 70 % yield (Scheme 3).



Scheme 3: First experiments conducted by *Victor Grignard* in 1900

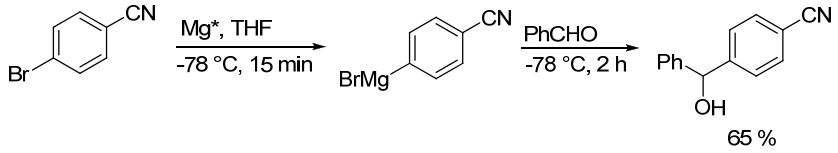
Subsequently, *Grignard* investigated the behavior of organomagnesium reagents towards different electrophiles such as esters and CO_2 and explored occurring side reactions such as homo-couplings.[10] For his pioneering work in this field he was awarded the Nobel Prize in Chemistry in 1912.

The exact mechanism of the magnesium insertion into organic halides is not yet completely elucidated. According to *Garst* and *Ungváry* the mechanism "remains rich in speculation and short on discriminating fact, a disturbing status for what may be the most-often-used non-trivial reaction."[11] A radical mechanism is generally accepted but there is much controversy concerning possible reaction pathways. While *M. S. Kharasch* and *H. M. Walborsky* support

[9] V. Grignard, *Compt. Rend. Acad. Sci. Paris*, **1900**, *130*, 1322.
[10] V. Grignard, *Ann. Chim.* **1901**, *24*, 433.
[11] H. G. Richey, Jr. (Ed.), *Grignard Reagents, New Developments*, Wiley-VCH, Weinheim, **2000**.

the hypothesis that the formed radicals stay on the metal surface (A Model)[12] *J. F. Garst* strongy believes in the theory that the formed radicals can freely diffuse into the solvent (D Model).[13]

A major limitation of the insertion reaction is that it is usually conducted at high temperatures, which strongly limits the scope of functional groups that can be used. In a ground-breaking series of publications, *Rieke* and co-workers showed that using highly reactive magnesium powder (Mg*), prepared by the reduction of $MgCl_2$ with lithium and naphthalene, it is possible to lower the temperature of the insertion to up to –78 °C.[14] For the first time functionalized magnesium compounds bearing functional groups such as an ester or a nitrile became available via insertion reactions (Scheme 4).[15]

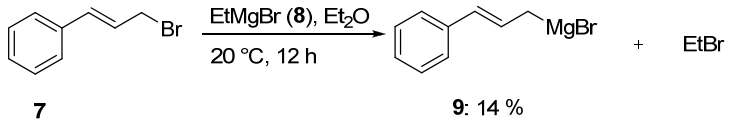


Scheme 4: Preparation a functionalized magnesium reagent using highly reactive magnesium powder (Mg*)

2.2. The Halogen-Magnesium Exchange Reaction

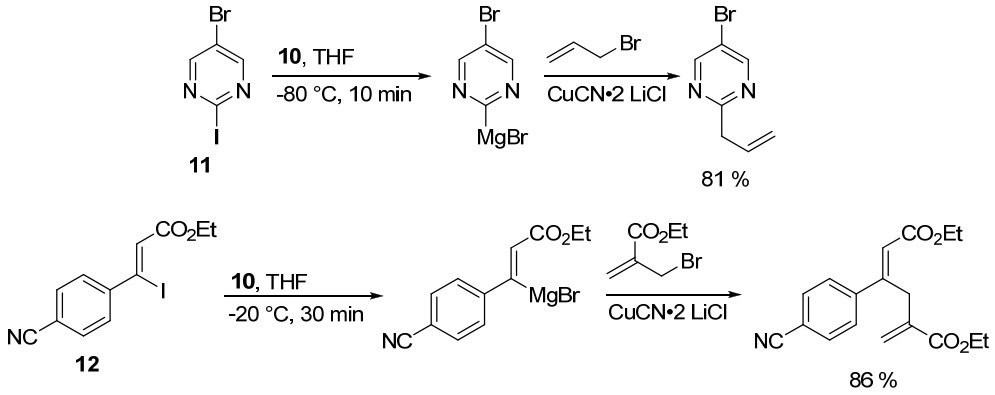
An alternative preparation of organomagnesium reagents lies in the halogen-magnesium exchange reaction. It was first described by *Prévost* in 1931 when reacting cinnamyl bromide (**7**) with ethylmagnesium bromide (**8**) furnishing cinnamylmagnesium bromide (**9**) in low yield (Scheme 5).[16]

[12] a) M. S. Kharasch, O. Reihmuth, *Grignard Reactions of Nonmetallic Substances*, Prantice-Hall, New York, **1954**; b) H. M. Walborsky, *Acc. Chem. Res.* **1990**, *23*, 286.
[13] J. F. Garst, *Acc. Chem. Res.* **1991**, *24*, 95.
[14] a) R. D. Rieke, *Science* **1989**, *246*, 1260; b) R. D. Rieke, P. M. Hudnall, *J. Am. Chem. Soc.* **1972**, *94*, 7178; c) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925; d) R. D. Rieke, *Top. Curr. Chem*. **1975**, *59*, 1; e) R. D. Rieke, *Acc. Chem. Res.* **1977**, *10*, 301; f) T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 3674; g) R. D. Rieke, *Aldrichchim. Acta* **2000**, *33*, 52.
[15] J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem*. **2000**, *65*, 5428.
[16] C. Prévost, *Bull. Soc. Chim. Fr*. **1931**, *49*, 1372.



Scheme 5: First example of a halogen-magnesium exchange reaction

The requirement of the halogen-magnesium exchange reaction is that the generated magnesium reagent has to be more stable than the exchange reagent.[17] *Knochel* and co-workers could demonstrate the significance of the iodine-magnesium exchange reaction using *i*PrMgBr (**10**).[18] Since the reaction proceeds at low temperatures down to –80 °C, sensitive heterocycles such as the polyhalogenated pyrimidine **11**[19] and the iodoalkene **12**[20] can be magnesiated using *i*PrMgBr (**10**) and quenched with typical electrophiles (Scheme 6).

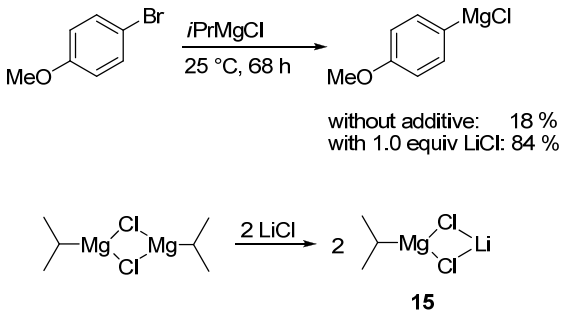


Scheme 6: Examples of the iodine-magnesium exchange reaction using *i*PrMgBr (**10**)

An extension of this work was published in 2004 and 2006 when *Knochel* reported the preparation of the mixed lithium and magnesium reagents *i*PrMgCl·LiCl (**13**) and *s*Bu_2Mg·LiCl (**14**).[21] These reagents are a tremendous improvement compared to earlier methods because they allow even electron-rich organic bromides to be used in halogen-magnesium exchange reactions compared to the usually more expensive and less stable iodides. Experimental as well as theoretical considerations support the proposed mechanism

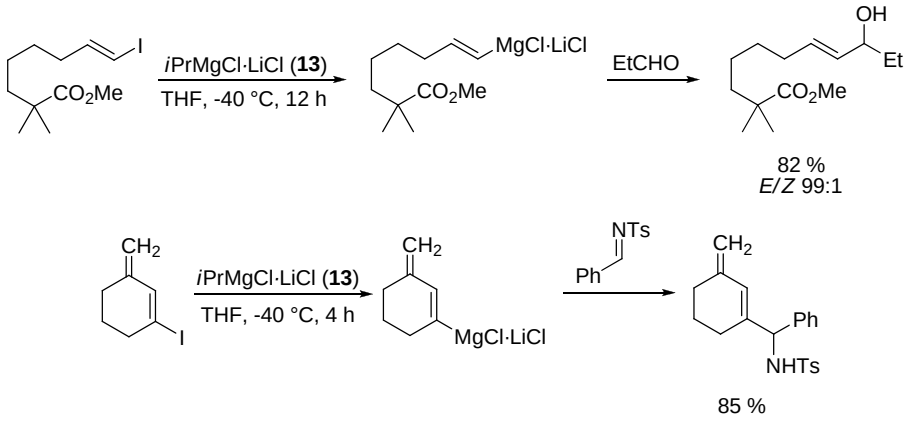
[17] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev*. **2006**, *10*, 733.
[18] For a review see: P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V.-A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.
[19] a) M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 7449; b) M. Abarbri, J. Thibonnet, L. Bérillon, F. Dehmel, M. Rottländer, P. Knochel, *J. Org. Chem*. **2000**, *65*, 4618.
[20] I. Sapountzis, W. Dohle, P. Knochel, *Chem. Commun.* **2001**, 2068.
[21] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed*. **2004**, *43*, 3333; b) A. Krasovskiy, B. Straub, P. Knochel, *Angew. Chem. Int. Ed*. **2006**, *45*, 15.

which involves the break-up of polymeric *i*PrMgCl by LiCl and formation of the magnesium-lithium ate complex **15** (Scheme 7).



Scheme 7: Rate acceleration of the bromine-magnesium exchange reaction by LiCl

The halogen-magnesium exchange reaction is also an excellent method for the stereoselective preparation of alkenylmagnesium reagents.[22] With the use of *i*PrMgCl·LiCl (**13**) it is now possible to stereoselectively prepare functionalized alkenylmagnesium reagents at low temperatures (Scheme 8).[23]



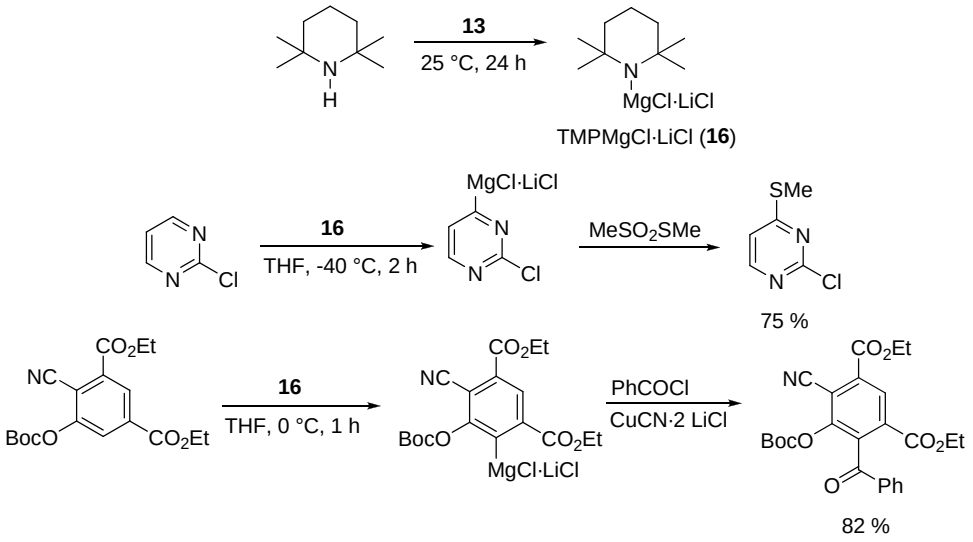
Scheme 8: Preparation of alkenylmagnesium reagents using *i*PrMgCl·LiCl (**13**)

[22] The magnesium insertion into alkenyl iodides and bromides is rarely selective: H. Lehmkuhl, *Bull. Soc. Chim. II,* **1981**, 87.
[23] a) H. Ren, A. Krasovskiy, P. Knochel, *Org. Lett.* **2004**, *6*, 4215; b) H. Ren, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2005**, 543.

2.3. Directed Deprotonation Using Magnesium Amide Bases

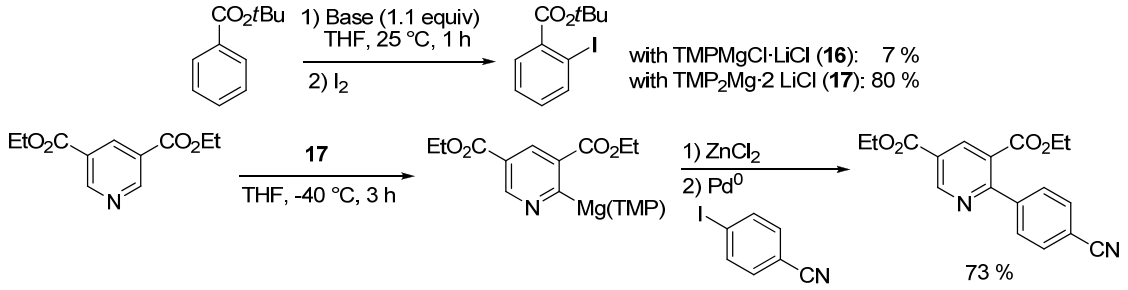
Yet another approach for the preparation of organomagnesium compounds is the directed metalation reaction using magnesium amide bases. Diethyl- and diisopropylaminomagnesium bromides were first used by *Hauser* for the self condensation of esters.[24] *Eaton* then demonstrated their synthetic utility by preparing various *ortho*-magnesiated aromatics using TMPMgBr and TMP_2Mg .[25] In 1995 *Mulzer* and coworkers used for the first time TMPMgCl for the directed metalation of various pyridine derivatives.[26] However, the limited solubility of such bases in common organic solvents as well as the requirement for an excess of the magnesium bases (2-7 equiv) to achieve high conversions has precluded their general use. Recently, *Knochel* et al. have developed the mixed lithium and magnesium amide base TMPMgCl·LiCl (**16**)[27] which has many advantages compared to earlier magnesium amide bases or lithium amide bases.[28] It is easily prepared, offers long term stability at ambient temperatures and is compatible with sensitive functional groups even in non-cryogenic conditions (Scheme 9).

[24] a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295; b) C. R. Hauser, F. C. Frostig, *J. Am. Chem. Soc.* **1949**, *71*, 1350.
[25] P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016.
[26] W. Schlecker, A. Huth, E. Ottow, J. Mulzer*, J. Org. Chem.* **1995**, *60*, 8414.
[27] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed*. **2006**, *45*, 2958; b) W. Lin, O. Baron, P. Knochel, *Org. Lett*, **2006**, *8*, 5673.
[28] a) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376; b) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489; c) M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3975; d) D. M. Hodgson, C. D. Bray, N. D. Kindon, *Org. Lett.* **2005**, *7,* 2305; e) J.-C. Plaquevent, T. Perrard, D. Cahard, *Chem. Eur. J.* **2002**, *8*, 3300; f) C.-C. Chang, M. S. Ameerunisha, *Coord. Chem. Rev.* **1999**, *189*, 199; g) J. Clayden, *Organolithiums: Selectivity for Synthesis* (Eds.: J. E. Baldwin, R. M. Williams), Elsevier, Amsterdam, **2002**; h) "The Preparation of Organolithium Reagents and Intermediates": F. Leroux, M. Schlosser, E. Zohar, I. Marek, *Chemistry of Organolithium Compounds* (Eds.: Z. Rappoport, I. Marek), Wiley, New York, **2004**, p. 435; i) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; j) G. Queguiner, F. Marsais , V. Snieckus, J. Epsztajn, *Adv. Heterocycl. Chem*. **1991**, *52*, 187.



Scheme 9: Preparation of TMPMgCl·LiCl (**16**) and its use in deprotonation reactions

In an extension from this work, the mixed magnesium and lithium bisamide $TMP_2Mg·2\ LiCl$ (**17**) was prepared by the reaction of TMPMgCl·LiCl (**16**) with TMPLi.[29] It features an improved kinetic basicity compared to TMPMgCl·LiCl (**16**) and is able to metalate even inactivated substrates such as unsubstituted benzoates (Scheme 10).

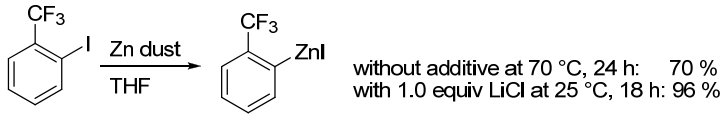


Scheme 10: Comparison of reaction rates between TMPMgCl·LiCl (**16**) and $TMP_2Mg·2\ LiCl$ (**17**)

[29] a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed*. **2007**, *46*, 7681; b) C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel, *Org. Synth*. **2009**, *86,* 374.

3. Preparation of Zinc Reagents

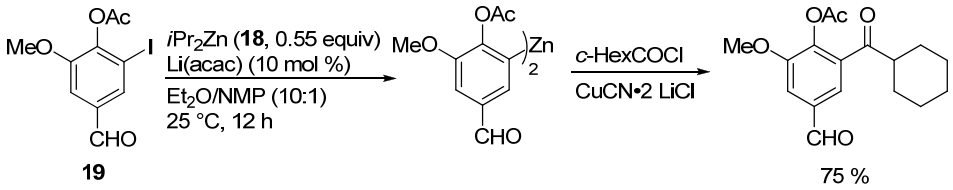
Similarly to organomagnesium compounds, multiple methods for the generation of organozinc reagents are known.[30] The classical insertion of zinc dust or foil into organic halides is the most common method for the preparation of functionalized organozinc halides. This method offers a great tolerance towards functional groups such as esters, ketones and nitriles.[31] A drawback of the classical zinc insertion is that it requires long reaction times and that expensive organic iodides have to be used almost exclusively. Improvements came with the development of highly active zinc powder (Zn*) pioneered by *Rieke*[14a, 32] and most recently in 2007 with the LiCl-mediated insertion of zinc powder by *Knochel* and co-workers.[33] They could show that the simple addition of LiCl considerably increases reaction rates for the insertion into organic iodides and bromides (Scheme 11).



Scheme 11: LiCl accelerated insertion of zinc dust to 2-iodobenzotrifluoride

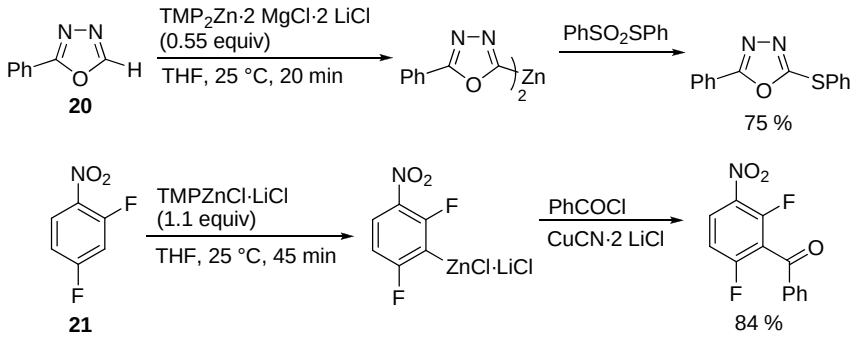
The iodine-zinc exchange is a convenient method for the preparation of diorganozinc compounds. A wide range of alkyl iodides undergo a iodine-zinc exchange using diethylzinc and catalytic amounts of a Cu(I) salt.[34] In 2004, it was shown that *i*Pr_2Zn (**18**) combined with catalytic amounts of Li(acac) enabled for the first time to perform an iodine-zinc exchange on aromatic substrates such as the functionalized aldehyde **19** (Scheme 12).[35]

[30] a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117; b) P. Knochel, J. Almena, P. Jones, *Tetrahedron* **1998**, *54*, 8275.
[31] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem*. **1988**, *53*, 2390.
[32] R. D. Rieke, P. T. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323.
[33] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358.
[34] a) M. J. Rozema, R. S. Achyutha, 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.
[35] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed*. **2004**, *43*, 1017.



Scheme 12: Li(acac) catalyzed iodine-zinc exchange reaction on the functionalized aldehyde **19**

Directed metalations offer another method for the synthesis of organozinc reagents. This interesting field was first explored by *Kondo* who developed highly active zincate bases for the directed *ortho* metalation.[36] More recently, the group of *Knochel* developed highly chemoselective and sensitive TMP-derived zinc bases for the deprotonation of functionalized aromatics and heteroaromatics.[37] These bases tolerate very sensitive heterocycles and functional groups such as the oxadiazole **20** or the nitroarene **21** (Scheme 13).



Scheme 13: TMP-derived zinc bases for the deprotonation of sensitive substrates

[36] a) Y. Kondo, H. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539; b) T. Imahori, M. Uchiyama, Y. Kondo, *Chem. Commun.* **2001**, 2450; c) P. F. H. Schwab, F. Fleischer, J. Michl, *J. Org. Chem.* **2002**, *67*, 443; d) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otami, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124,* 8514.

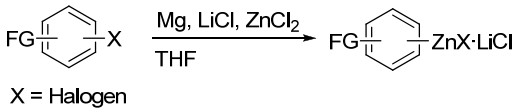
[37] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705; c) S. H. Wunderlich, P. Knochel, *Chem. Commun.* **2008**, 6387; d) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837.

4. Objectives

In a first project, the influence of LiCl towards the insertion of magnesium into aromatic bromides and chlorides will be investigated. The goal of this project is to enable the preparation of functionalized organomagnesium reagents by a simple magnesium insertion under very mild reaction conditions (Scheme 14).

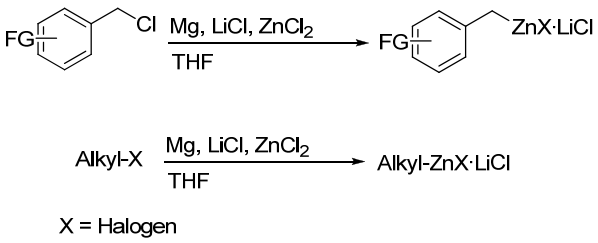
Scheme 14: Magnesium insertion in the presence of LiCl

In an extension of this method, the functionalization of very sensitive substrates such as aromatic esters and heterocycles will be explored using a magnesium insertion in the presence of $ZnCl_2$ (Scheme 15).



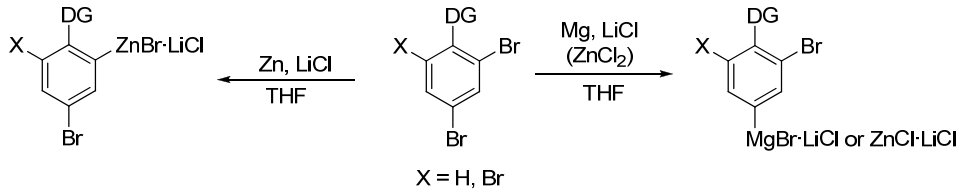
Scheme 15: Preparation of functionalized zinc reagents by a magnesium insertion in the presence of $ZnCl_2$

It is then planned to apply the above mentioned reaction sequence for the convenient and expedient preparation of highly functionalized benzylic and alkylzinc reagents (Scheme 16).



Scheme 16: Proposed synthesis of functionalized benzylic and alkylzinc reagents

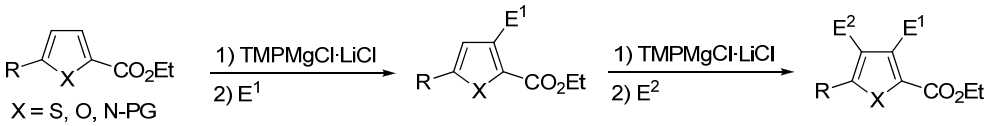
Based on the results of the regioselective Zn-insertion into polyhalogenated aromatics,[33b] the behavior of the magnesium insertion into similar substrates bearing a directing group (DG) will be ascertained (Scheme 17).



Scheme 17: Regioselective zinc and magnesium insertions

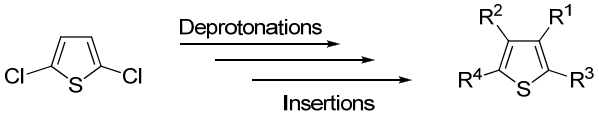
Due to the relevance of organometallic reagents for industrial applications, the preparation of organomagnesium and organozinc compounds will be studied on a larger scale using the above mentioned methodologies.

The second project will involve the use of magnesium amide bases such as TMPMgCl·LiCl (**16**) for the preparation of functionalized 5-membered ring heterocycles. Starting from substrates bearing an ester group at the 2-position the full functionalization of these heterocycles will be attempted (Scheme 18).



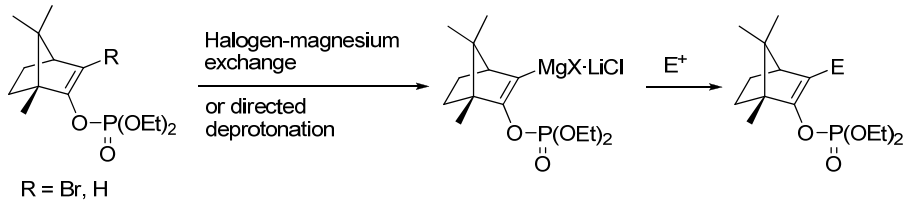
Scheme 18: Proposed full functionalization of 5-membered ring heterocycles

Furthermore, starting from readily available 2,5-dichlorothiophene, the synthesis of fully substituted thiophenes will be investigated using deprotonation and insertion reactions (Scheme 19).



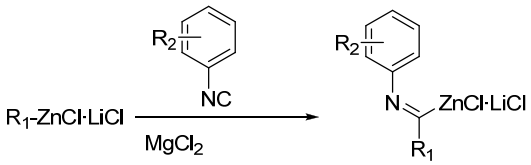
Scheme 19: Preparation of fully substituted thiophenes starting from 2,5-dichlorothiophene

A third topic will be the metalation of enol phosphates based on D(+)-camphor derivatives. Employing bromine-magnesium exchange and deprotonation reactions the functionalization of this important framework will be probed (Scheme 20).



Scheme 20: Functionalization of enol phosphates

The fourth project will be devoted to the preparation of 1-aryliminozinc reagents as acyl anion equivalents. The role of $MgCl_2$ in the α-addition of several organozinc reagents to various arylisonitriles will be explored (Scheme 21).



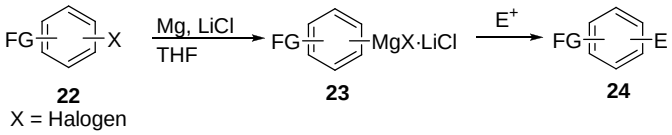
Scheme 21: $MgCl_2$ mediated α-addition of zinc reagents to isonitriles

B. RESULTS AND DISCUSSION

1. LiCl-Mediated Direct Insertion of Magnesium Into Aryl, Heteroaryl and Benzylic Halides

1.1. Magnesium Insertion in the Presence of LiCl Into Aryl and Heteroaryl Bromides

As mentioned above, organomagnesium compounds are frequently used reagents in organic synthesis. The insertion of magnesium metal into carbon-halogen bonds is the most commonly used method of preparation for these reagents. Due to the harsh reaction conditions however, the magnesium insertion cannot be used for the synthesis of functionalized magnesium reagents. Based on the observation that lithium salts such as Li(acac)[35] and LiCl greatly enhance the halogen-metal exchange reaction[21] as well as the insertion reaction of zinc dust into organic halides,[33] the influence of LiCl on the traditional magnesium insertion was investigated (Scheme 22).

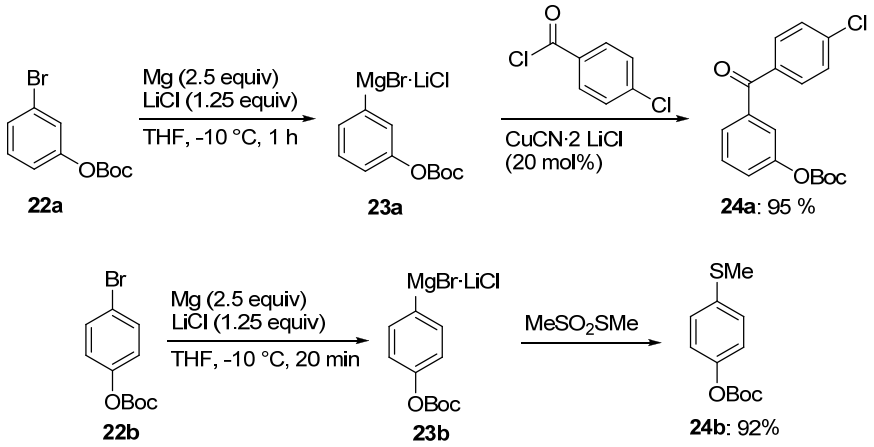


Scheme 22: LiCl-mediated preparation of functionalized magnesium reagents

The presence of LiCl (ca. 1.2 equiv) strongly facilitates the magnesium insertion into various aryl bromides. Because of these mild conditions, some additional functional groups can be present in the aromatic bromide. Thus, the Boc-protected bromophenols **22a** and **22b** reacted readily with magnesium turnings (2.5 equiv) in the presence of LiCl (1.25 equiv) at –10 °C in THF. The magnesium turnings were treated with *i*Bu_2AlH (1 mol%) which ensures a smooth reaction start.[38] In case of the *meta*-substituted aryl bromide **22a**, the insertion was completed within 60 min, whereas for the *para*-substituted substrate **22b** the insertion required only 20 min. In the absence of LiCl, no reaction was observed under these reaction conditions. The resulting magnesium reagent **23a** and **23b** reacted cleanly with electrophiles. In the presence of CuCN·2 LiCl (20 mol%),[31] an acylation with 4-chlorobenzoyl chloride (0.7 equiv) produced the ketone **24a** in 95 % yield. Alternatively, the reaction of the Grignard reagent

[38] U. Tilstam, H. Weinmann, *Org. Process Res. Dev*. **2002**, *6*, 906.

23b with $MeSO_2SMe$ (0.7 equiv) furnished the functionalized thioether **24b** in 92 % yield (Scheme 23). The Boc-group is perfectly tolerated during the organometallic reaction step.



Scheme 23: Magnesium insertion into Boc-protected bromophenols with magnesium turnings in the presence of LiCl

Similarly, a tosyloxy group is also compatible with the Mg insertion conditions. Thus, the treatment of 1-tosyloxy-3-bromobenzene (**22c**) with Mg (2.5 equiv) and LiCl (1.25 equiv) at 0 °C for 2 h provided the corresponding Grignard reagent **23c** which reacted with DMF (0.7 equiv) to give the aldehyde **24c** in 77 % yield (Table 1, entry 1). Even a sensitive pivalate protection group for the dibromophenol **22d** could be used. The magnesium reagent **23d** was regioselectively prepared within 1 h at –20 °C and underwent addition to benzaldehyde to yield the alcohol **24d** in 86 % (entry 2). Various bromochlorobenzenes such as **22e-f** undergo a selective insertion in the carbon-bromine bond leading to the magnesium reagents **23e-f**. Pd-catalyzed Negishi cross-coupling[39] reaction of the corresponding zinc reagent derived from **23e** using $Pd(dba)_2$ (3 mol%), tris(2-furyl)phosphine[40] (tfp; 6 mol%) and ethyl 4-iodobenzoate as electrophile furnished the biphenyl **24e** in 94 % yield (entry 3). A copper(I)-catalyzed acylation[31] of **23e** with pivaloyl chloride (0.7 equiv) gave the ketone **24f** in 69 % yield (entry

[39] a) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) X. Zeng, M. Quian, Q. Hu, E. Negishi, *Angew. Chem. Int. Ed.* **2004**, *43*, 2259; d) G. Manolikakes, M. A. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765; e) C. J. O'Brien, E. A. B. Kantchev, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem, Eur. J.* **2006**, *12*, 4743; f) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem, Eur. J.* **2006**, *12*, 4743; g) S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, *J. Org. Chem.* **2008**, *73*, 7380.

[40] a) V. Farina, B. Krishnan, *J. Am. Chem. Soc*. **1991**, *113*, 9585; b) V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem*. **1994**, *59*, 5905; c) I. Klement, M. Rottländer, C. E. Tucker, T. N. Majid, P. Knochel, P. Venegas, G. Cahiez, *Tetrahedron* **1996** *52*, 7201.

4). Also, the Grignard reagent **23f** derived from 1-bromo-4-chlorobenzene (**22f**) added readily to benzaldehyde giving the benzhydryl alcohol **24g** in 89 % yield (entry 5). The bromofluorobiphenyl **22g** reacts with Mg/LiCl within 30 min at 25 °C. The reaction of the resulting magnesium reagent with $MeSO_2SMe$ led to the expected thioether **24h** in 84 % yield (entry 6).

The formation of magnesium reagents containing a trifluoromethyl group is dangerous and difficult to perform especially at temperatures between 30 and 50 °C due to the exothermic reaction of magnesium with the trifluoromethyl moiety.[41] By using magnesium turnings in the presence of LiCl, Grignard reagents from *ortho*, *meta, para* or *meta,meta*-substituted benzotrifluorides **22h-k** can safely be prepared at 0 °C within 30 min. After transmetallation to the corresponding zinc reagents and Negishi cross-coupling reactions[39] with ethyl 4-iodobenzoate, the desired trifluoromethyl-substituted biphenyls **24i-l** were obtained in 83-97 % yield (entries 7-10). Remarkably, the yield remains excellent regardless of the substitution pattern. Alternatively, the Grignard reagent **23l** derived from 2-bromo-1-chloro-4-(trifluoromethyl)benzene (**22l**) could be prepared and subsequently reacted with 4-chlorobenzaldehyde which gave the alcohol **24m** in 88 % yield (entry 11).

Electron-rich bromobenzenes such as **22m-o** containing either a dimethylamino group or a methylene-dioxy group reacted also within 30 min with Mg/LiCl providing the corresponding magnesium reagents **23m-o**. Addition to an aldehyde or reaction with a sulfonothioate afforded the polyfunctionalized anilines **24n-o** in 65-91 % yield (entries 12-13). The reaction of magnesium reagents with ketones is often accompanied by several side reactions. Nevertheless, the magnesium reagent **23o** adds to the α-acidic methyl benzyl ketone in the presence of $LaCl_3 \cdot 2\ LiCl$[42] yielding the tertiary alcohol **24p** in 91 % yield (entry 14).

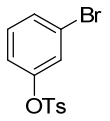
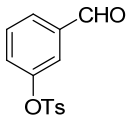
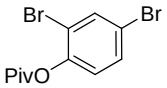
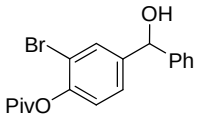
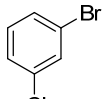
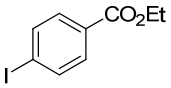
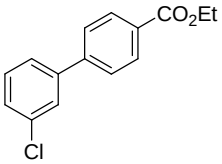
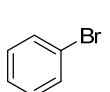
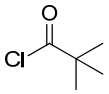
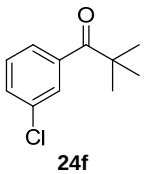
The expeditious preparation of heterocyclic organometallics is of central importance in modern pharmaceutical and agrochemical research.[43] The LiCl-mediated magnesium insertion is suitable for the preparation of polyfunctional heteroaryl magnesium reagents. Heterocyclic halides like 5-bromo-2-chloro-pyridine **22p** reacted rapidly with Mg/LiCl (0 °C, 30 min) and the resulting magnesium compound **23p** underwent a Negishi cross-coupling reaction or a

[41] J. L. Leazer, R. Cvetovich, F.-R. Tsay, U. Dolling, T. Vickery, D. Bachert, *J. Org. Chem*. **2003**, *68*, 3695.
[42] a) A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497; b) A. Metzger, A. Gavryushin, P. Knochel, *Synlett*, **2009**, 1433.
[43] A. F. Pozharskii, A. T. Soldatenkov, A. R. Katritzky, *Heterocycles in Life and Society,* Wiley, New York, **1997**, 135.

copper(I)-catalyzed allylation reaction leading to the pyridines **24q-r** in 62-84 % yield (entries 15-16).

Finally, the LiCl-mediated insertion of Mg turnings to bromobenzonitrile derivatives was examined. Despite the presence of the electronegative cyano substituent, the insertion reaction requires 35-45 min at 25 °C. The formation of the Grignard reagents **23q-s** is accompanied by reduction products in variable amounts, showing a possible limitation for this direct insertion. Nevertheless, the magnesium reagents **23q-s** could be prepared and reacted with typical electrophiles such as 1-bromo-4-(trifluoromethyl)benzene via a cross-coupling reaction using $Pd(OAc)_2$ (1 mol%) and S-Phos (2 mol%) as a catalytic system.[44] The resulting biphenyl **24s** is then obtained in 68 % yield (entry 17). Copper(I)-catalyzed acylation[31] of **23r-s** with various acid chlorides provided the expected ketones **24t-u** in 57-60 % yield (entries 18-19).

Table 1: Preparation of functionalized aromatics and heterocycles of type **24** by the reaction of magnesium in the presence of LiCl with aryl bromides of type **22** followed by quenching with an electrophile

Entry	Substrate	T [°C], *t* [min]	Electrophile	Product	Yield [%][a]
1	 **22c**	0, 120	DMF	 **24c**	77
2	 **22d**	-20, 60	PhCHO	 **24d**	86
3	 **22e**	25, 10		 **24e**	94[b]
4	 **22e**	25, 10		 **24f**	69[c]

[44] a) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685; b) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.

Table 1 (continued)

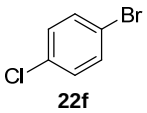
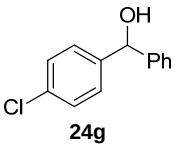
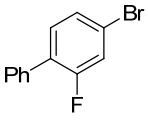
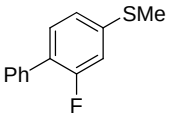
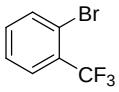
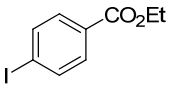
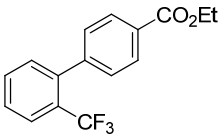
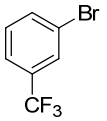
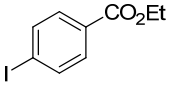
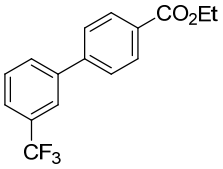
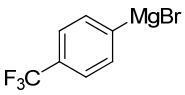
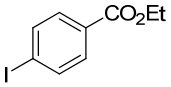
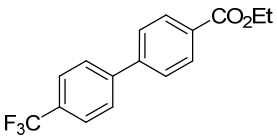
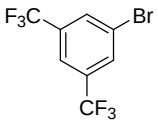
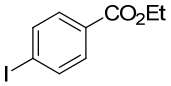
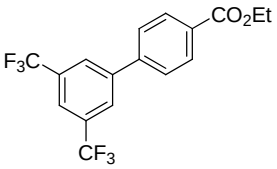
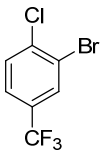
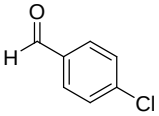
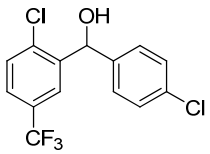
Entry	Substrate	T [°C], *t* [min]	Electrophile	Product	Yield [%][a]
5	 **22f**	25, 10	PhCHO	 **24g**	89
6	 **22g**	25, 30	$MeSO_2SMe$	 **24h**	84
7	 **22h**	0, 30		 **24i**	97[b]
8	 **22i**	0, 30		 **24j**	91[b]
9	 **22j**	0, 30		 **24k**	97[b]
10	 **22k**	0, 30		 **24l**	83[b]
11	 **22l**	0, 30		 **24m**	88

Table 1 (continued)

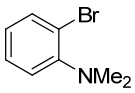
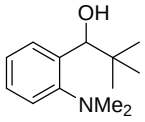
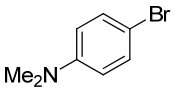
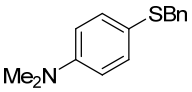
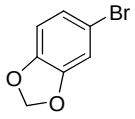
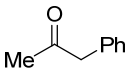
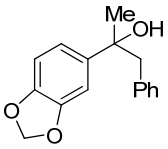
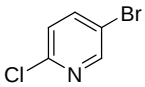
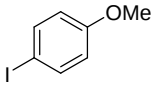
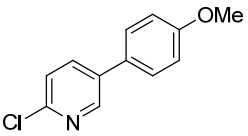
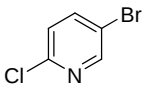
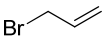
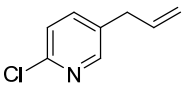
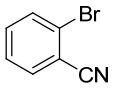
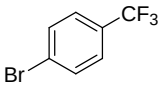
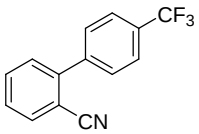
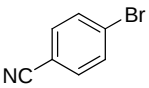
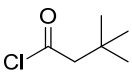
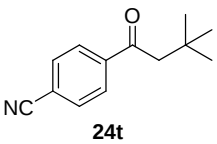
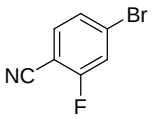
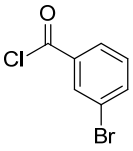
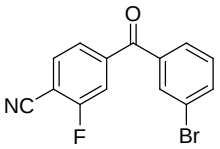
Entry	Substrate	T [°C], *t* [min]	Electrophile	Product	Yield [%][a]
12	 **22m**	25, 30		 **24n**	91
13	 **22n**	25, 30	$PhSO_2SBn$	 **24o**	65
14	 **22o**	25, 30		 **24p**	91[d]
15	 **22p**	0, 30		 **24q**	84[b]
16	 **22p**	0, 30		 **24r**	62[c]
17	 **22q**	25, 35		 **24s**	68[b]
18	 **22r**	25, 45		 **24t**	57[c]

Table 1 (continued)

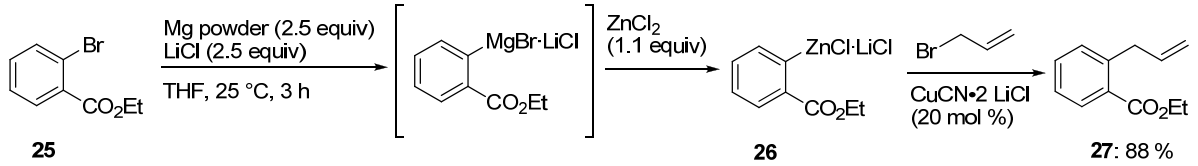
Entry	Substrate	T [°C], *t* [min]	Electrophile	Product	Yield [%][a]
19	 **22s**	25, 45		 **24u**	60[c]

[a] Yield of analytically pure product; [b] Obtained after a Pd-catalyzed cross-coupling reaction; [c] The organomagnesium reagent was transmetalated with CuCN·2 LiCl (20-100 mol%); [d] Obtained in the presence of $LaCl_3$·2 LiCl (100 mol%).

1.2. Preparation of Aryl- and Heteroarylzinc Reagents by Magnesium Insertion in the Presence of LiCl and $ZnCl_2$

The previously described LiCl-mediated magnesium insertion displays a remarkable tolerance towards functional groups but fails in the case of ester-containing substrates or highly sensitive heterocyles. Bromo-substituted aromatic esters also underwent a magnesium insertion in the presence of LiCl, but the resulting arylmagnesium compounds decomposed rapidly. However, in the presence of $ZnCl_2$ (1.1 equiv), the generated arylmagnesium species was transmetalated in situ to the corresponding stable organozinc reagent.

Thus, ethyl 2-bromobenzoate (**25**, 1.0 equiv) was readily converted to the arylzinc reagent **26** using magnesium powder (2.5 equiv), LiCl (2.5 equiv) and $ZnCl_2$ (1.1 equiv) within 3 h at 25 °C. After a Cu(I)-catalyzed reaction with allyl bromide,[31] the expected product **27** was isolated in 88 % yield (Scheme 24). Magnesium powder was used in these experiments preferentially over Mg turnings since shorter reaction times can be achieved in this way.

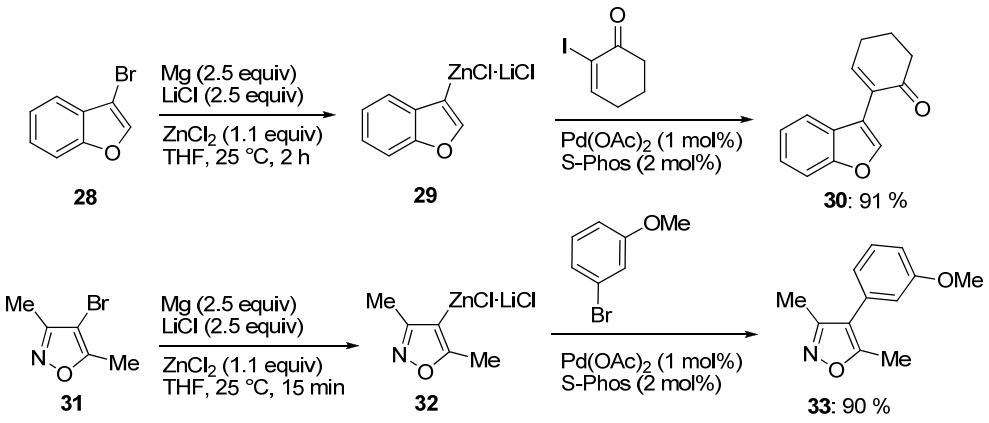


25 **26** **27**: 88 %

Scheme 24: LiCl-promoted insertion of magnesium into ethyl 2-bromobenzoate **25** and direct transmetalation with $ZnCl_2$

This method was successfully used for the preparation of various interesting zincated heterocycles. The zincation of the 3-position of benzofuran is of special interest since the bromide does not directly react with Zn and LiCl. The strong reduction potential of Mg

compared to Zn ensures, however, a rapid formation of the organometallic species. Thus, 3-bromobenzofuran (**28**) was converted by the treatment with Mg/LiCl/$ZnCl_2$ within 2 h at 25 °C into the corresponding zinc reagent **29**. A Negishi cross-coupling[39] with 2-iodocyclohexenone[45] using $Pd(OAc)_2$ (1 mol%) and S-Phos (2 mol%) as ligand provided the cyclohexenone **30** in 91 % yield. The metalation of 5-membered ring heterocycles often requires mild conditions since these metalated ring systems often have the tendency to undergo fragmentation reactions.[46] Still, their functionalization is a desirable task, because they are often found in natural products and frequently display important pharmaceutical properties. The isoxazole framework for example is found in ibotenic acid which is a strong neurotoxin.[47] 3,5-Dimethyl-4-bromoisoxazole (**31**) was smoothly converted to the corresponding zinc reagent **32** within 15 min at 25 °C by the treatment with Mg/LiCl/$ZnCl_2$. After a Negishi cross-coupling reaction with 3-bromoanisole, the arylated isoxazole **33** was isolated in 90 % yield (Scheme 25).

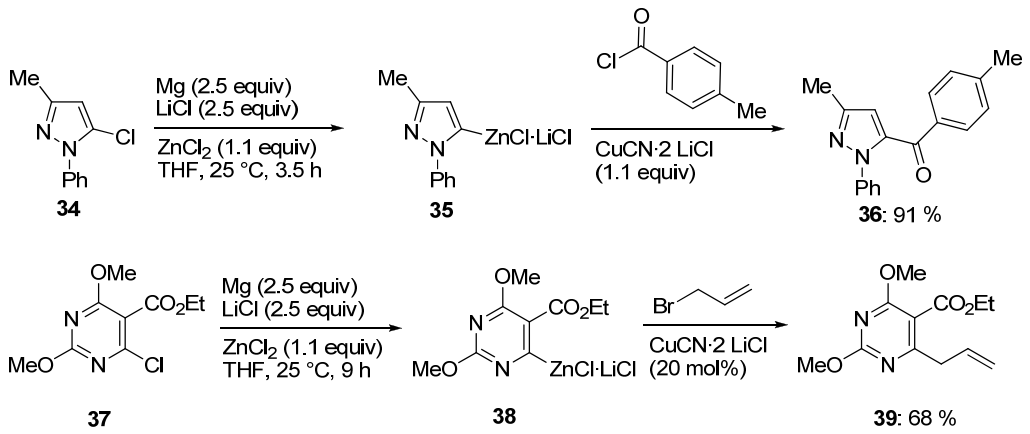


Scheme 25: Preparation and reaction of zincated heterocycles using Mg/LiCl/$ZnCl_2$

Pyrazoles are important heterocyclic structures that have attracted considerable interest in medicinal chemistry.[48] Surprisingly, in the case of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole **34** even the less reactive heterocyclic chloride could be used for the insertion to give the

[45] U. K. Tambar, T. Kano, J. F. Zepernick, B. M. Stoltz, *Tetrahedron Lett.* **2006**, *48*, 345.
[46] a) R. G. Micetich, *Can. J. Chem*. **1970**, *48*, 2006; b) A. I. Meyers, G. N. Knaus, *J. Am. Chem. Soc*. **1973**, *95*, 3408; c) G. N. Knaus, A. I. Meyers, *J. Org. Chem.* **1974**, *39*, 1189; d) R. A. Miller, M. R. Smith, B. Marcune, *J. Org. Chem.* **2005**, *70*, 9074; e) C. Hilf, F. Bosold, K. Harms, M. Marsch, G. Boche, *Chem. Ber.* **1997**, *130*, 1213; f) D. K. Anderson, J. A. Sikorski, D. B. Reitz, L. T. Pilla, *J. Heterocycl. Chem.* **1986**, *23*, 1257; g) M. R. Grimmett, B. Iddon, *Heterocycles* **1995**, *41*, 1525.
[47] P. K. Larsen, E. Nielsen, D. R. Curtis, *J. Med. Chem.* **1984**, *27*, 585.
[48] J. Elguero, P. Goya, N. Jagerovic, A. M. S. Silva, *Targets in Heterocyclic Systems* **2002**, *6*, 52.

zincated pyrazole **35**. A CuCN·2 LiCl-mediated acylation[31] with 4-chlorobenzoyl chloride provided the ketone **36** in 91 % yield. More functionalized substrates such as the chloropyrimidine **37** also reacted with Mg/LiCl/$ZnCl_2$ (25 °C, 9 h) and led after a copper(I)-catalyzed allylation to the allylated uracil derivative **39** in 68 % yield (Scheme 26).

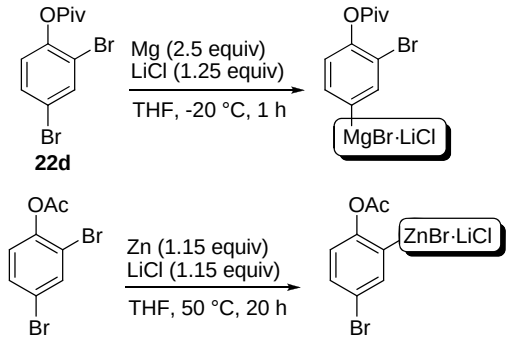


Scheme 26: Magnesium insertion into heterocyclic chlorides in the presence of LiCl and $ZnCl_2$

1.3. Regioselectivity of Zinc and Magnesium Insertions into Polybrominated Arenes

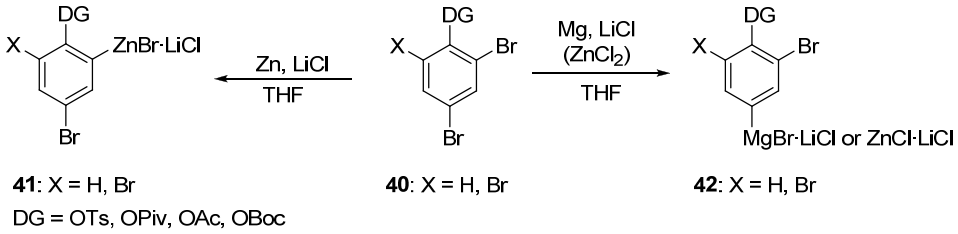
In the case of di- or tribromo-aromatics, the question of regioselective metal insertion arises. As shown above, the magnesium insertion into the 2,4-disubstituted dibromide **22d** is highly selective and only metalation in the *para*-position is observed (Table 1, entry 2). This is consistent with the results obtained by Rieke who observed the same selectivity using Rieke magnesium (Mg*).[49] This is surprising, given the fact that in 2007, *Knochel* have shown that the LiCl-mediated zinc insertion into polyhalogenated aromatics bearing a directing group (DG) was entirely *ortho*-selective (Scheme 27).[33b]

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



Scheme 27: Examples of regioselective magnesium and zinc insertions in polybrominated aromatics

Further investigations revealed that zinc reagents obtained by in situ transmetalation from the corresponding magnesium reagents with $ZnCl_2$ showed the same selectivity as the regular magnesium insertion. This means that the insertion metal is responsible for the regioselectivity and not the resulting metal species. This behavior can be explained by assuming that the zinc insertion requires a coordination to the directing group (DG) of **40**, whereas magnesium metal which has a much stronger reducing power does not need this *ortho*-coordination site and preferably inserts to the least sterically hindered carbon-bromine bond (Scheme 28).

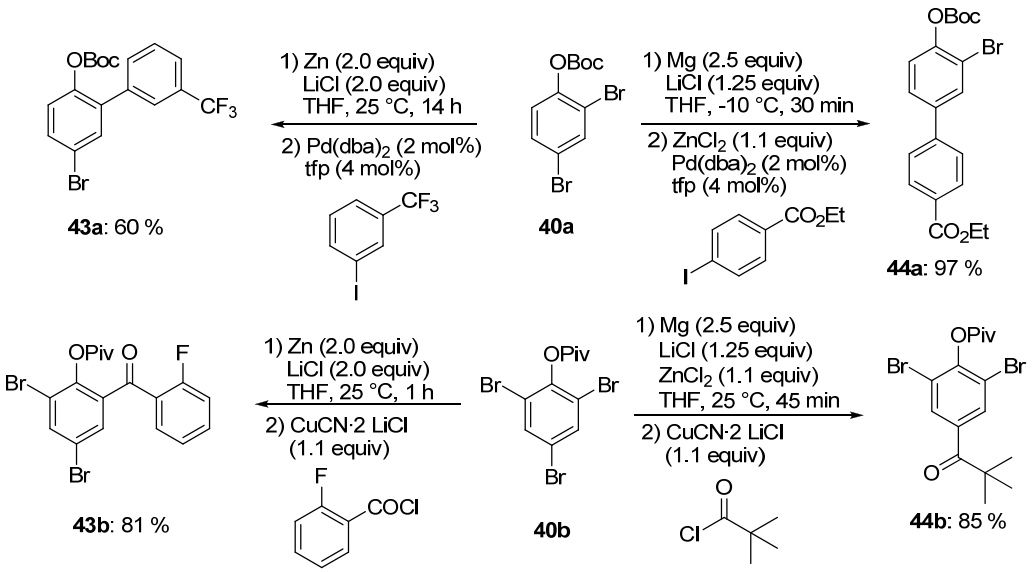


Scheme 28: Orthogonal regioselectivity pattern of magnesium and zinc insertions into polyhalogenated arenes

The reaction of *tert*-butyl 2,4-dibromophenyl carbonate (**40a**) with Zn/LiCl led only to the *ortho*-insertion zinc reagent.[50] After cross-coupling with 3-iodo-trifluoromethylbenzene the biphenyl **43a** was isolated in 60 % yield. However, by treating **40a** with Mg/LiCl (THF, – 20 °C) the insertion of magnesium occured only in *para*-position providing, after a Pd-catalyzed cross-coupling[39] with ethyl 4-iodobenzoate, the biphenyl derivative **44a** in 97 % isolated yield.

[50] All regioselective zinc insertions in this chapter were performed by M. A. Schade and are given here for the sake of completeness.

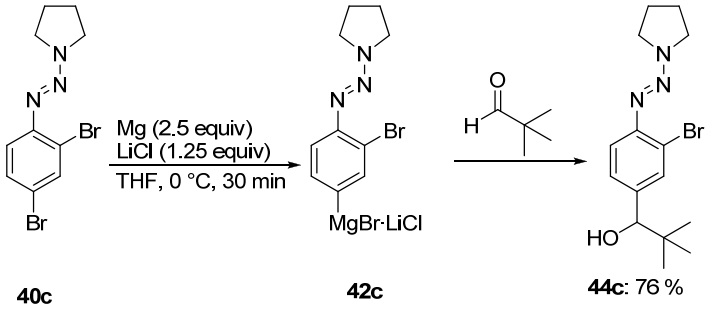
A similar reaction was observed with 2,4,6-tribromo-1-pivaloyloxybenzene (**40b**) as the insertion with Zn/LiCl provided the corresponding *ortho*-inserted zinc reagent. After transmetalation with CuCN·2 LiCl and acylation with 2-fluorobenzoyl chloride, the polyfunctional ketone **43b** was isolated in 81 % yield. Alternatively, the reaction of **40b** with $Mg/LiCl/ZnCl_2$ leads only to an insertion in *para*-position and the resulting intermediate can be converted to the ketone **44b** via a Cu(I)-mediated acylation[31] in 85 % yield (Scheme 29).



Scheme 29: *Ortho*- and *para*-functionalization of polybrominated aromatics using zinc or magnesium insertions

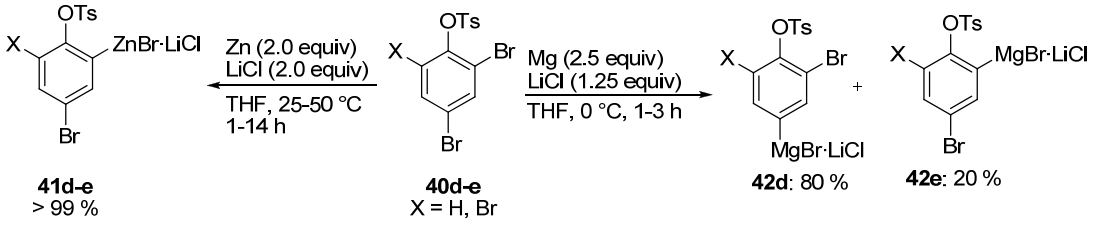
This method can also be applied advantageously to substrates bearing sensitive functionalities like triazenes, which are a synthetic equivalent of diazonium salts.[51] Thus, the treatment of the 2,4-dibromoaryltriazene derivative **40c** with Mg/LiCl (THF, 0 °C, 30 min) provided regioselectively the *para*-inserted magnesium derivative **42c**. After the addition of pivaldehyde, the functionalized benzylic alcohol **44c** was obtained in 76 % yield (Scheme 30).

[51] a) S. Braese, *Acc. Chem. Res.* **2004**, *37*, 805; b) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543; c) C.-Y. Liu, P. Knochel, *Synlett* **2007**, 2081; d) C.-Y. Liu, P. Knochel, *J. Org. Chem.* **2007**, *72*, 7106.



Scheme 30: Regioselective magnesium insertion into a functionalized triazene derivative

This regioselective insertion is triggered by several directing groups. Whereas the zinc insertion was always selective in the tested substrates, the magnesium insertion sometimes gave product mixtures. The di- and tri-brominated tosyl-protected phenols **40d-e** for example inserted zinc smoothly and selectively in the presence of LiCl. The magnesium insertion, on the other hand, produced the two possible magnesium reagents **42d-e** in 80:20 ratios (Scheme 31).[52]

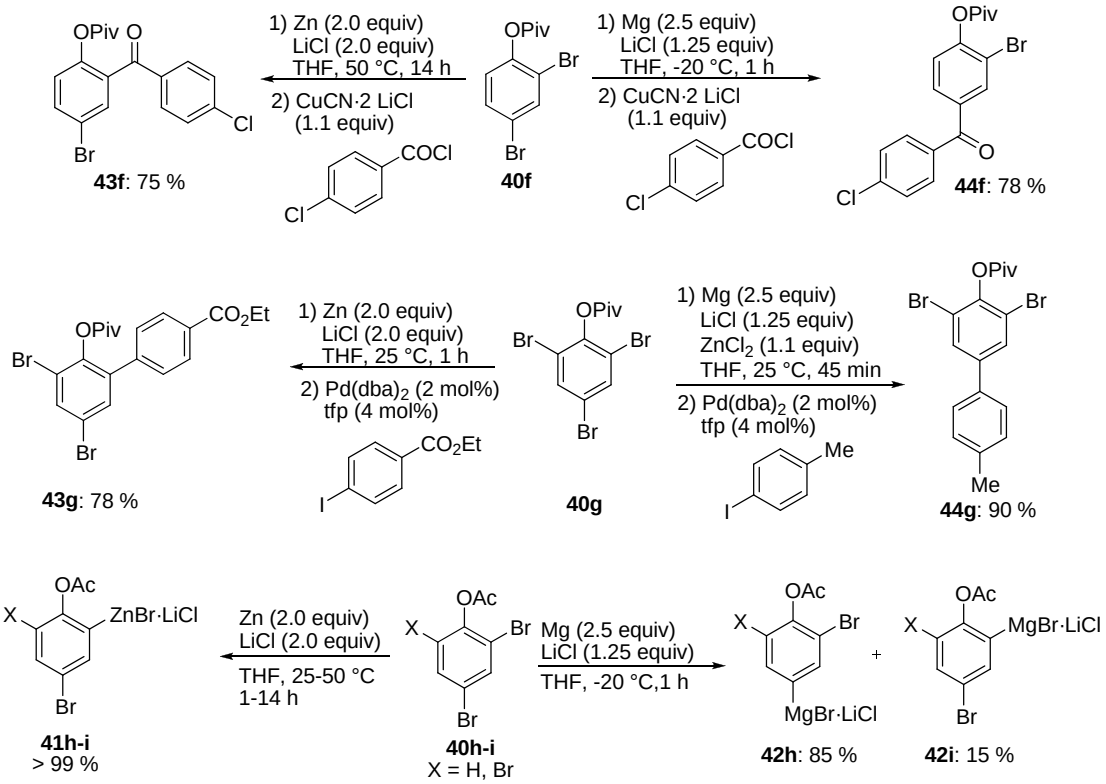


Scheme 31: Regioselectivity of the zinc and magnesium insertion into tosyl-protected polybrominated phenols

Even a slight variation of the directing group sometimes decreased the selectivity of the magnesium insertion. As described above, the pivaloyloxy directing group induces selectivity for both the zinc and the magnesium insertion. Thus, when treating the dibromopivaloyloxybenzene derivative **40f** with Zn/LiCl or Mg/LiCl the expected insertion products **41f** and **42f** were obtained. Quenching of these organometallic reagents with 4-chlorobenzoyl chloride in the presence of CuCN·2 LiCl[31] provided the benzophenone derivatives **43f** and **44f** in 75 % and 78 % yield respectively. The tribrominated derivative **40g** reacted similarly. After LiCl-mediated insertions and Pd-catalyzed cross-coupling reactions[39] with ethyl 4-iodobenzoate or 4-iodotoluene the *ortho*- or *para*-substituted biaryls **42g** and **44g** were obtained in 78-90 % yield.

[52] The selectivity and the product ratio were determined by ^{1}H-NMR measurement of the hydrolyzed magnesium or zinc reagents.

When changing the directing group to an acetyl group, the selectivity of the magnesium insertion surprisingly dropped to a ratio of 85:15 for both the di- and the tribrominated aromatics **40h-i**. Then again, the selectivity of the zinc insertion still remained excellent (Scheme 32).



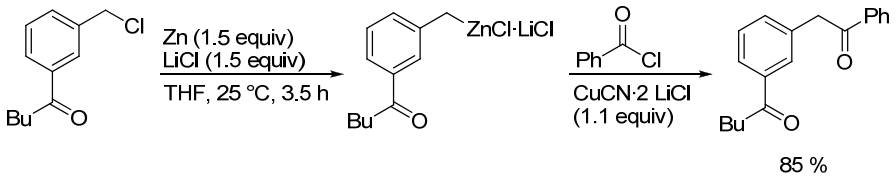
Scheme 32: Regioselective zinc and magnesium insertions using a pivalate or acetate as a directing group

1.4. Preparation of Benzylic Zinc Reagents by the Insertion of Magnesium in the Presence of LiCl and $ZnCl_2$

Benzylic organometallics are valuable synthetic intermediates. Because of the more ionic nature of the carbon-metal bond, these organometallics have especially high reactivity. Benzylic zinc compounds are of particular interest since, in contrast to benzylic lithium[53] and magnesium[54] reagents, they tolerate numerous functional groups.[55]

[53] J. N. Reed, *Science of Synthesis* **2006**, *8a*, 329.
[54] A. H. Stoll, A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 606.
[55] a) M. Gaudemar, *Bull. Soc. Chim. Fr.* **1962**, *5,* 974; b) M. A. Schade, A. Metzger, S. Hug, P. Knochel, *Chem. Commun.* **2008**, 3046; c) G. Manolikakes, M. A. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765; d) M. M. Yugushi, M. Tokuda, K. Orito, *J. Org. Chem*. **2004**, *69*, 908; d) C. Piazza, N. Millot, P.

These reagents can be prepared by the direct zinc insertion into benzylic bromides but often require elevated temperatures and polar co-solvents.[55f] In 2008, the group of *Knochel* reported the LiCl-mediated zinc insertion into commercially available benzylic chlorides.[56] This mild method allowed for the preparation of a vast variety of functionalized benzylic zinc reagents bearing functional groups such as ketones, esters or nitriles (Scheme 33).



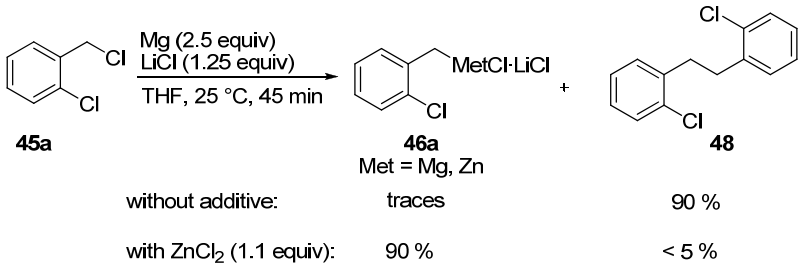
Scheme 33: LiCl-mediated zinc insertion into benzylic chlorides

The new procedure using magnesium turnings in the presence of $ZnCl_2$ and LiCl as described above, was successfully used to prepare a range of functionalized benzylic zinc reagents of type **46** starting from the corresponding benzylic chlorides **45** via an intermediate benzylic magnesium compound which was transmetalated in situ to **46**.

In a typical experiment, the addition of 2-chlorobenzyl chloride (**45a**) to magnesium turnings (2.5 equiv), LiCl (1.25 equiv) and $ZnCl_2$ (1.1 equiv) in THF led to the benzylic zinc chloride **46a** within 45 min at 25 °C as indicated by iodometric titration. Prior activation of the magnesium turnings was not required. The intermediate benzylic magnesium reagent was transmetalated in situ to the corresponding zinc organometallic. In the absence of $ZnCl_2$ the resulting magnesium reagent decomposes rapidly and a considerable amount of homo-coupling product **48** is observed. Interestingly, in the presence of $ZnCl_2$ the amount of homo-coupling formed is below 5 % (Scheme 34).

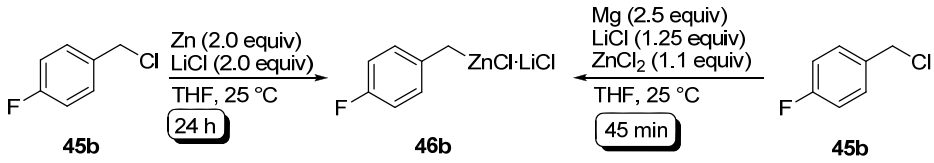
Knochel*, J. Organomet. Chem.* **2001**, *624*, 88; e) J. X. Wang, Y. Fu, Y. L. Hu, *Chin. Chem. Lett.* **2002**, *5*, 405; f) S. C. Berk, M. C. P. Yeh, N. Jeong, P. Knochel, *Organometallics* **1990**, *9*, 3053; e) T. Harada, T. Kaneko, T. Fujiwara, A. Oku*, J. Org. Chem*. **1997**, *62,* 8966.

[56] A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.



Scheme 34: Effect of $ZnCl_2$ on the magnesium insertion into benzylic halides

Although Zn in the presence of LiCl also led to a smooth reaction with various benzylic chlorides, the use of a stronger reducing metal such as magnesium allows shorter insertion times. Thus, the treatment of 4-fluorobenzyl chloride (**45b**) with Zn powder (2.0 equiv) in the presence of LiCl (2.0 equiv) provided the corresponding zinc reagent **46b** with a reaction time of 24 h at 25 °C. On the other hand, the reaction of **45b** with Mg turnings (2.5 equiv), $ZnCl_2$ (1.1 equiv) and LiCl (1.25 equiv) in THF leads to a complete conversion within 45 min (Scheme 35).



Scheme 35: Comparison of the zinc and magnesium insertion into 4-fluorobenzyl chloride

The Pd-catalyzed cross-coupling of **46b** with 4-bromobenzonitrile (0.7 equiv) provided the expected diarylmethane **47b** in 75 % yield (Table 2, entry 1). Functional groups such as an ester were also tolerated. Thus, the reaction of ethyl 3-chloromethyl benzoate (**45c**) with Mg/LiCl/$ZnCl_2$ at 25 °C for 2 h provided the corresponding zinc reagent **46c**. Its copper(I)-mediated reaction with an allylic bromide,[31] such as ethyl (2-bromomethyl)acrylate led to the diester **47c** in 67 % yield (entry 2).

Other halogen atoms on the aromatic ring are readily tolerated. 3-Trifluoromethylbenzyl chloride (**45d**) was converted to the benzylic zinc organometallic **46d** within 30 min at 25 °C. The reaction with 4-chlorobenzoyl chloride (after transmetalation with CuCN·2LiCl[31]) gave the desired ketone **47d** in 91 % yield (entry 3). Similarly, the chloro-substituted benzylic chlorides **45a** and **45e** reacted smoothly with magnesium turnings in the presence of LiCl and $ZnCl_2$ within 15 to 45 min at 25 °C. The resulting zinc reagents **46a** and **46e** were treated with

a sulfonothioate or acetyl chloride and the expected products **47a** and **47e** were obtained in 76-89 % yield (entries 4-5).

Also, electron-rich benzylic chlorides were converted to the corresponding zinc reagents without the formation of significant amounts of homo-coupling products. The methoxy-substituted benzylic zinc chlorides **46f-g** were obtained after 1 h of stirring at 25 °C. After a Cu(I)-mediated treatment with 4-bromobenzoyl chloride or 3,3-dimethylbutanoyl chloride the products **47f-g** were isolated in 81-82 % yield (entries 6-7).

Secondary benzylic chlorides can be converted to their corresponding organozinc reagents as well. Thus, 1,1-diphenylchloromethane (**45h**) reacted cleanly with Mg/LiCl/$ZnCl_2$ to the secondary benzylic zinc compound **46h** and could subsequently be reacted with an acid chloride to give the expected ketone **47h** in 81 % yield (entry 8). However, the treatment of a tertiary benzylic chloride such as cumyl chloride or trityl chloride with Mg, LiCl and $ZnCl_2$ only led to decomposition products.

Table 2: Preparation and reactions of benzylic zinc reagents **46** from the corresponding benzylic chlorides **45** using Mg, LiCl and $ZnCl_2$ at 25 °C

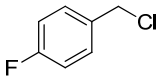
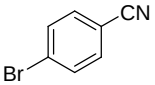
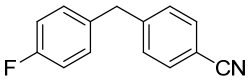
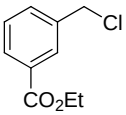
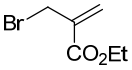
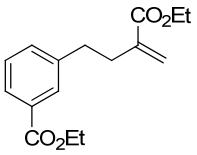
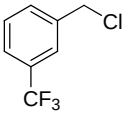
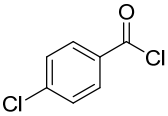
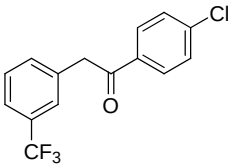
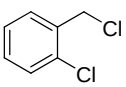
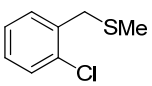
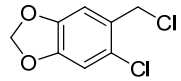
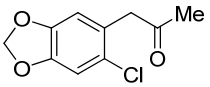
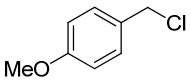
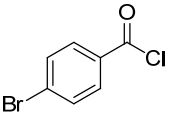
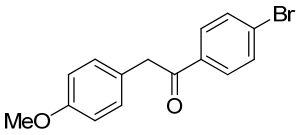
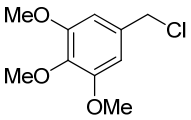
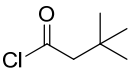
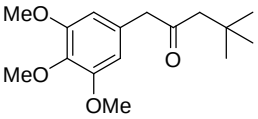
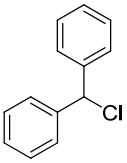
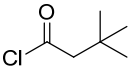
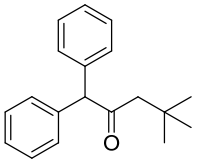
Entry	Substrate	*t* [min]	Electrophile	Product	Yield [%][a]
1	 **45b**	45		 **47b**	75[b]
2	 **45c**	120		 **47c**	67[c]
3	 **45d**	30		 **47d**	91[c]
4	 **45a**	45	$MeSO_2SMe$	 **47a**	89

Table 2 (continued)

Entry	Substrate	*t* [min]	Electrophile	Product	Yield [%][a]
5	 **45e**	15		 **47e**	76[c]
6	 **45f**	120		 **47f**	81[c]
7	 **45g**	60		 **47g**	82[c]
8	 **45h**	30		 **47h**	81[c]

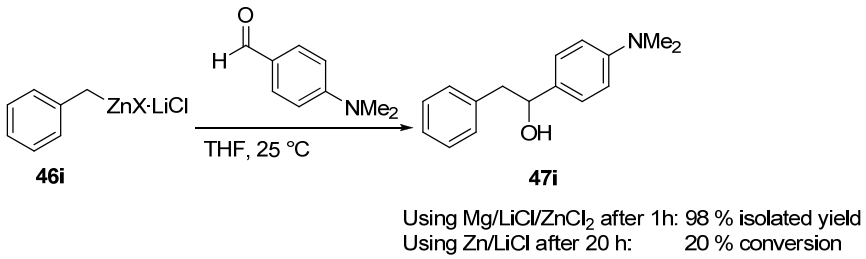
[a] Yield of analytically pure product; [b] Obtained after a Pd-catalyzed cross-coupling reaction; [c] The organozinc reagent was transmetalated with CuCN·2 LiCl (20-100 mol%).

This in situ method (Mg, LiCl, $ZnCl_2$) has two important advantages:

1. By adding just 0.5 equivalents of $ZnCl_2$ it is possible to prepare highly reactive dibenzylic zinc reagents.
2. The in situ method produces more reactive benzylic zinc reagents due to the presence of $MgCl_2$ generated during the reaction which accelerates the addition reaction to carbonyl derivatives.

Thus, the addition of benzylzinc chloride (**46i**) generated by using Zn/LiCl leads to less than 20 % conversion in the case of the addition to 4-dimethylaminobenzaldehyde after 20 h reaction time at 25 °C. In contrast, by generating benzylzinc chloride (**46i**) using

Mg/LiCl/$ZnCl_2$, the desired benzylic alcohol **47i** was obtained in 98 % isolated yield after a reaction time of only 1 h at 25 °C (Scheme 36).[57]



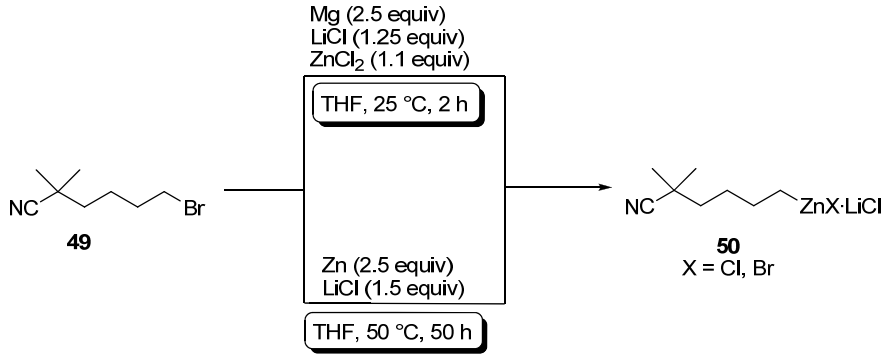
Scheme 36: Reactivity of benzylzinc chloride (**47i**) depending on its preparation method

1.5. Preparation of Alkylzinc Reagents by the Insertion of Magnesium in the Presence of LiCl and $ZnCl_2$

The insertion of zinc dust into alkyl iodides is a well known and often used reaction.[30] The corresponding alkyl bromides react much slower and require harsh reaction conditions for their formation such as *Rieke* zinc (Zn*)[32, 58] or zinc dust in the presence of LiCl at elevated temperatures.[33a] In many cases this precludes the presence of sensitive functional groups. Based on the results of the magnesium insertion in the presence of LiCl and $ZnCl_2$ into benzylic chlorides described above, these reaction conditions were also investigated using alkyl bromides as insertion substrates.

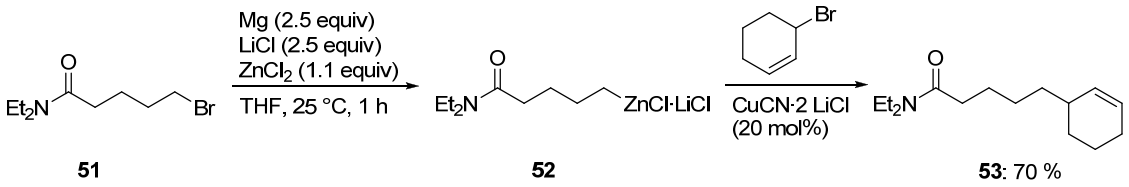
Thus, the reaction of 6-bromo-2,2-dimethylhexanenitrile (**49**) with Mg turnings (2.5 equiv) in the presence of dry $ZnCl_2$ (1.1 equiv) and dry LiCl (1.25 equiv) in THF (~ 0.28 M solution) was complete within 2.5 h at 25 °C providing the desired zinc reagent **50** in approximately 70 % yield. Alternatively, the treatment of 6-bromo-2,2-dimethylhexanenitrile (**49**) with zinc dust (2.5 equiv) in the presence of LiCl (1.25 equiv) required a reaction time of 50 h at 50 °C to reach completion[59] (Scheme 37).

[57] This experiment was performed by A. Metzger and is given here for the sake of completeness.
[58] A. Guijarro, D. M. Rosenberg, R. D. Rieke, *J. Am. Chem. Soc.* **1999**, *121*, 4155.
[59] T. D. Blümke, *Diploma Thesis*, Ludwig-Maximilians-Universität, Munich, **2009**.



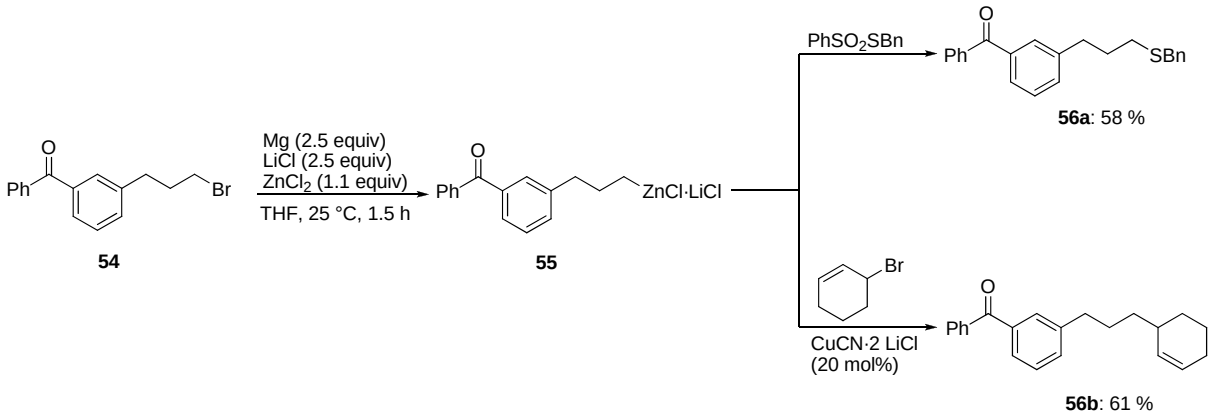
Scheme 37: Comparison of reaction rates using Mg/LiCl/$ZnCl_2$ and Zn/LiCl

The amide function is an important structural motif present in many natural products. Therefore, 5-bromo-*N*,*N*-diethylpentanamide (**51**) was chosen as a substrate. Its treatment with Mg turnings (2.5 equiv), $ZnCl_2$ (1.1 equiv) and LiCl (2.5 equiv) provided the functionalized Zn-reagent **52**, which reacted well in a Cu(I)-mediated allylation reaction[31] with 3-bromocyclohexene (0.7 equiv) yielding the unsaturated amide **53** in 70 % yield (Scheme 38).



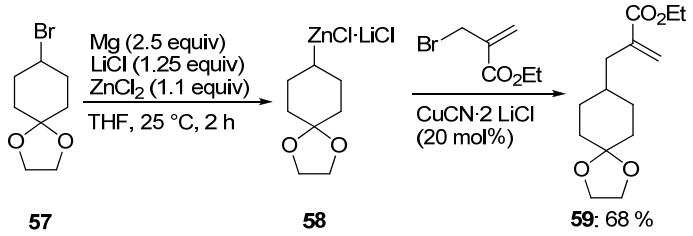
Scheme 38: Magnesium insertion in the presence of LiCl and $ZnCl_2$ into 5-bromo-*N*,*N*-diethylpentanamide

Interestingly, in the presence of an aromatic ketone, the corresponding zinc reagent **55** was obtained from [3-(3-bromopropyl)phenyl] (phenyl)methanone (**54**). It reacted cleanly with *S*-benzyl benzenesulfonothioate to afford the thioether **56a** in 58 % yield. Also, treatment of **55** with 3-bromocyclohexene (0.7 equiv) in the presence of CuCN·2 LiCl[31] (20 mol%) led to the allylated ketone **56b** in 61 % yield (Scheme 39).



Scheme 39: Preparation of alkylzinc reagent **55** bearing a keto group

The preparation of secondary alkylzinc compounds was also investigated. Thus, the reaction of the secondary cyclic alkyl bromide **57** with magnesium powder (2.5 equiv), LiCl (2.5 equiv) and $ZnCl_2$ (1.1 equiv) afforded the cyclohexylzinc reagent **58** after 2 h at 25 °C. A subsequent Cu(I)-catalyzed allylation[31] with ethyl (2-bromomethyl)acrylate led to the unsaturated ester derivative **59** in 68 % yield (Scheme 40).



Scheme 40: Magnesium insertion in the presence of LiCl and $ZnCl_2$ into the cyclohexyl derivative **59**

1.6. Larger Scale Preparations of Organomagnesium and Organozinc Reagents

The larger scale preparation of organomagnesium and organozinc reagents is an important task for industrial process chemists. One of the problems of the large scale magnesium insertion into organic halides is the often uncontrollable reaction start which is accompanied by a large evolution of heat. As the addition of LiCl allows the use of lower temperatures for the magnesium insertion, the larger scale preparation of magnesium and zinc compounds was studied for potential industrial applications.

Thus, 2-bromo-1-pivaloyloxybenzene (**22v**, 40 mmol) was treated with Mg (2.5 equiv) and LiCl (1.25 equiv) in THF at –20 °C. After slow addition and stirring for 30 min at –20 °C the conversion of the starting bromide **22v** was complete and the magnesium reagent **23v** was obtained in 93 % yield as indicated by titration (Table 3, entry 1).[60] The insertion started promptly and the internal temperature never exceeded –14 °C. Similarly, 3-bromo-1-pivaloyloxybenzene (**22w**, 40 mmol) could be inserted using the same protocol and the corresponding magnesium reagent **23w** was furnished in 86 % yield (entry 2). The Boc protecting group was also compatible with the magnesium insertion on an 86 mmol scale at –20 °C. When maintaining a slow addition rate, the internal temperature did not rise above –16 °C and led to the Boc-protected organometallic **23b** reagent in 91 % yield (entry 3).

Electron-rich or sterically demanding substrates such as 4-bromoanisole (**22x**) or bromomesitylene (**22y**) were smoothly converted to their respective magnesium reagents **23x-y** at 0 °C and a yield of 93-97 % could be obtained within 30 min, as indicated by iodometric titrations (entries 4 and 5).

As an example of a heterocyclic bromide, 3-bromopyridine (**22z**) was converted to the corresponding Grignard reagent **23z** in 90 % yield on a 100 mol scale (entry 6). When performing the reaction at ambient temperatures, the inside temperature ranged between 20 °C and 38 °C. When cooling the reaction mixture in an ice/water-bath, the inside temperature could be maintained between 1 °C and 7 °C.

The magnesium reagent of a typical alkyl bromide such as (3-bromopropyl)benzene (**60**) could conveniently be prepared at 0 °C in 91 % yield without the formation of homo-coupling by-products (entry 7).

Additionally, benzylic zinc reagents could be prepared on a larger scale. Using the system consisting of Mg/LiCl/$ZnCl_2$ 2-chlorobenzyl chloride (**45a**) was smoothly converted to the corresponding benzylic zinc reagent **46a** in excellent yield (entry 8).

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

Table 3: Scale-up experiments for the preparation of functionalized magnesium and zinc reagents

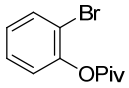
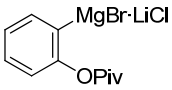
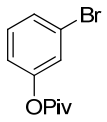
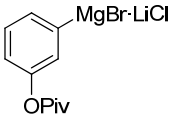
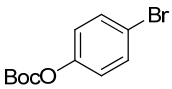
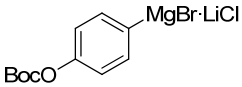
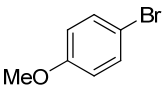
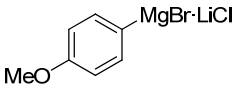
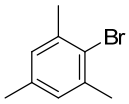
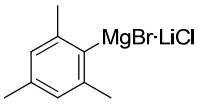
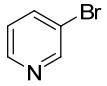
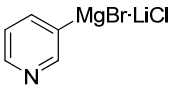
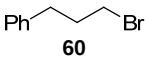
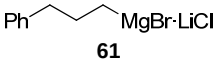
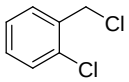
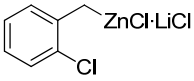
Entry	Substrate	T [°C]	Scale [mmol]	Product	Yield [%]
1	 **22v**	-20	40	 **23v**	93
2	 **22w**	-20	40	 **23w**	86
3	 **22b**	-20	86	 **23b**	91
4	 **22x**	0	50	 **23x**	97
5	 **22y**	0	50	 **23y**	93
6	 **22z**	0	100	 **23z**	90
7	 **60**	0	50	 **61**	91

Table 3 (continued)

Entry	Substrate	T [°C]	Scale [mmol]	Product	Yield [%]
8	 **45a**	0	50	 **46a**	90

In order to show that the reactivity of magnesium reagents prepared on a larger scale was equal to the smaller scale experiments, 10 mmol aliquots of selected Grignard reagents were reacted with electrophiles. Addition of freshly titrated 2-pivaloyloxyphenylmagnesium bromide (**22v**) to a solution of DMF (1.2 equiv) in THF at –20 °C furnished the benzaldehyde **24v** in 83 % yield (Table 4, entry 1). Similarly, the Grignard reagent derived from Boc-protected 4-bromophenol **23b** could be reacted with 4-chlorobenzaldehyde to give the diarylmethane **24w** in 90 % yield (entry 2). A 10 mmol aliquot of the heterocyclic 3-pyridylmagnesium bromide (**23z**) was added to anisaldehyde and the resulting benzylic alcohol **24x** could be isolated in 94 % yield (entry 3).

Finally, the magnesium compounds prepared in a large scale from 4-bromoanisole and bromomesitylene **23x-y** showed the same reactivity as their smaller scale counterparts. Their reaction with 4-isopropylbenzaldehyde or a Cu(I)-catalyzed acylation[31] with 4-anisoyl chloride afforded the expected products **24y-z** in 89-96 % yield (entries 4-5).

Table 4: Reactions of functionalized magnesium reagents of type **23** prepared on a big scale with typical electrophiles

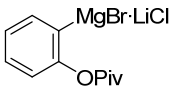
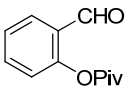
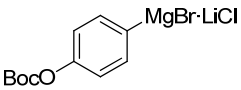
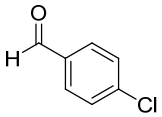
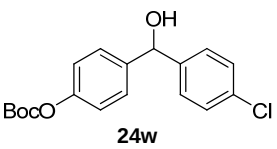
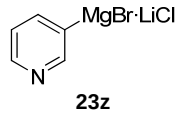
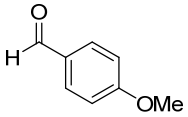
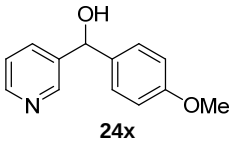
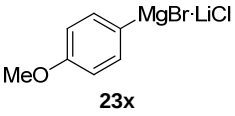
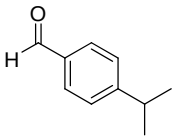
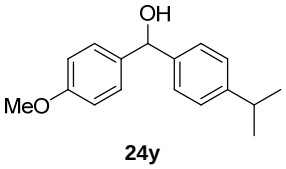
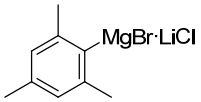
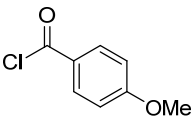
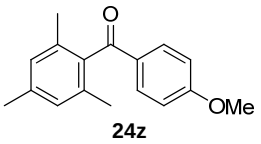
Entry	Magnesium Reagent	T [°C]	Electrophile	Product	Yield [%][a]
1	 **23v**	-20	DMF	 **24v**	83
2	 **23b**	-20		 **24w**	90

Table 4 (continued)

Entry	Magnesium Reagent	T [°C]	Electrophile	Product	Yield [%][a]
3	 **23z**	0		 **24x**	94
4	 **23x**	0		 **24y**	96
5	 **23y**	0		 **24z**	89[b]

[a] Yield of analytically pure product; [b] The organomagnesium reagent was transmetalated with CuCN·2 LiCl (20 mol%).

2. Regio- and Chemoselective Synthesis of Functionalized 5-Membered-Ring Heterocycles

2.1. Preparation of Polyfunctional Furan, Thiophene, Indole and Pyrrole Derivatives

The quest for new biologically active molecules is probably the most important task in synthetic organic chemistry today. As these molecules are mostly manufactured in chemical laboratories, the development of new methods for their synthesis is an incredibly important mission. Heteroatoms play a large role in most biologically active compounds because of their ability to interact with enzymatic centers or receptors through H-bonding or their lone electron pairs. Important classes of molecules bearing heteroatoms are heterocycles, which are found in many natural products. Six of seven of America's top-selling drugs in the year 2008 all included at least one heterocycle, and therefore their selective synthesis and functionalization is of great chemical, biological and medicinal interest.[61]

Directed lithiations of 5-membered ring heterocycles are well known reactions, but they often require low temperatures or have a poor functional group tolerance.[62] Magnesiations or zincations using amide bases or ate-complexes are compatible with some functional groups, but can only be performed at the activated 2- or 5-positions.[63]

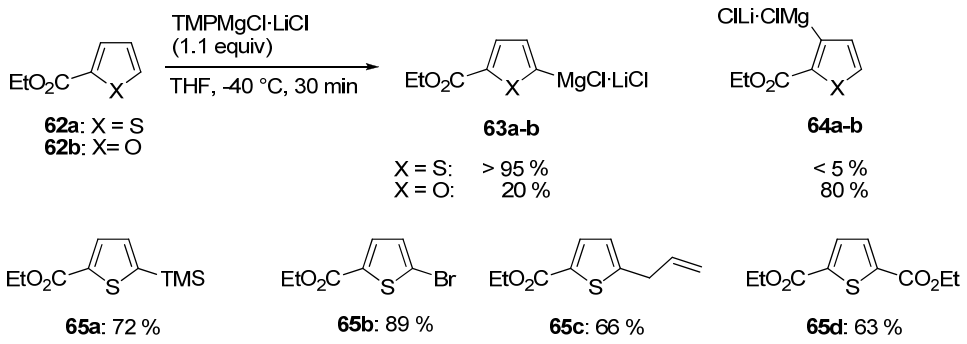
With the recent development of new and mild magnesium amide bases such as TMPMgCl·LiCl (**16**)[27] the metalation of functionalized furans and thiophenes was investigated.

In first experiments, the regioselectivity of the deprotonation of ethyl thiophene-2- and furan-2-caboxylate (**62a-b**) with TMPMgCl·LiCl (**16**) was determined. Thus, ethyl thiophene-2-carboxylate **62a** was treated with TMPMgCl·LiCl (**16**, 1.1 equiv) at –40 °C. Complete and selective metalation in the 5-position was achieved within 30 min and the resulting

[61] a) M. S. Butler, *J. Nat. Prod.* **2004**, *67*, 2141; b) E. Lamb, *Pharmacy Times,* **2008**, 20.
[62] a) A. J. Carpenter, D. J. Chadwick, *J. Org. Chem.* **1985**, *50*, 4362. b) E. G. Doat, V. Snieckus, *Tetrahedron Lett*. **1985**, *26*, 1149.
[63] a) M. Shilai, Y. Kondo, T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, **2001**, 442; b) O. Bayh, H. Awad, F. Mongin, C. Hoarau, F. Trécourt, G. Quéguiner, F. Marsais, F. Blanco, B. Abarca, R. Ballesteros, *Tetrahedron*, **2005**, *61*, 4779; c) J.-M. L'Helgoual'ch, A. Seggio, F. Chevallier, M. Yonehara, E. Jeanneau, M. Ushiyama, F. Mongin, *J. Org. Chem.* **1998**, *73*, 177; d) F. Mongin, A. Bucher, J. P. Bazureau, O. Bayh, H. Awad, F. Trécourt, *Tetrahedron Lett*. **2005**, *46*, 7989.

magnesium reagent **63a** was reacted with TMS-CN furnishing the silylated thiophene **65a** in 72 % yield. Additionally, the magnesium compound **63a** could be reacted with 1,2-dibromo-1,1,2,2-tetrachloroethane or with allyl bromide in a copper-(I)-catalyzed allylation[31] reaction, to give the expected products **65b-c** in 66-89 % yield. The diester **65d** could be prepared in 63 % yield by the reaction of **63a** with ethyl cyanoformate (Scheme 41).

The reaction of ethyl furan-2-carboxylate **62b** with TMPMgCl·LiCl (**16**) did not lead to a selective metalation. Contrary to the thiophene analogue, deprotonation is favored in the 3-position but a product ratio of 80:20 is obtained (Scheme 41).



Scheme 41: Regioselectivity of the deprotonation of ethyl 2-thiophene- and furancarboxylate using TMPMgCl·LiCl

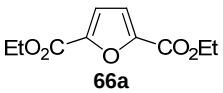
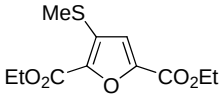
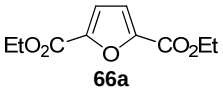
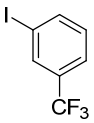
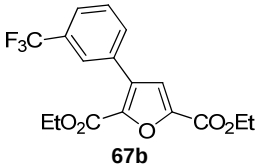
A further functionalization of 5-membered ring heterocycles could be achieved. Using TMPMgCl·LiCl (**16**), 2,5-disubstituted furans and thiophenes could be metalated in the 3-position for the first time. Thus, treatment of the diester **66a** with TMPMgCl·LiCl (**16**, 1.1 equiv) at –78 °C furnished the corresponding magnesium reagent within 10 min. The subsequent reaction with $MeSO_2SMe$ afforded the thioether **67a** in 93 % yield (Table 5, entry 1). After a transmetalation with $ZnCl_2$ and a subsequent Pd-catalyzed cross-coupling reaction with 3-iodobenzotrifluoride the arylated furan **67b** could be obtained in 79 % yield (entry 2). Similarly, a copper(I)-catalyzed[31] reaction with an acid chloride yielded the expected ketone **67c** in 85 % (entry 3) Furthermore, the addition of TsCN to this magnesium reagent produced the nitrile **67d** in 66 % yield (entry 4). The corresponding thiophene derivative **67e** could also be prepared in 58 % yield by deprotonation of the diester **65d** with TMPMgCl·LiCl (–60 °C, 30 min) and quenching with TsCN (entry 5).

The furan **66b** and the thiophene **65a** bearing a trimethylsilyl group in the 5-position could both be selectively metalated in the 3-position at –30 °C within 1 h. Reaction of the furan-

derived magnesium reagent with hexachloroethane furnished the chlorinated product **67f** in 48 % yield (entry 6). Both magnesium reagents could be reacted with TsCN and the polyfunctional heterocycles **65g-h** were obtained in 52-69 % yield (entries 7-8). The corresponding thiophene derivative was reacted in a Cu(I)-catalyzed allylation[31] reaction yielding the tri-substituted thiophene **67i** in 54 % (entry 9).

Treatment of the brominated furan derivative **66c** with TMPMgCl·LiCl (**16**) at –78 °C leads to the magnesiated furan within 30 min. After copper-catalyzed acylation reactions with benzoyl chloride the expected ketone (**67j**) could be isolated in 75% yield (entries 10). Additionally, the reaction with benzenesulfonyl chloride or TsCN led to the expected products **67k-l** in 59-63 % yield (entries 11-12). After a transmetalation with $ZnCl_2$ the resulting zinc reagent could be used in a Negishi cross-coupling reaction[39] with ethyl 4-iodobenzoate and the diester **67m** was obtained in 86 % yield (entry 13). Treatment of the zinc reagent with chloranil as an oxidizing agent[64] afforded the corresponding homo-coupling product **67n** in 80 % yield (entry 14). The magnesium reagent derived from the brominated thiophene **65b** was also obtained by deprotonation with TMPMgCl·LiCl (**16**, 1.1 equiv, -50 °C, 30 min). Subsequent reactions with a sulfonothioate or TsCN gave the 2,3,5-trisubstituted thiophenes **67o-p** in 50-68 % yield (entries 15-16).

Table 5: Preparation of 2,3,5-trisubstituted furans and thiophenes

Entry	Substrate	T [°C], *t* [min]	Electrophile	Product	Yield [%][a]
1	 **66a**	-78, 10	$MeSO_2SMe$	 **67a**	93
2	 **66a**	-78, 10		 **67b**	79[b]

[64] A. Krasovskiy, A. Tishkov, V. del Amo, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 5010.

Table 5 (continued)

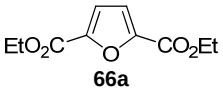
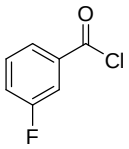
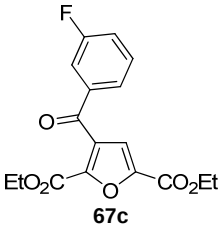
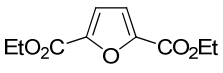
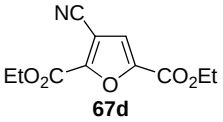
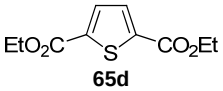
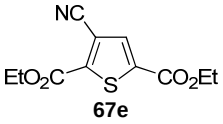
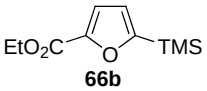
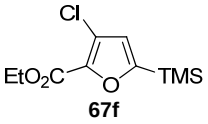
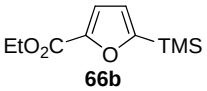
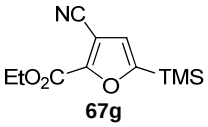
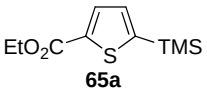
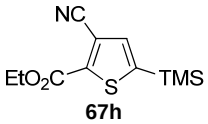
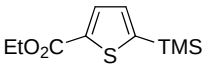
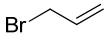
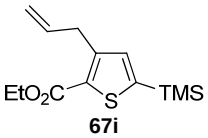
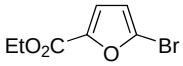
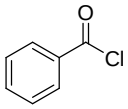
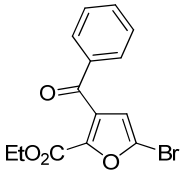
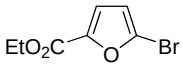
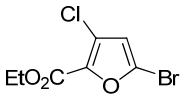
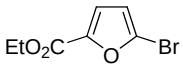
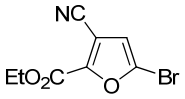
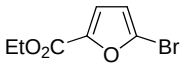
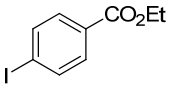
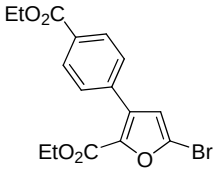
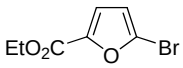
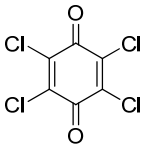
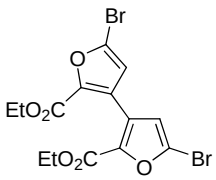
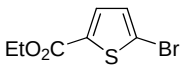
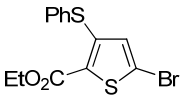
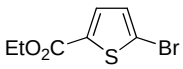
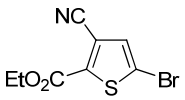
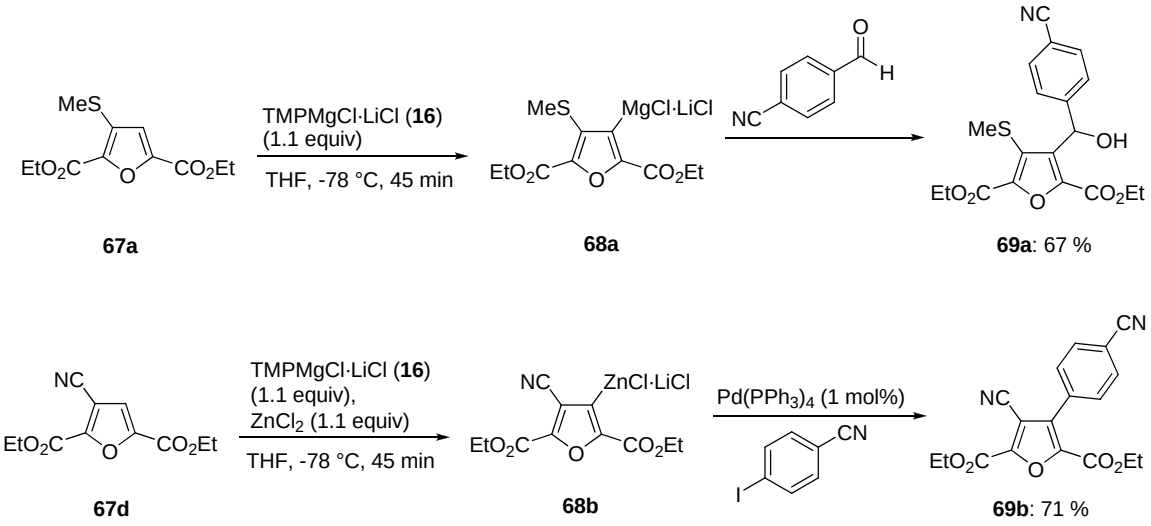
Entry	Substrate	T [°C], *t* [min]	Electrophile	Product	Yield [%][a]
3	 **66a**	-78, 10		 **67c**	85[c]
4	 **66a**	-78, 10	TsCN	 **67d**	66
5	 **65d**	-60, 30	TsCN	 **67e**	58
6	 **66b**	-30, 60	C_2Cl_6	 **67f**	48
7	 **66b**	-30, 60	TsCN	 **67g**	52
8	 **65a**	-35, 60	TsCN	 **67h**	69
9	 **65a**	-35, 60		 **67i**	54[c]

Table 5 (continued)

Entry	Substrate	T [°C], *t* [min]	Electrophile	Product	Yield [%][a]
10	 **66c**	-78, 30		 **67j**	75[c]
11	 **66c**	-78, 30	$PhSO_2Cl$	 **67k**	59
12	 **66c**	-78, 30	TsCN	 **67l**	63
13	 **66c**	-78, 30		 **67m**	86[b]
14	 **66c**	-78, 30		 **67n**	80[d]
15	 **65b**	-50, 30	$PhSO_2SPh$	 **67o**	68
16	 **65b**	-50, 30	TsCN	 **67p**	50

[a] Yield of analytically pure product; [b] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv) and a Pd-catalyzed cross-coupling reaction; [c] The organomagnesium reagent was transmetalated with CuCN·2 LiCl (20-100 mol%); [d] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv).

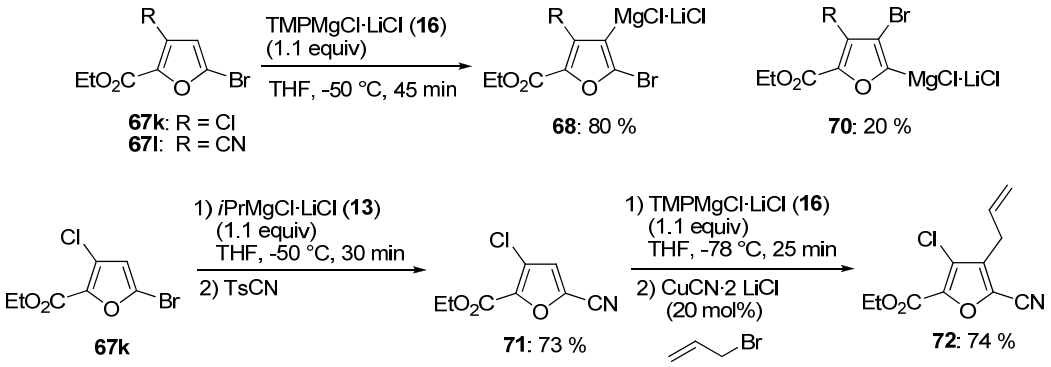
A further functionalization of the 4-position could also be achieved. Thus, the thiomethyl-substituted furan **67a** could be deprotonated using TMPMgCl·LiCl (**16**, 1.1 equiv) within 45 min at –78 °C. A subsequent reaction with 4-cyanobenzaldehyde furnished the alcohol **69a** in 67 % yield. On the other hand, when metalating the nitrile **67d** with TMPMgCl·LiCl (1.1 equiv) the resulting magnesium reagent was not stable even at –78 °C. However, when performing the reaction in the presence of 1.1 equiv of $ZnCl_2$ the magnesium reagent could be transmetalated in situ to the more stable zinc compound **68b**. After a Pd-catalyzed cross-coupling reaction[39] with 4-iodobenzonitrile the fully substituted furan **69b** was isolated in 71 % yield (Scheme 42).



Scheme 42: Preparation of fully substituted furan derivatives

When trying to deprotonate the 5-brominated furans **67k-l** two metalation products were formed. The 4-metalated products of type **68** partly rearranged in a halogen dance reaction and gave the two magnesiated furans of type **68** and **70** in 80:20 ratios.[65] This problem can be avoided when first functionalizing the 5-position. Thus, the brominated furan **67k** was subjected to a halogen-magnesium exchange reaction with *i*PrMgCl·LiCl (**13**, 1.1 equiv) and the magnesium reagent was obtained after 30 min at –50 °C. Reaction with TsCN then afforded the 2,3,5-trisubstituted furan **71** in 73 % yield. Subsequent deprotonation proceeds smoothly (**16**, –78 °C, 25 min) and the allylated product **72** could be isolated in 74 % yield after a Cu(I)-catalyzed reaction with allyl bromide (Scheme 43).

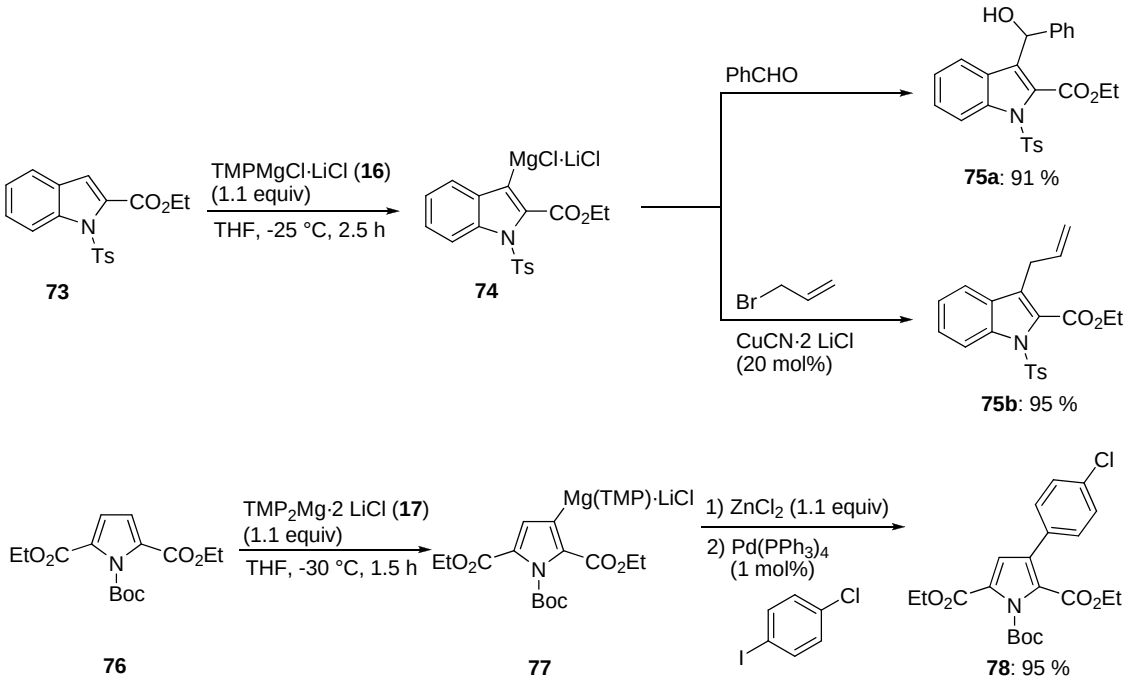
[65] a) J. Fröhlich, *Prog. Het. Chem.* **1994**, *6*, 1. b) J. Fröhlich, *Bull. Soc. Chim. Belg*. **1996**, *105*, 615.



Scheme 43: Halogen dance and functionalization of brominated furans of type **67**

Nitrogen-containing heterocycles are an important substance class in pharmaceutical and medicinal chemistry. The tosyl-protected indole **73**, bearing an ester group in the 2-position could be metalated selectively in the 3-position using TMPMgCl·LiCl (**16**, 1.1 equiv, –25 °C, 2.5 h). Subsequent reaction with benzaldehyde furnished the benzhydryl alcohol **75a** in 91 % yield. The magnesium reagent **74** could also be trapped with allyl bromide in a Cu(I)-catalyzed reaction,[31] to yield the allylated indole **75b** in 95 %.

The Boc-protected pyrrole **76** could not be metalated with TMPMgCl·LiCl (**16**). At temperatures below 0 °C no reaction was observed, and above 0 °C the resulting magnesium reagent decomposed rapidely. Using the more reactive base $TMP_2Mg·2$ LiCl (**17**)[29] **76** could be deprotonated at –30 °C within 1.5 h. A Negishi cross-coupling reaction[39] using $Pd(PPh_3)_4$ and 4-chloroiodobenzene then provided the arylated pyrrole **78** in 95 % yield (Scheme 44).



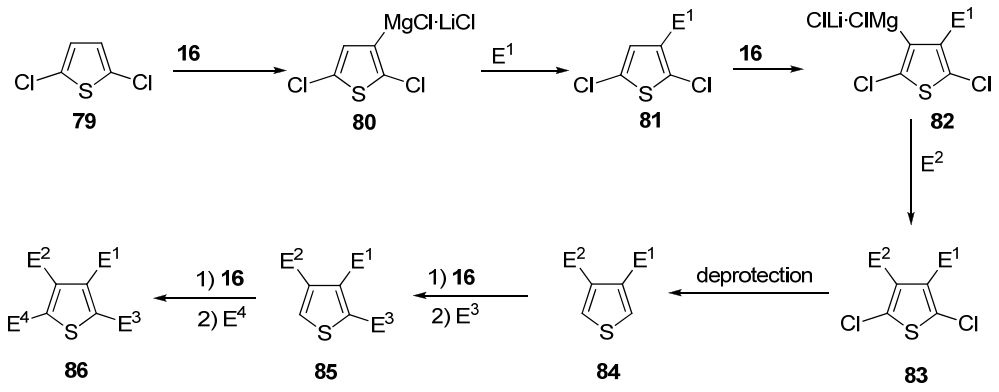
Scheme 44: Deprotonation and functionalization of indole and pyrrole derivatives

2.2. Regio- and Chemoselective Synthesis of Fully Substituted Thiophenes

The thiophene moiety is an important building block for various new materials[66] and modern drug design.[67] Therefore, the selective functionalization of every position of the thiophene ring is of particular interest. Based upon the results of the functionalization of 5-membered ring heterocycles mentioned above, a general reaction scheme was developed for the selective preparation of fully substituted thiophenes (Scheme 45).

[66] a) I. Osaka, R. D. McCullough, *Acc. Chem. Res*. **2008**, *41*, 1202; b) I. F. Perepichka, D. F. Perepichka, H. Meng, F. Wudl, F. *Adv. Mater.* **2005**, *17*, 2281; c) R. D. McCullough, *Adv. Mater.* **1998**, *10*, 93. d) M. Sebastian, M. Hissler, C. Fave, J. Rault-Berthelot, C. Odin, R. Réau, *Angew. Chem. Int. Ed.* **2006**, *45*, 6152.

[67] a) J. Swanston, "Thiophenes" in *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, **2006;** b) J. B. Sperry, D. L. Wright, *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723; For recent examples see: c) R. Romagnoli, P. G. Baraldi, M. D. Carrion, C. L. Cara, O. Cruz-Lopez, M. A. Iaconinoto, D. Preti, J. C. Shryock, A. R. Moorman, F. Vincentzi, K. Varani, P. A. Borea, *J. Med. Chem.* **2008**, *51*, 5875. d) L. Aurelio, H. Figler, B. L. Flynn, J. Linden, P. J. Scammells, *Bioorg. Med. Chem.* **2008**, *16*, 1319.



Scheme 45: Reaction sequence for the synthesis of fully substituted thiophenes of type **86**

Thus, it was envisioned to start from 2,5-dichlorothiophene **79**. The use of chlorine atoms as protecting groups was chosen because of the following requirements:

- It needed to possess directing ability in order to enable the metalation in the 3- and 4-position
- It needed to be easily cleft to give access to the 2- and 5-positions

After deprotonation and functionalization of the 3- and 4-positions using TMPMgCl·LiCl and subsequent quenching with an electrophile (E^1 and E^2) both Cl atoms are cleft, furnishing 3,4-disubstituted thiophenes of type **84**. Selective magnesation and quenching with electrophiles (E^3 and E^4) on the remaining 2- and 5-position then lead to fully substituted thiophenes of type **86**.

The use of chlorine atoms as a protecting group for the 2- and 5-position turned out to be the method of choice. They have a suitable directing ability and can easily be cleft reductively.

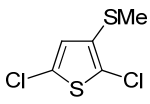
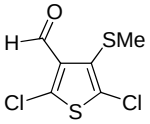
Thus, the reaction of 2,5-dichlorothiophene (**79**) with TMPMgCl·LiCl (**16**; 1.1 equiv, 25 °C, 30 min) led to the corresponding 3-magnesiated thiophene **80**, which could be trapped with $PhSO_2SMe$ giving the thiomethylated compound **81a** in 92 % yield. The subsequent deprotonation of **81a** using TMPMgCl·LiCl (**16**) also proceeded smoothly (–10 °C, 30 min) and the resulting magnesiated intermediate was reacted with DMF, yielding the aldehyde **83a** in 95 % (Table 6, entry 1).

Treatment of the magnesiated intermediate **80** with ethyl cyanoformate yielded the ester **81b** in 76% yield. A subsequent deprotonation of **81b**, proceeded smoothly (–30 °C, 30 min) and the expected products **83b-d** were isolated in 76-95 % yield after a Pd-catalyzed cross-

coupling reaction,[39] a reaction with an acid cyanide[68] or a Cu(I)-catalyzed allylation[31] (entries 2-4). Similarly, the 3-magnesiated thiophene **80** reacted directly with Boc_2O affording the ester **81e** in 82 % yield. Subsequent metalation and again trapping with Boc_2O provided the diester **83e** in 79 % yield (entry 5). Ketones are sensitive functional groups and often react with polar organometallics. However, the Cu(I)-catalyzed quenching of the 3-thienylmagnesium reagent **80** with acid chlorides[31] afforded the ketones **81f** and **81g**. These ketones readily underwent metalation using **16** (–78 to –50 °C, 30 to 45 min) and, after Negishi cross-coupling reactions with 4-iodobenzonitrile or 4-chloroiodobenzene, the arylated products **83f** and **83g** were obtained in 77-86 % yield (entries 6-7). Similarly, a cyano function is tolerated as well. Thus, the treatment of the magnesium reagent **80** with TsCN furnished the nitrile **81h** in 73 % yield. After a subsequent metalation of **81h** (–30 °C, 15 min) and trapping of the resulting magnesium reagent with DMF, the functionalized aldehyde **83h** was obtained in 86 % yield (entry 8).

The synthesis of 3,4-substituted chlorothiophenes of type **5** is also possible using the crude intermediate products of type **81**. Thus, the reaction of the magnesium compound **80** with ethyl cyanoformate gave the corresponding 3-substituted dichlorothiophene. After an aqueous workup, the crude mixture was again treated with TMPMgCl·LiCl (**1**; –30 °C, 30 min) and quenched with $NCCO_2Et$, yielding the diester **83i** in 87% overall yield (entry 9). Similarly, $PhSO_2SMe$ or an acid chloride could be used as a second electrophile (E^2) leading to the 3,4-substituted thiophenes **83j** and **83k** in 67-73 % overall yield (entries 10-11). When quenching the thienylmagnesium reagent **80** with $PhSO_2SMe$, the subsequent deprotonation of the crude reaction mixture proceeded smoothly (–10 °C, 30 min) and the resulting magnesium reagent could be used in a Pd-catalyzed cross-coupling reaction to give the expected product **83l** in 84 % overall yield (entry 12).

Table 6: Synthesis of 3,4-difunctionalized dichlorothiophenes of type **83**

Entry	E^1	Product of type 4 (yield[a])	E^2	Product of type 5 (yield[a])
1	$MeSO_2SMe$	 **81a**: 92 %	DMF	 **83a**: 95 %

[68] C. Duplais, F. Bures, I. Sapountzis, T. J. Korn, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 2968.

Table 6 (continued)

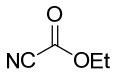
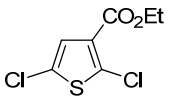
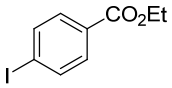
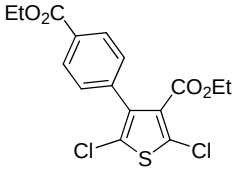
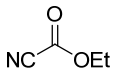
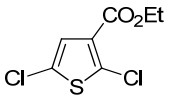
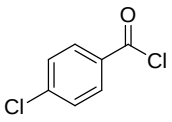
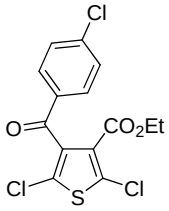
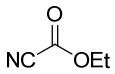
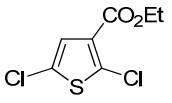
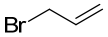
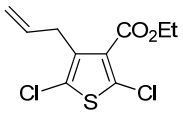
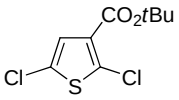
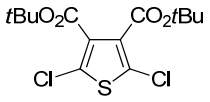
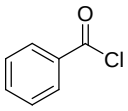
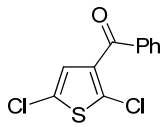
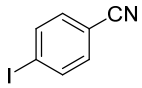
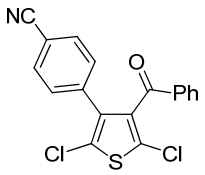
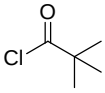
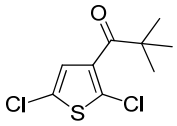
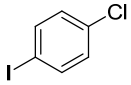
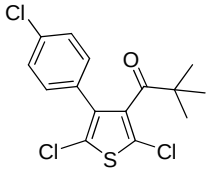
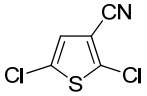
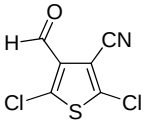
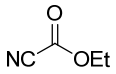
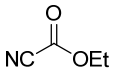
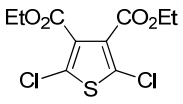
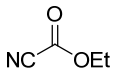
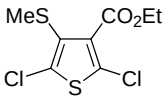
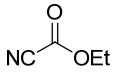
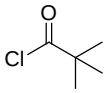
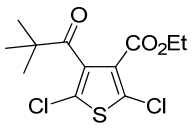
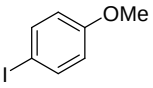
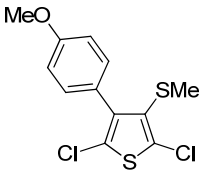
Entry	E^1	Product of type 4 (yield[a])	E^2	Product of type 5 (yield[a])
2		 **81b**: 76 %		 **83b**: 95 %[b]
3		 **81b**: 76 %		 **83c**: 76 %[c]
4		 **81b**: 76 %		 **83d**: 85 %[c]
5	Boc_2O	 **81c**: 82 %	Boc_2O	 **83e**: 79 %
6		 **81e**: 78 %[c]		 **83f**: 84 %[b]
7		 **81f**: 75 %[c]		 **83g**: 77 %[b]
8	TsCN	 **81f**: 73 %	DMF	 **83h**: 86 %

Table 6 (continued)

Entry	E^1	Product of type 4 (yield[a])	E^2	Product of type 5 (yield[a])
9				 **83i**: 87 %[d]
10			$MeSO_2SMe$	 **83j**: 73 %[d]
11				 **83k**: 67 %[d]
12	$MeSO_2SMe$			 **83l**: 84 %[b] [d]

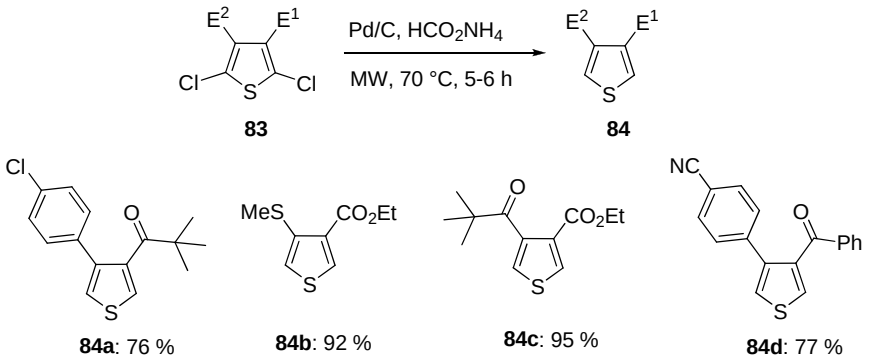
[a] Yield of analytically pure product; [b] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv) and a Pd-catalyzed cross-coupling reaction; [c] The organomagnesium reagent was transmetalated with CuCN·2 LiCl (20 mol%); [d] Overall yield over two steps.

The reductive cleavage of a carbon-chlorine bond can be achieved by various metal-catalyzed reactions.[69] The method developed by *Schlosser* using Pd/C and ammonium formate as a reductive system was chosen.[70] However, it was observed that conventional heating led to a sluggish reaction. For example, the reduction of the dichlorothiophene **83g** in EtOH at 80 °C using a sealed tube required 5 days to achieve completion. However, by using microwave irradiation (100 W, 70 °C, open vessel), the reduction was complete within 5 h and the dechlorinated thiophene **84a** was isolated in 76 % yield.

Remarkably, this reduction was completely selective, and only reduced the carbon-chlorine bonds at the thiophene ring without affecting other aromatic C-Cl-bonds (see Scheme 46, compound **84a**). The same procedure was used for the chlorothiophenes **83f**, **83j** and **83k** (5-6

[69] F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2002**, *102*, 4009.
[70] a) E. Marzi, C. Bobbio, F. Cottet, M. Schlosser, *Eur. J. Org. Chem.* **2005**, 2116; b) C. Bobbio, T. Rausis, M. Schlosser *Chem. Eur. J.* **2005**, *11*, 1903.

h, 100 W, 70 °C, open vessel) furnishing the dechlorinated products **84b-d** in 77-95 % yield (Scheme 46).

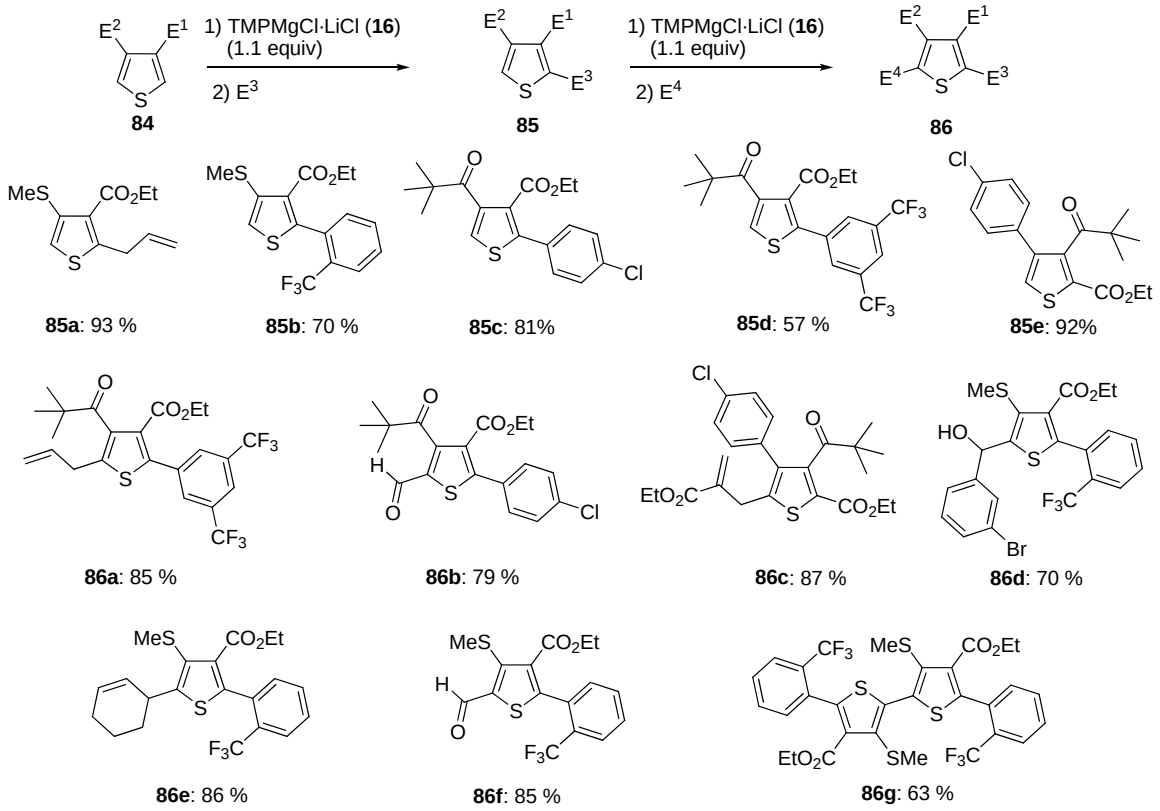


Scheme 46: Reduction of dichlorothiophenes of type **83** using Pd/C and HCO_2NH_4 under microwave irradiation

A further deprotonation of the dechlorinated thiophenes of type **84** was achieved with complete regioselectivity. When treating the thiophene **84b** and **84c** with TMPMgCl·LiCl (**16**; 1.1 equiv, –40 to –30 °C, 30-60 min) the ester moiety is acting as a directing group[71] and magnesiation occurs regioselectively next to this ester group. Cu(I)-catalyzed allylation[31] or Pd-catalyzed cross-coupling reactions afforded the expected products **85a-85d** in 57-93 % yield. Similarly, a ketone can also play the role of an efficient directing group and the product **85e** was isolated in 92 % yield after deprotonation of **84a** and quenching with $NCCO_2Et$.

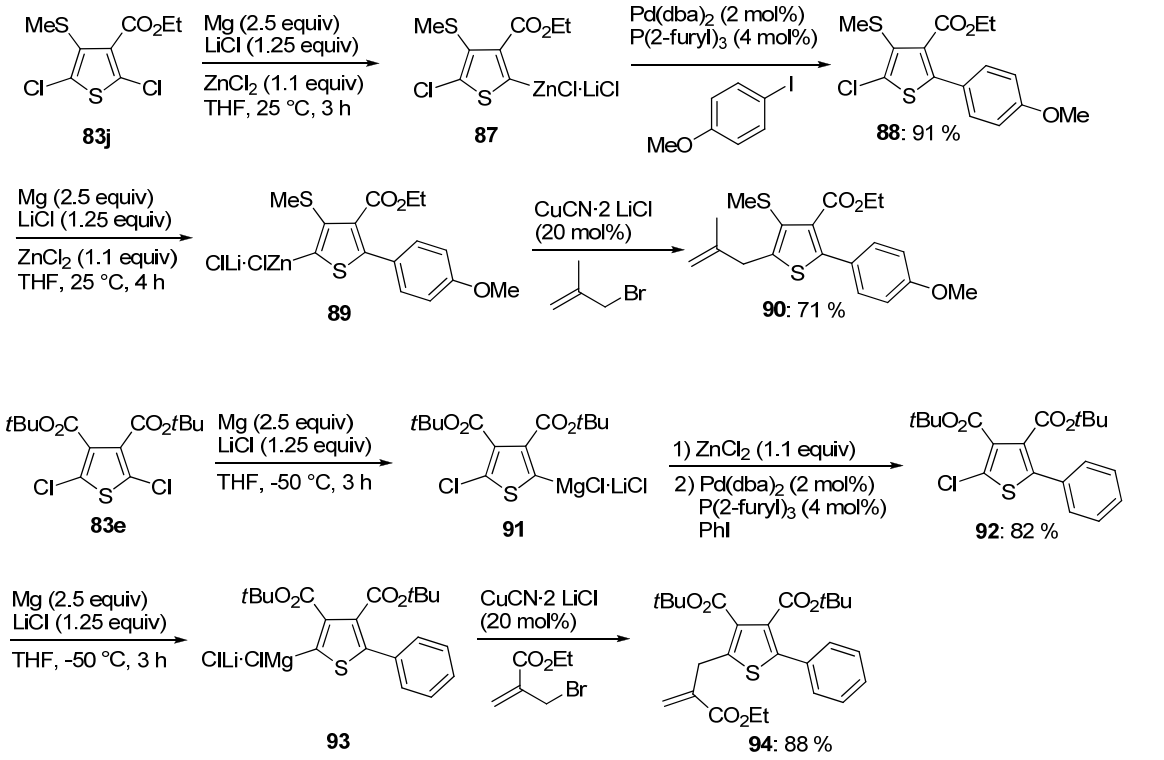
The remaining 5-position could be metalated as well between –50 and –20 °C with TMPMgCl·LiCl (**1**; 1.1 equiv, 30-45 min). The resulting magnesiated intermediates were trapped with aldehydes and DMF or can be used in allylations or cross-coupling reactions[39] furnishing the fully substituted thiophene derivatives **86a-86f** in 70-87% yield. Moreover, the magnesiated thiophene derived from thiophene **85b** could be subjected to a transition metal-free homo-coupling reaction using chloranil[64] and the highly functionalized dithiophene **86g** was obtained in 63 % yield (Scheme 47).

[71] a) T. Macklin, V. Snieckus in *Handbook of C–H Transformations* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**, 106; b) C. G. Hartung, V. Snieckus in *Modern Arene Chemistry* (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**, 330.



Scheme 47: Preparation of fully substituted thiophenes of type **86**

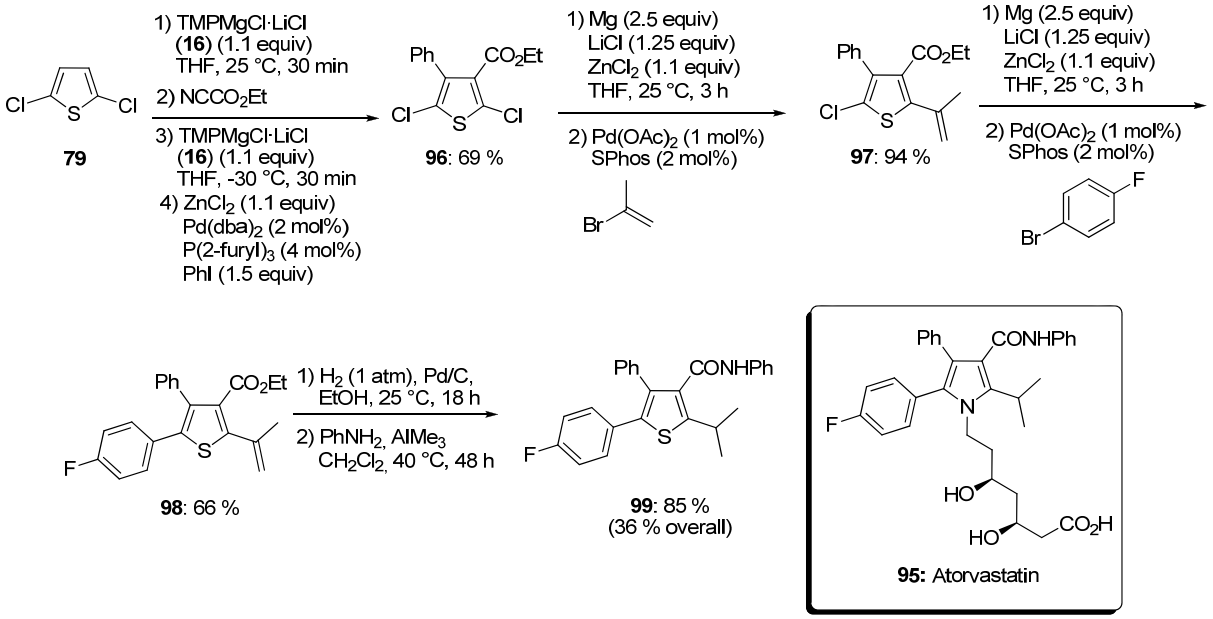
Dichlorothiophenes of type **83** could also be magnesiated directly at the 2- and 5-positions using a LiCl-mediated magnesium insertion. Thus, the addition of the dichlorothiophene **83j** to Mg-turnings (2.5 equiv), LiCl (1.25 equiv) and $ZnCl_2$ (1.1 equiv) in THF regioselectively gave the zincated intermediate **87** (25 °C, 3 h) which could be arylated in a Pd-catalyzed reaction[39] with 4-iodoanisole leading to the arylated product **88** in 91 % yield. Repeated treatment of **88** with magnesium turnings, LiCl and $ZnCl_2$ (25 °C, 4 h) afforded the zinc compound **89** and following an allylation reaction catalyzed by CuCN·2 LiCl[31] (20 mol%) the fully functionalized thiophene **90** was isolated 71 % yield. Additionally, the magnesium insertion into the dichlorothiophene **83e** could be conducted at –50 °C within 3 h. A subsequent Negishi cross-coupling reaction with iodobenzene furnished the arylated thiophene **92** in 82 % yield. The second insertion also proceeded smoothly at –50 °C within 3 h and after a Cu(I)-catalyzed allylation reaction the fully substituted thiophene **94** could be isolated in 88 % yield (Scheme 48).



Scheme 48: Magnesium insertion in the presence of LiCl into dichlorothiophenes of type **83**

As an application, a thiophene analogue of Atorvastatin (**95**; Lipitor®, HMG-CoA reductase inhibitor, anti-cholesterol agent) was prepared starting from 2,5-dichlorothiophene (**79**).[72] Using the procedure described above, selective deprotonations and successive quenching with ethyl cyanoformate and iodobenzene in a Negishi cross-coupling reaction furnished the 3,4-disubstituted dichlorothiophene **96** in 69 % yield. Regioselective magnesium insertion in the presence of LiCl and $ZnCl_2$ (25 °C, 3 h) and subsequent Pd-catalyzed cross-coupling[39] with 2-bromopropene (using $Pd(OAc)_2$ and SPhos as a catalytic system) afforded the alkene **97** in 94 % yield. The Mg-insertion into the remaining C-Cl bond of **97** proceeded smoothly (25 °C, 3 h). A Negishi cross-coupling reaction with 4-bromofluorobenzene, then yielded the arylated product **98** in 66 % yield. After hydrogenation of the double-bond and amide formation using *Weinreb's* method[73] ($PhNH_2$, $AlMe_3$) the thiophene analogue **99** of the Atorvastatin core (**95**) was obtained in 85 % yield (36 % overall yield, Scheme 49).

[72] Similar structures have been reported as steroid nuclear receptor modulators and protein kinase inhibitors: a) B. Flatt. X. H. Gu, R. Martin, R. Mohan, B. Murphy, M. Nyman, W. C. Stevens, T. L. Wang, L. C. Bannen, WO 2007024744, **2007;** b) G. Brenchley, J.-D. Charrier, S. Durrant, R. Knetgel, S. Ramaya, WO 2007139816, **2007**.
[73] A. Basha, M. Lipton, S. M. Weinreb, *Tetrahedron Lett.* **1977**, *48*, 4171.

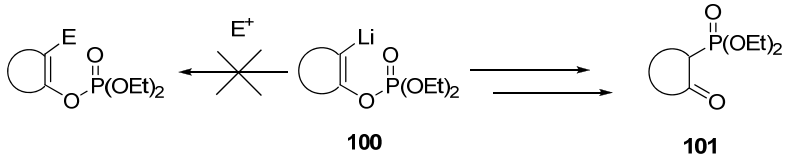


Scheme 49: Application to the synthesis of a thiophene-based Atorvastatin (Lipitor ®) derivative

3. Preparation of Functionalized Enol Phosphates by Halogen-Magnesium Exchange and Directed Deprotonation Reactions

Enol phosphates are an important class of organic compounds that have found applications as insecticides[74] and phosphatase inactivators.[75] Additionally, they can be used as versatile intermediates for the regioselective preparation of substituted double bonds. Several methods have been developed allowing efficient transition metal-catalyzed cross-coupling reactions with this kind of substrates.[76] In fact, enol phosphates are a useful synthetic alternative to the corresponding triflates since they are generally less expensive and more stable. Their preparation is conveniently performed starting either from enolizable ketones or α-halo carbonyl compounds.[74]

The synthesis of lithiated enol phosphates of type **100** via halogen-lithium exchange or deprotonation using LDA has already been described by Wiemer.[77] However, these lithium reagents do not react with electrophiles (E^+) but rearrange to the corresponding β-keto phosphonates **101** in good yields (Scheme 50).



Scheme 50: Rearrangement of lithiated enol phosphates to the corresponding β-keto phosphonate

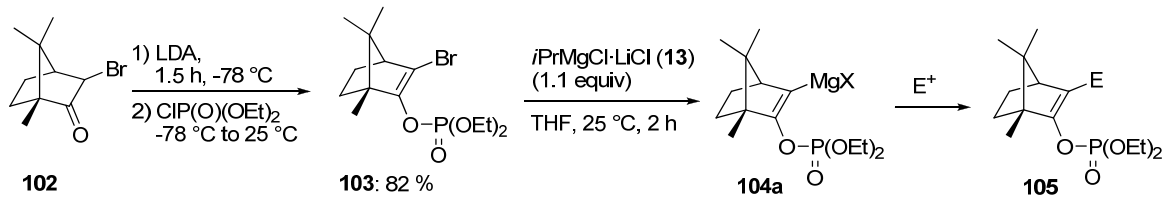
As organomagnesium reagents are less reactive than organolithium reagents it is expected that the corresponding magnesium reagents are more stable. Hence, the preparation of magnesiated enol phosphates derived from D(+)-camphor was investigated using halogen-magnesium exchange and directed deprotonation reactions. Camphor derivatves are often

[74] a) F. W. Lichtenthaler, *Chem. Rev.* **1961**, *61*, 607; b) Y. Ding, X. Huang, *Heteroatom Chem.* **2003**, *14*, 304.
[75] a) J. K. Stowell, T. S. Widlanski, *J. Am. Chem. Soc.* **1994**, *116*, 789; b) T.S. Widlanski, US Patent 5,714,361.
[76] a) K. Takai, M. Sato, K. Oshima, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 108; b) G. Cahiez, O. Gager, V. Habiak, *Synthesis* **2008**, *16*, 2636; c) J. A. Miller, *Tetrahedron Lett.* **2002**, *43*, 7111; d) U. S. Larsen, L. Martiny, M. Begtrup, *Tetrahedron Lett.* **2005**, *46*, 4261.
[77] a) T. Calogeropoulou, G. B. Hammond, D. F. Wiemer, *J. Org. Chem.* **1987**, *52*, 4185; b) T. J. Baker, D. F. Wiemer, *J.Org. Chem.* **1998**, *63*, 2613.

used as chiral auxiliaries in stereoselective reactions.[78] Developing a functionalization of the camphor skeleton would therefore be a highly desirable process.

Starting from commercially available D(+)-bromocamphor (**102**) the enol phosphate **103** was prepared by deprotonation with LDA (1.1 equiv, –78 °C, 1.5 h) and quenching of the resulting enolate with diethyl chlorophosphate in 82 % yield.

The corresponding magnesium reagent **104a** was smoothly generated by treatment of **103** with *i*PrMgCl·LiCl (**13**, 1.1 equiv, 25 °C, 2 h). No rearrangement to the β-keto phosphonate was observed (Scheme 51).



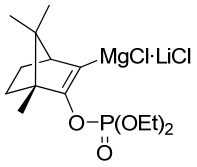
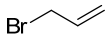
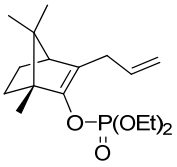
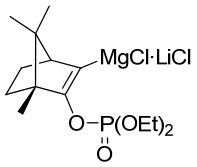
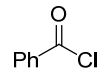
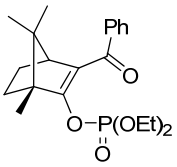
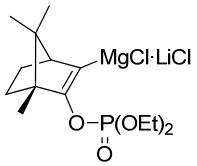
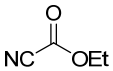
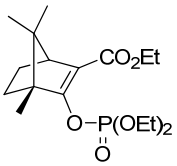
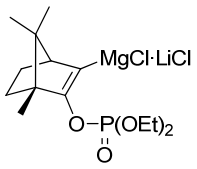
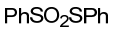
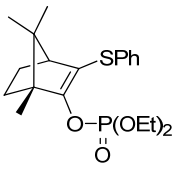
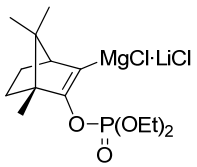
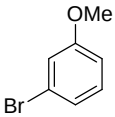
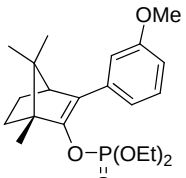
102 **103**: 82 % **104a** **105**

Scheme 51: Preparation and magnesation of enol phosphate **103**

The magnesium reagent **104** reacted well with electrophiles (E^+). Thus, treatment of **104** with allyl bromide using copper(I)-catalysis gave the allylated product **105a** in 62 % yield (Table 7, entry 1). Similarly, the cycloalkenylmagnesium reagent **104a** could be used in an acylation reaction with benzoyl chloride using CuCN·2 LiCl[31] (20 mol%) and the expected ketone **105b** was obtained in 67 % yield (entry 2). Additionally, the use of ethyl cyanoformate allowed the synthesis of the ester **105c** in 72 % yield (entry 3). Thioethers are easily prepared by quenching the Grignard reagents with sulfonothioates. Using $PhSO_2SPh$ as an electrophile, the corresponding phenyl thioether **105d** was obtained in 65 % yield (entry 4). After a transmetalation with $ZnCl_2$ (1.1 equiv), the resulting organozinc reagent underwent a Negishi cross-coupling reaction.[39] The electron rich 3-bromoanisole could be used as an electrophile by using *Buchwald's* S-Phos ligand (4 mol%) and $Pd(OAc)_2$ (2 mol%) yielding the arylated camphor derivative **105e** in 69 % yield (entry 5).

[78] a) W. Oppolzer, *Tetrahedron* **1987**, *43*, 1969; b) G. Chelucci, *Chem. Soc. Rev.* **2006**, *35*, 1230.

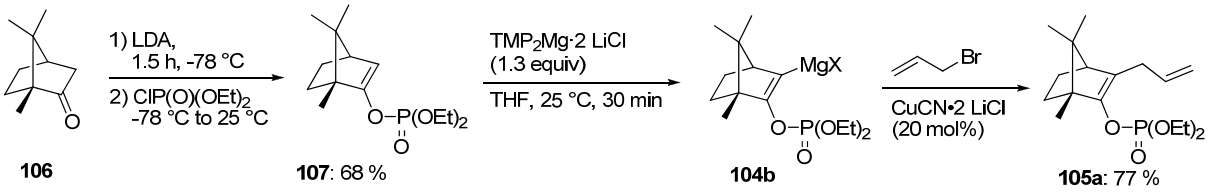
Table 7: Products obtained by the reaction of magnesium reagent **104a** with various electrophiles

Entry	Magnesium Reagent	Electrophile	Product	Yield [%][a]
1	 **104a**		 **105a**	62[b]
2	 **104a**		 **105b**	67[b]
3	 **104a**		 **105c**	72
4	 **104a**		 **105d**	65
5	 **104a**		 **105e**	68[c]

[a] Yield of analytically pure product; [b] The organomagnesium reagent was transmetalated with CuCN·2 LiCl (20 mol%); [c] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv) and a Pd-catalyzed cross-coupling reaction.

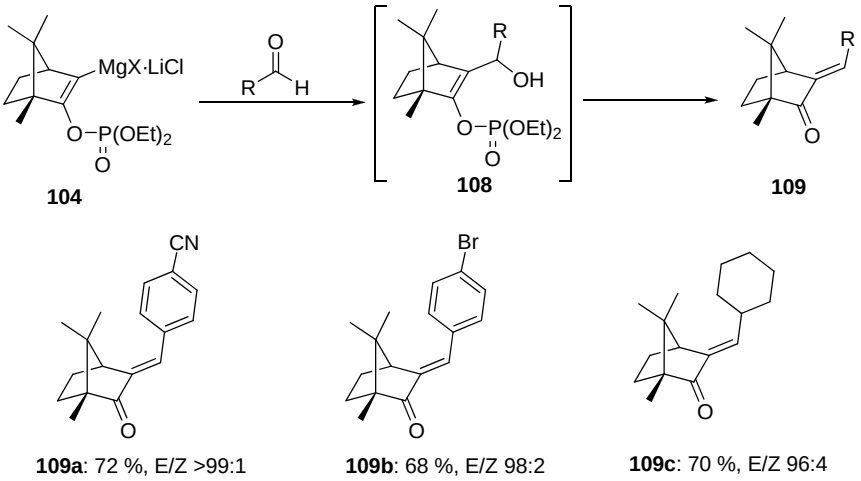
Starting from the enol phosphate **107** (prepared from D(+)-camphor **106**) the magnesium reagent **104a** could be prepared by a deprotonation reaction. Treatment of **104b** with TMPMgCl·LiCl (**16**, 1.1 equiv, 25 °C) furnished the corresponding magnesium reagent in reasonable yield (~80 %) but required 12 h to reach completion. Using the more reactive bisamide $TMP_2Mg·2$ LiCl (**17**, 1.1 equiv) full conversion to the Grignard reagent **104b** could be achieved with in 30 min at 25 °C. The magnesium reagent **104b** had a similar reactivity, regardless of its preparation method. Thus, the Grignard reagent **104b** generated by deprotonation with $TMP_2MgCl·2$ LiCl (**17**) could be trapped with allyl bromide using

copper(I) catalysis[31] (20 mol %) and led to the expected product **105a** in 77 % yield (Scheme 52).



Scheme 52: Preparation of magnesium reagent **104b** using $TMP_2Mg{\cdot}2\ LiCl$

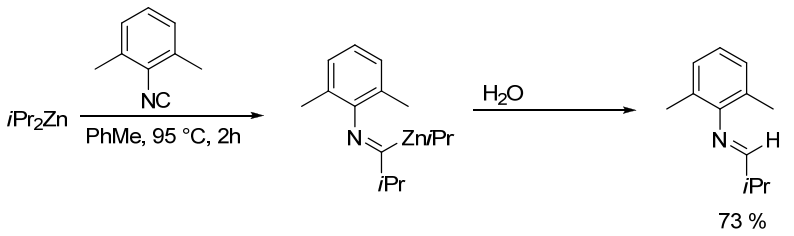
An unexpected reaction pathway was observed when reacting the Grignard reagent **104** with aldehydes. Instead of giving the expected allylic alcohols of type **108** the products underwent a spontaneous elimination to give the α,β-unsaturated ketones **109a-c** with an excellent *E/Z*-selecitivity as shown by NMR analysis. Thus, after reaction of **104** with 4-cyanobenzaldehyde the ketone **109a** was obtained in 72 % yield and >99:1 *E/Z*-selectivity. Similarly, 4-bromobenzaldehyde gave a similar elimination and yielded the unsaturated ketone **109b** in 68 % yield and 98:2 *E/Z*-selectivity. Aliphatic aldehydes reacted as well, and after the treatment of cyclohexanecarbaldehyde with the magnesium reagent **104** the elimination product **109c** was isolated in 70 % yield and 96:4 *E/Z*-selectivity (Scheme 53).



Scheme 53: Reaction of magnesium reagent **104** with various aldehydes and rearrangement to α,β-unsaturated ketones of type **109**

4. 1-Aryliminozinc Reagents as Acyl Anion Equivalents

Acyl anion equivalents are valuable synthetic intermediates in organic chemistry.[79] One member of this class of compounds are iminozinc reagents. They were first prepared in 1904 by *Sachs* and *Loevy* by the reaction of phenylmagnesium bromide and methyl isocyanide.[80] Since then, the α-addition of organometallic reagents to isonitriles has attracted considerable attention for example by *Gilman*[81] and *Ugi*.[82] A breakthrough was accomplished by *Walborsky* who showed in a series of papers that organolithium reagents could be added to isonitriles.[83] Later, *Ito* and co-workers prepared [1-(arylimino)alkyl]zinc reagents by the reaction of diorganozinc compounds with aromatic isonitriles (Scheme 54).[84]

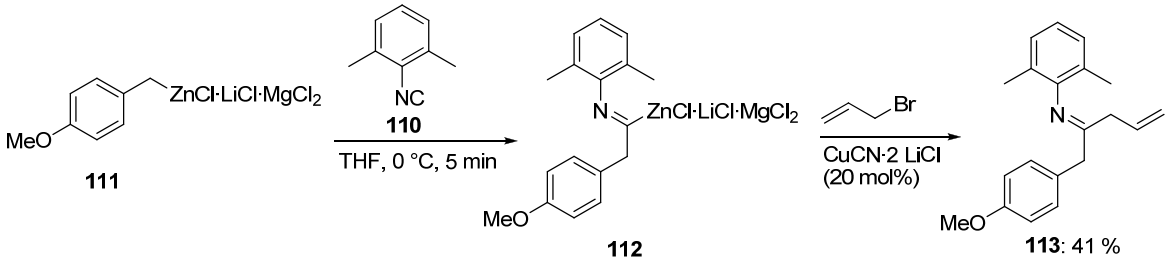


Scheme 54: Reaction of iPr$_2$Zn with 2,6-dimethylphenyl isonitrile according to *Ito*

Drawbacks of this reaction are a low functional group tolerance due harsh reaction conditions (95 °C in toluene) and the need to use diorganozinc compounds. Recently, *Knochel* and co-workers reported an accelerated attack of functionalized organozinc reagents to carbonyl compounds by the addition of $MgCl_2$.[85] Reagents of such kind are conveniently prepared by a direct insertion of magnesium in the presence of LiCl and $ZnCl_2$ as described earlier. Based on this report, the addition of organozinc reagents to aryl isonitriles was reinvestigated.

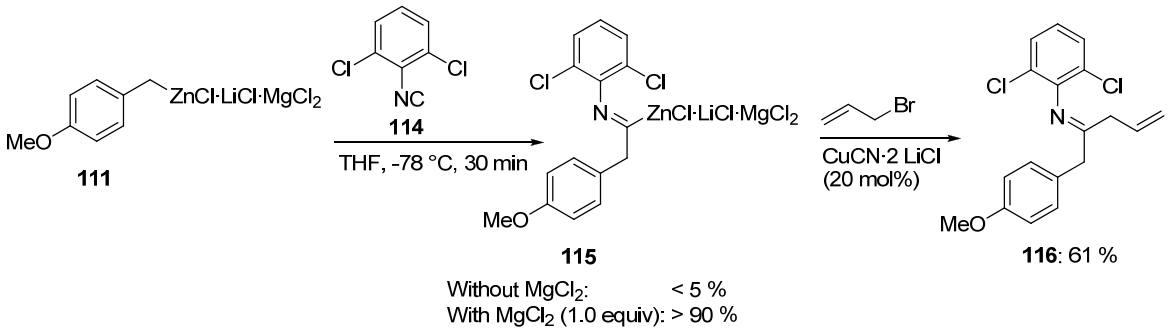
[79] a) O. W. Lever, *Tetrahedron* **1976**, *32*, 1943; b) D. J. Ager in *Umpoled Synthons: A Survey of Sources and Uses in Synthesis* (Ed.: T. A. Hase), Wiley, New York, **1987**.
[80] F. Sachs, H. Loevy, *Chem. Ber*. **1904**, *37*, 874.
[81] H. Gilman, L. C. Heckert, *Bull. Soc. Chim*. *Fr*. **1928**, *43*, 224.
[82] I. Ugi, U. Fetzer, *Chem. Ber*. **1961**, *94*, 2239.
[83] a) H. M. Walborsky, G. E. Niznik, *J. Am. Chem. Soc*. **1969**, *91*, 7778; b) H. M. Walborsky, W. H. Morrison, III, G. E. Niznik, *J. Am. Chem. Soc*. **1970**, *92*, 6675; c) H. M. Walborsky, W. H. Morrison, III, G. E. Niznik, *J. Org. Chem.* **1974**, *39*, 600.
[84] a) M. Murakami, H. Ito, Y. Ito, *J. Org. Chem*. **1988**, *53*, 4158; b) M. Murakami, H. Ito, W. A. b. W. A. Bakar, A. B. b. Baba, Y. Ito, *Chem. Lett.* **1989**, 1603.
[85] A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010***, in press.*

In preliminary experiments, various zinc reagents were reacted with commercially available 2,6-dimethylphenyl isonitrile (**110**) in the presence of $MgCl_2$. While alkyl and aromatic zinc reagents did not show any reactivity towards the isonitrile **110**, the benzylic zinc reagent **111** added to 2,6-dimethylphenyl isonitrile (**110**) within 15 min at 0 °C. The resulting aryliminozinc reagent **112** could be trapped with allyl bromide under Cu(I)-catalysis[31] (20 mol%) and the resulting imine **113** could be isolated in moderate yield (Scheme 55).



Scheme 55: Reaction of benzylic zinc reagent **111** with 2,6-dimethylphenyl isonitrile

During the reaction, it was observed that the aryliminozinc reagent **112** decomposed slowly, even at 0 °C. When lowering the temperature below 0 °C however, the reaction did not proceed to completion. It was envisioned that with the use of a more electron-poor isonitrile, the reaction could be performed at lower temperatures. Thus, 2,6-dichlorophenyl isonitrile (**114**) reacted with 4-methoxybenzylzinc chloride (**111**) in the presence of $MgCl_2$ at –78 °C within 30 min. Without $MgCl_2$ no reaction was observed under these reaction conditions. The resulting zinc reagent **115** was allyated in a Cu(I)-catalyzed reaction with allyl bromide and the resulting imine **116** could be isolated in 61 % yield (Scheme 56).



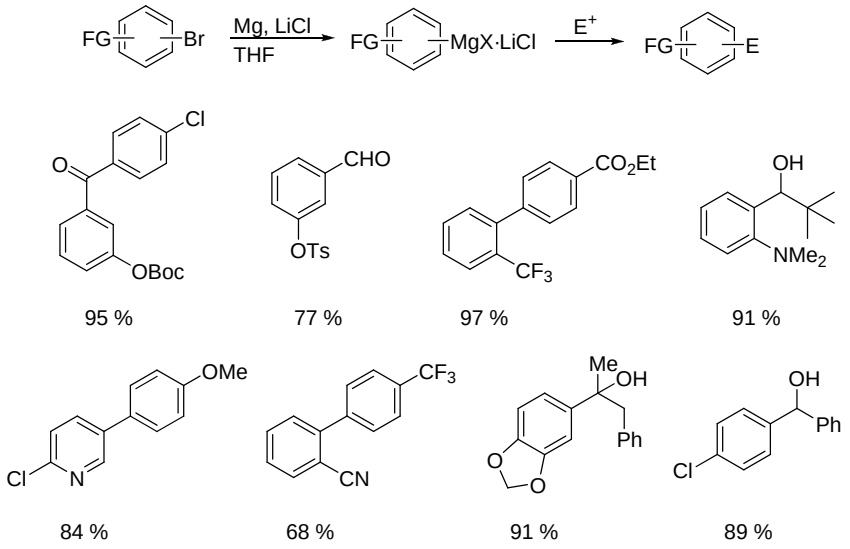
Scheme 56: Influence of $MgCl_2$ on the addition of benzylic zinc reagent **111** to 2,6-dichlorophenyl isonitrile (**114**)

5. Summary and Outlook

This work was focused on the preparation of organomagnesium and organozinc reagents by magnesium insertion reactions and directed deprotonations. Furthermore, functionalized enol phosphates derived from D(+)-camphor were synthesized and preliminary experiments towards the $MgCl_2$-mediated reaction of zinc reagents with aryl isonitriles were conducted.

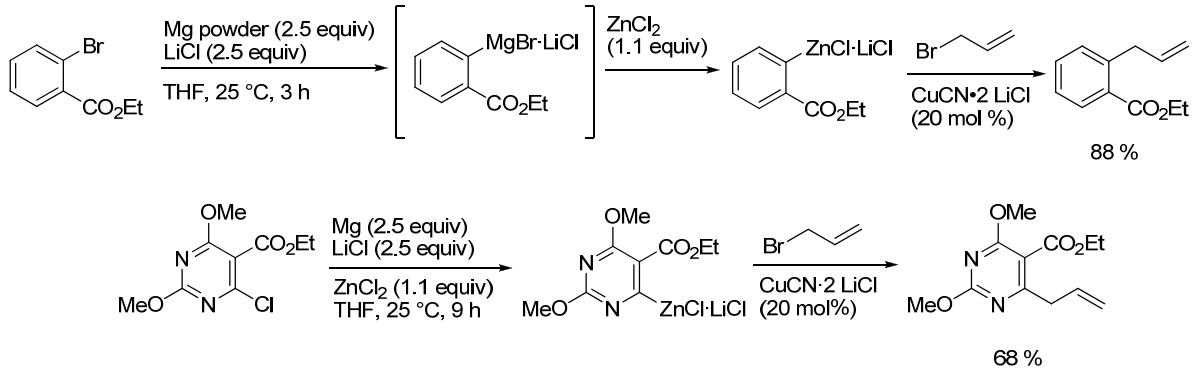
5.1. LiCl-Mediated Direct Insertion of Magnesium Into Aryl, Heteroaryl and Benzylic Halides

The insertion of readily available magnesium turnings into aryl bromides in the presence of LiCl was described. This method allowed the preparation of various functionalized magnesium reagents using a practical and economical procedure (Scheme 57).



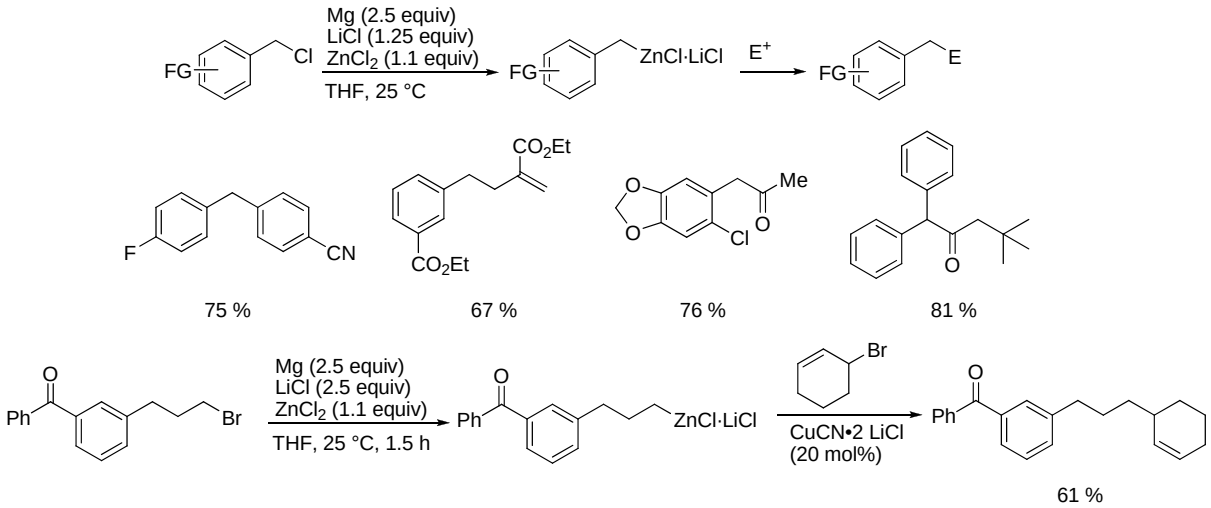
Scheme 57: Magnesium insertion in the presence of LiCl

Sensitive substrates such as aromatic esters or sophisticated heterocycles could also be converted by transmetalation with $ZnCl_2$ in situ to the corresponding organozinc reagents which then underwent reactions with various electrophiles (Scheme 58).



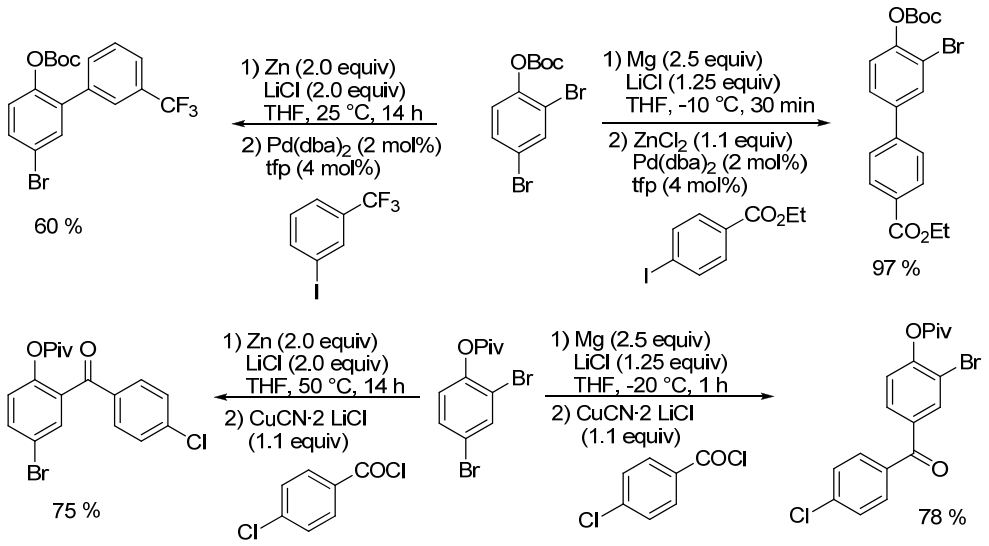
Scheme 58: Preparation of functionalized zinc reagents

This methodology was then successfully transferred to the preparation of benzylic zinc chlorides and alkylzinc bromides. In both cases, the reaction times using Mg/LiCl/$ZnCl_2$ were greatly accelerated compared to the corresponding zinc insertion (Scheme 59).



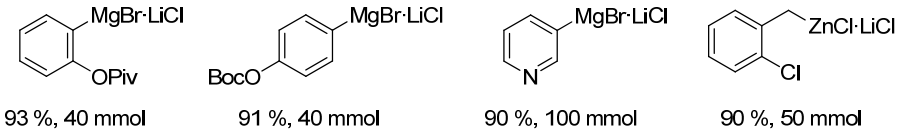
Scheme 59: Preparation of functionalized benzylic and alkylzinc reagents

Additionally, the magnesium and zinc insertion into 2,4-dibrominated and 2,4,6-tribrominated arenes was investigated. A highly useful regioselective insertion procedure was developed giving access to selectively metalated bromoarenes (Scheme 60).



Scheme 60: Orthogonal regioselectivity pattern of zinc and magnesium insertions

Due to the relevance of organometallic reagents for industrial applications, all of the procedures described above were performed on a larger scale. Functionalized organomagnesium and organozinc reagents were prepared by insertion of magnesium in the presence of LiCl on a 25-100 mmol scale (Scheme 61).

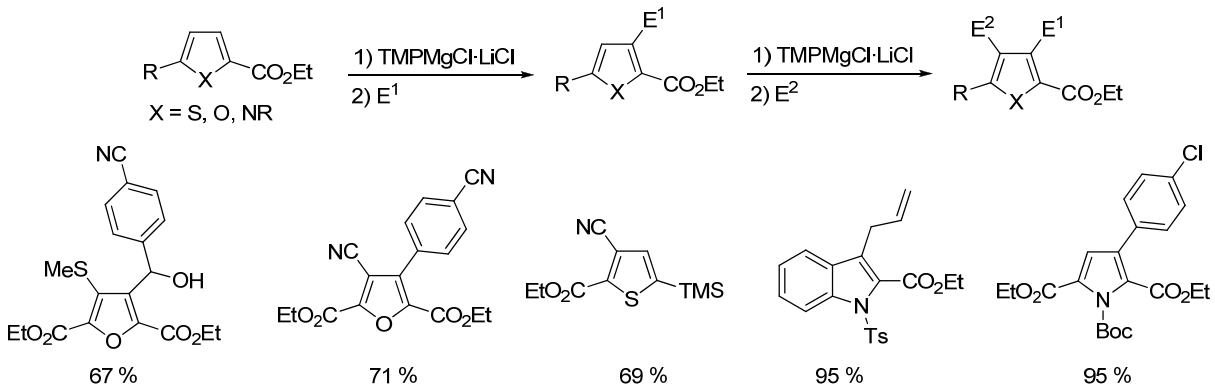


Scheme 61: Magnesium reagents obtained after larger-scale experiments

Since the LiCl-mediated magnesium insertion allows the use of low temperatures, it might be possible to insert into alkenyl bromides without isomerisation of the double bond. Furthermore, the direct transmetalation with metal halides such as $AlCl_3$ or $LaCl_3$ would open an easy access to new interesting organometallics.

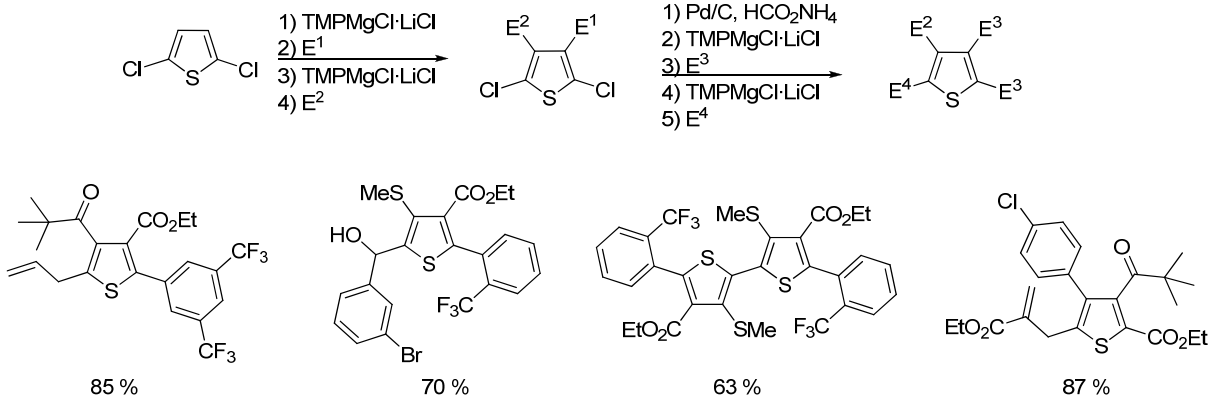
5.2. Regio- and Chemoselective Synthesis of Functionalized 5-Membered-Ring Heterocycles

The synthesis of various furan, thiophene, pyrrole and indole derivatives bearing an ester group in the 2-position was described. Using the magnesium amide bases TMPMgCl·LiCl and $TMP_2Mg·2$ LiCl all positions of the heterocyclic core could be functionalized (Scheme 62).



Scheme 62: Functionalized 5-membered-ring heterocycles prepared by directed deprotonations

Furthermore, a practical method for the preparation of fully substituted thiophenes was developed. Starting from commercially available 2,5-dichlorothiophene, a sequence of directed deprotonations using TMPMgCl·LiCl or magnesium insertions in the presence of LiCl afforded a broad range of fully substituted thiophenes (Scheme 63).

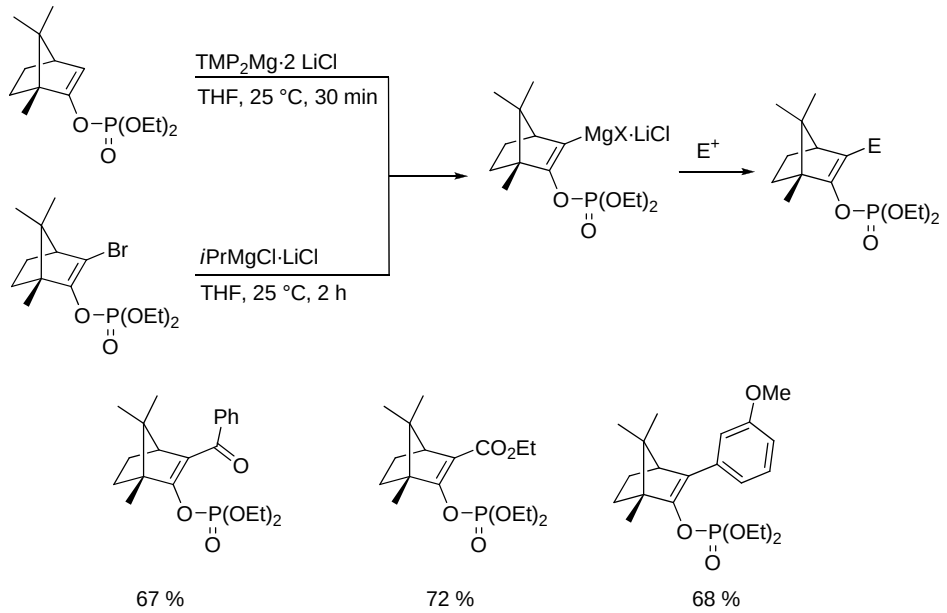


Scheme 63: Preparation of fully substituted thiophenes

Extensions of this work could include the preparation of functionalized materials such as organic conductors or organic solar cells based on thiophene and other heterocycles.

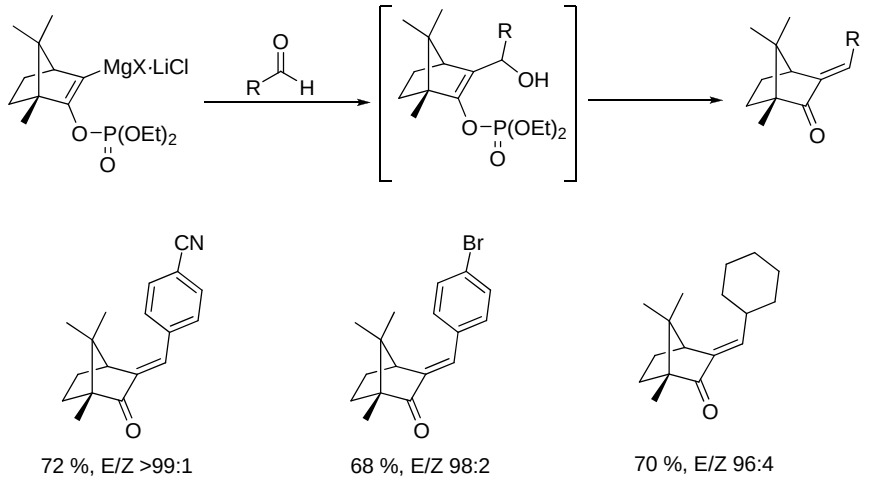
5.3. Preparation of Functionalized Enol Phosphates by Halogen-Magnesium Exchange and Directed Deprotonation Reactions

The functionalization of cyclic enol phosphates based on D(+)-camphor was achieved by either halogen/magnesium exchange reactions or directed deprotonations using TMP-derived magnesium amide bases (Scheme 64).



Scheme 64: Preparation of functionalized enol phosphaes derivatives

Furthermore, the reaction of a camphor derived magnesium reagent with aldehydes furnished, after elimination, the corresponding α,β-unsaturated enones in excellent *E/Z*-selectivity (Scheme 65).

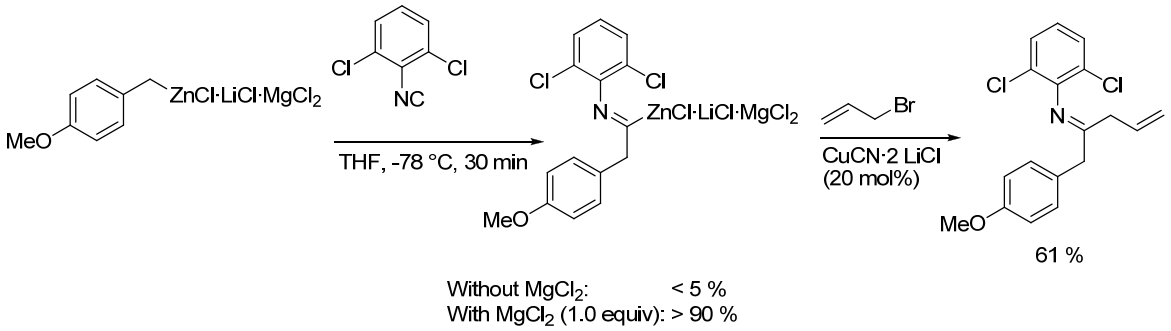


Scheme 65: Reaction of aldehydes with a D(+)camphor-derived magnesium reagent

As an application of this work, this method could be used for the convenient preparation of chiral *P,N*-ligands based on the camphor-core.

5.4. 1-Aryliminozinc Reagents as Acyl Anion Equivalents

Finally, preliminary experiments were conducted concerning the role of $MgCl_2$ towards the addition of organozinc reagents to aryl isonitriles. It was found that in the presence of $MgCl_2$ monoorganozinc reagents were able to attack 2,6-dichlorophenyl isonitrile even at –78 °C (Scheme 66).



Scheme 66: Influence of $MgCl_2$ on the addition of zinc reagents to isonitriles

Further investigations regarding the nature of the aryl isonitrile will need to be conducted. Possible targets could include CF_3-containing isonitriles. Moreover, due to their electronic similarity to *N*-heterocyclic carbenes, the use of isonitriles as ligands in palladium-catalyzed reactions could be investigated.

C. EXPERIMENTAL SECTION

1. General Considerations

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

Solvents

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

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.
Et_2O was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.
EtOH was treated with phthalic anhydride (25 g/L) and sodium, heated to reflux for 6 h and distilled.
DMF was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

Solvents for column chromatography were distilled prior to use.

Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid aldehydes and acid chlorides were distilled prior to use. Following compounds were prepared according to literature procedures:
O-Boc-Protected phenols,[27b] tosyl-protected phenols,[86] aromatic pivalates,[15] enol phosphates,[77] 2-iodocyclohex-2-en-1-one,[87] sulfonothioate derivatives,[54] 1-[(2,4-dibromophenyl)-diazenyl]-pyrrolidine,[88] ethyl 1-[(4-methylphenyl)sulfonyl]-1*H*-indole-2-

[86] I. Sapountzis, W. Lin, M. Fischer, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 4364.
[87] M. E. Krafft, J. W. Cran, *Synlett* **2005**, 1263.
[88] C.-Y. Liu, P. Knochel, *J. Org. Chem.*, **2007**, 72 , 7106.

carboxylate, [89] 1-*tert*-butyl 2,5-diethyl pyrrole-1,2,5-tricarboxylate,[90] ethyl 5-bromo-2-furoate.[91]

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

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

TMPMgCl·LiCl was prepared by slowly adding TMPH (105 mmol, 14.8 g) to a *i*PrMgCl·LiCl solution in THF (100 mmol, 1.4 M, 71.4 mL) and stirring of the resulting mixture at ambient temperature for 3 days.

TMP_2Mg·2 LiCl was prepared according to a literature procedure.[29]

CuCN·2 LiCl solution (1 M) was prepared by drying CuCN (80 mmol, 7.17 g) and LiCl (160 mmol, 6.77 g) in a *Schlenk*-tube under vacuum at 140 °C for 5 h. After cooling, 80 mL dry THF were added and stirring was continued until the salt was dissolved.

$ZnCl_2$ solution (1 M) was prepared by drying $ZnCl_2$ (100 mmol, 136.3 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.

LiCl solution (0.5 M) was prepared by drying LiCl (100 mmol, 4.23 g) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling, 200 mL dry THF were added and stirring was continued until the salt was dissolved.

Content Determination of Organometallic Reagents

Organzinc and organomagnesium reagents were titrated against I_2 in a 0.5 M LiCl solution in THF.[60]

Organolithium reagents were titrated against menthol using 1,10-phenanthroline as indicator in THF.[92]

TMPMgCl·LiCl and TMP_2Mg·2 LiCl were titrated against benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.

Chromatography

[89] R. Silvestri, G. Da Martino, G. La Regina, M. Artico, S. Massa, L. Vargui, M. Mura, A. G. Loi, T. Marceddu, P. La Colla, *J. Med. Chem*. **2003**, 46, 2482.
[90] T. J. Donahoe, C. E. Headley, R. P. C. Cousins, A. Cowley, *Org. Lett*. **2003**, *5,* 999.
[91] R. Chandraratna, *Eur. Pat. Appl.* 272921, **1988**.
[92] H.-S. Lin, A. Paquette, *Synth. Commun*. **1994**, *24*, 2503.

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 UV light at 254 nm and/or by staining of the TLC plate with one of the solutions given below followed by heating with a heat gun:

- $KMnO_4$ (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).

Analytical Data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the residual solvent peak of $CHCl_3$ (δ_H : 7.25, δ_C : 77.0). For the characterization of the observed signal multiplicities the following appreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet) as well as br (broad).

Mass spectroscopy: High resolution (HR-MS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an electron energy of 70 eV.
For the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890 / MSD 5973 was used.

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. The absorption bands are reported in wavenumbers (cm^{-1})

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

2. LiCl-Mediated Magnesium Insertions into Organic Halides

2.1. Magnesium Insertion in the Presence of LiCl into Aryl and Heteroaryl Bromides

2.1.1. Typical Procedure for the Magnesium Insertion in the Presence of LiCl (TP1)

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with magnesium turnings (122 mg, 5 mmol). LiCl (5.0 mL, 0.5 M in THF, 2.5 mmol) was added and the magnesium was activated with *i*Bu_2AlH (0.2 mL, 0.1 M in THF, 0.02 mmol). After 5 min of stirring the aryl chloride or bromide (2.0 mmol) was added in one portion at the given temperature. The reaction mixture was stirred for the indicated time and then cannulated to a new *Schlenk*-flask for the reaction with an electrophile.

2.1.2. Typical Procedure for Cross-Coupling Reactions (TP2)

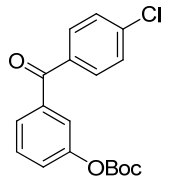
$ZnCl_2$ (2.0 mL, 1.0 M in THF, 2.0 mmol) was added to the freshly prepared magnesium reagent and the reaction mixture was stirred for 15 min. $Pd(dba)_2$ (23 mg, 2 mol%) and tfp (19 mg, 4 mol%) were added, followed by the addition of the corresponding aryl iodide or bromide (1.4 mmol), and the reaction mixture was stirred for the given time at 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash column chromatography.

2.1.3. Typical Procedure for Acylations and Allylations (TP3)

CuCN·2 LiCl (0.4 mL, 1.0 M in THF, 20 mol%) was added to the freshly prepared magnesium or zinc reagent and the reaction mixture was stirred for 15 min. After the addition of the corresponding acid chloride or allyl bromide (1.4 mmol) the reaction mixture was stirred for the given time at 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash column chromatography.

2.1.4. Preparation of Title Compounds

Preparation of *tert*-butyl 3-(4-chlorobenzoyl)phenyl carbonate (24a):



The magnesium reagent **23a** was prepared according to **TP1** from 3-bromophenyl *tert*-butyl carbonate (**22a**, 546 mg, 2.0 mmol) in 1 h at -10 °C. An acylation reaction was performed according to **TP3** with 4-chlorobenzoyl chloride (245 mg, 1.4 mmol) in 1 h. Flash column chromatography (pentane/CH_2Cl_2 = 3:2) furnished **24a** as a colorless solid (440 mg, 95 %).

M.p.: 83-84 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (d, J = 8.6 Hz, 2H), 7.62 (td, J = 2.3 Hz, J = 8.6 Hz, 1H), 7.59-7.58 (m, 1H), 7.51-7,45 (m, 3H), 7.42-7.39 (m, 1H), 1.55 (s, 9H).

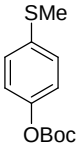
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 194.1, 151.5, 151.0, 139.1, 138.5, 135.4, 131.4, 129.4, 128.7, 127.2, 125.6, 122.8, 84.1, 27.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2985, 1749, 1653, 1580, 1439, 1369, 1248, 1138, 1085, 1004, 906, 824, 778.

MS (70 eV, EI) *m/z* (%): 232 (45) [M^+-Boc], 139 (52), 57 (100).

HRMS (EI) for $C_{13}H_9O_2Cl$ (232.0291 [M^+-Boc]): 232.0275.

Preparation of *tert*-butyl 4-(methylthio)phenyl carbonate (24b):



The magnesium reagent **23b** was prepared according to **TP1** from 4-bromophenyl *tert*-butyl carbonate (22**b**, 546 mg, 2.0 mmol) in 20 min at –10 °C. $MeSO_2SMe$ (177 mg, 1.4 mmol) was

added at -10 °C, the mixture was warmed to 25 °C and stirred for 1 h. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane/CH_2Cl_2 = 4:1) furnished **24b** as a colorless solid (309 mg, 92 %).

M.p.: 58-60 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.26 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 2.46 (s, 3H), 1.54 (s, 9H).

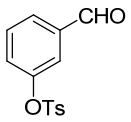
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2985, 1749, 1493, 1430, 1368, 1277, 1218, 1135, 1013, 890, 816, 779, 745.

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 151.8, 148.9, 135.5, 128.0, 121.7, 83.6, 27.7, 16.6.

MS (70 eV, EI) *m/z* (%): 240 (2) [M^+], 207 (5), 140 (100), 125 (27), 69 (10), 57 (84).

HRMS (EI) for $C_{12}H_{16}O_3S$ (240.0820): 240.0817.

Preparation of 3-formylphenyl 4-methylbenzenesulfonate (24c):



The magnesium reagent **23c** was prepared according to **TP1** from 3-bromophenyl 4-methylbenzenesulfonate (**22c**, 654 mg, 2.0 mmol) in 2 h at 0 °C. DMF (102 mg, 1.4 mmol) was added at 0 °C, the mixture warmed to 25 °C and stirred for 30 min. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (CH_2Cl_2) furnished **24c** as a colorless solid (299 mg, 77 %).

M.p.: 64-66 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 9.91 (s, 1H), 7.77 (td, J = 1.3 Hz, J = 8.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.50-7.45 (m, 2H), 7.33-7.27 (m, 3H), 2.44 (s, 3H).

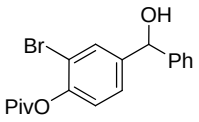
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 190.5, 150.2, 145.8, 137.8, 132.0, 130.4, 129.9, 128.4, 128.3, 128.2, 123.0, 21.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3092, 3056, 2846, 2740, 1691, 1579, 1482, 1439, 1364, 1282, 1220, 1188, 1178, 1126, 1090, 933, 802, 736.

MS (70 eV, EI) *m/z* (%): 276 (21) [M^+], 155 (74), 91 (100), 65 (21).

HRMS (EI) for $C_{14}H_{12}O_4S$ (276.0456): 276.0447.

Preparation of 2-bromo-4-[hydroxy(phenyl)methyl]phenyl pivalate (24d):



The magnesium reagent **23d** was prepared according to **TP1** from 2,4-dibromophenyl pivalate (**22d**, 672 mg, 2.0 mmol) in 1 h at –20 °C. Benzaldehyde (149 mg, 1.4 mmol) was added at -20 °C and the mixture stirred for 30 min at this temperature. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane/CH_2Cl_2 = 2:1 to CH_2Cl_2) furnished **24d** as a pale yellow oil (435 mg, 86 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (d, J = 2.1 Hz, 1H), 7.37-7.30 (m, 6H), 7.06 (d, J = 8.6 Hz, 1H), 5.81 (s, 1H), 2.25 (brs, 1H) 1.40 (s, 9H).

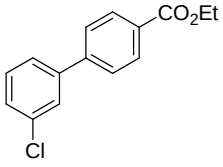
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 176.0, 147.6, 143.0, 142.9, 131.2, 128.7, 128.0, 126.6, 126.5, 123.5, 116.1, 75.2, 39.3, 27.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3433, 2971, 1755, 1477, 1215, 1099, 1041, 892, 697.

MS (70 eV, EI) *m/z* (%): 362 (6) [M^+], 280 (25), 201 (20), 105 (100), 57 (95).

HRMS (EI) for $C_{18}H_{19}BrO_3$ (362.0518): 362.0508.

Preparation of ethyl 3'-chlorobiphenyl-4-carboxylate (24e):



The magnesium reagent **23e** was prepared according to **TP1** from 3-chlorobromobenzene (**22e**, 383 mg, 2.0 mmol) in 10 min at 25 °C. A cross-coupling reaction was performed according to **TP2** with ethyl 4-iodobenzoate (386 mg, 1.4 mmol) in 2 h. Flash column chromatography (pentane/CH_2Cl_2 = 4:1) furnished **24e** as a colorless solid (341 mg, 94 %).

M.p.: 67-69 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.11 (d, J = 8.7 Hz, 2H), 7.63-7.59 (m, 3H), 7.50-7.47 (m, 1H), 7.41-7.34 (m, 2H), 4.40 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).

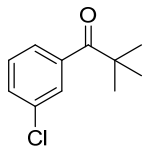
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.3, 144.0, 141.9, 134.8, 130.1, 130.1, 129.8, 128.1, 127.4, 127.0, 125.4, 61.0, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3061, 2977, 1703, 1608, 1595, 1559, 1471, 1393, 1364, 1274, 1183, 1099, 1018, 851, 761, 704, 690.

MS (70 eV, EI) *m/z* (%): 260 (49) [M^+], 232 (29), 215 (100), 152 (63), 76 (16).

HRMS (EI) for $C_{15}H_{13}ClO_2$ (260.0604): 260.0601.

Preparation of 1-(3-chlorophenyl)-2,2-dimethylpropan-1-one (24f):



The magnesium reagent **23e** was prepared according to **TP1** from 3-chlorobromobenzene (**23e**, 383 mg, 2.0 mmol) in 10 min at 25 °C. An acylation reaction was performed according to **TP3** with pivaloyl chloride (169 mg, 1.4 mmol) in 1 h. Flash column chromatography (pentane/CH_2Cl_2 = 4:1) furnished **24f** as a colorless oil (190 mg, 69 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62-7.61 (m, 1H), 7.54-7.52 (m, 1H), 7.44-7.41 (m, 1H), 7.35-7.31 (m, 1H), 1.33 (s, 9H).

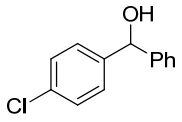
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 207.9, 140.2, 134.3, 130.7, 129.4, 127.9, 125.7, 44.3, 27.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2872, 1676, 1567, 1476, 1462, 1411, 1395, 1366, 1279, 1265, 1180, 1098, 1081, 984, 970, 884, 826, 798, 765, 739, 680, 663.

MS (70 eV, EI) *m/z* (%): 196 (8) [M^+], 139 (100), 111 (19), 75 (11), 57 (48).

HRMS (EI) for $C_{11}H_{13}ClO$ (196.0655): 196.0644.

Preparation of 1-(4-chlorophenyl)-1-phenylmethanol (24g):



The magnesium reagent **23f** was prepared according to **TP1** from 1-bromo-4-chlorobenzene (**22f**, 383 mg, 2.0 mmol) in 10 min at 25 °C. Benzaldehyde (149 mg, 1.4 mmol) was added and the mixture stirred for 15 min at 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (CH_2Cl_2) furnished **24g** as a colorless solid (271 mg, 89 %).

M.p.: 69-71 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32-7.21 (m, 9H), 5,71 (s, 1H), 2.45 (brs, 1H).

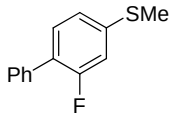
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 143.4, 142.1, 133.2, 128.6, 128.5, 127.8, 127.7, 126.5, 75.5.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3351, 1588, 1485, 1453, 1402, 1191, 1086, 1011, 847, 791, 759.

MS (70 eV, EI) *m/z* (%): 218 (41) [M^+], 165 (30), 139 (100), 105 (66), 78 (36).

HRMS (EI) for $C_{13}H_{11}OCl$(218.0498): 218.0491.

Preparation of 2-fluoro-4-(methylthio)biphenyl (24h):



The magnesium reagent **23g** was prepared according to **TP1** from 4-bromo-2-fluorobiphenyl (**22g**, 502 mg, 2.0 mmol) in 30 min at 25 °C. $MeSO_2SMe$ (177 mg, 1.4 mmol) was added at 0 °C and the reaction mixture was warmed to 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane) furnished **24h** as a colorless solid (257 mg, 84 %).

M.p.: 70-72 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.55-7.51 (m, 2H), 7.46-7.41 (m, 2H), 7.38-7.33 (m, 2H), 7.10-7.01 (m, 2H), 2.51 (s, 3H).

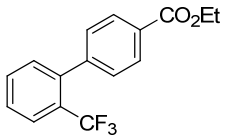
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 159.8 (d, J = 249.3 Hz), 140.0 (d, J = 8.3 Hz), 135.4, 130.7 (d, J = 4.4 Hz), 128.8 (d, J = 3.1 Hz), 128.5, 127.5, 125.5 (d, J = 13.7 Hz), 122.2 (d, J = 3.4 Hz), 113.6 (d, J = 25.8 Hz), 15.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1610, 1578, 1552, 1542, 1508, 1478, 1444, 1418, 1401, 1391, 1338, 1321, 1282, 1260, 1211, 1192, 1186, 1152, 1140, 1113, 1085, 1078, 1034, 1006, 994, 972, 963, 950, 915, 894, 850, 817, 764, 725, 713, 698, 660, 640.

MS (70 eV, EI) *m/z* (%): 218 (100) [M^+], 203 (51), 170 (24), 42 (47).

HRMS (EI) for $C_{13}H_{11}FS$ (218.0565): 218.0578.

Preparation of ethyl 2'-(trifluoromethyl)biphenyl-4-carboxylate (24i):



The magnesium reagent **23h** was prepared according to **TP1** from 1-bromo-2-(trifluoromethyl)benzene (**22h**, 450 mg, 2.0 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to **TP2** with ethyl 4-iodobenzoate (386 mg, 1.4 mmol) in 2 h at 25 °C. Flash column chromatography (pentane/CH_2Cl_2 = 4:1) furnished **24i** as a colorless oil (400 mg, 97 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (d, J = 7.9 Hz, 2H), 7.76 (d, J = 7.8 Hz, 1H), 7.59-7.47 (m, 2H), 7.40 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 8.0 Hz, 1H), 4.40 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H).

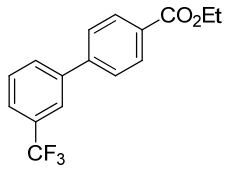
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 144.6, 140.3, 131.6, 131.4, 129.8, 129.0, 128.3 (q, J = 30.2 Hz), 127.8, 126.2 (q, J = 5.3 Hz), 124.0 (q, J = 274.0 Hz), 61.0, 14.3. (1 quarternary carbon not detected)

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 1713, 1611, 1604, 1579, 1486, 1479, 1465, 1448, 1405, 1367, 1312, 1299, 1270, 1168, 1124, 1107, 1099, 1069, 1034, 1026, 1006, 957, 881, 859, 767, 753, 739, 707, 664.

MS (70 eV, EI) *m/z* (%): 249 (100) [M^+], 201 (41), 97 (13), 83 (12), 69 (13).

HRMS (EI) for $C_{16}H_{13}F_3O_2$ (294.0868): 294.0855.

Preparation of ethyl 3'-(trifluoromethyl)biphenyl-4-carboxylate (24j):



The magnesium reagent **23i** was prepared according to **TP1** from 1-bromo-3-(trifluoromethyl)benzene (**22i**, 450 mg, 2.0 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to **TP2** with ethyl 4-iodobenzoate (386 mg, 1.4 mmol) in 1.5 h at 25 °C. Flash column chromatography (pentane/CH_2Cl_2 = 4:1) furnished **24j** as a colorless solid (375 mg, 91 %).

M.p.: 85-87 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.14 (d, J = 8.0 Hz, 2H), 7.85 (s, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.66-7.63 (m, 3H), 7.59-7.56 (m, 1H), 4.41 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).

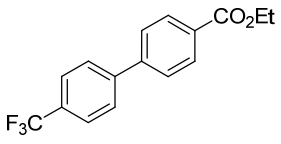
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 166.3, 143.9, 140.9, 131.4 (q, J = 32.3 Hz), 130.5, 130.2, 130.0, 129.4, 124.7 (q, J = 3.7 Hz), 124.0 (q, J = 272 Hz), 124.0 (q, J = 3.7 Hz), 61.1, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3065, 2982, 2943, 2909, 2873, 1704, 1664, 1609, 1595, 1571, 1491, 1475, 1456, 1440, 1401, 1368, 1332, 1309, 1300, 1274, 1264, 1188, 1178, 1157, 1119, 1105, 1099, 1076, 1034, 1017, 976, 962, 928, 920, 875, 853, 840, 825, 816, 806, 766, 737, 701, 669.

MS (70 eV, EI) *m/z* (%): 249 (100) [M^+], 266 (82), 250 (45), 201 (81), 152 (52).

HRMS (EI) for $C_{16}H_{13}F_3O_2$ (294.0868): 294.0877.

Preparation of ethyl 4'-(trifluoromethyl)biphenyl-4-carboxylate (24k):



The magnesium reagent **23j** was prepared according to **TP1** from 4-bromo benzotrifluoride (**22j**, 450 mg, 2.0 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to **TP2** with ethyl 4-iodobenzoate (386 mg, 1.4 mmol) in 1 h. Flash column chromatography (pentane/CH_2Cl_2 = 4:1) furnished **24k** as a colorless solid (398 mg, 97 %).

M.p.: 91-93 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, J = 8.8 Hz, 2H), 7.71 (s, 4H), 7.65 (d, J = 8.8 Hz, 2H), 4.41 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H).

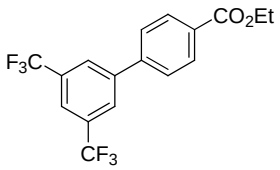
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.2, 143.9, 143.6, 130.2, 130.2, 130.1 (q, J = 33 Hz), 127.6, 127.2, 125.8 (q, J = 4 Hz), 124.1 (q, J = 272 Hz), 61.1, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984, 1708, 1608, 1481, 1395, 1280, 1110, 838.

MS (70 eV, EI) *m/z* (%): 294 (38) [M^+], 249 (100), 201 (29), 152 (27), 71 (33), 57 (54).

HRMS (EI) for $C_{16}H_{13}F_3O_2$ (294.0868): 294.0864.

Preparation of ethyl 3',5'-bis(trifluoromethyl)biphenyl-4-carboxylate (24l):



The magnesium reagent **23k** was prepared according to **TP1** from 1-bromo-3,5-bis(trifluoromethyl)benzene (**22k**, 586 mg, 2.0 mmol) in 30 min at 0 °C at 25 °C. A cross-coupling reaction was performed according to **TP2** with ethyl 4-iodobenzoate (386 mg, 1.4 mmol) in 1 h. Flash column chromatography (pentane/CH_2Cl_2 = 4:1) furnished **24l** as a colorless solid (420 mg, 83 %).

M.p.: 98-100 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.17 (d, J = 8.2 Hz, 2H), 8.03 (s, 2H), 7.90 (s, 1H), 7.67 (d, J = 8.2 Hz, H), 4.42 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).

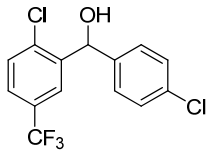
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 166.0, 142.3, 142.2, 132.3 (q, J = 33.3 Hz), 130.9, 130.5, 127.4, 127.2, 123.2 (q, J = 273 Hz), 121.7 (sept., J = 3.7 Hz), 61.3, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1714, 1670, 1610, 1572, 1515, 1478, 1465, 1453, 1402, 1382, 1370, 1327, 1309, 1286, 1278, 1258, 1180, 1169, 1123, 1114, 1104, 1053, 1026, 1016, 964, 941, 919, 895, 874, 859, 845, 837, 828, 792, 780, 772, 727, 703, 682, 667.

MS (70 eV, EI) *m/z* (%): 362 (25) [M^+], 334 (44), 317 (100), 269 (29), 220 (11).

HRMS (EI) for $C_{18}H_{19}BrO_3$ (362.0741): 362.0740

Preparation of (4-chlorophenyl)[2-chloro-5-(trifluoromethyl) phenyl]methanol (24m):



The magnesium reagent **23l** was prepared according to **TP1** from 2-bromo-1-chloro-4-(trifluoromethyl)benzene (**22l**, 519 mg, 2.0 mmol) in 30 min at 25 °C. 4-Chlorobenzaldehyde (197 mg, 1.4 mmol) was added at 0 °C and the mixture warmed to 25 °C. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (CH_2Cl_2) furnished **24m** as a colorless solid (395 mg, 88 %).

M.p.: 121-122 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.98-7.97 (m, 1H), 7.51-7.43 (m, 2H), 7.33-7.27 (m, 4H), 6.16 (s, 1H), 2.43 (brs, 1H).

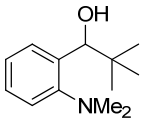
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 141.6, 139.8, 135.9, 134.1, 130.2, 129.7 (q, J = 33 Hz), 128.9, 128.4, 125.7 (q, J = 4 Hz), 124.7 (q, J = 4 Hz), 123.7 (q, J = 272 Hz), 71.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3256, 1608, 1596, 1582, 1490, 1475, 1412, 1324, 1286, 1254, 1231, 1181, 1163, 1122, 1104, 1079, 1060, 1032, 1016, 966, 953, 946, 920, 908, 831, 825, 768, 731, 713, 699, 660, 636, 621, 606.

MS (70 eV, EI) *m/z* (%): 319 (23) [M^+], 207 (100), 179 (31), 141 (23), 111 (33).

HRMS (EI) for $C_{14}H_9Cl_2F_3O$ (319.9983): 319.9958.

Preparation of 1-[2-(dimethylamino)phenyl]-2,2-dimethylpropan-1-ol (24n):



The magnesium reagent **23m** was prepared according to **TP1** from 2-bromo-*N*,*N*-dimethylaniline (**22m**, 400 mg, 2.0 mmol) in 30 min at 25 °C. Pivaldehyde (121 mg, 1.4 mmol) was added at 0 °C and the mixture warmed to 25 °C. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic

layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane/EtOAc = 9:1) furnished **24n** as a colorless oil (263 mg, 91 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34-7.22 (m, 2H), 7.14-7.07 (m, 2H), 4.56 (s, 1H), 2.68 (s, 6H), 0.93 (s, 9H).

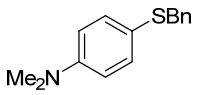
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 152.6, 136.2, 130.3, 127.7, 124.9, 122.7, 83.2, 46.8, 37.4, 26.5.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3408, 3156, 3062, 3024, 2950, 2905, 2866, 2826, 2786, 1597, 1578, 1481, 1459, 1450, 1406, 1391, 1361, 1301, 1276, 1237, 1214, 1178, 1162, 1154, 1146, 1098, 1066, 1040, 1009, 945, 935, 903, 870, 827, 769, 750, 734, 714, 648, 636.

MS (70 eV, EI) *m/z* (%): 207 (9) [M^+], 150 (100), 120 (20).

HRMS (EI) for $C_{13}H_{21}NO$ (207.1623): 207.1618.

Preparation of 4-(benzylthio)-*N*,*N*-dimethylaniline (24o):



The magnesium reagent **23n** was prepared according to **TP1** from 4-bromo-*N*,*N*-dimethylaniline (**22n**, 400 mg, 2.0 mmol) in 30 min at 25 °C. *S*-benzyl benzenesulfonothioate (370 mg, 1.4 mmol) was added at 0 °C and the mixture warmed to 25 °C. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane/Et_2O = 9:1) furnished **24o** as a pale orange solid (221 mg, 65 %).

M.p.: 93-94 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.30-7.18 (m, 7H), 6.63 (d, J = 8.6 Hz, 2H), 3.96 (s, 2H), 2.95 (s, 6H).

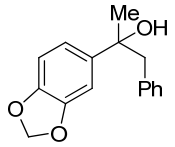
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 149.8, 138.5, 134.5, 128.9, 128.2, 126.8, 120.6, 112.7, 41.9, 40.5.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3060, 3029, 2923, 2852, 2799, 1860, 1595, 1501, 1446, 1353, 1227, 1204, 1167, 1068, 1025, 947, 806, 715, 695, 611.

MS (70 eV, EI) *m/z* (%): 243 (41) [M^+], 152 (100), 136 (7), 108 (3).

HRMS (EI) for $C_{15}H_{17}NS$ (243.1082s): 243.1080.

Preparation of 2-(1,3-benzodioxol-5-yl)-1-phenylpropan-2-ol (24p):



The magnesium reagent **23o** was prepared according to **TP1** from 5-bromo-1,3-benzodioxole (**22o**, 402 mg, 2.0 mmol) in 30 min at 25 °C. In a second flask, 1-phenylacetone (188 mg, 1.4 mmol) and $LaCl_3 \cdot 2$ LiCl (2.7 mL, 1.4 mmol, 0.52 M in THF) were stirred at 25 °C for 30 min. **2m** was then slowly added at 0 °C, the reaction mixture warmed to 25 °C and stired for 2h. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane/EtOAc = 9:1 → 4:1) furnished **24p** as a colorless solid (326 mg, 91 %).

M.p.: 45-48 °C.

^{1}H-NMR (300 MHz, C_6D_6) δ (ppm): 7.10-6.94 (m, 6H), 6.69-6.62 (m, 2H), 5.35-5.33 (m, 2H), 2.93-2.78 (m, 2H), 1.60 (s, H), 1.29 (s, 3H).

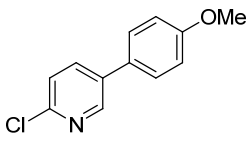
^{13}C-NMR (75 MHz, C_6D_6) δ (ppm): 147.6, 146.2, 142.2, 137.2, 130.6, 127.8, 127.7, 127.4, 126.4, 118.3, 107.4, 106.3, 100.5, 74.0, 50.5, 29.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3550, 3318, 3027, 2980, 2891, 2773, 1603, 1582, 1502, 1487, 1453, 1435, 1394, 1374, 1351, 1273, 1239, 1228, 1183, 1155, 1135, 1122, 1103, 1091, 1072, 1035, 971, 931, 910, 897, 878, 848, 833, 809, 801, 753, 728, 698, 650, 622, 609.

MS (70 eV, EI) *m/z* (%): 256 (1) [M^+], 238 (8), 165 (100).

HRMS (EI) for $C_{16}H_{16}O_3$ (256.1099): 256.1093.

Preparation of 2-chloro-5-(4-methoxyphenyl)pyridine (24q):



The magnesium reagent **23p** was prepared according to **TP1** from 5-bromo-2-chloropyridine (**22p**, 385 mg, 2.0 mmol) in 30 min at 0 °C. A cross-coupling reaction was performed according to **TP2** with 4-iodoanisole (328 mg, 1.4 mmol) in 6 h at 25 °C. Flash column chromatography (CH_2Cl_2) furnished **24q** as a colorless solid (258 mg, 84 %).

M.p.: 127-128 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.55 (d, J = 2.2 Hz, 1H), 7,78 (dd, J = 2.2 Hz, J = 8.2 Hz, 1H), 7.49-7.46 (m, 2H), 7.35 (d, J = 8.2 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 3.85 (s, 3H).

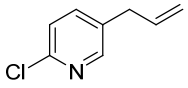
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 160.0, 149.6, 147.5, 136.7, 135.3, 128.8, 128.1, 124.1, 114.7, 55.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3015, 2963, 2935, 2838, 1607, 1584, 1516, 1451, 1366, 1288, 1253, 1186, 1039, 814.

MS (70 eV, EI) *m/z* (%): 219 (100) [M^+], 204 (50), 176 (39), 140 (21).

HRMS (EI) for $C_{12}H_{10}ONCl$ (219.0451): 219.0428.

Preparation of 5-allyl-2-chloropyridine (24r):



The magnesium reagent **23p** was prepared according to **TP1** from 5-bromo-2-chloropyridine (**22p**, 385 mg, 2.0 mmol) in 30 min at 0 °C. An allylation reaction was performed according to **TP3** with allyl bromide (169 mg, 1.4 mmol) in 15 min. Flash column chromatography (CH_2Cl_2) furnished **24r** as a colorless oil (134 mg, 62 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.20 (d, J = 2.4 Hz, 1H), 7.48-7.44 (m, 1H), 7.26-7.23 (m, 1H), 5.97-5.83 (m, 1H), 5.15-5.04 (m, 2H), 3.35 (d, J = 6.6 Hz, 2H).

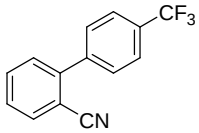
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 149.7, 149.3, 139.0, 135.5, 134.2, 123.9, 117. 3, 36.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3082, 3045, 2980, 2908, 1640, 1584, 1564, 1457, 1433, 1414, 1380, 1289, 1210, 1136, 1100, 1023, 992, 917, 841, 813, 742, 700, 684, 654.

MS (70 eV, EI) *m/z* (%): 153 (100) [M^+], 118 (63), 91 (35).

HRMS (EI) for C_8H_8ClN (153.0345): 153.0339.

Preparation of 4'-(trifluoromethyl)biphenyl-2-carbonitrile (24s):



The magnesium reagent **23q** was prepared according to **TP1** from 2-bromobenzonitrile (**22q**, 364 mg, 2.0 mmol) in 35 min at 25 °C. A cross-coupling reaction was performed according to **TP2** with 1-bromo-4-(trifluoromethyl)benzene (315 mg, 1.4 mmol) using $Pd(OAc)_2$ (5 mg, 1 mol%) and S-Phos (16 mg, 2 mol%) in 16 h. Flash column chromatography (pentane/CH_2Cl_2 = 2:1) furnished **24s** as a colorless solid (235 mg, 68 %).

M.p.: 103-104 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.82-7.65 (m, 6H), 7.53-7.48 (m, 2H).

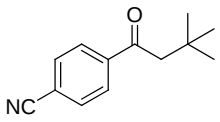
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 143.9, 141.5, 133.9, 133.0, 131.3 (q, J = 33 Hz), 130.0, 129.2, 128.4, 125.7 (q, J = 3 Hz), 124.0 (q, J = 272 Hz), 118.2, 111.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2226, 1619, 1596, 1566, 1481, 1408, 1328, 1270, 1260, 1245, 1198, 1182, 1165, 1116, 1104, 1070, 1048, 1020, 1007, 974, 964, 958, 886, 844, 799, 766, 733, 708, 668, 660, 641, 636, 626, 611.

MS (70 eV, EI) *m/z* (%): 247 (100) [M^+], 218 (34), 203 (19), 177 (11).

HRMS (EI) for $C_{14}H_8F_3N$ (247.0609): 247.0620.

Preparation of 4-(3,3-dimethylbutanoyl)benzonitrile (24t):



The magnesium reagent **23r** was prepared according to **TP1** from 4-bromobenzonitrile (**22r**, 362 mg, 2.0 mmol) in 45 min at 25 °C. The freshly prepared magnesium reagent wascooled to -20 °C and CuCN·2 LiCl (2.0 mL, 1.0 m in THF, 2.0 mmol) was added. After stirring for 30 min, 3,3-dimethylbutanoyl chloride (188 mg, 1.4 mmol) was added and the reaction mixture was warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL) followed by 25% aq. NH_3 solution (5 mL) and extracted with Et_2O (3x 30 mL). The

combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane/CH_2Cl_2 = 2:1) furnished **24t** as a colorless oil (161 mg, 57 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.01 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 2.86 (s, 2H), 1.05 (s, 9H).

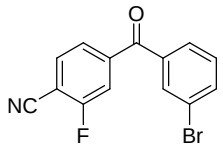
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 198.9, 141.1, 132.4, 128.5, 118.0, 116.0, 50.3, 31.5, 29.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3067, 2956, 2906, 2869, 2232, 1759, 1695, 1679, 1606, 1566, 1500, 1466, 1446, 1404, 1390, 1364, 1318, 1290, 1248, 1229, 1198, 1186, 1172, 1146, 1109, 1074, 1055, 1036, 1009, 931, 909, 855, 826, 794, 778, 736, 718, 698, 644, 618.

MS (70 eV, EI) *m/z* (%): 201 (9) [M^+], 145 (98), 130 (100), 102 (31), 99 (19).

HRMS (EI) for $C_{13}H_{15}NO$ (201.1154): 201.1154.

Preparation of 4-(3-bromobenzoyl)-2-fluorobenzonitrile (24u):



The magnesium reagent **23s** was prepared according to **TP1** from 4-bromo-2-fluorobenzonitrile (**22s**, 400 mg, 2.0 mmol) in 45 min at 25 °C. An acylation reaction was performed according to **TP3** with 3-bromobenzoyl chloride (307 mg, 1.4 mmol) in 1 h. Flash column chromatography (pentane/CH_2Cl_2 = 1:1) furnished **24u** as a colorless solid (254 mg, 60 %).

M.p.: 89-91 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.91-7.90 (m, 1H), 7.81-7.76 (m, 2H), 7.69-7.59 (m, 3H), 7.43-7.38 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 192.1, 162.4 (d, J = 261 Hz), 142.9 (d, J = 6.2 Hz), 137.6, 136.5, 133.8, 132.7, 130.3, 128.7, 125.7 (d, J = 4 Hz), 123.1, 117.4 (d, J = 21 Hz), 113.0, 105.3 (d, J = 16 Hz).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3063, 2237, 1662, 1631, 1564, 1493, 1471, 1412, 1290, 1276, 1260, 1211, 1183, 1172, 1149, 1098, 1074, 998, 982, 922, 908, 889, 882, 844, 800, 751, 736, 720, 708, 686, 657, 635.

MS (70 eV, EI) *m/z* (%): 302 (51) [M^+], 183 (100), 148 (59), 120 (35).

HRMS (EI) for $C_{14}H_7BrFNO$ (302.9695): 302.9670.

2.2. Preparation of Aryl- and Heteroarylzinc Reagents by Magnesium Insertion in the Presence of LiCl and $ZnCl_2$

2.2.1. Typical Procedure for the Magnesium Insertion in the Presence of $ZnCl_2$ (TP4)

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (212 mg, 5.0 mmol) and was heated under high vacuum for 5 min. $ZnCl_2$ (300 mg, 2.2 mmol) was added and was similarly heated under high vacuum. Magnesium powder (122 mg, 5.0 mmol) and 5 mL THF were added and the magnesium powder was activated with *i*Bu_2AlH (0.2 mL, 0.1 m in THF, 0.02 mmol). After 5 min of stirring the aryl or alkyl bromide (2.0 mmol) was added in one portion at the given temperature. The reaction mixture was stirred for the given time and then cannulated to a new *Schlenk*-flask for the reaction with an electrophile.

2.2.2. Typical Procedure for Cross-Coupling Reactions of Arylzinc Reagents (TP5)

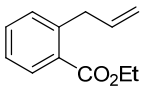
$Pd(dba)_2$ (32 mg, 2 mol%), P(2-furyl)$_3$ (26 mg, 4 mol%) were added to the freshly prepared zinc reagent followed by the aryliodide (1.4 mmol) and the mixture was stirred for the given time at 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) extracted with EtOAc (3x 10 mL). 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.

2.2.3. Typical Procedure for Acylation Reactions of Arylzinc Reagents (TP6)

The freshly prepared zinc reagent was cooled to -20 °C, CuCN·2 LiCl (2 mL, 2.0 mmol, 1 M in THF) was added and the reaction mixture was stirred for 15 min. After the addition of the acid chloride, the reaction mixture was allowed to warm to 25 °C and stirred 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, 2x 10 mL) extracted with EtOAc (3x 10 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.

2.2.4. Preparation of Title Compounds

Preparation of ethyl 2-allylbenzoate (27):



The zinc reagent **26** was prepared according to **TP4** from ethyl 2-bromobenzoate (**25**, 458 mg, 2.0 mmol) in 3 h at 25 °C. An allylation reaction was performed according to **TP3** with allyl bromide (169 mg, 1.4 mmol) in 30 min. Flash column chromatography (pentane/Et_2O = 3:1) furnished **27** as a colorless oil (232 mg, 88 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.90 (dd, J = 1.3 Hz, J = 8.2 Hz, 1H), 7.47-7.25 (m, 1H), 7.23 (t, J = 8.2 Hz, 2H), 6.11-5.98 (m, 1H), 5.07-5.01 (m, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.79 (d, J = 5.4 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).

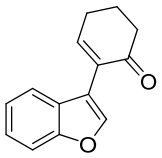
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.6, 141.3, 137.4, 131.8, 130.8, 130.4, 130.1. 126.1, 115.4, 60.7, 38.3, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3056, 2982, 1423, 1266.

MS (70 eV, EI) *m/z* (%): 190 (53) [M^+], 175 (63), 147 (74), 145 (73), 144 (37), 117 (81), 116 (45), 115 (100).

HRMS (EI) for $C_{12}H_{14}O_2$ (190.0994): 190.0996.

Preparation of 2-(1-benzofuran-3-yl)cyclohex-2-en-1-one (30):



According to **TP4**, the zinc reagent **29** was prepared from 3-bromo-1-benzofuran (**28**, 394 mg, 2.0 mmol) in 2 h at 25 °C. The Palladium-catalyzed cross-coupling reaction with 2-iodocyclohex-2-en-1-one (311 mg, 1.4 mmol) using $Pd(OAc)_2$ (5 mg, 1 mol%) and S-Phos (16 mg, 2 mol%) was performed according to **TP5** in 30 min at 25 °C. Flash column chromatography (pentane/CH_2Cl_2 = 1:1) furnished **30** as a pale yellow oil (271 mg, 91 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.09 (s, 1H), 7.66-7.63 (m, 1H), 7.52-7.49 (m, 1H), 7.44-7.41 (m, 1H), 7.33-7.23 (m, 2H), 2.65-2.57 (m, 4H), 2.17-2.08 (m, 2H).

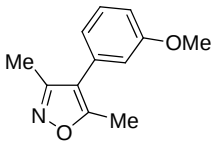
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 197.4, 154.8, 146.5, 144.5, 131.5, 126.2, 124.1, 122.6, 120.3, 114.8, 111.6, 39.0, 26.4, 22.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3344, 3150, 2942, 2865, 1674, 1544, 1451, 1377, 1306, 1240, 1193, 1156, 1106, 1086, 1070, 958, 905, 856, 801, 752, 714.

MS (70 eV, EI) *m/z* (%): 212 (100) [M^+], 184 (49), 167 (23), 156 (28), 149 (69), 128 (21).

HRMS (EI) for $C_{16}H_{15}ClO_2S$ (212.0837): 212.0828.

Preparation of 4-(3-methoxyphenyl)-3,5-dimethylisoxazole (33):



According to **TP4**, the zinc reagent **32** was prepared from 4-bromo-3,5-dimethylisoxazole (**31**, 352 mg, 2.00 mmol) in 15 min at 25 °C. The Pd-catalyzed cross-coupling reaction with 1-bromo-3-methoxybenzene (212 mg, 1.4 mmol) using $Pd(OAc)_2$ (5 mg, 1 mol%) and S-Phos (16 mg, 2 mol%) was performed according to **TP5** in 1 h at 25 °C. Flash column chromatography (pentane/EtOAc = 9:1) furnished **33** as colorless oil (257 mg, 90 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37-7.32 (m, 1H), 6.91-6.87 (m, 1H), 6.85-6.81 (m, 1H), 6.78-6.77 (m, 1H), 3.83 (s, 3H), 2.40 (s, 3H), 2.27 (s, 3H).

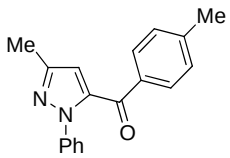
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.2, 159.7, 158.7, 131.8, 19.8, 121.5, 116.5, 115.1, 112.6, 55.3, 11.6, 10.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2998, 2934, 2836, 1630, 1600, 1577, 1502, 1483, 1464, 1420, 1408, 1382, 1369, 1317, 1296, 1283, 1247, 1210, 1180, 1170, 1095, 1055, 1025, 1009, 995, 982, 875, 859, 844, 834, 784, 761, 705, 694, 677, 616.

MS (70 eV, EI) *m/z* (%): 203 (100) [M^+], 188 (50), 160 (37), 146 (16), 134 (22), 119 (30), 91 (20).

HRMS (EI) for $C_{12}H_{13}NO_2$ (203.0946): 203.0935.

Preparation of (4-toluoyl)(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)methanone (36):



According to **TP4**, the zinc reagent **35** was prepared from 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole (**34**, 385 mg, 2.0 mmol) in 3.5 h at 25 °C. The acylation reaction with 4-toluoyl chloride (216 mg, 1.4 mmol) was performed according to **TP6** in 1 h at 25 °C. Flash column chromatography (pentane/EtOAc = 9:1) furnished **36** as colorless solid (352 mg, 91 %).

M.p.: 131-132 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.83 (d, J = 8.3 Hz, 2H), 7.38-7.25 (m, 7H), 6.55 (s, 1H), 2.42 (s, 3H), 2.39 (s, 3H).

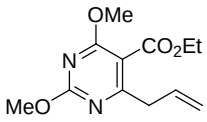
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 185.4, 148.7, 144.5, 140.1, 139.9, 134.7, 129.9, 129.2, 128.8, 127.7, 124.6, 113.1, 21.7, 13.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3056, 3034, 2928, 2854, 2360, 2342, 1738, 1650, 1598, 1502, 1462, 1434, 1360, 1288, 1240, 1148, 1134, 902, 832, 810, 794, 768, 752, 694, 668, 656, 638, 612.

MS (70 eV, EI) *m/z* (%): 276 (100) [M^+], 247 (30), 185 (13), 119 (26), 91 (20).

HRMS (EI) for $C_{18}H_{16}N_2O$ (276.1263): 276.1256.

Preparation of ethyl 4-allyl-2,6-dimethylpyrimidine-5-carboxylate (39):



According to **TP4**, the zinc reagent **38** was prepared from ethyl 4-chloro-2,6-dimethylpyrimidine-5-carboxylate (**37**, 437 mg, 2.0 mmol) in 9 h at 25 °C. The allylic substitution reaction with allyl bromide (170 mg, 1.4 mmol) was performed according to **TP3** in 1 h at 25 °C. Flash column chromatography (pentane/Et_2O = 6:1) furnished **39** as colorless oil (240 mg, 68 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.05-5.91 (m, 1H), 5.16-5.06 (m, 2H), 4.34 (q, J = 7.1 Hz, 2H), 3.99 (s, 6H), 3.50 (td, J = 1.5, J = 6.6 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 169.4, 169.2, 165.7, 164.6, 133.7, 117.4, 107.9, 61.5, 54.9, 54.5, 40.1, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984, 2958, 2904, 2876, 2362, 2342, 1726, 1638, 1558, 1482, 1458, 1374, 1360, 1298, 1256, 1244, 1206, 1196, 1120, 1106, 1078, 1058, 996, 974, 944, 916, 868, 848, 814, 780, 746, 728, 684, 668, 652, 616.

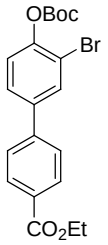
MS (70 eV, EI) *m/z* (%): 252 (47) [M^+], 223 (100), 205 (28), 179 (9).

HRMS (EI) for $C_{12}H_{16}N_2O_4$ (252.1110): 252.1104

2.3. Regioselectivity of Zinc and Magnesium Insertions into Polybrominated Arenes

2.3.1. Preparation of Title Compounds

Preparation of ethyl 3'-bromo-4'-[(*tert*-butoxycarbonyl)oxy]biphenyl-4-carboxylate (44a):



The magnesium reagent **42a** was prepared according to **TP1** from *tert*-butyl 2,4-dibromophenyl carbonate (**40a**, 704 mg, 2.0 mmol) in 30 min at -10 °C. A cross-coupling reaction was performed according to **TP2** with ethyl 4-iodobenzoate (386 mg, 1.4 mmol) in 3 h. Flash column chromatography (pentane/CH_2Cl_2 = 2:1) furnished **44a** as a pale brown solid (572 mg, 97 %).

M.p.: 59-61 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.10 (d, J = 8.6 Hz 2H), 7.83 (d, J = 2.1 Hz, 1H), 7.60-7.53 (m, 3H), 7.29 (d, J = 8.3 Hz, 1H), 4.39 (q, J = 7.2 Hz, 2H), 1.58 (s, 9H), 1.41 (t, J = 7.2 Hz, 3H).

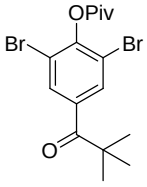
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.3, 150.8, 148.3, 143.2, 139.6, 132.1, 130.2, 129.9, 127.4, 127.0, 123.8, 116.9, 84.5, 61.1, 27.7, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 2938, 2906, 1756, 1704, 1656, 1610, 1580, 1564, 1518, 1478, 1458, 1418, 1394, 1370, 1340, 1276, 1252, 1230, 1144, 1126, 1108, 1052, 1042, 1034, 1016, 956, 896, 854, 832, 770, 752, 726, 696, 678.

MS (70 eV, EI) *m/z* (%): 420 (<1) [M^+], 320 (100), 294 (20), 277 (71), 168 (47), 139 (33).

HRMS (EI) for $C_{20}H_{21}BrO_5$ (420.0572): 420.0573.

Preparation of 2,6-dibromo-4-(2,2-dimethylpropanoyl)phenyl pivalate (44b):



The zinc reagent **42b** was prepared according to **TP4** from 2,4,6-dibromophenyl pivalate (**40b**, 4.15 g, 10.0 mmol) in 45 min at 25 °C. An acylation reaction was performed according

to **TP6** with pivaloyl chloride (844 mg, 7.0 mmol) in 6 h. Flash column chromatography (pentane/CH_2Cl_2 = 4:1 → 1:1) furnished **44b** as a colorless solid (2.50 g, 85 %).

M.p.: 84-86 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.88 (s, 2H), 1.43 (s, 9H), 1.33 (s, 9H).

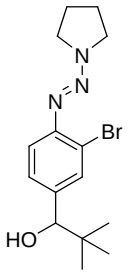
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 205.0, 174.2, 148.4, 137.6, 132.1, 117.1, 44.4, 39.5, 27.9, 27.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2968, 2934, 2910, 2872, 1764, 1684, 1550, 1478, 1456, 1396, 1380, 1366, 1286, 1270, 1236, 1226, 1194, 1158, 1078, 1046, 1026, 990, 946, 886, 852, 784, 750, 732, 714, 702, 680, 602, 584.

MS (70 eV, EI) *m/z* (%): 418 (<1) [M^+], 336 (9), 279 (65), 192 (17), 165 (9), 84 (58), 57 (100).

HRMS (EI) for $C_{16}H_{20}Br_2O_3$ (417.9779): 417.9768.

Preparation of 1-{3-bromo-4-[pyrrolidin-1-yldiazenyl]phenyl}-2,2-dimethylpropan-1-ol (44c):



The magnesium reagent **42c** was prepared according to **TP1** from 1-[(2,4-dibromophenyl)diazenyl]pyrrolidine (**40c**, 666 mg, 2.0 mmol) in 30 min at 0 °C. Pivaldehyde (121 mg, 1.4 mmol) was added at 0 °C and the mixture was warmed to 25 °C. The reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (CH_2Cl_2) furnished **44c** as a light brown solid (364 mg, 76 %).

M.p.: 164-166 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.51 (d, J = 1.8 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.15 (dd, J = 1.8 Hz, J = 8.3 Hz, 1H), 4.32 (s, 1H), 3.93-3.73 (brm, 4H), 2.03 (brs, 4H), 1.89 (s, 1H), 0.9 (s, 9H).

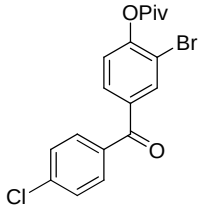
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 147.8, 140.3, 131.9, 127.1, 118.6, 117.5, 81.5, 51.1, 46.8, 35.7, 25.9, 23.9, 23.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3352, 2978, 2964, 2952, 2930, 2900, 2868, 2830, 2360, 1908, 1748, 1728, 1682, 1598, 1554, 1476, 1464, 1452, 1446, 1410, 1394, 1360, 1342, 1310, 1290, 1268, 1236, 1224, 1210, 1188, 1176, 1160, 1134, 1102, 1066, 1040, 1010, 972, 934, 908, 894, 876, 856, 830, 792, 766, 726, 710, 664, 638, 606, 580, 570, 556.

MS (70 eV, EI) *m/z* (%): 339 (7) [M^+], 282 (100), 185 (18), 77 (25).

HRMS (EI) for $C_{15}H_{22}BrN_3O$ (339.0946): 339.0940.

Preparation of 2-bromo-4-(4-chlorobenzoyl)phenyl pivalate (44f):



The magnesium reagent **42f** was prepared according to **TP1** from 2,4-dibromophenyl pivalate (**40f**, 672 mg, 2.0 mmol) in 1 h at -20 °C. An acylation reaction was performed according to **TP3** with 4-chlorobenzoyl chloride (245 mg, 1.4 mmol) in 1 h at 25 °C. Flash column chromatography (pentane/CH_2Cl_2 = 3:1) furnished **44f** as a colorless solid (430 mg, 78 %).

M.p.: 54-56 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.02 (d, J = 2.0 Hz, 1H), 7.74-7.71 (m, 3H), 7.47 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 1H), 1.41 (s, 9H).

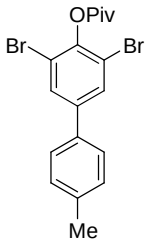
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 193.0, 175.6, 151.9, 139.3, 136.0, 135.2, 135.0, 131.3, 130.1, 128.8, 123.7, 116.6, 39.4, 27.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972, 2934, 2908, 2874, 1760, 1652, 1586, 1566, 1476, 1460, 1396, 1382, 1366, 1300, 1276, 1254, 1234, 1216, 1174, 1152, 1088, 1044, 1028, 1012, 958, 942, 898, 888, 852, 840, 800, 754, 704, 678, 658, 648, 628, 604, 590, 582.

MS (70 eV, EI) *m/z* (%): 394 (2) [M^+], 312 (100), 199 (58), 139 (88), 85 (62).

HRMS (EI) for $C_{18}H_{16}BrClO_3$ (393.9971): 393.9980.

3,5-dibromo-4'-methylbiphenyl-4-yl pivalate (44g):



The zinc reagent **42g** was prepared according to **TP4** from 2,4,6-tribromophenyl pivalate (**40g**, 830 mg, 2.0 mmol) in 45 min at 25 °C. A cross-coupling reaction was performed according to **TP5** with 4-iodotoluene (305 mg, 1.4 mmol) in 3 h at 25 °C. Flash column chromatography (pentane/CH_2Cl_2 = 7:1) furnished **44g** as a colorless solid (535 mg, 90 %).

M.p.: 84-86 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.72 (s, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 2.39 (s, 3H), 1.46 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 174.7, 145.1, 141.5, 138.3, 135.0, 130.7, 129.7, 126.9, 117.8, 39.5, 27.2, 21.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 2934, 2908, 2872, 1758, 1700, 1588, 1574, 1542, 1520, 1476, 1452, 1414, 1396, 1380, 1368, 1310, 1286, 1272, 1256, 1234, 1222, 1212, 1188, 1078, 1026, 962, 944, 884, 874, 860, 836, 814, 772, 750, 726, 692, 660, 644, 628, 614, 586, 572, 554.

MS (70 eV, EI) *m/z* (%): 423 (5) [M^+], 340 (100), 153 (25).

HRMS (EI) for $C_{18}H_{18}Br_2O_2$ (423.9674): 423.9678.

2.4. Preparation of Benzylic Zinc Reagents by the Insertion of Magnesium in the Presence of LiCl and $ZnCl_2$

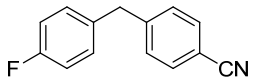
2.4.1. Typical Procedure for the Magnesium Insertion in the Presence of $ZnCl_2$ into Benzylic Chlorides (TP7)

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (122 mg, 5.0 mmol). LiCl (5.0 mL, 0.5 M in THF, 2.5 mmol) and $ZnCl_2$ (2.2 mL, 1.0 M in THF, 2.2 mmol) were added. The benzylic chloride (2.0 mmol) was added in one portion at the given temperature. The reaction mixture was

stirred for the given time and then cannulated to a new *Schlenk*-flask for the reaction with an electrophile.

2.4.2. Preparation of Title Compounds

Preparation of 4-(4-fluorobenzyl)benzonitrile (47b):



The zinc reagent **46b** was prepared according to **TP7** from 4-fluorobenzyl chloride (**45b**, 289 mg, 2.0 mmol) in 45 min at 25 °C. A dry and argon-fushed *Schlenk*-flask was charged with 4-bromobenzonitrile (255 mg, 1.4 mmol), $Pd(OAc)_2$ (5 mg, 1 mol%) and S-Phos (16 mg, 2 mol%). THF (2.0 mL) was added. The mixture was stirred for 15 min and cooled to 0 °C. The freshly prepared zinc reagent **46b** was added, the reaction mixture warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane/CH_2Cl_2 = 4:1) furnished **47b** as a colorless solid (222 mg, 75 %).

M.p.: 67-69 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.57 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.13-7.08 (m, 2H), 7.02-6.96 (m, 2H), 4.00 (s, 2H).

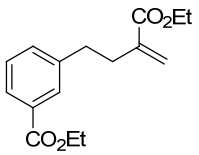
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 163.3, 160.1, 146.5, 135.0 (d, J = 3 Hz), 132.3, 130.3 (d, J = 8 Hz), 118.9, 115.5 (d, J = 21 Hz), 110.2, 41.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3040, 2934, 2222, 1920, 1884, 1606, 1500, 1470, 1446, 1428, 1412, 1310, 1302, 1290, 1258, 1214, 1178, 1154, 1116, 1104, 1088, 1016, 984, 968, 954, 938, 922, 868, 844, 814, 796, 764, 734, 708, 682, 648, 624, 564.

MS (70 eV, EI) *m/z* (%): 211 (100) [M^+], 183 (15), 109 (16).

HRMS (EI) for $C_{14}H_{10}NF$ (211.0797): 211.0771.

Preparation of ethyl 3-[3-(ethoxycarbonyl)but-3-en-1-yl]benzoate (47c):



The zinc reagent **46c** was prepared according to **TP7** from 3-ethoxycarbonylbenzyl chloride (**45c**, 397 mg, 2.0 mmol) in 2 h at 25 °C. The freshly prepared zinc reagent **46c** was added to ethyl (2-bromomethyl)acrylate (270 mg, 1.4 mmol) in 1.0 mL THF at 25 °C. CuCN·2 LiCl (0.4 mL, 1.0 M in THF, 0.4 mmol) was added and the mixture was stirred for 15 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution (45 mL) followed by 25% aq. NH_3 solution (5 mL) and extracted with CH_2Cl_2 (3x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (pentane/CH_2Cl_2 = 1:1) furnished **16c** as a colorless oil (290 mg, 75 %).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.87-7.86 (m, 2H), 7.37-7.32 (m, 2H), 6.15 (s, 1H), 5.48 (s, 1H), 4.37 (q, J = 7.2 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 2.85-2.82 (m, 2H), 2.64-2.61 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H).

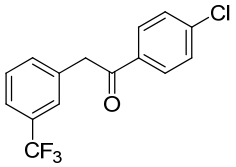
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 167.0, 166.7, 141.7, 139.8, 133.0, 130.6, 129.5, 128.3, 127.3, 125.4, 60.9, 60.7, 34.7, 33.8, 14.3, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2936, 2906, 2872, 1712, 1630, 1608, 1588, 1478, 1464, 1444, 1410, 1392, 1368, 1278, 1186, 1134, 1104, 1082, 1024, 944, 906, 862, 818, 750, 696, 668, 630, 624, 618, 582, 576, 568, 558.

MS (70 eV, EI) *m/z* (%): 276 (13) [M^+], 230 (55), 202 (100), 184 (25), 163 (56), 129 (32), 84 (96).

HRMS (EI) for $C_{16}H_{20}O_4$ (276.1362): 276.1356

Preparation of 1-(4-chlorophenyl)-2-[3-(trifluoromethyl)phenyl]ethanone (47d):



The zinc reagent **46d** was prepared according to **TP7** from 3-(trifluoromethyl)benzyl chloride (**45d**, 389 mg, 2.0 mmol) in 30 min at 25 °C. The freshly prepared zinc reagent **46d** was cooled to -20 °C and CuCN·2 LiCl (2.0 mL, 1.0 M in THF, 2.0 mmol) was added. After stirring for 15 min, 4-chlorobenzoyl chloride (245 mg, 1.4 mmol) was added, the mixture warmed to 25 °C and was stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL) followed by 25% aq. NH_3 solution (2 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo.* Flash column chromatography (pentane/CH_2Cl_2 = 3:1) furnished **47d** as a colorless solid (382 mg, 91 %).

M.p.: 54-56 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.96-7.92 (m, 2H), 7.55-7.41 (m, 6H), 4.32 (s, 2H).

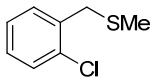
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 195.4, 140.0, 135.0, 134.6, 133.0, 131.0 (q, J = 32.2 Hz), 129.8, 129.1, 129.1, 126.3 (q, J = 4 Hz) 124.0 (q, J = 4 Hz), 124.0 (q, J = 272 Hz), 44.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1694, 1682, 1588, 1572, 1488, 1454, 1400, 1334, 1302, 1284, 1210, 1186, 1176, 1156, 1118, 1106, 1092, 1074, 1014, 1004, 990, 960, 942, 922, 904, 878, 852, 832, 818, 812, 792, 784, 762, 754, 720, 700, 656, 628, 620, 598, 584, 562.

MS (70 eV, EI) *m/z* (%): 279 (2), 139 (100), 111 (18), 75 (6).

HRMS (EI) for $C_{15}H_{10}OClF_3$ (298.0372): 298.0352.

Preparation of 2-chlorobenzyl methyl sulphide (47a):



The zinc reagent **46a** was prepared according to **TP7** from 2-chlorobenzyl chloride (**45a**, 322 mg, 2.0 mmol) in 45 min at 25 °C. $MeSO_2SMe$ (177 mg, 1.4 mmol) was added to the freshly prepared zinc reagent **46a** and the mixture was stirred for 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (pentane) furnished **47b** as a colorless oil (214 mg, 89 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.38-7.32 (m, 2H), 7.24-7.15 (m, 2H), 3.80 (s, 2H), 2.05 (s, 3H).

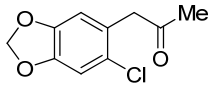
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 136.0, 134.1, 130.7, 129.8, 128.3, 126.7, 35.7, 15.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2914, 1572, 1472, 1442, 1424, 1240, 1120, 1050, 1036, 978, 958, 944, 850, 822, 762, 738, 718, 686, 668, 626, 618, 598, 578.

MS (70 eV, EI) *m/z* (%): 172 (100) [M^+], 127 (94), 89 (24), 63 (10).

HRMS (EI) for C_8H_9ClS (172.0113): 172.0109.

Preparation of 1-(6-chloro-1,3-benzodioxol-5-yl)acetone (47e):



The zinc reagent **46e** was prepared according to **TP7** from 5-chloro-6-(chloromethyl)-1,3-benzodioxole (**45e**, 410 mg, 2.0 mmol) in 15 min at 25 °C. The freshly prepared zinc reagent **46e** was cooled to -20 °C and CuCN·2 LiCl (2.0 mL, 1.0 M in THF, 2.0 mmol) was added. After stirring for 15 min, acetyl chloride (110 mg, 1.4 mmol) was added, the mixture warmed to 25 °C and was stirred for 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL) followed by 25% aq. NH_3 solution (2 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (pentane/CH_2Cl_2 = 1:1) furnished **47e** as a colorless solid (227 mg, 76 %).

m.p.: 79-80 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.85 (s, 1H), 6.65 (s, 1H), 5.96 (s, 2H), 3.72 (s, 2H), 2.18 (s, 3H).

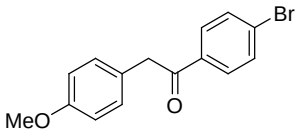
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 205.1, 147.5, 146.8, 126.0, 125.6, 110.8, 109.9, 101.8, 48.1, 29.5.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2912, 1718, 1504, 1488, 1422, 1406, 1394, 1356, 1320, 1256, 1236, 1202, 1192, 1160, 1122, 1034, 990, 968, 924, 874, 858, 846, 784, 696, 654, 596.

MS (70 eV, EI) *m/z* (%): 212 (23) [M^+], 169 (100), 111 (6), 75 (9).

HRMS (EI) for $C_{10}H_9O_3Cl$ (212.0240): 212.0225.

Preparation of 1-(4-bromophenyl)-2-(4-methoxyphenyl)ethanone (47f):



The zinc reagent **46f** was prepared according to **TP7** from 4-methoxybenzyl chloride (**45f**, 276 mg, 1.8 mmol) in 1 h at 25 °C. The freshly prepared zinc reagent **46f** was cooled to -20 °C and CuCN·2 LiCl (2.0 mL, 1.0 M in THF, 2.0 mmol) was added. After stirring for 15 min, 4-bromobenzoyl chloride (285 mg, 1.3 mmol) was added, the mixture warmed to 25 °C and was stirred for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL) followed by 25% aq. NH_3 solution (2 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane/CH_2Cl_2 = 3:1) furnished **4g** as a colorless solid (323 mg, 81 %).

M.p.: 117-118 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.85 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.17 (s, 2H), 3.77 (s, 3H).

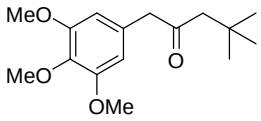
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 196.9, 158.6, 135.3, 131.9, 130.4, 130.1, 128.3, 126.1, 114.2, 55.2, 44.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3310, 2914, 1754, 1494, 1488, 1434, 1424, 1404, 1092, 1058, 1008, 1000, 882, 822, 792, 716.

MS (70 eV, EI) *m/z* (%): 304 (6) [M^+], 183 (19), 121 (100).

HRMS (EI) for $C_{15}H_{13}BrO_2$ (304.0099): 304.0085.

Preparation of 4,4-dimethyl-1-(3,4,5-trimethoxyphenyl)pentan-2-one (47g):



The zinc reagent **46g** was prepared according to **TP7** from 3,4,5-trimethoxybenzyl chloride (**45g**, 433 mg, 2.0 mmol) in 1 h at 25 °C. The freshly prepared zinc reagent **46g** was cooled to -20 °C and CuCN·2 LiCl (2.0 mL, 1.0 M in THF, 2.0 mmol) was added. After stirring for 15 min, 3,3-dimethylbutanoyl chloride (188 mg, 1.4 mmol) was added, the mixture warmed to 25 °C and was stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution

(10 mL) followed by 25% aq. NH_3 solution (2 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (CH_2Cl_2) furnished **47g** as a colorless solid (323 mg, 82 %).

M.p.: 65-66 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.37 (s, 2H), 3.83 (s, 6H), 3.82 (s, 3H), 2.35 (s, 2H), 1.00 (s, 9H).

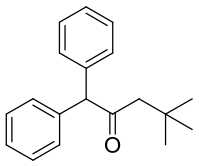
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 207.9, 153.3, 137.0, 129.8, 106.5, 60.8, 56.1, 53.9, 52.2, 31.0, 29.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984, 2954, 2902, 2868, 1708, 1586, 1508, 1464, 1454, 1438, 1422, 1384, 1360, 1350, 1328, 1268, 1240, 1188, 1148, 1124, 1072, 1030, 994, 970, 922, 834, 822, 780, 678, 618.

MS (70 eV, EI) *m/z* (%): 280 (15) [M^+], 181 (100), 99 (4), 57 (12).

HRMS (EI) for $C_{16}H_{24}O_4$ (280.1675): 280.1675.

Preparation of 4,4-dimethyl-1,1-diphenylpentan-2-one (47h):



The zinc reagent **46h** was prepared according to **TP7** from 1,1'-(chloromethylene)dibenzene (**45h**, 405 mg, 2.0 mmol) in 30 min at 0 °C. The freshly prepared zinc reagent **46h** was cooled to -20 °C and CuCN·2LiCl (2.0 mL, 1.0 M in THF, 2.0 mmol) was added. After stirring for 15 min, 3,3-dimethylbutanoyl chloride (188 mg, 1.4 mmol) was added, the mixture warmed to 25 °C and was stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL) followed by 25% aq. NH_3 solution (2 mL) and extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (pentane → pentane/CH_2Cl_2 = 3:2) furnished **47h** as a colorless solid (302 mg, 81 %).

M.p.: 45-47 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.35-7.20 (m, 10H), 5.09 (s, 1H), 2.44 (s, 2H), 1.01 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 207.8, 138.4, 129.0, 128.6, 127.1, 65.7, 54.9, 31.3, 29.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3060, 3028, 2980, 2956, 2904, 2868, 1714, 1596, 1582, 1492, 1464, 1452, 1398, 1388, 1360, 1348, 1306, 1294, 1272, 1252, 1230, 1190, 1154, 1126, 1084, 1060, 1032, 1004, 990, 948, 916, 902, 758, 746, 720, 702, 692, 628, 616, 604.

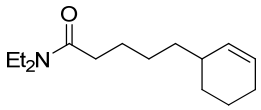
MS (70 eV, EI) *m/z* (%): 183 (1), 167 (100), 152 (10), 99 (18).

HRMS (EI) for $C_{19}H_{22}O$ (266.1671): 266.1659.

2.5. Preparation of Alkylzinc Reagents by the Insertion of Magnesium in the Presence of LiCl and $ZnCl_2$

2.5.1. Preparation of Title Compounds

Preparation of 5-cyclohex-2-en-1-yl-*N*,*N*-diethylpentanamide (53):



The zinc reagent **52** was prepared according to **TP4** from 5-bromo-*N*,*N*-diethylpentanamide (**51**, 472 mg, 2 mmol) in 1 h at 25 °C. CuCN·2 LiCl (0.4 mL, 1 M in THF, 20 mol%) was added at -20 °C and the mixture stirred for 30 min. 3-Bromocyclohexene (225 mg, 1.4 mmol, 0.7 equiv) was added at -20 °C under argon. The mixture was stirred for 1 h and allowed to warm up slowly to 20 °C before being quenched with sat. aqueous NH_4Cl solution (20 mL) and conc. ammonia (20 mL). The aqueous layer was extracted with diethyl ether three times. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (EtOAc/pentane = 1:4) to yield compound **53** (232 mg, 70 %) as colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 5.64-5.51 (m, 2H), 3.37-3.23 (m, 4H), 2.28-2.23 (m, 2H) 2.03-1.09 (m, 21H).

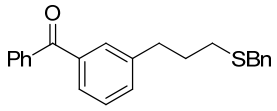
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 172.2, 132.1, 126.7, 41.9, 40.0 36.1, 35.0, 33.1, 29.0, 26.8, 25.7, 25.3, 21.5, 14.4, 13.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2967, 2931, 2861, 1616, 1480, 1448, 1430, 1380, 1362, 1264, 1221.

MS (EI, 70 eV) *m/z* (%): 237 (9) [M^+], 156 (15), 115 (100), 100 (59), 58 (38).

HRMS (EI) for $C_{15}H_{27}NO$ (237.2093): 237.2097.

Preparation of {3-[3-(benzylthio)propyl]phenyl}(phenyl)methanone (56a):



The zinc reagent **55** was prepared according to **TP4** from [3-(3-bromopropyl)phenyl] (phenyl)methanone (**54**, 606 mg, 2 mmol) in 1.5 h at 25 °C. *S*-benzyl benzenesulfonothioate (370 mg, 1.4 mmol, 0.7 equiv) was added at -20 °C and the mixture stirred for 1 h. The solution was allowed to warm up slowly to 20 °C before being quenched with sat. aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with diethyl ether three times. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (Et_2O/pentane = 1:19) to yield compound **56a** (254 mg, 58 %) as colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.79-7.70 (m, 4H), 7.60-7.44 (m, 3H), 7.31-7.22 (m, 7H), 3.70 (s, H), 2.75 (t, J = 7.3 Hz, 2H), 2.44 (t, J = 7.0 Hz, 2H), 1.95-1.85 (m, 2H).

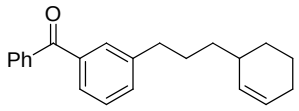
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 196.4, 146.7, 138.4, 137.9, 137.5, 137.5, 135.4, 132.2, 130.4, 129.9, 128.8, 128.5, 128.4, 128.2, 127.0, 36.6, 34.7, 30.6, 30.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3059, 3027, 2922, 2857, 1653, 1604, 1578, 1568, 1494, 1446, 1412, 1315, 1310, 1276, 1202, 1176, 1148, 1072, 1028, 1020, 1000, 938, 922, 847, 787, 768, 740, 697, 680.

MS (EI, 70 eV) *m/z* (%): 346 (52) [M^+] 255 (12), 222 (21), 209 (100), 196 (18), 145 (28), 105 (55), 91 (79).

HRMS (EI) for $C_{23}H_{22}OS$ (346.1391): found 346.1394.

Preparation of [3-(3-cyclohex-2-en-1-ylpropyl)phenyl](phenyl)methanone (56b):



The zinc reagent **55** was prepared according to **TP4** from [3-(3-bromopropyl)phenyl] (phenyl)methanone (**54**, 606 mg, 2 mmol) in 1.5 h at 25 °C. CuCN·2 LiCl (0.4 mL, 1 M in THF, 20 mol%) was added at -20 °C and the mixture stirred for 30 min. 3-Bromocyclohexene (225 mg, 1.4 mmol, 0.7 equiv) was added at -20 °C under argon. The mixture was stirred for 1 h and allowed to warm up slowly to 20 °C before being quenched with sat. aqueous NH_4Cl solution (20 mL) and conc. ammonia (20 mL). The aqueous layer was extracted with diethyl ether three times. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (Et_2O/pentane = 1:9) to yield compound **56b** (261 mg, 61 %) as colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.43-6.97 (m, 9H), 5.70-5.56 (m, 2H), 3.02 (s, 1H) 2.60-2.53 (m, 2H), 2.10 (brs, 1H), 1.79-1.17 (m, 9H).

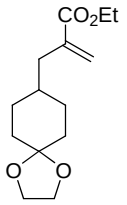
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 144.5, 141.5, 141.3, 132.1, 128.6, 128.4, 127.3, 127.2, 126.8, 126.8, 126.8, 126.7, 35.9, 35.6, 35.0, 29.0, 28.5, 25.4, 21.5.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2971, 2941, 2859, 1659, 1610, 1582, 1560, 1493, 1314, 1321, 1275, 1243, 1153, 1144, 1111, 1022, 1020, 998, 846, 787, 768, 740, 690, 680.

MS (EI, 70 eV) *m/z* (%): 304 (59) [M^+], 209 (100), 196 (42), 183 (22), 118 (18), 105 (92), 77 (75).

HRMS (EI) for $C_{22}H_{24}O$ (304.1827): 304.1804.

Preparation of ethyl 2-(1,4-dioxaspiro[4.5]dec-8-ylmethyl)acrylate (59):



The zinc reagent **58** was prepared according to **TP4** from 8-bromo-1,4-dioxaspiro[4.5]decane (**57**, 442 mg, 2 mmol) in 2 h at 25 °C. CuCN·2 LiCl (1 M solution in THF, 0.4 mL, 0.2 equiv)

was added at -20 °C and the mixture stirred for 30 min. ethyl 2-(bromomethyl)acrylate (270 mg, 1.4 mmol, 0.7 equiv) was added at -20 °C under argon. The mixture was stirred for 1 h and allowed to warm up slowly to 20 °C before being quenched with sat. aqueous NH_4Cl solution (20 mL) and 25% NH_3 (20 mL). The aqueous layer was extracted with diethyl ether three times. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (EtOAc/pentane = 1:9) to yield compound **59** (245 mg, 68 %) as colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.13 (d, J = 1.7 Hz, 1H), 5.46-5.45 (m, 1H), 4.18 (q, J = 7.3 Hz, 2H), 3.90 (s, 4H), 2.21 (d, J = 6.8 Hz, 2H), 1.74-1.64 (m, 4H), 1.53-1.43 (m, 3H), 1.27 (t, J = 7.3 Hz, 3H), 1.23-1.21 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 167.3, 139.3, 125.8, 109.0, 64.2, 60.5, 38.8, 35.1, 34.3, 29.9, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2930, 2879, 2860, 1713, 1629, 1477, 1446, 1410, 1371, 1329, 1301, 1284, 1200, 1174, 1156, 1133, 1104, 1076, 1067, 1033, 1001, 982, 929, 884, 857, 820, 768, 661.

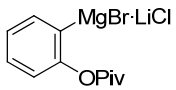
MS (EI, 70 eV) *m/z* (%): 254 (<1) [M^+], 198 (3), 181 (5), 99 (100), 86 (13).

HRMS (EI) for $C_{14}H_{22}O_4$ (254.1518): 254.1494.

2.6. Larger Scale Preparations of Organomagnesium and Organozinc Reagents

2.6.1. Preparation of Title Compounds

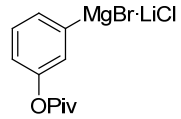
Preparation of 2-[(2,2-dimethylpropanoyl)oxy]phenylmagnesium bromide (23v):



A dry and argon-flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (2.12 g, 50 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (2.43 g, 100 mmol) and THF (100 mL) were added and the

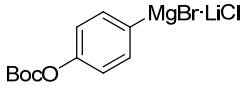
magnesium was activated with *i*Bu_2AlH (0.07 mL, 57 mg, 0.4 mmol). After 5 min of stirring, the suspension was cooled to –20 °C and 2-bromo-1-pivaloyloxybenzene (**22v**, 10.3 g, 40 mmol) was added slowly, so that the reaction temperature is kept below –15 °C. After complete addition, the reaction mixture was stirred for additional 30 min at –20 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed *Schlenk*-flask and the yield of the magnesium reagent was determined by iodometric titration (106 mL, 0.35 M, 37.1 mmol, 93 %).

Preparation of 3-[(2,2-dimethylpropanoyl)oxy]phenylmagnesium bromide (23w):



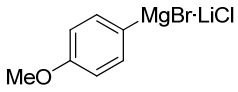
A dry and argon-flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (2.12 g, 50 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (2.43 g, 100 mmol) and THF (100 mL) were added and the magnesium was activated with *i*Bu_2AlH (0.07 mL, 57 mg, 0.4 mmol). After 5 min of stirring, the suspension was cooled to –20 °C and 3-bromo-1-pivaloyloxybenzene (**22w**, 10.3 g, 40 mmol) was added slowly, so that the reaction temperature is kept below –15 °C. After complete addition, the reaction mixture was stirred for additional 30 min at –20 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed *Schlenk*-flask and the yield of the magnesium reagent was determined by iodometric titration (108 mL, 0.32 M, 34.6 mmol, 86 %).

Preparation of 4-[(tert-butoxycarbonyl)oxy]phenylmagnesium bromide (23b):



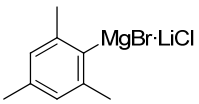
A dry and argon-flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (4.58 g, 108 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (5.23 g, 215 mmol) and THF (215 mL) were added and the magnesium was activated with *i*Bu_2AlH (0.14 mL, 114 mg, 0.8 mmol). After 5 min of stirring, the suspension was cooled to –20 °C and 4-bromophenyl *tert*-butyl carbonate (**22b**, 23.49 g, 86 mmol) was added slowly, so that the reaction temperature is kept below –15 °C. After complete addition, the reaction mixture was stirred for additional 30 min at –20 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed *Schlenk*-flask and the yield of the magnesium reagent was determined by iodometric titration (270 mL, 0.29 M, 78.3 mmol, 91 %).

Preparation of 4-methoxyphenylmagnesium bromide (23x):



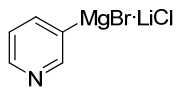
A dry and argon-flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (2.67 g, 63 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (3.04 g, 125 mmol) and THF (125 mL) were added and the magnesium was activated with *i*Bu_2AlH (0.07 mL, 57 mg, 0.4 mmol). After 5 min of stirring, the suspension was cooled to 0 °C and 4-bromoanisole (**22x**, 9.35 g, 50 mmol) was added slowly, so that the reaction temperature is kept below 10 °C. After complete addition, the reaction mixture was stirred for additional 30 min at 0 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed *Schlenk*-flask and the yield of the magnesium reagent was determined by iodometric titration (126 mL, 0.38 M, 47.9 mmol, 97 %).

Preparation of mesitylmagnesium bromide (23y):



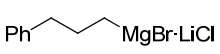
A dry and argon-flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (2.67 g, 63 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (**22y**, 3.04 g, 125 mmol) and THF (125 mL) were added and the magnesium was activated with *i*Bu_2AlH (0.07 mL, 57 mg, 0.4 mmol). After 5 min of stirring, the suspension was cooled to 0 °C and 2-bromo-1,3,5-trimethylbenzene (9.95 g, 50 mmol) was added slowly, so that the reaction temperature is kept below 10 °C. After complete addition, the reaction mixture was stirred for additional 30 min at 0 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed *Schlenk*-flask and the yield of the magnesium reagent was determined by iodometric titration (129 mL, 0.36 M, 46.3 mmol, 93 %).

Preparation of pyridine-3-ylmagnesium bromide (23z):



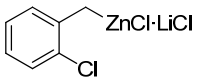
A dry and argon-flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (5.30 g, 125 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (6.08 g, 250 mmol) and THF (250 mL) were added and the magnesium was activated with *i*Bu_2AlH (0.14 mL, 114 mg, 0.8 mmol). After 5 min of stirring, the suspension was cooled to 0 °C and 3-bromopyridine (**22z**, 15.80 g, 100 mmol) was added slowly, so that the reaction temperature is kept below 10 °C. After complete addition, the reaction mixture was stirred for additional 30 min at 0 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed *Schlenk*-flask and the yield of the magnesium reagent was determined by iodometric titration (266 mL, 0.34 M, 90.4 mmol, 90 %).

Preparation of 3-phenylpropyl-1-magnesium bromide (61):



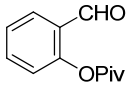
A dry and argon-flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (2.67 g, 63 mmol) and heated with a heat gun under high vacuum (20 min). Magnesium turnings (3.04 g, 125 mmol) and THF (125 mL) were added and the magnesium was activated with *i*Bu_2AlH (0.07 mL, 57 mg, 0.4 mmol). After 5 min of stirring, the suspension was cooled to 0 °C and (3-bromopropyl)benzene (**60**, 9.95 g, 50 mmol) was added slowly, so that the reaction temperature is kept below 10 °C. After complete addition, the reaction mixture was stirred for additional 30 min at 0 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed *Schlenk*-flask and the yield of the magnesium reagent was determined by iodometric titration (124 mL, 0.37 M, 45.7 mmol, 91 %).

Preparation of 2-chlorobenzylzinc chloride (46a):



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with LiCl (2.65 g, 62.5 mmol) and was heated under high vacuum for 20 min. $ZnCl_2$ (3.60 g, 55.0 mmol) was added and was similarly heated under high vacuum. Magnesium turnings (3.04 g, 125 mmol) and THF (125 mL) were added. The suspension was cooled to 0 °C and 2-chlorobenzyl chloride (**45a**, 8.05 g, 50 mmol) was slowly, so that the reaction temperature is kept below 10 °C. After complete addition, the reaction mixture was stirred for additional 30 min at 0 °C. GC-analysis of a quenched reaction aliquot showed complete conversion. Then, the supernatant solution was cannulated to a new dry and argon-flushed *Schlenk*-flask and the yield of the zinc reagent was determined by iodometric titration (132 mL, 0.34 M, 44.9 mmol, 90 %).

Preparation of 2-formylphenyl pivalate (24v):



Freshly prepared and titrated 3-[(2,2-dimethylpropanoyl)oxy]phenylmagnesium bromide (**23v**, 28.6 mL, 0.35 M, 10.0 mmol) was added to a solution of DMF (886 mg, 12 mmol) in THF (5 mL) at -20 °C. The reaction mixture was stirred for 15 min and then warmed to 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane/CH_2Cl_2 = 2:1) furnished **24v** as colorless oil (1.71 g, 83 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 9.99 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.59-7.52 (m, 2H), 7.34-7.31 (m, 1H), 1.36 (s, 9H).

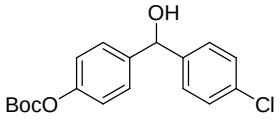
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 191.3, 176.8, 151.7, 137.7, 130.0, 127.8, 127.2, 122.1, 39.1, 27.1.

IR (ATR): $\tilde{\nu}$ (cm^{-1}): 2976, 2937, 2909, 2874, 2730, 1752, 1697, 1606, 1589, 1480, 1449, 1397, 1388, 1368, 1272, 1235, 1162, 1135, 1101, 1030, 1001, 922, 897, 867, 820, 779, 756, 680, 645, 619.

MS (70 eV, EI) *m/z* (%): 206 (1) [M$^+$], 122 (45), 57 (66), 48 (100).

HRMS (EI) for $C_{12}H_{14}O_3$ (206.0943): 206.0917.

Preparation of *tert*-butyl 4-[(4-chlorophenyl)(hydroxy)methyl]phenyl carbonate (24w):



Freshly prepared and titrated 4-[(tert-butoxycarbonyl)oxy]phenylmagnesium bromide (**23b**, 35.5 mL, 0.29 M, 10.0 mmol) was added to a solution of 4-chlorobenzaldehyde (1.69 g, 12 mmol) in THF (5 mL) at –20 °C. The reaction mixture was stirred for 15 min and then warmed to 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane/EtOAc = 4:1) furnished **24w** as colorless oil (3.01 g, 90 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.33 (d, J = 8.5 Hz, 2H), 7.29 (s, 4H), 7.13 (d, J = 8.5 Hz, 2H), 5.80 (s, 1H), 2.01 (brs, 1H), 1.54 (s, 9H).

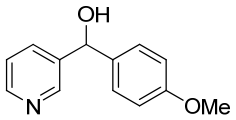
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 151.8, 150.5, 141.9, 140.9, 133.4, 128.6, 127.9, 127.6, 121.4, 83.7, 75.0, 27.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3493, 1728, 1526, 1508, 1496, 1380, 1303, 1294, 1261, 1219, 1150, 1086, 1040, 1013, 898, 824, 814, 806, 784, 614.

MS (70 eV, EI) *m/z* (%): 334 (1) [M^+], 276 (12), 234 (77), 215 (52), 153 (67), 139 (66), 57 (100).

HRMS (EI) for $C_{18}H_{19}ClO_4$ (334.0972): 334.0980.

Preparation of (4-methoxyphenyl)(pyridin-3-yl)methanol (24x):



Freshly prepared and titrated pyridine-3-ylmagnesium bromide (**23z**, 29.4 mL, 0.34 M, 10.0 mmol) was added to a solution of 4-methoxybenzaldehyde (1.63 g, 12 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 15 min and then warmed to 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane/EtOAc = 1:1) furnished **24x** as a pale brown solid (2.02 g, 94 %).

M.p.: 92-93 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 8.31 (d, J = 3.6 Hz, 1H), 7.69 (td, J = 1.7 Hz, J = 7.8 Hz, 1H), 7.27-7.19 (m, 3H), 6.85 (d, J = 8.8 Hz, 2H), 5.77 (s, 1H), 4.56 (s, 1H),3.77 s, 3H).

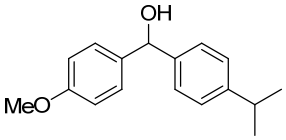
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 159.1, 147.8, 147.7, 140.1, 135.5, 134.4, 127.8, 123.4, 113.9, 73.3, 55.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3184, 3086, 3067, 3050, 3036, 2993, 2966, 2935, 2837, 1511, 1426, 1250, 1171, 1053, 1029, 805, 715.

MS (70 eV, EI) *m/z* (%): 215 (100) [M^+], 198 (17), 137 (51), 109 (99).

HRMS (EI) for $C_{13}H_{13}NO_2$ (215.0946): 215.0935.

Preparation of (4-isopropylphenyl)(4-methoxyphenyl)methanol (24y):



Freshly prepared and titrated 4-methoxyphenylmagnesium bromide (**23x**, 29.4 mL, 0.34 M, 10.0 mmol) was added to a solution of 4-isopropylbenzaldehyde (1.78 g, 12 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 15 min and then warmed to 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (pentane/EtOAc = 2:1) furnished **24y** as a colorless oil (2.46 g, 96 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.32-7.14 (m, 6H), 6.88 (d, J = 8.8 Hz, 2H), 5.77 (s, 1H) 3.79 (s, 3H), 2.90 (sept, J = 7.0 Hz, 1H), 2.29 (brs, 1H), 1.25 (d, J = 7.0 Hz, 6H).

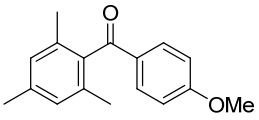
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 158.9, 148.0, 141.5, 136.2, 127.8, 126.4, 126.4, 113.7, 75.6, 55.2, 33.7, 23.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2966, 2921, 1665, 1602, 1574, 1415, 1272, 1260, 1161, 1024, 909, 845.

MS (70 eV, EI) *m/z* (%): 256 (88) [M^+], 239 (42), 213 (20), 147 (61), 135 (100), 109 (40).

HRMS (EI) for $C_{17}H_{20}O_2$ (256.1463): 256.1458.

Preparation of mesityl(4-methoxyphenyl)methanone (24z):



Freshly prepared and titrated mesitylmagnesium bromide (**23y**, 27.8 mL, 0.36 M, 10.0 mmol) was slowly added to a solution of 4-methoxybenzoyl chloride (2.05 g, 12 mmol) and CuCN·2 LiCl (2 mL, 1 M in THF, 2 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 30 min and then warmed to 25 °C. The reaction mixture was quenched with sat. NH_4Cl/NH_3 (9:1) solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (pentane/EtOAc = 4:1) furnished **24z** as a colorless oil (2.26 g, 89 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.76 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 6.87 (s, 2H), 3.85 (s, 3H), 2.32 (s, 3H), 2.08 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 199.2, 163.9, 138.2, 137.2, 134.1, 1318, 130.5, 128.2, 114.0, 55.5, 21.1, 19.3.

MS (70 eV, EI) *m/z* (%): 254 (71) [M^+], 239 (33), 223 (100), 147 (23), 135 (40).

HRMS (EI) for $C_{13}H_{15}NO$ (201.1154): 201.1154.

3. Regio- and Chemoselective Synthesis of 5-Membered Ring Heterocycles

3.1. Preparation of Polyfunctional Furan, Thiophene, Indole and Pyrrole Derivatives

3.1.1. Typical Procedure for the Deprotonation of Heterocycles (TP8)

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with the starting thiophene in THF (approx. 1 M solution) and cooled to the appropriate temperature. TMPMgCl·LiCl was added dropwise and the reaction mixture stirred for the indicated time (the completion of the reaction was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in THF).

3.1.2. Typical Procedure for Cross-Coupling Reactions (TP9)

To the freshly prepared magnesium reagent was added $ZnCl_2$ (1 M in THF, 1.1 equiv) and the reaction mixture was stirred for 15 min at the indicated temperature. The catalytic system and the aryl iodide or bromide (1.5 equiv) were added and the reaction mixture was warmed to 25 °C. After stirring for the indicated time the reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and

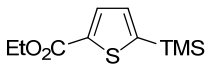
concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel.

3.1.3. Typical Procedure for Allylation or Acylation Reactions (TP10)

To the freshly prepared magnesium reagent was added CuCN·2 LiCl (1 M in THF, 20 mol %) and the reaction mixture was stirred for 15 min at the indicated temperature. The allyl bromide or acyl chloride was added and the reaction mixture was warmed to 25 °C. After stirring for the indicated time the reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel.

3.1.4. Preparation of Title Compounds

Preparation of ethyl 5-(trimethylsilyl)thiophene-2-carboxylate (65a):



Prepared according to **TP8** from ethyl thiophene-2-carboxylate (**62a**, 5.0 mmol, 781 mg) in 5 mL THF and trimethylsilylcyanide (6.0 mmol, 595 mg). Deprotonation time: 30 min at –40 °C. Reaction time with electrophile: 2 h at –40 °C. The crude residue was purified by flash column chromatography (pentane/CH_2Cl_2 = 4:1) yielding **65a** (821 mg, 72 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.81 (d, J = 3.7 Hz, 1H), 7.19 (d, J = 3.7 Hz, 1H), 4.34 (q, J = 7.0 Hz, 2H), 1.36 (t, J = 7.0 Hz, 3H), 0.32 (s, 9H).

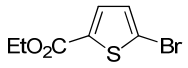
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 162.2, 149.2, 138.6, 134.1, 134.0, 61.0, 14.4, -0.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1426, 1366, 1310, 1274, 1238, 1088, 986, 836, 824, 750.

MS (70 eV, EI) *m/z* (%): 228 (18) [M^+], 213 (100), 185 (22), 84 (7), 75 (10).

HRMS (EI) for $C_{10}H_{16}O_2SSi$ (228.0640): 228.0624.

Preparation of ethyl 5-bromothiophene-2-carboxylate (65b):



Prepared according to **TP8** from ethyl thiophene-2-carboxylate (**62a**, 1.0 mmol, 156 mg) in 1 mL THF and 1,2-dibromo-1,1,2,2-tetrachloroethane (1.1 mmol, 358 mg) in 1 mL THF. Deprotonation time: 30 min at –40 °C. Reaction time with electrophile: 30 min at –40 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/CH_2Cl_2 = 10:1) **65b** (209 mg, 89 %) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (d, J = 3.9 Hz, 1H), 7.06 (d, J = 3.9 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H).

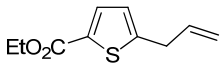
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 161.1, 135.2, 133.5, 130.8, 120.0, 61.4, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 1706, 1532, 1414, 1366, 1326, 1278, 1246, 1172, 1084, 1048, 808, 742.

MS (70 eV, EI) *m/z* (%): 236 (43) [M^+, ^{81}Br], 234 (42) [M^+, ^{79}Br], 208 (39), 206 (37), 191 (100), 189 (98), 82 (18).

HRMS (EI) for $C_7H_7BrO_2S$ (233.9350): 233.9324.

Preparation of ethyl 5-allylthiophene-2-carboxylate (65c):



Prepared according to **TP8** from ethyl thiophene-2-carboxylate (**62a**, 1.0 mmol, 156 mg) in 1 mL THF and ally bromide (1.1 mmol, 133 mg). Deprotonation time: 30 min at -40 °C. An allylation reaction was performed according to **TP10** using allyl bromide (1.1 mmol, 133 mg) at -40 °C during 1 h. The crude residue was purified by flash column chromatography (pentane/CH_2Cl_2 = 7:1) yielding **65c** (130 mg, 66%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.63 (d, J = 3.6 Hz, 1H), 6.80 (d, J = 3.6 Hz, 1H), 5.99-5.92 (m, 1H), 5.18-5.13 (m, 2H), 4.31 (q, J = 7.2 Hz, 2H), 3.57 (d, J = 7.7 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H).

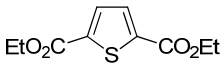
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 162.3, 150.8, 135.3, 133.6, 131.9, 125.6, 117.2, 61.0, 34.6, 14.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 1704, 1640, 1540, 1456, 1368, 1278, 1256, 1086, 990, 918, 816, 748.

MS (70 eV, EI) *m/z* (%): 196 (89) [M^+], 168 (13), 151 (100), 123 (75), 79 (12).

HRMS (EI) for $C_{10}H_{12}O_2S$ (196.0558): 196.0567.

Preparation of diethyl thiophene-2,5-dicarboxylate (65d):



Prepared according to **TP8** from ethyl thiophene-2-carboxylate (**62a**, 5.0 mmol, 781 mg) in 5 mL THF and ethyl cyanoformate (5.5 mmol, 545 mg). Deprotonation time: 30 min at –40 °C. Reaction time with electrophile: 30 min at –40 °C and warming to 25 °C. The crude residue was purified by recrystallization (heptane) yielding **65d** (714 mg, 63 %) as a slightly yellow solid

M.p.: 49-50 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.72 (s, 2H), 4.37 (q, J = 7.2 Hz, 4H), 1.38 (t, J = 7.2 Hz, 6H).

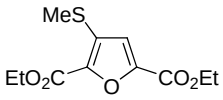
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 161.6, 139.2, 132.9, 61.7, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 2938, 1700, 1536, 1464, 1366, 1346, 1244, 1088, 1012, 746.

MS (70 eV, EI) *m/z* (%): 228 (34) [M^+], 213 (7), 200 (18), 183 (100), 172 (26), 155 (65), 111 (9).

HRMS (EI) for $C_{10}H_{12}O_4S$ (228.0456): 228.0460.

Preparation of diethyl 3-(methylthio)furan-2,5-dicarboxylate (67a):



Prepared according to **TP8** from diethyl furan-2,5-dicarboxylate (**66a**, 2.0 mmol, 424 mg) in 2 mL THF and $PhSO_2SMe$ (2.5 mmol, 471 mg). Deprotonation time: 10 min at -78 °C. Reaction time with electrophile: 3 h min at –50 °C The crude residue was purified by flash column chromatography (CH_2Cl_2) yielding **67a** (481 mg, 93 %) as a pale yellow solid.

M.p.: 69-70 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.14 (s, 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 2.47 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H).

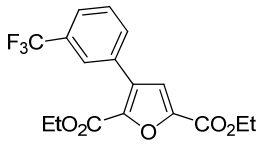
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 158.4, 157.8 145.9, 139.3, 133.6, 118.2, 116.5, 61.8, 61.4, 15.6, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2988, 2940, 2908, 2872, 1728, 1696, 1560, 1508, 1476, 1432, 1392, 1368, 1296, 1276, 1192, 1168, 1116, 1100, 1028, 1012, 972, 876, 860, 836, 768, 716.

MS (70 eV, EI) *m/z* (%): 258 (100) [M^+], 228 (7) 212 (17), 196 (20).

HRMS (EI) for $C_{11}H_{14}N_5S$ (258.0562): 258.0555.

Preparation of diethyl 3-[3-(trifluoromethyl)phenyl]furan-2,5-dicarboxylate (67b):



Prepared according to **TP8** from diethyl furan-2,5-dicarboxylate (**66a**, 1.0 mmol, 212 mg) in 1 mL THF. Deprotonation time: 10 min at -78 °C. A cross-coupling reaction was performed according to **TP9** using 3-iodobenzotrofluoride (1.1 mmol, 299 mg) and $Pd(PPh_3)_4$ (1 mol%, 12 mg) at 25 °C for 3 h. The crude residue was purified by flash column chromatography (CH_2Cl_2) yielding **67b** (281 mg, 79 %) as a colorless solid.

M.p.: 78-79 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.82 (s, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.65 (d, J = 8.6, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.30 (s, 1H), 4.42 (q, J = 7.3 Hz, 2H), 4.34 (q, J = 7.3 Hz, 2H), 1.41 (t, J = 7.3 Hz, 3H), 1.30 (t, J = 7.3 Hz, 3H).

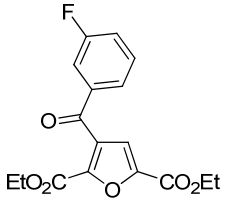
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 158.3, 157.9, 145.8, 141.4, 133.2, 132.6, 131.7, 10.6, 128.7, 126.3, 125.4, 123.0, 119.8, 61.8, 61.7, 14.3, 14.0.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2988, 1712, 1672, 1604, 1588, 1540, 1484, 1456, 1380, 1368, 1332, 1292, 1272, 1224, 1188, 1164, 1144, 1104, 1076, 1020, 972, 924, 900, 872, 848, 824, 796, 776, 760, 692.

MS (70 eV, EI) *m/z* (%): 356 (100) [M^+], 311 (32), 283 (34), 256 (17).

HRMS (EI) for $C_{17}H_{15}O_5F_3$ (356.0872): 356.0862.

Preparation of diethyl 3-(3-fluorobenzoyl)furan-2,5-dicarboxylate (67c):



Prepared according to **TP8** from diethyl furan-2,5-dicarboxylate (**66a,** 1.0 mmol, 212 mg) in 1 mL THF. Deprotonation time: 10 min at -78 °C. An acylation reaction was performed according to **TP10** using 3-fluorobenzoyl chloride (1.1 mmol, 174 mg) at -20 °C for 1 h. The crude residue was purified by flash column chromatography (pentane/Et_2O = 4:1) yielding **67c** (285 mg, 85 %) as a colorless solid.

M.p.: 73-75 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.59-7.53 (m, 2H), 7.48-7.41 (m, 1H), 7.34-7.27 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H).

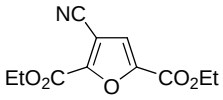
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 188.3, 164.5, 161.2, 157.2 (d, *J* = 36 Hz), 146.5, 143.9, 138.7 (d, *J* = 7 Hz), 130.8, 130.4 (d, *J* = 8 Hz), 125.4, 121.0 (d, *J* = 22 Hz), 118.2, 115.7 (d, *J* = 23 Hz), 62.1, 62.1, 14.2, 13.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3144, 3108, 3088, 2988, 2944, 2908, 2880, 1796, 1712, 1668, 1588, 1540, 1480, 1444, 1404, 1384, 1364, 1312, 1260, 1220, 1192, 1168, 1148, 1084, 1008, 968, 900, 856, 808, 780, 752, 684, 672.

MS (70 eV, EI) *m/z* (%): 334 (100) [M^+], 289 (34), 262 (34), 239 (30), 210 (79), 187 (37), 122 (76).

HRMS (EI) for $C_{17}H_{15}O_6F$ (334.0853): 334.0857.

Preparation of diethyl 3-cyanofuran-2,5-dicarboxylate (67d):



Prepared according to **TP8** from diethyl furan-2,5-dicarboxylate (**66a**, 5.0 mmol, 1.06 g) in 5 mL THF and tosylcyanide (6.0 mmol, 1.09 g). Deprotonation time: 10 min at –78 °C. Reaction time with electrophile: 30 min at –78 °C. The crude residue was purified by flash column chromatography (pentane/Et_2O = 5:1) yielding **67d** (781 mg, 66 %) as a colorless solid.

M.p.: 93-95 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37 (s, 1H), 4.48 (q, J = 7.3 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.3 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H).

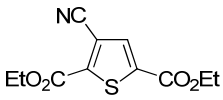
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 156.6, 155.6, 150.2, 147.0, 119.2, 110.8, 104.1, 63.0, 62.4, 14.1, 14.0.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3112, 3092, 3000, 2968, 2948, 2904, 2248, 1744, 1724, 1584, 1524, 1496, 1472, 1452, 1412, 1388, 1364, 1308, 1288, 1216, 1196, 1156, 1132, 1112, 1088, 1008, 964, 888, 872, 848, 820, 780, 764, 736, 704, 680.

MS (70 eV, EI) *m/z* (%): 237 (36) [M^+], 209 (37), 192 (59), 181 (100), 164 (53), 137 (23).

HRMS (EI) for $C_{11}H_{11}NO_5$ (237.0637): 237.0624.

Preparation of diethyl 3-cyanothiophene-2,5-dicarboxylate (67e):



Prepared according to **TP8** from diethyl thiophene-2,5-dicarboxylate (**65d**, 1.7 mmol, 380 mg) in 2 mL THF and tosylcyanide (2.0 mmol, 362 mg). Deprotonation time: 30 min at –60 °C. Reaction time with electrophile: 30 min at –50 °C. The crude residue was purified by flash column chromatography (pentane/Et_2O = 3:1) yielding **67e** (249 mg, 58 %) as a colorless solid.

M.p.: 78-80 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.91 (s, 1H), 4.45 (q, J = 7.1 Hz, 2H), 4.40 (q, J = 7.4 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H), 1.39 (t, J = 7.4 Hz, 3H).

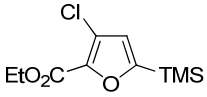
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 160.0, 159.1, 144.6, 139.2, 135.3, 114.1, 112.8, 63.0, 62.6, 14.2, 14.0.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3092, 2984, 2940, 2236, 1732, 1700, 1536, 1476, 1452, 1400, 1368, 1300, 1284, 1260, 1204, 1160, 1120, 1088, 1012, 900, 860, 832, 804, 764, 716.

MS (70 eV, EI) *m/z* (%): 253 (53) [M^+], 225 (46), 208 (100), 197 (91), 180 (82).

HRMS (EI) for $C_{11}H_{11}NO_4S$ (253.0409): 253.0409.

Preparation of ethyl 3-chloro-5-(trimethylsilyl)furan-2-carboxylate (67f):



Prepared according to **TP8** from ethyl 5-(trimethylsilyl)furan-2-carboxylate (**66b**, 2.0 mmol, 414 mg) in 2 mL THF and hexachloroethane (3 mmol, 710 mg) in 3 mL THF. Deprotonation time: 4 h at –50 °C. Reaction time with electrophile: 15 h at –50 °C. The crude residue was purified by flash column chromatography (pentane/CH_2Cl_2 = 2:1) yielding **(67f)** (237 mg, 48 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.64 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H), 0.29 (s, 9H).

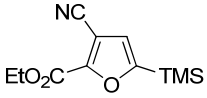
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.3, 158.2, 143.0, 123.6, 123.1, 61.0, 14.3, -2.0.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2962, 1720, 1570, 1482, 1370, 1342, 1276, 1252, 1176, 1142, 1094, 1038, 932, 838, 758.

MS (70 eV, EI) *m/z* (%): 246 (53) [M^+], 231 (100), 203 (33), 174 (6), 103 (28), 75 (41).

HRMS (EI) for $C_{10}H_{15}ClO_3Si$ (246.0479): 246.0454.

Preparation of ethyl 3-cyano-5-(trimethylsilyl)furan-2-carboxylate (67g):



Prepared according to **TP8** from ethyl 5-(trimethylsilyl)furan-2-carboxylate (**66b**, 1.0 mmol, 212 mg) in 1 mL THF and tosyl cyanide (1.2 mmol, 217 mg) in 1 mL THF. Deprotonation time: 1 h at –30 °C. Reaction time with electrophile: 15 min at –30 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/CH_2Cl_2 = 1:1) yielding **67g** (141 mg, 52 %) as a colorless solid.

M.p.: 100-102 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.84 (s, 1H), 4.44 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H), 0.32 (s, 9H).

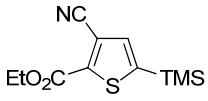
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 167.3, 156.7, 152.4, 122.3, 112.3, 103.0, 62.2, 14.1, -2.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3118, 2962, 2904, 2246, 1722, 1576, 1476, 1376, 1296, 1248, 1200, 1106, 1074, 1016, 932, 838.

MS (70 eV, EI) *m/z* (%): 237 (21) [M^+], 222 (100), 194 (47), 43 (9).

HRMS (EI) for $C_{11}H_{15}NO_3Si$ (237.0821): 237.0828.

Preparation of ethyl 3-cyano-5-(trimethylsilyl)thiophene-2-carboxylate (67h):



Prepared according to **TP8** from ethyl 5-(trimethylsilyl)thiophene-2-carboxylate (**65a**, 1.0 mmol, 228 mg) in 1 mL THF and tosyl cyanide (1.2 mmol, 218 mg) in 1 mL THF. Deprotonation time: 1 h at –35 °C. Reaction time with electrophile: 30 min at –35 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/CH_2Cl_2 = 1:1) yielding **67h** (174 mg, 69 %) as a colorless solid.

M.p.: 61-62 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40 (s, 1H), 4.42 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H), 0.35 (s, 9H).

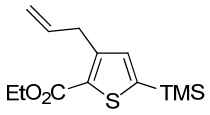
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 159.9, 150.0, 145.0, 137.3, 115.4, 114.1, 62.6, 14.4, -0.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3082, 2956, 2940, 2898, 2234, 1694, 1520, 1420, 1328, 1282, 1248, 1100, 1028, 952, 836, 758.

MS (70 eV, EI) *m/z* (%): 253 (13) [M^+], 238 (100), 210 (25), 97 (4), 83 (7).

HRMS (EI) for $C_{11}H_{15}NO_2SSi$ (253.0593): 253.0576.

Preparation of ethyl 3-allyl-5-(trimethylsilyl)thiophene-2-carboxylate (67i):



Prepared according to **TP8** from ethyl 5-(trimethylsilyl)thiophene-2-carboxylate (**65a**, 0.5 mmol, 114 mg) in 0.5 mL THF. Deprotonation time: 1 h at -35 °C. An allylation reaction was performed according to **TP10** using allyl bromide (0.6 mmol, 73 mg) at -35 °C for 15 min. The crude residue was purified by flash column chromatography (pentane/CH_2Cl_2 = 6:1) yielding **67i** (72 mg, 54 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.04 (s, 1H), 6.02-5.95 (m, 1H), 5.09-5.04 (m, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.77 (d, J = 6.5 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H), 0.31 (s, 9H).

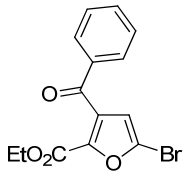
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 162.5, 148.5, 146.7, 137.0, 136.3, 131.5, 115.8, 60.7, 33.8, 14.4, -0.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958, 1706, 1638, 1532, 1426, 1248, 1210, 1172, 1078, 1012, 972, 912, 834, 756.

MS (70 eV, EI) *m/z* (%): 268 (27) [M^+], 251 (100), 225 (28), 207 (9), 179 (5), 149 (13), 73 (45).

HRMS (EI) for $C_{13}H_{20}O_2SSi$ (268.0953): 268.0981.

Preparation of ethyl 3-benzoyl-5-bromofuran-2-carboxylate (67j):



Prepared according to **TP8** from ethyl 5-bromofuran-2-carboxylate (**66c**, 1.0 mmol, 219 mg) in 1 mL THF. Deprotonation time: 30 min at –40 °C. An acylation reaction was performed according to **TP10** using benzoyl chloride (1.2 mmol, 169 mg) at -40 °C for 15 h. The crude residue was purified by flash column chromatography (pentane/CH_2Cl_2 = 5:4) yielding **67j** (242 mg, 75 %) as a colorless solid.

M.p.: 95-96 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.85 (d, J = 7.0 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 2H), 6.61 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 0.96 (t, J = 7.1 Hz, 3H).

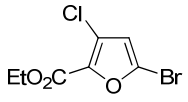
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 189.5, 156.7, 143.3, 136.7, 134.0, 132.8, 129.5, 128.6, 127.8, 114.4, 61.6, 13.5.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3116, 3066, 2982, 2360, 1720, 1668, 1574, 1478, 1400, 1304, 1250, 1176, 1100, 934, 830, 716, 686.

MS (70 eV, EI) *m/z* (%): 324 (98) [M^+, ^{81}Br], 322 (100) [M^+, ^{79}Br], 278 (25), 250 (45), 219 (37), 217 (36), 170 (18), 143 (15), 105 (46), 77 (36).

HRMS (EI) for $C_{14}H_{11}BrO_4$ (321.9841): 321.9834.

Preparation of ethyl 5-bromo-3-chlorofuran-2-carboxylate (67k):



Prepared according to **TP8** from ethyl 5-bromofuran-2-carboxylate (**66c**, 5.0 mmol, 1.095 g) in 5 mL THF and benzenesulfonyl chloride (7.5 mmol, 1.325 g). Deprotonation time: 30 min at –78 °C. Reaction time with electrophile: 3 h at -78 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/CH_2Cl_2 = 8:1) yielding **67k** (748 mg, 59 %) as a colorless solid.

M.p.: 98-100 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.48 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H).

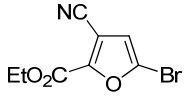
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 156.8, 141.7, 127.2, 125.3, 116.1, 61.5, 14.3.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3108, 2984, 2360, 1698, 1564, 1478, 1466, 1376, 1354, 1290, 1170, 1098, 932, 834, 764.

MS (70 eV, EI) *m/z* (%): 256 (14) [M^+, ^{37}Cl ^{81}Br], 254 (53) [M^+, ^{37}Cl ^{79}Br, ^{35}Cl ^{81}Br], 252 (43) [M^+, ^{35}Cl ^{79}Br], 226 (93), 209 (100), 182 (64), 153 (24), 129 (23), 72 (21).

HRMS (EI) for $C_7H_6BrClO_3$ (251.9189): 251.9185.

Preparation of ethyl 5-bromo-3-cyanofuran-2-carboxylate (67l):



Prepared according to **TP8** from ethyl 5-bromofuran-2-carboxylate (**66c**, 5.0 mmol, 1.095 g) in 5 mL THF and tosyl cyanide (5.5 mmol, 997 mg) in 6 mL THF. Deprotonation time: 30 min at –78 °C. Reaction time with electrophile: 30 min at –78 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/CH_2Cl_2 = 3:1) yielding **67l** (765 mg, 63 %) as a colorless solid.

M.p.: 103-105 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.69 (s, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H).

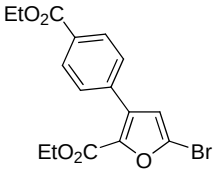
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 155.3, 150.2, 128.7, 115.3, 110.6, 105.2, 62.7, 14.1.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3116, 3066, 2982, 1720, 1668, 1596, 1574, 1478, 1400, 1304, 1250, 1176, 1100, 1016, 934, 830, 716.

MS (70 eV, EI) *m/z* (%): 245 (30), [M^+, ^{81}Br], 243 (34) [M^+, ^{79}Br], 217 (96), 215 (100), 200 (54), 198 (55), 173 (34), 171 (34), 144 (16), 142 (18), 108 (9), 63 (18).

HRMS (EI) for $C_8H_6BrNO_3$ (242.9531): 242.9521.

Preparation of ethyl 5-bromo-3-[4-(ethoxycarbonyl)phenyl]-2-furoate (67m):



Prepared according to **TP8** from ethyl 5-bromofuran-2-carboxylate (**66c**, 1.0 mmol, 219 mg) in 1 mL THF. Deprotonation time: 10 min at -78 °C. A cross-coupling reaction was performed according to **TP9** using ethyl 4-iodobenzoate (1.1 mmol, 304 mg) and $Pd(PPh_3)_4$ (1 mol%, 12 mg) at 25 °C for 6 h. The crude residue was purified by flash column chromatography (pentane/Et_2O = 8:1) yielding **67m** (314 mg, 86 %) as a colorless solid.

M.p.: 71-72 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.06 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 6.57 (s, 1H), 4.39 (q, J = 7.1, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H).

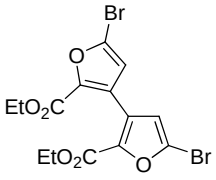
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.1, 157.8, 142.2, 135.5, 135.3, 130.6, 129.3, 129.2, 127.0, 115.9, 61.3, 61.1, 14.3, 14.1.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3744, 3392, 3112, 2988, 2936, 2908, 2876, 2532, 2400, 2244, 2188, 1980, 1940, 1704, 1664, 1612, 1584, 1568, 1536, 1516, 1476, 1444, 1420, 1392, 1368, 1312, 1280, 1260, 1236, 1184, 1164, 1124, 1108, 1080, 1020, 980, 936, 876, 860, 828, 764, 704, 668.

MS (70 eV, EI) *m/z* (%): 368 (100), [M^+, ^{81}Br], 366 (99) [M^+, ^{79}Br], 233 (54), 295 (33).

HRMS (EI) for $C_{16}H_{15}BrO_5$ (368.0082): 368.0062.

Preparation of diethyl 5,5'-dibromo-3,3'-bifuran-2,2'-dicarboxylate (67n):



Prepared according to **TP8** from ethyl 5-bromofuran-2-carboxylate (**66c**, 1.0 mmol, 219 mg) in 1 mL THF. Deprotonation time: 10 min at -78 °C. $ZnCl_2$ (1.1 mmol, 1 M in THF, 1.1 mL) was added and the mixture stirred for 15 min. Chloranil (1.5 mmol, 369 mmol) in 7 mL THF

was slowly added and the solution stirred for 2 h at -40 °C. The reaction mixture was quenched with sat. NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (CH_2Cl_2) furnished **67n** (174 mg, 80 %) as a pale brown solid.

M.p.: 168-170 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.61 (s, 2H), 4.29 (q, J = 7.1 Hz, 4H), 1.30 (t, J = 7.1 Hz, 6H).

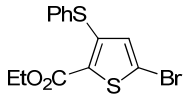
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 157.8, 142.8, 126.7, 125.6, 116.9, 61.6, 14.4.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3960, 3852, 3380, 3180, 3148, 2996, 2980, 2940, 2904, 2872, 2572, 2384, 2336, 2236, 2168, 2112, 2044, 2024, 1952, 1880, 1752, 1712, 1628, 1596, 1556, 1468, 1448, 1432, 1384, 1364, 1332, 1272, 1168, 1148, 1088, 1020, 956, 940, 864, 816, 764, 720, 684, 660.

MS (70 eV, EI) *m/z* (%): 438 (26) [M^+, ^{81}Br, ^{81}Br], 436 (53) [M^+, ^{79}Br, ^{81}Br], 434 ([M^+, ^{79}Br, ^{79}Br], 357 (83), 327 (100), 299 (30), 227 (27).

HRMS (EI) for $C_{14}H_{12}Br_2O_6$ (435.8980): 435.8980.

Preparation of ethyl 5-bromo-3-(phenylthio)thiophene-2-carboxylate (67o):



Prepared according to **TP8** from ethyl 5-bromothiophene-2-carboxylate (**65b**, 2.9 mmol, 671 mg) in 3.0 mL THF and phenyl benzenesulfonothioate (3.2 mmol, 801 mg) in 3.5 mL THF. Deprotonation time: 30 min at –50 °C. Reaction time with electrophile: 1 h at –50 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/CH_2Cl_2 = 5:1) yielding **67o** (674 mg, 68 %) as a colorless solid.

M.p.: 56-58 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.60-7.57 (m, 2H), 7.46-7.41 (m, 3H), 6.26 (s, 1H), 4.36 (q, J = 7.0 Hz, 2H), 1.37 (t, J = 7.0 Hz, 3H).

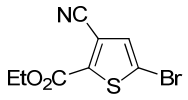
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 161.1, 145.6, 135.0, 131.8, 130.4, 129.8, 129.6, 122.6, 118.9, 61.4, 14.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2360, 2340, 1696, 1502, 1422, 1310, 1266, 1152, 1086, 1018, 986, 816, 744, 690.

MS (70 eV, EI) *m/z* (%): 344 (100) [M^+, ^{81}Br], 342 (93) [M^+, ^{79}Br], 299 (33), 197 (30), 272 (14), 270 (16), 223 (41), 199 (36).

HRMS (EI) for $C_{13}H_{11}BrO_2S_2$ (341.9384): 341.9362.

Preparation of ethyl 5-bromo-3-cyanothiophene-2-carboxylate (67p):



Prepared according to **TP8** from ethyl 5-bromothiophene-2-carboxylate (**65b**, 1.0 mmol, 235 mg) in 1 mL THF and tosyl cyanide (1.1 mmol, 199 mg) in 3 mL THF. Deprotonation time: 30 min at –50 °C. Reaction time with electrophile: 50 min at –50 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (pentane/Et_2O = 10:1) yielding **67p** (130 mg, 50 %) as a colorless solid.

M.p.: 94-96 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.30 (s, 1H), 4.42 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).

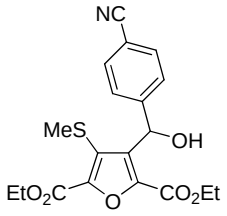
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 158.6, 141.8, 133.3, 120.2, 114.5, 112.3, 62.8, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3852, 3788, 3584, 3376, 3128, 3096, 3036, 3008, 2980, 2936, 2904, 2868, 2760, 2728, 2700, 2592, 2528, 2384, 2360, 2288, 2236, 2168, 2148, 2044, 2024, 1956, 1792, 1692, 1552, 1524, 1468, 1412, 1368, 1348, 1292, 1180, 1152, 1120, 1100, 1028, 1000, 940, 880, 860, 820, 760, 692.

MS (70 eV, EI) *m/z* (%): 261 (52) [M^+, ^{81}Br], 259 (53) [M^+, ^{79}Br], 216 (100), 189 (41), 107 (55).

HRMS (EI) for $C_8H_6BrNO_2S$ (258.9303): 258.9307.

Preparation of diethyl 3-[(4-cyanophenyl)(hydroxy)methyl]-4-(methylthio)furan-2,5-dicarboxylate (69a):



Prepared according to **TP8** from diethyl 3-(methylthio)furan-2,5-dicarboxylate (**76a**, 1.0 mmol, 253 mg) in 4 mL THF and 4-cyanobenzaldehyde (1.5 mmol, 197 mg) in 3 mL THF. Deprotonation time: 45 min at –78 °C. Reaction time with electrophile: 3 h at –78 °C and warming to 25 °C. The crude residue was purified by flash column chromatography (CH_2Cl_2) yielding **69a** (262 mg, 67 %) as a pale yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.59 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 6.26 (d, J = 11.9 Hz, 1H), 5.50 (d, J = 11.9 Hz, 1H), 4.48-4.36 (m, 4H), 2.39 (s, 3H), 1.43 (t, J = 7.3 Hz, 3H), 1.38 (t, J = 7.2 Hz, 3H).

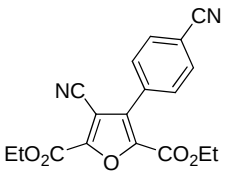
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 160.1, 157.5, 147.9, 146.2, 140.7, 140.5, 132.5, 128.0, 126.8, 118.9, 111.7, 67.7, 63.1, 62.3, 19.6, 14.5, 14.3.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3416, 2984, 2932, 2908, 2872, 2228, 1780, 1712, 1688, 1608, 1580, 1520, 1504, 1468, 1444, 1396, 1380, 1368, 1284, 1236, 1180, 1128, 1108, 1028, 1016, 976, 904, 856, 828, 776, 696.

MS (70 eV, EI) *m/z* (%): 389 (98) [M^+], 360 (52), 341 (37), 313 (100), 297 (20), 131 (55).

HRMS (EI) for $C_{19}H_{19}NO_6S$ (389.0933): 389.0934.

Preparation of diethyl 3-cyano-4-(4-cyanophenyl)furan-2,5-dicarboxylate (69b):



Diethyl 3-cyanofuran-2,5-dicarboxylate (**67d**, 1 mmol, 237 mg) was dissolved in 4 mL THF and $ZnCl_2$ (1.1 mmol, 1 M in THF, 1.1 mL) and cooled to -78 °C. TMPMgCL·LiCl (1.2 mmol, 1.1 M in THF, 1.1 mL) was added and the reaction mixture stirred for 20 min. $Pd(PPh_3)_4$ (1 mol%, 12 mg) and 4-iodobenzonitrile (1.2 mmol, 275 mg) were added and the mixtued warmed to 25 °C. After stirring for 3 h, the reaction was quenched with sat. NH_4Cl

solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (CH_2Cl_2) furnished **69b** (239 mg, 71 %) as a pale brown solid.

M.p.: 156-158 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.79 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.6 Hz, 2H), 4.52 (q, J = 7.1 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H).

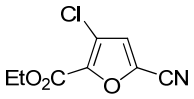
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 156.8, 155.5, 149.6, 142.1, 133.1, 132.1, 130.5, 118.0, 113.8, 110.2, 105.3, 63.3, 62.6, 14.1, 14.0.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2988, 2232, 1720, 1612, 1592, 1552, 1504, 1472, 1452, 1424, 1388, 1368, 1324, 1284, 1240, 1216, 1180, 1108, 1080, 1012, 984, 916, 888, 856, 844, 808, 776, 736, 704, 672.

MS (70 eV, EI) *m/z* (%): 338 (100) [M^+], 310 (34), 293 (24), 281 (34), 264 (33).

HRMS (EI) for $C_{18}H_{14}N_2O_5$ (338.0903): 338.0888.

Preparation of ethyl 3-chloro-5-cyanofuran-2-carboxylate (71):



Ethyl 5-bromo-3-chlorofuran-2-carboxylate (**67k**, 3.0 mmol, 748 mg) in 5 mL THF was cooled to -50 °C, and *i*PrMgCl·LiCl (3.3 mmol, 1.36 M in THF, 2.4 mL) was added. The reaction mixture was stirred for 30 min and tosyl cyanide was added. The reaction mixture was warmed to 25 °C and after stirring for 3 h was quenched with sat. NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (pentane/CH_2Cl_2 = 1:1) furnished **71** (440 mg, 73 %) as a colorless solid.

M.p.: 80-81 °C.

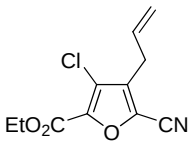
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.12 (s, 1H), 4.42 (q, J = 7.0 Hz, 2H), 1.40 (t, J = 7.0 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 156.2, 142.9, 127.3, 124.0, 123.4, 109.5, 62.3, 14.1.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3148, 3132, 2986, 2238, 1718, 1547, 1516, 1374, 1280, 1236, 1190, 1114, 1052, 1012, 972, 856, 768.

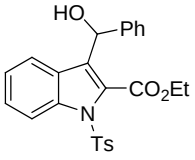
MS (70 eV, EI) *m/z* (%): 199 (25) [M^+], 171 (82), 154 (100), 127 (20), 98 (15).
HRMS (EI) for $C_8H_6ClNO_3$ (199.0036): 199.0020.

Synthesis of ethyl 4-allyl-3-chloro-5-cyanofuran-2-carboxylate (72):



Prepared according to **TP8** from ethyl 3-chloro-5-cyanofuran-2-carboxylate (**71**, 0.68 mmol, 136 mg) in 1.4 mL THF. An allylation reaction was performed according to **TP10** using allyl bromide (1.0 mmol, 121 mg) at -78 °C for 15 min. The crude residue was purified by flash column chromatography (pentane/CH_2Cl_2 = 1:1) yielding **72** (120 mg, 74 %) as a colorless oil.
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 5.93-5.80 (m, 1H), 5.22-5.13 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 3.37-3.34 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 156.4, 142.8, 136.1, 131.3, 125.6, 124.4, 119.0, 109.9, 62.4, 27.9, 14.4.
IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2986, 2234, 1726, 1532, 1406, 1286, 1184, 1032, 992, 924, 848, 768.
MS (70 eV, EI) *m/z* (%): 239 (68) [M^+], 211 (30), 194 (100), 167 (21), 136 (27), 102 (29).
HRMS (EI) for $C_{11}H_{10}ClNO_3$ (239.0349): 239.0357.

Preparation of ethyl 3-(hydroxy(phenyl)methyl)-1-tosylindole-2-carboxylate (75a):



Prepared according to **TP8** from ethyl 1-tosylindole-2-carboxylate (**73**, 0.5 mol, 172 mg) in 2.5 mL THF and benzaldehyde (0.6 mmol, 64 mg). Deprotonation time: 30 min at –45 °C.

Reaction time with electrophile: 30 min at –45 °C. The crude residue was purified by flash column chromatography (CH_2Cl_2) yielding **75a** (205 mg, 91 %) as a colorless solid.

M.p.: 51-52 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.00 (d, J = 8.7, 1H), 7.75 (d, J = 8.4, 2H), 7.44-7.12 (m, 10H), 6.15 (d, J = 5.2 Hz, 1H), 4.45 (q, J = 7.0 Hz, 2H), 2.82 (d, J = 5.2, 1H), 2.32 (s, 3H) 1.37 (t, J = 7.0 Hz, 3H).

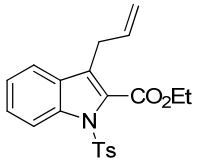
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 163.2, 145.1, 141.5, 136.9, 134.2, 129.9, 129.6, 128.7, 128.3, 127.9, 127.6, 127.2, 126.7, 126.1, 124.3, 121.9, 115.4, 68.9, 62.7, 21.6, 13.9.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3526 (w, br), 2984, 1716, 1596, 1448, 1368, 1258, 1174, 1016, 748, 668.

MS (70 eV, EI) *m/z* (%): 449 (4) [M^+], 294 (54), 248 (100), 220 (14), 204 (9), 165 (6), 105 (12), 91 (13), 77 (6).

HRMS (EI) for $C_{25}H_{23}NO_5S$ (449.1297): 449.1281.

Synthesis of ethyl 3-allyl-1-tosylindole-2-carboxylate (75b):



Prepared according to **TP8** from ethyl 1-tosylindole-2-carboxylate (**73**, 0.5 mol, 172 mg) in 2.5 mL THF. Deprotonation time: 30 min at -45 °C. An allylation reaction was performed according to **TP10** using allyl bromide (0.6 mmol, 73 mg) at -45 °C for 30 min. The crude residue was purified by flash column chromatography (CH_2Cl_2/pentane = 5:4) yielding **75b** (182 mg, 95 %) as a colorless solid.

M.p.: 66-68 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.02 (d, J = 8.3 Hz, 1H), 7.76 (d, J = 6.6 Hz, 2H), 7.47 (d, J = 7.9 Hz, 1H), 7.37 (t, J = 5.9 Hz, 1H), 7.23 (t, J = 7.0 Hz, 1H), 7.17 (d, J = 6.8 Hz, 2H), 5.93-5.80 (m, 1H), 5.03-4.93 (m, 2H), 4.45 (q, J = 7.1 Hz, 2H), 3.51 (td, J = 6.2 Hz, J = 1.7 Hz, 2H), 2.31 (s, 3H), 1.41 (t, J = 7.1 Hz, 3 H).

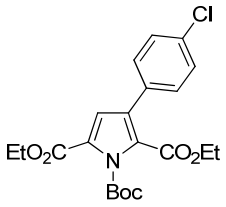
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 162.4, 144.8, 137.1, 134.6, 134.5, 129.8, 129.4, 128.8, 127.2, 126.7, 126.5, 124.0, 120.7, 116.3, 115.6, 62.1, 28.7, 21.6, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 1712, 1640, 1598, 1440, 1366, 1308, 1260, 1180, 1146, 1104, 1088, 1020, 810, 750, 666.

MS (70 eV, EI) *m/z* (%): 383 (33) [M^+], 338 (8), 228 (100), 200 (16), 183 (27), 154 (77), 128 (28), 91 (34).

HRMS (EI) for $C_{21}H_{21}NO_4S$ (383.1191): 383.1186.

Preparation of 1-*tert*-butyl 2,5-diethyl 3-(4-chlorophenyl)pyrrole-1,2,5-tricarboxylate (78):



Prepared according to **TP8** from 1-*tert*-butyl 2,5-diethylpyrrole-1,2,5-tricarboxylate (**76**, 1.0 mmol, 311 mg) in 1 mL THF and $TMP_2Mg{\cdot}2$ LiCl (1.1 mmol, 0.58 M in THF, 1.9 mL). Deprotonation time: 1.5 h at -30 °C. A cross-coupling reaction was performed according to **TP9** using 4-iodochlorobenzene (1.5 mmol, 358 mg) and $Pd(PPh_3)_4$ (1 mol%, 12 mg) at 25 °C for 1.5 h. The crude residue was purified by flash column chromatography (CH_2Cl_2) yielding **78** (339 mg, 95 %) as a colorless solid.

M.p.: 80-81 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.35-7.31 (m, 4H), 6.82 (s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 1.65 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 160.1, 159.5, 148.5, 133.5, 132.6, 130.9, 129.9, 127.9, 125.9, 123.2, 117.3, 86.3, 61.2, 61.2, 27.4, 14.3, 13.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984, 2944, 2900, 1780, 1724, 1704, 1600, 1572, 1548, 1496, 1472, 1440, 1384, 1372, 1344, 1296, 1264, 1228, 1152, 1124, 1084, 1032, 1012, 984, 928, 896, 824, 784, 772, 756, 732, 680.

MS (70 eV, EI) *m/z* (%): 421 (4) [M^+], 321 (100), 274 (14), 202 (13).

HRMS (EI) for $C_{21}H_{24}ClNO_6$ (421.1292): 421.1270.

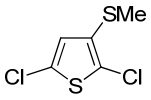
3.2. Regio- and Chemoselective Synthesis of Fully Substituted Thiophenes

3.2.1. Typical Procedure for Dechlorination Reactions (TP11)

A round bottom flask equipped with a stirring bar and a reflux condenser was charged with the dichlorothiophene in EtOH. Pd/C and NH_4CO_2 were added and the reaction mixture was heated by using a Discover BenchMate® system (100 W, 70 °C) for 1 h. The mixture was allowed to cool to 25 °C, another portion of Pd/C was added and the mixture was again heated for 1 h in the microwave (100 W, 70 °C). This procedure was repeated for the indicated time. After the last reaction cycle the mixture was allowed to cool to 25 °C and filtered through Celite®. The crude residue was purified by flash column chromatography on silica gel if necessary.

3.2.2. Preparation of Title Compounds

Preparation of 2,5-dichloro-3-(methylthio)thiophene (81a):



Prepared according to **TP8** from **79** (3.06 g, 20.0 mmol) and TMPMgCl·LiCl (19.6 mL, 1.12 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. $PhSO_2SMe$ (4.70 g, 25.0 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded **81a** (3.66 g, 92 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.75 (s, 1H), 2.42 (s, 3H).

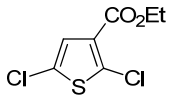
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 131.3, 127.2, 126.5, 124.0, 17.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3090, 2921, 1510, 1429, 1411, 1308, 1151, 1032, 1014, 970, 849, 806, 695, 686.

MS (70 eV, EI) *m/z* (%): 198 (100) [M^+], 183 (74), 163 (21), 139 (24).

HRMS (EI) for $C_5H_4Cl_2S_2$ (197.9131): 197.9124.

Preparation of ethyl 2,5-dichlorothiophene-3-carboxylate (81b):



Prepared according to **TP8** from **79** (3.06 g, 20.0 mmol) and TMPMgCl·LiCl (19.6 mL, 1.12 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. Ethyl cyanoformate (2.97 g, 30.0 mmol) was added at 0 °C and the reaction mixture stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel (pentane/CH_2Cl_2 = 6:1) afforded **81b** (3.41 g, 76 %) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.18 (s, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 4.0 Hz, 3H).

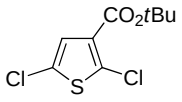
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 160.8, 134.2, 128.6, 127.3, 126.2, 61.2, 14.2.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3108, 2984, 1728, 1712, 1536, 1440, 1376, 1344, 1220, 1148, 1048, 1020, 932, 840, 768, 684.

MS (70 eV, EI) *m/z* (%): 224 (67) [M^+], 196 (40), 181 (100), 107 (13).

HRMS (EI) for $C_7H_6Cl_2O_2S$ (223.9466): 223.9474.

Preparation of *tert*-butyl 2,5-dichlorothiophene-3-carboxylate (81e):



Prepared according to **TP8** from **79** (3.06 g, 20.0 mmol) and TMPMgCl·LiCl (19.6 mL, 1.12 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. Boc_2O (6.55 g, 30 mmol) was added at -20 °C and the reaction mixture stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **81e** (4.14 g, 82 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.11 (s, 1H), 1.55 (s, 9H).

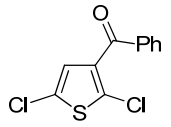
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 159.9, 133.3, 130.0, 127.5, 125.7, 82.3, 28.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 2931, 1708, 1534, 1475, 1456, 1439, 1393, 1366, 1346, 1241, 1163, 1145, 1046, 1035, 1002, 935, 919, 846, 790, 770, 744, 733, 685.

MS (70 eV, EI) *m/z* (%): 252 (17) [M^+], 196 (100), 179 (59), 107 (8).

HRMS (EI) for $C_9H_{10}Cl_2O_2S$ (251.9779): 251.9774.

Preparation of (2,5-dichloro-3-thienyl)(phenyl)methanone (81f):



Prepared according to **TP8** from **79** (3.06 g, 20.0 mmol) and TMPMgCl·LiCl (19.6 mL, 1.15 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. An acylation reaction was performed according to **TP10** using benzoyl chloride (3.51 g, 25.0 mmol) at -30 °C during 1 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **81f** (4.01 g, 78 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.83-7.80 (m, 2H), 7.63-7.57 (m, 1H), 7.51-7.45 (m, 2H), 6.97 (s, 1H).

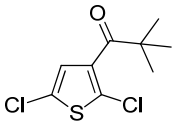
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 188.7, 136.9, 136.5, 133.5, 130.8, 129.7, 128.6, 127.4, 127.0.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 4062, 4058, 4052, 3309, 3191, 3093, 3059, 3033, 2981, 2932, 2842, 1714, 1659, 1596, 1578, 1524, 1488, 1447, 1429, 1420, 1354, 1335, 1315, 1306, 1275, 1237, 1177, 1168, 1103, 1075, 1057, 1049, 1026, 1001, 989, 973, 932, 838, 821, 804, 789, 715, 692, 672, 661.

MS (70 eV, EI) *m/z* (%): 256 (24) [M^+], 179 (32), 105 (100).

HRMS (EI) for $C_{11}H_6Cl_2OS$ (255.9516): 255.9515.

Preparation of 1-(2,5-dichloro-3-thienyl)-2,2-dimethylpropan-1-one (81g):



Prepared according to **TP8** from **79** (3.06 g, 20.0 mmol) and TMPMgCl·LiCl (19.6 mL, 1.15 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. An acylation reaction was performed according to **TP10** using pivaloyl chloride (3.02 g, 25.0 mmol) at -20 °C during 1 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **81g** (3.54 g, 75 %) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.85 (s, 1H), 1.24 (s, 9H).

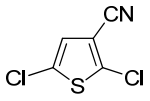
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 204.2, 137.3, 127.0, 126.9, 124.7, 45.0, 26.6.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2968, 2903, 2870, 1725, 1687, 1602, 1528, 1476, 1461, 1420, 1394, 1365, 1330, 1278, 1259, 1241, 1225, 1200, 1175, 1119, 1071, 1031, 997, 937, 917, 909, 905, 901, 894, 883, 869, 843, 824, 783, 753, 733, 728, 725, 718, 710, 700, 690, 667, 657.

MS (70 eV, EI) *m/z* (%): 236 (26) [M^+], 179 (100), 57 (19)

HRMS (EI) for $C_9H_{10}Cl_2OS$ (235.9829): 235.9819.

Preparation of 2,5-dichlorothiophene-3-carbonitrile (81h):



Prepared according to **TP8** from **79** (3.06 g, 20.0 mmol) and TMPMgCl·LiCl (19.6 mL, 1.12 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. TsCN (3.81 g, 21.0 mmol) was added at -20 °C and the reaction mixture stirred for 18 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **81h** (2.60 g, 73 %) as a colorless solid.

M.p.: 51-53 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.95 (s, 1H).

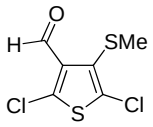
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 137.9, 129.0, 126.2, 111.9, 110.3.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3098, 2231, 1671, 1525, 1427, 1344, 1174, 1053, 1019, 923, 836, 828, 686.

MS (70 eV, EI) *m/z* (%): 177 (100) [M^+], 142 (8), 98 (13), 79 (12).

HRMS (EI) for C_5HCl_2NS (176.9207): 176.9211.

Preparation of 2,5-dichloro-4-(methylthio)thiophene-3-carbaldehyde (83a):



Prepared according to **TP8** from **81a** (1.99 g, 10.0 mmol) and TMPMgCl·LiCl (10.3 mL, 1.17 M in THF, 12.0 mmol). Deprotonation time: 30 min at -10 °C. DMF (1.10 g, 15.0 mmol) was added at -10 °C and the reaction mixture stirred for 30 min. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **83a** (2.15 g, 95 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 10.09 (s, 1H), 2.38 (s, 3H).

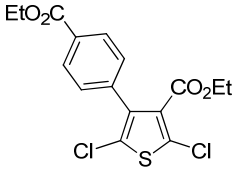
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 184.2, 137.6, 133.8, 131.4, 131.2, 19.2.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3970, 3343, 2933, 2881, 2779, 2588, 2093, 1699, 1677, 1645, 1489, 1415, 1400, 1313, 1290, 1095, 970, 839, 713.

MS (70 eV, EI) *m/z* (%): 226 (100) [M^+], 183 (25), 163 (15), 103 (26).

HRMS (EI) for $C_6H_4Cl_2OS_2$ (225.9081): 225.9067.

Preparation of ethyl 2,5-dichloro-4-[4-(ethoxycarbonyl)phenyl]thiophene-3-carboxylate (83b):

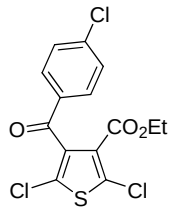


Prepared according to **TP8** from **81b** (675 mg, 3.0 mmol) and TMPMgCl·LiCl (3.4 mL, 1.15 M in THF, 3.9 mmol). Deprotonation time: 30 min at -30 °C. A cross-coupling reaction was performed according to **TP9** using ethyl 4-iodobenzoate (1.24 g, 4.5 mmol) and $Pd(PPh_3)_4$ (36 mg, 1 mol %) at -30 °C during 16 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 1:1) afforded **83b** (1.06 g, 95 %) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.08 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 4.39 (q, J = 7.0 Hz, 2H), 4.09 (q, J = 7.4 Hz, 2H), 1.40 (t, J = 7.0 Hz, 3H), 1.00 (t, J = 7.4 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.2, 161.5, 138.0, 137.8, 131.6, 130.2, 130.1, 129.4, 129.4, 124.1, 61.4, 61.1, 14.3, 13.7.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2979, 2935, 2904, 1712, 1610, 1577, 1571, 1540, 1505, 1443, 1406, 1389, 1366, 1268, 1243, 1174, 1154, 1100, 1052, 1016, 935, 864, 834, 772, 741, 710.
MS (70 eV, EI) *m/z* (%): 372 (93) [M^+], 327 (100), 299 (28), 255 (49),
HRMS (EI) for $C_{16}H_{15}Cl_2O_4S$ [$M^+ + H^+$] (373.0063): 373.0057.

Preparation of ethyl 2,5-dichloro-4-(4-chlorobenzoyl)thiophene-3-carboxylate (83c):

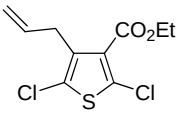


Prepared according to **TP8** from **81b** (225 mg, 1.0 mmol) and TMPMgCl·LiCl (1.0 mL, 1.15 M in THF, 1.2 mmol). Deprotonation time: 30 min at -30 °C. (4-Chlorophenyl)(oxo)acetonitrile (248 mg, 1.5 mmol) and $Fe(acac)_3$ (18 mg, 5 mol %) were added at -30 °C and the reaction mixture stirred for 30 min. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 3:2) afforded **83c** (276 mg, 76 %) as a colorless solid.
M.p.: 67-69 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.76 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 4.07 (q, J = 7.28 Hz, 2H), 1.03 (t, J = 7.28 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 188.3, 159.9, 140.5, 140.5, 137.9, 134.7, 130.6, 129.2, 128.4, 125.4, 61.7, 13.5.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3088, 3057, 2989, 1706, 1698, 1676, 1585, 1571, 1475, 1455, 1445, 1378, 1270, 1241, 1221, 1177, 1097, 1088, 1012, 980, 930, 868, 848, 822, 815, 782, 774, 750, 719.

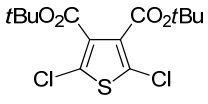
MS (70 eV, EI) *m/z* (%): 362 (64) [M^+], 317 (27), 223 (34), 141 (32), 139 (100).
HRMS (EI) for $C_{14}H_9Cl_3O_3S$ 361.9338: 361.9322.

Preparation of ethyl 4-allyl-2,5-dichlorothiophene-3-carboxylate (83d):



Prepared according to **TP8** from **81b** (712 mg, 3.2 mmol) and TMPMgCl·LiCl (3.2 mL, 1.17 M in THF, 3.8 mmol). Deprotonation time: 30 min at -30 °C. An allylation reaction was performed according to **TP10** using allyl bromide (581 mg, 4.8 mmol) at -30 °C during 1 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **83d** (724 mg, 85 %) as a colorless oil.
M.p.: 51-53 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 5.89-5.76 (m, 1H), 5.03-4.94 (m, 2H), 4.33 (q, J = 7.2 Hz, 2H), 3.53 (td, J = 1.7 Hz, J = 5.9 Hz, 2 H), 1.36 (t, J = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 161.8, 136.6, 134.4, 131.9, 129.0, 123.2, 116.0, 61.3, 31.6, 14.1.
IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3080, 2980, 1714, 1639, 1536, 1439, 1377, 1249, 1237, 1202, 1097, 1014, 991, 968, 910, 858, 784, 774, 742, 709, 674, 667, 658.
MS (70 eV, EI) *m/z* (%): 264 (100) [M^+], 219 (51), 183 (58), 157 (20)
HRMS (EI) for $C_{10}H_{10}Cl_2O_2S$ (263.9779): 263.9801.

Preparation of di-*tert*-butyl 2,5-dichlorothiophene-3,4-dicarboxylate (83e):



Prepared according to **TP8** from **81e** (3.72 g, 14.7 mmol) and TMPMgCl·LiCl (12.1 mL, 1.32 M in THF, 16.0 mmol). Deprotonation time: 30 min at -20 °C. Boc_2O (4.80 g, 22.0 mmol) was added at -20 °C and the reaction mixture stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with

Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **83e** (4.09 g, 79 %) as a colorless solid.

M.p.: 82-84 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.54 (s, 18H).

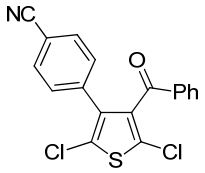
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 160.1, 132.0, 128.9, 83.1, 28.0.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 2934, 1728, 1707, 1669, 1536, 1472, 1455, 1391, 1385, 1365, 1286, 1257, 1230, 1153, 1088, 1038, 1028, 1015, 948, 928, 910, 845, 820, 789, 782, 773, 732, 714, 691, 687, 670, 662.

MS (70 eV, EI) *m/z* (%): 352 (6) [M^+], 240 (100), 223 (41), 196 (22).

HRMS (EI) for $C_{14}H_{18}Cl_2O_4S$ (352.0303): 352.0294.

Preparation of 4-(4-benzoyl-2,5-dichloro-3-thienyl)benzonitrile (83f):



Prepared according to **TP8** from **81f** (452 mg, 1.8 mmol) and TMPMgCl·LiCl (1.7 mL, 1.17 M in THF, 2.0 mmol). Deprotonation time: 45 min at -78 °C. A cross-coupling reaction was performed according to **TP9** using 4-iodo benzonitrile (618 mg, 2.7 mmol), $Pd(dba)_2$ (22 mg, 2 mol %) and P(*o*-furyl)$_3$ (18 mg, 4 mol %) at -78 °C during 1 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 13:7) afforded **83f** (543 mg, 84 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.77-7.74 (m, 2H), 7.59-7.53 (m, 3H), 7.44-7.32 (m, 4H).

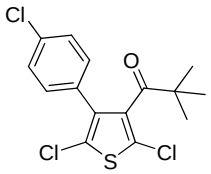
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 190.1, 137.7, 136.7, 136.7, 136.2, 134.3, 132.1, 130.1, 129.7, 128.8, 127.4, 125.1, 118.3, 112.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2917, 2849, 2227, 1655, 1594, 1502, 1449, 1442, 1351, 1299, 1274, 1261, 1169, 1059, 1023, 973, 937, 867, 846, 838, 824, 794, 754, 726, 695, 683, 654.

MS (70 eV, EI) *m/z* (%): 357 (68) [M^+], 280 (30), 217 (14), 105 (76), 77 (34), 44 (100).

HRMS (EI) for $C_{18}H_9Cl_2NOS$ (356.9782): 356.9776.

Preparation of 1-[2,5-dichloro-4-(4-chlorophenyl)-3-thienyl]-2,2-dimethylpropan-1-one (83g):



Prepared according to **TP8** from **81g** (2.92 g, 12.3 mmol) and TMPMgCl·LiCl (12.1 mL, 1.17 M in THF, 14.2 mmol). Deprotonation time: 30 min at -50 °C. A cross-coupling reaction was performed according to **TP9** using 4-chloroiodobenzene (4.29 g, 18.0 mmol) and $Pd(PPh_3)_4$ (142 mg, 1 mol %) at -50 °C during 8 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 7:1) afforded **83g** (3.28 g, 77 %) as a colorless solid.

M.p.: 77-78 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.36 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 0.89 (s, 9H).

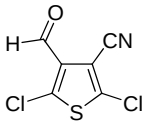
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 209.1, 140.2, 135.3, 134.8, 134.8, 131.1, 128.9, 124.0, 121.6, 45.3, 26.7.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2973, 2930, 2902, 2867, 1685, 1595, 1491, 1475, 1433, 1363, 1341, 1266, 1204, 1187, 1092, 1076, 1034, 1013, 999, 870, 847, 825, 819, 798, 758, 724, 704, 694.

MS (70 eV, EI) *m/z* (%): 346 (13) [M^+], 291 (93), 262 (100), 226 (21), 183 (90), 108 (33).

HRMS (EI) for $C_{15}H_{13}Cl_3OS$ (345.9753): 345.9767.

Preparation of 2,5-dichloro-4-formylthiophene-3-carbonitrile (83h):



Prepared according to **TP8** from **81h** (196 mg, 1.1 mmol) and TMPMgCl·LiCl (1.0 mL, 1.20 M in THF, 1.2 mmol). Deprotonation time: 15 min at -30 °C. DMF (110 mg, 1.5 mmol)

was added at -30 °C the reaction mixture warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (CH_2Cl_2) afforded **83h** (195 mg, 86 %) as a colorless solid.

M.p.: 128-130 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 9.97 (s, 1H).

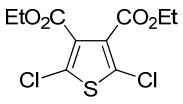
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 179.8, 139.8, 139.6, 134.4, 110.4, 109.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2857, 2814, 2230, 1678, 1651, 1511, 1446, 1392, 1384, 1378, 1200, 1169, 964, 959, 889, 872, 805.

MS (70 eV, EI) *m/z* (%): 205 (16) [M^+], 177 (10), 132 (6), 57 (100).

HRMS (EI) for C_6HCl_2NOS (204.9156): 204.9138.

Preparation of diethyl 2,5-dichlorothiophene-3,4-dicarboxylate (83i):



Prepared according to **TP8** from **79** (3.06 g, 20.0 mmol) and TMPMgCl·LiCl (19.6 mL, 1.12 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. Ethyl cyanoformate (2.38 g, 24.0 mmol) was added at 0 °C and the reaction mixture stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was solved in THF and deprotonated according to **TP8** using TMPMgCl·LiCl (19.6 mL, 1.12 M in THF, 22.0 mmol). Deprotonation time: 30 min at -30 °C. Ethyl cyanoformate (2.38 g, 24.0 mmol) was added at -30 °C, the reaction mixture warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **83i** (5.17 g, 87 %) as a colorless oil.

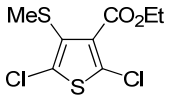
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 4.33 (q, J = 7.0 Hz, 4H), 1.34 (t, J = 7.0 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 161.1, 130.4, 130.2, 62.0, 14.0.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 2937, 2904, 1726, 1535, 1451, 1378, 1367, 1354, 1298, 1260, 1201, 1170, 1113, 1085, 1014, 944, 910, 862, 794, 779, 751, 727, 667.

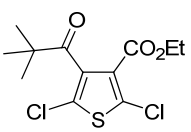
MS (70 eV, EI) *m/z* (%): 296 (24) [M^+], 251 (23), 223 (100).
HRMS (EI) for $C_{10}H_{10}Cl_2O_4S$ (295.9677): 295.9675.

Preparation of diethyl ethyl 2,5-dichloro-4-(methylthio)thiophene-3-carboxylate (83j):



Prepared according to **TP8** from **79** (3.06 g, 20.0 mmol) and TMPMgCl·LiCl (20.0 mL, 1.11 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. Ethyl cyanoformate (2.38 g, 24.0 mmol) was added at 0 °C and the reaction mixture stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was solved in THF and deprotonated according to **TP8** using TMPMgCl·LiCl (20.0 mL, 1.11 M in THF, 22.0 mmol). Deprotonation time: 30 min at -30 °C. $PhSO_2SMe$ (4.14 g, 22.0 mmol) was added at -30 °C, the reaction mixture warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 7:1) afforded **83j** (3.95 g, 73 %) as a colorless oil.
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 4.39 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.39 (t, J = 4.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 161.9, 133.2, 131.2, 130.3, 129.2, 61.9, 19.1, 14.1.
IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2981, 2925, 1721, 1592, 1509, 1474, 1464, 1442, 1419, 1389, 1367, 1331, 1202, 1113, 1094, 1073, 1014, 973, 959, 937, 931, 863, 838, 787, 732, 693, 674.
MS (70 eV, EI) *m/z* (%): 270 (100) [M^+], 225 (76), 209 (30), 196 (30), 115 (22).
HRMS (EI) for $C_8H_8Cl_2O_2S_2$ (269.9343): 269.9330.

Preparation of ethyl 2,5-dichloro-4-(2,2-dimethylpropanoyl)thiophene-3-carboxylate (83k):



Prepared according to **TP8** from **79** (3.06 g, 20.0 mmol) and TMPMgCl·LiCl (18.3 mL, 1.20 M in THF, 22.0 mmol). Deprotonation time: 30 min at 25 °C. Ethyl cyanoformate (2.38 g, 24.0 mmol) was added at 0 °C and the reaction mixture stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was solved in THF and deprotonated according to **TP8** using TMPMgCl·LiCl (18.3 mL, 1.20 M in THF, 22.0 mmol). Deprotonation time: 30 min at -30 °C. An acylation reaction was performed according to **TP10** using pivaloyl chloride (3.62 g, 30.0 mmol) at -30 °C during 18 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **83k** (4.41 g, 67 %) as a colorless solid.

M.p.: 44-46 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 4.30 (q, J = 4.2 Hz, 2H), 1.33 (t, J = 4.2 Hz, 3H), 1.23 (s, 9H).

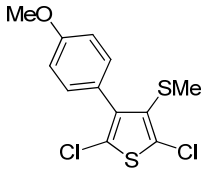
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 206.7, 160.6, 140.1, 134.4, 127.9, 121.6, 61.9, 45.5, 27.2, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2986, 2970, 2940, 2904, 2871, 1706, 1696, 1666, 1478, 1462, 1456, 1439, 1391, 1379, 1363, 1350, 1267, 1239, 1193, 1162, 1113, 1040, 1018, 998, 932, 874, 847, 806, 789, 755, 751, 704, 691, 687, 668, 657.

MS (70 eV, EI) *m/z* (%): 308 (2) [M^+], 251 (78), 223 (94), 57 (100).

HRMS (EI) for $C_{12}H_{14}Cl_2O_3S$ (308.0041): 308.0027.

Preparation of 2,5-dichloro-3-(4-methoxyphenyl)-4-(methylthio)thiophene (83l):



Prepared according to **TP8** from **79** (3.12 g, 20.4 mmol) and TMPMgCl·LiCl (19.7 mL, 1.14 M in THF, 22.5 mmol). Deprotonation time: 30 min at 25 °C. $PhSO_2SMe$ (4.70 g, 25.0 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over

Na_2SO_4 and concentrated *in vacuo*. The crude residue was solved in THF and deprotonated according to **TP8** using TMPMgCl·LiCl (19.7 mL, 1.14 M in THF, 22.5 mmol). A cross-coupling reaction was performed according to **TP9** using 4-iodo anisole (5.85 g, 25.0 mmol), $Pd(dba)_2$ (235 mg, 2 mol%) and P(2-furyl)$_3$ (189 mg, 4 mol%) at -30 °C during 2 h. Flash column chromatographical purification on silica gel (pentane) afforded **83l** (5.23 g, 84 %) as a pale yellow solid.

M.p.: 86-87 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.32 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.03 (s, 3H).

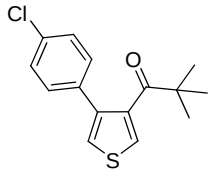
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 159.5, 140.4, 131.1, 131.0, 129.0, 125.5, 122.5, 113.6, 55.2, 18.1.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3017, 2962, 2919, 2837, 1607, 1571, 1534, 1495, 1460, 1450, 1441, 1431, 1422, 1309, 1300, 1283, 1248, 1174, 1165, 1108, 1041, 1024, 1009, 971, 886, 835, 807, 762, 665.

MS (70 eV, EI) *m/z* (%): 304 (100) [M^+], 254 (31), 239 (12), 211 (11).

HRMS (EI) for $C_{12}H_{10}Cl_2OS_2$ (303.9550): 303.9556.

Preparation of 1-[4-(4-chlorophenyl)-3-thienyl]-2,2-dimethylpropan-1-one (84a):



Prepared according to **TP11** from **83g** (836 mg, 2.4 mmol) in 20 mL EtOH, NH_4CO_2 (630 mg, 10 mmol), and Pd/C (128 mg, 5 mol %). Total reaction time: 5 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 17:3) afforded **84a** (507 mg, 76 %) as a colorless solid.

M.p.: 83-85 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.41 (d, J = 3.0 Hz, 1H), 7.33-7.29 (m, 2H), 7.26-7.23 (m, 2H), 7.21 (d, J = 3.0 Hz, 1H), 1.10 (s, 9H).

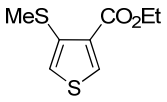
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 209.4, 141.0, 140.5, 134.8, 133.5, 129.7, 128.6, 125.0, 123.5, 45.0, 27.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3116, 3089, 2968, 2953, 2927, 2864, 1670, 1523, 1485, 1471, 1459, 1431, 1395, 1360, 1269, 1224, 1176, 1155, 1087, 1014, 998, 907, 865, 838, 822, 807, 801, 771, 754, 723, 694.

MS (70 eV, EI) *m/z* (%): 278 (37) [M^+], 223 (100).

HRMS (EI) for $C_{15}H_{15}ClOS$ (278.0532): 278.0525.

Preparation of ethyl 4-(methylthio)thiophene-3-carboxylate (84b):



Prepared according to **TP11** from **83j** (3.58 g, 13.0 mmol) in 50 mL EtOH, NH_4CO_2 (2.46 g, 39.0 mmol) and Pd/C (415 mg, 3 mol %). Total reaction time: 5 h. **84b** (2.42 g, 92 %) was afforded as a colorless solid without further purification.

M.p.: 40-41 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.17 (d, J = 3.3 Hz, 1H), 6.68 (d, J = 3.3 Hz, 1H), 4.33 (q, J = 7.0 Hz, 2H), 2.46 (s, 3H), 1.36 (t, J = 7.0, 3H).

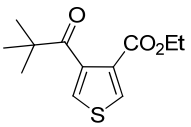
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 162.2, 137.7, 134.6, 130.7, 115.2, 60.8, 16.2, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3108, 2987, 2969, 2917, 1694, 1656, 1498, 1458, 1440, 1432, 1412, 1375, 1354, 1246, 1172, 1161, 1128, 1118, 1032, 998, 950, 861, 821, 772, 722.

MS (70 eV, EI) *m/z* (%): 202 (9) [M^+], 157 (10), 45 (100).

HRMS (EI) for $C_8H_{10}O_2S_2$ (202.0122): 202.0105.

Preparation of ethyl 4-(2,2-dimethylpropanoyl)thiophene-3-carboxylate (84c):



Prepared according to **TP11** from **83k** (3.47 g, 11.0 mmol) in 50 mL EtOH, NH_4CO_2 (3.15 g, 50.0 mmol) and Pd/C (351 mg, 3 mol %). Total reaction time: 5 h. **84c** (2.43 g, 95 %) was afforded as a colorless oil without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.06 (d, J = 3.2 Hz, 1H), 7.13 (d, J = 3.2 Hz, 1H), 4.27 (q, J = 7.0 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H), 1.23 (s, 9H).

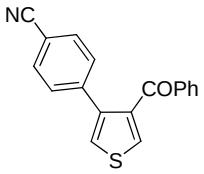
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 209.2, 161.9, 142.0, 133.2, 132.6, 122.5, 61.1, 45.0, 26.6, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3106, 2973, 2907, 2904, 1711, 1692, 1512, 1479, 1462, 1439, 1390, 1381, 1363, 1298, 1242, 1196, 1166, 1159, 1079, 1030, 937, 928, 880, 867, 829, 805, 778, 748, 729, 693.

MS (70 eV, EI) *m/z* (%): 240 (2) [M^+], 183 (65), 155 (100).

HRMS (EI) for $C_{12}H_{16}O_3S$ (240.0820): 240.0806.

Preparation of 4-(4-benzoyl-3-thienyl)benzonitrile (84d):



Prepared according to **TP11** from **83f** (520 mg, 1.5 mmol) in 7 mL EtOH, NH_4CO_2 (504 mg, 8 mmol) and Pd/C (80 mg, 5 mol %). Total reaction time: 6 h. Flash column chromatographical purification on silica gel (CH_2Cl_2) afforded **84d** (333 mg, 77 %) as a colorless solid.

M.p.: 108-109 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.84-7.79 (m, 3H), 7.58-7.53 (m, 3H), 7.45-7.39 (m, 5H).

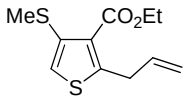
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 191.1, 141.9, 140.3, 139.6, 137.7, 133.6, 133.3, 132.1, 129.9, 129.2, 128.5, 125.8, 118.8, 111.0.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3081, 2224, 1644, 1606, 1598, 1579, 1526, 1492, 1448, 1421, 1410, 1260, 1165, 1128, 1081, 1001, 993, 910, 870, 855, 835, 829, 798, 763, 728, 721, 697, 661.

MS (70 eV, EI) *m/z* (%): 289 (100) [M^+], 260 (18), 212 (68), 140 (22), 105 (21).

HRMS (EI) for $C_{18}H_{11}NOS$ (289.0561): 289.0531.

Preparation of ethyl 2-allyl-4-(methylthio)thiophene-3-carboxylate (85a):



Prepared according to **TP8** from **84b** (990 mg, 4.9 mmol) and TMPMgCl·LiCl (4.9 mL, 1.10 M in THF, 5.4 mmol). Deprotonation time: 30 min at -30 °C. An allylation reaction was performed according to **TP10** using allyl bromide (714 mg, 5.9 mmol) at -30 °C during 1 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **85a** (1103 mg, 93 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.49 (s, 1H), 6.04 – 5.91 (m, 1H), 5.17-5.09 (m, 2H), 4.35 (q, J = 7.0 Hz, 2H), 3.86 (td, J = 1.3 Hz, J = 6.6 Hz, 2H), 2.41 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H).

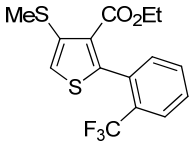
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 163.2, 153.2, 138.1, 135.3, 126.2, 117.3, 112.0, 60.7, 34.7, 16.4, 14.3.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3112, 3079, 2978, 2916, 1701, 1639, 1569, 1508, 1475, 1463, 1441, 1426, 1393, 1374, 1348, 1319, 1298, 1281, 1238, 1171, 1133, 1112, 1095, 1058, 1023, 992, 971, 917, 859, 830, 784, 768, 745, 710, 657.

MS (70 eV, EI) *m/z* (%): 242 (54) [M^+], 196 (62), 163 (100), 122 (29).

HRMS (EI) for $C_{11}H_{14}O_2S_2$ (242.0435): 242.0419.

Preparation of ethyl 4-(methylthio)-2-[2-(trifluoromethyl)phenyl]thiophene-3-carboxylate (85b):



Prepared according to **TP8** from **84b** (1.96 g, 9.7 mmol) and TMPMgCl·LiCl (8.9 mL, 1.20 M in THF, 10.7 mmol). Deprotonation time: 30 min at -30 °C. A cross-coupling reaction was performed according to **TP9** using 2-iodobenzotrifluoride (3.54 g, 13.0 mmol), $Pd(dba)_2$ (224 mg, 4 mol %) and P(*o*-furyl)$_3$ (180 mg, 8 mol %) at -30 °C. The reaction mixture was then heated to 50 °C for 6 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 3:1) afforded **85b** (2.36 g, 70 %) as a colorless solid.

M.p.: 87-70 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.74-7.70 (m, 1H), 7.56-7.50 (m, 2H), 7.37-7.34 (m, 1H), 6.75 (s, 1H), 3.98 (q, J = 7.0 Hz, 2H), 2.49 (s, 3H), 0.81 (t, J = 7.0, 3H).

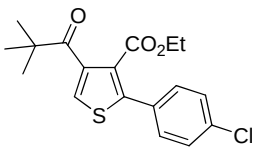
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 162.3, 147.2, 137.8, 134.6, 133.2, 132.2, 130.8, 129.4 (q, J = 30.4 Hz), 128.4, 125.9 (q, J = 5.2 Hz), 120.0 (q, J = 273.7 Hz), 114.6, 60.3, 16.3, 13.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3099, 2989, 2901, 1705, 1604, 1580, 1524, 1482, 1443, 1376, 1347, 1313, 1265, 1249, 1218, 1173, 1166, 1138, 1124, 1105, 1063, 1034, 1026, 998, 966, 765, 733.

MS (70 eV, EI) *m/z* (%): 346 (100) [M^+], 301 (44), 271 (15), 231 (15).

HRMS (EI) for $C_{15}H_{13}F_3O_2S_2$ (346.0309): 346.0285.

Preparation of ethyl 2-(4-chlorophenyl)-4-(2,2-dimethylpropanoyl)thiophene-3-carboxylate (85c):



Prepared according to **TP8** from **84c** (712 mg, 3.0 mmol) and TMPMgCl·LiCl (3.1 mL, 1.18 M in THF, 3.6 mmol). Deprotonation time: 1 h at -40 °C. A cross-coupling reaction was performed according to **TP9** using 4-chloroiodobenzene (1.07 g, 4.5 mmol), $Pd(dba)_2$ (35 mg, 2 mol %) and P(*o*-furyl)$_3$ (28 mg, 4 mol %) at -40 °C during 16 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 2:1) afforded **85c** (852 mg, 81 %) as a pale orange solid.

M.p.: 78-80 °C.

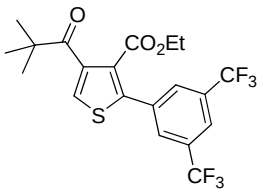
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.42-7.33 (m, 5H), 4.17 (q, J = 7.2 Hz, 2H), 1.32 (s, 9H), 1.14 (t, J = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 205.9, 164.1, 146.7, 142.5, 135.3, 131.2, 130.9, 130.3, 128.7, 124.2, 61.6, 44.8, 27.5, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3111, 3072, 2980, 2972, 2934, 2915, 2867, 1687, 1651, 1591, 1565, 1552, 1522, 1492, 1476, 1462, 1453, 1444, 1398, 1389, 1381, 1361, 1357, 1280, 1265, 1230, 1211, 1192, 1168, 1154, 1134, 1094, 1089, 1046, 1028, 1012, 964, 958, 950, 937, 930, 910, 881, 858, 834, 824, 812, 797, 764, 739, 715, 700, 667.

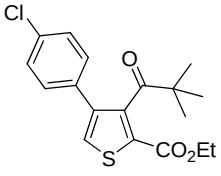
MS (70 eV, EI) *m/z* (%): 350 (28) [M^+], 294 (100), 266 (95), 149 (34).
HRMS (EI) for $C_{18}H_{19}ClO_3S$ (350.0743): 350.0734.

Preparation of ethyl 2-[3,5-bis(trifluoromethyl)phenyl]-4-(2,2-dimethylpropanoyl) thiophene-3-carboxylate (85d):



Prepared according to **TP8** from **84c** (1.45 g, 6.0 mmol) and TMPMgCl·LiCl (6.3 mL, 1.12 M in THF, 7.0 mmol). Deprotonation time: 1 h at -40 °C. A cross-coupling reaction was performed according to **TP9** using 1-bromo-3,5-bis(trifluoromethyl)benzene (2.34 g, 8.0 mmol) and $Pd(PPh_3)_4$ at -40 °C. The reaction mixture was then heated to 50 °C for 16 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **85d** (1.55 g, 57 %) as a colorless solid.
M.p.: 100-103 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.92-7.90 (m, 3H), 7.45 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.33 (s, 9H), 1.10 (t, J = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 205.8, 162.9, 144.1, 143.0, 134.8, 131.6 (q, J = 33.7 Hz), 131.1, 129.7, 127.4, 123.0 (q, J = 273.1 Hz), 122.5, 61.6, 44.7, 27.1, 13.6.
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3123, 2969, 1718, 1685, 1618, 1525, 1478, 1456, 1449, 1439, 1399, 1384, 1361, 1320, 1276, 1272, 1254, 1209, 1197, 1175, 1154, 1127, 1104, 1096, 1037, 1018, 1002, 947, 911, 896, 867, 843, 808, 791, 779, 748, 734, 702, 683, 666, 652.
MS (70 eV, EI) *m/z* (%): 452 (0.3) [M^+], 395 (63), 367 (100), 347 (22), 303 (11), 125 (11).
HRMS (EI) for $C_{20}H_{18}F_6O_3S$ (452.0881): 452.0870.

Preparation of ethyl 4-(4-chlorophenyl)-3-(2,2-dimethylpropanoyl)thiophene-2-carboxylate (85e):



Prepared according to **TP8** from **84a** (460 mg, 1.6 mmol) and TMPMgCl·LiCl (1.5 mL, 1.17 M in THF, 1.8 mmol). Deprotonation time: 3 h at -50 °C. Ethyl cyanoformate (198 mg, 2.0 mmol) was added at -50 °C, the reaction mixture was stirred for 1 h and then warmed to 25 °C. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 1:1) afforded **85e** (515 mg, 92 %) as a colorless solid.

M.p.: 92-93 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.41 (s, 1H), 7.34-7.26 (m, 4H), 4.32 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H).

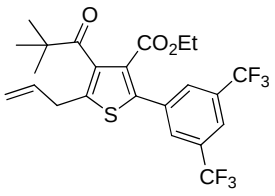
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 211.9, 161.3, 146.5, 140.1, 134.4, 134.0, 130.2, 130.0, 129.4, 128.8, 61.8, 45.4, 27.1, 14.3.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2967, 2934, 2869, 1701, 1685, 1526, 1500, 1479, 1462, 1444, 1436, 1362, 1265, 1246, 1232, 1214, 1173, 1163, 1093, 1076, 1053, 1018, 1006, 906, 891, 835, 823, 806, 793, 757, 732, 681.

MS (70 eV, EI) *m/z* (%): 350 (10) [M^+], 293 (91), 265 (100).

HRMS (EI) for $C_{18}H_{19}ClO_3S$ (350.0743): 350.0733.

Preparation of ethyl 5-allyl-2-[3,5-bis(trifluoromethyl)phenyl]-4-(2,2-dimethylpropanoyl) thiophene-3-carboxylate (86a):



Prepared according to **TP8** from 5**8d** (452 mg, 1.0 mmol) and TMPMgCl·LiCl (0.92 mL, 1.20 M in THF, 1.1 mmol). Deprotonation time: 45 min at -50 °C. An allylation reaction was

performed according to **TP10** using allyl bromide (145 mg, 1.2 mmol) at -50 °C during 1 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **86a** (421 mg, 85 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.89-7.86 (m, 3H), 5.97-5.90 (m, 1H), 5.24-5.18 (m, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.45 (td, J = 1.2 Hz, J = 6.6 Hz, 2H), 1.24 (s, 9H), 1.02 (t, J = 7.1 Hz, 3H).

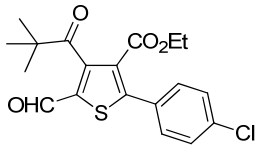
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 210.1, 162.3, 144.3, 140.6, 140.5, 135.4, 134.8, 131.3 (q, J = 34 Hz), 130.2, 128.4, 123.1 (q, J = 272 Hz), 122.2, 118.3, 61.4, 45.5, 33.1, 27.4, 13.5.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2979, 1710, 1693, 1641, 1619, 1536, 1481, 1458, 1447, 1404, 1392, 1370, 1275, 1171, 1157, 1129, 1108, 1034, 1018, 1004, 936, 897, 872, 847, 834, 798, 781, 737, 703, 683.

MS (70 eV, EI) *m/z* (%): 492 (3) [M^+], 435 (95), 407 (100), 257 (43).

HRMS (EI) for $C_{23}H_{22}F_6O_3S$ (492.1194): 492.1187.

Preparation of ethyl 2-(4-chlorophenyl)-4-(2,2-dimethylpropanoyl)-5-formylthiophene-3-carboxylate (86b):



Prepared according to **TP8** from **85c** (351 mg, 1.0 mmol) and TMPMgCl·LiCl (0.93 mL, 1.18 M in THF, 1.1 mmol). Deprotonation time: 30 min at -40 °C. DMF (110 mg, 1.5 mmol) was added at -40 °C and the reaction mixture was warmed to 25 °C. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 1:1) afforded **86b** (300 mg, 79 %) as a colorless solid.

M.p.: 105-107 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 9.67 (s, 1H), 7.43-7.36 (m, 4H), 4.14 (q, J = 7.0, 2H), 1.27 (s, 9H), 1.10 (t, J = 7.0 Hz, 3H).

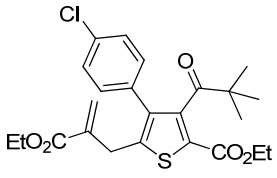
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 208.3, 181.8, 161.9, 156.4, 150.5, 138.0, 136.2, 130.9, 130.4, 128.6, 128.5, 61.7, 45.3, 27.1, 13.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976, 2935, 2894, 2869, 2839, 1699, 1681, 1674, 1593, 1520, 1471, 1446, 1405, 1383, 1362, 1356, 1290, 1268, 1201, 1159, 1117, 1090, 1013, 968, 874, 856, 846, 836, 825, 811, 800, 766, 715, 707, 670, 660.

MS (70 eV, EI) *m/z* (%): 378 (2) [M^+], 322 (68), 293 (100), 276 (39), 249 (17), 149 (16).

HRMS (EI) for $C_{19}H_{19}ClO_4S$ (378.0693): 378.0690.

Preparation of ethyl 4-(4-chlorophenyl)-3-(2,2-dimethylpropanoyl)-5-[2-(ethoxycarbonyl) prop-2-en-1-yl]thiophene-2-carboxylate (86c):



Prepared according to **TP8** from **85e** (379 mg, 1.1 mmol) and TMPMgCl·LiCl (1.03 mL, 1.17 M in THF, 1.2 mmol). Deprotonation time: 30 min at -50 °C. An allylation reaction was performed according to **TP10** using ethyl 2-(bromomethyl)acrylate (290 mg, 1.5 mmol) at -50 °C during 30 min. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 1:1) afforded **86c** (441 mg, 87 %) as a colorless solid.

M.p.: 74-76 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.34 (d, *J* = 7.6 Hz, 2H), 7.19 (d, *J*= 7.6 Hz, 2H), 6.25 (s, 1H), 5.45 (s, 1H), 4.29 (q, *J* = 7. 6 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.69 (brs, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.84 (s, 9H).

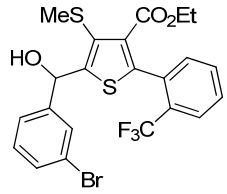
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 211.8, 165.8, 161.3, 148.3, 145.2, 138.3, 136.9, 134.3, 132.6, 131.5, 128.8, 127.3, 126.0, 61.6, 61.6, 44.7, 31.0, 27.1, 14.3, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 2905, 1703, 1691, 1629, 1529, 1497, 1479, 1463, 1444, 1413, 1405, 1390, 1367, 1362, 1328, 1292, 1278, 1252, 1231, 1215, 1193, 1182, 1174, 1153, 1113, 1105, 1083, 1069, 1027, 1016, 977, 969, 942, 895, 879, 843, 834, 816, 778, 759, 739, 721, 706, 699.

MS (70 eV, EI) *m/z* (%): 462 (2) [M^+], 405 (100), 377 (28), 331 (22).

HRMS (EI) for $C_{24}H_{31}ClO_5NS$ [$M^+ + NH_4^+$] (480.1611): 480.1614.

Preparation of ethyl 5-[(4-bromophenyl)(hydroxy)methyl]-4-(methylthio)-2-[2-(trifluoromethyl)phenyl]thiophene-3-carboxylate (86d):



Prepared according to **TP8** from **85b** (346 mg, 1.0 mmol) and TMPMgCl·LiCl (0.94 mL, 1.17 M in THF, 1.1 mmol). Deprotonation time: 1 h at -30 °C. 4-bromobenzaldehyde (222 mg, 1.2 mmol) was added at -30 °C, the reaction mixture was warmed to 25 °C and stirred for 16 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (CH_2Cl_2) afforded **86d** (374 mg, 70 %) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.71-7.70 (m, 1H), 7.54-7.47 (m, 4H), 7.39-7.35 (m, 3H), 6.45 (d, 1H), 3.97 (q, J = 7.1 Hz, 2H), 2.95 (brs, 1H), 2.32 (s, 3H), 0.79 (t, J = 7.1 Hz, 3H).

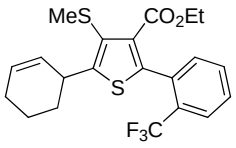
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 162.6, 151.7, 144.0, 141.2, 134.0, 132.6, 132.4, 131.7, 131.0, 129.3 (q, J = 29 Hz), 128.8, 128.6, 128.4, 126.0 (q, 5 Hz), 123.6 (q, 274 Hz), 122.1, 70.7, 60.4, 20.3, 13.3.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3380, 2982, 2924, 1769, 1703, 1604, 1590, 1578, 1526, 1486, 1441, 1421, 1396, 1374, 1344, 1312, 1279, 1265, 1250, 1193, 1169, 1125, 1108, 1065, 1022, 1009, 972, 962, 949, 899, 858, 834, 824, 766, 736, 707, 696, 689, 683, 658.

MS (70 eV, EI) *m/z* (%): 530 (10) [M^+], 517 (10), 486 (53), 471 (50), 441 (35), 344 (100).

HRMS (EI) for $C_{22}H_{18}BrF_3O_3S_2$ (529.9833): 529.9828.

Preparation of ethyl 5-cyclohex-2-en-1-yl-4-(methylthio)-2-[2-(trifluoromethyl)phenyl] thiophene-3-carboxylate (86e):



Prepared according to **TP8** from **85b** (346 mg, 1.0 mmol) and TMPMgCl·LiCl (0.94 mL, 1.17 M in THF, 1.1 mmol). Deprotonation time: 1 h at -30 °C. An allylation reaction was performed according to **TP10** using 3-bromo-1-cyclohexene (209 mg, 1.3 mmol) at -30 °C during 2 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 3:2) afforded **86e** (367 mg, 86 %) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.71-7.69 (m, 1H), 7.53-7.47 (m, 2H), 7.39-7.37 (m, 1H), 5.91-5.87 (m, 1H), 5.74-5.72 (m, 1H), 4.29-4.27 (m, 1H), 3.98 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 2.13-2.07 (m, 3H), 1.83-1.78 (m, 1H), 1.72-1.63 (m, 2H), 0.81 (t, J = 7.1 Hz, 3H).

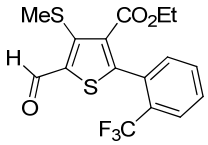
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 163.2, 155.1, 141.5, 134.0, 133.4, 132.6, 130.9, 129.6, 129.5 (q, J = 29 Hz), 129.1, 128.5, 127.3, 125.9 (q, J = 5 Hz), 123.7 (q, J = 274 Hz), 60.3, 36.0, 31.9, 24.8, 20.9, 20.8, 13.4.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3021, 2982, 2925, 2860, 1720, 1604, 1578, 1527, 1485, 1453, 1441, 1394, 1372, 1341, 1312, 1276, 1264, 1239, 1187, 1164, 1127, 1108, 1065, 1032, 997, 970, 960, 948, 899, 888, 865, 837, 828, 802, 766, 733, 723, 704, 680, 672.

MS (70 eV, EI) *m/z* (%): 426 (10) [M^+], 380 (98), 337 (100).

HRMS (EI) for $C_{21}H_{21}F_3O_2S_2$ (426.0935): 426.0923.

Preparation of ethyl 5-formyl-4-(methylthio)-2-[2-(trifluoromethyl)phenyl]thiophene-3-carboxylate (86f):



Prepared according to **TP8** from **85b** (260 mg, 0.75 mmol) and TMPMgCl·LiCl (0.71 mL, 1.17 M in THF, 0.83 mmol). Deprotonation time: 1 h at -30 °C. DMF (73 mg, 1.0 mmol) was added at -30 °C, the reaction mixture was warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical

purification on silica gel (pentane/CH_2Cl_2 = 13:7) afforded **86f** (238 mg, 85 %) as a colorless solid.

M.p.: 81-82 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 10.36 (s,1H), 7.76-7.75 (m, 1H), 7.60-7.56 (m, 2H), 7.38-7.37 (m, 1H), 4.01 (q, J = 4.1 Hz, 2H), 2.58 (s, 3H), 0.83 (t, J =4.1 Hz, 3H).

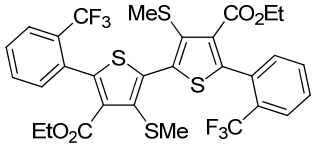
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 184.2, 161.7, 152.2, 143.8, 142.7, 135.5, 131.8, 131.6, 131.2, 129.5, 129.1 (q, J = 30 Hz), 126.2 (q, J = 4 Hz), 123.5 (q, J = 273 Hz), 60.9, 21.3, 13.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2988, 2942, 2900, 1713, 1638, 1604, 1581, 1521, 1484, 1427, 1375, 1334, 1314, 1296, 1269, 1209, 1175, 1160, 1123, 1105, 1063, 1037, 1025, 992, 987, 966, 948, 763, 740, 712, 662, 657.

MS (70 eV, EI) *m/z* (%): 374 (100) [M^+], 300 (20), 271 (14).

HRMS (EI) for $C_{16}H_{13}F_3O_3S_2$ (374.0258): 374.0246.

Preparation of diethyl 3,3'-bis(methylthio)-5,5'-bis[2-(trifluoromethyl)phenyl]-2,2'-bithiophene-4,4'-dicarboxylate (86g):



Prepared according to **TP8** from **85b** (260 mg, 0.75 mmol) and TMPMgCl·LiCl (0.71 mL, 1.17 m in THF, 0.83 mmol). Deprotonation time: 1 h at -30 °C. $ZnCl_2$ (0.83 mL, 1 M in THF, 1.1 equiv) was added at -30 °C and the reaction mixture stirred for 15 min. Chloranil (101 mg, 0.41 mmol) was added, the reaction mixture was warmed to 25 °C and stirred for 7 h. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded **86g** (162 mg, 63 %) as a brown solid.

M.p.: 139-141 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.76-7.75 (m, 2H), 7.60-7.53 (m, 4H), 7.49-7.48 (m, 2H), 4.02 (q, J = 7.1 Hz, 4H), 2.38 (s, 6H), 0.85 (t, J = 7.1 Hz, 6H).

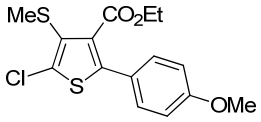
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 162.8, 145.1, 135.5, 134.2, 132.8, 132.6, 132.2, 131.1, 129.5 (q, J = 30 Hz), 129.0, 126.1 (q, J = 5 Hz), 123.7 (q, J = 273), 60.6, 20.0, 13.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2989, 2934, 2919, 2236, 2161, 2148, 1981, 1955, 1723, 1683, 1651, 1602, 1578, 1522, 1477, 1446, 1420, 1395, 1373, 1335, 1313, 1268, 1253, 1232, 1193, 1172, 1161, 1127, 1107, 1066, 1028, 1005, 986, 973, 965, 951, 896, 883, 870, 843, 834, 807, 796, 784, 766, 738, 730, 701, 680, 662.

MS (70 eV, EI) *m/z* (%): 690 (100) [M^+], 673 (7), 271 (18).

HRMS (EI) for $C_{30}H_{28}F_6NO_4S_4$ [$M^+ + NH_4^+$] (708.0805): 708.0810.

Preparation of ethyl 5-chloro-2-(4-methoxyphenyl)-4-(methylthio)thiophene-3-carboxylate (88):



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (286 mg, 11.8 mmol), LiCl (12.0 mL, 0.5 M in THF, 6.0 mmol) and $ZnCl_2$ (5.2 mL, 1.0 M in THF, 5.2 mmol). **83j** (1.29 g, 4.7 mmol) was added in one portion at 25 °C and the mixture was stirred for 3 h. The reaction mixture was cannulated to a new dry and argon-flushed *Schlenk*-flask and $Pd(dba)_2$ (54 mg, 2 mol%), P(2-furyl)$_3$ (43 mg, 4 mol%) and 4-iodoanisole (772 mg, 3.3 mmol) were added. The mixture was stirred for 3 h and then quenched with concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 13:7) afforded **88** (1.03 g, 91%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.33 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 4.24 (q, J = 4.1 Hz, 2H), 3.82 (s, 3H), 2.41 (s, 3H), 1.19 (t, J = 4.1 Hz, 3H).

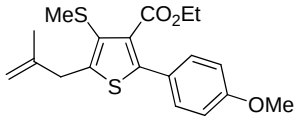
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 164.8, 160.2, 142.0, 132.8, 132.2, 130.2, 129.8, 124.6, 114.1, 61.5, 55.4, 19.0, 13.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2926, 2904, 2836, 1720, 1606, 1574, 1534, 1498, 1462, 1440, 1428, 1392, 1370, 1338, 1310, 1292, 1246, 1192, 1176, 1112, 1094, 1060, 1030, 1018, 972, 942, 926, 864, 830, 810, 790, 778, 736, 718, 702, 636, 618, 572.

MS (70 eV, EI) *m/z* (%): 342 (100) [M^+], 297 (33).

HRMS (EI) for $C_{15}H_{15}ClO_3S_2$ (342.0151): 342.0144.

Synthesis of ethyl 2-(4-methoxyphenyl)-5-(2-methylprop-2-en-1-yl)-4-(methylthio) thiophene-3-carboxylate (90):



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (122 mg, 5.0 mmol), LiCl (5.0 mL, 0.5 M in THF, 2.5 mmol) and $ZnCl_2$ (2.2 mL, 1.0 M in THF, 2.2 mmol). **88** (685 mg, 2 mmol) was added in one portion at 25 °C and the mixture was stirred for 4 h. The reaction mixture was cannulated to a new dry and argon-flushed *Schlenk*-flask and CuCN·2 LiCl (0.40 mL, 20 mol%) was added and the reaction mixture was stirred for 15 min. 3-Bromo-2-methylprop-1-ene (189 mg, 1.4 mmol) was added, the mixture was stirred for 3 h and then quenched with concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 7:3) afforded **90** (358 mg, 71%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.35 (d, J = 8.92 Hz, 2H), 6.88 (d, J = 8.92 Hz, 2H), 4.87 – 4.82 (m, 2H), 4.26 (q, J = 7.19 Hz, 2H), 3.82 (s, 3H), 3.69 (brs, 2H), 2.33 (s, 3H), 1.78 (brs, 3H), 1.19 (t, J = 7.19 Hz, 3H).

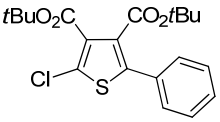
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.0, 159.8, 145.9, 143.9, 142.4, 133.0, 129.6, 129.0, 125.8, 113.9, 112.8, 61.2, 55.3, 37.0, 22.2, 20.4, 14.0.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 2924, 2836, 2360, 2342, 1718, 1652, 1608, 1574, 1536, 1502, 1462, 1440, 1418, 1392, 1372, 1342, 1292, 1248, 1176, 1132, 1112, 1094, 1024, 986, 972, 948, 932, 894, 864, 830, 810, 778, 742, 716, 668, 654, 636.

MS (70 eV, EI) *m/z* (%): 362 (100) [M^+], 301 (75), 260 (42), 247 (25), 175 (10).

HRMS (EI) for $C_{19}H_{22}O_3S_2$ (362.1010): 362.1011.

Preparation of di-*tert*-butyl 2-chloro-5-phenylthiophene-3,4-dicarboxylate (92):



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (292 mg, 12 mmol). LiCl (12.5 mL, 0.5 M in THF, 6.3 mmol) was added and the magnesium was activated with DIBAL-H (0.5 mL, 0.1 M in THF, 0.05 mmol). Di-*tert*-butyl 2,5-dichlorothiophene-3,4-dicarboxylate (**83e**, 1.77 g, 5.0 mmol) was added in one portion at -50 °C. The reaction mixture was stirred for 3 h and then cannulated to a new *Schlenk*-flask. $ZnCl_2$ (5.0 mL, 1 m in THF, 5.0 mmol) was added to the freshly prepared magnesium reagent and the reaction mixture was stirred for 15 min. $Pd(dba)_2$ (86 mg, 3 mol%) and tfp (69 mg, 6 mol%) were added, followed by the addition of iodobenzene (714 mg, 3.5 mmol), and the reaction mixture was stirred for 3 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution (15 mL) and extracted with Et_2O (3x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (pentane/CH_2Cl_2 = 4:1 to 1:1) furnished **92** as a colorless solid (1.13 g, 82 %).

M.p.: 84-86 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.42-7.35 (m, 5H), 1.59 (s, 9H), 1.34 (s, 9H).

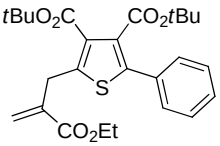
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 162.3, 161.1, 142.4, 132.5, 131.9, 131.3, 131.2, 129.2, 128.9, 128.3, 82.7, 82.2, 28.1, 27.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976, 1727, 1708, 1365, 1233, 1149, 765.

MS (70 eV, EI) *m/z* (%): 394 (9) [M^+], 282 (100), 265 (30), 238 (21), 57 (18).

HRMS (EI) for $C_{20}H_{23}ClO_4S$ (394.1006): 394.0992.

Preparation of di-*tert*-butyl 2-[2-(ethoxycarbonyl)prop-2-en-1-yl]-5-phenylthiophene-3,4-dicarboxylate (94):



The magnesium insertion was performed according to **TP1** from **92** (790 mg, 2.0 mmol) in 3 h at -50 °C. A allylation reaction was performed according to **TP3** with ethyl (2-bromomethyl)acrylate (270 mg, 1.4 mmol) in 30 min. Flash column chromatography (CH_2Cl_2) furnished **94** as a colorless oil (580 mg, 88 %).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.42-7.40 (m, 2H), 7.37-7.33 (m, 3H), 6.30 (d, J = 1.1 Hz, 1H), 5.60 (d, J = 1.1 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 4.00 (m, 2H), 1.53 (s, 9H), 1.36 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H).

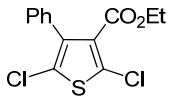
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 166.3, 163.7, 162.6, 144.4, 142.2, 138.5, 132.8, 132.5, 132.1, 129.1, 128.4, 128.2, 126.9, 81.9, 81.8, 61.0, 30.8, 28.1, 27.8, 14.2.

MS (70 eV, EI) *m/z* (%): 472 (1) [M^+], 360 (31), 342 (100), 270 (27), 57 (16).

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2977, 1707, 1631, 1475, 1392, 1365, 1244, 1150, 1122, 950, 847, 696.

HRMS (EI) for $C_{26}H_{32}O_6S$ (472.1920): 472.1929.

Preparation of ethyl 2,5-dichloro-4-phenylthiophene-3-carboxylate (96):



Prepared according to **TP8** from **79** (2.14 g, 14.0 mmol) and TMPMgCl·LiCl (14.0 mL, 1.10 M in THF, 15.4 mmol). Deprotonation time: 30 min at 25 °C. Ethyl cyanoformate (1.59 g, 16.0 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was quenched with half concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was solved in THF and deprotonated according to **TP8** using TMPMgCl·LiCl (14.0 mL, 1.10 M in THF, 15.4 mmol). A cross-coupling reaction was performed according to **TP9** using iodobenzene (4.08 g, 21.0 mmol), $Pd(dba)_2$ (161 mg, 2 mol%) and P(*o*-furyl)$_3$ (129 mg, 4 mol%) at -30 °C during 6 h. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 4:1) afforded **96** (2.93 g, 69 %) as a colorless solid.

M.p.: 55-56 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.44-7.37 (m, 3H), 7.29 – 7.26 (m, 2H), 4.09 (q, J = 7.1 Hz, 2H), 0.99 (t, J = 7.1 Hz, 3H).

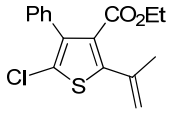
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 161.9, 138.9, 133.2, 130.7, 130.6, 120.2, 128.2, 128.1, 123.5, 61.3, 13.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 2932, 1722, 1544, 1498, 1482, 1464, 1446, 1384, 1366, 1280, 1246, 1176, 1156, 1098, 1072, 1054, 1014, 932, 862, 842, 806, 766, 702, 656, 630.

MS (70 eV, EI) *m/z* (%): 300 (40) [M^+], 255 (43), 207 (32), 192 (20), 44 (100).

HRMS (EI) for $C_{13}H_{10}Cl_2O_2S$ (299.9779): 299.9774.

Preparation of ethyl 5-chloro-2-isopropenyl-4-phenylthiophene-3-carboxylate (97):



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (462 mg, 19.0 mmol), LiCl (19.0 mL, 0.5 M in THF, 9.5 mmol) and $ZnCl_2$ (8.4 mL, 1.0 M in THF, 8.4 mmol). **96** (2.30 g, 7.6 mmol) was added in one portion at 25 °C and the mixture was stirred for 3 h. The reaction mixture was cannulated to a new dry and argon-flushed *Schlenk*-flask and $Pd(OAc)_2$ (36 mg, 1 mol %), SPhos (62 mg, 2 mol %) and 2-bromopropene (641 mg, 5.3 mmol) were added. The mixture was stirred for 2 h and then quenched with concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 3:1) afforded **97** (1.53 g, 94 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.42-7.28 (m, 5H), 5.26 (brs, 1H), 5.20-5.18 (m, 1H), 4.03 (q, J = 7.0 Hz, 2H), 2.11-2.10 (m, 3H), 0.97 (t, J =7.0 Hz, 3H).

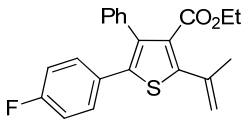
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 164.8, 144.4, 138.8, 136.6, 133.6, 129.4, 129.2, 128.1, 127.9, 124.5, 117.5, 61.2, 23.3, 13.5.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2936, 2164, 2030, 1974, 1720, 1498, 1442, 1368, 1282, 1232, 1174, 1152, 1094, 1072, 1018, 902, 698.

MS (70 eV, EI) *m/z* (%): 306 (100) [M^+], 277 (87), 249 (56), 197 (33).

HRMS (EI) for $C_{16}H_{15}ClO_2S$ (306.0481): 306.0475.

Preparation of ethyl 5-(4-fluorophenyl)-2-isopropenyl-4-phenylthiophene-3-carboxylate (98):



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with magnesium turnings (182 mg, 7.5 mmol), LiCl (7.5 mL, 0.5 M in THF, 3.8 mmol) and $ZnCl_2$ (3.3 mL, 1.0 M in THF, 3.3 mmol). **97** (918 mg, 3.0 mmol) was added in one portion at 25 °C and the mixture was stirred for 3 h. The reaction mixture was cannulated to a new dry and argon-flushed *Schlenk*-flask and $Pd(OAc)_2$ (14 mg, 1 mol%), SPhos (25 mg, 2 mol%) and 4-bromofluorobenzene (368 mg, 2.1 mmol) were added. The mixture was stirred for 1 h and then quenched with concentrated aqueous NH_4Cl solution, extracted three times with Et_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (toluene) afforded **98** (426 mg, 66 %) as a pale yellow solid.

M.p.: 55-57 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.27-7.26 (m, 3H), 7.18-7.16 (m, 2H), 7.12 – 7.10 (m, 2H), 6.88 (t, J = 8.5 Hz, 2H), 5.33 (s, 1H), 5.19 (s, 1H), 4.03 (q, J = 7.1 Hz, 2H), 2.16 (s, 3H), 0.98 (t, J = 7.1, 3H).

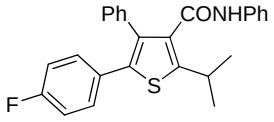
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.0, 162.2 (d, J = 248), 144.9, 137.7, 136.9, 136.7, 135.4, 131.5, 130.8 (d, J = 8 Hz), 129.8, 129.4 (d, J = 3 Hz), 128.2, 127.4, 116.6, 115.3 (d, J = 21 Hz), 61.1, 23.5, 13.6.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2976, 2936, 2352, 1714, 1536, 1504, 1462, 1454, 1442, 1390, 1374, 1366, 1306, 1220, 1208, 1170, 1158, 1136, 1090, 1076, 1024, 1016, 900, 832, 812, 792, 754, 726, 712, 700.

MS (70 eV, EI) *m/z* (%): 366 (100) [M^+], 337 (65), 309 (38), 139 (8), 91 (35).

HRMS (EI) for $C_{22}H_{19}FO_2S$ (366.1090): 360.1080.

Preparation of 5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenylthiophene-3-carboxamide (99):



To a solution of **98** (117 mg, 0.32 mmol) in EtOH (10 mL) Pd/C (17 mg, 5 mol %) was added. The mixture was hydrogenated at 25 °C under 1 atm of H_2 for 18 h. The catalyst was removed by filtration through Celite® by using a short-pad column. The solvents were evaporated *in vacuo* and the crude material was used in the next step without purification.

In a dry and argon-flushed *Schlenk*-flask $AlMe_3$ (1.0 mL, 1 M in heptane, 1.0 mmol) was added slowly to a solution of aniline (93 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) and the mixture was stirred for 15 min at 25 °C. The crude hydrogenated product was added, the reaction mixture was warmed to 40 °C and stirred for 48 h. After cooling, the mixture was transferred to an Erlenmeyer-flask and carefully quenched by the addidion of 1 M HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 20 mL), the organic layer dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane/CH_2Cl_2 = 1:1) afforded **99** (113 mg, 85 %) as a colorless solid.

M.p.: 231-232 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.33-7.00 (m, 12H), 6.90 (t, J = 8.7 Hz, 2H), 6.70 (brs, 1H), 3.89 (sept, J = 6.8 Hz, 1H), 1.42 (d, J = 6.8 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 163.3, 162.1 (d, J = 247 Hz), 156.5, 137.4, 135.6, 135.3, 135.2, 133.4, 130.8 (d, J = 8 Hz), 130.0, 129.8 (d, J = 3 Hz), 129.0, 128.8, 127.9, 124.3, 119.9, 115.3 (d, J = 21 Hz), 29.0, 25.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3234, 2978, 2166, 1998, 1750, 1716, 1640, 1596, 1552, 1534, 1514, 1500, 1456, 1442, 1368, 1332, 1252, 1234, 1158, 1096, 1004, 828, 798, 758, 742, 722, 700.

MS (70 eV, EI) *m/z* (%): 415 (24) [M^+], 323 (100), 281 (21), 139 (13).

HRMS (EI) for $C_{26}H_{22}FNOS$ (415.1406): 415.1393.

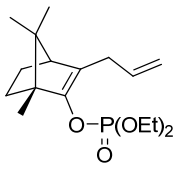
4. Preparation of Functionaized Enol Phosphates by Halogen-Magnesium Exchange and Directed Deprotonation Reactions

4.1. Typical Procedure for the Br-Mg-Exchange on Enol Phosphates (TP12)

To neat **21** (367 mg, 1.0 mmol) was added *i*PrMgCl·LiCl (0.96 mL, 1.1 mmol, 1.14 M in THF) at 25 °C and the resulting mixture was stirred for 2 h at this temperature. Further functionalizations were performed as described.

4.2. Preparation of Title Compounds

Preparation of 3-allyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl diethyl phosphate (105a):



103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to **TP12**. CuCN·2 LiCl (1 M solution in THF, 0.2 mL) and allyl bromide (132 mg, 1.1 mmol) were then added dropwise and the reaction mixture was stirred for 1 h at 25 °C. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/EtOAc = 6:1) furnished the compound **105a** (203 mg, 62 %) as a colourless oil.

Preparation by deprotonation:

107 (1.0 mmol) in THF (2.0 mL) was reacted with freshly titrated TMP_2Mg·2 LiCl (1.3 mmol, 0.55 M in THF, 2.36 mL) at 25 °C and stirred for 30 min. CuCN·2 LiCl (1 M solution in THF, 0.2 mL) and allyl bromide (132 mg, 1.1 mmol) were then added dropwise and the reaction mixture was stirred for 1 h at 25 °C. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL) extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash

chromatography (pentane/EtOAc = 6:1) furnished the compound **105a** (252 mg, 77 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 5.83-5.69 (m, 1 H), 5.10-4.97 (m, 2 H), 4.20-4.10 (m, 4 H), 3.07-2.99 (m, 1 H), 2.79-2.69 (m, 1 H), 2.18 (d, J = 3.7 Hz, 1 H), 1.85-1.74 (m, 1 H), 1.62-1.53 (m, 1 H), 1.47-1.39 (m, 1 H), 1.34 (tq, J = 7.1 Hz, J = 1.0 Hz, J = 0.51 Hz, 6 H), 1.11-1.03 (m, 1 H), 1.00 (s, 3 H), 0.89 (s, 3 H), 0.72 (s, 3 H).

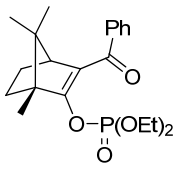
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 135.4, 124.6 (d, J = 6 Hz), 115.8, 64.2, 55.1, 54.4, 52.4 (d, J = 1 Hz), 32.5 (d, J = 1 Hz), 30.2 (d, J = 1 Hz), 25.4 (d, J = 5 Hz), 19.7 (d, J = 28 Hz), 16.2 (d, J = 6 Hz), 10.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 2873, 1672, 1639, 1476, 1444, 1388, 1368, 1319, 1271, 1211, 1167, 1133, 1054, 1028, 1008, 977, 928, 858, 820, 756, 647, 603.

MS (70 eV, EI) *m/z* (%): 328 (2) [M^+], 111 (54), 97 (70), 85 (44), 83 (67), 71 (65), 69 (69), 57 (100), 55 (55), 43 (50).

HRMS (EI) for $C_{17}H_{29}O_4P$ (328.1803): 328.1784.

Preparation of 3-benzoyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl diethyl phosphate (105b):



103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to **TP12**. The reaction mixture was cooled to –20 °C and CuCN·2 LiCl (1 M solution in THF, 0.2 mL) was added and the reaction mixture was stirred at this temperature for 30 min. Benzoyl chloride (155 mg, 1.1 mmol) was then added and the mixture was allowed to warm up to 25 °C over night. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/EtOAc = 2:1) furnished the compound **105b** (263 mg, 67 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.83-7.79 (m, 2 H), 7.50-7.37 (m, 3 H), 3.76-3.53 (m, 4 H), 2.82 (d, J = 3.4 Hz, 1 H), 2.06-1.95 (m, 1 H), 1.77-1.62 (m, 2 H), 1.49-1.41 (m, 1 H), 1.09 (m, 12 H), 0.83 (s, 3 H).

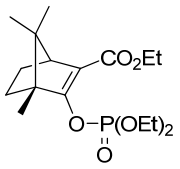
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 191.8 (d, J = 2 Hz), 158.5 (d, J = 12 Hz), 139.0, 132.0, 129.1, 128.0, 64.3 (t, J = 6 Hz), 56.8, 55.1, 52.8, 31.5 (d, J = 2 Hz), 26.0 (d, J = 3 Hz), 19.4 (d, J = 6 Hz), 15.9 (q, J = 3 Hz), 9.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2964, 2879, 1638, 1614, 1578, 1478, 1450, 1341, 1317, 1283, 1276, 1251, 1204, 1168, 1127, 1107, 1032, 1010, 977, 921, 894, 880, 827, 820, 775, 723, 703, 694, 657, 621.

MS (70 eV, EI) *m/z* (%): 392 (32) [M^+], 238 (23), 223 (34), 210 (33), 195 (38), 167 (13), 155 (13), 105 (100), 91 (9), 77 (34).

HRMS (EI) for $C_{21}H_{29}O_5P$: (392.1753): 392.1746.

Preparation of ethyl 3-[(diethoxyphosphoryl)oxy]-4,7,7-trimethylbicyclo[2.2.1]hept-2-ene-2-carboxylate (105c):



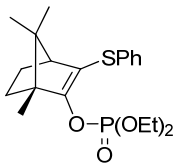
103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to **TP12**. The reaction mixture was cooled to –20 °C and ethyl cyanoformate (109 mg, 1.1 mmol) was added and the reaction mixture was slowly warmed to 25 °C. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/EtOAc = 3:1) furnished the compound **105c** (260 mg, 72 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 4.26-4.14 (m, 6H), 2.70 (d, J = 3.5 Hz, 1H), 1.95-1.90 (m, 1H), 1.68-1.64 (m, 1H), 1.53-1.49 (m, 1H), 1.34 (td, J = 7.1 Hz, J = 1.1 Hz, 6H), 1.28 (t, J = 7.1 Hz, 3H), 1.26-1.22 (m, 1H), 1.07 (s, 3H), 0.91 (s, 3H), 0.77 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 163.6, 162.6 (d, J = 11 Hz), 120.0 (d, J = 6 Hz), 64.6, 59.9, 56.6, 55.3, 50.9, 31.3 (d, J = 2 Hz), 25.6, 19.4, 19.1, 16.1 (d, J = 7 Hz), 14.3, 9.8.

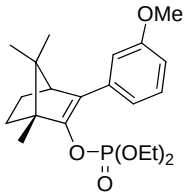
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 1703, 1635, 1392, 13709, 1339, 1275, 1246, 1186, 1025, 921.
MS (70 eV, EI) *m/z* (%): 360 (10) [M^+], 332 (14), 314 (95), 286 (82), 258 (37), 230 (38), 178 (100).
HRMS (EI) for $C_{17}H_{29}O_6P$ (360.1702): 360.1708.

Preparation of diethyl 1,7,7-trimethyl-3-(phenylthio)bicyclo[2.2.1]hept-2-en-2-yl phosphate (105d):



103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to **TP12**. The reaction mixture was cooled to –20 °C and benzenethiosulfonic acid *S*-phenyl ester (275 mg, 1.1 mmol) was added and the reaction mixture was slowly warmed to 25 °C. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/Et_2O = 3:1) furnished the compound **105d** (257 mg, 65 %) as a colorless oil.
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40-7.37 (m, 2H), 7.28-7.15 (m, 3H), 4.26-4.16 (m, 4H), 2.19 (d, *J* = 3.5 Hz, 1H), 1.81-1.71 (m, 1H), 1.67-1.59 (m, 1H), 1.53-1.45 (m, 1H), 1.36-1.30 (m, 6H), 1.25-1.16 (m, 1H), 1.07 (s, 3H), 0.99 (s, 3H), 0.70 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 155.1 (d, *J* = 11 Hz), 134.9, 130.7, 128.7, 126.5, 117.7 (d, *J* = 7 Hz), 64.5, 55.99, 54.2, 53.2, 32.9, 25.8, 19.4, 16.0 (d, *J* = 7 Hz), 10.0.
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958, 16919, 1477, 1440, 1280, 1133, 1034, 965, 823.
MS (70 eV, EI) *m/z* (%): 396 (75) [M^+], 368 (71), 319 (80), 287 (87), 214 (93), 105 (100).
HRMS (EI) for $C_{20}H_{29}O_4PS$ (396.1524): 396.1532.

Preparation of diethyl 3-(3-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl phosphate (105e):



103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to **TP12** and then transmetallated with $ZnCl_2$ (1.1 equiv) at 0 °C. $Pd(OAc)_2$ (4.5 mg, 2 mol%), S-Phos (16.5 mg, 4 mol%) and 3-bromoanisole (281 mg, 1.5 mmol) were then added to the reaction mixture. The resulting mixture was stirred at 25 °C overnight and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/EtOAc = 3:1) furnished the compound **105e** (273 mg, 69 %) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.21 (t, J = 7.9 Hz, 1H), 7.07-7.02 (m, 2H), 6.73 (dd, J = 7.9 Hz, J = 2.2 Hz, 1H), 4.11-3.90 (m, 4H), 3.81 (s, 3H), 2.65 (d, J = 3.7 Hz, 1H), 2.13 (brs, 1H), 1.99-1.94 (m, 1H), 1.70 (t, J = 6.3 Hz, 2H), 1.35-1.27 (m, 1H), 1.22 (td, J = 7.2 Hz, J = 1.0 Hz, 3H), 1.15 (td, J = 7.2 Hz, J = 1.0 Hz, 3H), 1.13 (s, 3H), 0.97 (s, 3H), 0.81 (s, 3H).

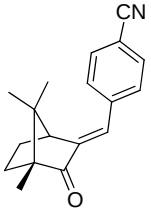
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 159.4, 150.7 (d, J = 12 Hz), 135.7 (d, J = 2), 129.0, 126.3 (d, J = 7 Hz), 119.4, 112.4, 112.2, 64.2, 55.7, 55.5, 55.2, 53.5, 32.4, 25.8 (d, J = 3 Hz), 19.5 (d, J = 43 Hz), 15.9, 10.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 1636, 1597, 1483, 1271, 1161, 1129, 1025, 1003, 960, 922, 875, 784, 686.

MS (70 eV, EI) *m/z* (%): 394 (22) [M^+], 240 (30), 225 (33), 212 (100), 197 (17).

HRMS (EI) for $C_{21}H_{31}O_5P$ (394.1909): 394.1908.

Preparation of 4-[(*E*)-(4,7,7-trimethyl-3-oxobicyclo[2.2.1]hept-2-ylidene)methyl]benzonitrile (109a):



103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to **TP12**. The reaction mixture was cooled to –20 °C and 4-cyanobenzaldehyde (144 mg, 1.1 mmol) was added and the reaction mixture was slowly warmed to 25 °C. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/Et_2O = 3:1) furnished the compound **109a** (191 mg, 72 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.65 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.18 (s, 1H), 3.03 (d, J = 4.5 Hz, 2H), 2.25-2.13 (m, 1H), 1.86-1.76 (m, 1H), 1.63-1.47 (m, 2H), 1.02 (s, 3H), 1.00 (s, 3H), 0.76 (s, 3H).

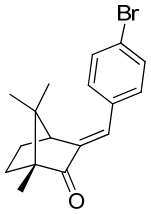
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 207.4, 145.1, 140.3, 132.3, 130.09, 125.1, 118.6, 111.8, 57.1, 49.2, 46.6, 30.4, 25.9, 20.6, 18.2, 9.2.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3436, 2959, 2228, 1724, 1648, 1504, 1324, 1295, 1064, 1016, 837.

MS (70 eV, EI) *m/z* (%): 265 (100) [M^+], 250 (58), 222 (57), 183 (59), 154 (54).

HRMS (EI) for $C_{18}H_{17}NO$ (265.1467): 265.1492.

Preparation of (3*E*)-3-(4-bromobenzylidene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (109b):



103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to **TP12**. The reaction mixture was cooled to –20 °C and 4-bromobenzaldehyde (204 mg, 1.1 mmol) was added and the reaction mixture was slowly warmed to 25 °C. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/Et_2O = 4:1) furnished the compound **109b** (220 mg, 68 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.50 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.14 (s, 1H), 3.03 (d, J = 4.0 Hz, 1H), 2.22-2.09 (m, 1H), 1.84-1.73 (m, 1H), 1.59-1.46 (m, 2H), 1.02 (s, 3H), 0.99 (s, 3H), 0.76 (s, 3H).

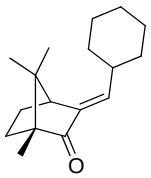
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 207.9, 142.8, 134.6, 131.9, 131.1, 126.2, 122.8, 57.1, 49.2, 46.7, 30.6, 25.9, 20.6, 18.3, 9.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3420, 2957, 1720, 1641, 1586, 1491, 1323, 1071, 1064, 1008, 796.

MS (70 eV, EI) *m/z* (%): 320 (100) [M^+], 318 (98) [M^+], 303 (37), 275 (22), 249 (19), 236 (38), 196 (21), 128 (37).

HRMS (EI) for $C_{17}H_{19}OBr$ (318.0619): 318.0621.

(3*E*)-3-(Cyclohexylmethylene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (109c):



103 (367 mg, 1.0 mmol) was reacted at 25 °C for 2 h according to **TP12**. The reaction mixture was cooled to –20 °C and cyclohexanecarbaldehyde (123 mg, 1.1 mmol) was added and the reaction mixture was slowly warmed to 25 °C. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/Et_2O = 4:1) furnished the compound **109c** (173 mg, 70 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 6.18 (d, J = 8.9 Hz, 1H), 2.67 (d, J = 4.4 Hz, 1H), 2.22-2.10 (m, 1H), 2.03-1.93 (m, 1H), 1.72-1.56 (m, 6H), 1.42-1.07 (m, 7H), 0.93 (s, 3H), 0.92 (s, 3H), 0.75 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 208.0, 141.0, 135.5, 57.7, 47.7, 46.0, 37.99, 32.3, 32.2, 30.09, 26.8, 25.8, 25.5, 20.5, 18.3, 9.2.

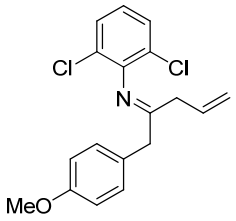
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2848, 1725, 1662, 1446, 1257, 1109, 1065, 940.

MS (70 eV, EI) *m/z* (%): 246 (95) [M^+], 231 (98), 218 (81), 203 (100), 95 (94).

HRMS (EI) for $C_{17}H_{26}O$ (246.1984): 246.1963.

5. 1-Aryliminozinc Reagents as Acyl Anion Equivalents

Preparation of (2,6-dichlorophenyl)[1-(4-methoxybenzyl)but-3-en-1-ylidene]amine (116):



A flame-dried and argon-flushed *Schlenk*-flask was charged with 2,6-dichlorophenyl isonitrile (**114,** 1.1 mmol, 189 mg) in 3 mL THF and cooled to –78 °C. 4-Methoxybenzylzinc chloride (**111**, 1.0 mmol, 0.44 M in THF, 2.3 mL) was added slowly and the reaction mixture stirred for 30 min. CuCN·2 LiCl (0.2 mmol, 1 M in THF, 0.2 mmol) and allyl bromide (1.2 mmol, 145 mg) were added and the solution stirred for 15 min. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatographical purification (pentane/EtOAc = 4:1) furnished **116** (202 mg, 61 %) as a yellow oil.

D. APPENDIX

Fabian Michel Piller

-Curriculum Vitae-

Personal Information:

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	81377 Munich	
	Germany	
Telephone:	+49-89-72484675	
Mobile:	+49-163-2522437	
E-Mail:	fabian.piller@cup.lmu.de	
Date of Birth:	January 4th 1981	
Place of Birth:	Paris, France	
Nationality:	German, French	
Marital Status:	Single	
Languages:	German:	mother-tongue
	French:	mother-tongue
	English:	fluent

Education:

12/2006-02/2010	**Ph.D. Thesis** in the group of Prof. Dr. Paul Knochel, Ludwig-Maximilians-Universität Munich.
10/2004-09/2006	**Graduate studies (M.Sc.)** at the Department of Chemistry, Ludwig-Maximilians-Universität Munich, Grade: sehr gut (very good)
10/2001-10/2004	**Undergraduate studies (B.Sc.)** at the Department of Chemistry, Ludwig-Maximilians-Universität Munich
9/1991-6/2000	**High School** at the Luisengymnasuim, Munich and Pacifica High School, Garden Grove, CA, U.S.A. Average Grade: 1.4 (A)

Research and Work Experience:

12/2006-02/2010	**Research Associate** in the Group of Prof. Dr. Paul Knochel, Ludwig-Maximilians-Universität Munich Topic: LiCl-Mediated Direct Insertion of Magnesium Into Aryl-, Heteroaryl and Benzylic Halides. Regio- and Chemoselective Synthesis of 5-Membered Ring Heterocycles**.** Tasks included: Supervision of two Master's Theses and one Bachelor's Thesis, Teaching and supervising students in their sophomore organic chemistry course
03/2006-09/2006	**Master's Thesis** in the group of Prof. Dr. Paul Knochel, Ludwig-Maximilians-Universität Munich Topic: Regioselective Synthesis of Highly Functionalized Heterocycles
07/2005-09/2005	**Visiting student** in the group of Prof. Dr. Victor Snieckus, Queen's University, Kingston, ON, Canada
11/2004-07/2005	**Student Internship** in the group of Prof. Dr. Paul Knochel, Ludwig-Maximilians-Universität Munich

Awards:

2008	Award of the Dr. Klaus Römer-Foundation for excellence during the Ph.D. thesis
2000	FCI-Award (Fund of the Chemical Industry, Germany) for the best Chemistry-Diploma in High School

Extracurricular Activities:

2002-2004	Elected student representative in the council of the Faculty of Chemistry and Pharmacy, Ludwig-Maximilians-Universität Munich
2002-2004	President of the Chemistry Students' Association, Ludwig-Maximilians-Universität Munich
Interests:	Music, playing the guitar, traveling, reading, cooking

Fabian Michel Piller

-Publication List-

Communications and Full Papers:

F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, **Convenient Preparation of Polyfunctional Arylmagnesium Reagents Using a Direct Magnesium Insertion in the Presence of LiCl**, *Angew. Chem. Int. Ed*. **2008**, *47*, 6802-6806; *Angew. Chem.* **2008**, *120*, 6907-6911.
Highlighted in *Synfacts* **2008**, *11*, 1160.

A. Metzger, F. M. Piller, P. Knochel, **Polyfunctional Benzylic Zinc Chlorides by the Direct Insertion of Magnesium in the Presence of LiCl and $ZnCl_2$**, *Chem. Commun.* **2008**, 5824-5826.

F. M. Piller, P. Knochel, **Regio- and Chemoselective Synthesis of Fully Substituted Thiophenes,** *Org. Lett.* **2009**, *11*, 445-448.

F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, **Preparation of Polyfunctional Arylmagnesium, Arylzinc and Benzylic Zinc Reagents Using Magnesium in the Presence of LiCl**, *Chem. Eur. J.* **2009**, *15*, 7192-7202.

T. D. Blümke, F. M. Piller, P. Knochel, **Preparation of Highly Functionalized Alkylzinc Halides from Alkyl Bromides using Mg, $ZnCl_2$ and LiCl,** *Chem. Commun*. **2010**, DOI:10.1039/c001845g.

F. M. Piller, T. Bresser, M. K. R. Fischer, P. Knochel, **Preparation of Functionalized Cyclic Enol Phosphates by Halogen-Magnesium Exchange and Directed Deprotonation Reactions**, *manuscript in preparation*.

F. M. Piller, P. Knochel, **Functionalization of Furan, Thiophene, Pyrrole and Indol Derivatives via** *Ortho*-**Magnesiation Reactions,** *manuscript in preparation.*

Reviews:

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