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Synthesis of Functionalized Heterocycles Using Magnesium and Zinc Reagents. Diastereoselective Addition of Allylic Aluminum Reagents to Carbonyl Compounds. Preparation and Application of Aromatic and Benzylic Manganese Reagents

von

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aus

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Erklärung

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Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig, ohne unerlaubte Hilfe bearbeitet.

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…..……

Zhihua Peng

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1. Gutachter: Prof. Dr. Paul Knochel
2. Gutachter: Prof. Dr. Manfred Heuschmann

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Parts of this Ph.D. thesis have been published

1) Benjamin Haag, Zhihua Peng, and Paul Knochel*, Preparation of Polyfunctional Indazoles and Heteroarylazo Compounds Using Highly Functionalized Zinc Reagents, *Org. Lett.* **2009**, *11*, 4270-4273.
2) Tobias Blümke, Yi-Hung Chen, Zhihua Peng and Paul Knochel*, Preparation of functionalized organoaluminiums by direct insertion of aluminium to unsaturated halides, *Nat. Chem.* **2010**, *2*, 313-318.
3) Zhihua Peng, Benjamin A. Haag, and Paul Knochel*, Preparation of 2-Magnesiated 1,3,5-Triazines via an Iodine-Magnesium Exchange, *Org. Lett*. **2010**, *12*, 5398-5401.
4) Zhihua Peng, Tobias D. Blümke, Peter Mayer, and Paul Knochel*, Diastereoselective Synthesis of Homoallylic Alcohols with Adjacent Tertiary and Quaternary Centers by Using Functionalized Allylic Aluminum Reagents, *Angew. Chem. Int. Ed.* **2010,** *49*, 8516 –8519.
5) Zhihua Peng, and Paul Knochel*, Preparation of Functionalized Organomanganese(II) Reagents by Direct Insertion of Manganese to Aromatic and Benzylic Halides, *Org. Lett*. **2011**, *13*, 3198-3201.

To Yilei, with love

Table of Contents

Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl
*n*Bu	*n*-butyl
*s*Bu	*s*-butyl
*t*Bu	*t*-butyl
calc.	calculated
conc.	concentrated
δ	chemical shifts in parts per million
d	doublet
dba	*trans,trans*-dibenzylideneacetone
dr	diastereomeric ratio
EI	electron-impact ionization
eq.	equation
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectroscopy
IR	infrared
LA	Lewis acid
LDA	lithium diisopropylamide

J	coupling constant (NMR)
M	molarity
m	meta
m	multiplet
Me	methyl
min	minute
mmol	millimole
m.p.	melting point
MS	mass spectroscopy
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
o	ortho
Oct	octyl
p	para
PEPPSI	pyridine, enhanced, precatalyst, preparation, stabilization, and initiation
Ph	phenyl
*i*Pr	*iso*-propyl
q	quartet
R	organic substituent
s	singulet
sat.	saturated
tfp	tris-2-furylphosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TES	triethylsilyl
TP	typical procedure
X	halogen (F, Cl, Br, I)

A. General Introduction

1. Overview

"*Today it is not only unwise but rather difficult to accomplish an efficient and selective multiple synthesis without using organometallics*".[1]

The synthesis of biologically active compounds or natural products for the pharmaceutical and agrochemical industries is one of the most important areas of research. Considering that the construction of complex molecules constantly demands new, straightforward and efficient methods for achieving chemical transformations, undoubtly, developing novel strategies and new reagents for meeting this challenge is a major task of modern organic chemists. Since the first preparation of organometallic reagent (diethylzinc) was performed by *Frankland,*[2] it has been proven that organometallics are the most powerful tools in the formation of carbon-carbon and carbon-heteroatom bonds, and they also offer access to complex and biological molecules to organic chemists. Up to now, nearly every metal in the periodic table has been used in synthetic organic chemistry. Among them, a large number of metals were used to prepare organometallic reagents and their displayed reactivities to electrophiles and compatibilities with functional groups have been studied in detail.[3] For instance, organolithium compounds have high reactivity to electrophiles, but they display low selectivity and reduced functional group tolerance. In the case of organomagnesium reagents and organozinc reagents which possess a more covalent character of the carbon-metal bond, they have good reactivity and can tolerate a wide range of sensitive functional groups. Moreover, organoaluminum reagents have significant functional group tolerance but suffer from decreased reactivity.

[1] *Organometallics in Organic Synthesis*, E.-I. Negishi, Wiley-VCH; Weinheim, 1980.
[2] a) E. Frankland, *Liebigs Ann. Chem.* **1848-9**, *71*, 171; b) E. Frankland, *J. Chem. Soc.* **1848-9**, *2*, 263.
[3] a) *Handbook of Functionalized Organometallics*, P. Knochel, Ed., Wiley-VCH: Weinheim, **2005**; b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., A. de Meijere, F. Diederich, Wiley-VCH: Weinheim, **2004**.

Additionally, organomanganese reagents can behave like transition metal derivatives, which leads to a much different reactivity than that of the previously mentioned organometallic species. Because of their different properties, organometallics offered sufficient optional approaches to perform efficient total synthesis of complex molecules. Therefore, developing methods for the reliable preparation of various organometallics and studying the reactivity of these organometallics are continuously necessary and important, and they are also the main goals of this work.

2. Halogen-Metal Exchange Reaction

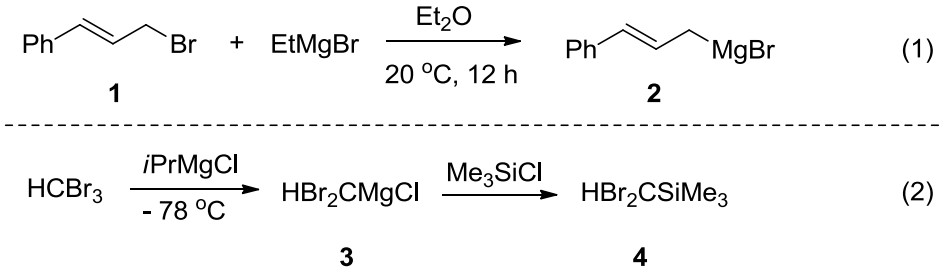
Organomagnesium reagents, characterized by excellent reactivity and good function tolerance to a variety of electrophiles, still occupy a central place in organometallic chemistry. Since *Victor Grignard* reported the first preparation of organomagnesium reagents in 1901,[4] these so-called Grignard reagents have been utilized widely in the areas of academic and process chemistry. The well-established methodologies concerning organomagnesium reagents include addition to carbonyl functions, Kumada cross-coupling, carboxylation with carbon dioxide, and so on.[3] Especially, the reactivity and selectivity of organomagnesium reagents can be tuned after the transmetallation with many metallic salts, which dramatically broadened their scope.

The most common way for the preparation of organomagnesium reagents is the oxidative insertion of magnesium metal to organic halides. However, this insertion method is usually hindered by low functional group tolerance.[5] An alternative method for synthesizing organomagnesium reagents is the halogen-magnesium exchange reaction.[6]

The first reaction of a halogen-magnesium exchange was disclosed by *Prévost* who showed that cinnamyl bromide (**1**) reacted with EtMgBr, affording

[4] V. Grignard, *Ann. Chim.* **1901**, *24*, 433.
[5] *Grignard Reagents-New Developments* (Ed.: H. G.. Richey), Wiley, New York, **2000.**
[6] For selected reviews, see: a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; b) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; c) H. Ila, O. Baron, A. J. Wagner, P. Knochel, *Chem. Commun*. **2006**, 583.

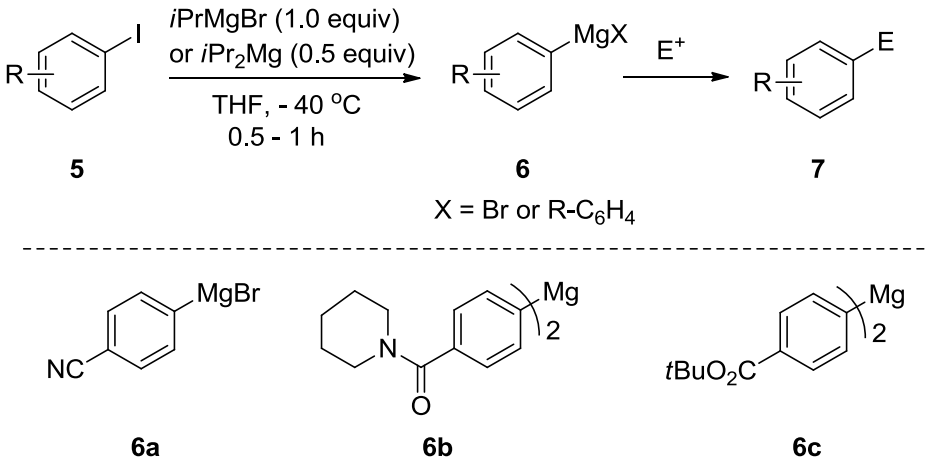
cinnamylmagnesium bromide (**2**) in a moderate yield (Scheme 1, Eq. 1).[7] In 1967, *Villiéras* demonstrated that the treatment of $CHBr_3$ with *i*PrMgCl afforded the corresponding magnesium carbenoid **3** (Scheme 1, Eq. 2).[8] A few years later, the work of *Tamborski* and *Moore* as well as similar work done by *Furukawa* confirmed this halogen-magnesium exchange reaction.[9] These excellent pioneer breakthroughs allowed access to polyfunctionalized organomagnesium reagents by a halogen-magnesium exchange reaction.



Scheme 1. First example of a halogen-magnesium exchange (Eq. 1) and bromine-magnesium exchange (Eq. 2).

Subsequently, this convenient method has received attention from several research groups. In 1998, *Knochel* and co-workers discovered that the halogen-magnesium exchange displays a remarkable functional group tolerance.[10] A variety of arylmagnesium halides bearing sensitive functional groups such as nitriles, esters, or amides can be prepared *via* an I/Mg exchange (Scheme 2).

[7] C. Prévost, *Bull. Soc. Chim. Fr*. **1931**, *49*, 1372.
[8] a) J. Villiéras, *Bull. Chem. Soc. Fr.* **1967**, *5*, 1520; b) J. Villiéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Chem. Soc. Fr*. **1986**, 470.
[9] a) C. Tamborski, G. J. Moore, *J. Organomet. Chem*. **1971**, *26*, 153; b) N. Furukawa, T. Shibutani, H, Fujihara, *Tetrahedron Lett*. **1987**, *28*, 5845.
[10] L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.



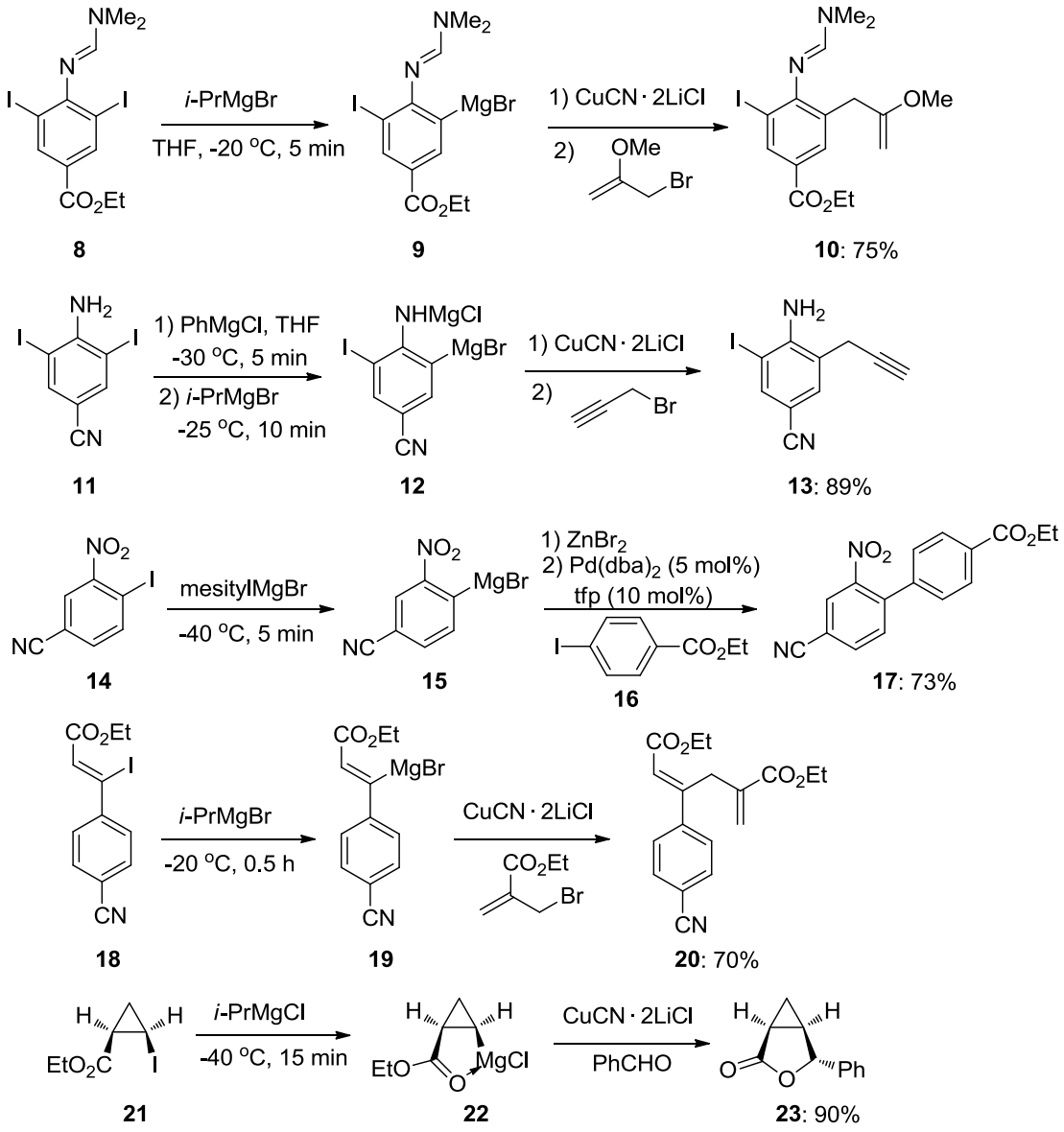
Scheme 2. Preparation of highly functionalized Grignard reagents by an I/Mg exchange.

Over the years, the scope of substrates in halogen-magnesium exchange reaction has been considerably enhanced. For instance, the reaction of amidine-protected diiodoamidine **8** with *i*-PrMgBr in THF afforded the corresponding arylmagnesium species **9** within 5 min. After transmetallation of **9** with CuCN·2LiCl, the resulting copper reagent underwent allylation with 2-methoxyallyl bromide, furnishing the desired allylation product **10**.[11] Interestingly, the treatment of unprotected iodoaniline **11** with PhMgCl and *i*PrMgCl formed the dimagnesium derivative **12**. Transmetallation with CuCN·2LiCl, followed by the addition of 3-bromoprop-1-yne, gave the desired product **13** in 89% yield.[12] Substrates with highly electrophilic functionalities such as a nitro group can also be used to prepare Grignard reagent. Thus, 4-iodo-3-nitrobenzonitrile **14** reacted with the sterically hindered mesitylMgBr within 5 min at -40 °C, affording the corresponding Grignard reagent **15**. After transmetallation with $ZnBr_2$, the reaction of the resulting zinc reagent with ethyl 4-iodobenzoate (**16**) in the presence of [$Pd(dba)_2$] (5 mol%) and tfp (10 mol%) furnished biaryl derivative **17** in 73% yield (Scheme 3).[13] In comparison to aryl iodides, an I/Mg exchange reaction of alkenyl iodides is slower. However, the

[11] D. M. Lindsay, W. Dohle, A. E. Jensen, F. Kopp, P. Knochel, *Org. Lett.* **2002**, *4*, 1819.
[12] G.. Varchi, C. Kofink, D. M. Lindsay, A. Ricci, P. Knochel, *Chem. Commun*. **2003**, 396.
[13] I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed*. **2002**, *41*, 1610.

presence of an electron-withdrawing functionality directly linked to the double bond facilitates the iodine-magnesium exchange reaction. Thus, the alkenyl magnesium reagent **19** was readily obtained by an iodine-magnesium exchange of ethyl 3-iodo-*p*-cyanocinnamate (**18**) with *i*PrMgBr. Transmetallation with CuCN·2LiCl and reaction with ethyl (2-bromomethyl)-acrylate led to the expected allylation product **20** in 70% yield.[14] In the case of alkyl substrates, the preparation of alkyl magnesium reagents is difficult due to the high reactivity of the resulting alkyl magnesium reagents. Remarkably, the treatment of 2-iodocyclopropanecarboxylate **21** with *i*PrMgCl within 15 min at -40 ^{o}C afforded stable *cis*-cyclopropylmagnesium chloride **22**. Reaction with benzaldehyde after transmetallation with CuCN·2LiCl furnished the lactone **23**.[15]

[14] I. Sapountzis, W. Dohle, P. Knochel, *Chem. Commun*. **2001**, 2068.
[15] V. A. Vu, I. Marek, K. Polborn, P. Knochel, *Angew. Chem. Int. Ed*. **2002**, *41*, 351.

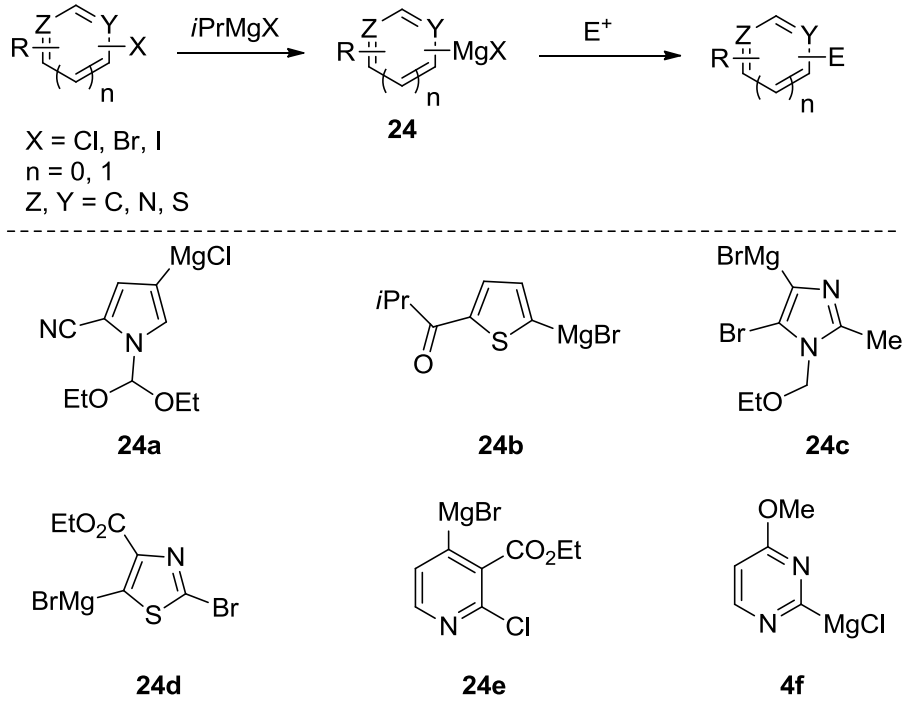


Scheme 3. The scope of the halogen-magnesium exchange reaction.

Additionally, an important application of the halogen-magnesium exchange is the construction of polyfunctionalized heterocycles which are becoming more significant in many fields. To date, a wide range of functionalized five-membered and six-membered heteroaryl magnesium compounds have been synthesized by a halogen-magnesium exchange reaction such as **24a**,[16] **24b**,[17] **24c**,[18] **24d**,[19] **24e**,[20]

[16] M. Bergauer, P. Gmeiner, *Synthesis*, **2001**, 2281.
[17] M. Abarbri, J. Thibonnet, L. Bérillon, F. Dehmel, M. Rottländer, P. Knochel, *J. Org. Chem.* **2000**, *65*, 4618.
[18] F. Dehmel, M. Abarbri, P. Knochel, *Synlett* **2000**, 345.
[19] C. J. Lovely, H. Du, H. V. Rasika Dias, *Org. Lett.* **2001**, *3*, 1319.

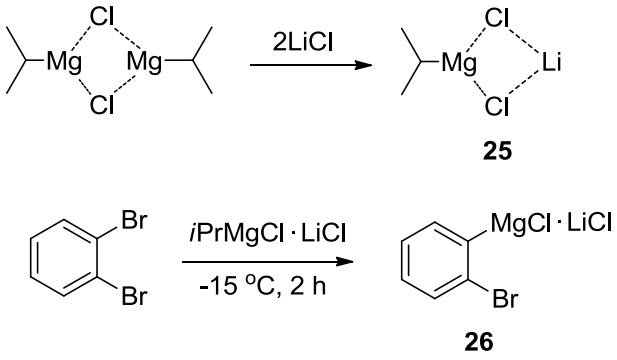
and **24f**[21] (Scheme 4).



Scheme 4. Preparation of functionalized heteroaryl magnesium compounds.

A recent improvement accomplished by *Knochel et al.* demonstrated that by using a stoichiometric amount of LiCl, the rate of the halogen-magnesium exchange was increased and the reactivity of the resulting Grignard reagent was enhanced. The proposed mechanism is that LiCl breaks the aggregates of *i*PrMgCl affording a more reactive complex **25**. By using this new reagent *i*PrMgCl·LiCl, *ortho*-bromophenylmagnesium halide **26** which is difficult to prepare from 1,2-dibromobenzene was readily generated *via* a Br/magnesium exchange (Scheme 5).[22]

[20] L. Bérillon, A. Leprêtre, A. Turck, N. Plé, G. Quéguiner, G. Cahiez, P. Knochel, *Synlett* **1998**, 1359.
[21] A. Leprêtre, A. Turck, N. Plé, P. Knochel, G. Quéguiner, *Tetrahedron*, **2000**, *56*, 265.
[22] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed*. **2004**, *43*, 3333.



Scheme 5. The supposed reactive intermediate **25** and selective Br/Mg exchange.

3. Allylic Aluminum Reagents

3.1 Allylic Metals

The addition of allylmetal reagents to carbonyl groups is one of the most common strategies to perform highly stereoselective syntheses of an important structural subunit bearing sequences of stereocenters which is commonly found in polyether antibiotics and polyhydroxylated natural products.[23] To date, allylic organometallic reagents which are derived from a wide range of metals, including magnesium, boron, silicon, aluminum, indium, lithium and so on,[24] have been extensively studied. Especially, the excellent pioneering studies of *Heathcock*,[25] *Hoffmann*[26] and *Yamamoto*[27] from 1978 to 1980 have shown the potential of allylic organometallics reagents for the control of the stereochemistry of the carbon-carbon formed in additional reactions. Since then, the asymmetric addition of allylic organometallic reagents to carbonyl group or imines has emerged and has been widely used in a variety of asymmetric total synthesis.

Mechanistically, allylic organometallic reagents can be classified in three categories.[28] In addition reactions of allylic organometallic reagents of type **I** to carbonyl group, chair-like transition state is presumed. An *anti*-homoallylic alcohol is obtained when (*E*)-alkene precursor is employed. On the contrary, (*Z*)-alkene precursor gives a *syn*-homoallylic alcohol (Scheme 6).[24]

[23] a) P. A. Bartlett, *Tetrahedron* **1980**, *36*, 3; b) I. Paterson, M. M. Mansuri, *Tetrahedron* **1984**, *41*, 3569; c) R. W. Hoffmann, *Angew. Chem. Int. Ed.* **1987**, *26*, 489.

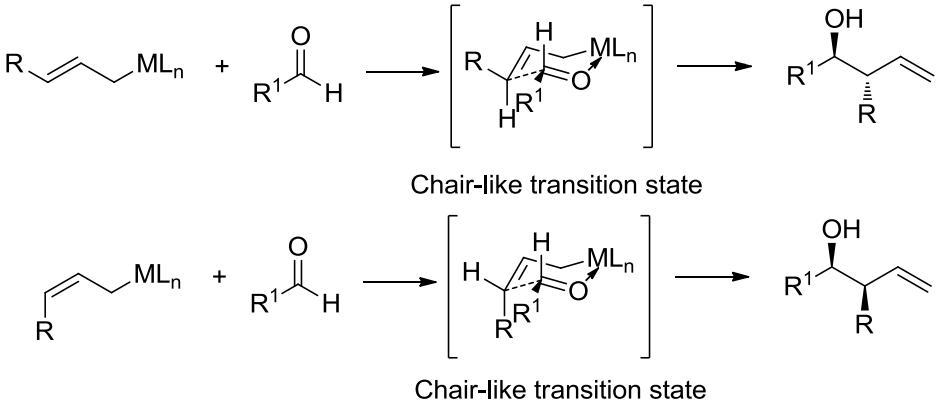
[24] For selected reviews, see: a) Roush, W. R. In *Compreh. Org. Synth.;* Heathcock, C. H., Ed.; Pergamon: Oxford 1990, Vol. 2, p; b) Y. Yamamoto and N. Asao, *Chem. Rev*. **1993**, *93*, 2207; c) J.W. J. Kennedy and D. G. Hall, *Angew. Chem. Int. Ed.* **2003**, *42*, 4732; d) S. E. Denmark, J. Fu, *Chem. Rev*. **2003**, *103*, 2763; e) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243.

[25] C. T. Buse, C. H. Heathcock, *Tetrahedron Lett.* **1978**, 1685.

[26] R. W. Hoffmann, H.-J. Zeiss, *Angew. Chem. Int. Ed.* **1979**, *18*, 306.

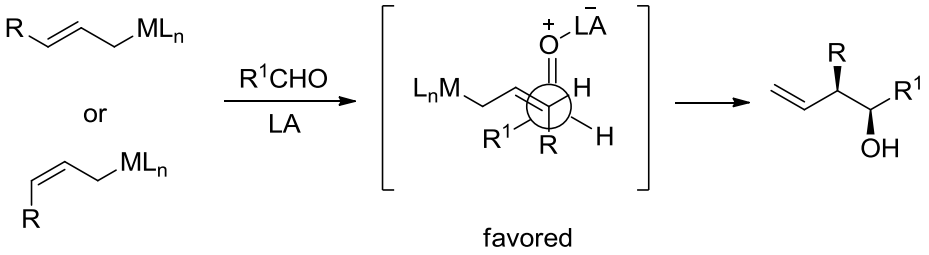
[27] Y. Yamamoto, H. Yatagai, Y. Naruta, K. Maruya, *J. Am. Chem. soc.* **1980**, *102*, 7107.

[28] S. E. Denmark, E. J. Weber, *Helv. Chim. Acta* **1983**, *66*, 1655.



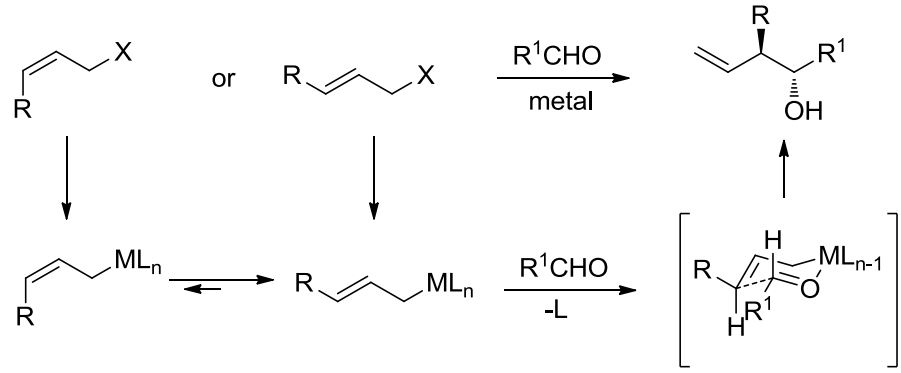
Scheme 6. The addition of allylic organometallic reagents of type **I** to an aldehyde.

Allylic organometallic reagents of type Ⅱ undergo addition reaction catalyzed or mediated by a Lewis acid. The postulated pathway allows the generation of only *syn*-diastereomer regardless of the geometry of alkene precursor (Scheme 7).[24]



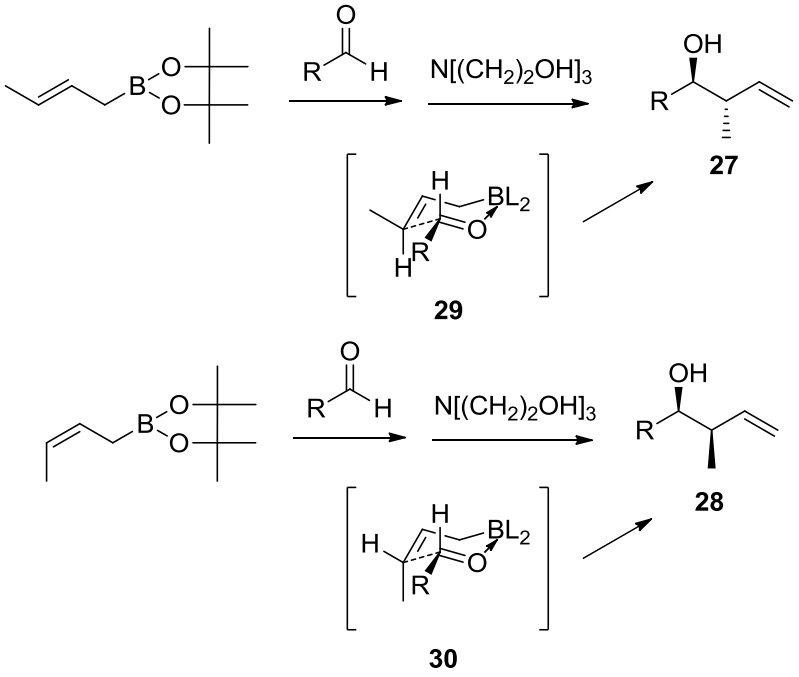
Scheme 7. The addition of allylic organometallic reagents of type Ⅱ to an aldehyde.

Allylic organometallic reagents of type Ⅲ, which typically are formed *in situ* and presumably equilibrated to the more stable (*E*)-isomer, reacted with aldehydes or ketones mainly leading to the *anti* adduct (Scheme 8).[24]



Scheme 8. The addition of allylic organometallic reagents of type Ⅲ to an aldehyde.

In the case of allylboron reagent which belongs in type **I**, cyclic transition state allows to predict the stereochemistry of carbon-carbon bond formed in addition to carbonyl compounds with regards to the geometry of the double bond in the allylic group. For instance, the addition of (*E*)-crotylboron derivative to aldehyde leads to *anti* homoallylic alcohol **27**, whereas the treatment of (*Z*)-crotylboron derivative with aldehyde results in the formation of *syn* adduct **28**. This stereospecific selectivity is well rationalized by cyclic transition states **29** and **30** (Scheme 9).[29]



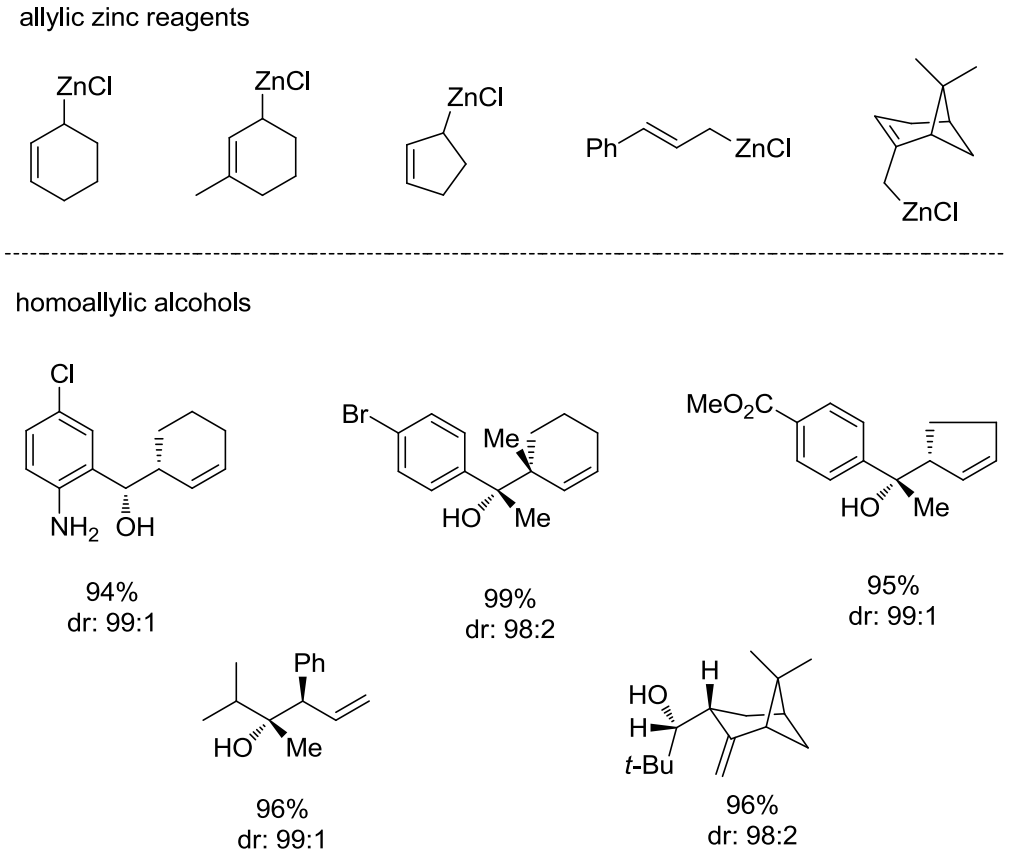
Scheme 9. Cyclic TS in the addition of croylboron to aldehyde.

The scope of the addition reaction of allylic boron or boronate reagents to carbonyl compounds has been extended to enantiomerically pure allylic boranes and borinates bearing chiral auxiliaries. The extensively developed chiral structures in allylic compounds include (+)-*α*-pinene, (-)-*α*-pinene, (+)-limonene, (-)-*β*-pinene, (+)-longifolene, (-)-10-methyl-*α*-pinene, (+)-3-carene as well as tartrate esters. These enantiomerically pure allylic boron reagents react with aldehydes generating the corresponding homoallylic alcohols in both excellent diastereoselectivities and

[29] a) R. W. Hoffmann and H.-J. Zeiss, *J. Org. Chem.* **1981**, *46*, 1309; b) K. Fujita, M. Schlosser, *Helv. Chim. Acta*, **1982**, *65*, 1258.

enantioselectivities.[30]

Allylic zinc reagents have also proven to be an effective tool to form carbon-carbon bond in diastereoselective manner. Recently, *Knochel et al.* reported that substituted allylic zinc reagents can be obtained by using a direct insertion of zinc dust into allyl halides in the presence of LiCl and the resulting allylic zinc reagents reacted with aldehydes or ketones affording homoallylic alcohols bearing adjacent quaternary centers in high diastereoselectivities (Scheme 10).[31]



Scheme 10. Allylic zinc reagents and selected reaction products.

Allylsilanes as well as allylstannanes have also been studied in detail in stereoselective reactions to aldehydes. The diastereoselectivity can be tuned by adding

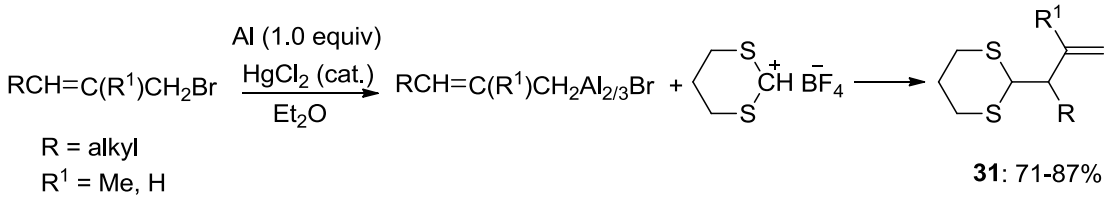
[30] a) H. C. Brown, P. K. Jadhav, *J. Am. Chem. Soc.* **1983**, *105*, 2092; b) W. R. Roush, A. E. Walts, L. K. Hoong, *J. Am. Chem. Soc.* **1985**, *107*, 8186; c) H. C. Brown, K. S. Baht, *J. Am. Chem. Soc.* **1986**, *108*, 293; d) H. C. Brown, P. K. Jadhav, K. S. Baht, *J. Am. Chem. Soc.* **1988**, *110*, 1535; e) W. R. Roush, L. Banfi, J. C. Park, L. K. Hoong, *Tetrahedron Lett.* **1989**, *30*, 6457; f) J. Garcia, S. Masamune, *J. Org. Chem.* **1987**, *52*; g) H. C. Brown, P. K. Jadhav, *J. Org. Chem.* **1984**, *49*, 4089. h) F. Peng, D. G. Hall, *J. Am. Chem. Soc.* **2007**, *129*, 3070.

[31] a) H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc*. **2007,** *129*, 5376; b) M. D. Helm, P. Mayer, P. Knochel, *Chem. Commun*. **2008**, 1916.

Lewis acids.[24]

3.2 Allylic Aluminum Reagents

Aluminum powder hardly inserts into organic halides to generate organoaluminum reagents even with reactive allyl compounds because of the passivation of the metal surface. However, *Gaudemar*[32] and *Miginiac*[33] demonstrated that allylic aluminum reagents could be prepared from allylic bromides using diethyl ether as solvent in the presence of a catalytic amount of $HgCl_2$. The treatment of these resulting allylic aluminium reagents with dithienium tetrafluoroborate yielded the expected dithianes of type **31** in good yields (Scheme 11).



Scheme 11. The preparation of allylic aluminum reagents in the presence of $HgCl_2$.

Later, a number of additives such as $SnCl_2$, $PbCl_2$, $V(Cp)_2Cl_2$ and $TiCl_4$ were used to activate the aluminum powder and these Al/additive systems underwent Barbier-type allylation with carbonyl compounds or imines.[34]

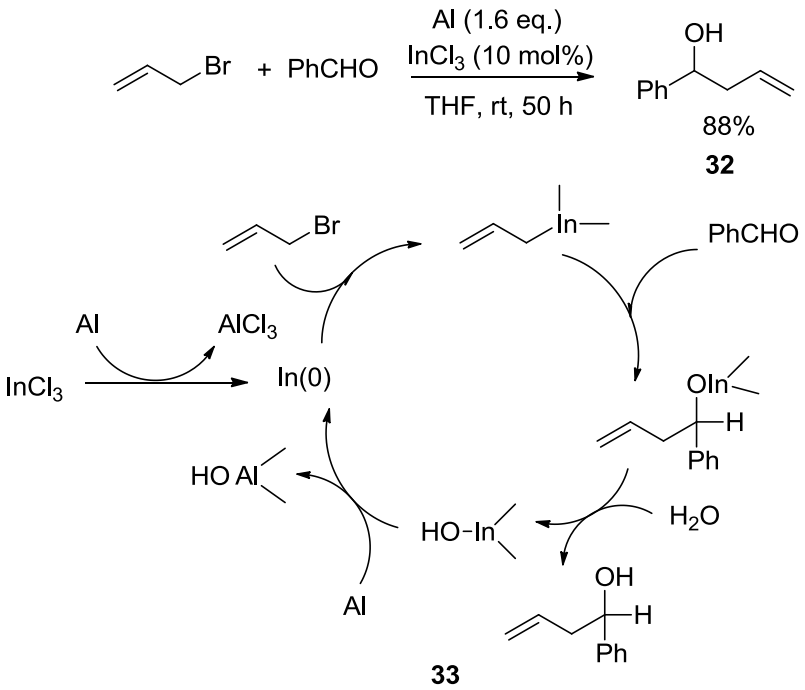
The Barbier-type allylation of aldehydes and ketones was also achieved by using aluminum and catalytic amount of $InCl_3$. Thus, the reaction of benzaldehyde, allyl bromide, aluminum and $InCl_3$ in one pot gave the alcohol **32** in 88% yield. The generation of product can be rationalized by the postulated pathway **33** illustrated in

[32] a) M. Gaudemar, *Bull. Soc. Chim. Fr.* **1958**, 1475; b) A. Stefani, P. Pino, *Hel. Chim. Acta*, **1972**, 55, 1110.

[33] a) G. Picotin, P. Miginiac, *J. Org. Chem*. **1985**, *50*, 1299; b) L. Miginiac-Groizeleau, *Bull. Soc. Chim. Fr.* **1963**, 1449.

[34] a) For general activation of aluminum powder, see: S. Saito in *Science of Synthesis* (Ed.: H. Yamamoto), **2004**, vol. 7, p 5; b) K, Uneyama, N. Kamaki, A. Moriya, S. Torii, *J. Org. Chem*. **1985**, *50*, 5396; c) H. Tanaka, T. Nakahara, H. Dhimane, S. Torii, *Tetrahedron Lett*. **1989**, *30*, 4161; d) H. Tanaka, K. Inoue, Ulrike Pokorski, M. Taniguchi, S. Torii, *Tetrahedron Lett*. **1990**, *31*, 3023; e) T. Hirano, B. Hatano, Y. Imamoto, A. Ogawa, *J. Org. Chem*. **1999**, *64*, 7665.

Scheme 12.[35]

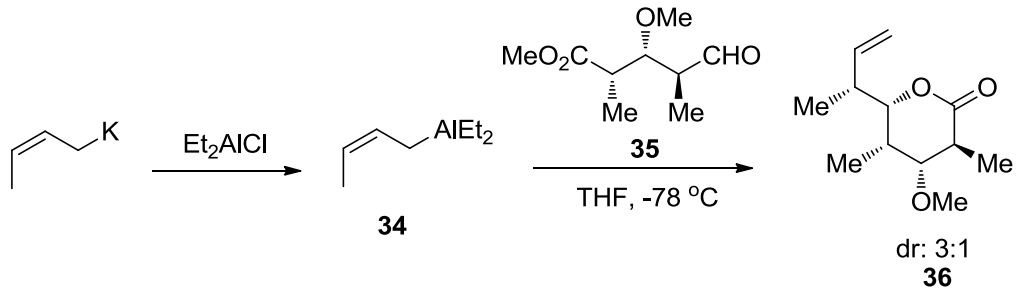


Scheme 12. Barbier-type allylation of aldehydes and ketones using aluminum and catalytic amount of $InCl_3$.

In 2002, *Takai et al.* reported that allylic aluminum reagents could be prepared by the insertion of aluminum (cut foil, 2 mm-2 mm, 1.0 mmol) to allyl bromide (1.5 mmol) in the presence of a catalytic amount of indium(0) powder (0.050 mmol) in THF (5 mL) at 25 °C within 30 min. The subsequent Grignard-type addition of the allylic aluminum reagent to cyclododecanone (1.0 mmol) at 10 °C within 30 min afforded the desired alcohol in 98% yield. The catalytic amount of $InCl_3$ in this reaction allows the similar generation of the allylaluminum reagent.[36]

A reliable method for the preparation of allylic aluminum reagents is by transmetallation from the corresponding allylic lithium, allylic magnesium as well as allylic potassium. The addition of (*Z*)-crotyldiethylaluminum **34** derived from (*Z*)-crotylpotassium and diethylaluminum chloride to chiral aldehyde **35** led to the expected lactone **36** in good 3,4-syn selectivity (Scheme 13).[37]

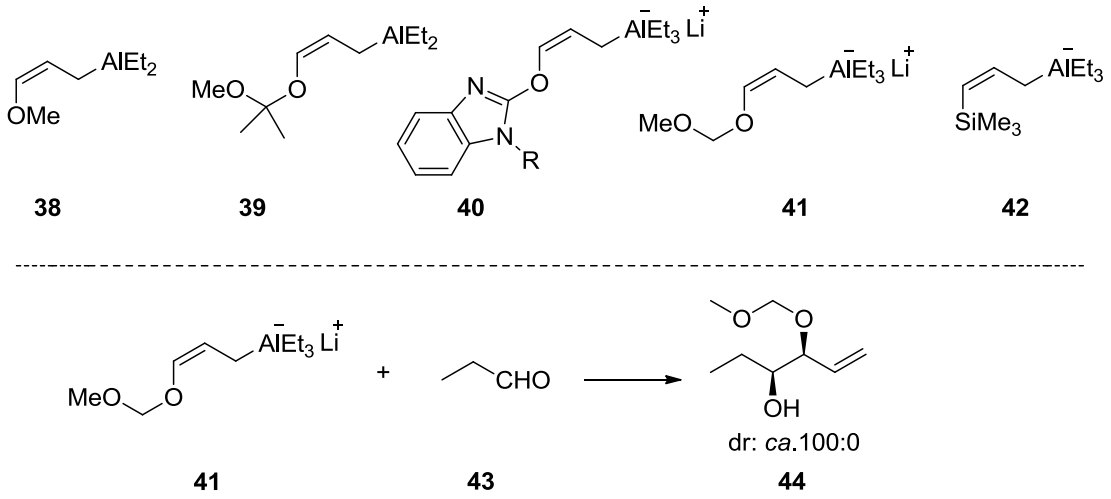
[35] S. Araki, S.-J. Jin, Y. Idou, Y. Butsugan, *Bull. Chem. Soc. Jpn*. **1992**, *65*, 1736.
[36] K. Takai, Y. Ikawa, *Org. Lett*. **2002**, *4*, 1727.
[37] D. B. Collum, J. H. McDonald, III, W. C. Still, *J. Am. Chem. Soc*. **1980**, *102*, 2118.



Scheme 13. Diastereoselective addition of allylic aluminum reagent **34** derived from crotyl potassium to an aldehyde.

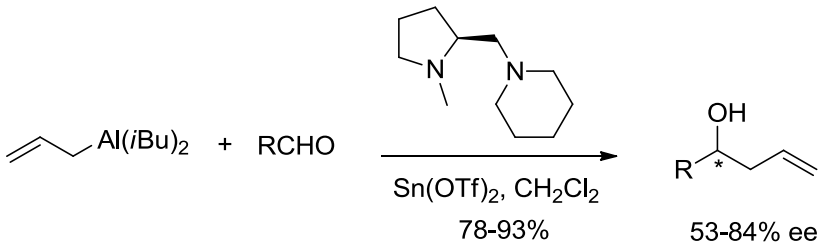
Furthermore, allylic aluminum reagent **37** bearing alkoxy functionality has been prepared by transmetallation of the corresponding alkoxyallyllithiums with diethylaluminum chloride. The treatment of (*E*)- and (*Z*)-crotyllithium derivatives with *i*Bu_2AlCl or *i*Bu_2AlOMe generated the corresponding (*E*)- and (*Z*)-crotylaluminum reagents **38** and **39**.[38] Moreover, heterosubstituted aluminate complexes such as **40**,[39] **41**[40] and **42**[41] have been prepared in a similar manner. The reactions of these allylic aluminum reagents to aldehydes and ketones displayed good diastereoselectivity. For example, the *syn* adduct **44** was observed as the sole product in the addition reaction of allylic aluminum reagent **41** to propionaldehyde **43** (Scheme 14).

[38] M. Koreeda, Y. Tanaka, *J. Chem. Soc., Chem. Commun.* **1982**, 845.
[39] M. Yamaguchi, T. Mukaiyama, *Chem. Lett*, **1982**, 237.
[40] Y. Yamamoto, H. Yatagai, Y. Saito, K. Maruyama, *J . Org. Chem.* **1984,** *49*, 1096.
[41] Y. Yamamoto, Y. Saito, K. Maruyama, *J. Chem. Soc. Chem. Commun.*, **1982**, 1326.



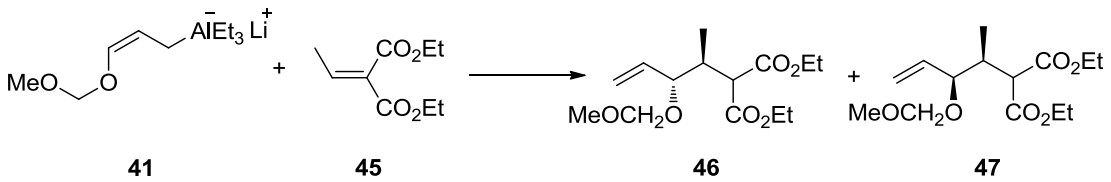
Scheme 14. Selected allylic aluminum reagents.

Allylaluminum reagent reacted with prochiral aldehydes in the presence of $Sn(OTf)_2$ and chiral diamine providing homoallylic alcohol in good yield and moderate optical purity (Scheme 15).[42]



Scheme15. Asymmetric addition of allylaluminum reagent to prochiral aldehydes.

Finally, allylic aluminum reagents could smoothly undergo Michael addition. Thus, the alkoxy-substituted allylic aluminum reagent **41** reacted with diesters **45** affording a mixture of *anti* and *syn* adducts (**46** and **47**) in the ratio of 1:1 (Scheme 16).[43]



Scheme 16. Michael addition of allylic aluminum reagent **41**.

[42] T. Mukaiyama, N. Minowa, T. Origama, K. Narasaka, *Chem. Lett.* **1986**, 97.
[43] Y. Yamamoto, S. Nishii, *J. Org. Chem*. **1988**, *53*, 3597.

4. Organomanganese Reagents

In 1937, the first examples of organomanganese compounds were disclosed by *Gilman* and *Bailie* who showed the preparation of phenylmanganese iodide and diphenylmanganese by the treatment of phenyllithium with manganese iodide.[44] Since then, organomanganese compounds have been studied widely due to their excellent chemoselectivity, low toxicity and good availability.[45]

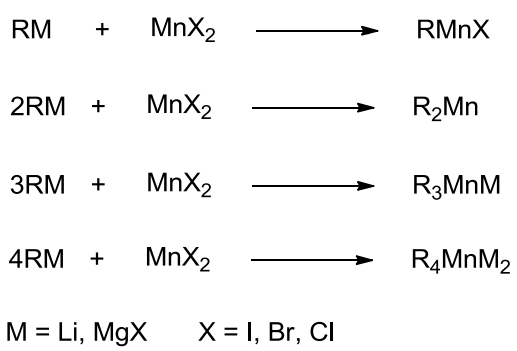
4.1 Preparation of Organomanganese Reagents

4.1.1 Transmetallation from The Corresponding Organolithium or Organomagnesium Reagents

To date, the most commonly used way to prepare organomanganese reagents is by transmetallation from the corresponding organomagnesium or organolithium reagents with manganese halides. As showed in Scheme 17, several types of organomanganese reagents including RMnX, R_2Mn, R_3MnM and R_4MnM_2 have been synthesized depending on the ratio of RMg/MnX_2 or RLi/MnX_2. The stability of these organomanganese reagents increased in the following order: R_2Mn < RMnX < R_3MnM/ R_4MnM_2 (Scheme 17).[45a]

[44] a) H. Gilman, J. C. Bailie, *J. Org. Chem*. **1937**, *2*, 84; b) H. Gilman, R. Kirby, *J. Am. Chem. Soc.* **1941**, *63*, 2046.

[45] For selected reviews, see: a) G. Cahiez, C. Duplais, J. Buendia, *Chem. Rev*. **2009**, *109*, 1434; b) S.-H. Kim, R. D. Rieke, *Molecules* **2010**, *15*, 8006; c) J. M. Concellón, H. Rodríguez-Solla, V. del Amo, *Chem.—Eur. J.* **2008**, *14*, 10184; d) K. Oshima, *J. Organomet. Chem.* **1999**, *575*, 1; (e) H. Shinokubo, K. Oshima, *Eur. J. Org. Chem*. **2004**, 2081.



Scheme 17. Types of organomanganese reagents.

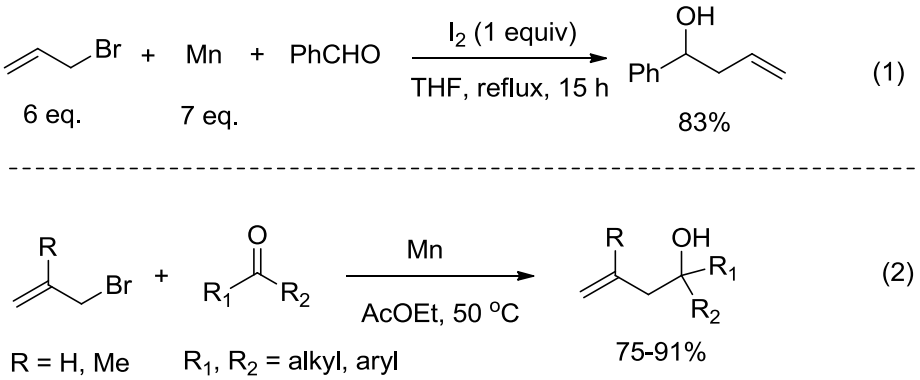
The manganese halides used in transmetallation reactions include manganese iodide, manganese bromide and manganese chloride. LiBr or LiCl allows the preparation of the ate-complexes $MnX_2 \cdot LiX$ and the resulting organomanganese reagents which are more stable and more soluble in the solvent. Among various solvents, THF and ether are the commonly used solvents in the preparation of organomanganese reagents.[45a] This approach allows the generation of a large variety of organomanganese reagents such as aryl, benzyl, allyl, alkyl, alkenyl, alkynyl and heteroarylmanganese reagents and this method displays an excellent functional group tolerance.[46]

4.1.2 Commercial Manganese Insertion into Reactive Organic Halides

The direct insertion of commercial manganese powder into organic halides is difficult because the surface of Mn metal mostly consists of hydroxides and oxides. According to the literature, only reactive substrates such as allylic halides and α-halogenesters can be used to react with commercial Mn powder giving the corresponding organomanganese reagents, which are trapped immediately with ketones or aldehydes (Barbier conditions), affording the desired alcohols. The first example was disclosed by *Hiyama* who described that Mn (7 eq.) reacted with allyl bromide (6 eq.) in the

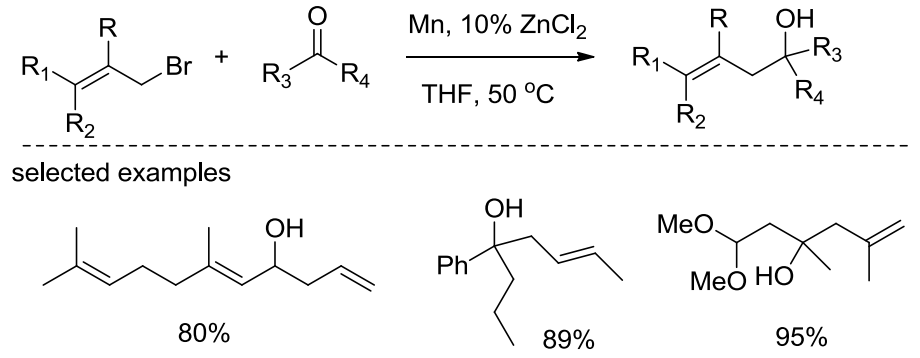
[46] a) G. Cahiez, D. Bernard, J. F. Normant, *Synthesis* **1977**, 130; b) G. Friour, G. Cahiez, J. F. Normant, *Synthesis* **1984**, 37; c) G. Cahiez, M. Alami, *Tetrahedron* **1989**, *45*, 4163; d) G. Cahiez, B. Laboue, *Tetrahedron Lett.* **1989**, *30*, 3545; e) G. Cahiez, L. Razafintsalama, B. Laboue, F. Chau, *Tetrahedron Lett.* **1998**, *39*, 849; f) G. Cahiez, B. Laboue, P. Tozzolino, Eur. Patent 283359, **1988**; g) *Chem. Abstr.* **1989**, *110*, 114306; h) G. Cahiez, B. Laboue, P. Tozzolino, Eur. Patent 374015, 1990; (i) *Chem. Abstr*. **1990**, *113*, 191644.

presence of an aldehyde or a ketone leading to homoallylic alcohol in 83% yield (Scheme 18, Eq. 1).[47] In 1989, *Cahiez et al.* reported that the scope of this reaction can be extended to substituted allylic halides when ethyl acetate was employed as a solvent (Scheme 18, Eq. 2).[48]



Scheme 18. Insertion of commercial Mn into allylic halides.

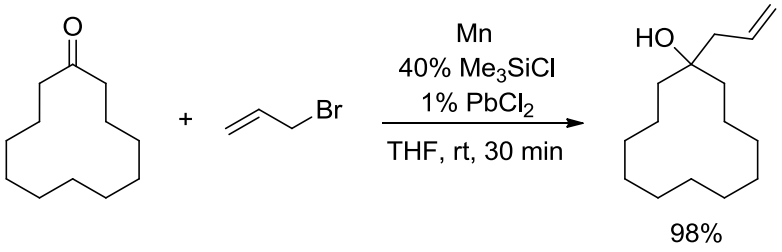
Later, *Cahiez* and co-workers found that a catalytic amount of metallic halide such as $ZnCl_2$, $CuCl_2$, $CdCl_2$ or $HgCl_2$ can activate commercial manganese powder. This activated system allows the preparation of crotylmanganese reagents and prenylmanganese reagents (Scheme 19).[48]



Scheme 19. Activation of Mn surface by catalytic $ZnCl_2$.

Takai also reported that allylmanganese reagents were formed in the presence of catalytic amounts of both $PbCl_2$ and TMSCl (Scheme 20).[49]

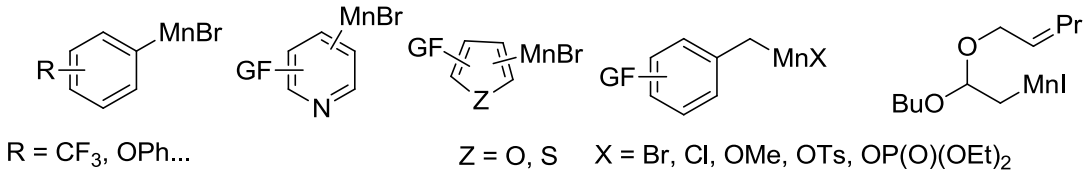
[47] T. Hiyama, M. Sawahata, M. Obayashi, *Chem. Lett.* **1983**, *8*, 1237.
[48] a) G. Cahiez, P.-Y. Chavant, *Tetrahedron Lett.* **1989**, *30*, 7373; b) G. Cahiez, P.-Y. Chavant, P. Tozzolino, Eur. Patent 323332, **1989**; c) *Chem. Abstr.* **1990**, *112*, 38679; d) G. Cahiez, P.-Y. Chavant, P. Tozzolino, Fr. Patent 2625500, **1989**; e) *Chem. Abstr.* **1990**, *112*, 35281.
[49] K. Takai, T. Ueda, T. Hayashi, T. Moriwake, *Tetrahedron Lett.* **1996**, *37*, 7049.



Scheme 20. Activation of commercial Mn by both $PbCl_2$ and TMSCl.

4.1.3 Activated Manganese Insertion into Organic Halides

Although the direct insertion reaction of commercial manganese powder to organic halides is straightforward, effective and inexpensive, the scope of this reaction is limited as previously shown. The activated manganese metal prepared from manganese halides, namely *Rieke*-metal, is highly reactive. By using *Rieke*-Mn, a wide range of functionalized substrates such as aryl halides, heteroaryl halides, benzyl sulfonates and alkyl halides were readily converted to the corresponding organomanganese reagents (Scheme 21).[50]



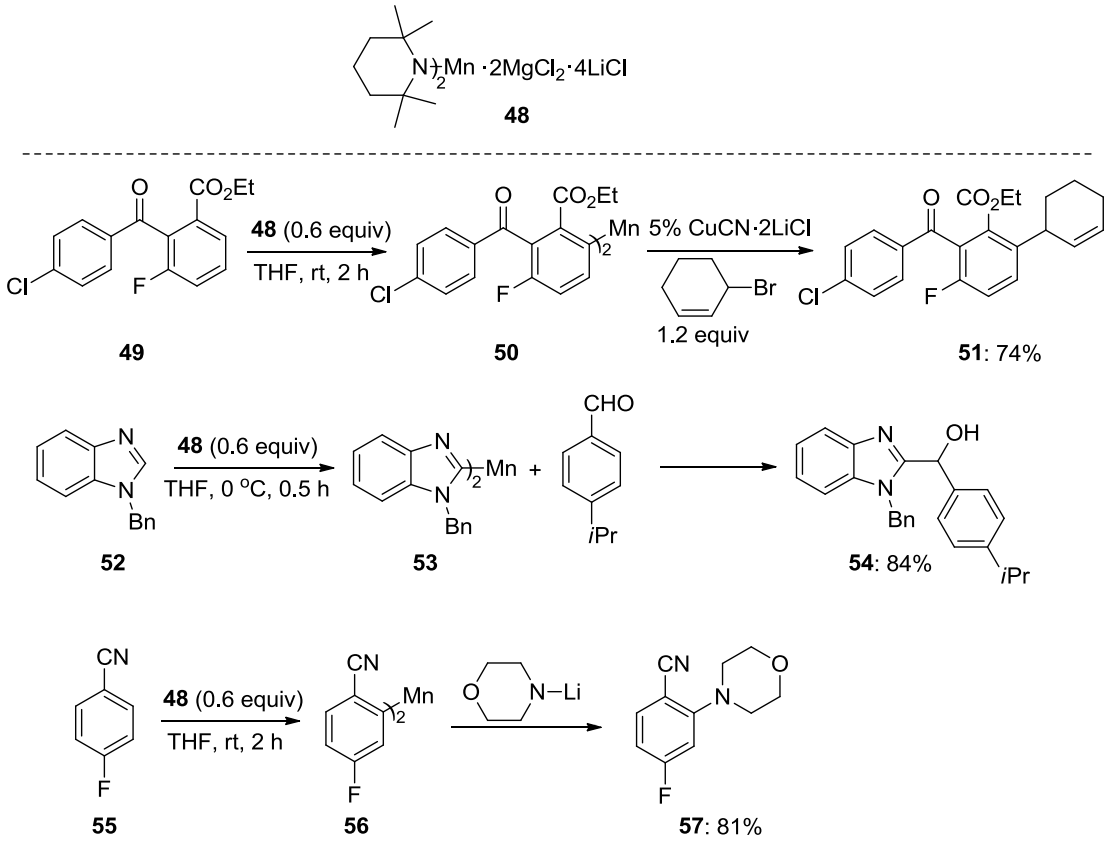
Scheme 21. The scope of substrates in the oxidative addition of Rieke-Mn.

4.1.4 Deprotonation Using TMP_2Mn·LiCl Base

Recently, *Knochel et al.* demonstrated that a direct deprotonation using TMP_2Mn allowed smooth preparation of functionalized aryl manganese reagents. A variety of functionalized aromatic substrates including arenes and heterocycles are readily

[50] a) S.-H. Kim, R. D. Rieke, *Synth. Commun.* **1998**, *28*, 1065; b) R. D. Rieke, S.-H. Kim, X. Wu, *J. Org. Chem.* **1997**, *62*, 6921; c) R. D. Rieke, Y. S. Suh, S.-H. Kim, *Tetrahedron Lett.* **2005**, *46*, 5961; d) S.-H. Kim, R. D. Rieke, *Tetrahedron Lett.* **1999**, *40*, 4931; e) G. Cahiez, A. Martin, T. Delacroix, *Tetrahedron Lett.* **1999**, *40*, 6407; f) J. Tang, H. Shinokubo, K. Oshima, *Synlett* **1998**, 1075.

manganated under mild conditions. Thus, the highly functionalized aryl manganese reagent **50** was prepared by the treatment of benzophenone derivative **49** with base **48**. Its Cu-catalyzed allylation reaction with 3-bromocyclohex-1-ene furnished the polyfunctional benzophenone **51** in 74% yield. Similarly, N-benzylbenzimidazole **52** is converted to the corresponding heterocyclic manganese reagent **53** using base **48**. Its addition to the aldehyde gave the desired alcohol **54** in 84% yield. The arylmanganese reagent **56** prepared under the similar condition underwent an oxidative amination with lithium amine providing the aniline **57** in 81% yield (Scheme 22).[51]



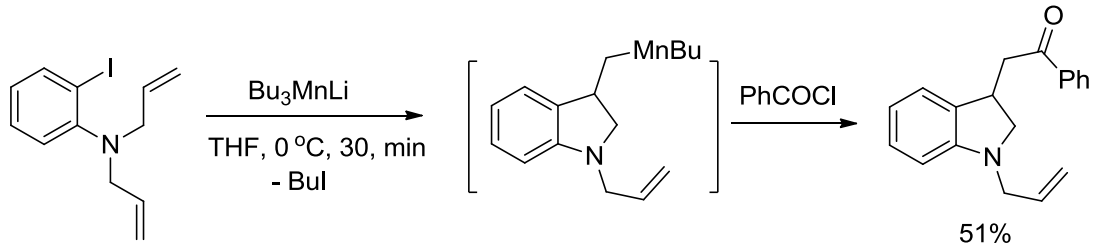
Scheme 22. The deprotonation of arenes and heterocycles by TMP_2Mn base.

4.1.5 Halogen-Manganese Exchange Reaction

Only few halogen-manganese exchange reactions have been reported. *Hosomi*

[51] S. H. Wunderlich, K. Marcel, P. Knochel, *Angew. Chem. Int. Ed*. **2009**, *48*, 7256.

demonstrated that the reaction of allylbromide with Bu_4MnLi_2 in THF afforded an allylic manganese reagent.[52] The treatment of various unsaturated organic iodides with Bu_4MnLi_2 or Bu_3MnLi leads to intramolecular cyclization (Scheme 23).[53]

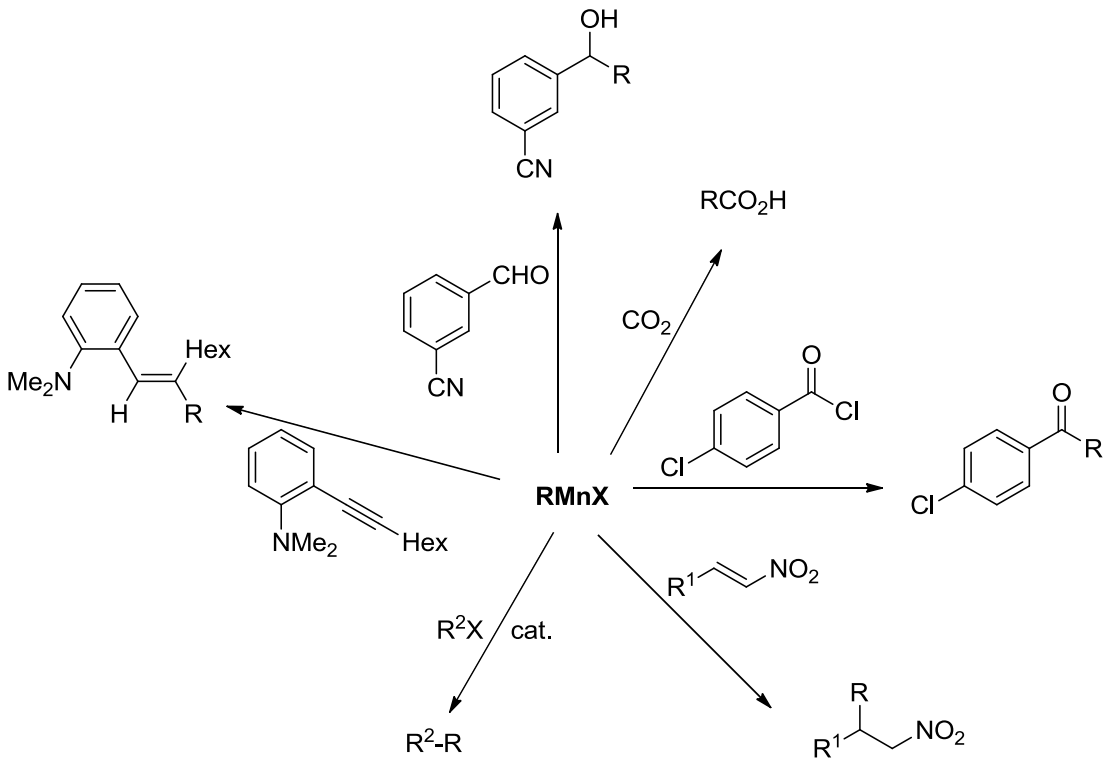


Scheme 23. Radical cyclization promoted by trialkylmanganate reagent.

4.2 Reactions of Organomanganese Reagents

Organomanganese compounds can be used to perform chemoselective 1,2-additions, acylations, metal catalyzed cross-coupling reactions, carbometalations, as well as copper-catalyzed conjugate additions (Scheme 24).[54]

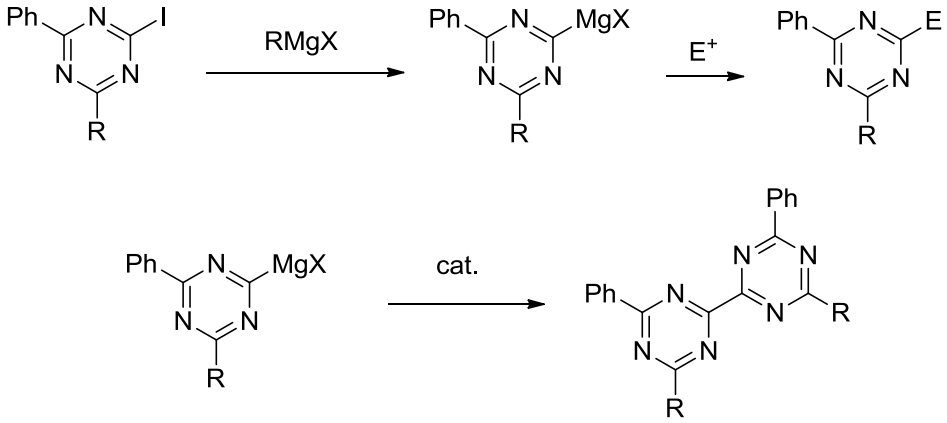
[52] M. Hojo, H. Harada, H. Ito, A. Hosomi, *Chem. Commun.* **1997**, *21*, 2077.
[53] a) J. Nakao, R. Inoue, H. Shinokubo, K. Oshima, *J. Org. Chem.* **1997**, *62*, 1910; b) R. Inoue, J. Nakao, H. Shinokubo, K. Oshima, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2039.
[54] Reference 45a and its cited references.



Scheme 24. Reactions of organomanganese compounds.

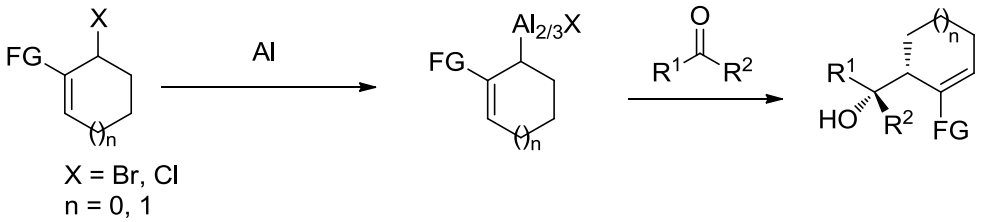
5. Objectives

Heteroarylmetal reagents are key intermediates for the construction of complex heterocyclic compounds. Among heterocycles, 1,3,5-triazine and its derivatives have been proven to be important in many aspects. In the first project, using highly efficient halogen-magnesium exchange reaction, we planned to prepare functionalized magnesiated 1,3,5-triazine derivatives which could be a powerful tool to synthesize various complex 1,3,5-triazine derivatives. Especially, we tried to meet the challenge of the syntheses of dimeric and trimeric 1,3,5-triazine derivatives (Scheme 25).



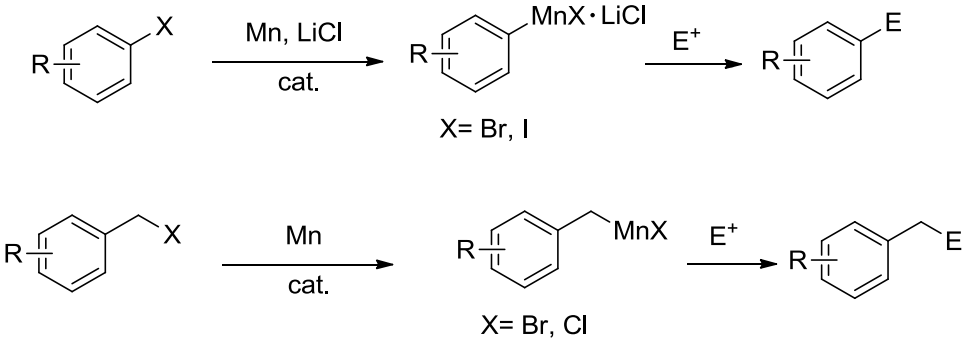
Scheme 25. Preparation of 2-magnesiated 1,3,5-triazine and 1,3,5-triazine derivatives.

Another subject dealt with the development of allylic aluminum reagents. The goal of this project was to prepare allylic aluminum species bearing various sensitive functional groups. Additionally, the diastereoselectivity of the addition of these reagents to aldehydes or ketones was investigated (Scheme 26).



Scheme 26. Diastereoselective addition of allylic aluminum reagents to carbonyl compounds.

Finally, the preparation of aromatic and benzylic manganese species was studied. Although organomanganese reagents have a lot of advantages, the efficient methods for the preparation of organomanganese reagents are limited. The objective was to develop a new, straightforward and effective method for the preparation of aromatic and benzylic manganese reagents from commercial manganese powder. Also, their reactivity towards various electrophiles was investigated (Scheme 27).



Scheme 27. Preparation of organomanganese reagents.

B. Results and Discussion

1. Preparation of 2-Magnesiated 1,3,5-Triazines via an Iodine-Magnesium Exchange

1.1 Introduction: The Chemistry of 1,3,5-Triazine

Heterocycles have gained increased significance in modern chemistry.[55] Among N-containing heterocycles, 1,3,5-triazine derivatives[56] have found numerous industrial applications as pharmaceuticals,[57] liquid crystals,[58] reactive dyes,[59] and organic light-emitting diodes (OLEDs).[60] Four types of methods for the construction of 1,3,5-triazine derivatives are well established: (1) Ring-closure reactions are the most commonly used strategy for the successful synthesis of a large variety of 1,3,5-triazine derivatives (Scheme 28, Eq. 1).[61, 56a] (2) 1,3,5-Triazine derivatives can be prepared by using ring enlargement (Scheme 28, Eq. 2).[62, 56a] (3) Aromatization has been proven to be a useful approach towards 1,3,5-triazine derivatives (Scheme 28, Eq. 3).[63, 56a] (4) Substitution of existing substituents allows the smooth preparation of

[55] a) A. F. Pozharskii, A. T. Soldatenkov, A. R. Katritzky, In *Heterocycles in Life and Society*; Wiley-VCH: Weinheim, 1997; b) T. S. Eicher, S. Hauptmann, In *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, 2003; c) A. R. Katritzky, In *Advances in Heterocyclic Chemistry*; Academic Press: Oxford, 2002; Vol. 82.

[56] For reviews, see: a) S. V. Angerer, In *Science of Synthesis*; Weinreb, S. M., Ed.; Thieme: Stuttgart, 2003; Vol. 17, pp 449; b) G. Giacomelli, A. Porcheddu, In *Comprehensive Heterocyclic Chemistry III*; Turnbull, K., Ed.; Elsevier Science: Oxford, 2008; Vol. 9, pp 197; c) G. Blotny, *Tetrahedron* **2006**, *62*, 9507.

[57] a) A. Dhainaut, G. Regnier, A. Tizot, A. Pierre, S. Leonce, N. Guilbaud, L. Kraus-Berthier, G. Atassi, *J. Med. Chem.* **1996**, *39*, 4099; b) S. Ronchi, D. Prosperi, F. Compostella, L. Panza, *Synlett* **2004**, 1007.

[58] a) A. Kohlmeier, D. Janietz, S. Diele, *Chem. Mater.* **2006**, *18*, 1483; b) H. C. Holst, T. Pakula, H. Meier, *Tetrahedron* **2004**, *60*, 6765; c) E. Beckel, N. Cramer, A. Harant, C. Bowman, *Liq. Cryst.* **2003**, *30*, 1343.

[59] K. Xie, Y. Sun, A. Hou, *J. Appl. Polym. Sci.* **2007**, *103*, 2166.

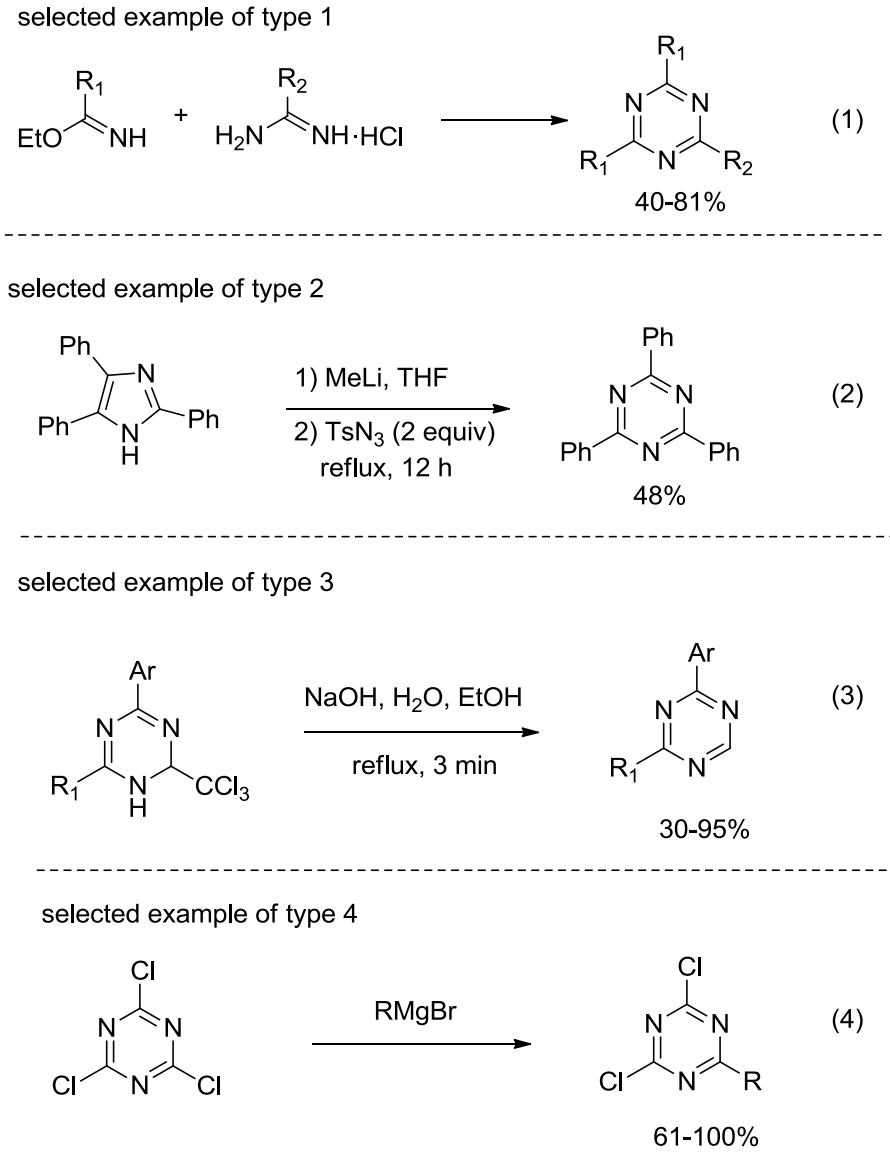
[60] a) A. Kulkarni, C. Tonzola, A. Babel, S. Jenekhe, *Chem. Mater.* **2004**, *16*, 4556; b) J.-W. Kang, D.-S. Lee, H.-D. Park, Y.-S. Park, J. W. Kim, W.-I. Jeong, K.-M. Yoo, K. Go, S.-H. Kim, J.-J. Kim, *J. Mater. Chem.* **2007**, *17*, 3714; c) T.-Y. Chu, M.-H. Ho, J.-F. Chen, C. H. Chen, *Chem. Phys. Lett.* **2005**, *415*, 137; d) H. Inomata, K. Goushi, T. Masuko, T. Konno, T. Imai, H. Sasabe, J. Brown, C. Adachi, *Chem. Mater* **2004**, *16*, 1285; e) J. Pang, Y. Tao, S. Freiberg, X.-P. Yang, M. D'Iorio, S. Wang, *J. Mater. Chem.* **2002**, *12*, 206.

[61] F. C. Schaefer, *J. Org. Chem.* **1962**, *27*, 3608.

[62] K. Sakai, J.-P. Anselme, *Bull. Chem, Soc. Jpn.* **1972**, *45*, 306.

[63] T. P. Popovich, B. S. Drach, *J. Org. Chem.* **1987**, *23*, 2158.

a large number of functionalized 1,3,5-triazine derivatives (Scheme 28, Eq. 4).[64, 56a]



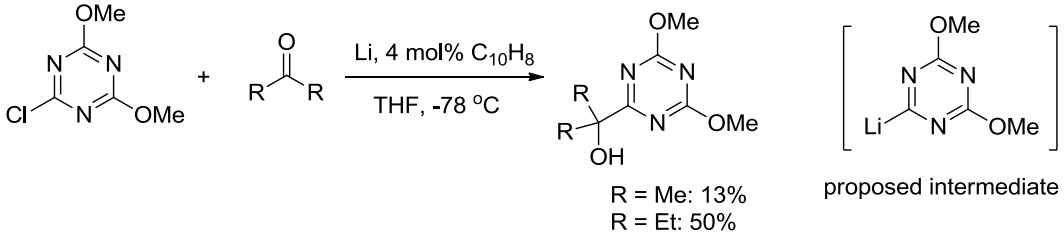
Scheme 28. Preparations of 1,3,5-triazine derivatives.

However, the efficient syntheses of polyfunctional 1,3,5-triazines, including dimeric and trimeric triazine derivatives by using known methodologies, remain a synthetic challenge. As shown previously, metalated heterocyclic intermediates have proven to possess great potential for the concise synthesis of functionalized heterocycles.[65] Especially, polyfunctionalized organomagnesium compounds show a high tolerance

[64] R. Menicagli, S. Samaritani, V. Zucchelli, *Tetrahedron*, **2000**, *56*, 9705.

[65] a) T. Delacroix, L. Bérillon, G. Cahiez, P. Knochel, *J. Org. Chem.* **2000**, *65*, 8108; b) M. Poirier, F. Chen, C. Bernard, Y.-S. Wong, G. G. Wu, *Org. Lett.* **2001**, *3*, 3795; c) W. Dohle, A. Staubitz, P. Knochel, *Chem.—Eur. J.* **2003**, *9*, 5323; d) M. Mosrin, M. Petrera, P. Knochel, *Synthesis* **2008**, 3697; e) G. Monzon, P. Knochel, *Synlett* **2010**, 304.

toward a wide range of functional groups and are easily accessible, e.g., via Br/Mg or I/Mg exchange reaction.[66, 6a-c] It has been reported that the reactions of 2-chloro-4,6-dimethoxy-1,3,5-triazine with ketones using lithium powder and substoichiometric amounts of naphthalene involving a lithiated 1,3,5-triazine intermediate afford the corresponding alcohols in 13-50% yield (Scheme 29).[67] Therefore, metalated 1,3,5-triazine intermediate is a potential reagent for carbon-carbon bond formation in the area of complex 1,3,5-triazine derivatives.



Scheme 29. The postulated lithiated 1,3,5-triazine intermediate.

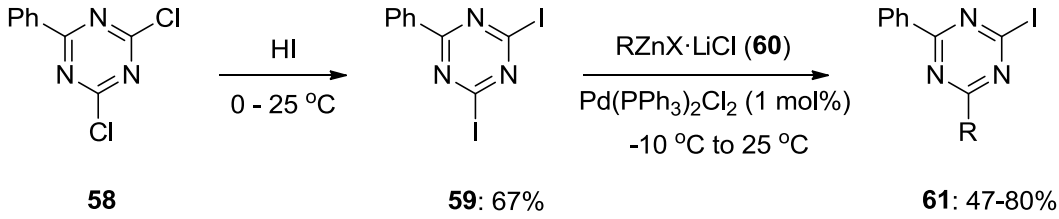
We planned to develop a straightforward and practical preparation of fully substituted 1,3,5-triazines *via* magnesiated triazines as well as synthetic routes to highly functionalized 1,3,5-triazine dimers and trimers which are expected to be valuable advanced materials.

1.2 Preparation of Functionalized Iodotriazine Derivatives

First of all, in order to investigate the reactivity of metalated 1,3,5-triazine reagents, we designed a short route to synthesize iodotriazine derivatives of type **61** bearing various sensitive functional groups. Starting from inexpensive and commercial 2,4,6-trichloro-1,3,5-triazine, the raw material 2,4-dichloro-6-phenyl-1,3,5-triazine (**58**) was readily obtained in 72% yield.[56a] The treatment of 2,4-dichloro-6-phenyl-1,3,5-triazine **58** with HI (57%) between 0 °C and 25 °C over 12 h furnished 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**) in 67% yield.[68] We envisioned

[66] a) F. Cresty, P. Knochel, *Synthesis* **2010**, 1097; b) L. Melzig, C. Rauhut, P. Knochel, *Synthesis* **2009**, 1041.
[67] I. Gómez, E. Alonso, D. J. Ramón, M. Yus, *Tetrahedron* **2000**, *56*, 4043.
[68] G. Vlád, I. T. Horváth, *J. Org. Chem.* **2002**, *67*, 6550.

that the functionalized iodotriazine derivatives of type **61** could be prepared by using a well-established Negishi cross-coupling[69] reaction of the intermediate **59** with functionalized organozinc reagents. After screening the palladium catalysts, $Pd(PPh_3)_2Cl_2$ was employed as an effective catalyst and allowed a smooth preparation of functionalized iodotriazine derivatives in 47-80% yield (Scheme 30).



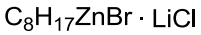
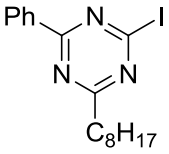
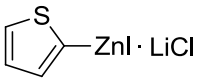
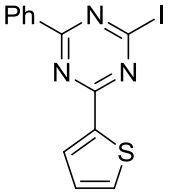
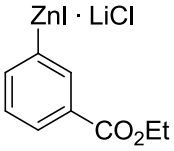
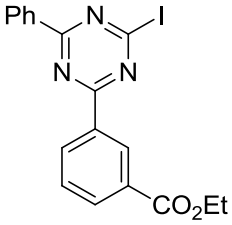
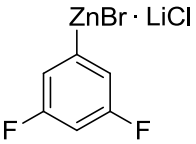
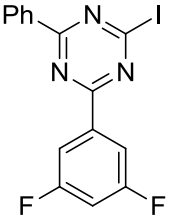
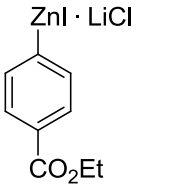
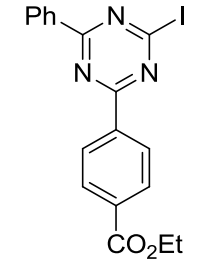
Scheme 30. Preparation of functionalized iodotriazine derivatives.

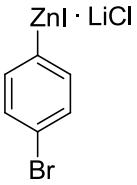
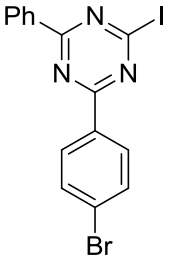
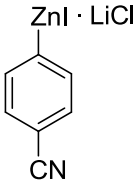
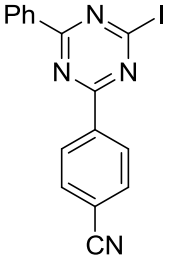
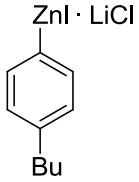
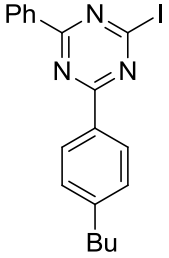
Thus, the reaction of 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**) with $C_8H_{17}ZnBr{\cdot}LiCl$ obtained after transmetallation of the corresponding Grignard reagent with $ZnBr_2{\cdot}2LiCl$ in the presence of 1 mol% $Pd(PPh_3)_2Cl_2$ afforded the iodotriazine derivative **61a** in 60% yield (entry 1, Table 1). In addition, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**) reacted with thienyl zinc reagent **60b**[70] in THF within 5 h in the presence of 1 mol% $Pd(PPh_3)_2Cl_2$ leading to the iodotriazine derivative **61b** (entry 2). Similarly, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**) smoothly undergoes Pd-catalyzed cross-coupling reactions with various organozinc reagents **60e-k** furnishing the desired adducts **61e-k** in 47-72% yield (entries 3-9).

[69] a) J.-X. Wang, J. McCubbin, M. Jin, R. Laufer, Y. Mao, A. Crew, M. Mulvihill, V. Snieckus, *Org. Lett.* **2008**, *10*, 2923; b) A. de Meijere, P. von Zezschwitz, S. Braese, *Acc. Chem. Res.* **2005**, *38*, 413; (c) K. Albrecht, O. Reiser, M. Weber, B. Knieriem, A. de Meijere, *Tetrahedron* **1994**, *50*, 383; d) E. Negishi, A. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; e) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; f) Ø. Rist, M. Begtrup, *J. Chem. Soc., Perkin Trans.* **2001**, *1*, 1566; g) C. James, A. Coelho, M. Gevaert, P. Forgione, V. Snieckus, *J. Org. Chem.* **2009**, *74*, 4094; h) Z. Zhao, A. Jaworski, I. Piel, V. Snieckus, *Org. Lett.* **2008**, *10*, 2617; i) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; j) X. Zeng, M. Quian, Q. Hu, E. Negishi, *Angew. Chem.* **2004**, *116*, 2309; *Angew. Chem., Int. Ed.* **2004**, *43*, 2259; k) G. Manolikakes, M. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765; l) Z. Dong, G. Manolikakes, J. Li, P. Knochel, *Synthesis* **2009**, 681.

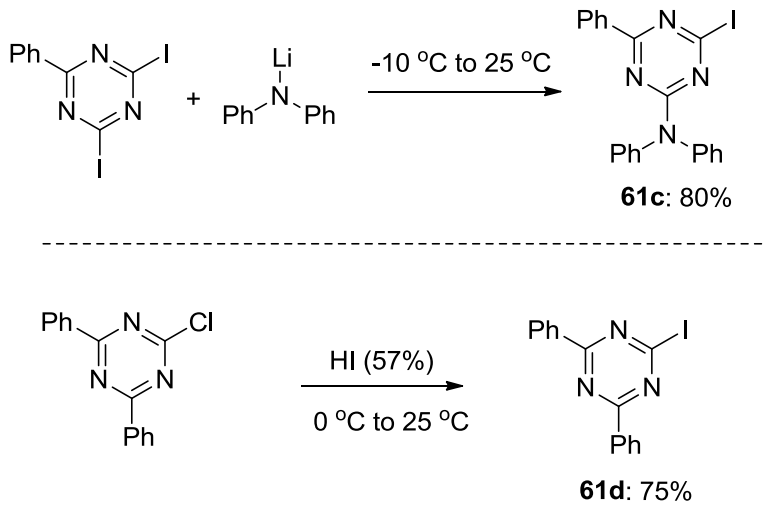
[70] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.

Table 1 Preparation of functionalized iodotriazine derivatives *via* Negishi Cross-Coupling

entry	organozinc reagent	product, yield (%)
1	 **60a**	 **61a**: 60%
2	 **60b**	 **61b**: 80%
3	 **60e**	 **61e**: 55%
4	 **60f**	 **61f**: 72%
5	 **60g**	 **61g**: 51%
6	**60h**	**61h**: 66%

		
7	**60i**	**61i**: 47%
		
8	**60j**	**61j**: 56%
		
9	**60k**	**61k**: 62%

In the case of 4-iodo-*N*,*N*,6-triphenyl-1,3,5-triazin-2-amine (**61c**), it was obtained in 80% yield by the treatment of 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**) with lithium diphenylamide prepared by addition of BuLi to a solution of diphenylamine in THF (Scheme 31). 2-chloro-4,6-diphenyl-1,3,5-triazine reacted with HI (57%) between 0 ^{o}C and 25 ^{o}C over 12 h furnished 2-iodo-4,6-diphenyl-1,3,5-triazine **61d** in 75% yield (Scheme 31).



Scheme 31. Preparation of iodotriazine derivatives **61c** and **61d**.

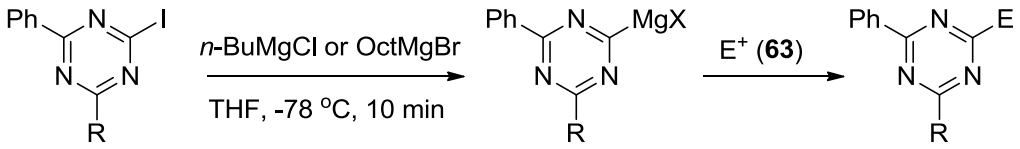
1.3 Preparation of 2-Magnesiated 1,3,5-Triazines and Their Subsequent Reactions with Various Electrophiles

With key functionalized iodotriazine derivatives at hand, we started to seek an effective I/Mg exchange reagent for these iodotriazine derivatives. We found that in comparison to well-established Hal/Mg exchange reagents such as *i*PrMgCl,[71, 3a] the Grignard reagents BuMgCl and OctMgBr are less nucleophilic and more selective, avoiding undesired substitution products. Thus, the reaction of 6-iodo-4-octyl-2-phenyl-1,3,5-triazine (**61a**) with BuMgCl (1.1 equiv, -78 °C, 10 min) provided the corresponding triazinylmagnesium chloride (**62a**), which after transmetallation with $ZnBr_2$·LiCl (1.1 equiv, -20 °C, 30 min) undergoes a cross-coupling with ethyl 4-iodobenzoate (**63a**) in the presence of $Pd(dba)_2$ (5 mol%) and tfp (10 mol%), affording the trisubstituted 1,3,5-triazine derivative **64a** in 62% yield (entry 1, Table 2). Additionally, a copper-catalyzed allylation (CuCN·2LiCl, 20 mol%) of **62a** with ethyl (2-bromomethyl)acrylate (**63b**) produced the acrylate **64b** in 73% yield (entry 2). In the same manner, a range of 1,3,5-triazinylmagnesium reagents bearing electron-donating functional groups such as a 2-thienyl group (**62b**), a diphenylamino group (**62c**), or an aryl group bearing various substituents (**62d**-**j**)

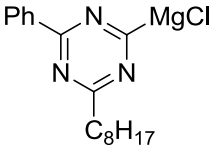
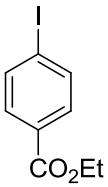
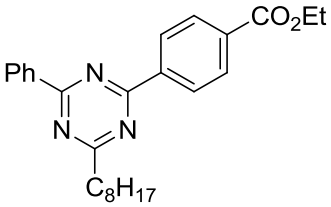
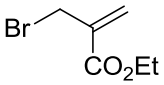
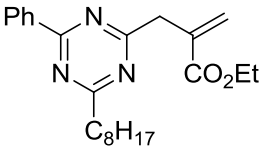
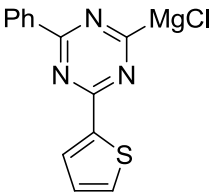
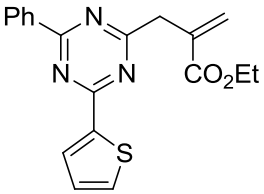
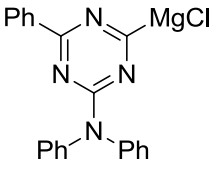
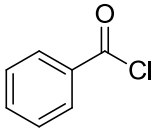
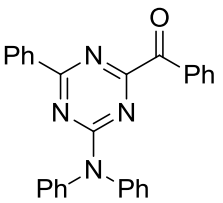
[71] C. Rauhut, C. Cervino, A. Krasovskiy, P. Knochel, *Synlett* **2009**, 67.

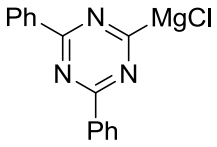
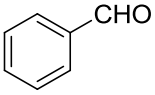
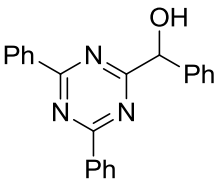
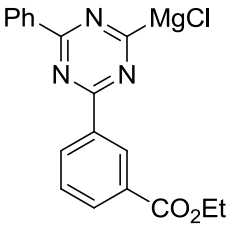
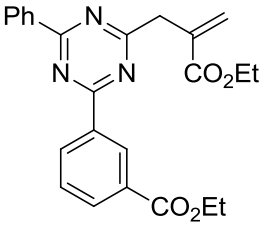
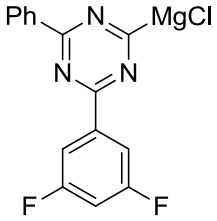
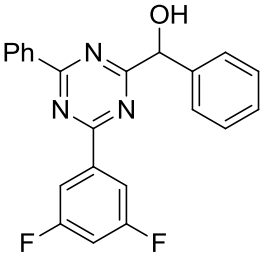
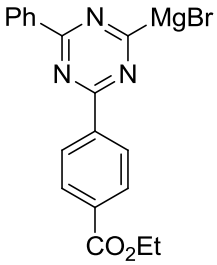
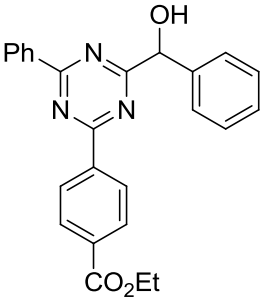
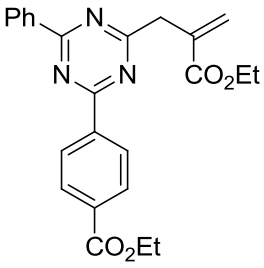
were prepared by reaction with BuMgCl or OctMgBr (1.1 equiv, -78 °C, 10 min) with 2-iodo-1,3,5-triazine derivatives (**61a**-**j**). The resulting 1,3,5-triazinylmagnesium reagents **62b**-**j** reacted with various electrophiles **63b**-**e** affording the fully substituted 1,3,5-triazines **64c**-**m** in 59-75% yield (entries 3-13). Thus, a Cu(I)-catalyzed allylation (CuCN·2LiCl, 20 mol%) of the magnesiated triazine **62b** with ethyl 2-(bromomethyl)acrylate (**63b**) furnished the trisubstituted acrylate **64c** in 59% yield (entry 3). Similarly, the magnesium reagent **62c** afforded, after a Cu(I)-mediated benzoylation with **63c** (CuCN·2LiCl, 1.1 equiv), the triazinyl ketone **64d** in 71% yield (entry 4). Moreover, the substituted 2-triazinyl alcohol **64e** was obtained after addition of the organomagnesium reagent **62d** to PhCHO (**63d**) in 61% yield (entry 5). Remarkably, also electron-poor triazines **61e**,**f** underwent a smooth I/Mg-exchange with BuMgCl (1.1 equiv, -78 °C, 10 min) affording the functionalized 1,3,5-triazinylmagnesium reagents **62e**,**f**. Subsequent Cu(I)-catalyzed allylation (CuCN·2LiCl, 20 mol%) with ethyl 2-(bromomethyl)acrylate (**63b**) or addition to PhCHO (**63d**) afforded the trisubstituted 1,3,5- triazines **64f** and **64g** in 54-71% yield (entries 6 and 7). The 1,3,5-triazine-based Grignard reagents **62g**-**j** bearing electron-withdrawing functional groups such as ester, cyano, and halo groups in the *ortho*- or *para*-position of the phenyl substituent were prepared via a rapid I/Mg exchange with OctMgBr (1.1 equiv, -78 °C, 10 min) from the corresponding substituted 2-iodo-1,3,5-triazines **61g**-**j**. In comparison to BuMgCl, OctMgBr avoids side products due to a nucleophilic substitution of the triazine ring. Thus, the 1,3,5-triazinylmagnesium reagent **62g** afforded, after addition to PhCHO (**63d**) or *p*-NC-C_6H_4CHO (**63e**), the functionalized 1,3,5-triazinyl alcohols **64h-i** in 63-75% yield (entries 8 and 9). Similarly, a Cu-catalyzed allylation of **62g** provided the triazinylsubstituted acrylate **64j** in 71% yield (entry 10). The ethoxycarbonyl-, bromo-, and cyano-substituted triazinylmagnesium reagents **62h**-**j** underwent similar additions to PhCHO (**63d**) or Cu-mediated benzoylation with PhCOCl (**63c**), leading to trisubstituted 1,3,5-triazine derivatives **64k**-**m** in 63-68% yield (entries 11-13).

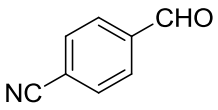
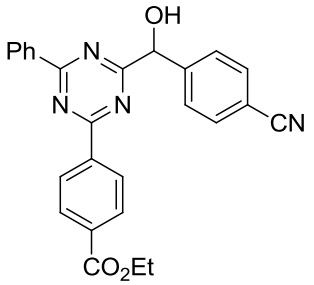
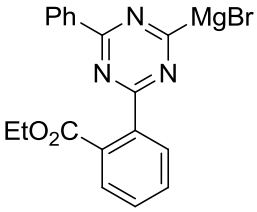
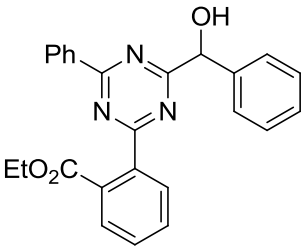
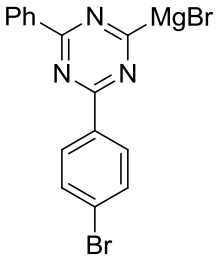
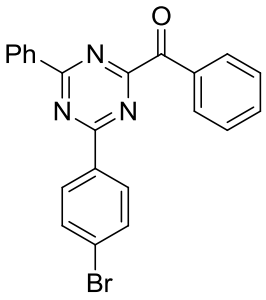
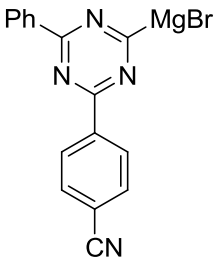
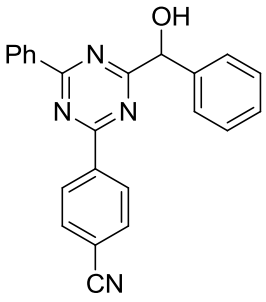
Table 2. Functionalized 1,3,5-triazine derivatives of type **64** obtained by I/Mg exchange and subsequent quenching with an electrophile



61 **62** **64**

entry	magnesium reagent	electrophile	product, yield[a]
			
1	**62a**[b]	**63a**	**64a**: 62%[d]
			
2	**62a**[b]	**63b**	**64b**: 73%[b]
			
3	**62b**[b]	**63b**	**64c**: 59%[e]
			
4	**62c**[b]	**63c**	**64d**: 71%[f]

			
5	**62d**[b]	**63d**	**64e**: 61%
			
6	**62e**[b]	**63b**	**64f**: 71%[e]
			
7	**62f**[b]	**63d**	**64g**: 54%
			
8	**62g**[c]	**63d**	**64h**: 75%
			
9	**62g**[c]	**63b**	**64i**: 71%

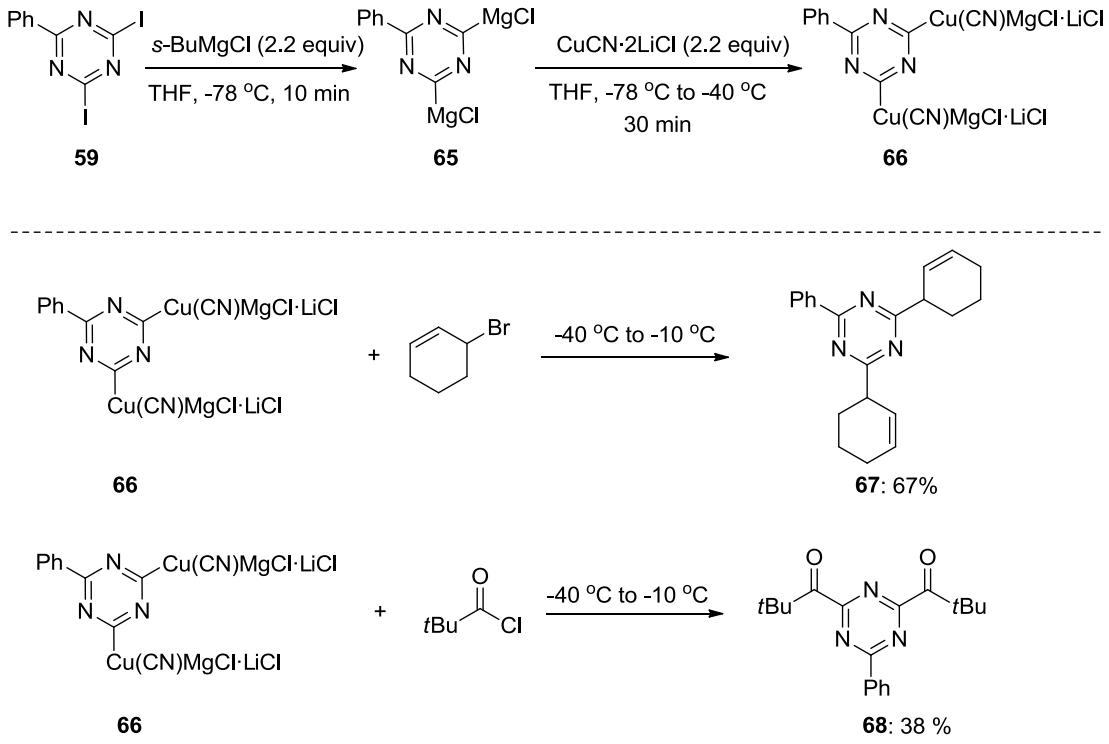
			
10	**62g**[c]	**63e**	**64j**: 63%
			
11	**62h**[c]	**63d**	**64k**: 63%
			
12	**62i**[c]	**63c**	**64l**: 68%[f]
			
13	**62j**[c]	**63d**	**64m**: 64%

[a] Isolated yield of analytically pure product. [b] Obtained after I/Mg exchange with BuMgCl (-78 °C, 10 min). [c] Obtained after I/Mg- exchange with OctMgBr (-78 °C, 10 min). [d] Obtained after transmetallation with $ZnBr_2$·LiCl (1.1 equiv) and subsequent Negishi cross-coupling with ethyl 4-iodobenzoate in the presence of $Pd(dba)_2$ (5 mol%) and tfp (10 mol%). [e] Obtained after addition of CuCN·2LiCl (20 mol%). [f] Obtained after transmetallation with CuCN·2LiCl (1.1 equiv).

1.4 Doubly Magnesiated 1,3,5-Triazine

In general, the preparation of bis-magnesiated aromatics requires harsh reaction conditions, and only a few examples have been reported.[72] However, the I/Mg exchange of 2,4-diiodo-1,3,5-triazine (**59**) with *s*BuMgCl (2.2 equiv, -78 °C, 10 min) readily furnished the doubly magnesiated 1,3,5-triazine **65** (>90% yield). Transmetallation of **65** with CuCN·2LiCl (2.2 equiv, -78 °C to -40 °C) afforded the biscopper derivatives which after allylation or acylation produced the bis-functionalized triazines **67** and **68** in yields of 67% and 38%, respectively (Scheme 32).

[72] a) R. D. Rieke, S. E. Bales, *J. Am. Chem. Soc.* **1974**, *96*, 1775; b) F. Bickelhaupt, *Angew. Chem., Int. Ed.* **1987**, *26*, 990; c) E. Bartmann, B. Bogdanovic, N. Janke, S. Liao, K. Schlichte, B. Spliethoff, J. Treber, U. Westeppe, U. Wilczok, *Chem. Ber.* **1990**, *123*, 1517; d) D. R. Armstrong, W. Clegg, S. H. Dale, D. V. Graham, E. Hevia, L. M. Hogg, G. W. Honeyman, A. R. Kennedy, R. E. Mulvey, *Chem. Commun.* **2007**, 598; e) C. E. Reck, C. H. Winter, *Organometallics* **1997**, *16*, 4493; f) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A .Gavryushin, P. Knochel, *Chem.—Eur. J.* **2009**, *15*, 7192; g) I. Marek, *Chem. Rev.* **2000**, *100*, 2887; h) H. J. R. DeBoer, F. J. J. DeKanter, O. S. Akkerman, F. Bickelhaupt, *Main Group Met. Chem.* **2001**, *24*, 841.



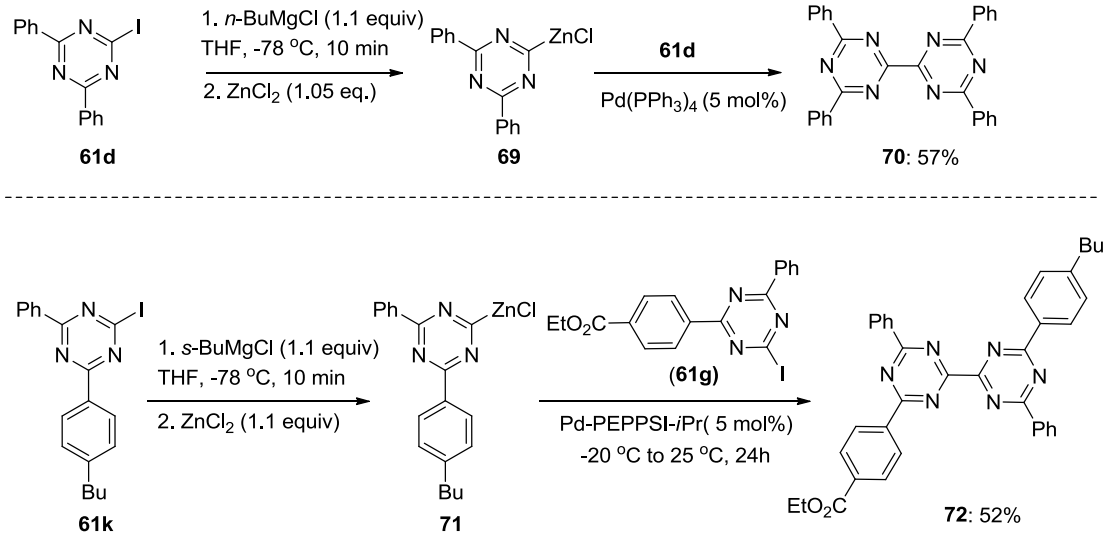
Scheme 32. Preparation of the dimagnesiated 1,3,5-triazine derivatives **67** and **68**

1.5 Syntheses of Trimeric and Dimeric Derivatives

Conjugated molecules bearing 1,3,5-triazine moieties may exhibit useful opto-electronic properties.[73] We have used the functionalized triazinylmagnesium reagents of type **62** for the syntheses of dimeric and trimeric derivatives **70**, **72** and **74** (Scheme 33 and 34). Thus, 2-iodo-4,6-diphenyl-1,3,5-triazine (**61d**) undergoes a smooth I/Mg exchange with BuMgCl (1.1 equiv, -78 °C, 10 min) and leads after a transmetallation with $ZnCl_2$ (1.05 equiv, -78 °C, 10 min) to the corresponding 1,3,5-triazinylzinc chloride **69** (>90% yield). Subsequent Pd(0)-catalyzed cross-coupling with the iodotriazine **61d** (1.0 equiv, -78 to 25 °C, 24 h) provided the dimeric triazine **70** in 57% yield (Scheme 33). Similarly, the I/Mg exchange reaction of 2-iodo-4-(4-butylphenyl)-6-phenyl-1,3,5-triazine (**61k**) with *s*BuMgCl (1.1 equiv, -78 °C, 10 min) followed by $ZnCl_2$ addition furnished the 1,3,5-triazinylzinc reagent

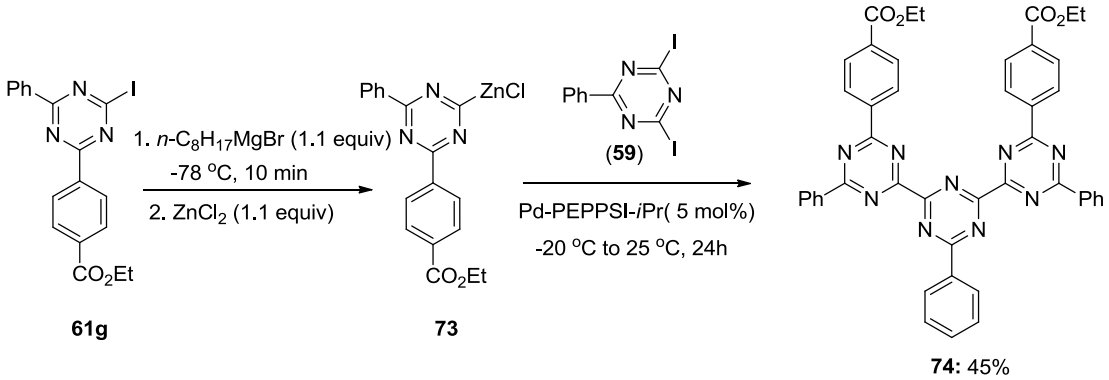
[73] H. Zhong, E. Xu, D. Zeng, J. Du, J. Sun, S. Ren, B. Jiang, Q. Fang, *Org. Lett.* **2008**, *10*, 709.

71. Subsequent Negishi cross-coupling with **61g** (1.0 equiv) using Pd-PEPPSI-*i*Pr[74] (5 mol%, 25 °C, 24 h) led to the dimeric triazine **72** in 52% yield (Scheme 33).



Scheme 33. Preparation of dimeric triazines **70** and **72**.

The trimeric triazine derivative **74** was prepared from the iodotriazine **61g** by I/Mg exchange and transmetallation with $ZnCl_2$, leading to the zinc reagent **73** (>90% yield). Negishi cross-coupling of **73** with 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**) in the presence of Pd-PEPPSI-*i*Pr[74] (5 mol%, 25 °C, 24 h) affords the triazine **74** in 45% yield (Scheme 34).



Scheme 34. Preparation of tristriazine derivative **74**.

[74] a) 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; b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O. Brien, C. Valente, *Chem, —Eur. J.* **2006**, *12*, 4749; c) S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, *J. Org. Chem.* **2008**, *73*, 7380.

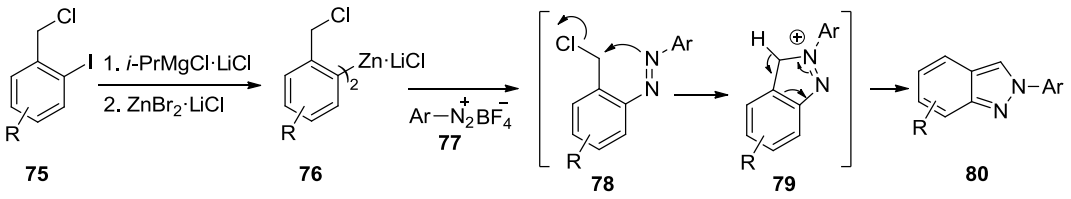
1.6 Conclusion

In summary, we have developed a new method for the preparation of stable mono- and bis(1,3,5-triazinyl)magnesium reagents, which react with aldehydes, acid chlorides, and allylic halides, furnishing a wide range of new functionalized fully substituted 1,3,5-triazine derivatives. Remarkably, dimeric and trimeric triazine derivatives were also prepared using triazinylzincs as key intermediates.

2. Preparation of Polyfunctional Indazoles Using Highly Functionalized Zinc Reagents

2.1 Synthetic Strategy

Among various heterocyclic compounds, indazoles have found numerous applications in the areas of pharmaceuticals, agrochemicals, and polymers.[75] As previously shown, organometallics are versatile reagents for the preparation of complex heterocycles. Especially, organozinc compounds have excellent compatibility with nitrogen functionalities at high oxidation degree such as nitro groups, azides, and triazenes.[76] It has been reported that diphenylzinc species reacted with diazonium salts giving azo compounds.[77] We envisioned that the treatment of diarylzinc reagent **76** (which can be prepared by an I/Mg exchange and a subsequent transmetallation with $ZnBr_2 \cdot LiCl$) with diazonium salt **77** can provide the desired indazole of type **80** by intramolecular nucleophilic substitution of the 2-chloromethylarylazo intermediate **78** and the subsequent proton abstraction (Scheme 35).



Scheme 35. Tentative synthesis of indazole of type **80**.

2.2 Preparation of Highly Functionalized Zinc Reagents

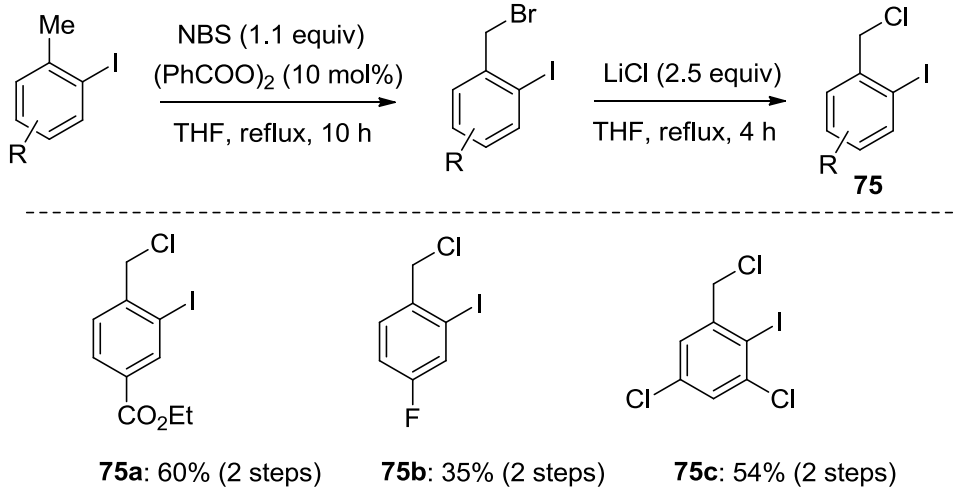
Functionalized 2-iodobenzyl chlorides of type **75** were generated in two steps in

[75] a) A. Schmidt, A. Beutler, B. Snovydovych, *Eur. J. Org. Chem.* **2008**, 4073; b) W. Stadlbauer, *Sci. Synth.* **2002**, *12*, 227; c) H. Cerecetto, A. Gerpe, M. González, V. Arán, C. Ochoa de Ocáriz, *Mini-Rev. Med. Chem.* **2005**, *5*, 869; d) V. Minkin, D. Garnovskii, J. Elguero, A. Katritzky, O. Denisko, *Adv. Heterocycl. Chem.* **2000**, *76*, 157; e) J. van Ooijen, J. Reedijk, *J. Magn. Magn. Mater.* **1979**, *12*, 4; f) G. Sagi, K. Szucs, L. Otvos, *J. Med. Chem.* **1992**, *35*, 4549; g) O. Dann, P. Nickel, *Liebigs Ann. Chem.* **1963**, *667*, 101; h) M. De Angelis, F. Stossi, K. Carlson, B. Katzenellenbogen, J. Katzenellenbogen, *J. Med. Chem.* **2005**, *48*, 1132.

[76] a) I. Sapountzis, P. Knochel, *Angew. Chem., Int. Ed.* **2002**, *41*, 1610; b) C.-Y. Liu, P. Knochel, *J. Org. Chem.* **2007**, *72*, 7106; c) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543.

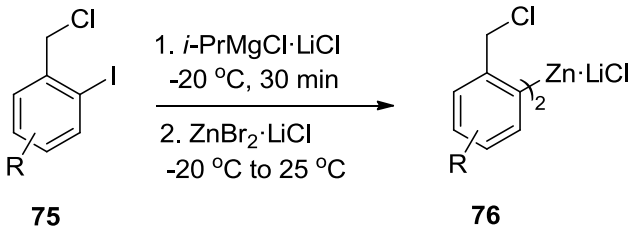
[77] D. Curtin, J. Tveteen, *J. Org. Chem.* **1961**, *26*, 1764.

35-53% yield (Scheme 36). For example, the reaction of 3-iodo-4-methyl-benzoic acid ethyl ester with *N*-bromosuccinimide (1.1 equiv) in the presence of dibenzoylperoxide (10 mol%) in THF provided crude 4-bromomethyl-3-iodobenzoic acid ethyl ester. Subsequent treatment with LiCl (2.5 equiv) led to the expected product **75a** in 60% yield (two steps). 2-Iodobenzyl chlorides **75b** and **75c** were obtained respectively in similar manner (Scheme 36).



Scheme 36. Preparation of functionalized 2-iodobenzyl chlorides of type **75**

With functionalized 2-iodobenzyl chlorides at hand, the corresponding diarylzinc reagents were prepared by using the well-established I/Mg exchange reaction. Thus, the treatment of functionalized 2-iodobenzyl chlorides of type **75** with *i*-PrMgCl·LiCl (1.05 equiv, -20 °C, 30 min) furnished 2-chloromethylphenylmagnesium chlorides. Transmetallation with $ZnBr_2$·LiCl (0.55 equiv, -20 °C to 25 °C, 20 min) provided the desired diarylzinc reagents of type **76** (Scheme 37).

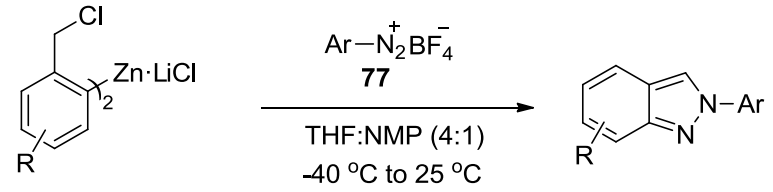


Scheme 37. Preparation of functionalized diarylzinc reagents of type **76**.

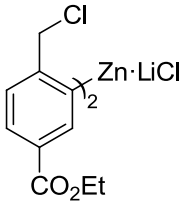
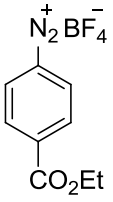
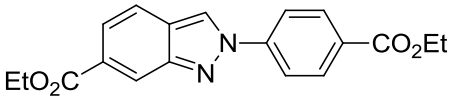
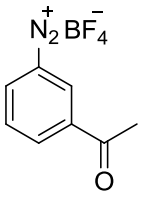
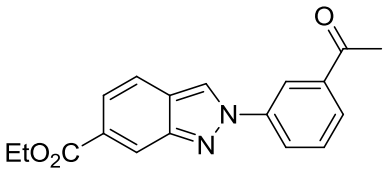
2.3 Preparation of Polyfunctionalized Indazoles

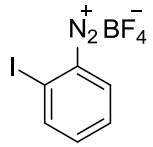
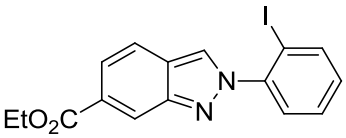
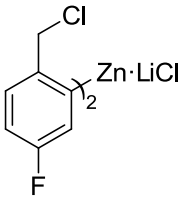
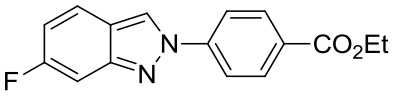
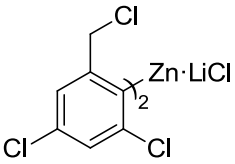
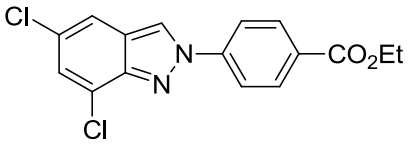
The resulting zinc reagent **76a** was then added to aryldiazonium tetrafluoroborate **77a** in a 1:1 THF:NMP mixture (NMP = *N*-methyl-2-pyrrolidone) at -40 °C. After stirring the reaction mixture at 25 °C (30 min) and warming the solution to 50 °C for 1 h, 2-(4-ethoxycarbonyl-phenyl)-2*H*-indazole-6-carboxylic acid ethyl ester (**80a**) was isolated in 71% yield (entry 1, Table 3). Similarly, the diarylzinc reagent **76a** reacted with aryldiazonium tetrafluoroborate **77b-c** affording the corresponding indazoles **80b-c** in 68-90% yield (entries 2-3). In addition, the diarylzinc reagents **76b** and **76c** were converted to the desired adducts **80d** (75% yield) and **80e** (66% yield) respectively under similar conditions (entries 4-5).

Table 3. Aryl-2*H*-indazole synthesis by the reaction of di(2-chloromethylaryl) zinc with aryldiazonium tetrafluoroborate



76 **80**

entry	zinc reagent[a]	diazonium salt	product, yield[b]
			
1	**76a**	**77a**	**80a**: 71%
			
2	**76a**	**77b**	**80b**: 68%

			
3	**76a**	**77c**	**80c**: 90%
			
4	**76b**	**77a**	**80d**: 75%
			
5	**76c**	**77a**	**80e**: 66%

[a] With $ZnBr_2$·LiCl (0.55 equiv), a transmetallation was performed. [b] Yield of analytically pure product.

2.4 Conclusion

Therefore, we have developed a short and convenient synthetic route to 2-aryl-2*H*-indazoles by using highly functionalized arylzinc reagents.

3. Diastereoselective Synthesis of Homoallylic Alcohols with Adjacent Tertiary and Quaternary Centers by Using Functionalized Allylic Aluminum Reagents

3.1 Introduction

Addition reactions of nucleophiles to carbonyl compounds are excellent reactions for generating quaternary centers in a diastereoselective manner.[78] Especially the addition of allylic organometallics to aldehydes or ketones proceeds in several cases with high diastereoselectivity.[79] This novel strategy has been widely applied for the construction of the complex molecules. For instance, *Paterson* and co-workers used this methodology in the total synthesis of Swinholide A. Homoallylic alcohol **82** was prepared in 60% yield with complete diasteroselectivity by exposing aldehyde to the (+)-Ipc-derived crotylboration reagent[80] (Scheme 38).[81] As previously shown, the scope of this reaction has been extended to allylic zinc reagents, allylic silane reagents, allylic aluminum reagents, allylic titanium reagents and so on.[82]

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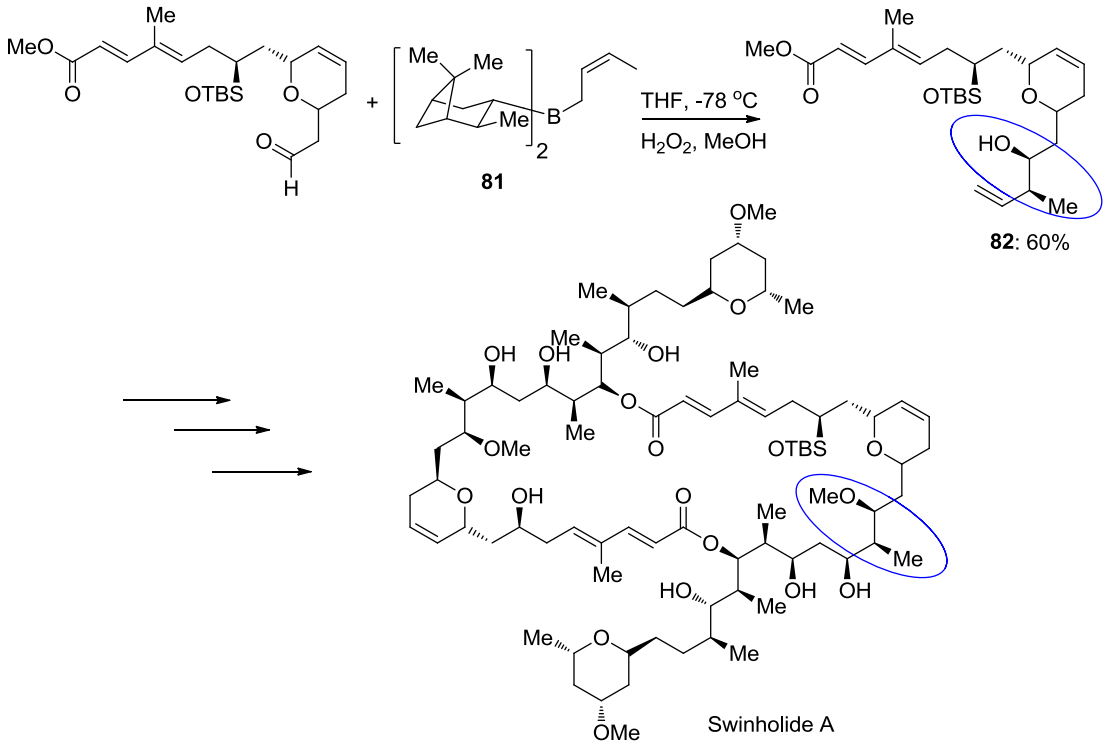
[78] a) E. J. Corey, A. Guzman-Perez, *Angew. Chem*. **1998**, *110*, 402; *Angew. Chem. Int. Ed*. **1998**, *37*, 388; b) J. Christoffers, A. Mann, *Angew. Chem*. **2001**, *113*, 4725; *Angew. Chem. Int. Ed*. **2001**, *40*, 4591; c) M. d_Augustin, L. Palais, A. Alexakis, *Angew. Chem*. **2005**, *117*, 1400; *Angew*. *Chem. Int. Ed*. **2005**, *44*, 1376; d) G. Sklute, D. Amsallem, A. Shabli, J. P. Varghese, I. Marek, *J. Am*. *Chem. Soc*. **2003**, *125*, 11776; e) G. Sklute, I. Marek, *J. Am. Chem. Soc*. **2006**, *128*, 4642; f) B. Breit, P. Demel, C. Studte, *Angew. Chem*. **2004**, *116*, 3874; *Angew. Chem. Int. Ed*. **2004**, *43*, 3786; g) H. Li, P. J. Walsh, *J. Am. Chem. Soc*. **2004**, *126*, 6538; h) J. W. J. Kennedy, D. G. Hall, *J. Am. Chem. Soc*. **2002**, *124*, 898; i) S. E. Denmark, J. Fu, *J. Am. Chem. Soc*. **2001**, *123*, 9488; j) S. E. Denmark, J. Fu, *Org. Lett*. **2002**, *4*, 1951; k) J.-N. Heo, G. C. Micalizio,W. R. Roush, *Org. Lett*. **2003**, *5*, 1693; l) J. P. Das, H. Chechik, I. Marek, *Nat. Chem*. **2009**, *1*, 128.

[79] For additions of allylic organometallics to carbonyls, see: a) S. R. Chemler, W. R. Roush in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, Germany, **2000**, Chapter 10; b) S. E. Denmark, N. G. Almstead in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, Germany, **2000**, Chapter 11; c) *Stereoselective Synthesis*, *Methods of Organic Chemistry (Houben-Weyl)*, (Eds.: G. Helmchen, R. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1996**, Vol. 3; d) S.-W. Li, R. A. Batey, *Chem. Commun.* **2004**, 1382; e) C. T. Buse, C. H. Heathcock, *Tetrahedron Lett.* **1978**, 1685; f) Y. Yamamoto, H. Yatagai, Y. Naruta, K. Maruyama, *J. Am. Chem. Soc.* **1980**, *102*, 7107; g) Y. Yatsumonji, T. Nishimura, A. Tsubouchi, K. Noguchi, T. Takeda, *Chem. Eur. J*. **2009**, *15*, 2680.

[80] a) H. C. Brown, K. S. Bhat, R. S. Randad, *J. Org. Chem.* **1989**, *54*, 1570; b) H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 5919.

[81] a) I. Paterson, K.-S. Yeung, R. A. Ward, J. G. Cumming, J. D. Smith, *J. Am. Chem. Soc.* **1994**, *116*, 9391; b) I. Paterson, J. D. Smith, R. A. Ward, J. G. Cumming, *J. Am. Chem. Soc.* **1994**, *116*, 2615. c) K. C. Nicolaou, S. A. Synder, *Classics in Total Synthesis ⅡI* Wiley-VCH, Weiheim, 2003.

[82] For references, see: Chapter **A**.



Scheme 38. Addition reaction of allylboron reagent in total synthesis of Swinholide A

Recently, *Knochel* and co-workers have shown that functionalized allylic zinc reagents can be prepared from allylic chlorides by the reaction of zinc powder in the presence of LiCl. Their addition to aldehydes and ketones proceeds with high diastereoselectivities.[31] Nevertheless, the preparation of allylic zinc reagents bearing sensitive functional groups (such as a cyano or an ester function) is limited due to the high reactivity of such allylic organometallics.[83] Besides zinc, aluminum is a metal which has many attractive features: it is of low toxicity, inexpensive and due to the low ionic character of the carbon-aluminum bond, it may tolerate a number of important functional groups. [84] The preparation of unsaturated aluminum organometallics from commercial Al-powder is in general difficult, but a proper activation of the aluminum surface allows an effective insertion of aluminum to aryl

[83] a) N. E. Alami, C. Belaud, J. Villieras, *J. Organomet. Chem.* **1988**, *348*, 1-9; b) N. E. Alami, C. Belaud, J. Villieras, *J. Organomet. Chem.* **1988**, *353*, 157-168; c) M. Gaudemar, *Bull. Soc. Chim. Fr.* **1963**, *7*, 1475.

[84] Organoaluminum reagents: a) E.-i. Negishi, T. Takahashi, S. Baba, D. E. Van Horn, N. Okukado, *J. Am. Chem. Soc.* **1987**, *109*, 2393; b) E.-i. Negishi, *Acc. Chem. Res.* **1982**, *15*, 304; c) S.-L. Ku, X.-.Hui, C.-A. Chen, Y.-Y. Kuo, H.-M. Gau, *Chem. Commun.* **2007**, 3847; d) G. Zweifel, J. A. Miller in *Organic Reactions* (Ed.: W. G. Dauben), John Wiley & Sons, New York, **1984**.

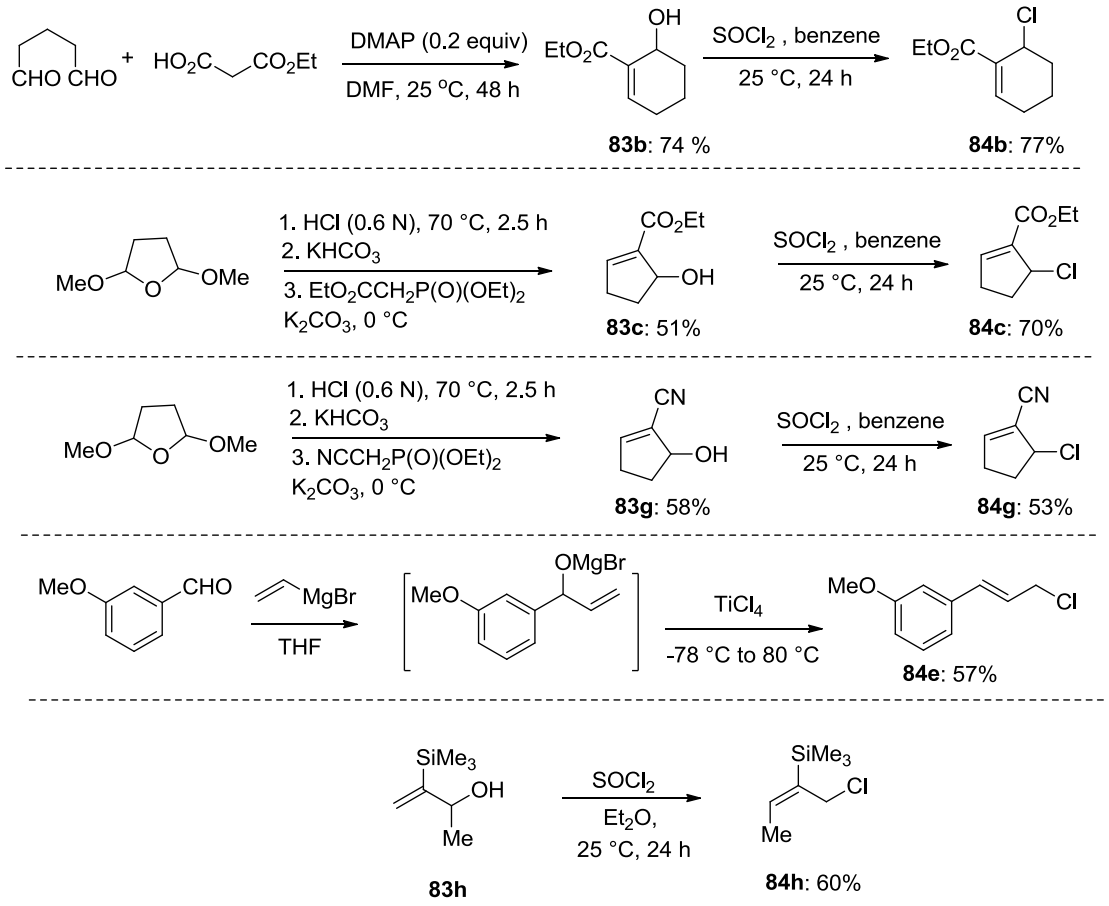
halides.[85] Previously, allylic aluminum reagents were prepared from allylic bromides according to *Gaudemar*[32] and *Miginiac*[33] using diethyl ether as solvent in the presence of a catalytic amount of $HgCl_2$.

We wish to develop a practical synthesis of functionalized allylic aluminum reagents bearing various substituents by performing an insertion of commercial Al-powder to various allylic chlorides or bromides as well as their diastereoselective addition to aldehydes and ketones.

3.2 Preparation of Functionalized Allylic Chlorides

Starting from readily available allylic alcohol, the corresponding functionalized allylic halides were obtained by treatment with chlorination reagent such as thionyl chloride. Thus, the reaction of 6-hydroxy-cyclohex-1-enecarboxylic acid ethyl ester[86] (**83b**) with thionyl chloride in benzene at 25 ^{o}C within 24 h afforded the desired allylic chloride **84b** in 77% yield. Similarly, starting from ethyl 5-hydroxycyclopent-1-enecarboxylate[87] (**83c**), the corresponding allylic chloride **84c** was given in 70% yield. This condition can be applied for preparing the allylic chloride bearing a cyano function **84g** from 5-hydroxycyclopent-1-enecarbonitrile[87] (**83g**). The treatment of 3-methoxybenzaldehyde with vinylmagnesium bromide and subsequent reaction with $TiCl_4$ provided the functionalized cinnamyl chloride **84e** in 57% yield.[88] (E)-(1-chlorobut-2-en-2-yl)trimethylsilane (**84h**) was prepared in 60% yield from the corresponding allylic alcohol **83h**[89] in ether at 25 ^{o}C within 24h (Scheme 39).

[85] T. D. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313.
[86] Prepared according to: List, A. Dochring, M. T. H. Fonseca, A. Job, R. R. Torres, *Tetrahedron* **2006**, *62*, 476.
[87] Prepared according to: T. Yamane, M. Takahashi, K. Ogasawara, *Synthesis*, **1995**, 444.
[88] M. J. Fuchter, J.-N. Levy, *Org. Lett.* **2008**, *19*, 4919.
[89] Prepared according to: R. K. Boeckman, JR., D. M. Blum, B, Ganem, N. Halvey, *Org. Synth.* **1978**, *58*, 152



Scheme 39. Preparation of functionalized allylic halides.

3.3 Preparation of Functionalized Allylic Aluminum Reagents and Their Addition to Aldehydes and Ketones

3.3.1 Cyclic Aluminum Reagents

Preliminary studies have shown that an appropriate activation of aluminum is essential for achieving a smooth insertion to organic halides.[90] Thus, 3-bromocyclohex-1-ene (**84a**) reacts with Al-powder (1.5 equiv) and $InCl_3$ (1 mol%)[91]

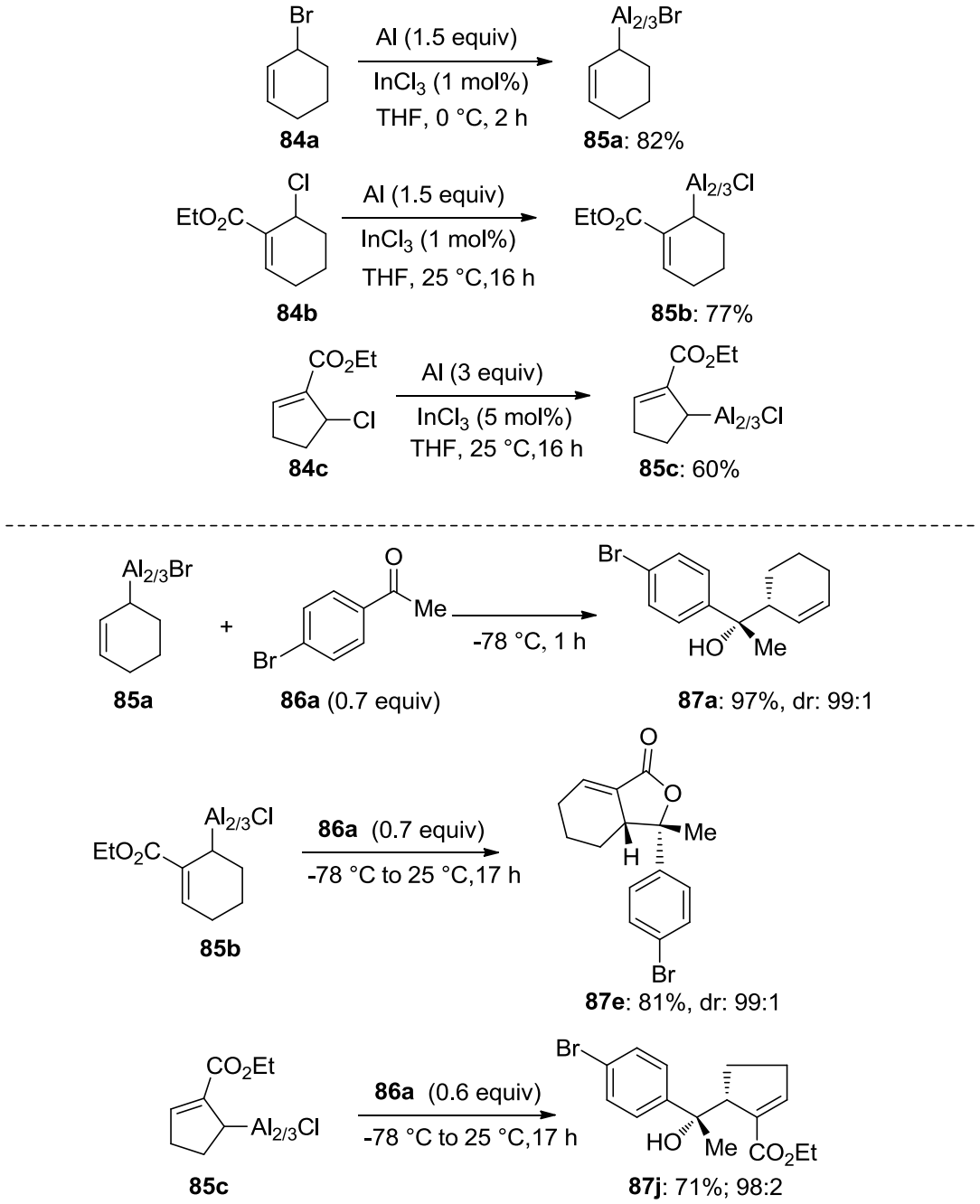
[90] Aluminum powder has been previously activated by $PbCl_2$, $SnCl_2$, $TiCl_4$ for insertion into allyl bromides and chlorides, see: a) K, Uneyama, N. Kamaki, A. Moriya, S. Torii, *J. Org. Chem*. **1985**, *50*, 5396; b) H. Tanaka, T. Nakahara, H. Dhimane, S. Torii, *Tetrahedron Lett*. **1989**, *30*, 4161; c) H. Tanaka, K. Inoue, Ulrike Pokorski, M. Taniguchi, S. Torii, *Tetrahedron Lett*. **1990**, *31*, 3023. For general activation of aluminum powder, see: S. Saito in *Science of Synthesis* (Ed.: H. Yamamoto), **2004**, vol. 7, p 5.

[91] We assume that $InCl_3$ activates the Al-surface; see also: a) K. Takai, Y. Ikawa, *Org. Lett*. **2002**, *4*, 1727; b) S. Araki, S.-J. Jin, Y. Idou, Y. Butsugan, *Bull. Chem. Soc. Jpn*. **1992**, *65*, 1736.

in THF at 0 °C within 2 h and provides the corresponding allylic aluminum reagent **85a** in 82% yield.[92] Its reaction with 4´-bromoacetophenone (**86a**, 0.7 equiv, 1 h, -78 °C) leads to the *syn*-homoallylic alcohol (**87a**) in 97% yield as only diastereoisomer (dr > 99:1).[93] Functional groups like an ester are readily compatible with this procedure. Thus, starting from ethyl 6-chloro-cyclohex-1-enecarboxylate (**84b**), the functionalized allylic aluminum reagent (**85b**) is obtained in 77% yield (25 °C, 16 h). It also reacted well with 4´-bromoacetophenone (**86a**, 0.7 equiv) affording the homoallylic lactone (**87e**) with excellent diastereoselectivity (dr > 99:1 and 81% yield). In addition, ethyl 5-chlorocyclopent-1-enecarboxylate (**84c**) reacted with Al-powder (3 equiv) and $InCl_3$ (5 mol%) in THF affording the aluminum reagent **85c** within 16 h at 25 °C (60% yield). However, in contrast to the six-membered analogue (**85b**), a lactone formation is disfavoured and the reaction with 4´-bromoacetophenone (**86a**) yields the ester-substituted homoallylic alcohols (**87j**) in 71% yield (Scheme 40).

[92] Yields were determined by iodometric titration after transmetallation with $ZnCl_2$: A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890.

[93] The stereochemistry has been established by a comparison with the literature (^{1}H-NMR and ^{13}C-NMR spectra): M. Yasuda, K. Hirata, M. Nishino, A. Yamamoto, A. Baba, *J. Am. Chem. Soc.* **2002**, *124*, 13442.

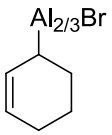
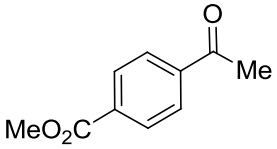
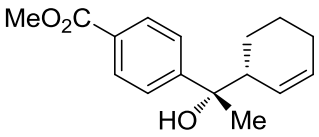
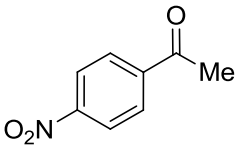
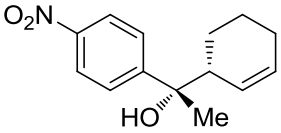
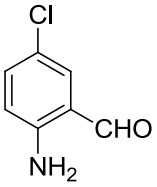
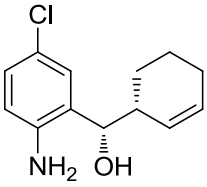
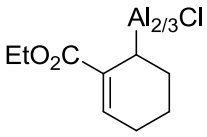
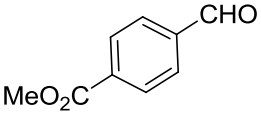
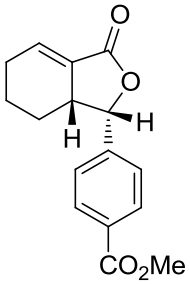


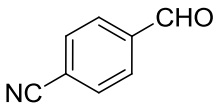
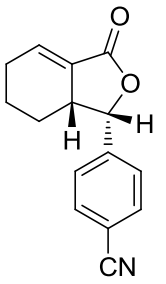
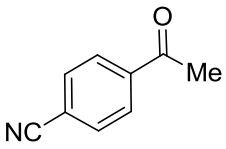
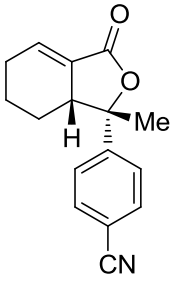
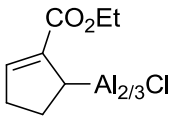
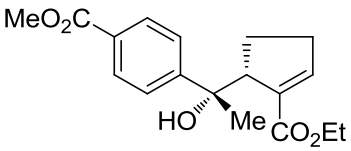
Scheme 40. Preparation of the allylic aluminum reagents **85a-c** and their addition to 4´-bromoacetophenone (**86a**).

The reaction scope of such additions has been studied and we found that the allylic aluminum reagent **85a** reacts well with variously substituted aromatic ketones. Thus, the addition to methyl 4-acetylbenzoate (**86b**, 0.7 equiv) furnishes the homoallylic alcohol **87b** (dr > 99:1; 98% yield; Table 4, entry 1). Remarkably, despite the seemingly high nucleophilicity of the allylic aluminum reagent, the reagent **85a** adds

smoothly to 1-(4-nitrophenyl)ethanone (**86c**, 0.7 equiv) without reacting with the nitro group and the homoallylic alcohol **87c** (dr > 99:1) is isolated in 95% yield (entry 2). An unprotected amino group is also compatible with the aluminum reagent under these reaction conditions and the addition of **85a** to 2-amino-5-chlorobenzaldehyde (**86d,** 0.7 equiv) affords the amino-alcohol **87d** (dr > 99:1) in 95% yield (entry 3). Various aromatic aldehydes and ketones (**86e-g**) react with the functionalized allylic aluminum reagent **85b**, leading to the corresponding lactones (**87f-h**) in 77-87% yield (dr > 98:2, entries 4-6). Also, the reaction of the functionalized allylic aluminum reagent **85c** with 4-acetylbenzoate (**86b**) provides the ester-substituted homoallylic alcohols **87i** in 70% yield (entries 7).

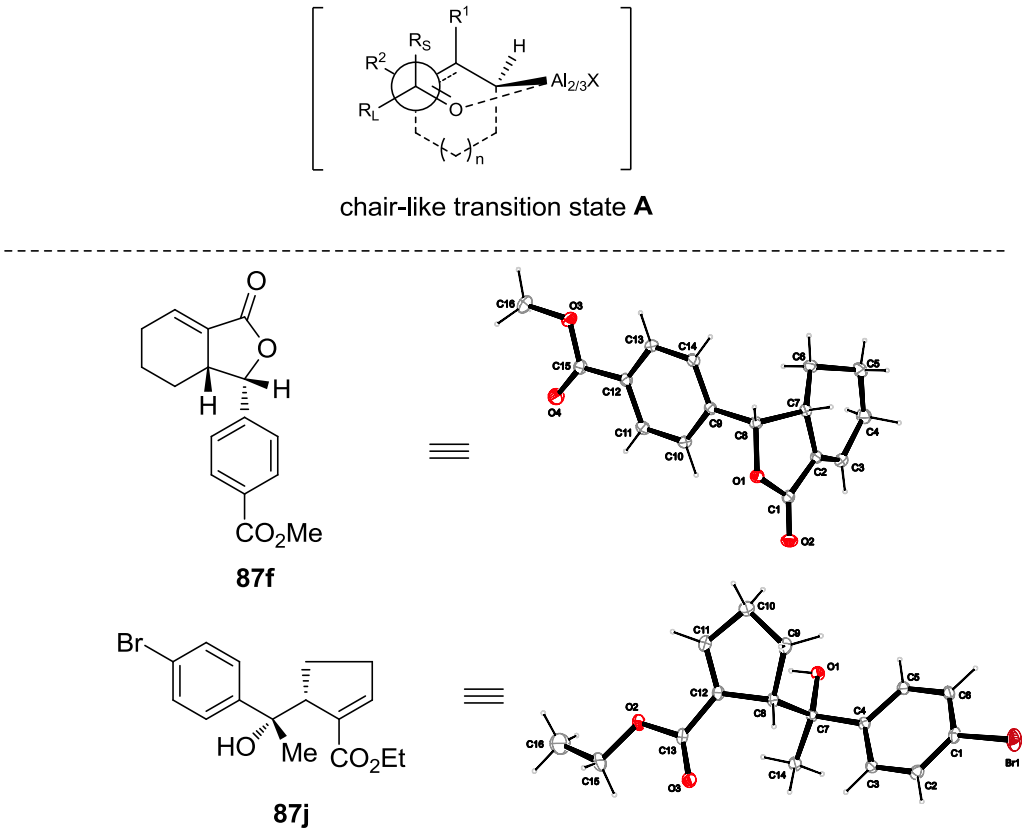
Table 4. Diastereoselective preparation of homoallylic alcohols and lactones of type **87** using allylic aluminum reagents of type **85.**

entry	aluminum reagent[a]	carbonyl electrophile[b]	product[c, d]
			
1	**85a**	**86b**	**87b**: 98%; 99:1
			
2	**85a**	**86c**	**87c**: 95%; 99:1
			
3	**85a**	**86d**	**87d**: 95%; 99:1
			
4	**85b**	**86e**	**87f**: 78%; 99:1[e]

			
5	**85b**	**86f**	**87g**: 87%; 99:1
			
6	**85b**	**86g**	**87h**: 79%; 98:2
			
7	**85c**	**86b**	**87i**: 70%; 98:2

[a] All reactions were carried out on a 1-4 mmol scale. [b] 0.6-0.7 equivalents of electrophiles have been used. [c] Isolated yield of analytically pure products. [d] The diastereoselectivities were determined by ^{1}H-NMR analysis. [e] The structures have been established by X-ray analysis.

The diastereoselectivity can be best rationalized by a chair-like transition state **A** (Scheme 41). Also, the stereochemistry of homoallylic alcohols **87a** and **87d** has been established by comparison with the literature.[93, 31] The structure of the bicyclic lactone **87f** has been proven by X-ray analysis (CCDC-775024) and the structures of the analogue **87e** and **87h** were determined by ^{1}H NMR and NOESY NMR analysis. Again, X-ray analysis of **87j** has been used to establish its structure (CCDC-775025) (Scheme 41)



Scheme 41. Chair-like transition state and X-ray analysis of **87f** and **87j**.

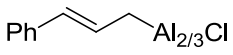
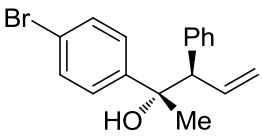
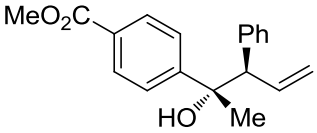
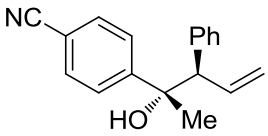
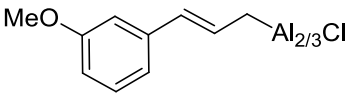
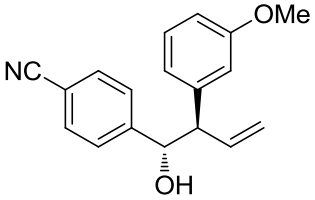
3.3.2 Cinnamylaluminum Reagents

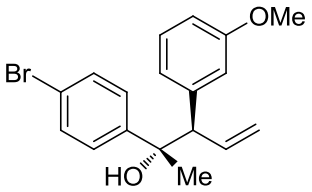
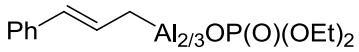
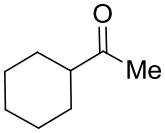
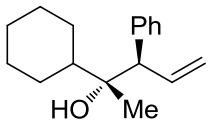
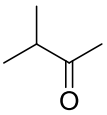
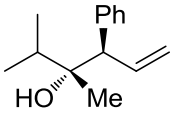
Similarly, the reaction of Al-powder (1.5 equiv) and $InCl_3$ (1 mol%) with cinnamyl chloride (**84d**) provides the aluminum reagent **85d** (73% yield) within 2 h at 25 °C. Addition to methyl ketones such as 4´-bromoacetophenone (**86a**, 0.7 equiv), methyl 4-acetylbenzoate (**86b**, 0.7 equiv) or 4-acetylbenzonitrile (**86g**, 0.7 equiv), affords the corresponding alcohols **87k-m** in almost quantitative yields, with high diastereoselectivities (>98% yield, entries 1-3, Table 5). Remarkably, in contrast to the preparation of the corresponding cinnamylzinc reagent[94], little homo-coupling of the allylic reagent is observed. Even a more electron-rich cinnamyl chloride (**84e)** bearing a methoxy group provides the corresponding aluminum reagent **85e** using Al-powder (1.5 equiv) and $InCl_3$ (1 mol%; 25 °C, 11 h, 71% yield). It adds smoothly to

[94] M. Gaudemar, *Bull. Soc. Chim. Fr*. **1962**, 974.

4-cyanobenzaldehyde (**86f**, 0.7 equiv) or 4´-bromoacetophenone (**86a**, 0.7 equiv) affording the polyfunctional *anti*-homoallyllic alcohols (**87n-o**) in 74-95% yield (entries 4-5). Interestingly, a cinnamylaluminum phosphate (**85f**) could be readily prepared by reacting the phosphoric cinnamyl ester (**84f**) with Al-powder (1.5 equiv) and $InCl_3$ (1 mol%) in THF (25 °C, 12 h, 70% yield). Trapping this new organometallic reagent with aliphatic methyl ketones such as 1-cyclohexylethanone (**86h**, 0.7 equiv) or 3-methylbutan-2-one (**86i**, 0.7 equiv) furnishes the corresponding homoallylic alcohols bearing two adjacent stereo-controlled tertiary and quaternary centers **87p-q** (dr > 97:3) in 62-90% yield (entries 6-7). The structures of all homoallylic alcohols resulting from the addition to ketones and aldehydes could be established either by literature comparison[31, 93] or X-ray analysis in the case of **87n** (CCDC-775023) (Scheme 42).

Table 5. Diastereoselective preparation of homoallylic alcohols and lactones of type **87** using allylic aluminum reagents of type **85.**

entry	aluminum reagent[a]	carbonyl electrophile[b]	product[c, d]
			
1	**85d**	**86a**	**87k**: 99%; 98:2
			
2	**85d**	**86b**	**87l**: 99%; 96:4
			
3	**85d**	**86g**	**87m**: 98%; 94:6
			

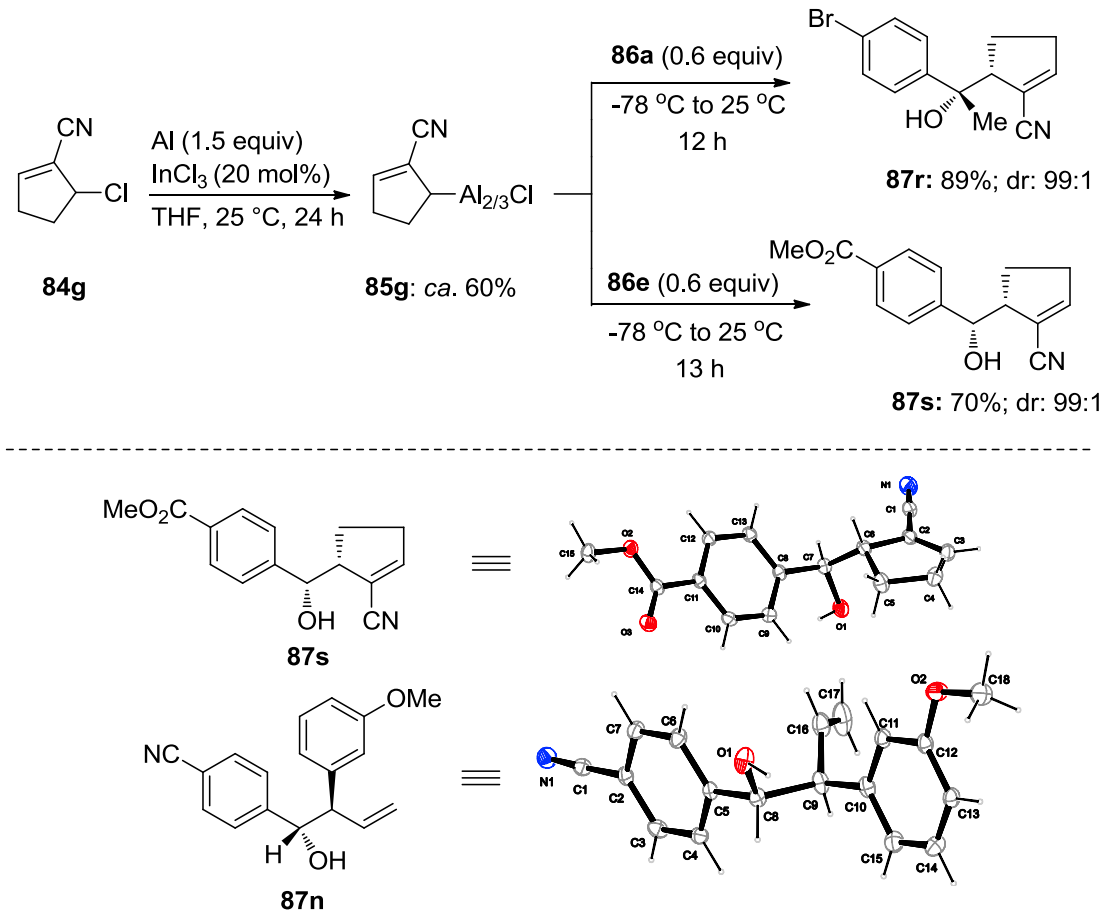
4	**85e**	**86f**	**87n**: 95%; 97:3[e] 
5	**85e** 	**86a** 	**87o**: 74%; 92:8 
6	**85f**	**86h** 	**87p**: 62%; 97:3 
7	**85f**	**86i**	**87q**: 90%; 98:2

[a] All reactions were carried out on a 1-4 mmol scale. [b] 0.6-0.7 equivalents of electrophiles have been used. [c] Isolated yield of analytically pure products. [d] The diastereoselectivities were determined by ^{1}H-NMR analysis. [e] The structures have been established by X-ray analysis.

3.3.3 Cyano-Substituted Cyclopentylaluminum Reagent

Usually, cyano-substituents react rapidly with allylic organometallics such as zinc reagents (Blaise reaction).[95] Remarkably, a cyano function is well tolerated during the Al-insertion reaction. Thus, the preparation of a cyano-substituted cyclopentyl-aluminum reagent (**85g**) can be achieved starting from 5-chloro-cyclopent-1-enecarbonitrile (**84g**) using Al-powder (1.5 equiv) and $InCl_3$ (20 mol%) in 24 h at 25 °C (*ca.* 60% yield). The addition of this aluminum reagent to a ketone or an aldehyde affords the homoallylic alcohols **87r** and **87s** in 70-89% yield (dr > 99:1, Scheme 42). An X-ray analysis for **87s** has been performed (CCDC-775026) (Scheme 42).

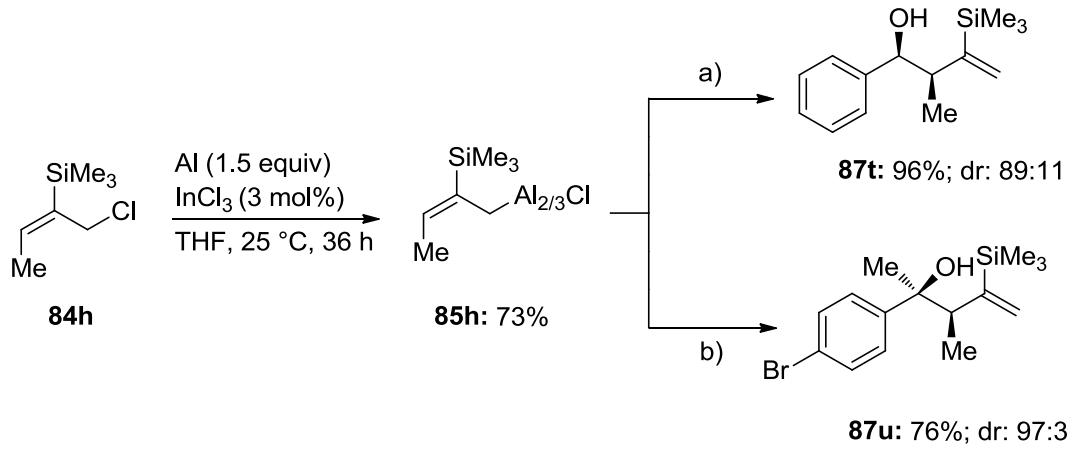
[95] a) P. Knochel, J. F. Normant, *J. Organomet. Chem.* **1986**, *309*, 1; b) E. E. Blaise, *Compt. Rend.* **1901**, *132*, 478.



Scheme 42. Preparation of a cyano-substituted allylic aluminum reagent (**85g**) and X-ray analysis of **87n** and **87s**.

3.3.4 *β*-Silyl-Substituted Crotylaluminum Reagent

In the case of a *β*-silyl-substituted crotylaluminum reagent (**85h**), which was prepared starting from the *β*-silyl-substituted crotyl chloride **84h**, the addition to benzaldehyde (**86j**, 0.7 equiv) and 4´-bromoacetophenone (**86a**, 0.7 equiv) was also selective, and the *syn*-homoallylic alcohols **87t** (dr > 89:11, 96% yield) and **87u** (dr > 97:3, 76% yield) were obtained (Scheme 43).



Scheme 43*:* Preparation of a trimethylsilyl-substituted allylaluminum reagent (**85h**) and its addition reactions. Reactions and conditions: a) benzaldehyde (**86j**, 0.7 equiv), -78 °C, 1 h; b) 4´-bromoacetophenone (**86a**, 0.7 equiv), -78 °C, 1 h.

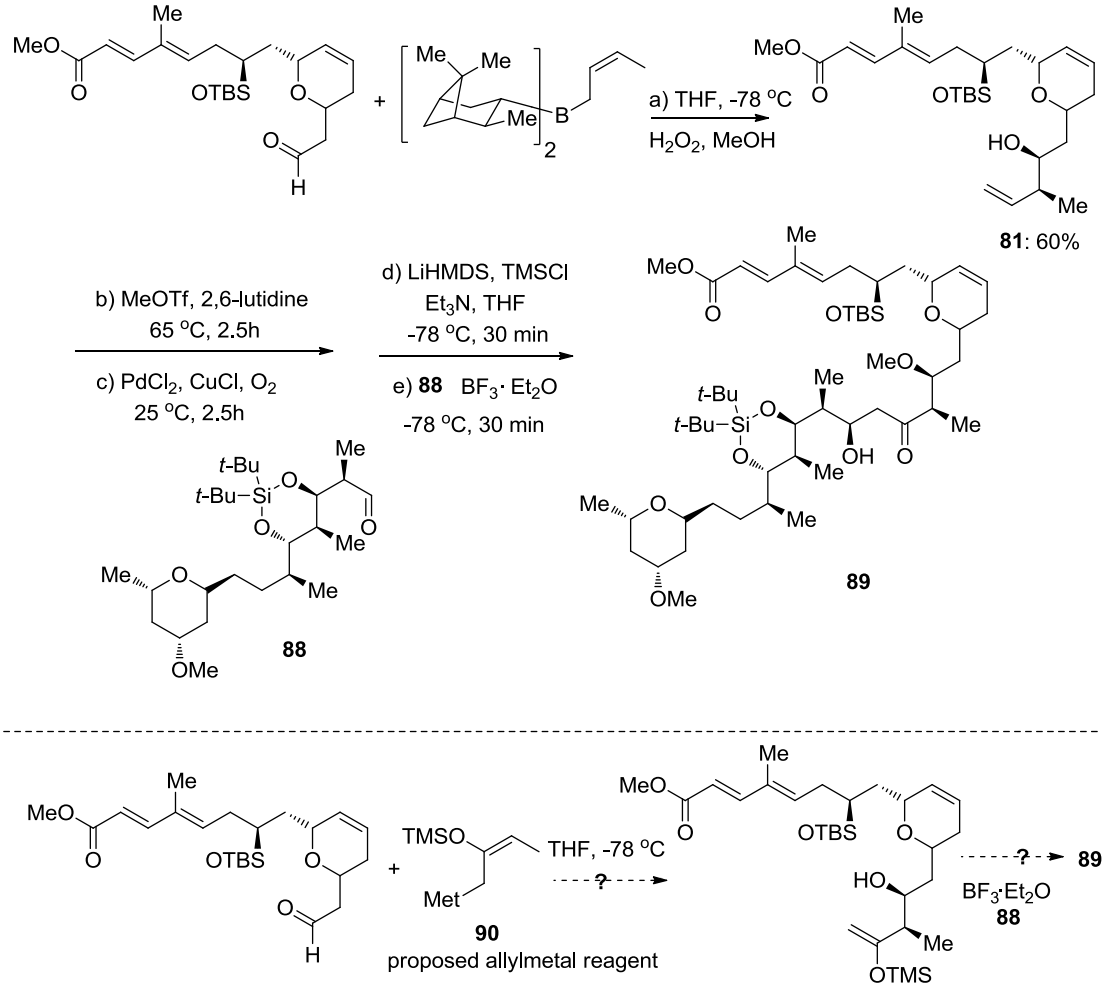
3.4 Conclusion

In summary, we have demonstrated that allylic aluminum reagents can be conveniently prepared using aluminum powder in the presence of catalytic amounts of $InCl_3$ from allylic chlorides or bromides under mild conditions. The addition to various functionalized aldehydes or ketones affords polyfunctionalized homoallylic alcohols, bearing adjacent tertiary and quaternary centers with good diastereoselectivity.

3.5 Extension of Functionalized Allylic aluminum Reagents

3.5.1 Introduction

As previously mentioned, *Paterson* constructed homoallylic alcohol **81** using addition reaction of the (+)-Ipc-derived crotylboration reagent to an aldehyde in the total synthesis of Swinholide A.[80, 81] The subsequent protection, Wacker oxidation, generation of enolate and Mukaiyama aldol reaction afforded the adduct **89** in 5 overall steps (Scheme 44).

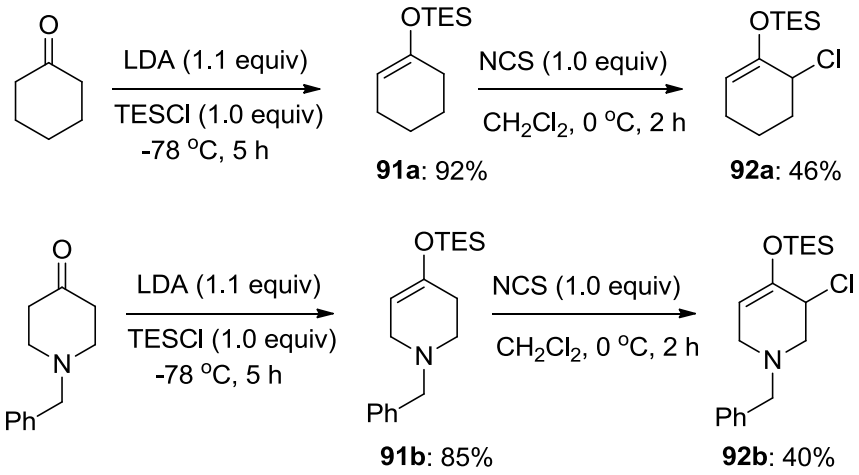


Scheme 44. The proposed allylmetal reagent

We envisioned the development of a new allylic metal reagent of type **90** with masked ketone moiety which would allow the generation of product **89** in only two steps (Scheme 44).

3.5.2 Preparation of Allylic Chlorides

Inspired by the need of the mentioned new allylic metal reagent, we prepared the starting allylic chlorides **92a** and **92b** according to literature.[96] Thus, the treatment of cyclohexanone with LDA and TESCl at -78 °C within 5 h led to (cyclohex-1-en-1-yloxy)triethylsilane (**91a**) in 92% yield. Its reaction with NCS at 0 °C furnished the expected allylic chloride **92a** in 46% yield. Similarly, starting from 1-benzylpiperidin-4-one, the corresponding 1-benzyl-3-chloro-4-((triethylsilyl)oxy)-1,2,3,6-tetrahydropyridine (**92b**) was obtained in 40% yield (Scheme 45).



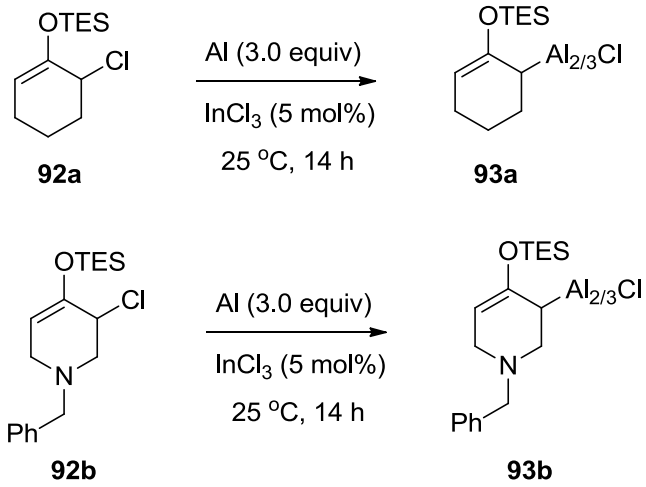
Scheme 45. Preparation of starting allylic chlorides **92a** and **92b**.

3.5.3 Preparation of Allylic Aluminum Reagents and Their Addition to Aldehydes and Ketones

To our delight, using the well-established method for the preparation of allylic aluminum reagents developed in our laboratories,[97] ((6-chlorocyclohex-1-en-1-yl)oxy) triethylsilane (**92a**) reacts with Al-powder (3.0 equiv) and $InCl_3$ (5 mol%) in THF at 25 °C within 14 h and provides the corresponding allylic aluminum reagent **93a** in 70% yield. Also, the preparation of allylic aluminum reagent **93b** can be achieved

[96] a) T. V. Lee, J. Toczek, *Tetrahedron Lett.* **1982**, *23*, 2917; b) G. F. Hambly, T. H. Chan, *Tetrahedron Lett.* **1986**, *27*, 2563.
[97] Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed*. **2010**, *49*, 8516.

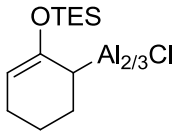
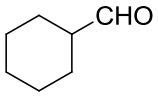
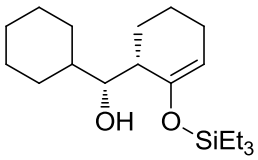
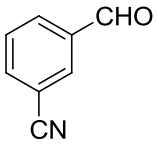
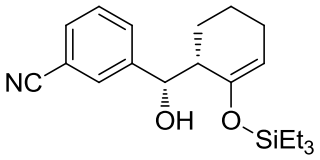
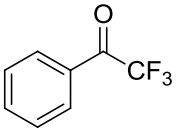
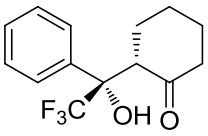
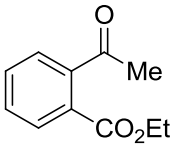
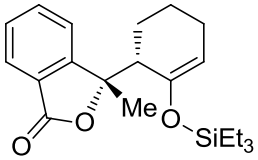
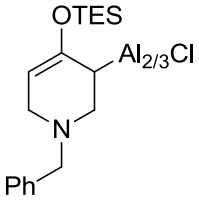
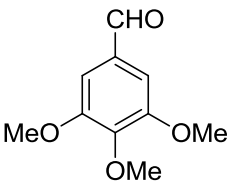
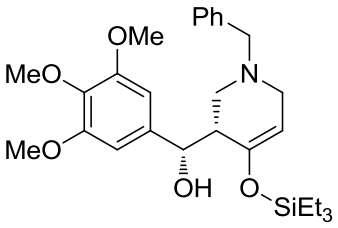
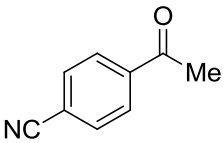
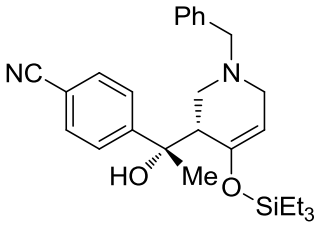
starting from 1-benzyl-3-chloro-4-((triethylsilyl)oxy)-1,2,3,6-tetrahydropyridine **92b** using Al-powder (3.0 equiv) and $InCl_3$ (5 mol%) in 14 h at 25 °C (70% yield, Scheme 46).

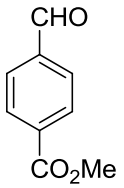
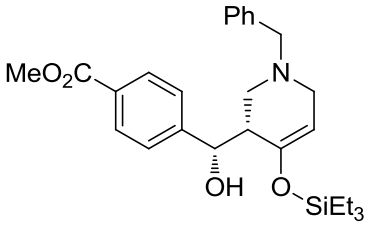
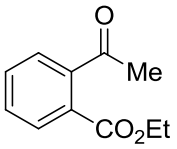
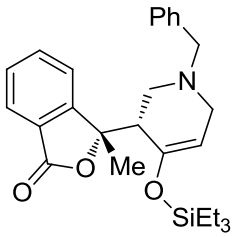


Scheme 46. Preparation of allylic aluminum reagents **93a** and **93b**.

The reaction of the allylic aluminum reagent **93a** with cyclohexanecarboxaldehyde (**94a**, 0.7 equiv, -78 °C, 2 h) afforded the homoallylic alcohol **95a** in 75% yield (dr > 90:10, entry 1, Table 6). Various aromatic aldehydes and ketones (**94b-d**) react with the allylic aluminum reagent **93a**, leading to the corresponding alcohols (**95b-d**) in 57-76% yield (dr > 90:10, entries 2-4). In addition, the allylic aluminum reagent **93b** reacted with aldehydes and methyl ketones such as 3,4,5-trimethoxybenzaldehyde (**94e**, 0.7 equiv), 4-acetylbenzonitrile (**94f**, 0.7 equiv) or methyl 4-formylbenzoate (**94g**, 0.7 equiv), providing the corresponding alcohols **95e-j** in 61-70% yield, with high diastereoselectivities (dr > 93:7, entries 5-7, Table 6). Interestingly, the allylic aluminum reagent **93b** reacted with ethyl 2-acetylbenzoate (**94f**, 0.7 equiv) giving the homoallylic lactone **95h** in 70% yield with high diastereoselectivity (dr > 97:3, entry 8, Table 6).

Table 6. Diastereoselective preparation of homoallylic alcohols and lactones of type **95** using allylic aluminum reagents of type **93**.

entry	aluminum reagent[a]	carbonyl electrophile[b]	product[c, d]
			
1	**93a**	**94a**	**95a**: 72%, dr: 90:10
			
2	**93a**	**94b**	**95b**: 76%, 93:7
			
3	**93a**	**94c**	**95c**: 57%, dr: 95:5
			
4	**93a**	**94d**	**95d**: 63%, dr: 90:10
			
5	**93b**	**94e**	**95e**: 62%, dr: 95:5
			
6	**93b**	**94f**	**95f**: 70%, dr: 93:7

			
7	**93b**	**94g**	**95g**: 61%, dr: 95:5
			
8	**93b**	**94d**	**95h**: 70%, dr: 97:3

[a] All reactions were carried out on a 1-4 mmol scale. [b] 0.6-0.7 equivalents of electrophiles have been used. [c] Isolated yield of analytically pure products. [d] The diastereoselectivities were determined by ^{1}H-NMR analysis.

3.5.4 Conclusion

Preliminary study showed that these special allylic aluminum reagents can be conveniently prepared using aluminum powder in the presence of catalytic amounts of $InCl_3$ from allylic chlorides under mild conditions. The addition to various functionalized aldehydes or ketones affords polyfunctionalized homoallylic alcohols, bearing adjacent tertiary and quaternary centers with good diastereoselectivity. The application of this new allylic aluminum reagent and the subsequent Mukaiyama reaction of the resulting polyfunctionalized homoallylic alcohols are ongoing in our laboratory.

4. Preparation of Functionalized Organomanganese(II) Reagents by Direct Insertion of Manganese to Aromatic and Benzylic Halides

4.1 Introduction

Functionalized organometallics are versatile reagents for forming carbon-carbon bonds reactions in organic synthesis.[1, 3a] Organomanganese reagents,[45] due to their excellent chemoselectivity, low toxicity and good availability, have found widespread applications for performing chemoselective 1,2-additions, [98] acylations, [99] cross-coupling reactions, [100] as well as copper-catalyzed conjugate additions. [101] Despite these advantages, the preparation methods of organomanganese(II) reagents are limited. Most organomanganese(II) reagents are prepared by transmetallation from the corresponding organolithium or organomagnesium reagents with manganese halides.[46] Recently, a directed manganation using $TMP_2Mn{\cdot}2LiCl$ allows the generation of the functionalized arylmanganese compounds by a directed deprotonation.[51] Moreover, organomanganese(II) reagents are difficult to generate by an oxidative addition to organic halides using commercial manganese powder due to the passivation exhibited by commercial Mn. To date, commercial manganese powder

[98] a) Y. Ahn, W. W. Doubleday, T. Cohen, *Synth. Commun.* **1995**, *25*, 33; b) T. Kauffmann, H. Kieper, H. Pieper, *Chem. Ber.* **1992**, *125*, 899; c) G. Cahiez, B. Figadère, *Tetrahedron Lett.* **1986**, *27*, 4445; d) M. T. Reetz, K. Rölfing, N. Griebenow, *Tetrahedron Lett.* **1994**, *35*, 1969; e) C. Boucley, G. Cahiez, S. Carini, V. Cerè, M. Comes-Franchini, P. Knochel, S. Pollicino, A. Ricci, *J. Organomet. Chem.* **2001**, *624*, 223.

[99] a) G. Cahiez, A. Masuda, D. Bernard, J. F. Normant, *Tetrahedron Lett.* **1976**, *36*, 3155; b) K. Ritter, M. Hanack, *Tetrahedron Lett.* **1985**, *26*, 1285; c) G. Cahiez, B. Laboue, *Tetrahedron Lett.* **1989**, *30*, 7369; d) G. Cahiez, D. Luart, F. Lecomte, *Org. Lett.* **2004**, *6*. 4395.

[100] a) G. Cahiez, F. Lepifre, P. Ramiandrasoa, *Synthesis* **1999**, 2138; b) M. Rueping, W. Ieawsuwan, *Synlett* **2007**, 247; c) E. Riguet, M. Alami, G. Cahiez, *J. Organomet. Chem.* **2001**, *624*, 376; d) A. Leleu, Y. Fort, R. Schneider, *Adv. Synth. Catal.* **2006**, *348*, 1086; e) G. Cahiez, S. Marquais, *Tetrahedron Lett.* **1996**, *37*, 1773; f) J. G. Donkervoort, J. L. Vicario, J. T. B. H. Jastrzebski, R. A. Gossage, G. Cahiez, G. van Koten, *J. Organomet. Chem.* **1998**, *558*, 61; g) H. Kakiya, R. Inoue, H. Shinokubo, K. Oshima, *Tetrahedron Lett.* **1997**, *38*, 3275.

[101] a) G. Cahiez, M. Alami, *Tetrahedron* **1989**, *45*, 4163; b) S. Marquais, M. Alami, G. Cahiez, *Org. Synth.* **1995**, *72*, 135.

inserts only into reactive organic halides such as allylic halides or α-halogenoesters.[47, 48, 49] By using highly activated Mn (*Rieke*-Mn), the insertion to aromatic and benzylic halides can be achieved.[102, 50] Recently, we have reported that LiCl facilitates the insertion of various metals (Zn,[103] Mg,[104] In[105]). By adding small amounts of a metallic salt like $InCl_3$ and $PbCl_2$ as pioneered by *Takai*,[106] we were able to prepare functionalized aromatic, benzylic and allylic aluminum reagents under mild conditions.[107]

We envisioned that commercial manganese activated by adding suitable metallic salts could be insert into aromatic or benzylic halides affording the corresponding organomanganese reagents.

4.2 Optimization of The Reaction Conditions

An extensive sceening of various metallic salts on the insertion of commercial manganese powder(3.0 equiv) to 1-chloro-3-iodobenzene (**96**) in the presence of LiCl (1.5 equiv) in THF was undertaken. Preliminary experiments showed that several additives such as $TiCl_4$, $ZrCl_4$, CeF_3 and $ZnBr_2$ provided a trace of arylmanganese reagent **97** (entries 1-4, Table 7). The addition of only $PbCl_2$ or only $InCl_3$ led to the corresponding arylmanganese species **97** in 10-15% yield (entries 5-6). The yield of the arylmanganese species **97** can be improved by the addition of both metallic salts (entries 7-10). The combination of $InCl_3$ (2.5 mol%) and $PbCl_2$ (2.5 mol%) allows the generation of the arylmanganese species **97** (43% yield, entry 7).

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[102] a) T. Hiyama, M. Obayashi, A. Nakamura, *Organometallics* **1982**, *1*, 1249; b) A. Fürstner, H. Brunner, *Tetrahedron Lett.* **1996**, *37*, 7009; c) S.-H. Kim, M. V. Hanson, R. D. Rieke, *Tetrahedron Lett.* **1996**, *37*, 2197; d) S.-H. Kim, R. D. Rieke, *Synth. Commun.* **1998**, *28*, 1065; e) R. D. Rieke, S.-H. Kim, X. Wu, *J. Org. Chem.* **1997**, *62*, 6921; f) H. Kakiya, S. Nishimae, H. Shinokubo, K. Oshima, *Tetrahedron* **2001**, *57*, 8807.

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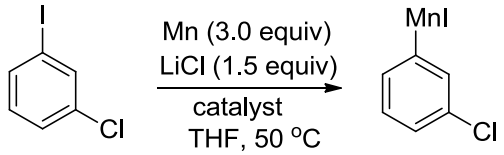
Table 7. Catalyst optimization of insertion reaction of commercial manganese powder to aryliodide.



96 **97**

entry	catalyst	yield of **97**[a]
1	$TiCl_4$ (10 mol%)	trace
2	$ZrCl_4$ (10 mol%)	trace
3	CeF_3 (10 mol%)	trace
4	$ZnBr_2$ (10 mol%)	8%
5	$PbCl_2$ (5 mol%)	10%
6	$InCl_3$ (5 mol%)	15%
7	$InCl_3$ (2.5 mol%), $PbCl_2$ (2.5 mol%)	43%
8	$InCl_3$ (2.5 mol%), $BiCl_3$ (2.5 mol%)	26%
9	$InCl_3$ (2.5 mol%), $SnCl_2$ (2.5 mol%)	16%
10	$ZnCl_2$ (2.5 mol%), $PbCl_2$ (2.5 mol%)	33%

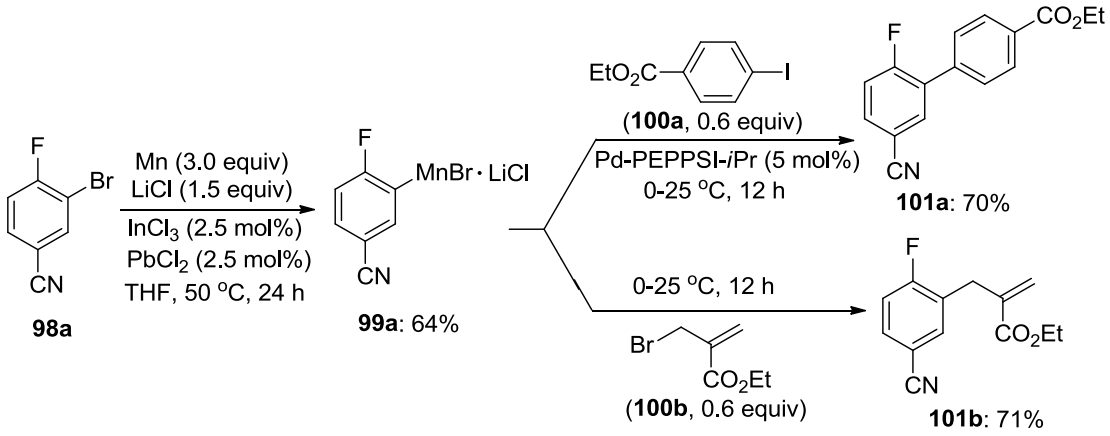
[a] The yield was determined by GC.

Next, we investigated the scope of this insertion reaction of commercial mangenese powder to organic halides.

4.3 Preparation of Aromatic Manganese Reagents

The reaction of 3-bromo-4-fluorobenzonitrile (**98a**) in THF with manganese powder (3 equiv) in the presence of LiCl (1.5 equiv), 2.5% $InCl_3$ and 2.5% $PbCl_2$ at 50 °C was complete within 24 h and led to the corresponding arylmanganese reagent (**99a)** in 64% yield. Subsequent Negishi cross-coupling with ethyl 4-iodobenzoate (**100a**, 0.6 equiv) in the presence of Pd-PEPPSI-*i*Pr (5 mol%) afforded the biphenyl derivative **101a** in 70% yield. Additionally, a smooth allylic substitution of **99a** with ethyl (2-bromomethyl)acrylate (**100b**, 0.6 equiv) furnished the acrylate **101b** in 71% yield (Scheme 47). Both catalytic amounts of $InCl_3$ and $PbCl_2$ and a stoichiometric amount of LiCl are required for an efficient insertion reaction. By using only $InCl_3$ or only $PbCl_2$, only a trace of the arylmanganese species is formed. This salt combination

allows a unique activation of the Mn-surface.

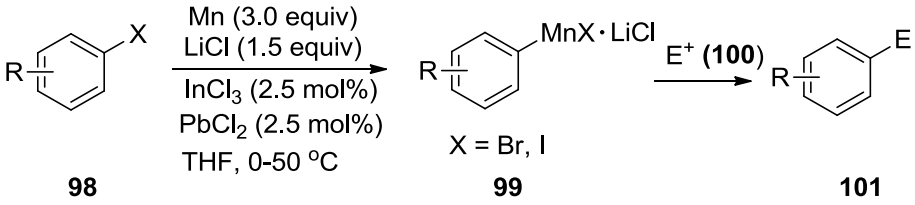


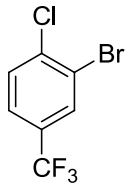
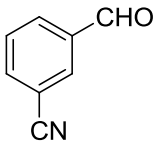
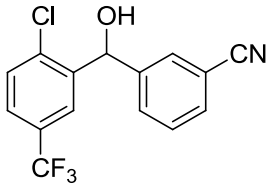
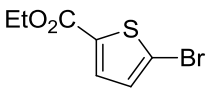
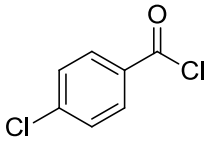
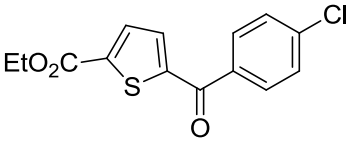
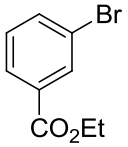
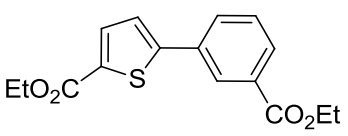
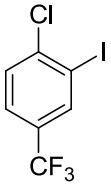
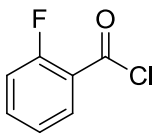
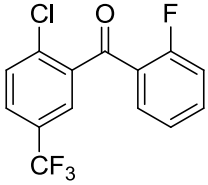
Scheme 47. Preparation of (5-cyano-2-fluorophenyl)manganese(II) bromide (**99a**) and subsequent reaction with electrophiles.

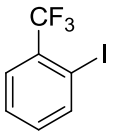
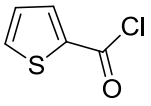
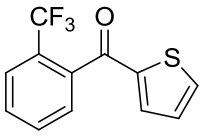
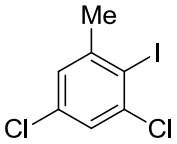
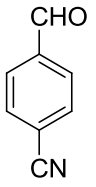
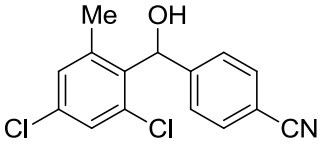
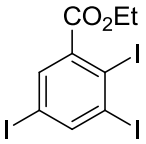
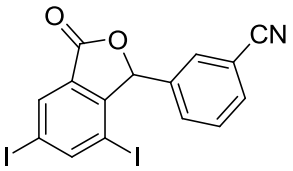
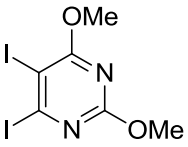
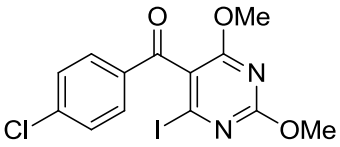
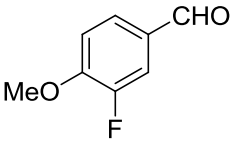
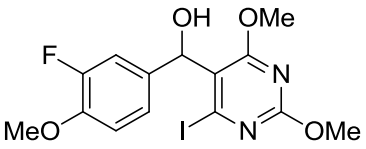
Similarly, 2-bromo-1-chloro-4-(trifluoromethyl)benzene (**98b**) was converted to the corresponding organomanganese reagent **99b** (50 °C, 24 h, 72% yield). It readily underwent a 1,2-addition to 3-formylbenzonitrile (**100c**) providing the functionalized alcohol **101c** in 73% yield (entry 1, Table 8). Manganese powder inserted into the functionalized thiophene (**98c**) in the presence of LiCl (1.5 equiv), 2.5% $InCl_3$ and 2.5% $PbCl_2$ between 0-25 °C within 12 h giving the arylmanganese reagent **99c** (70% yield). It was converted to the functionalized ketone derivative **101d** (68% yield) and the biaryl derivative **101e** (77% yield) respectively by an acylation reaction with 4-chlorobenzoyl chloride (**100d**, 0.6 equiv) and a Pd-catalyzed cross-coupling reaction with ethyl 3-bromobenzoate (**100e**, 0.6 equiv) (entries 2-3). In the same manner, various substituted aryl iodides such as **98d-f**, bearing substituents such as chloride or a trifluoromethyl group, were readily converted to the corresponding arylmanganese reagents at 25 °C within 12-24 h. Subsequent acylation and 1,2-addition afforded the expected polyfunctionalized adducts **101f-h** in 72-85% yield (entries 4-6). Remarkably, manganese powder chemoselectively inserted into ethyl 2,3,5-triiodobenzoate (**98g**), yielding (2-(ethoxycarbonyl)-4,6-diiodophenyl)manganese(II) iodide (**99g**). Its treatment with aldehyde **100c** (0.6 equiv) afforded the desired lactone **101i** in 68% yield (entry 7). Moreover, heterocyclic

4,5-diiodo-2,6-dimethoxypyrimidine (**98h**) was converted selectively to the organomanganese reagent (**99h**) which underwent acylation and 1,2-addition giving the functionalized benzophenone derivative **101j** and alcohol derivative **101k** in 71-78% yield (entries 8-9).

Table 8. Functionalized aromatic manganese(II) halides obtained by direct insertion of commercial manganese powder into aromatic halides and subsequent quenching with electrophiles



entry	substrate	conditions (temperature, time)	electrophile	product (Yield, %)[a]
		50 °C 24 h		
1	**98b**		**100c**[b]	**101c**: 73%
		0-25 °C 12 h		
2	**98c**		**100d**[c]	**101d**: 68%
				
3	**98c**		**100e**[c]	**101e**: 77%[d]
		25 °C 18 h		
4	**98d**		**100f**[b]	**101f**: 85%

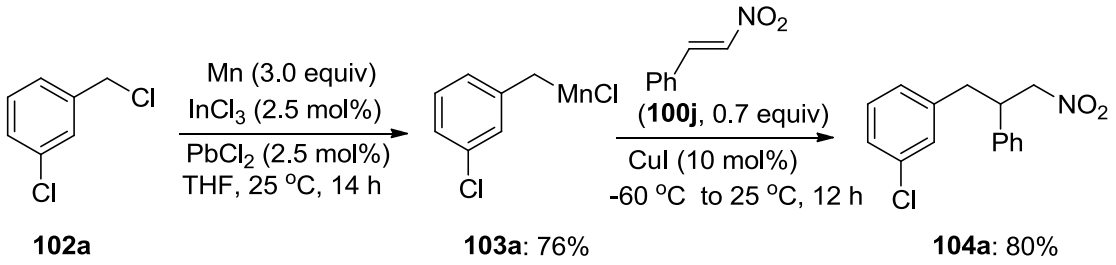
		25 °C 23 h		
5	**98e**		**100g**[b]	**101g**: 74%
		25 °C 12 h		
6	**98f**		**100h**[b]	**101h**: 72%
		25 °C 16 h		
7	**98g**		**100c**[c]	**101i**: 68%
		0-25 °C 12 h		
8	**98h**		**100d**[c]	**101j**: 71%
				
9	**98h**		**100i**[c]	**101k**: 78%

[a] Isolated yield of analytically pure product. [b] 0.7 Equivalents of electrophile were used. [c] 0.6 Equivalents of electrophile were used. [d] Obtained after cross-coupling with ethyl 3-bromobenzoate (**100e**) in the presence of Pd-PEPPSI-*i*Pr (5 mol%).

4.4 Preparation of Benzylic Manganese Reagents

In the case of benzylic chlorides or bromides, a smooth manganese insertion occurs at 25 °C in the presence of 2.5% $InCl_3$ and 2.5% $PbCl_2$. These insertions proceed best in the absence of LiCl since this salt favors extensive homo-coupling reactions. Thus, the reaction of 1-chloro-3-(chloromethyl)benzene (**102a**) with Mn powder (3.0 equiv) in the presence of 2.5% $InCl_3$ and 2.5% $PbCl_2$ afforded the benzylic manganese reagent **103a** within 14 h at 25 °C. A Cu-catalyzed 1,4-addition reaction with

nitrostyrene (**100j**, 0.7 equiv) provided the nitro derivative (**104a**) in 80% yield (Scheme 48).

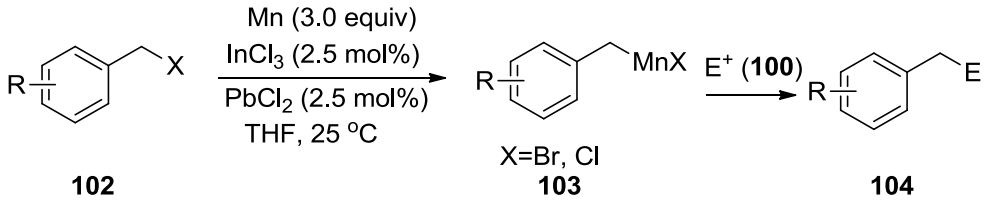


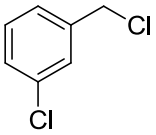
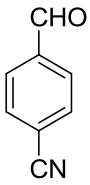
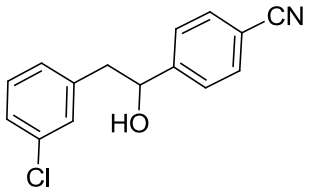
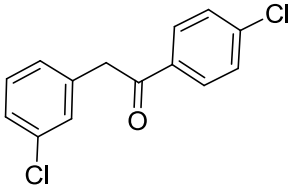
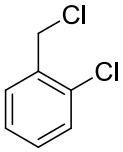
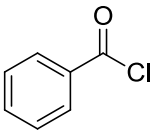
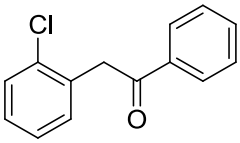
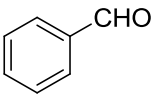
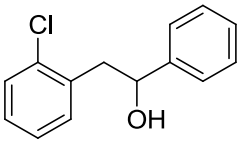
Scheme 48. Preparation of (3-chlorobenzyl)manganese(II) chloride (**103a**) and its 1,4-addition to nitrostyrene (**100j**)

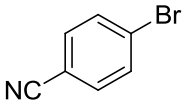
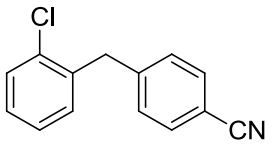
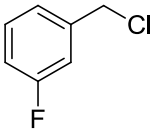
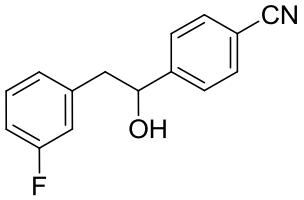
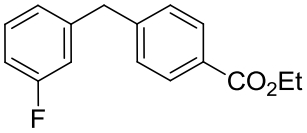
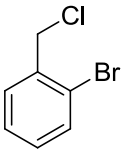
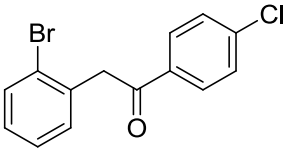
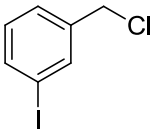
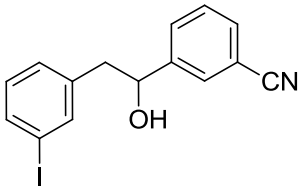
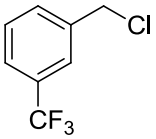
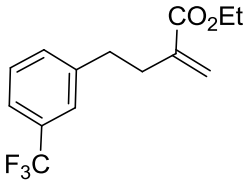
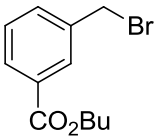
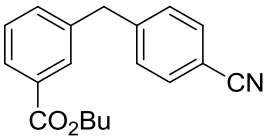
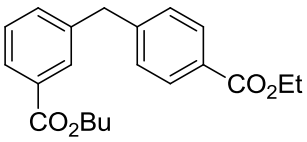
A smooth addition of the benzylic manganese reagent **103a** to the benzaldehyde **100h** (0.7 equiv) generated the functionalized alcohol derivative **104b** in 73% yield (entry 1, Table 9). Also, the treatment of the benzylic manganese reagent **103a** with 4-chlorobenzoyl chloride (**100d**, 0.7 equiv) produced the ketone derivative **104c** in 75% yield (entry 2). Several functionalized benzylic substrates (**102b-f**) readily underwent a manganese insertion in the presence of 2.5% $InCl_3$ and 2.5% $PbCl_2$ as catalysts, followed by quenching with various electrophiles, affording the desired products **104d-k** in 66-88% yield (entries 3-10). However, the manganese insertion into benzylic chlorides bearing an ester and a cyano group led to unsatisfactory yields. In comparison, by using benzylic bromides, a smooth insertion proceeds at 25 °C allowing the direct preparation of ester- or cyano-functionalized benzylmanganese bromides. For instance, the reaction of butyl 3-(bromomethyl)benzoate (**102g**) with Mn powder (3 equiv) in the presence of 2.5% $InCl_3$ and 2.5% $PbCl_2$ furnished the benzylic manganese bromide **103g** within 17 h at 25 °C. A Pd-catalyzed cross-coupling with 4-bromobenzonitrile (**100m**, 0.6 equiv) or ethyl 4-iodobenzoate (**100a**, 0.6 equiv) generated the expected products **104l-m** in 67-71% yield (entries 11-12). Similarly, 3-(bromomethyl)benzonitrile (**102h**) was converted to the corresponding benzylic manganese reagent **103h**, followed by an allylic substitution with ethyl (2-bromomethyl)acrylate (**100b**, 0.6 equiv), producing the allylated product

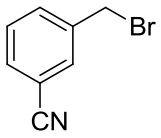
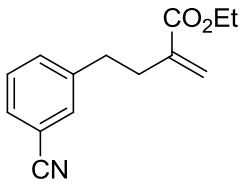
104n in 45% yield (entry 13).

Table 9. Functionalized benzylmanganese(II) halides obtained by direct insertion of commercial manganese powder into benzylic halides and subsequent reaction with electrophiles



entry	substrate	conditions (temperature, time)	electrophile	product (yield, %)[a]
1	 **102a**		 **100h**[b]	 **104b**: 73%
2	**102a**		**100d**[b]	 **104c**: 75%
3	 **102b**	25 °C 16 h	 **100k**[b]	 **104d**: 88%
4	**102b**		 **100l**[b]	 **104e**: 74%

				
5	**102b** 	25 °C 16 h	**100m**[b]	**104f**: 84%[c] 
6	**102c**		**100h**[b]	**104g**: 75% 
7	**102c** 	25 °C 13 h	**100a**[b]	**104h**: 80%[d] 
8	**102d** 	25 °C 16 h	**100d**[b]	**104i**: 67% 
9	**102e** 	25 °C 24 h	**100c**[b]	**104j**: 70% 
10	**102f** 	25 °C 17 h	**100b**[b]	**104k**: 70% 
11	**102g**		**100l**[e]	**104l**: 71%[f] 
12	**102g**		**100a**[e]	**104m**: 67%[g]

		25 °C 17 h		
13	**102h**		**100b**[e]	**104n**: 45%

[a] Isolated yield of analytically pure product. [b] 0.7 Equivalents of electrophile were used. [c] Obtained after cross-coupling with 4-bromobenzonitrile (**100m**) in the presence of $Pd(PPh_3)_4$ (10 mol%). [d] Obtained after cross-coupling with ethyl 4-iodobenzoate (**100a**) in the presence of $Pd(PPh_3)_4$ (10 mol%). [e] 0.6 Equivalents of electrophile were used. [f] Obtained after cross-coupling with ethyl 4-bromobenzonitrile (**100m**) in the presence of Pd-PEPPSI-*i*Pr (5 mol%). [g] Obtained after cross-coupling with ethyl 4-iodobenzoate (**100a**) in the presence of Pd-PEPPSI-*i*Pr (5 mol%).

4.5 Conclusion

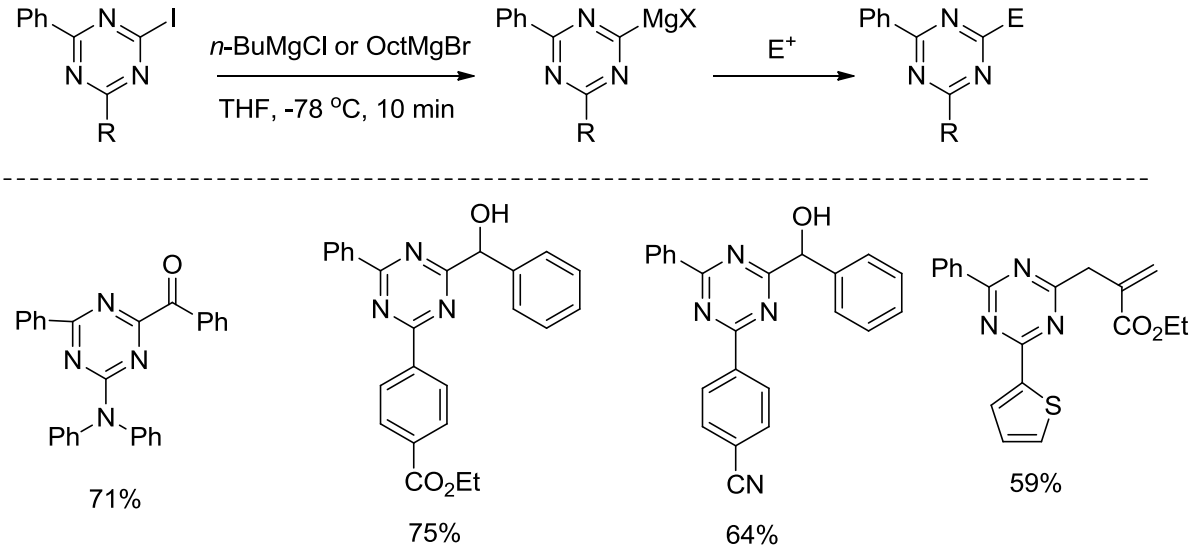
In summary, we have developed a convenient method for the preparation of functionalized arylmanganese halides and benzylic manganese halides by direct insertion of commercial manganese powder into aromatic and benzylic halides in the presence of 2.5% $InCl_3$ and 2.5% $PbCl_2$. These organomanganese reagents smoothly undergo 1,2-addition, acylation, allylic substitution, Pd-catalyzed cross-coupling, and copper-catalyzed conjugate addition with various electrophiles affording the desired products in good yields.

5. Summary and outlook

This work includes three topics: the first part was focused on the construction of heterocycles such as 1,3,5-triazines and indazoles by using organomagnesium or organozinc reagents. Furthermore, the addition of allylic aluminum reagents to aldehydes or ketones in a diastereoselective manner was investigated in detail. Finally, we developed a new method for the preparation of aromatic and benzylic manganese reagents by a direct insertion of commercial manganese powder to aromatic or benzylic halides.

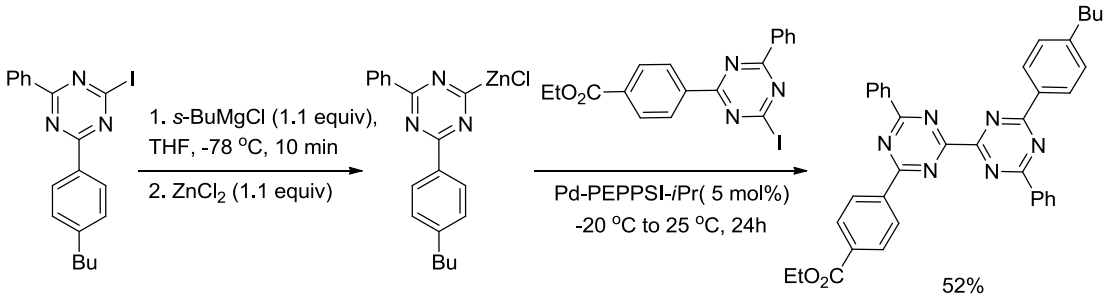
5.1 Preparation of 2-Magnesiated 1,3,5-Triazines and Trimeric and Dimeric Derivatives

A convenient method for the preparation of stable mono- and bis(1,3,5-triazinyl)magnesium reagents has been developed. This kind of Grignard reagents having good compatibility with a variety of sensitive functional groups react with aldehydes, acid clorides, and allylic halides, furnishing a wide range of new functionalized fully substituted 1,3,5-triazine derivatives (Scheme 49).



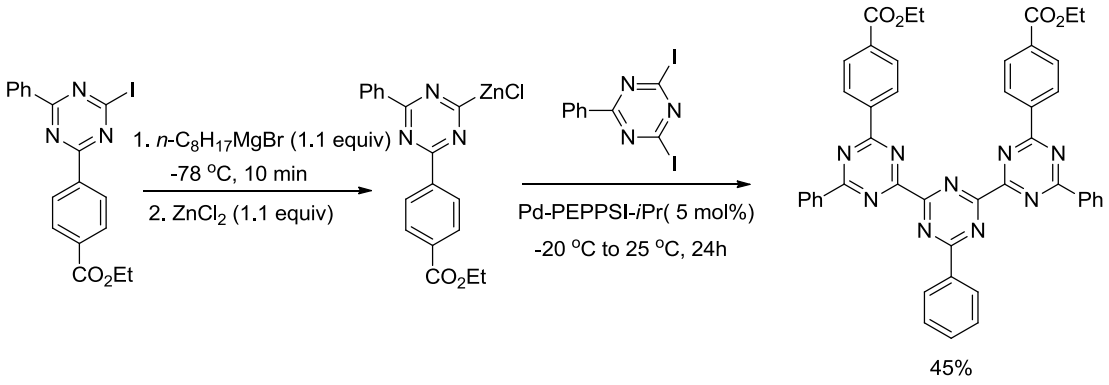
Scheme 49. Preparation of 1,3,5-triazine derivatives using 2-magnesiated 1,3,5-triazines.

2-Magnesiated 1,3,5-triazine has been utilized successfully to synthesize a dimeric 1,3,5-triazine derivative which may exhibit useful opto-electronic properties (Scheme 50).



Scheme 50. Preparation of dimeric 1,3,5-triazine derivative.

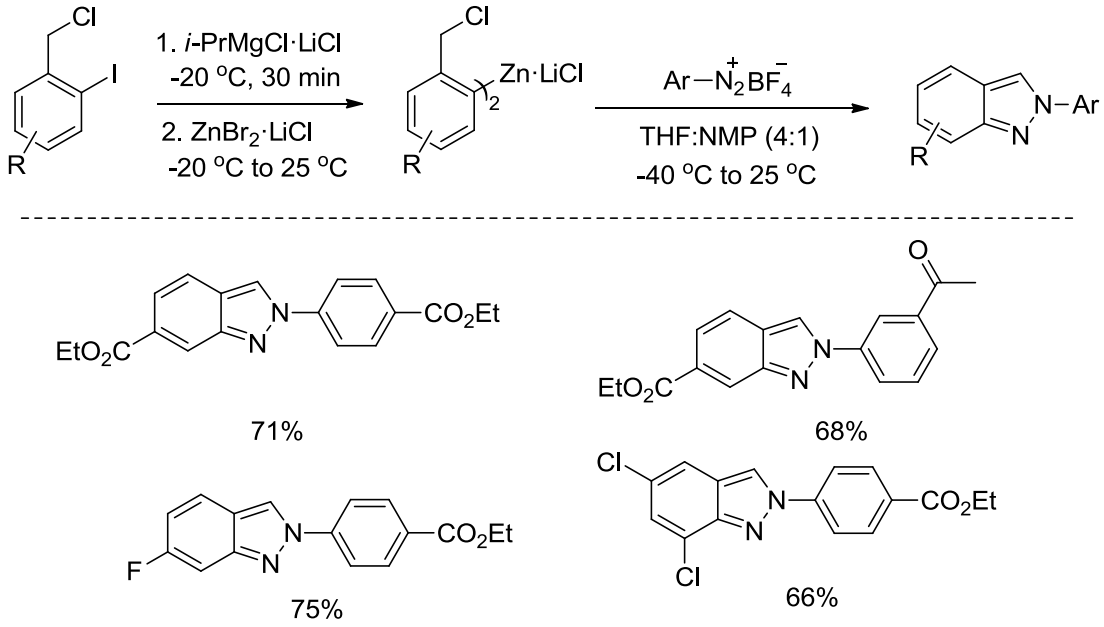
A remarkable preparation of a trimeric 1,3,5-triazine derivative was performed (Scheme 51).



Scheme 51. Preparation of trimeric 1,3,5-triazine derivative.

5.2 Preparation of Functionalized Indazoles

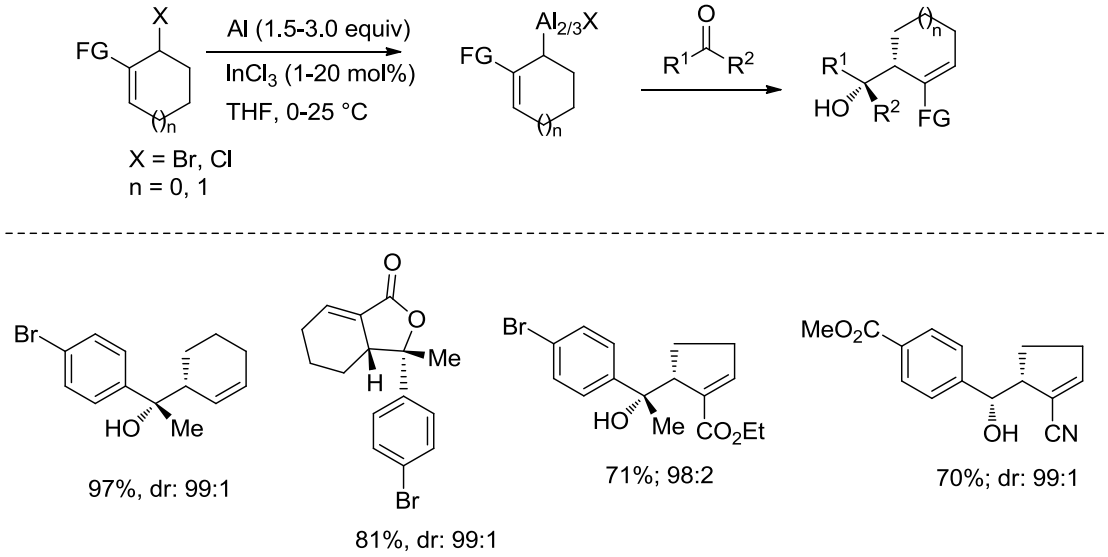
We have developed a short and convenient synthetic route to 2-aryl-2*H*-indazoles by using highly functionalized arylzinc reagents. This reaction displays an excellent functional group tolerance (Scheme 52).



Scheme 52. Preparation of functionalized indazoles.

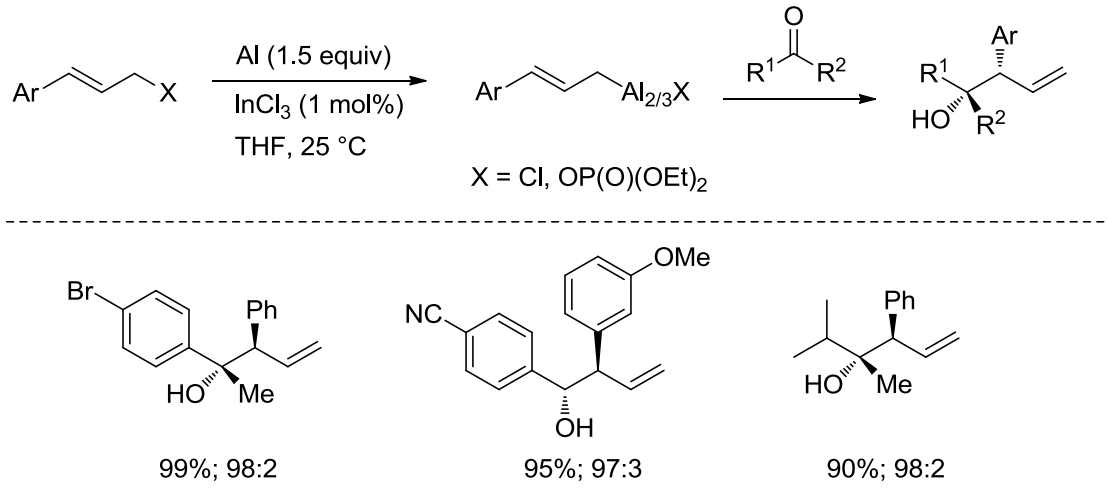
5.3 Diastereoselective Synthesis of Homoallylic Alcohols

A practical protocol for the generation of allylic aluminum reagents was developed. In addition, the addition to various functionalized aldehydes or ketones affords polyfunctionalized homoallylic alcohols, bearing adjacent tertiary and quaternary centers with good diastereoselectivity (Scheme 53).



Scheme 53. Diastereoselective synthesis of homoallylic alcohols using functionalized allylic aluminum reagents.

The scope of this method was extended to cinnamyl substrates. Cinnamyl aluminum reagents can be conveniently prepared using aluminum powder in the presence of catalytic amounts of $InCl_3$ and their addition to carbonyl compounds showed also high diastereoselectivities (Scheme 54)

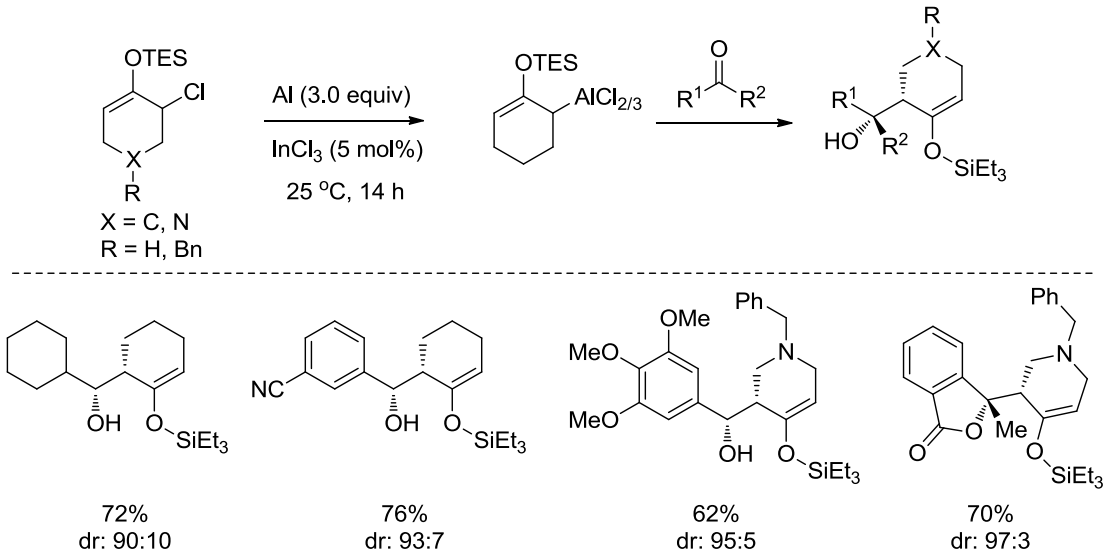


Scheme 54. Diastereoselective addition of cinnamyl aluminum reagents to carbonyl compounds

The diastereoselectivity can be best rationalized by a chair-like transition state and the structures of the homoallylic alcohols have been proven by X-ray or NOESY NMR analysis.

5.4 Extension of Functionalized Allylic Aluminum Reagents

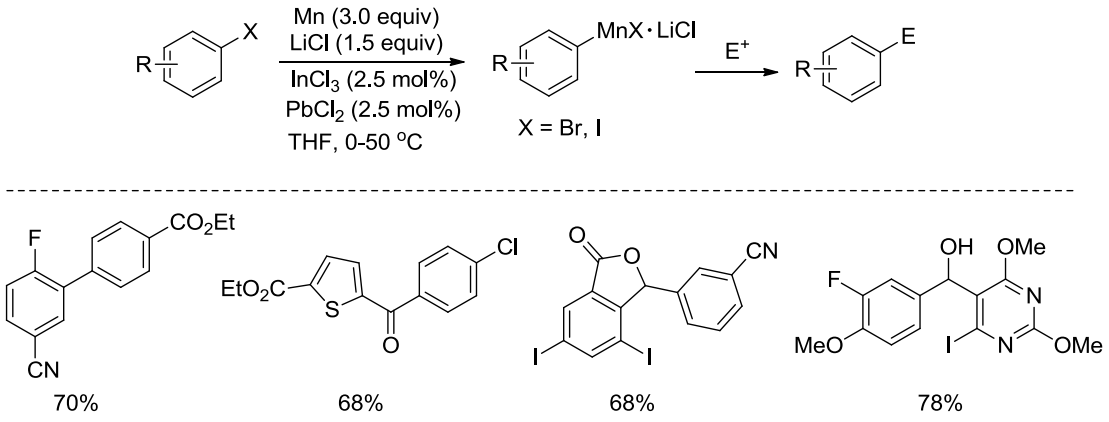
The allylic aluminum reagents can be conveniently prepared using aluminum powder in the presence of catalytic amounts of $InCl_3$ from allylic chlorides under mild conditions. The addition to various functionalized aldehydes or ketones affords polyfunctionalized homoallylic alcohols, bearing adjacent tertiary and quaternary centers with good diastereoselectivities (Scheme 55).



Scheme 55. Diastereoselective preparation of homoallylic alcohols.

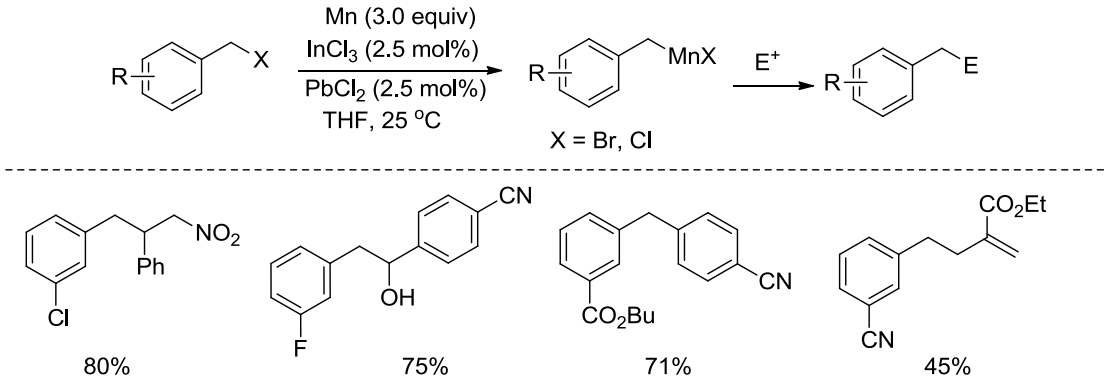
5.5 Preparation of Functionalized Organomanganese(II) Reagents by Direct Insertion of Manganese to Aromatic and Benzylic Halides

We have developed a convenient method for the preparation of functionalized arylmanganese halides by direct insertion of commercial manganese powder into aromatic halides in the presence of LiCl with both 2.5% $InCl_3$ and 2.5% $PbCl_2$ as catalysts. These organomanganese reagents smoothly undergo 1,2-addition, acylation, allylic substitution, Pd-catalyzed cross-coupling, and copper-catalyzed conjugate addition with various electrophiles affording the desired products in good yields (Scheme 56).



Scheme 56. Preparation of functionalized arylmanganese halides and their reactions with electrophiles.

The extension to the preparation of benzylic manganese halides was performed. Benzylic manganese reagents can be obtained by direct insertion of commercial manganese powder into aromatic halides in the presence of 2.5% $InCl_3$ and 2.5% $PbCl_2$ (Scheme 57).



Scheme 57. Preparation of functionalized benzylic manganese halides.

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.

1.1. Solvents

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

CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2.

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

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

Et_2O was predried over CaH_2 and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

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

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

Triethylamine was dried over KOH and distilled.

Solvents for column chromatography were distilled prior to use.

1.2. 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.

Preparation of Organometallic Reagents:

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

***i*PrMgCl** solution in THF was purchased from Chemetall

PhMgCl solution in THF was purchased from Chemetall

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

Zinc reagents were prepared according to: (a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; (b) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107; (c) S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, P. *J. Org. Chem.* **2008**, *73*, 7380.

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

Preparation of the reagent OctMgBr (1 M in THF)

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

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

A dry and argon-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with $ZnCl_2$ (20.45 g, 0.15 mol). The salt was heated to 140 °C under high vacuum for 6 h. After cooling to 25 °C, dry THF (150 mL) was added slowly and stirring was continued until the salt was dissolved (4 h) forming a clear colourless solution, which was kept over molecular sieves (4 Å).

Preparation of $ZnBr_2$·LiCl solution (1 M in THF)

A dry and argon-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with $ZnBr_2$ (33.81 g, 0.15 mol) and LiCl (6.35 g, 0.15 mol). The salts were heated to 140 °C under high vacuum for 6 h. After cooling to 25 °C, dry THF (150 mL) was added slowly and stirring was continued until the salts were dissolved (4 h) forming a clear colourless solution, which was kept over molecular sieves (4 Å).

1.3. Content Determination of Organometallic Reagents

Organzinc and organomagnesium reagents were titrated against I_2 in a 0.5 M LiCl solution in THF according to: A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.
Organolithium reagents were titrated against menthol using 1,10-phenanthroline as indicator in THF according to: H.-S. Lin, L. A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.

1.4. Chromatography

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from Merck.
Thin layer chromatography was performed using SiO_2 pre-coated aluminium plates (Merck 60, F-254). The chromatograms were examined under 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).

1.5. 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 $CHCl_3$ (dH: 7.26, dC: 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).

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

2.1 Preparation of 1,3,5-Triazine Derivatives.

2.1.1 Typical Procedures (TP)

TP1: Typical procedure for the preparation of iodo-1,3,5-triazine derivatives (61a-k).

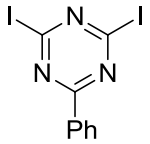
To a solution of 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 2.0 mmol) and $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol) in THF (20 mL) in a dry and argon-flushed Schlenk-flask was added dropwise a solution of organozinc reagent (1.2 equiv) in THF prepared according to literature procedure at -10 °C followed by continously stirring for 2 h. After stirring for 13 h at 25 °C, the reaction mixture was quenched with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography affording the corresponding iodo-1,3,5-triazines **61a-k**.

TP2: Typical procedure for the preparation of 1,3,5-triazin-2-ylmagnesium halides (62a-j)

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with iodo-1,3,5-triazine derivative (1 mmol) in THF (1 mL) followed by dropwise addition of a solution of alkylmagnesium reagent (1.1 equiv) at -78 °C. The reaction mixture was stirred for 10 min at the same temperature. Complete iodine-magnesium exchange was monitored by GC analysis of reaction aliquots, quenched with brine using tetradecane as internal standard.

2.1.2 Preparation of 2-Magnesiated 1,3,5-Triazines and 1,3,5-triazine derivatives.

Synthesis of 2,4-diiodo-6-phenyl-1,3,5-triazine (59).



A 50 mL round-bottom flask was charged with HI (57% solution, 20 mL). The solution was cooled to 5 °C and 2,4-dichloro-6-phenyl-1,3,5-triazine (4.52 g, 20 mmol) was added at the same temperature. The reaction mixture was allowed to warm up to 25 °C slowly and stirred for 48 h at 25 °C. The mixture was neutralized carefully with solid potassium carbonate, and decolorized with a saturated aqueous solution of sodium disulfite. Water was added until the solution was formed. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 50:1) afforded 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 5.5 g, 67%) as a white solid.

m. p. = 188.5-190.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.49-8.42 (m, 2H), 7.68-7.48 (m, 3H).

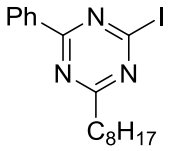
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.2, 139.6, 134.4, 132.3, 129.8, 128.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3065 (W), 2924 (W), 1469 (S), 1369 (M), 1237 (W), 1205 (M), 1170 (M), 1084 (W), 802 (W), 759 (S), 688 (M), 640 (W).

MS (EI, 70 eV): m/z (%) = 408 (M^+, 46), 282 (5), 281 (45), 230 (1), 229 (12), 178 (11). 130 (8), 129 (100), 128 (1), 103 (12), 77 (11).

HRMS (EI): Calcd. for $[C_9H_5I_2N_3]^+$: 408.8573; found: 408.8567.

Synthesis of 2-iodo-4-octyl-6-phenyl-1,3,5-triazine (61a).



According to **TP1**, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 820 mg) reacted with OctZnCl (0.89 M, 2.5 mL). Purification by flash column chromatography (silica gel, pentane / EtOAc = 100:1) afforded 2-iodo-4-octyl-6-phenyl-1,3,5-triazine (**61a**, 474

mg, 60%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.52-8.48 (m, 2H), 7.63-7.49 (m, 3H), 2.89 (t, *J* = 7.8 Hz, 2H), 1.93-1.82 (m, 2H), 1.44-1.26 (m, 10H), 0.91 (t, *J* = 7.1 Hz, 3H).

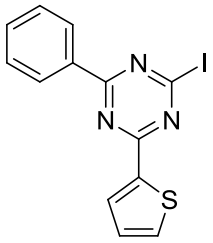
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 180.1, 170.7, 142.2, 134.0, 133.4, 129.3, 128.8, 38.7, 31.8, 29.3, 29.3, 29.2, 27.7, 22.7, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2923 (W), 2853 (W), 1600 (VW), 1517 (S), 1483 (VS), 1360 (W), 1236 (M), 1175 (W), 1117 (W), 1026 (W), 908 (W), 800 (M), 767 (M), 689 (S).

MS (EI, 70 eV): m/z (%) = 395 (M^+, 0.2), 309 (1), 297 (6), 267 (2), 129 (100), 103 (20), 77 (21).

HRMS (EI): Calcd. for $[C_{17}H_{22}IN_3]^+$: 395.0858; found: 395.0887.

Synthesis of 2-iodo-4-phenyl-6-(thiophen-2-yl)-1,3,5-triazine (61b).



According to **TP1**, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 820 mg, 2 mmol) reacted with thiophen-2-ylzinc(II) iodide (0.72 M, 3.3 mL, 2.4 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 50:1) afforded 2-iodo-4-phenyl-6-(thiophen-2-yl)-1,3,5-triazine (**61b**, 453 mg, 62%) as a white solid.

m. p. = 122.8-124.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.57-8.52 (m, 2H), 8.27 (dd, *J* = 3.8 Hz, 1.3 Hz, 1H), 7.69 (dd, *J* = 4.9 Hz, 1.3 Hz, 1H), 7.67-7.50 (m, 3H), 7.23 (dd, *J* = 4.9 Hz, 3.8 Hz, 1H).

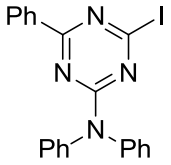
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.8, 166.9, 142.2, 139.7, 133.9, 133.8, 133.4, 133.1, 129.3, 128.8, 128.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2926 (VW), 2247 (VW), 1509 (S), 1474 (VS), 1426 (M), 1364 (M), 1246 (W), 1209 (W), 1086 (W), 1019 (W), 819 (W), 768 (S), 726 (M), 692 (M), 655 (W).

MS (EI, 70 eV): m/z (%) = 364 (M^+, 43), 321 (13), 281 (9), 275 (3), 273 (12), 239 (15), 238 (100), 229 (2), 137 (4), 136 (7), 135 (93), 129 (75), 108 (18), 77 (12).

HRMS (EI): Calcd. for $[C_{13}H_8IN_3S]^+$: 364.9484; found: 364.9477.

Synthesis of 4-iodo-N,N,6-triphenyl-1,3,5-triazin-2-amine (61c).



2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 409 mg, 1 mmol) reacted with lithium diphenylamide (1.1 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 50:1) afforded 4-iodo-N,N,6-triphenyl-1,3,5-triazin-2-amine (**1c**, 358 mg, 80%) as a white solid.

m. p. = 205.3-207.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.18 (d, *J* = 7.1 Hz, 2H), 7.51-7.35 (m, 7H), 7.34-7.27 (m, 6H).

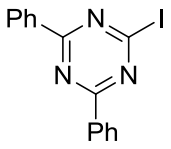
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.1, 163.6, 142.5, 141.5, 134.5, 132.7, 129.1, 128.9, 128.4, 127.5, 126.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3036 (VW), 1584 (W), 1471 (S), 1436 (S), 1371 (S), 1309 (W), 1225 (M), 1165 (M), 1024 (W), 995 (W), 773 (M), 747 (M), 692 (S), 636 (M).

MS (EI, 70 eV): m/z (%) = 451 (17), 450 (M^+, 83), 449 (27), 323 (29), 296 (16), 220 (100), 167 (53), 129 (27), 103 (21), 77 (74).

HRMS (EI): Calcd. for $[C_{21}H_{15}IN_4]^+$: 450.0341; found: 450.0333.

Synthesis of 2-iodo-4,6-diphenyl-1,3,5-triazine (61d).



A 50 mL round-bottom flask was charged with HI (57% solution, 20 mL). The solution was cooled to 5 °C and 2-chloro-4,6-diphenyl-1,3,5-triazine (2.67 g, 10

mmol) was added at the same temperature. The reaction mixture was allowed to warm up to 25 °C slowly and stirred for 48 h at 25 °C. The mixture was neutralized carefully with solid potassium carbonate, and decolorized with a saturated aqueous solution of sodium disulfite. Water was added until the solution was formed. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 100:1) afforded 2-iodo-4,6-diphenyl-1,3,5-triazine (**61d**, 2.69 g, 75%) as a white solid.

m. p. = 146.5-147.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.64-8.59 (m, 4H), 7.67-7.53 (m, 6H).

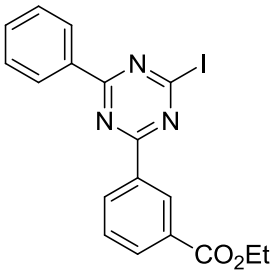
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.1, 142.6, 134.2, 133.4, 129.3, 128.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3043 (VW), 2924 (VW), 1587 (W), 1515 (VS), 1480 (VS),1432 (M), 1359 (S), 1314 (W), 1212 (W), 1067 (W),795 (M), 747 (S), 685 (S), 637 (M).

MS (EI, 70 eV): m/z (%) = 358 (M^+, 2), 232 (36), 207 (10), 130 (10), 129 (100), 127 (1), 126 (1), 103 (22), 77 (35).

HRMS (EI): Calcd. for $[C_{15}H_{10}IN_3]^+$: 358.9919; found: 358.9938.

Synthesis of ethyl 3-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzoate (61e).



According to **TP1**, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 820 mg, 2 mmol) reacted with (3-(ethoxycarbonyl)phenyl)zinc iodide (0.75 M, 3.2 mL, 2.4 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 20:1) afforded ethyl 3-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzoate (**61e**, 474 mg, 55%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.19 (t, *J* = 1.5 Hz, 1H), 8.75 (dt, *J* = 7.7 Hz,

1.5 Hz, 1H), 8.60-8.57 (m, 2H), 8.28-8.26 (m, 1H), 7.63-7.59 (m, 2H), 7.55-7.51 (m, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H).

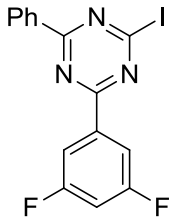
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.1, 170.2, 165.9, 142.7, 134.7, 134.1, 133.9, 133.6, 133.3, 131.3, 130.3, 129.4, 128.9, 128.8, 61.4, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3070 (VW), 2981 (VW), 1716 (S), 1511 (VS), 1490 (VS), 1430 (S), 1354 (M), 1260 (S), 1221 (S), 1149 (M), 1070 (M), 906 (S), 799 (M), 728 (VS), 686 (VS), 638 (M).

MS (EI, 70 eV): m/z (%) = 431 (M^+, 3), 385 (17), 305 (18), 304 (100), 298 (4), 282 (1), 277 (1), 255 (3), 201 (48), 173 (10), 129 (23), 103 (4).

HRMS (EI): Calcd. for $[C_{18}H_{14}IN_3O_2]^+$: 431.0131; found: 431.0117.

Synthesis of 2-(3,5-difluorophenyl)-4-iodo-6-phenyl-1,3,5-triazine (61f).



According to **TP1**, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 820 mg, 2 mmol) reacted with (3,5-difluorophenyl)zinc bromide (0.68 M, 3.5 mL, 2.4 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 50:1) afforded 2-(3,5-difluorophenyl)-4-iodo-6-phenyl-1,3,5-triazine (**61f**, 529 mg, 67%) as a white solid.

m. p. = 150.0-152.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.61-8.56 (m, 2H), 8.17-8.09 (m, 2H), 7.69-7.53 (m, 3H), 7.08 (tt, *J* = 8.4 Hz, 2.4 Hz, 2.3Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.3, 168.9 (t, *J* = 3.7 Hz, 1C), 164.9 (d, *J* = 12.1 Hz, 1C), 161.5 (d, *J* = 12.1 Hz, 1C), 142.6, 137.7 (t, *J* = 9.7 Hz, 1C), 133.8, 133.7, 129.4, 128.9, 112.2 (d, *J* = 8.9 Hz, 1C), 111.9 (d, *J* = 8.9 Hz, 1C), 108.6 (t, *J* = 25.5 Hz, 1C).

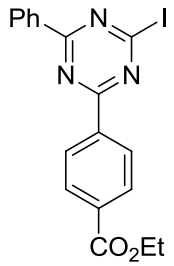
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3078 (VW), 2925 (VW), 1600 (W), 1516 (S),

1491 (VS), 1361 (M), 1235 (M), 1119 (W), 987 (W), 774 (M), 730 (M), 685 (M), 647 (W).

MS (EI, 70 eV): m/z (%) = 394 (M^+, 15), 382 (6), 381 (23), 281 (6), 269 (11), 267 (62), 240 (4), 229 (2), 165 (97), 139 (33), 129 (100), 103 (36), 77 (28).

HRMS (EI): Calcd. for $[C_{15}H_8F_2IN_3]^+$: 394.9731; found: 394.9711.

Synthesis of ethyl 4-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzoate (61g).



According to **TP1**, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 820 mg, 2 mmol) reacted with (4-(ethoxycarbonyl)phenyl)zinc iodide (0.72 M, 3.4 mL, 2.4 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 20:1) afforded ethyl 4-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzoate (**61g**, 440 mg, 51%) as a white solid.

m. p. = 172.3-174.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.68-8.57 (m, 4H), 8.22-8.17 (m, 2H), 7.68-7.51 (m, 3H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H),

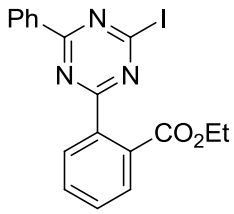
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.2, 170.1, 165.9, 142.7, 138.0, 134.6, 133.9, 133.6, 129.8, 129.4, 129.2, 128.8, 61.4, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3054 (VW), 2981 (VW), 1709 (S), 1482 (VS), 1353 (M), 1271 (S), 1221 (S), 1069 (M), 1018 (W), 827 (W), 797 (M), 754 (S), 688 (M), 647 (W).

MS (EI, 70 eV): m/z (%) = 432 (100), 322 (6), 217 (13), 145 (1).

HRMS (ESI): Calcd. for $[C_{18}H_{14}IN_3O_2 + H]^+$: 432.0209; found: 432.0200 ($[C_{18}H_{14}IN_3O_2 + H]^+$).

Synthesis of ethyl 2-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzoate (61h).



According to **TP1**, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 820 mg, 2 mmol) reacted with (2-(ethoxycarbonyl)phenyl)zinc iodide (0.72 M, 3.4 mL, 2.4 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 20:1) afforded ethyl 2-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzoate (**61h**, 569 mg, 66%) as a white solid.

m. p. = 90.5-92.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.58-8.51 (m, 2H), 8.25-8.18 (m, 1H), 7.78-7.73 (m, 1H), 7.68-7.59 (m, 3H), 7.58-7.50 (m, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H).

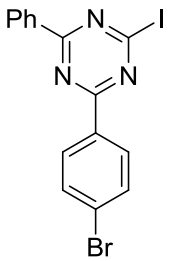
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.9, 170.7, 168.9, 141.8, 134.3, 134.2, 133.8, 133.7, 131.8, 130.7, 130.6, 129.5, 129.2, 128.9, 61.6, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3068 (VW), 2976 (VW), 1726 (S), 1509 (VS), 1472 (VS), 1357 (M), 1287 (M), 1237 (M), 1217 (M), 1124 (W), 797 (W), 750 (M), 685 (M).

MS (EI, 70 eV): m/z (%) = 431 (M^+, 7), 386 (9), 385 (18), 304 (65), 277 (5), 276 (26), 275 (6), 274 (9), 249 (2), 201 (14), 173 (37), 130 (27), 129 (100), 104 (3), 77 (12).

HRMS (EI): Calcd. for $[C_{18}H_{14}IN_3O_2]^+$: 431.0131; found: 431.0119.

Synthesis of 2-(4-bromophenyl)-4-iodo-6-phenyl-1,3,5-triazine (61i).



According to **TP1**, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 820 mg, 2 mmol) reacted with (4-bromophenyl)zinc iodide (0.68 M, 3.5 mL, 2.4 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 100:1) afforded

2-(4-bromophenyl)-4-iodo-6-phenyl-1,3,5-triazine (**61i**, 417 mg, 47%) as a white solid.

m. p. = 163.5-165.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.55 (d, *J* = 7.7 Hz, 2H), 8.44 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.64-7.50 (m, 3H).

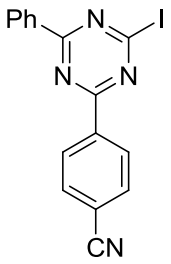
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.1, 170.1, 142.6, 133.9, 133.6, 133.1, 132.1, 130.7, 129.3, 128.8, 128.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3047 (VW), 1585 (W), 1510 (S), 1480 (VS), 1441 (M), 1354 (M), 1221 (M), 1063 (M),1011 (M), 818 (W), 800 (M), 766 (S), 647 (M), 614 (W).

MS (EI, 70 eV): m/z (%) = 436 (M^+, 9), 313 (5), 312 (27), 311 (5), 310 (31), 208 (43), 206 (45), 180 (7), 129 (100), 102 (16), 77 (21).

HRMS (EI): Calcd. for $[C_{15}H_9BrIN_3]^+$: 436.9025; found: 436.9009.

Synthesis of 4-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzonitrile (61j).



According to **TP1**, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 820 mg, 2 mmol) reacted with (4-cyanophenyl)zinc iodide (0.74 M, 3.2 mL, 2.4 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 10:1) afforded 4-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzonitrile (**61j**, 428 mg, 56%) as a white solid.

m. p. = 176.7-178.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.75-8.70 (m, 2H), 8.63-8.58 (m, 2H), 7.88-7.83 (m, 2H), 7.70-7.54 (m, 3H).

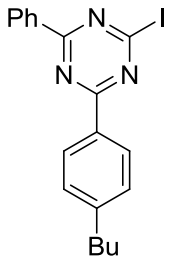
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.4, 169.3, 142.7, 138.3, 133.9, 133.7, 132.5, 129.7, 129.5, 128.9, 118.2, 116.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3067 (VW), 2918 (VW), 2227 (VW), 1511 (S), 1483 (VS), 1355 (M), 1224 (M), 1068 (W), 800 (W), 773 (M), 690 (W).

MS (EI, 70 eV): m/z (%) = 383 (M^+, 9), 292 (4), 258 (9), 257 (45), 191 (1), 155 (7), 154 (80), 129 (100), 103 (12), 77 (11).

HRMS (EI): Calcd. for $[C_{16}H_9IN_4]^+$: 383.9872; found: 383.9858.

Synthesis of 2-(4-butylphenyl)-4-iodo-6-phenyl-1,3,5-triazine (61k).



According to **TP1**, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 820 mg, 2 mmol) reacted with (4-butylphenyl)zinc iodide (0.72 M, 3.3 mL, 2.4 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 100:1) afforded 2-(4-butylphenyl)-4-iodo-6-phenyl-1,3,5-triazine (**61k**, 515 mg, 62%) as a white solid.

m. p. = 103.3-104.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.63-8.58 (m, 2H), 8.51 (d, *J* = 8.3 Hz, 2H), 7.67-7.51 (m, 3H), 7.36 (d, *J* = 8.3 Hz, 2H), 2.77-2.70 (m, 2H), 1.74-1.62 (m, 2H), 1.41 (qt, *J* = 7.5 Hz, 7.3 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

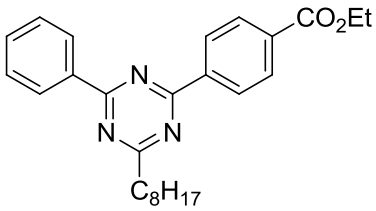
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.1, 170.9, 149.3, 142.6, 134.3, 133.3, 131.7, 129.4, 129.3, 128.9, 128.7, 35.8, 33.3, 22.4, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2956 (VW), 2928 (VW), 1609 (VW), 1511 (VS), 1479 (S), 1441 (W), 1358 (M), 1221 (M), 1070 (W), 801 (W), 767 (M), 693 (W), 618 (W).

MS (EI, 70 eV): m/z (%) = 416 (100), 306 (49), 257 (24), 177 (7).

HRMS (ESI): Calcd. for $[C_{19}H_{18}IN_3 + H]^+$: 416.0624; found: 416.0619 ($[C_{19}H_{18}IN_3 + H]^+$).

Synthesis of 4-(4-octyl-6-phenyl-[1,3,5]triazin-2-yl)-benzoic acid ethyl ester (64a).



According to **TP 2**, 2-iodo-4-octyl-6-phenyl-1,3,5-triazine (**61a**, 395 mg, 1 mmol) was converted to the corresponding triazinylmagnesium chloride (**62a**) after I/Mg exchange reaction with BuMgCl (1.43 M, 0.77 mL, 1.1 mmol) and was reacted with ethyl 4-iodobenzoate (**63a**, 305 mg, 1.1 mmol) after addition of $ZnBr_2 \cdot LiCl$ (1 M, 1.1 mL) in the presence of $Pd(dba)_2$ (5 mol%) and tfp (10 mol%). Purification by flash column chromatography (silica gel, pentane / EtOAc = 20:1) afforded 4-(4-octyl-6-phenyl-[1, 3, 5]triazin-2-yl)-benzoic acid ethyl ester (**64a**, 292 mg, 62%) as a pale yellow solid.

m. p. = 54.8 – 56.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.73 (d, *J* = 8.8 Hz, 2H), 8.68 (dd, *J* = 8.0 Hz, 1.5 Hz, 2H), 8.22 (d, *J* = 8.8 Hz, 2H), 7.66-7.52 (m, 3H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.08-3.00 (m, 2H), 2.04-1.93 (m, 2H), 1.56-1.22 (m, 10H), 1.47 (t, *J* = 7.2 Hz, 3H), 0.95-0.86 (m, 3H).

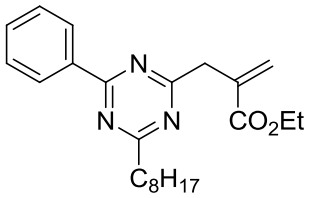
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 180.5, 171.3, 170.3, 166.2, 140.1, 135.9, 133.7, 132.6, 129.7, 128.9, 128.8, 128.7, 61.3, 39.3, 31.9, 29.5, 29.4, 29.3, 27.7, 22.7, 14.4, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3583 (W), 2913 (W), 1724 (M), 1529 (S), 1364 (M), 1278 (S), 1101 (M), 1021 (M), 759 (S), 689 (M), 665 (S).

MS (EI, 70 eV): m/z (%) = 417 (M^+, 7), 388 (2), 372 (3), 332 (12), 320 (18), 319 (100), 176 (10), 104 (16).

HRMS (EI): Calcd. for $[C_{26}H_{31}N_3O_2]^+$: 417.2416; found: 417.2408.

Synthesis of 2-(4-octyl-6-phenyl-[1,3,5]triazin-2-ylmethyl)-acrylic acid ethyl ester (64b).



According to **TP 2**, 2-iodo-4-octyl-6-phenyl-1,3,5-triazine (**61a**, 395 mg, 1 mmol) was converted to the corresponding triazinylmagnesium chloride (**62a**) after I/Mg exchange reaction with BuMgCl (1.43 M, 0.77 mL, 1.1 mmol) and was reacted with ethyl 2-(bromomethyl)acrylate (**63b**, 213 mg, 1.1 mmol) after addition of CuCN·2LiCl (1 M, 0.2 mL). Purification by flash column chromatography (silica gel, pentane / EtOAc = 20:1) afforded 2-(4-octyl-6-phenyl-[1,3,5]triazin-2-ylmethyl)-acrylic acid ethyl ester (**64b**, 279 mg, 73%) as yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.48 (d, *J* = 8.5 Hz, 2H), 7.57-7.44 (m, 3H), 6.36 (s, 1H), 5.68 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 2H), 2.92-2.85 (m, 2H), 1.89-1.79 (m, 2H), 1.44-1.23 (m, 10H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 6.7 Hz, 3H)

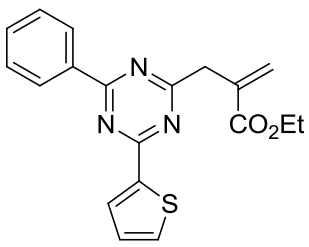
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 179.8, 176.8, 170.8, 166.8, 136.6, 135.7, 132.4, 128.9, 128.6, 127.1, 60.8, 41.7, 39.1, 31.8, 29.4, 29.3, 29.2, 27.8, 22.7, 14.2, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3583 (W), 2956 (W), 2927 (M), 2855 (W), 1720 (S), 1534 (VS), 1380 (M), 1148 (M), 1027 (W), 735 (W).

MS (EI, 70 eV): m/z (%) = 381 (M^+, 19), 380 (3), 352 (9). 336 (8), 308 (12), 296 (25), 284 (16), 283 (100), 237 (20), 211 (18), 104 (29).

HRMS (EI): Calcd. for $[C_{23}H_{31}N_3O_2]^+$: 381.2416; found: 381.2412.

Synthesis of ethyl 2-((4-phenyl-6-(thiophen-2-yl)-1,3,5-triazin-2-yl)methyl)-acrylate (64c).



According to **TP 2**, 2-iodo-4-phenyl-6-(thiophen-2-yl)-1,3,5-triazine (**61b**, 365 mg, 1 mmol) was converted to the corresponding triazinylmagnesium chloride (**62b**) after I/Mg exchange reaction with BuMgCl (1.43 M, 0.77 mL, 1.1 mmol) and was reacted with ethyl 2-(bromomethyl)acrylate (**63b**, 213 mg, 1.1 mmol) after addition of CuCN·2LiCl (1 M, 0.2 mL). Purification by flash column chromatography (silica gel, pentane / EtOAc = 20:1) afforded 2-((4-phenyl-6-(thiophen-2-yl)-1,3,5-triazin-2-yl)methyl)acrylate (**64c**, 213 mg, 59%) as yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.58 (d, *J* = 6.8 Hz, 2H), 8.28-8.23 (m, 1H), 7.65-7.48 (m, 4H), 7.24-7.18 (m, 1H), 6.41 (s, 1H), 5.76 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.06 (s, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

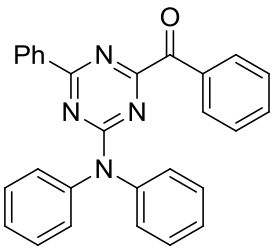
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 177.4, 171.1, 167.6, 166.9, 141.7, 136.6, 135.5, 132.6, 132.3, 131.7, 128.9, 128.6, 128.5, 127.1, 60.8, 41.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3583 (W), 3066 (W), 2979 (W), 2928 (W), 2253 (W), 1716 (VS), 1519 (VS), 1439 (S), 1375 (S), 1152 (M), 1027 (M), 774 (W), 732 (M), 704 (M), 665 (W).

MS (EI, 70 eV): m/z (%) = 351 (M^+, 60), 322 (36), 306 (19), 280 (13), 279 (56), 278 (100), 273 (18), 219 (10), 175 (30), 129 (18), 110 (31), 108 (29).

HRMS (EI): Calcd. for $[C_{19}H_{17}N_3O_2S]^+$: 351.1041; found: 351.1031.

Synthesis of (4-(diphenylamino)-6-phenyl-1,3,5-triazin-2-yl)(phenyl)methanone (64d).



According to **TP 2**, 4-iodo-N,N,6-triphenyl-1,3,5-triazin-2-amine (**61c**, 225 mg, 0.5 mmol) was converted to the corresponding triazinylmagnesium chloride (**62c**) after I/Mg exchange reaction with BuMgCl (1.43 M, 0.37 mL, 0.55 mmol) and was reacted with benzoyl chloride (**63c**, 60 mg, 0.55 mmol) after addition of CuCN·2LiCl (1 M,

0.55 mL). Purification by flash column chromatography (silica gel, pentane / EtOAc = 10:1) afforded (4-(diphenylamino)-6-phenyl-1,3,5-triazin-2-yl)(phenyl)methanone (**64d**, 154 mg, 71%) as a white solid.

m. p. = 212.6-214.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.31 (d, *J* = 7.3 Hz, 2H), 8.09 (d, *J* = 7.3 Hz, 2H), 7.71-7.21 (m, 16H).

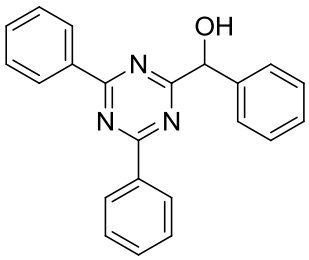
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 190.3, 171.7, 170.5, 165.9, 142.8, 135.5, 134.4, 133.9, 132.6, 130.8, 129.1, 129.0, 128.5, 128.3, 127.6, 126.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3583 (W), 3065 (W), 2254 (W), 1969 (W), 1691 (S), 1595 (M), 1537 (S), 1471 (S), 1372 (S), 1221 (M), 908 (S), 733 (M), 638 (W).

MS (EI, 70 eV): m/z (%) = 428 (M^+, 100), 323 (53), 296 (45), 220 (12), 193 (5), 180 (8), 167 (7), 105 (20), 77 (21).

HRMS (EI): Calcd. for $[C_{28}H_{20}N_4O]^+$: 428.1637; found: 428.1627.

Synthesis of (4, 6-diphenyl-[1,3,5]triazin-2-yl)-phenyl-methanol (64e).



According to **TP 2**, 2-iodo-4,6-diphenyl-1,3,5-triazine (**61d**, 359 mg, 1 mmol) was converted to the corresponding triazinylmagnesium chloride (**62d**) after I/Mg exchange reaction with BuMgCl (1.43 M, 0.77 mL, 1.1 mmol) and was reacted with benzaldehyde (**63d**, 117 mg, 1.1 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 10:1) afforded (4, 6-diphenyl-[1,3,5]triazin-2-yl)-phenyl-methanol (**64e**, 205 mg, 61%) as a white solid.

m. p. = 135.5 – 137.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.70-8.64 (m, 4H), 7.75-7,53 (m, 8H), 7.46 - 7.30 (m, 3H), 5.97 (s, 1H), 4.97 (br. s, 1H).

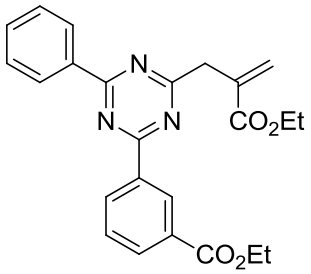
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 178.4, 171.3, 141.2, 135.2, 133.1, 129.1, 128.8, 128.5, 128.1, 126.8, 75.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3467 (W), 3064 (W), 2920 (W), 1959 (W), 1539 (S), 1520 (S), 1373 (M), 1372 (M), 1176 (W), 1061(W), 754 (M), 720 (M), 690 (M).

MS (EI, 70 eV): m/z (%) = 239(M^+, 100), 323 (11), 322 (23), 262 (39), 234 (12), 233 (53), 130 (30), 105 (14), 103 (60).

HRMS (EI): Calcd. for $[C_{22}H_{17}N_3O]^+$: 339.1372; found: 339.1366.

Synthesis of ethyl 3-(4-(2-(ethoxycarbonyl)allyl)-6-phenyl-1,3,5-triazin-2-yl) benzoate (64f).



According to **TP 2**, ethyl 3-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzoate (**61e**, 431 mg, 1 mmol) was converted to the corresponding triazinylmagnesium chloride (**62e**) after I/Mg exchange reaction with BuMgCl (1.43 M, 0.77 mL, 1.1 mmol) and was reacted with ethyl 2-(bromomethyl)acrylate (**63b**, 213 mg, 1.1 mmol) after addition of CuCN·2LiCl (1 M, 0.2 mL). Purification by flash column chromatography (silica gel, pentane / EtOAc = 10:1) afforded ethyl 3-(4-(2-(ethoxycarbonyl)allyl)-6-phenyl-1,3,5-triazin-2-yl)benzoate (**64f**, 286 mg, 71%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.26 (t, *J* = 1.7 Hz, 1H), 8.81-8.79 (m, 1H), 8.65-8.62 (m, 2H), 8.26-8.24 (m, 1H), 7.63-7.57 (m, 2H), 7.55-7.52 (m, 2H), 6.42 (d, *J* = 1.4 Hz, 1H), 5.77-5.76 (m, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.11 (s, 2H), 1.46 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H).

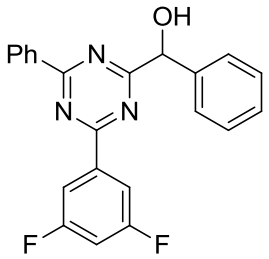
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 177.7, 171.4, 170.5, 166.9, 166.2, 136.6, 136.3, 135.6, 133.3, 133.1, 132.7, 131.2, 130.0, 129.0, 128.7, 128.6, 127.2, 61.3, 60.8, 41.8, 14.4, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3583 (W), 2981 (W), 2256 (W), 1721 (S), 1529 (S), 1366 (M), 1257 (M), 1152 (M), 1026 (W), 752 (M), 690 (W).

MS (EI, 70 eV): m/z (%) = 417 (M^+, 100), 388 (38), 372 (41), 345 (72), 344 (97), 273 (15), 241 (12), 213 (14), 169 (20), 149 (10), 130 (12), 104 (30).

HRMS (EI): Calcd. for $[C_{24}H_{23}N_3O_4]^+$: 417.1689; found: 417.1688.

Synthesis of (4-(3,5-difluorophenyl)-6-phenyl-1,3,5-triazin-2-yl)(phenyl)methanol (64g).



According to **TP 2**, 2-(3,5-difluorophenyl)-4-iodo-6-phenyl-1,3,5-triazine (**61f**, 395 mg, 1 mmol) was converted to the corresponding triazinylmagnesium chloride (**62f**) after I/Mg exchange reaction with BuMgCl (1.43 M, 0.77 mL, 1.1 mmol) and was reacted with benzaldehyde (**63d**, 117 mg, 1.1 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 20:1) afforded (4-(3,5-difluorophenyl)-6-phenyl-1,3,5-triazin-2-yl)(phenyl)methanol (**64g**, 202 mg, 54%) as a white solid.

m. p. = 145.2-147.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.66-8.61 (m, 2H), 8.17-8.12 (m, 2H), 7.69-7.60 (m, 3H), 7.58-7.54 (m, 2H), 7.41-7.37 (m, 2H), 7.33-7.29 (m, 1H), 7.06-7.02 (m, 1H), 5.94 (d, *J* = 6.1 Hz, 1H), 4.77 (d, *J* = 6.1 Hz, 1H).

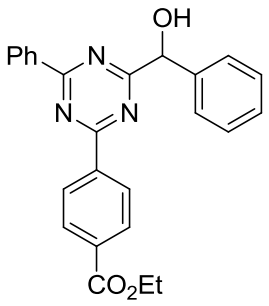
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 178.9, 171.7, 169.4 (t, *J* = 3.5 Hz, 1C), 164.0 (d, *J* = 12.3 Hz, 1C), 162.4 (d, *J* = 12.3 Hz, 1C), 140.8, 138.8 (t, *J* = 9.5 Hz, 1C), 134.7, 133.4, 129.2, 128.9, 128.5, 128.2, 126.7, 111.9 (d, *J* = 5.6 Hz, 1C), 111.1 (d, *J* = 5.6 Hz, 1C), 108.2 (t, *J* = 25.5 Hz, 1C), 75.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3477 (W), 3080 (VW), 2924 (W), 1522 (VS), 1369 (S), 1177 (W), 1117 (W), 1062 (W), 986 (W), 878 (W), 697 (M).

MS (EI, 70 eV): m/z (%) = 375 (M^+, 33), 323 (32), 298 (12), 269 (23), 220 (100), 180 (11), 167 (24), 129 (27), 117 (59), 104 (27), 77 (66).

HRMS (EI): Calcd. for $[C_{22}H_{15}F_2N_3O]^+$: 375.1183; found: 375.1182.

Synthesis of 4-[4-(hydroxy-phenyl-methyl)-6-phenyl-[1,3,5]triazin-2-yl]-benzoic acid ethyl ester (64h).



According to **TP 2**, ethyl 4-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzoate (**61g**, 431 mg, 1 mmol) was converted to the corresponding triazinylmagnesium chloride (**62g**) after I/Mg exchange reaction with OctMgBr (1 M, 1.1 mL, 1.1 mmol) and was reacted with benzaldehyde (**63d**, 117 mg, 1.1 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 10:1) afforded 4-[4-(hydroxy-phenyl-methyl)-6-phenyl-[1,3,5]triazin-2-yl]-benzoic acid ethyl ester (**64h**, 309 mg, 75%) as a white solid.

m. p. = 144.7-146.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.69 (dd, *J* = 12.8 Hz, 7.7 Hz, 4H), 8.22 (d, *J* = 8.3 Hz, 2H), 7.74-7.54 (m, 5H), 7.47-7.25 (m, 3H), 5.97 (s, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H).

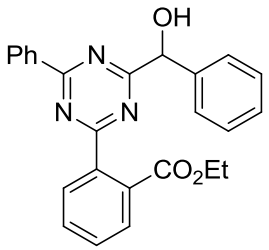
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 178.7, 171.6, 170.6, 166.0, 140.9, 139.1, 134.9, 134.2, 133.3, 129.8, 129.2, 128.9, 128.8, 128.5, 128.1, 126.7, 75.2, 61.4, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3467 (M), 3063 (W), 2982 (W), 2929 (W), 1717 (S), 1520 (S), 1372 (S), 1275 (S), 1104 (M), 909 (M), 760 (M), 731 (S), 698 (M).

MS (EI, 70 eV): m/z (%) = 411 (M^+, 67), 410 (17), 395 (28). 366 (11), 334 (28), 305 (22), 232 (12), 219 (15), 130 (16), 105 (100).

HRMS (EI): Calcd. for $[C_{25}H_{21}N_3O_3]^+$: 411.1583; found: 411.1573.

Synthesis of ethyl 2-(4-(hydroxy(phenyl)methyl)-6-phenyl-1,3,5-triazin-2-yl) benzoate (64k).



According to **TP 2**, ethyl 2-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzoate (**61h**, 431 mg, 1 mmol) was converted to the corresponding triazinylmagnesium chloride (**62h**) after I/Mg exchange reaction with OctMgBr (1 M, 1.1 mL, 1.1 mmol) and was reacted with benzaldehyde (**63d**, 117 mg, 1.1 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 10:1) afforded ethyl 2-(4-(hydroxy(phenyl)methyl)-6-phenyl-1,3,5-triazin-2-yl)benzoate (**64k**, 261 mg, 63%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.61-8.58 (m, 2H), 8.21-8.16 (m, 1H), 7.77-7.73 (m, 1H), 7.65-7.59 (m, 5H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.32-7.28 (m, 1H), 5.92 (s, 1H), 4.77 (br. s, 1H), 4.17-4.06 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H).

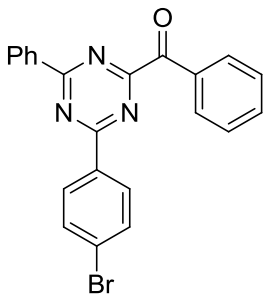
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 178.3, 172.6, 171.2, 169.1, 140.9, 135.5, 134.8, 134.1, 133.3, 131.4, 130.7, 130.4, 129.2, 129.1, 128.8, 128.5, 128.1, 126.7, 75.1, 61.5, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3469 (W), 3064 (W), 2918 (W), 2250 (W), 1725 (S), 1536 (S), 1521 (S), 1374 (M), 1287 (M), 1253 (M), 1177 (W), 1121 (W), 1061 (W), 910 (W), 731 (M), 697 (M), 608 (W).

MS (EI, 70 eV): m/z (%) = 411 (M^+, 100), 410 (25), 409 (82), 394 (11), 366 (13), 364 (32), 349 (23), 335 (15), 288 (24), 276 (20), 259 (20), 234 (38), 173 (23), 130 (71), 105 (86), 77 (46).

HRMS (EI): Calcd. for $[C_{25}H_{21}N_3O_3]^+$: 411.1583; found: 411.1580.

Synthesis of (4-(4-bromophenyl)-6-phenyl-1,3,5-triazin-2-yl)(phenyl)methanone (64l).



According to **TP 2**, 2-(4-bromophenyl)-4-iodo-6-phenyl-1,3,5-triazine (**61i**, 438 mg, 1 mmol) was converted to the corresponding triazinylmagnesium chloride (**62i**) after I/Mg exchange reaction with OctMgBr (1 M, 1.1 mL, 1.1 mmol) and was reacted with benzoyl chloride (**63c**, 169 mg, 1.2 mmol) after addition of CuCN·2LiCl (1 M, 1.1 mL). Purification by flash column chromatography (silica gel, pentane / EtOAc = 10:1) afforded (4-(4-bromophenyl)-6-phenyl-1,3,5-triazin-2-yl)(phenyl)methanone (**64l**, 289 mg, 68%) as a white solid.

m. p. = 144.3-146.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.69 (d, *J* = 7.1 Hz, 2H), 8.58 (d, *J* = 8.5 Hz, 2H), 8.14 (d, *J* = 7.1 Hz, 2H), 7.75-7.63 (m, 4H), 7.62-7.52 (m, 4H).

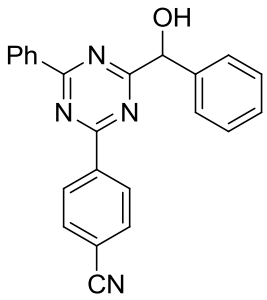
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 190.3, 172.3, 171.5, 170.9, 134.9, 134.4, 134.1, 134.0 133.5, 132.1, 130.9, 130.8, 129.3, 128.9, 128.7, 128.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3583 (W), 3064 (W), 2923 (W), 2248 (W), 1686 (S), 1588 (M), 1528 (VS), 1367 (S), 1222 (M), 1176 (W), 1068 (W), 1011 (W), 909 (W), 835 (W), 774 (W), 665 (W), 646 (W).

MS (EI, 70 eV): m/z (%) = 416 (22), 415 (M^+, 54), 414 (9), 387 (4), 313 (4), 234 (17), 206 (4), 156 (2), 105 (100), 77 (30).

HRMS (EI): Calcd. for $[C_{22}H_{14}BrN_3O]^+$: 415.0320; found: 415.0320.

Synthesis of 4-(4-(hydroxy(phenyl)methyl)-6-phenyl-1,3,5-triazin-2-yl) benzonitrile (64m).



According to **TP 2**, 4-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzonitrile (**61j**, 300 mg, 0.78 mmol) was converted to the corresponding triazinylmagnesium chloride (**62j**) after I/Mg exchange reaction with OctMgBr (1 M, 0.86 mL, 1.1 mmol) and was reacted with benzaldehyde (**63d**, 91 mg, 0.86 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 10:1) afforded 4-(4-(hydroxy(phenyl)methyl)-6-phenyl-1,3,5-triazin-2-yl)benzonitrile (**64m**, 186 mg, 64%) as a white solid.

m. p. = 192.0-194.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.76 (d, *J* = 8.5 Hz, 2H), 8.70-8.62 (m, 2H), 7.86 ((d, *J* = 8.5 Hz, 2H). 7.71-7.54 (m, 5H), 7.45-7.29 (m, 3H), 5.98 (s, 1H), 4.79 (br. s, 1H).

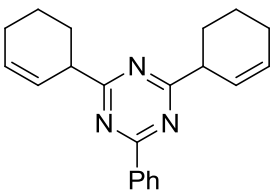
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 179.0, 171.8, 169.9, 140.8, 139.3, 134.7, 133.6, 132.5, 129.5, 129.2, 128.9, 128.6, 128.2, 126.7, 118.3, 116.2, 75.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3445 (W), 3062 (W), 2923 (W), 2230 (W), 1575 (W), 1519 (VS), 1371 (S), 1344 (M), 1191 (W), 1020 (W), 910 (W), 821 (W), 695 (W), 665 (W).

MS (EI, 70 eV): m/z (%) = 364 (M^+, 20), 363 (12), 362 (39). 348 (21), 347 (11), 258 (14), 244 (7), 129 (11), 117 (11), 105 (100).

HRMS (EI): Calcd. for $[C_{23}H_{16}N_4O]^+$: 364.1324; found: 364.1315.

Synthesis of 2,4-di(cyclohex-2-en-1-yl)-6-phenyl-1,3,5-triazine (67).



According to **TP 2**, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 409 mg, 1 mmol) as converted to the corresponding doubly magnesiated 1,3,5-triazine (**65**) after I/Mg exchange reaction with sBuMgCl (1.77 M, 1.25 mL, 2.2 mmol) and was reacted with 3-bromocyclohex-1-ene (354 mg, 2.2 mmol) after addition of CuCN·2LiCl (1 M, 2.2 mL). Purification by flash column chromatography (silica gel, pentane / EtOAc = 100:1) afforded 2,4-di(cyclohex-2-en-1-yl)-6-phenyl-1,3,5-triazine (**67**, 211 mg, 67%) as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.55 (dd, *J* = 7.7 Hz, 1.7 Hz 2H), 7.60-7.41 (m, 3H), 6.07-5.85 (m, 4H), 3.76-3.61 (m, 2H), 2.28-1.59 (m, 12H).

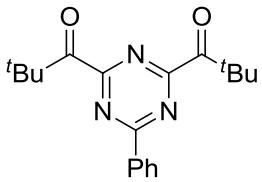
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 181.4, 170.9, 136.2, 132.2, 128.9, 128.7, 128.5, 127.2, 44.5, 27.8, 24.8, 21.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3058 (W), 2959 (W), 1674 (M), 1516 (VS), 1378 (W), 1260 (W), 1231 (W), 1025 (M), 776 (M), 699 (M), 650 (W).

MS (EI, 70 eV): m/z (%) = 318 (16), 317 (M^+, 64), 316 (21), 276 (43), 252 (12), 236 (16), 281 (10), 106 (33), 104 (100), 79 (33), 77 (41).

HRMS (EI): Calcd. for $[C_{21}H_{23}N_3]^+$: 317.1892; found: 317.1893.

Synthesis of 1,1'-(6-phenyl-1,3,5-triazine-2,4-diyl)bis(2,2-dimethylpropan-1-one) (68).



According to **TP 2**, 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 409 mg, 1 mmol) as converted to the corresponding doubly magnesiated 1,3,5-triazine (**65**) after I/Mg exchange reaction with sBuMgCl (1.77 M, 1.25 mL, 2.2 mmol) and was reacted with 3-bromocyclohex-1-ene (354 mg, 2.2 mmol) after addition of CuCN·2LiCl (1 M, 2.2 mL, 2.2 mmol). Purification by flash column chromatography (silica gel, pentane / EtOAc = 50:1) afforded 1,1'-(6-phenyl-1,3,5-triazine-2,4-diyl) bis(2,2-dimethylpropan-1-one) (**68**, 121 mg, 38%) as a white solid.

m. p. = 60.9-62.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.61-8.55 (m, 2H), 7.70-7.52 (m, 3H), 1.43 (s, 18H).

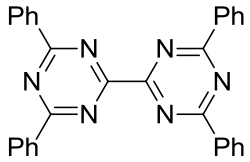
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 204.5, 172.1, 171.0, 134.2, 133.9, 129.4, 128.9, 43.8, 26.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3062 (W), 2968 (W), 1710 (S), 1528 (VS), 1477 (M), 1392 (S), 1061 (W), 990 (M), 839 (M), 749 (S), 699 (S), 650 (W).

MS (EI, 70 eV): m/z (%) = 325 (M^+, 4), 269 (3), 242 (2), 241 (15), 226 (14), 207 (2), 185 (3), 157 (2), 129 (6), 103 (11), 85 (11), 77 (10), 57 (100).

HRMS (EI): Calcd. for $[C_{19}H_{23}N_3O_2]^+$: 325.1790; found: 325.1813.

Synthesis of 4,4',6,6'-tetraphenyl-2,2'-bi(1,3,5-triazine) (70).



According to **TP 2**, 2-iodo-4,6-diphenyl-1,3,5-triazine (**61d**, 359 mg, 1 mmol) was converted to the corresponding triazinylmagnesium chloride (**62d**) after I/Mg exchange reaction with BuMgCl (1.43 M, 0.77 mL, 1.1 mmol) and was reacted with 2-iodo-4,6-diphenyl-1,3,5-triazine (**61d**, 359 mg, 1 mmol) after addition of $ZnCl_2$ (1 M, 1.1 mL 1.1 mmol) in the presence of $Pd(PPh_3)_4$ (5 mol%). Purification by flash column chromatography (silica gel, pentane / EtOAc = 10:1) afforded 4,4',6,6'-tetraphenyl-2,2'-bi(1,3,5-triazine) (**70**, 265 mg, 57%) as a yellow solid.

m. p. = 285.0-287.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.92-8.84 (m, 8H), 7.72-7.59 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.9, 170.4, 135.6, 133.1, 129.4, 128.8.

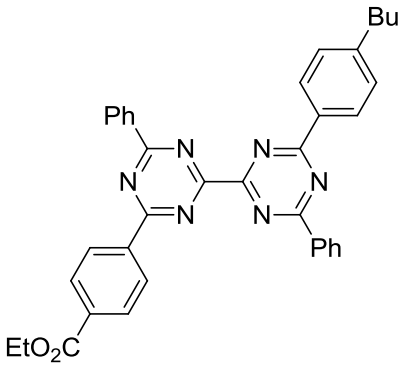
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3034 (VW), 2924 (VW), 1504 (VS), 1444 (M), 1355 (S), 1245 (W), 1177 (W), 1024 (M), 839 (M), 794 (M), 751 (S), 686 (S), 643 (M).

MS (EI, 70 eV): m/z (%) = 465 (100), 445 (3), 305 (12), 259 (8).

HRMS (ESI): Calcd. for $[C_{30}H_{20}N_6 + H]^+$: 465.1828; found: 465.1821 ($[C_{30}H_{20}N_6$ +

H]$^+$).

Synthesis of ethyl 4-(4'-(4-butylphenyl)-6,6'-diphenyl-[2,2'-bi(1,3,5-triazin)]-4-yl) benzoate (72).



According to **TP 2**, 2-(4-butylphenyl)-4-iodo-6-phenyl-1,3,5-triazine (**61k**, 249 mg, 0.6 mmol) was converted to the corresponding triazinylmagnesium chloride after I/Mg exchange reaction with sBuMgCl (1.77 M, 0.37 mL, 0.66 mmol) and was reacted with ethyl 4-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzoate (**61g**, 216 mg, 0.5 mmol) after addition of $ZnCl_2$ (1 M, 0.66 mL 0,66 mmol) in the presence of PEPPSI (5 mol%). Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1) afforded ethyl 4-(4'-(4-butylphenyl)-6,6'-diphenyl-[2,2'-bi(1,3,5-triazin)]-4-yl)benzoate (**72**, 154 mg, 52%) as a yellow solid.

m. p. = 164.6-166.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.91-8.88 (m, 2H), 8.85-8.81 (m, 4H), 8.73 (d, *J* = 8.2 Hz, 2H), 8.27 (d, *J* = 8.2 Hz, 2H), 7.68-7.57 (m, 6H), 7.41 (d, *J* = 7.9 Hz, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 2.77-2.73 (m, 2H), 1.72-1.66 (m, 2H), 1.46 (t, *J* = 7.1 Hz, 3H), 1.44-1.38 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

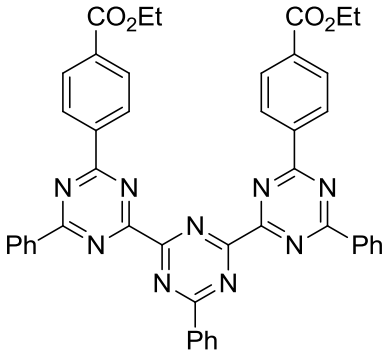
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 173.0, 172.9, 172.7, 171.9, 170.5, 169.9, 166.1, 148.9, 139.4, 135.6, 135.3, 134.2, 133.3, 133.0, 132.9, 129.9, 129.4, 129.4, 129.3, 129.2, 128.9, 128.8, 128.7, 61.4, 35.8, 33.3, 22.4, 14.3, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3065 (W), 2956 (W), 1715 (S), 1504 (VS), 1357 (M), 1271 (S), 1099 (M), 1017 (M), 829 (W), 764 (S), 688 (S), 648 (M).

MS (EI, 70 eV): m/z (%) = 592 (M^+, 100), 551 (9), 550 (29), 549 (40), 489 (13). 433 (8), 331 (9), 277 (9), 261 (14), 252 (24), 129 (9), 116 (11), 104 (21).

HRMS (EI): Calcd. for $[C_{37}H_{32}N_6O_2]^+$: 592.2587; found: 592.2591.

Synthesis of diethyl 4,4'-(6,6',6''-triphenyl-[2,2':4',2''-ter(1,3,5-triazine)]-4,4''-diyl)dibenzoate (74).



According to **TP 2**, ethyl 4-(4-iodo-6-phenyl-1,3,5-triazin-2-yl)benzoate (**61g**, 431 mg, 1 mmol) was converted to the corresponding triazinylmagnesium bromide after I/Mg exchange reaction with OctMgBr (0.72 M, 1.53 mL, 1.1 mmol) and was reacted with 2,4-diiodo-6-phenyl-1,3,5-triazine (**59**, 144 mg, 0.35 mmol) after addition of $ZnCl_2$ (1 M, 1.1 mL 1.1 mmol) in the presence of Pd-PEPPSI-*i*Pr (5 mol%). Purification by flash column chromatography (silica gel, pentane / EtOAc = 2:1) afforded diethyl 4,4'-(6,6',6''-triphenyl-[2,2':4',2''-ter(1,3,5-triazine)]-4,4''-diyl)dibenzoate (**74**, 121 mg, 45%) as a yellow solid.

m. p. = 185.0-187.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.92 (d, *J* = 7.9 Hz, 5H), 8.86 (d, *J* = 7.4 Hz, 4H), 8.27 (d, *J* = 7.4 Hz, 4H), 7.73-7.59 (m, 10H), 4.45 (q, *J* = 7.1 Hz, 4H), 1.45 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 174.3, 173.2, 172.1, 171.0, 169.9, 166.0, 139.2, 135.1, 134.7, 134.4, 133.9, 133.5, 129.9, 129.5, 129.3, 129.0, 128.9, 61.4, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3066 (VW), 2927 (VW), 1717 (S), 1504 (VS), 1361 (M), 1270 (S), 1101 (M), 1020 (M), 834 (M), 759 (M), 733 (M), 688 (M), 650 (W).

MS (EI, 70 eV): m/z (%) = 763 (M^+, 60), 718 (12), 588 (11), 487 (13), 486 (42), 336 (12), 309 (11), 285 (15), 277 (51), 249 (30), 208 (19), 176 (18), 148 (20), 129 (43), 104 (100), 77 (17).

HRMS (EI): Calcd. for $[C_{45}H_{33}N_9O_4]^+$: 763.2656; found: 763.2656.

2.2 Preparation of Functionalized Indazoles

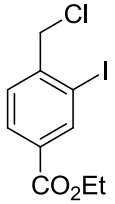
2.2.1 Typical Procedures (TP)

TP1: Typical procedure for the preparation of 2-aryl-2*H*-indazole derivatives (3a-r).

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

2.2.2 Preparation of Starting Materials and Functionalized Indazoles

Synthesis of 4-chloromethyl-3-iodo-benzoic acid ethyl ester (75a).



To a solution of 3-iodo-4-methyl-benzoic acid ethyl ester (1.16 g, 4 mmol) in THF (10 mL) was added N-bromosuccinimide (783 mg, 4.4 mmol) and dibenzoylperoxid

(97 mg, 0.4 mmol). The resulting mixture was refluxed for 9 h. The resulting mixture was refluxed for 9 h. Subsequently, the solvent was concentrated *in vacuo*, filtered through a plug of silica and washed with pentane. The solvent was removed *in vacuo*. In a 50 mL round bottom flask the residue was dissolved in THF (15 mL) and LiCl (433 mg, 10 mmol) was added. The resulting mixture was refluxed for 4 h. Subsequently, the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 100:1) provided 4-chloromethyl-3-iodobenzoic acid ethyl ester (**75a**, 776 mg, 60%) as a white solid.

m. p. = 79.2-80.4 °C.

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

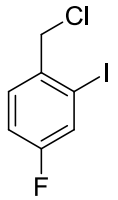
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 164.6, 144.3, 140.7, 131.9, 129.8, 129.8, 98.7, 61.5, 50.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 1708 (VS), 1292 (M), 727 (S).

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

HRMS ($C_{10}H_{10}ClIO_2$): Calc.: 323.9414; found: 323.9415 (M^+).

Synthesis of 1-chloromethyl-4-fluoro-2-iodo-benzene (75b).



To a solution of 4-fluoro-2-iodo-1-methyl-benzene (2.36 g, 10 mmol) in THF (10 mL) was added N-bromosuccinimide (1.96 g, 11 mmol) and dibenzoylperoxid (242 mg, 1 mmol). The resulting mixture was refluxed for 9 h. Subsequently, the solvent was concentrated *in vacuo*, filtered through a plug of silica and washed with pentane. The solvent was removed *in vacuo*. In a 50 mL round bottom flask the residue was dissolved in THF (15 mL) and LiCl (693 mg, 16 mmol) was added. The resulting mixture was refluxed for 4 h. Subsequently, the solvent was removed *in vacuo*.

Purification by flash column chromatography (silica, pentane) provided 4-fluoro-3-chloromethyl-2-iodo-benzene (**75b**, 908 mg, 35%) as colorless oil.

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

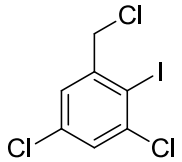
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 163.4 (d, *J* = 251.9 Hz), 136.1 (d, *J* = 3.5 Hz), 131.1 (d, *J* = 8.4 Hz), 126.9 (d, *J* = 23.6 Hz), 116.0 (d, *J* = 20.9 Hz), 99.0 (d, *J* = 8.6 Hz), 50.1 (d, *J* = 0.6 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 1693 (w), 1590 (M), 1225 (M), 863 (S).

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

HRMS (C_7H_5ClFI): Calc.: 269.9109; found: 269.9102 (M^+).

Synthesis of 1,5-dichloro-3-chloromethyl-2-iodo-benzene (75c)



To a solution of 1,5-dichloro-2-iodo-3-methyl-benzene (2.3 g, 8 mmol) in THF (10 mL) was added N-bromosuccinimide (1.6 g, 8.8 mmol) and dibenzoylperoxide (194 mg, 0.8 mmol). The resulting mixture was refluxed for 9 h. Subsequently, the solvent was concentrated *in vacuo*, filtered through a plug of silica and washed with pentane. The solvent was removed *in vacuo*. In a 50 mL round bottom flask the residue was dissolved in THF (15 mL) and LiCl (693 mg, 16 mmol) was added. The resulting mixture was refluxed for 4 h. Subsequently, the solvent was removed *in vacuo*. Purification by flash column chromatography (silica gel, pentane) provided 1,5-dichloro-3-chloromethyl-2-iodo-benzene (**75c**, 716 mg, 54 %) as colorless oil.

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

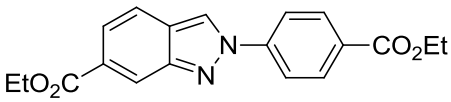
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 143.8, 140.7, 135.2, 128.8, 127.9, 101.4, 51.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2362 (S), 1551 (M), 1382 (M), 1266 (W), 1282 (M), 1017 (S), 862 (M), 811 (M).

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

HRMS ($C_7H_4Cl_3I$): Calc.: 319.8423; found: 319.8408 (M^+).

Synthesis of 2-(4-ethoxycarbonyl-phenyl)-2*H*-indazole-6-carboxylic acid ethyl ester (80a).



According t o **TP1,** 4-chloromethyl-3-iodo-benzoic acid ethyl ester (**75a**, 324 mg, 1 mmol) was converted to the diarylzinc compound and reacted with *p*-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (177 mg, 0.67 mmol). Purification by flash chromatograph (silica gel, pentane / EtOAc = 5:1 to 2:1) afforded 2-(4-ethoxycarbonyl-phenyl)-2H-indazole-6-carboxylic acid ethyl ester (**80a**, 161 mg, 71%) as a pale yellow solid.

m. p. = 140.6-142.4 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.61 (s, 1H), 8.54 (s, 1H), 8.26 (d, *J* = 8.7 Hz, 2H), 8.06 (d, *J* = 8.7 Hz, 2H), 7.70-7.78 (m, 2H), 4.40-4.50 (m, 4H), 1.40-1.45 (m, 6H).

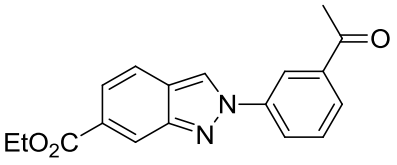
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.7, 165.6, 143.3, 131.2, 130.2, 129.6, 122.6, 121.8, 120.5, 120.5, 61.4, 61.2, 14.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3068 (VW), 2984 (W), 1697 (VS), 1604 (M), 1521 (M), 1363 (M), 1257 (S), 1098 (S), 856 (W), 769 (M) , 689 (W).

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

HRMS ($C_{19}H_{18}N_2O_4$): Calc.: 338.1267, found: 338.1242 (M^+).

Synthesis of 2-(3-acetylphenyl)-2*H*-indazole-6-carboxylic acid ethyl ester (80b).



According t o **TP1**, 4-chloromethyl-3-iodo-benzoic acid ethyl ester (**75a**, 243 mg, 0.75 mmol) was converted to the diarylzinc compound and reacted with 3-(acetyl)benzenediazonium tetrafluoroborate (117 mg, 0.5 mmol). Purification by

flash chromatograph (silica gel, pentane / EtOAc = 5:1 to 3:1) afforded 2-(3-acetyl-phenyl)-2H-indazole-6-carboxylic acid ethyl ester (**80b**, 104 mg, 68%) as a pale yellow solid.

m. p. = 128.8-130.6 °C

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

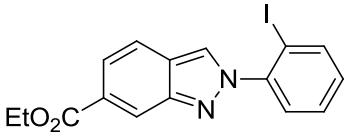
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 196.8, 166.8, 149.2, 140.7, 138.5, 130.1, 129.4, 128.0, 125.3, 124.7, 122.4, 121.7, 120.7, 120.5, 120.3, 61.1, 26.8, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3341 (VW), 3103 (W), 1707 (VS), 1678 (VS), 1441 (M), 1368 (M), 1317 (M), 1243 (S), 1060 (M), 795 (M), 741 (M) , 592 (M).

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

HRMS ($C_{18}H_{16}N_2O_3$): Calc.: 308.1161, found: 308.1148 (M^+).

Synthesis of 2-(2-iodophenyl)-2*H*-indazole-6-carboxylic acid ethyl ester (80c).



According t o **TP1**, 4-chloromethyl-3-iodo-benzoic acid ethyl ester (**75a**, 243 mg, 0.75 mmol) was converted to the diarylzinc compound and reacted with *o*-iodobenzenediazonium tetrafluoroborate (160 mg, 0.5 mmol). Purification by flash chromatograph (silica gel, pentane / EtOAc = 5:1) afforded 2-(2-iodo-phenyl)-2H-indazole-6-carboxylic acid ethyl ester (**80c**, 177 mg, 90%) as a yellow oil.

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

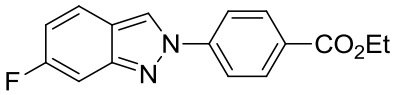
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.9, 148.6, 143.5, 140.1, 131.1, 129.1, 129.0, 128.1, 125.2, 123.8, 122.1, 121.8, 120.5, 94.0, 61.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2980 (W), 1710 (VS), 1504 (M), 1353 (W), 1314 (W), 1224 (M), 1088 (M), 1021 (W), 948 (W), 746 (M).

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

HRMS ($C_{16}H_{13}N_2O_2I$): Calc.: 392.0022, found: 392.0034 (M^+).

Synthesis of 4-(6-fluoro-indazol-2-yl)-benzoic acid ethyl ester (80d).



According to **TP1**, 1-chloromethyl-4-fluoro-2-iodo-benzene (**75**b, 406 mg, 1.5 mmol) was converted to the diarylzinc compound and reacted with *p*-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (264 mg, 1 mmol). Purification by flash chromatograph (silica gel, pentane / EtOAc = 5:1) afforded 4-(6-fluoro-indazol-2-yl)-benzoic acid ethyl ester (**80d**, 212 mg, 75%) as a yellow solid.

m. p. = 159.8-161.2 °C

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

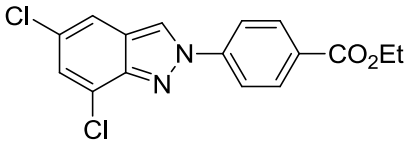
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 165.7, 162.3 (d, *J* = 244.3 Hz), 150.0 (d, *J* = 13.5Hz), 143.3, 131.1, 129.7, 122.4 (d, *J* = 10.5 Hz), 121.0 (d, *J* = 1.5 Hz), 120.3, 120.1, 115.0 (d, *J* = 28.6 Hz), 101.0 (d, *J* = 24.0 Hz), 61.35, 14.35.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3073 (W), 2986 (W), 1707 (VS), 1639 (M), 1607 (S), 1370 (M), 1270 (VS), 1101 (VS), 808 (M), 763 (S) , 728 (M).

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

HRMS ($C_{16}H_{13}FN_2O_2$): Calc.: 284.0961, found: 284.0955 (M^+)

Synthesis of 4-(5,7-dichloro-indazol-2-yl)-benzoic acid ethyl ester (80e).



According to **TP1**, 1,5-dichloro-3-chloromethyl-2-iodo-benzene (**75c**, 482 mg, 1.5 mmol) was converted to the diarylzinc compound and reacted with *p*-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (264 mg, 1 mmol). Purification by flash chromatograph (silica gel, pentane / EtOAc = 5:1) afforded 4-(5,7-dichloro-indazol-2-yl)-benzoic acid ethyl ester (**80e**, 219 mg, 66%) as a pale yellow solid.

m. p. = 139.6-141.3 °C.

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

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

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2987 (W), 1701 (VS), 1606 (M), 1517 (S), 1365 (M), 1276 (VS), 850 (S), 765 (S).

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

HRMS ($C_{16}H_{12}Cl_2N_2O_2$): Calc.: 334.0276; found: 334.0280 (M^+).

2.3 Diastereoselective Synthesis of Homoallylic Alcohols with Adjacent Tertiary and Quaternary Centers by Using Functionalized Allylic Aluminum Reagents

2.3.1 Typical Procedures (TP)

TP1: Typical procedure for the preparation of allylaluminum reagents (85a-h) using the Al/$InCl_3$ method.

Aluminum powder (1.5 equiv) and $InCl_3$ (1 mol%) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (2.5 mL / mmol) was added. A solution of the corresponding allyl bromide or chloride (1.0 equiv.) in THF (2.5 mL / mmol) was added at the appropriate temperature (0-20°C) and the reaction mixture was stirred until the conversion of the allyl halide reached >95% (monitored by GC-analysis of hydrolyzed reaction aliquots). The remaining aluminum powder was allowed to settle down and the allylaluminum reagent is obtained as a clear solution. Estimation of the yield was performed by iodometric titration after transmetallation with $ZnCl_2$ as follows: To the clear solution of the allylaluminum reagent was added $ZnCl_2$ solution (1M in THF, 1.0 equiv.) and the mixture stirred for 15 minutes at 20°C. The resulting allylzinc solution was added dropwise to a solution of iodine (0.5 equiv) in THF (1 mL) until the red colour disappeared.

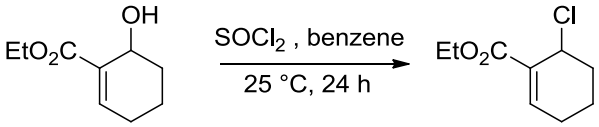
Typical procedures for preparation of homoallylic alcohols and lactones (87a-u) by the addition of allylic aluminum reagents to aldehydes or ketones:

Typical Procedure (**TP2**): The allylaluminum halides (**85a-h**) prepared according to **TP1** were added to a solution of an aldehyde or a ketone in THF at -78 °C and the mixture was stirred at this temperature for 1-2 h. After quenching with water (10 mL), the reaction mixture was extracted with ether (3 × 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography provided the pure compound.

Typical Procedure (TP3): The allylaluminum halides (**85a-h**) prepared according to **TP1** were added to a solution of an aldehyde or a ketone in THF at -78 °C and the mixture was stirred for 16-24 h warming from -78 °C to 25 °C. After quenching with water (10 mL), the reaction mixture was extracted with ether (3 × 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography provided the pure compound.

2.3.2 Preparation of Allylaluminum Reagents (85a-h).

Preparation of 6-chloro-cyclohex-1-enecarboxylic acid ethyl ester (84b):



6-Hydroxy-cyclohex-1-enecarboxylic acid ethyl ester was prepared according to a known literature procedure.[86] Thionyl chloride (2 mL) was slowly added to the solution of 6-hydroxy-cyclohex-1-enecarboxylic acid ethyl ester (3.4 g, 20 mmol) in benzene (40 mL) at 25 °C. The resulting mixture was stirred for 24 h at 25 °C. After the mixture was cooled with ice-bath, water (20 mL) was added slowly. The reaction mixture was extracted with diethyl ether (3 × 30 mL). The extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (eluent: pentane:ether = 1:30) provided the pure compound **84b** (3.3 g, 86%) as colorless oil.

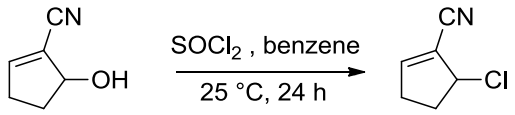
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.11 (dd, *J* = 5.1 Hz, 2.7 Hz, 1H), 5.09-5.04 (m, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.49-2.35 (m, 1H), 2.30-2.14 (m, 2H), 2.08-1.66 (m, 3H), 1.3 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 165.3, 142.9, 131.4, 60.7, 52.3, 31.3, 25.5, 15.8, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3418 (W), 2952 (W), 2361 (W), 1712 (VS), 1241 (VS), 1062 (S), 761 (S), 660 (M)； **MS** (EI, 70 eV): m/z (%) = 188 (M^+, 13), 160 (11), 152(49), 151 (27), 150 (10),123 (15), 80 (19), 79 (100).

HRMS (EI): Calcd. for $C_9H_{13}ClO_2$: 188.0604; found: 188.0607.

Preparation of 5-chloro-cyclopent-1-enecarbonitrile (84g):



5-Hydroxy-cyclopent-1-enecarbonitrile was prepared according to a known literature procedure.[87] Thionyl chloride (1 mL) was slowly added to the solution of 5-hydroxy-cyclopent-1-enecarbonitrile (1.09 g, 10 mmol) in benzene (10 mL) at 25 °C. The resulting mixture was stirred for 24 h at 25 °C. After the mixture was cooled with ice-bath, water (10 mL) was added slowly. The reaction mixture was extracted with diethyl ether (3 × 20 mL). The extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent: pentane:ether = 1:10) provided the pure compound **84g** (670 mg, 53%) as pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.90-6.84 (m, 1H), 5.07-4.98 (m, 1H), 2.92-2.25 (m, 4H).

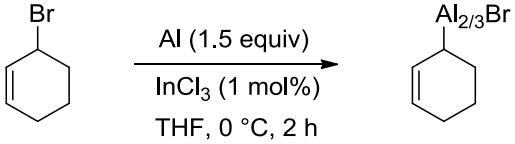
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 152.0, 118.0, 114.5, 63.0, 34.5, 32.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3317 (W), 2947 (W), 2228 (M), 1737 (S), 1442 (M), 1325 (M), 1233 (M), 1013 (VS), 881 (S), 811 (S), 718 (VS), 645 (S).

MS (EI, 70 eV): m/z (%) = 127 (M^+, 9), 92 (7), 91 (100), 64 (32).

HRMS (EI): Calcd. for C_6H_6ClN: 127.0189; found: 127.0181.

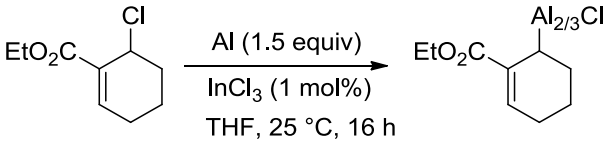
Preparation of 2-cyclohexenylaluminum bromide (85a):



According to the typical procedure (**TP1**), aluminum powder (81 mg, 3 mmol) and $InCl_3$ (4.4 mg, 0.02 mmol) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and

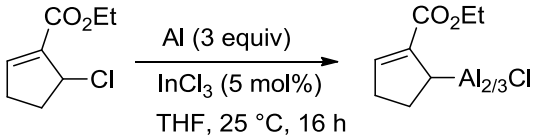
backfilled with argon three times and THF (5 mL) was added. A solution of 3-bromo-1-cyclohexene (**84a**, 322 mg, 2 mmol) in THF (5 mL) was added with a syringe pump within 1 h at 0 °C and the resulting solution was stirred at 0 °C for 1 h. The insertion reaction was monitored by GC analysis of hydrolyzed reaction aliquots. Yield determined by iodometric titration after transmetallation with $ZnCl_2$: 82%.

Preparation of 2-enecarboxylic acid ethyl ester-6-cyclohexenylaluminum chloride (85b):



According to the typical procedure (**TP1**), aluminum powder (81 mg, 3 mmol) and $InCl_3$ (4.4 mg, 0.02 mmol) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (2 mL) was added. A solution of 6-chloro cyclohex-1-enecarboxylic acid ethyl ester (**84b**, 377 mg, 2 mmol) in THF (2 mL) was added at 25 °C and the resulting solution was stirred at 25 °C for 16 h. The insertion reaction was monitored by GC analysis of hydrolyzed reaction aliquots. Yield: 77%.

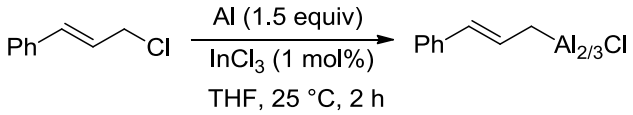
Preparation of 2-enecarboxylic acid ethyl ester-5-cyclopentenylaluminum chloride (85c):



According to the typical procedure (**TP1**), aluminum powder (81 mg, 3 mmol) and $InCl_3$ (11 mg, 0.05 mmol) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (1 mL) was added. A solution of 5-chloro-cyclopent-1-enecarboxylic acid ethyl ester (**84c**, 174 mg, 1 mmol) in THF (0.5 mL) was added at 25 °C and the resulting solution was stirred at 25 °C for 16 h.

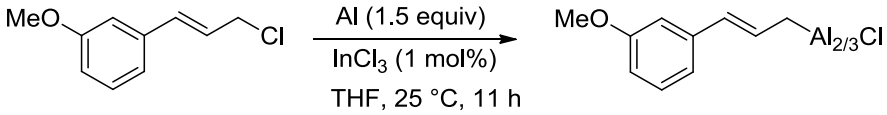
The insertion reaction was monitored by GC analysis of hydrolyzed reaction aliquots. Yield: 60%.

Preparation of cinnamylaluminum chloride (85d):



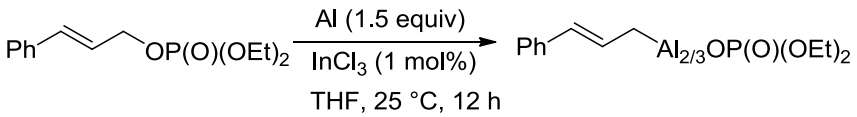
According to the typical procedure (**TP1**), aluminum powder (81 mg, 3 mmol) and $InCl_3$ (4.4 mg, 0.02 mmol) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (2 mL) was added. A solution of cinnamyl chloride (**84d**, 305 mg, 2 mmol) in THF (2 mL) was added at 25 °C and the resulting solution was stirred at 25 °C for 2 h. The insertion reaction was monitored by GC analysis of hydrolyzed reaction aliquots. Yield: 73%.

Preparation of 3-methoxycinnamylaluminum chloride (85e):



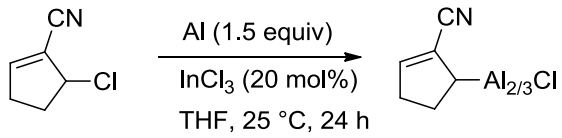
According to the typical procedure (**TP1**), aluminum powder (81 mg, 3 mmol) and $InCl_3$ (4.4 mg, 0.02 mmol) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (2 mL) was added. A solution of 1-(3-chloro-propenyl)-3-methoxy-benzene (**84e**, 364 mg, 2 mmol) in THF (2 mL) was added at 25 °C and the resulting solution was stirred at 25 °C for 11 h. The insertion reaction was monitored by GC analysis of hydrolyzed reaction aliquots. Yield: 71%.

Preparation of cinnamylaluminum phosphate (85f):



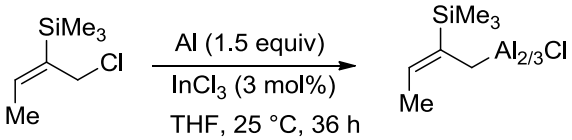
According to the typical procedure (**TP1**), aluminum powder (81 mg, 3 mmol) and $InCl_3$ (4.4 mg, 0.02 mmol) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (2 mL) was added. A solution of the cinnamyl phosphate (**84f**, 540 mg, 2 mmol) in THF (2 mL) was added at 25 °C and the resulting solution was stirred at 25 °C for 12 h. The insertion reaction was monitored by GC analysis of hydrolyzed reaction aliquots. Yield: 70%.

Preparation of 2-cyano-5-cyclopentenylaluminum chloride (85g):



According to the typical procedure (**TP1**), aluminum powder (41 mg, 1.5 mmol) and $InCl_3$ (44 mg, 0.2 mmol) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (1 mL) was added. A solution of 5-chloro-cyclopent-1-enecarbonitrile (**84g**, 127 mg, 1 mmol) in THF (1 mL) was added at 25 °C and the resulting solution was stirred at 25 °C for 24 h. The insertion reaction was monitored by GC analysis of hydrolyzed reaction aliquots. Yield: *ca.*60%.

Preparation of *β*-silyl-substituted crotylaluminum (85h):

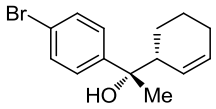


According to the typical procedure (**TP1**) aluminum powder (41 mg, 1.5 mmol) and $InCl_3$ (7 mg, 0.03 mmol) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (2 mL) was added. A solution of

β-silyl-substituted crotyl chloride (**84h**, 163 mg, 1 mmol) in THF (1 mL) was added at 25 °C and the resulting solution was stirred at 25 °C for 36 h. The insertion reaction was monitored by GC analysis of hydrolyzed reaction aliquots. Yield: 73%.

2.3.3 Preparation of Homoallylic Alcohols and Lactones (87a-u)

Synthesis of 1-(4-bromo-phenyl)-1-cyclohex-2-enyl-ethanol (87a):



The allylaluminum reagent **85a** (10 mL) was added to a solution of 4´-bromoacetophenone (**86a**, 279 mg, 1.4 mmol) in THF (1.5 mL) according to **TP2**. Purification by flash chromatography (eluent: pentane:ether = 10:1) provides the pure compound **87a** (384 mg, 97%) as colourless oil. dr > 99:1.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.44 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 5.98 - 5.89 (m, 1H), 5.76 (d, *J* = 10.5 Hz, 1H), 2.55 – 2.46 (m, 1H), 1.98 – 1.89 (m, 2H), 1.81 (s, 1H), 1.75 – 1.65 (m, 1H), 1.56 (s, 3H), 1.48 – 1.14 (m, 3H).

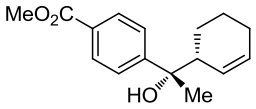
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 146.2, 132.2, 130.9, 127.2, 125.9, 120.3, 75.8, 46.4, 28.0, 25.1, 24.3, 21.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3435 (S, br.), 2930 (W), 1484 (M), 1393 (M), 1072 (S), 1007 (VS), 829 (M), 720 (M).

MS (EI, 70 eV): m/z (%) = 280 (M^+, 6), 200 (96), 198 (100), 183 (17), 80 (23).

HRMS (EI): Calcd. for $C_{14}H_{17}BrO$: 280.0463; found: 280.0258. Spectral data matching those reported in the literature.[93, 31]

Synthesis of 4-(1-cyclohex-2-enyl-1-hydroxy-ethyl)-benzoic acid methyl ester (87b):



The allylaluminum reagent **85a** (10 mL) was added to a solution of methyl 4-acetylbenzoate (**86b**, 250 mg, 1.4 mmol) in THF (1.5 mL) according to **TP2**.

Purification by flash chromatography (eluent: pentane:ether = 9:1) provides the pure compound **87b** (372 mg, 97%) as a white solid. dr > 99:1.

m. p. = 63.0 – 64.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.99 (d, *J* = 8.5 Hz, 2 H), 7.49 (d, *J* = 8.5 Hz, 2 H), 5.99 - 5.91 (m, 1 H), 5.79 (d, *J* = 10.5 Hz, 1 H), 3.90 (s, 3 H), 2.61 – 2.50 (m, 1 H), 1.99 – 1.89 (m, 2 H), 1.81 (s, 1 H), 1.77 – 1.63 (m, 1 H), 1.60 (s, 3 H), 1.51 – 1.15 (m, 3 H).

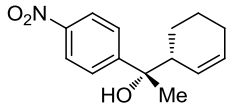
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 167.1, 152.5, 132.1, 129.3, 128.3, 125.7, 125.3, 76.0, 52.0, 46.4, 27.9, 25.1, 24.3, 21.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3506 (M), 2946 (W), 1696 (VS), 1279 (VS), 1112 (M), 711 (M).

MS (EI, 70 eV): m/z (%) = 261(1), 179 (100), 137 (8), 77 (5).

HRMS (EI): Calcd. for $[C_{16}H_{20}O_3 + H]^+$: 261.1491; found: 261.1491 $[C_{16}H_{20}O_3 + H]^+$.

Synthesis of 1-cyclohex-2-enyl-1-(4-nitro-phenyl)-ethanol (87c):



The allylaluminum reagent **85a** (10 mL) was added to a solution of 1-(4-nitrophenyl)ethanone (**86c**, 231 mg, 1.4 mmol) in THF (1.5 mL) according to **TP2**. Purification by flash chromatography (eluent: pentane:ether = 9:1) provides the pure compound **87c** (329 mg, 95%) as a yellow oil. dr > 99:1.

^{1}H NMR (300 MHz, C_6D_6): δ (ppm) = 7.85 - 7.80 (m, 2H), 7.07 – 7.02 (m, 2H), 5.75 - 5.68 (m, 1H), 5.54 – 5.48 (m, 1H), 2.17 – 2.08 (m, 1H), 1.76 – 1.60 (m, 1H), 1.50 – 1.42 (m, 1H), 1.26 (s, 1H), 1.24 – 1.15 (m, 1H), 1.12 (s, 3H), 1.09 – 1.04 (m, 2H).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 154.0, 146.5, 131.8, 125.9, 125.4, 122.7, 75.2, 46.0, 27.5, 24.9, 24.0, 21.6.

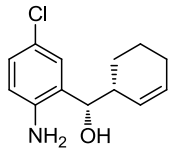
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3548 (W), 3028 (VW), 2974 (W), 2932 (W), 2860 (W), 2838 (W), 1600 (M), 1512 (VS), 1492 (M), 1448 (W), 1434 (W), 1408 (W),

1374(W), 1342 (VS), 1264 (W), 1232 (W), 1182 (W), 1142 (W), 1102 (M), 1078 (M), 1064 (M), 1046 (W), 1014 (W), 942 (W), 926 (VW), 906 (W), 894 (W), 880 (M), 852 (S), 770 (W), 756 (W), 740 (W),724 (M), 704 (S), 678 (W).

MS (EI, 70 eV): m/z (%) = 248 (M^+, 1), 166 (100), 150 (10), 120 (7).

HRMS (EI): Calcd. for $[C_{14}H_{17}NO_3 + H]^+$: 248.1287; found: 248.1276 $[C_{14}H_{17}NO_3 + H]^+$.

Synthesis of (2-amino-5-chloro-phenyl)-cyclohex-2-enyl-methanol (87d):



The allylaluminum reagent **85a** (10 mL) was added to a solution of 2-amino-5-chloro-benzaldehyde (**86d**, 218 mg, 1.4 mmol) in THF (1.5 mL) according to **TP2**. Purification by flash chromatography (eluent: pentane:ether = 2:1) provides the pure compound **87d** (315 mg, 95%) as a white solid. dr > 99:1.

m. p. = 114.1 - 115.8 °C.

^{1}H NMR (400 MHz, C_6D_6): δ (ppm) = 6.99 (s, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 5.98 (d, *J* = 8.4 Hz, 1H), 5.59-5.47 (m, 1H), 5.22-5.08 (m, 1H), 3.94 (d, *J* = 8.6 Hz, 1H), 3.71 – 3.26 (bs, 2H), 2.68 – 2.51 (m, 1H), 1.88 – 1.22 (m, 6H).

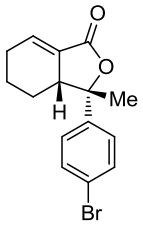
^{13}C NMR (100 MHz, C_6D_6): δ (ppm) = 143.7, 129.4, 128.5, 128.0, 127.9, 127.7, 122.1, 117.5, 77.0, 38.9, 25.1, 25.0, 20.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3358（W）, 3159 (W), 2919 (VW), 1604 (W), 1487.5 (M), 1420 (W), 826.5 (VS), 693.4 (S), 667.4 (M), 642.2 (S).

MS (EI, 70 eV): m/z (%) = 237 (M^+, 3), 220 (4), 158 (29), 156 (100), 93 (29).

HRMS (EI): Calcd. for $C_{13}H_{16}ClNO$: 237.0920; found: 237.0915.

Synthesis of 3-(4-bromophenyl)-3-methyl-3a,4,5,6-tetrahydro-3H-isobenzofuran-1-one (87e):



The allylaluminum reagent **85b** (2 mL) was added to a solution of 4´-bromoacetophenone (**86a**, 140 mg, 0.7 mmol) according to **TP3**. Purification by flash chromatography (eluent: pentane:ether = 5:1) provides the pure compound **87e** (172 mg, 81%) as colourless oil. dr > 99:1.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.44 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.83 (q, *J* = 3.3 Hz, 1H), 2.96-2.85 (m, 1H), 2.32-2.17 (m, 1H), 2.08-1.88 (m, 1H), 1.86 (s, 3H), 1.85 -1.70 (m, 2H), 1.58 -1.39 (m, 1H), 0.51 – 0.34 (m, 1H).

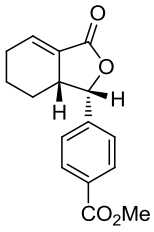
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.0, 140.2, 137.5, 131.4, 129.6, 126.9, 121.8, 87.5, 48.4, 27.8, 24.8, 24.5, 20.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm-1) = 2925 (W), 1755 (VS), 1239 (M), 1031 (S), 921 (M), 752 (M), 725 (W).

MS (EI, 70 eV): m/z (%) = 306 (M+, 2), 182 (5), 108 (100).

HRMS (EI): Calcd. for $C_{15}H_{15}BrO_2$: 306.0255; found: 306.0244.

Synthesis of 4-(3-oxo-1,3,5,6,7,7a-hexahydro-isobenzofuran-1-yl) benzoic acid methyl ester (87f):



The allylaluminum reagent **84b** (4 mL) was added to a solution of 4-formyl-benzoic acid methyl ester (**86e**, 230 mg, 1.4 mmol) in THF (1.5 mL) according to **TP3**. Purification by flash chromatography (eluent: pentane:ether = 3:1) provides the pure compound **87f** (297 mg, 78%) as a white solid. dr > 99:1.

m. p. = 171.3 – 173.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.01 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz,

2H), 6.95 (q, *J* = 3.3 Hz, 1H), 5.76 (d, *J* = 9.2 Hz, 1H), 3.91 (s, 3H), 3.41-3.27 (m, 1H), 2.37-2.23 (m, 1H), 2.13 -1.94 (m, 1H), 1.85 -1.63 (m, 2H), 1.63 -1.42 (m, 1H), 0.49 – 0.30 (m, 1H).

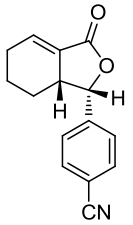
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.2, 166.5, 142.4, 138.4, 130.1, 129.7, 127.7, 125.6, 81.8, 52.2, 40.8, 24.9, 24.1, 20.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2956 (W), 1762 (S), 1715 (VS), 1292 (VS), 1182 (M), 990 (M), 759 (M).

MS (EI, 70 eV): m/z (%) = 272 (M^+, 1), 241 (7), 108 (100), 80 (21), 79 (26).

HRMS (EI): Calcd. for $C_{16}H_{16}O_4$: 272.1049; found: 272.1046.

Synthesis of 4-(3-oxo-1,3,5,6,7,7a-hexahydro-isobenzofuran-1-yl)benzonitrile (87g):



The allylaluminum reagent **85b** (4 mL) was added to a solution of 4-formyl-benzonitrile (**86f**, 184 mg, 1.4 mmol) in THF (1.5 mL) according to **TP3**. Purification by flash chromatography (eluent: pentane:ether = 2:1) provides the pure compound **87g** (291 mg, 87%) as a white solid. dr > 99:1.

m. p. = 153.2 – 155.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.65 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.97 (q, *J* = 3.4 Hz, 1H), 5.75 (d, *J* = 9.2 Hz, 1H), 3.43-3.29 (m, 1H), 2.39-2.25 (m, 1H), 2.15-1.97 (m, 1H), 1.89 -1.69 (m, 2H), 1.65 -1.45 (m, 1H), 0.46 – 0.29 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 169.9, 142.7, 138.9, 132.3, 127.2, 126.3, 118.3, 112.2, 81.2, 40.7, 24.9, 24.1, 20.8.

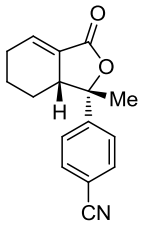
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2959 (W), 1751 (VS), 1029 (M), 990 (M), 856 (M).

MS (EI, 70 eV): m/z (%) = 240 (2), 239 (M^+, 0.4), 166 (2), 140 (5), 130 (7), 108

(100).

HRMS (EI): Calcd. for $C_{15}H_{13}NO_2$: 239.0946; found: 239.0953.

Synthesis of 4-(1-methyl-3-oxo-1,3,5,6,7,7a-hexahydro-isobenzofuran-1-yl)-benzonitrile (87h):



The allylaluminum reagent **85b** (4 mL) was added to a solution of 4-acetylbenzonitrile (**86g**, 203 mg, 1.4 mmol) in THF (1.5 mL) according to **TP3**. Purification by flash chromatography (eluent: pentane:ether = 1:1) provides the pure compound **87h** (281 mg, 79%) as a white solid. dr > 98:2.

m. p. = 165.4 – 167.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.62 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.94 (q, *J* = 3.4 Hz, 1H), 3.03-2.89 (m, 1H), 2.33-2.17 (m, 1H), 2.08-1.93 (m, 1H), 1.90(s, 3H), 1.87 -1.74 (m, 2H), 1.61 -1.40 (m, 1H), 0.45 – 0.25 (m, 1H).

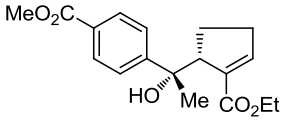
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 169.6, 146.4, 138.0, 132.1, 129.1, 126.1, 118.4, 111.7, 87.2, 48.4, 27.7, 24.8, 24.5, 20.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2943 (W), 2226 (W), 1756 (VS), 1679 (W), 1401 (W), 1252 (S), 1240 (VS), 1032 (VS), 1015 (M), 923 (M), 844 (S), 736 (S).

MS (EI, 70 eV): m/z (%) = 253 (0.5), 189 (0.6), 165 (1), 129 (6), 116 (1), 109 (8), 108 (100).

HRMS (EI): Calcd. for $C_{16}H_{15}NO_2$: 253.1103; found: 253.1093.

4-[1-(2-ethoxycarbonyl-cyclopent-2-enyl)-1-hydroxy-ethyl]-benzoic acid methyl ester (87i):



The allylaluminum reagent **85c** (1.5 mL) was added to a solution of methyl

4-acetylbenzoate (**86b**, 107 mg, 0.6 mmol) in THF (1 mL) according to **TP3**. Purification by flash chromatography (eluent: pentane:ether = 4:1) provides the pure compound **87i** (134 mg, 70%) as colourless oil. dr > 98:2.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.93 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.77 (q, *J* = 1.8 Hz, 1H), 4.21 (dd, *J* = 7.1 Hz, 3.9 Hz, 2H), 3.90 (s, 3H), 3.47-3.36 (m, 1H), 2.22-2.03 (m, 2H), 2.01-1.78 (m, 2H), 1.65 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

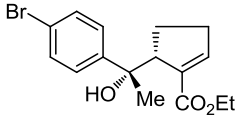
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 167.6, 167.1, 151.2, 148.9, 136.4, 128.9, 128.4, 125.9, 76.9, 61.1, 56.3, 51.9, 31.8, 28.8, 27.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3409 (br), 2978 (W), 2950 (W),1711 (VS), 1680 (VS), 1609 (W), 1434 (W), 1275 (VS), 1192 (M), 1097 (S), 1016 (M), 861 (M), 756 (M), 710 (M).

MS (EI, 70 eV): m/z (%) = 287 (4) 279 (3), 241 (6), 179 (56), 163 (9), 140 (100), 112 (30).

HRMS (ESI): Calcd. for $[C_{18}H_{22}O_5 - OH]^+$: 301.1440; found: 301.1433 $[C_{18}H_{22}O_5 - OH]^+$.

Synthesis of 5-[1-(4-bromo-phenyl)-1-hydroxy-ethyl]-cyclopent-1-enecarboxylic acid ethyl ester (87j):



The allylaluminum reagent **85c** (1.5 mL) was added to a solution of 4´-bromoacetophenone (**86a**, 119 mg, 0.6 mmol) in THF (1 mL) according to **TP3**. Purification by flash chromatography (eluent: pentane:ether = 10:1) provides the pure compound **87j** (144 mg, 71%) as a white solid. dr > 98:2.

m. p. = 75.1 – 76.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.38 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.79 (q, *J* = 2.2 Hz, 1H), 4.22 (dd, *J* = 7.2 Hz, 3.3 Hz, 2H), 3.43-3.35 (m, 1H), 2.23-2.02 (m, 2H), 1.97-1.80 (m, 2H), 1.61 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 167.7, 148.8, 144.9, 136.5, 130.6, 127.8,

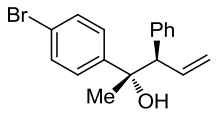
120.6, 76.6, 61.1, 56.3, 31.8, 28.9, 27.8, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3404 (W), 2976 (W), 1707 (S), 1679 (S), 1254 (M), 1096 (S), 1006 (S), 827 (M), 757 (S).

MS (EI, 70 eV): m/z (%) = 361 (87),323 (92), 277 (28), 164 (6).

HRMS (ESI): Calcd. for $[C_{16}H_{19}BrO_3 + Na]^+$: 361.0415; found: 361.0410 $[C_{16}H_{19}BrO_3 + Na]^+$.

Synthesis of 2-(4-bromo-phenyl)-3-phenyl-pent-4-en-2-ol (87k):



The allylaluminum reagent **85d** (4 mL) was added to a solution of 4´-bromoacetophenone (**86a**, 279 mg, 1.4 mmol) in THF (1.5 mL) according to **TP3**. Purification by flash chromatography (eluent: pentane:ether = 10:1) provides the pure compound **87k** (440 mg, 99%) as colourless oil. dr > 98:2.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.42 (d, *J* = 8.5 Hz, 2H), 7.32-7.05 (m, 7H), 6.19-6.05 (m, 1H), 5.08 (d, *J* = 10.3 Hz, 1H), 4.96 (d, *J* = 17.2 Hz, 1H), 3.58 (d, *J* = 8.8 Hz, 1H), 1.95 (br s, 1H), 1.43 (s, 3H).

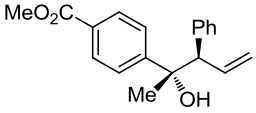
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 145.6, 139.9, 137.1, 130.9, 129.6, 128.3, 127.6, 127.0, 120.7, 118.4, 76.2, 61.9, 28.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3353 (W), 2974 (W), 1485 (M), 1075 (M), 1007 (M), 738 (M), 701 (VS).

MS (EI, 70 eV): m/z (%) = 334 (39), 283 (100), 255 (55), 227 (5), 117 (2).

HRMS (ESI): Calcd. for $[C_{17}H_{17}BrO + NH_4]^+$: 334.0807; found: 334.0801 $[C_{17}H_{17}BrO + NH_4]^+$.

Synthesis of 4-(1-hydroxy-1-methyl-2-phenyl-but-3-enyl)benzoic acid methyl ester (87l):



The allylaluminum reagent **85d** (4 mL) was added to a solution of methyl

4-acetylbenzoate (**86b**, 250 mg, 1.4 mmol) in THF (1.5 mL) according to **TP2**. Purification by flash chromatography (eluent: pentane:ether = 8:1) provides the pure compound **87l** (455 mg, 99%) as a white solid. dr > 96:4.

m. p. = 89.4 – 90.7 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) = 7.96 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.29-7.22 (m, 3H), 7.15-7.10 (m, 2H), 6.14-6.07 (m, 1H), 5.04 (d, *J* = 10.3 Hz, 1H), 4.92 (d, *J* = 17.2 Hz, 1H), 3.90 (s, 3H), 3.61 (d, *J* = 8.8 Hz, 1H), 2.05 (br s, 1H), 1.45 (s, 3H).

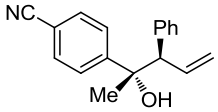
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 167.0, 151.6, 139.7, 136.8, 129.5, 129.1, 128.4, 128.2, 126.9, 125.6, 118.4, 76.3, 61.8, 52.0, 28.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3512 (W), 2974 (W), 2362 (W), 1698 (VS), 1274 (VS), 1101 (M), 916 (M), 699 (VS).

MS (EI, 70 eV): m/z (%) = 314(9), 248 (12).

HRMS (ESI): Calcd. for $[C_{19}H_{20}O_3 + NH_4]^+$: 314.1756; found: 314.1751 $[C_{19}H_{20}O_3 + NH_4]^+$.

Synthesis of 4-(1-hydroxy-1-methyl-2-phenyl-but-3-enyl)-benzonitrile (87m):



The allylaluminum reagent **85d** (4 mL) was added to a solution of 4-acetylbenzonitrile (**86g**, 203 mg, 1.4 mmol) in THF (1.5 mL) according to **TP2**. Purification by flash chromatography (eluent: pentane:ether = 6:1) provides the pure compound **87m** (363 mg, 98%) as a white solid. dr > 94:6.

m. p. = 101 – 102 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.58 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.32-7.23 (m, 3H), 7.13-7.10 (m, 2H), 6.13-6.06 (m, 1H), 5.05 (d, *J* = 10.4 Hz, 1H), 4.93 (d, *J* = 17.3 Hz, 1H), 3.56 (d, *J* = 9.1 Hz, 1H), 2.09 (br s, 1H), 1.44 (s, 3H).

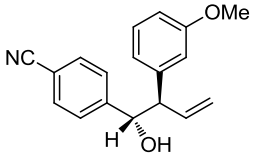
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 151.8, 139.3, 136.5, 131.6, 129.4, 128.4, 127.2, 126.5, 118.9, 118.7, 110.4, 76.2, 61.8, 28.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3475 (W), 2981 (W), 2231 (W), 1606 (W), 1367 (W), 922 (S), 839 (M), 716 (S), 696 (VS), 669 (M).

MS (EI, 70 eV): m/z (%) = 281 (100), 249 (8).

HRMS (ESI): Calcd. for $[C_{18}H_{17}NO + NH_4]^+$: 281.1654; found: 281.1648 $[C_{18}H_{17}NO + NH_4]^+$.

Synthesis of 4-[1-hydroxy-2-(3-methoxy-phenyl)-but-3-enyl] benzonitrile (87n):



The allylaluminum reagent **85e** (4 mL) was added to a solution of 4-cyanobenzaldehyde (**86f**, 184 mg, 1.4 mmol) in THF (1.5 mL) according to **TP2**. Purification by flash chromatography (eluent: pentane:ether = 2:1) provides the pure compound **87n** (371 mg, 95%) as a white solid. dr > 97:3.

m. p. = 97.1 – 98.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.66 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.11 (t, *J* = 7.9Hz, 1H), 6.75 (d, *J* = 7.4 Hz, 2H), 6.71-6.67 (m, 1H), 6.26-6.15 (m, 1H), 5.66 (d, *J* = 5.1 Hz, 1H), 5.01 (dd, *J* = 10.3 Hz, 2.1 Hz, 1H), 4.93-4.82 (m, 2H), 3.66 (s, 3H), 3.54-3.48 (m, 1H).

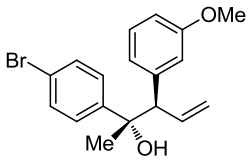
^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 159.4, 150.7, 143.7, 138.5, 131.9, 129.4, 128.1, 121.2, 119.4, 117.1, 114.7, 111.9, 109.7, 75.8, 57.7, 55.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3476 (M), 2873 (W), 2234 (W), 1605 (M), 1581 (M), 1454 (W), 1274 (M), 1224 (M), 1048 (M), 752 (S).

MS (EI, 70 eV): m/z (%) = 297 (100), 108 (1).

HRMS (ESI): Calcd. for $[C_{18}H_{17}NO_2 + NH_4]^+$: 297.1603; found: 297.1597 $[C_{18}H_{17}NO_2 + NH_4]^+$.

Synthesis of 2-(4-bromo-phenyl)-3-(3-methoxy-phenyl)-pent-4-en-2-ol (87o):



The allylaluminum reagent **85e** (4 mL) was added to a solution of

4´-bromoacetophenone (**86a**, 274 mg, 1.4 mmol) in THF (1.5 mL) according to **TP2**. Purification by flash chromatography (eluent: pentane:ether = 9:1) provides the pure compound **87o** (359 mg, 74%) as colourless oil. dr > 92:8.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.44 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.15 (t, *J* = 7.9 Hz, 1H), 6.89-6.84 (m, 2H), 6.77-6.72 (m, 1H), 6.09-6.98 (m, 1H), 5.17 (s, 1H), 4.76 (dd *J* = 10.1 Hz, 2.1 Hz, 1H), 4.61 (dd *J* = 17.2 Hz, 1.9 Hz, 1H), 3.69 (s, 3H), 3.52 (d, *J* = 9.2 Hz, 1H), 1.22 (s, 3H).

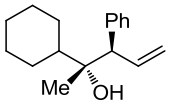
^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 159.0, 148.7, 143.4, 139.1, 130.6, 128.9, 128.5, 122.5, 119.5, 116.5, 115.9, 111.8, 75.6, 61.2, 55.2, 29.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3493 (W), 2973 (W), 1597 (M), 1581 (M), 1484 (M), 1260 (M), 1074 (M), 1006 (S), 763 (S).

MS (EI, 70 eV): m/z (%) = 364 (100), 355 (14), 177 (30).

HRMS (ESI): Calcd. for $[C_{18}H_{19}BrO_2 + NH_4]^+$: 364.0912; found: 364.0907 $[C_{18}H_{19}BrO_2 + NH_4]^+$.

Synthesis of 2-cyclohexyl-3-phenyl-pent-4-en-2-ol (87p):



The allylaluminum reagent **85f** (4 mL) was added to a solution of 1-cyclohexylethanone (**86h**, 177 mg, 1.4 mmol) in THF (1.5 mL) according to **TP2**. Purification by flash chromatography (eluent: pentane:ether = 10:1) provides the pure compound **87p** (212 mg, 62%) as colourless oil. dr > 97:3.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.37-7.21 (m, 5H), 6.37 (dt, *J* = 17.3 Hz, 9.8 Hz, 1H), 5.18 (dd, *J* = 10.2 Hz, 1.9 Hz, 1H), 5.10 (dd, *J* = 17.2 Hz, 1.9 Hz, 1H), 3.46 (d, *J* = 9.7 Hz, 1H), 2.06-1.58 (m, 6H), 1.58-0.94 (m, 6H), 0.91 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 141.9, 137.9, 129.5, 128.3, 126.5, 116.8, 75.7, 57.3, 44.6, 27.8, 26.8, 26.7, 21.5.

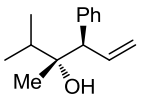
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2930 (W), 2252 (W), 1452 (W), 902 (S), 723 (VS), 649 (M).

MS (EI, 70 eV): m/z (%) = 226 (4), 128 (9), 127 (75), 118 (8), 115 (9), 109 (41), 83

(74), 43 (13).

HRMS (EI): Calcd. for $[C_{17}H_{24}O - H_2O]^+$: 226.1721; found: 226.1701 $[C_{17}H_{24}O - H_2O]^+$. Spectral data matching those reported in the literature. [93, 31]

Synthesis of 2,3-dimethyl-4-phenyl-hex-5-en-3-ol (87q):



The allylaluminum reagent **85f** (4 mL) was added to a solution of 3-methylbutan-2-one (**86i**, 120 mg, 1.4 mmol) in THF (1.5 mL) according to **TP2**. Purification by flash chromatography (eluent: pentane:ether = 10:1) provides the pure compound **87q** (257 mg, 90%) as colourless oil. dr > 98:2.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.22-7.38 (m, 5H), 6.39 (dt, *J* = 17.2 Hz, 9.9 Hz, 1H), 5.19 (dd, *J* = 10.2 Hz, 1.9 Hz, 1H), 5.13 (ddd, *J* = 17.2 Hz, 1.8 Hz, 0.7 Hz, 1H), 3.46 (d, *J* = 9.6 Hz, 1H), 2.00 (hept, *J* = 6.8 Hz, 1H), 1.40 (br s, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 3H).

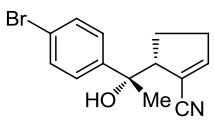
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 141.9, 137.9, 129.4, 128.3, 126.5, 116.9, 76.1, 57.7, 34.1, 20.2, 17.6, 16.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3581 (W), 3486 (W), 3076 (W), 2977 (W), 1635 (W), 1491 (W), 1387 (W), 1080 (W), 906 (S), 728 (VS), 701 (S).

MS (EI, 70 eV): m/z (%) = 186 (0.3), 161 (2), 128 (2), 118 (85), 117 (29), 87 (100), 71 (3).

HRMS (EI): Calcd. for $[C_{14}H_{20}O - H_2O]^+$: 186.1409; found: 186.1401 $[C_{14}H_{20}O - H_2O]^+$. Spectral data matching those reported in the literature.[93, 31]

Synthesis of 5-[1-(4-bromo-phenyl)-1-hydroxy-ethyl]-cyclopent-1-enecarbonitrile (87r):



The allylaluminum reagent **85g** (2 mL) was added to a solution of 4´-bromoacetophenone (**86a**, 119 mg, 0.6 mmol) in THF (1.5 mL) according to **TP3**.

Purification by flash chromatography (eluent: pentane:ether = 1:1) provides the pure compound **87r** (156 mg, 89%) as a colourless oil. dr > 99:1.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.47 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 6.85-6.77 (m, 1H), 3.38-3.27 (m, 1H), 2.32-2.13 (m, 2H), 1.96-1.77 (m, 2H), 1.74 (s, 3H).

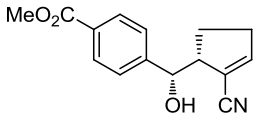
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 154.3, 144.9, 131.2, 127.3, 121.1, 117.8, 114.8, 76.4, 57.9, 32.8, 28.9, 26.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3460 (W), 2974 (W), 2217 (W), 1486 (M), 1076 (M), 1006 (S), 830 (M).

MS (EI, 70 eV): m/z (%) = 291 (M^+, 1), 199 (84), 184 (19), 182 (25), 102 (15), 97 (19).

HRMS (EI): Calcd. for $C_{14}H_{14}BrNO$: 291.0259; found: 291.0269.

Synthesis of 5-[(4-bromo-phenyl)-hydroxy-methyl]-cyclopent-1-enecarbonitrile (87s):



The allylaluminum reagent **85g** (2 mL) was added to a solution of 4-formyl-benzoic acid methyl ester (**86e**, 98 mg, 0.6 mmol) in THF (1.0 mL) according to **TP3**. Purification by flash chromatography (eluent: pentane:ether = 1:1) provides the pure compound **87s** (108 mg, 70%) as a white solid. dr > 99:1.

m. p. = 119.8 – 121.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.02 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 2.4 Hz, 1H), 5.15 (d, *J* = 3.2 Hz, 1H), 3.91 (s, 3H), 3.34-3.24 (m, 1H), 2.51-2.39 (m, 2H), 2.21 (s, 1H), 2.09-1.94 (m, 1H), 1.82-1.66 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.9, 151.9, 147.3, 129.7, 129.4, 125.9, 116.2, 115.8, 72.5, 54.3, 52.1, 32.9, 22.6.

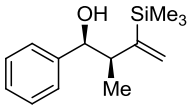
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3489 (M), 2955 (W), 1702 (VS), 1283 (VS), 1087 (M).

MS (EI, 70 eV): m/z (%) = 257 (M^+, 0.3), 226 (4), 166 (11), 165 (100), 133 (11), 93

(11).

HRMS (EI): Calcd. for $C_{15}H_{15}NO_3$: 257.1052; found: 257.1032.

Synthesis of 2-methyl-1-phenyl-3-trimethylsilanyl-but-3-en-1-ol (87t):



The allylaluminum reagent **85h** (3 mL) was added to a solution of benzaldehyde (**86j**, 74 mg, 0.7 mmol) in THF (1.0 mL) according to **TP2**. Purification by flash chromatography (eluent: pentane:ether = 20:1) provides the pure compound **87t** (158 mg, 96%) as colourless oil. dr: 89:11.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.32-7.12 (m, 5H), 5.73 (d, *J* = 2.0 Hz, 1H), 5.51 (d, ^{3}J = 2.0 Hz, 1H), 4.66 (d, *J* = 4.6 Hz, 1H), 2.69 (dq, *J* = 4.8 Hz, 7.0 Hz, 1H), 1,78 (br s, 1H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.00 (s, 9H).

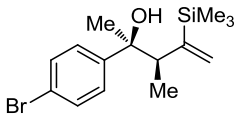
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 155.3, 143.2, 128.0, 126.9, 126.2, 125.6, 74.9, 44.8, 13.4, -0.12.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3564 (br), 2958 (W), 2362 (W), 1248 (M), 906 (S), 835 (S), 727 (VS), 699 (S).

MS (EI, 70 eV): m/z (%) = 217(5), 200 (3), 178(19), 128 (37), 113 (66), 107 (100), 79 (26), 77 (15).

HRMS (EI): Calcd. for $C_{14}H_{22}OSi$: 234.1440; found: 234.1416. Spectral data matching those reported in the literature.[93, 31]

Synthesis of 2-(4-bromo-phenyl)-3-methyl-4-trimethylsilanyl-pent-4en-2-ol (87u):



The allylaluminum reagent **85h** (3 mL) was added to a solution of 4´-bromoacetophenone (**86a**, 140 mg, 0.7 mmol) in THF (1.0 mL) according to **TP2**. Purification by flash chromatography (eluent: pentane:ether = 20:1) provides the pure compound **87u** (174 mg, 76%) as colourless oil. dr: 97:3.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.47 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz,

2H), 5.93 (d, *J* = 2.4 Hz, 1H), 5.64 (d, *J* = 2.4 Hz, 1H), 2.69 (q, *J* = 7.2 Hz, 1H), 1,73 (br s, 1H), 1,45 (s, 3H), 0.82 (d, *J* = 7.1 Hz, 3H), 0.15(s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 155.4, 146.9, 130.9, 127.2, 126.9, 120.2, 76.4, 47.4, 30.5, 16.8, -0.76.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3498 (W), 2955 (W), 1486 (W), 1246 (M), 1078 (M), 1008 (M), 852 (S), 832 (VS), 757 (M).

MS (EI, 70 eV): m/z (%) = 311(0.45), 295 (1), 201(96), 199 (100), 183 (10), 113 (26).

HRMS (EI): Calcd. for $[C_{15}H_{23}BrOSi - Me]^+$: 311.0467; found: 311.0482 $[C_{15}H_{23}BrOSi - Me]^+$.

2.4 Extension of Functionalized Allylic Aluminum Reagents

2.4.1 Typical Procedures (TP)

TP1: Typical procedure for the preparation of allylic aluminum reagents (93a-b).

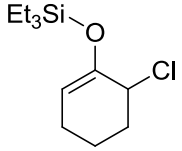
Aluminum powder (3.0 equiv) and $InCl_3$ (5 mol%) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (2.5 mL / mmol) was added. A solution of the corresponding allylic chloride (1.0 equiv.) in THF (2.5 mL / mmol) was added at the appropriate temperature (0-20°C) and the reaction mixture was stirred until the conversion of the allyl halide reached >95% (monitored by GC-analysis of hydrolyzed reaction aliquots). The remaining aluminum powder was allowed to settle down and the allylaluminum reagent is obtained as a clear solution.

TP2: Typical procedure for the preparation of homoallylic alcohols and lactones (95a-h).

The allylaluminum halides (**93a-b**) prepared according to **TP1** were added to a solution of an aldehyde or a ketone in THF at -78 °C and the mixture was stirred at this temperature for 1-2 h. After quenching with water (10 mL), the reaction mixture was extracted with ether (3 × 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography provided the pure compound.

2.4.2 Preparation of allylic chlorides

Synthesis of ((6-chlorocyclohex-1-en-1-yl)oxy)triethylsilane (92a).



N-Chlorosuccinimide (1.4 g, 10 mmol) was slowly added to the solution of (cyclohex-1-en-1-yloxy)triethylsilane (2.1 g, 10 mmol) in dichloromethane (100 mL) at 0 °C. The resulting mixture was stirred for 5 h at 0 °C. After the mixture was quench with ice water (20 mL) was added slowly. The reaction mixture was extracted with dichloromethane (3 × 20 mL). The extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (eluent: iso-hexane) provided the pure compound **92a** (1.15 g, 46%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.98 (dd, *J* = 4.6 Hz, 2.9 Hz, 1H), 4.38-4.33 (m, 1H), 1.52-0.66 (m, 6H), 1.05-0.93 (m, 9H), 0.76-0.62 (m, 6H).

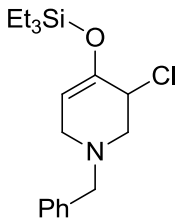
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 148.7, 107.6, 58.3, 32.9, 23.8, 22.9, 6.7, 5.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2952, 1659, 1456, 1231, 1195, 1008, 981, 895, 830, 727, 705.

MS (EI, 70 eV): m/z (%) = 246 (15), 212 (5), 211 (9), 210 (15), 190 (5), 188 (14), 182 (13), 180 (29), 150 (7), 121 (100).

HRMS (EI): Calcd. for $[C_{12}H_{23}ClOSi]^+$: 246.1207; found: 246.1207 $[C_{12}H_{23}ClOSi]^+$.

Synthesis of 1-benzyl-3-chloro-4-((triethylsilyl)oxy)-1,2,3,6-tetrahydropyridine (92b).



N-Chlorosuccinimide (705 g, 5.3 mmol) was slowly added to the solution of 1-benzyl-4-((triethylsilyl)oxy)-1,2,3,6-tetrahydropyridine (1.6 g, 5.3 mmol) in dichloromethane (50 mL) at -20 °C. The resulting mixture was stirred for 12 h between -20 °C and 25 °C. After the mixture was quench with ice water (20 mL) was added slowly. The reaction mixture was extracted with dichloromethane (3 × 20 mL). The extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (eluent: iso-hexane) provided the pure compound **92b** (0.72 g, 40%) as pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.47-7.27 (m, 5H), 5.01 (dd, *J* = 4.4 Hz, 3.0 Hz, 1H), 4.39-4.33 (m, 1H), 3.80 (d, *J* = 13.6 Hz, 1H), 3.62 (d, *J* = 13.6 Hz, 1H), 3.33-3.24 (m, 1H), 3.06-2.94 (m, 2H), 2.89-2.81 (m, 1H), 1.11-1.02 (m, 9H), 0.84-0.73 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 147.4, 137.8, 128.9, 128.3, 127.2, 105.1, 61.4, 57.7, 56.8, 51.4, 6.7, 5.0.

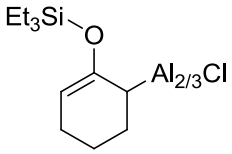
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2953, 2750, 1668, 1454, 1355, 1136, 1057, 1003, 976, 869, 803, 728.

MS (EI, 70 eV): m/z (%) = 336 (19), 316 (12), 303 (24), 302 (100), 301 (12), 300 (36), 246 (3), 210 (3), 189 (5), 121 (15), 91 (68).

HRMS (EI): Calcd. for $[C_{18}H_{28}ClNOSi - H]^+$: 336.1550; found: 336.1541 $[C_{18}H_{28}ClNOSi - H]^+$

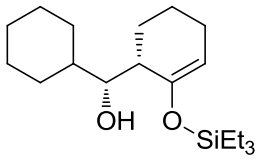
2.4.3 Preparation of allylic aluminum reagents, homoallylic alcohols and lactones.

Preparation of allylic aluminum reagent (93a).



According to the typical procedure (**TP1**), aluminum powder (162 mg, 6 mmol) and $InCl_3$ (22 mg, 0.1 mmol) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (2 mL) was added. A solution of ((6-chlorocyclohex-1-en-1-yl)oxy)triethylsilane (**92a**, 492 mg, 2 mmol) in THF (2 mL) was added at 25 °C and the resulting solution was stirred at 25 °C for 16 h. The insertion reaction was monitored by GC analysis of hydrolyzed reaction aliquots. Yield: 70%.

Synthesis of cyclohexyl(2-((triethylsilyl)oxy)cyclohex-2-en-1-yl)methanol (95a).



The allylaluminum reagent **93a** (4 mL) was added to a solution of cyclohexanecarbaldehyde (**94a**, 157 mg, 1.4 mmol) according to **TP2**. Purification by flash chromatography (eluent: iso-hexane:ether = 50:1) provides the pure compound **95a** (327 mg, 72%) as colourless oil. dr > 90:10.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.91-4.89 (m, 1H), 3.85 (dd, *J* = 8.5 Hz, 1.9Hz, 1H), 2.37-2.32 (m, 1H), 2.17-1.08 (m, 17H), 0.99-0.95 (m, 9H), 0.70-0.63 (m, 6H).

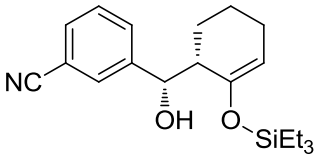
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 150.9, 106.7, 75.4, 42.0, 41.6, 33.1, 30.6, 29.9, 26.5, 26.0, 24.3, 22.0, 6.8, 5.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2928, 2252, 1615, 1449, 1222, 903, 723.

MS (EI, 70 eV): m/z (%) = 229 (5), 228 (17), 227 (100), 199 (6), 117 (11), 87 (21).

HRMS (EI): Calcd. for $[C_{19}H_{36}O_2Si - H_2O]^+$: 306.2379; found: 306.2377.

Synthesis of 3-(hydroxy(2-((triethylsilyl)oxy)cyclohex-2-en-1-yl)methyl) benzonitrile (95b).



The allylaluminum reagent **93a** (4 mL) was added to a solution of 3-formylbenzonitrile (**94b**, 183 mg, 1.4 mmol) according to **TP2**. Purification by flash chromatography (eluent: iso-hexane:ether = 15:1) provides the pure compound **95b** (363 mg, 76%) as colourless oil. dr > 93:7.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.61-7.58 (m, 1H), 7.53-7.47 (m, 2H), 7.42-7.35 (m, 1H), 5.18 (d, *J* = 3.3 Hz, 1H), 4.95-4.90 (m, 1H), 2.19-2.12 (m, 1H), 2.04-1.94 (m, 2H), 1.75-1.62 (m, 2H), 1.37-1.12 (m, 2H), 0.92-0.86 (m, 9H), 0.69-0.61 (m, 6H).

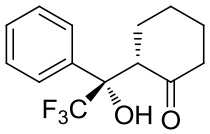
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 149.3, 146.9, 130.5, 130.1, 129.8, 128.5, 119.2, 111.8, 106.3, 72.6, 47.6, 24.1, 21.9, 20.9, 6.7, 4.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2953, 2231, 1670, 1457, 1219, 1009, 904, 727.

MS (EI, 70 eV): m/z (%) = 325 (1), 248 (5), 247 (17), 246 (100), 181 (1), 115 (28).

HRMS (EI): Calcd. for $[C_{20}H_{29}NO_2Si - H_2O]^+$: 325.1862; found: 325.1851.

Synthesis of 2,2,2-trifluoro-1-hydroxy-1-phenylethyl)cyclohexanone (95c).



The allylaluminum reagent **93a** (4 mL) was added to a solution of 2,2,2-trifluoro-1-phenylethanone (**94c**, 244 mg, 1.4 mmol) according to **TP2**. Purification by flash chromatography (eluent: iso-hexane:ether = 50:1) provides the pure compound **95c** (217 mg, 57%) as colourless oil. dr > 95:5.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.58-7.51 (m, 2H), 7.46-7.32 (m, 3H), 6.42 (s, 1H), 3.34-3.24 (m, 1H), 2.66-2.53 (m, 1H), 2.52-2.42 (m, 1H), 2.27-2.14 (m, 1H), 1.84-1.47 (m, 5H).

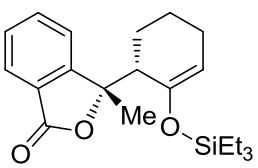
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 216.7, 136.3 (q, *J* = 1.1 Hz), 128.3, 128.2, 125.8 (q, *J* = 288.7 Hz), 125.7 (q, *J* = 1.7 Hz), 78.5 (q, *J* = 27.9 Hz), 52.0, 44.3, 32.1, 30.5, 25.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2944, 1697, 1450, 1265, 1154, 907, 712.

MS (EI, 70 eV): m/z (%) = 203 (3), 105 (21), 86 (12), 42 (100).

HRMS (EI): Calcd. for $[C_{14}H_{15}F_3O_2]^+$: 272.1024; found: 272.1083 $[C_{14}H_{15}F_3O_2]^+$

Synthesis of (2-((triethylsilyl)oxy)cyclohex-2-en-1-yl)(3,4,5-trimethoxyphenyl) methanol (95d).



The allylaluminum reagent **93a** (4 mL) was added to a solution of methyl ethyl 2-acetylbenzoate (**94d**, 269 mg, 1.4 mmol) according to **TP2**. Purification by flash chromatography (eluent: iso-hexane:ether = 15:1) provides the pure compound **95d** (326 mg, 63%) as colourless oil. dr > 90:10.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.86-7.81 (m, 1H), 7.62-7.58 (m, 1H), 7.48-7.42 (m, 2H), 4.94-4.88 (m, 1H), 2.77-2.69 (m, 1H), 2.16-1.93 (m, 2H), 1.73 (s, 3H), 1.70-1.52 (m, 2H), 1.40-1.25 (m, 2H), 0.97-0.89 (m, 9H), 0.70-0.61 (m, 6H).

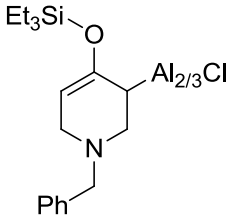
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.2, 154.2, 149.0, 133.5, 128.5, 126.5, 125.3, 121.4, 106.6, 89.7, 45.3, 26.5, 26.2, 23.7, 20.5, 6.7, 4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2934, 2253, 1759, 1466, 1223, 904.

MS (EI, 70 eV): m/z (%) = 358 (4), 330 (8), 329 (33), 213 (5), 212 (18), 211 (100), 183 (11), 148 (16), 147 (93), 115 (31), 87 (26).

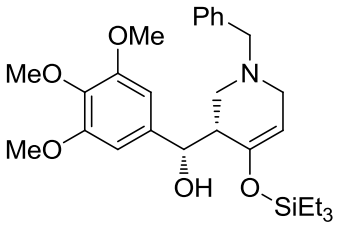
HRMS (EI): Calcd. for $[C_{21}H_{30}O_3Si]^+$: 358.1964; found: 358.1968 $[C_{21}H_{30}O_3Si]^+$

Preparation of allylic aluminum reagent (93b).



According to the typical procedure (**TP1**), aluminum powder (162 mg, 6 mmol) and $InCl_3$ (22 mg, 0.1 mmol) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (2 mL) was added. A solution of 1-benzyl-3-chloro-4-((triethylsilyl)oxy)-1,2,3,6-tetrahydropyridine (**92b**, 672 mg, 2 mmol) in THF (2 mL) was added at 25 °C and the resulting solution was stirred at 25 °C for 16 h. The insertion reaction was monitored by GC analysis of hydrolyzed reaction aliquots. Yield: 70%.

Synthesis of (1-benzyl-4-((triethylsilyl)oxy)-1,2,3,6-tetrahydropyridin-3-yl) (3,4,5-trimethoxyphenyl)methanol (95e).



The allylaluminum reagent **93b** (2 mL) was added to a solution of 3,4,5-trimethoxybenzaldehyde (**94e**, 137 mg, 0.7 mmol) according to **TP2**. Purification by flash chromatography (eluent: iso-hexane:ether = 4:1) provides the pure compound **95e** (216 mg, 62%) as colourless oil. dr > 95:5.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.42-7.27 (m, 5H), 6.61 (br s, 1H), 6.50 (s, 2H), 5.11 (s, 1H), 4.99 (dd, *J* = 4.9 Hz, 1.9 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 6H), 3.65-3.47 (m, 2H), 3.31 (dd, *J* = 15.3 Hz, 4.3 Hz, 1H), 2.98 (d, *J* = 12.5 Hz, 1H), 2.28-2.27 (m, 1H), 2.33-2.20 (m, 2H), 1.11-1.01 (m, 9H), 0.83-0.73 (m, 6H).

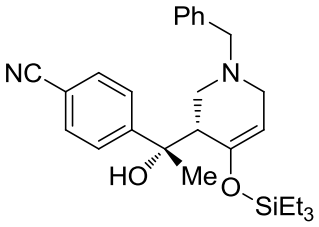
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 153.0, 149.2, 137.7, 136.4, 134.4, 129.4, 128.5, 127.7, 108.7, 102.4, 77.2, 60.8, 58.2, 56.1, 51.6, 50.5, 46.9, 6.7, 5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2958, 2251, 1591, 1128, 902, 721.

MS (EI, 70 eV): m/z (%) = 499 (0.01), 367 (1), 198 (1), 196 (3), 189 (2), 91 (100).

HRMS (EI): Calcd. for $[C_{28}H_{41}NO_5Si]^+$: 499.2754; found: 499.2759.

Synthesis of 4-(1-benzyl-4-((triethylsilyl)oxy)-1,2,3,6-tetrahydropyridin-3-yl)-1-hydroxyethyl)benzonitrile (95f).



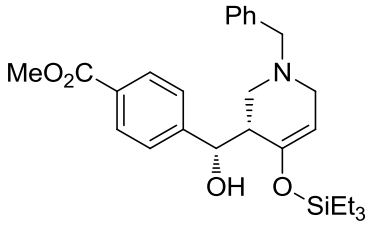
The allylaluminum reagent **93b** (2 mL) was added to a solution of 4-acetylbenzonitrile (**94f**, 102 mg, 0.7 mmol) according to **TP2**. Purification by flash chromatography (eluent: iso-hexane:ether = 5:1) provides the pure compound **95f** (219 mg, 70%) as colourless oil. dr > 93:7.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.48-7.15 (m, 9H), 5.00 (dd, *J* = 4.3 Hz, 2.4 Hz, 1H), 3.63 (d, *J* = 12.4 Hz, 1H), 3.43 (dd, *J* = 15.3 Hz, 4.3 Hz, 1H), 3.17 (d, *J* =

12.4 Hz, 1H), 2.85-2.76 (m, 1H), 2.49-2.41 (m, 1H), 2.30-2.25 (m, 1H), 2.15 (dd, *J* = 11.3 Hz, 3.6 Hz, 1H), 1.50 (s, 3H), 1.09-0.99 (m, 9H), 0.82-0.71 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 155.2, 148.7, 136.5, 131.6, 129.8, 128.5, 127.7, 125.7, 119.1, 109.5, 102.7, 77.4, 61.8, 51.9, 51.5, 48.3, 29.6, 6.8, 5.1.

Synthesis of methyl 4-((1-benzyl-4-((triethylsilyl)oxy)-1,2,3,6-tetrahydropyridin-3-yl)(hydroxy)methyl)benzoate (95g).



The allylaluminum reagent **93b** (2 mL) was added to a solution of methyl 4-formylbenzoate (**94g**, 115 mg, 0.7 mmol) according to **TP2**. Purification by flash chromatography (eluent: iso-hexane:ether = 8:1) provides the pure compound **95g** (199 mg, 61%) as colourless oil. dr > 95:5.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.81 (d, *J* = 8.2 Hz, 2H), 7.46-7.40 (m, 3H), 7.37-7.31 (m, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 6.70 (br s, 1H), 5.12 (s, 1H), 5.03 (dd, *J* = 4.9 Hz, 1.9 Hz, 1H), 3.91 (s, 3H), 3.72 (d, *J* = 12.4 Hz, 1H), 3.39 (dd, *J* = 14.8 Hz, 5.1 Hz, 1H), 3.26 (d, *J* = 12.4 Hz, 1H), 2.87-2.76 (m, 2H), 2.16-2.06 (m, 2H), 1.10-1.01 (m, 9H), 0.83-0.73 (m, 6H).

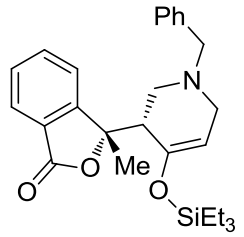
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 167.1, 150.4, 149.1, 136.9, 129.9, 129.3, 128.6, 128.2, 127.8, 125.6, 102.0, 73.5, 62.1, 52.3, 51.9, 48.9, 46.6, 6.7, 5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2952, 1703, 1443, 1280, 1193, 1103, 829, 728.

MS (EI, 70 eV): m/z (%) = 466 (4), 438 (6), 376 (3), 319 (6), 304 (6), 303 (22), 302 (62), 300 (10), 279 (11), 188 (41), 164 (8), 133 (15), 91 (100).

HRMS (EI): Calcd. for $[C_{27}H_{37}NO_4Si - H]^+$: 466.2414; found: 466.2407 $[C_{27}H_{37}NO_4Si - H]^+$

Synthesis of 3-(1-benzyl-4-((triethylsilyl)oxy)-1,2,3,6-tetrahydropyridin-3-yl)-3-methylisobenzofuran-1(3H)-one (95h).



The allylaluminum reagent **93b** (4 mL) was added to a solution of methyl ethyl 2-acetylbenzoate (**94d**, 269 mg, 1.4 mmol) according to **TP2**. Purification by flash chromatography (eluent: iso-hexane:ether = 7:1) provides the pure compound **95h** (478 mg, 70%) as colourless oil. dr > 97:3.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.76-7.69 (m, 2H), 7.56-7.51 (m, 1H), 7.41-7.37 (m, 1H), 7.33-7.22 (m, 5H), 4.62 (dd, *J* = 4.1 Hz, 3.0 Hz, 1H), 3.51-3.42 (m, 2H), 3.10 (dd, *J* = 15.2 Hz, 3.9 Hz, 1H), 2.89 (dd, *J* = 11.8 Hz, 3.0 Hz, 1H), 2.71-2.62 (m, 2H), 2.45 (dd, *J* = 11.8 Hz, 4.4 Hz, 1H), 1.59 (s, 3H), 0.85-0.80 (m, 9H), 0.56-0.50 (m, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 170.0, 153.4, 147.9, 137.8, 132.8, 129.3, 128.2, 128.1, 127.1, 126.4, 124.7, 123.6, 102.7, 89.7, 62.6, 52.3, 51.2, 46.9, 25.1, 6.5, 4.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2953, 2874, 1760, 1671, 1465, 1353, 1284, 1208, 1118, 1023, 855, 726, 696.

MS (EI, 70 eV): m/z (%) = 448 (8), 304 (6), 303 (24), 302 (100), 186 (8), 103 (18), 91 (64), 75 (11).

HRMS (EI): Calcd. for $[C_{27}H_{35}NO_3Si - H]^+$: 448.2308; found: 448.2302 $[C_{27}H_{35}NO_3Si - H]^+$

2.5 Preparation of Functionalized Organomanganese(II) Reagents by Direct Insertion of Manganese to Aromatic and Benzylic Halides

2.5.1 Typical Procedures (TP)

TP1: Typical procedure for the preparation of aromatic manganese reagents (99a-h).

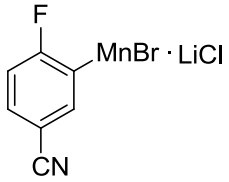
LiCl (1.5 equiv.) was placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). After cooled to room temperature, this flask was charged with manganese powder (3 equiv.), $InCl_3$ (2.5 mol %) and $PbCl_2$ (2.5 mol %) and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (2 mL) was added. Manganese powder was activated with TMSCl (1 mol%). The solution of organic halide in THF (2-8 mL) was then added at the appropriate temperature (0-25 °C) and the reaction mixture was stirred until the conversion of the organic halide reached >95% (monitored by GC-analysis of hydrolyzed reaction aliquots). Yields of these resulting aromatic manganese reagents were determined by iodolysis in THF.

TP2: Typical procedure for the preparation of benzylic manganese reagents (103a-h).

Manganese powder (3 equiv.), $InCl_3$ (2.5 mol %) and $PbCl_2$ (2.5 mol %) were placed in an argon-flushed flask and dried for 5 min at 380 °C (heat gun) under high vacuum (1 mbar). The flask was evacuated and backfilled with argon three times and THF (5 mL) was added. Manganese powder was activated with TMSCl (1 mol%). The solution of organic halide in THF (5 mL) was then added at 25 °C and the reaction mixture was stirred until the conversion of the organic halide reached >95% (monitored by GC-analysis of hydrolyzed reaction aliquots). Yields of these resulting benzylic manganese reagents were determined by iodolysis in THF.

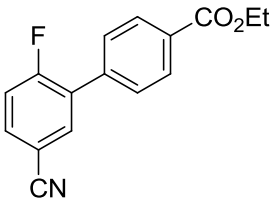
2.5.2 Preparation of Aromatic and Benzylic Manganese Reagents

Preparation of (5-cyano-2-fluorophenyl)manganese(II) bromide (99a).



According to **TP1**, 3-bromo-4-fluorobenzonitrile (**98a**, 400 mg, 2 mmol) reacted with manganese powder (330 mg, 6 mmol), LiCl (127 mg, 3 mmol), $InCl_3$ (11 mg, 2.5 mol %) and $PbCl_2$ (14 mg, 2.5 mol %) in THF (4 mL) within 24 h at 50 °C affording the corresponding aryl manganese reagent **99a** in 64% yield.

Synthesis of ethyl 5'-cyano-2'-fluoro-[1,1'-biphenyl]-4-carboxylate (101a).



Ethyl 4-iodobenzoate (**100a**, 334 mg, 1.2 mmol), Pd-PEPPSI-*i*Pr (47 mg, 5 mol%) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (5-cyano-2-fluorophenyl)manganese(II) bromide (**99a**, 4 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/Et_2O = 5:1) afforded **101a** (227 mg, 70%) as a white solid.

m. p. = 123.0 – 124.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.17 (d, *J* = 8.6 Hz, 2H), 7.81 (dd, *J* = 7.1 Hz, 2.1 Hz, 1H), 7.73-7.67 (m, 1H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.35-7.28 (m, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 165.9, 161.9 (d, *J* = 258.9 Hz), 137.6 (d, *J* = 1.5 Hz), 134.9 (d, *J* = 4.8 Hz), 133.7 (d, *J* = 9.8 Hz), 130.7, 129.9, 129.8 (d, *J* = 14.9

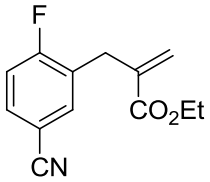
Hz), 128.9 (d, *J* = 3.1 Hz), 117.8 (d, *J* = 24.4 Hz), 117.7 (d, *J* = 0.6 Hz), 109.2 (d, *J* = 4.2 Hz), 61.2, 14.3.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3065 (W), 2983 (W), 2229 (M), 1882 (VW), 1705 (VS), 1608 (M), 1485 (M), 1365 (M), 1272 (VS), 1222 (S), 1100 (VS), 1014 (M), 824 (M), 705 (M).

MS (EI, 70 eV): m/z (%) = 269 (M^+, 73), 242 (11), 241 (81), 225 (39), 224 (100), 197 (8), 196 (49), 195 (45), 176 (11), 169 (31), 145 (4), 112 (6), 84 (3).

HRMS (EI): Calcd. for $[C_{16}H_{12}FNO_2]^+$: 269.0852; found: 269.0846.

Synthesis of ethyl 2-(5-cyano-2-fluorobenzyl)acrylate (101b).



Ethyl 2-(bromomethyl)acrylate (**100b**, 232 mg, 1.2 mmol), and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (5-cyano-2-fluorophenyl)manganese(II) bromide (**99a**, 4 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/Et_2O = 10:1) afforded **101b** (198 mg, 71%) as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.61-7.51 (m, 2H), 7.19-7.10 (m, 1H), 6.33 (s, 1H), 5.58 (d, *J* = 0.6 Hz, 1H), 4.21 (q, *J* = 7.4 Hz, 2H), 3.69 (s, 2H), 1.29 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 165.9, 163.4 (d, *J* = 255 Hz), 137.4 (d, *J* = 0.8 Hz), 135.4 (d, *J* = 6 Hz), 132.6 (d, *J* = 9.7 Hz), 128.1 (d, *J* = 16.5 Hz), 127.4 (d, *J* = 1.1 Hz), 118.1 (d, *J* = 0.6 Hz), 116.7 (d, *J* = 23.8 Hz), 108.4 (d, *J* = 3.9 Hz), 61.0, 30.8 (d, *J* = 2.8 Hz).14.0.

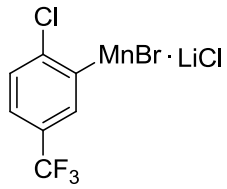
IR (Diamond-ATR, neat): ν (cm^{-1}) = 2984 (VW), 2232 (W), 1712 (VW), 1633 (W),

1495 (S), 1328 (M), 1249 (S), 1145 (S), 1026 (M), 908 (M), 825 (M), 730 (M), 699 (W), 648 (W).

MS (EI, 70 eV): m/z (%) = 233 (M^+, 100), 205 (53), 202 (42), 187 (53), 186 (14), 184 (41), 159 (97), 158 (92), 157 (64), 133 (52), 106 (16).

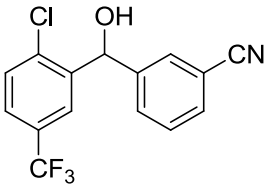
HRMS (EI): Calcd. for $[C_{13}H_{12}FNO_2]^+$: 233.0852; found: 233.0841.

Preparation of (2-chloro-5-(trifluoromethyl)phenyl)manganese(II) bromide (99b).



According to **TP1**, 2-bromo-1-chloro-4-(trifluoromethyl)benzene (**98b**, 519 mg, 2 mmol) reacted with manganese powder (330 mg, 6 mmol), LiCl (127 mg, 3 mmol), $InCl_3$ (11 mg, 2.5 mol %) and $PbCl_2$ (14 mg, 2.5 mol %) in THF (4 mL) within 24 h at 50 °C affording the corresponding aryl manganese reagent **99b** in 72% yield.

Synthesis of 3-((2-chloro-5-(trifluoromethyl)phenyl)(hydroxy)methyl) benzonitrile (101c).



3-Formylbenzonitrile (**100c**, 183 mg, 1.4 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (2-chloro-5-(trifluoromethyl)phenyl)manganese(II) bromide (**09b**, 4 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/Et_2O = 2:1) afforded **101c** (316 mg, 73%) as a white solid.

m. p. = 128.1 – 130.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.96 (d, *J* = 1.7 Hz, 1H), 7.73-7.44 (m, 6H), 6.27 (d, *J* = 3.3 Hz, 1H), 2.88 (s, 1H).

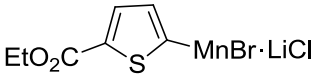
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 142.9, 141.1, 135.8 (q, *J* = 1.7 Hz), 131.7, 131.4, 130.6, 130.3, 129.5, 129.9 (q, *J* = 33.2 Hz) 126.0 (q, *J* = 3.7 Hz), 124.8 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.5 Hz), 118.5, 112.6, 71.4.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3455 (M), 3050 (VW), 2923 (VW), 2236 (M), 1609 (W), 1403 (W), 1326 (S), 1277 (M), 1165 (S), 1118 (VS), 1078 (S), 1036 (M), 898 (W), 828 (M), 694 (M), 641 (W).

MS (EI, 70 eV): m/z (%) = 311 (M^+, 65), 292 (14), 276 (15), 258 (14), 208 (52), 206 (71), 177 (15), 160 (21), 144 (28), 130 (73), 104 (100).

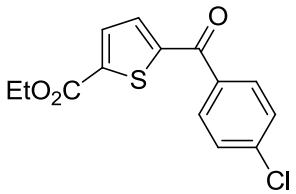
HRMS (EI): Calcd. for $[C_{15}H_9ClF_3NO]^+$: 311.0325; found: 311.0319.

Preparation of (5-(ethoxycarbonyl)thiophen-2-yl)manganese(II) bromide (99c).



According to **TP1**, ethyl 5-bromothiophene-2-carboxylate (**108c**, 470 mg, 2 mmol) reacted with manganese powder (330 mg, 6 mmol), LiCl (127 mg, 3 mmol), $InCl_3$ (11 mg, 2.5 mol %) and $PbCl_2$ (14 mg, 2.5 mol %) in THF (10 mL) within 12 h between 0-25 °C affording the corresponding aryl manganese reagent **99c** in 70% yield.

Synthesis of ethyl 5-(4-chlorobenzoyl)thiophene-2-carboxylate (101d).



4-Chlorobenzoyl chloride (**100d**, 210 mg, 1.2 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (5-(ethoxycarbonyl)thiophen-2-yl)manganese(II) bromide (**99c**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with

CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/Et_2O = 20:1) afforded **101d** (240 mg, 68%) as a white solid.

m. p. = 105.9 – 107.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.84 (d, *J* = 8.6 Hz, 2H), 7.79 (d, *J* = 4.1 Hz, 1H), 7.59 (d, *J* = 4.1 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

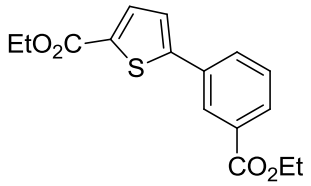
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 186.7, 161.5, 147.1, 140.6, 139.3, 135.5, 133.7, 132.9, 130.6, 128.9, 61.9, 14.2.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3073 (W), 2980 (W), 2961 (W), 2569 (VW), 1701 (VS), 1627 (S), 1585 (M), 1444 (W), 1399 (W), 1249 (VS), 1091 (S), 840 (M), 745 (S), 685 (M).

MS (EI, 70 eV): m/z (%) = 294 (M^+, 78), 265 (19), 249 (16), 248 (75), 220 (14), 183 (63), 154 (39), 140 (32), 139 (100), 111 (49), 75 (17).

HRMS (EI): Calcd. for $[C_{14}H_{11}ClO_3S]^+$: 294.0117; found: 294.0112.

Synthesis of ethyl 5-(3-(ethoxycarbonyl)phenyl)thiophene-2-carboxylate (101e).



Ethyl 3-bromobenzoate (**100e**, 206 mg, 0.9 mmol), Pd-PEPPSI-*i*Pr (30 mg, 5 mol%) and THF (1.0 mL) were placed in an argon-flushed flask. To this mixture was added (5-(ethoxycarbonyl)thiophen-2-yl)manganese(II) bromide (**99c**, 7.6 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/Et_2O = 10:1) afforded **101e** (210 mg, 77%) as a white solid.

m. p. = 80.9 – 82.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.32 (d, *J* = 1.7 Hz, 1H), 8.07-8.00 (m, 1H), 7.85-7.77 (m, 2H), 7.54-7.46 (m, 1H), 7.39-7.36 (m, 1H), 4.46-4.35 (m, 4H), 1.46-1.36 (m, 6H).

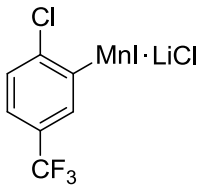
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 165.9, 162.1, 149.7, 134.2, 133.7, 133.2, 131.4, 130.2, 129.5, 129.1, 127.1, 124.2, 61.3, 61.2, 14.4, 14.3.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 2978 (W), 1717 (S), 1693 (VS), 1451 (M), 1366 (M), 1277 (VS), 1238 (S), 1100 (VS), 1080 (S), 1025 (M), 805 (M), 747 (VS), 683 (W).

MS (EI, 70 eV): m/z (%) = 304 (M^+, 100), 276 (22), 260 (15), 259 (77), 247 (10), 231 (12), 230 (38), 204 (5), 159 (16), 115 (10).

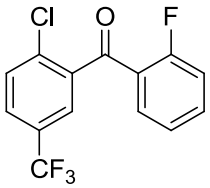
HRMS (EI): Calcd. for $[C_{16}H_{16}O_4S]^+$: 304.0769; found: 304.0761.

Preparation of (2-chloro-5-(trifluoromethyl)phenyl)manganese(II) iodide (99d).



According to **TP1**, 1-chloro-2-iodo-4-(trifluoromethyl)benzene (**98d**, 613 mg, 2 mmol) reacted with manganese powder (330 mg, 6 mmol), LiCl (127 mg, 3 mmol), $InCl_3$ (11 mg, 2.5 mol %) and $PbCl_2$ (14 mg, 2.5 mol %) in THF (4 mL) within 18 h at 25 °C affording the corresponding aryl manganese reagent **99d** in 84% yield.

Synthesis of (2-chloro-5-(trifluoromethyl)phenyl)(2-fluorophenyl)methanone (101f).



2-Fluorobenzoyl chloride (**100f**, 221 mg, 1.4 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (2-chloro-5-(trifluoromethyl)phenyl)manganese(II) iodide (**99d**, 4 mL) dropwise at

0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/Et_2O = 10:1) afforded **101f** (360 mg, 85%) as a white solid.

m. p. = 50.9 – 52.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.88-7.81 (m, 1H), 7.76-7.55 (m, 4H), 7.35-7.27 (m, 1H), 7.17-7.07 (m, 1H).

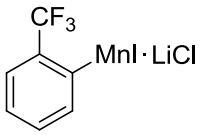
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 190.4 (d, *J* = 0.6 Hz), 161.7 (d, *J* = 257.5 Hz), 140.4 (d, *J* = 0.8 Hz), 135.7 (d, *J* = 8.9 Hz), 135.1 (m), 131.3 (d, *J* = 1.1 Hz), 130.7, 129.6 (q, *J* = 33.0 Hz), 128.2 (q, *J* = 3.7 Hz), 126.2 (m), 125.3 (d, *J* = 10.4 Hz), 123.3 (q, *J* = 270.8 Hz), 124.7 (d, *J* = 3.9 Hz), 116.7 (d, *J* = 22.2 Hz).

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3044 (VW), 1664 (S), 1607 (S), 1481 (M), 1455 (M), 1332 (S), 1289 (S), 1171 (S), 1123 (VS), 1079 (VS), 957 (W), 914 (W), 836 (S), 756 (M), 629 (W).

MS (EI, 70 eV): m/z (%) = 302 (M^+, 73), 209 (28), 207 (100), 180 (11), 178 (38), 143 (9), 123 (79), 95 (70).

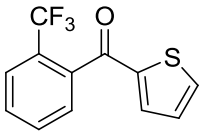
HRMS (EI): Calcd. for $[C_{14}H_7ClF_4O]^+$: 302.0122; found: 302.0120.

Preparation of (2-(trifluoromethyl)phenyl)manganese(II) iodide (99e)



According to **TP1**, 1-iodo-2-(trifluoromethyl)benzene (**98e**, 544 mg, 2 mmol) reacted with manganese powder (330 mg, 6 mmol), LiCl (127 mg, 3 mmol), $InCl_3$ (11 mg, 2.5 mol %) and $PbCl_2$ (14 mg, 2.5 mol %) in THF (10 mL) within 23 h at 25 °C affording the corresponding aryl manganese reagent **99e** in 76% yield.

Synthesis of thiophen-2-yl(2-(trifluoromethyl)phenyl)methanone (101g).



Thiophene-2-carbonyl chloride (**100g**, 205 mg, 1.4 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (2-(trifluoromethyl)phenyl)manganese(II) iodide (**99e**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/Et_2O = 20:1) afforded **101g** (266 mg, 74%) as a white solid.

m. p. = 58.1 – 59.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.83-7.75 (m, 2H), 7.69-7.59 (m, 2H), 7.57-7.49 (m, 1H), 7.35 (dd, *J* = 3.7 Hz, 1.2 Hz, 1H), 7.13 (dd, *J* = 4.8 Hz, 3.7 Hz, 1H).

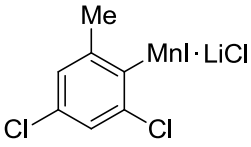
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 187.5, 143.8 (q, *J* = 0.9 Hz), 137.8 (q, *J* = 2.2 Hz), 136.0, 135.7, 131.4 (q, *J* = 1.0 Hz), 130.1, 128.3, 128.2, 128.0 (q, *J* = 32.3 Hz), 126.8 (q, *J* = 4.6 Hz), 123.5 (q, *J* = 274.0 Hz).

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3100 (VW), 1979 (VW), 1648 (VS), 1411 (S), 1315 (VS), 1286 (S), 1172 (S), 1149 (M), 1113 (VS), 1045 (M), 846 (M), 775 (M), 730 (W).

MS (EI, 70 eV): m/z (%) = 256 (M^+, 39), 237 (2), 173 (10), 145 (15), 111 (100), 95 (3), 82 (5).

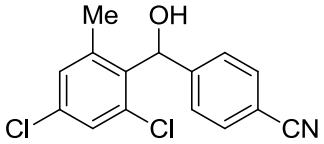
HRMS (EI): Calcd. for $[C_{12}H_7F_3OS]^+$: 256.0170; found: 256.0160.

Preparation of (2,4-dichloro-6-methylphenyl)manganese(II) iodide (99f).



According to **TP1**, 1,5-dichloro-2-iodo-3-methylbenzene (**98f**, 574 mg, 2 mmol) reacted with manganese powder (330 mg, 6 mmol), LiCl (127 mg, 3 mmol), $InCl_3$ (11 mg, 2.5 mol %) and $PbCl_2$ (14 mg, 2.5 mol %) in THF (6 mL) within 12 h at 25 °C affording the corresponding aryl manganese reagent **99f** in 70% yield.

Synthesis of 4-((2,4-dichloro-6-methylphenyl)(hydroxy)methyl)benzonitrile (101h).



4-Formylbenzonitrile (**100h**, 183 mg, 1.4 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (2,4-dichloro-6-methylphenyl)manganese(II) iodide (**99f**, 6 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/Et_2O = 10:1) afforded **101h** (294 mg, 72%) as a white solid.

m. p. = 156.0-158.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.66-7.59 (m, 2H), 7.57-7.41 (m, 2H), 7.34-7.30 (m, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 6.58 (d, *J* = 5.8 Hz, 1H), 2.82 (d, *J* = 5.8 Hz, 1H), 2.21 (s, 3H).

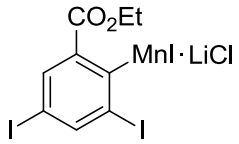
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 147.2, 141.4, 136.1, 134.5, 134.3, 132.1, 130.7, 127.4, 126.1, 118.8, 110.8, 70.6, 20.3.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3477 (M), 2927 (VW), 2360 (W), 2231 (M), 1735 (M), 1700 (M), 1392 (M), 1259 (W), 1053 (S), 910 (M), 849 (S), 813 (S), 766 (W), 688 (W).

MS (EI, 70 eV): m/z (%) = 290 (M^+, 42), 289 (66), 287 (100), 272 (13), 255 (14), 237 (19), 199 (15), 186 (78), 130 (63), 102 (65).

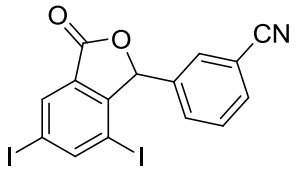
HRMS (EI): Calcd. for $[C_{15}H_{11}Cl_2NO]^+$: 291.0218; found: 290.9944.

Preparation of (2-(ethoxycarbonyl)-4,6-diiodophenyl)manganese(II) iodide (99g).



According to **TP1**, ethyl 2,3,5-triiodobenzoate (**98g**, 1.05 g, 2 mmol) reacted with manganese powder (330 mg, 6 mmol), LiCl (127 mg, 3 mmol), $InCl_3$ (11 mg, 2.5 mol %) and $PbCl_2$ (14 mg, 2.5 mol %) in THF (10 mL) within 16 h between 0-25 °C affording the corresponding aryl manganese reagent **99g** in 60% yield.

Synthesis of 3-(5,7-diiodo-3-oxo-1,3-dihydroisobenzofuran-1-yl)benzonitrile (101i).



3-Formylbenzonitrile (**100c**, 157 mg, 1.2 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (2-(ethoxycarbonyl)-4,6-diiodophenyl)manganese(II) iodide (**99g**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/Et_2O = 4:1) afforded **101i** (397 mg, 68%) as a yellow solid.

m. p. = 118.0-119.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.41 (d, *J* = 1.4 Hz, 1H), 8.34 (d, *J* = 1.4 Hz, 1H), 7.76-7.70 (m, 1H), 7.58-7.45 (m, 3H), 6.16 (s, 1H).

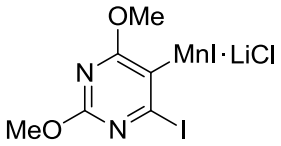
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.8, 151.6, 150.2, 135.1, 134.6, 133.4, 133.3, 132.8, 129.9, 129.5, 117.8, 113.2, 96.0, 90.9, 83.7.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3416 (W), 2964 (W), 2569 (W), 2232 (M), 1768 (S), 1681 (VS), 1435 (M), 1275 (VS), 1232 (S), 1065 (M), 911 (W), 802 (M), 753 (S), 675 (M).

MS (EI, 70 eV): m/z (%) = 486 (M^+, 53), 457 (4), 384 (13), 356 (100), 230 (5), 205 (4), 200 (10), 190 (6), 189 (22), 188 (29), 177 (11), 155 (20), 130 (19), 127 (66), 102 (10).

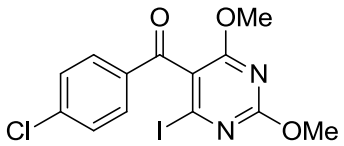
HRMS (EI): Calcd. for $[C_{15}H_7I_2NO_2]^+$: 486.8566; found: 486.8550.

Preparation of (4-iodo-2,6-dimethoxypyrimidin-5-yl)manganese(II) iodide (99h).



According to **TP1**, 4,5-diiodo-2,6-dimethoxypyrimidine (**98h**, 787 mg, 2 mmol) reacted with manganese powder (330 mg, 6 mmol), LiCl (127 mg, 3 mmol), $InCl_3$ (11 mg, 2.5 mol %) and $PbCl_2$ (14 mg, 2.5 mol %) in THF (10 mL) within 12 h at 25 °C affording the corresponding aryl manganese reagent **99h** in 65% yield.

Synthesis of (4-chlorophenyl)(4-iodo-2,6-dimethoxypyrimidin-5-yl)methanone (101j).



4-Chlorobenzoyl chloride (**100d**, 210 mg, 1.2 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (4-iodo-2,6-dimethoxypyrimidin-5-yl)manganese(II) iodide (**99h**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/Et_2O = 2:1) afforded **101j** (344 mg, 71%) as a white solid.

m. p. = 176.5-178.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.78 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 4.05 (s, 3H), 3.89 (s, 3H).

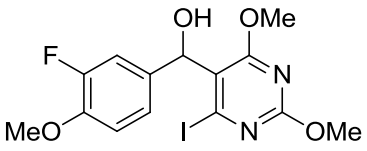
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 191.8, 167.2, 163.5, 140.8, 133.9, 131.0, 129.3, 126.7, 120.7, 55.7, 54.9.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 2953 (VW), 2360 (VW), 1738 (W), 1670 (M), 1564 (S), 1523 (S), 1477 (M), 1380 (S), 1314 (M), 1249 (M), 1073 (M), 1009 (S), 917 (S), 869 (M).

MS (EI, 70 eV): m/z (%) = 404 (100), 279 (18), 239 (8), 210 (21), 154 (4).

HRMS (ESI): Calcd. for ($[C_{13}H_{10}ClIN_2O_3]^+$ + H): 404.9503; found: 404.9496 ($[C_{13}H_{10}ClIN_2O_3]^+$ + H).

Synthesis of (3-fluoro-4-methoxyphenyl)(4-iodo-2,6-dimethoxypyrimidin-5-yl) methanol (101k).



3-Fluoro-4-methoxybenzaldehyde (**100i**, 185 mg, 1.2 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (4-iodo-2,6-dimethoxypyrimidin-5-yl)manganese(II) iodide (**99h**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/Et_2O = 1:1) afforded **101k** (393 mg, 78%) as a white solid.

m. p. = 155.6-157.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.15-6.86 (m, 3H), 5.96 (d, *J* = 7.7 Hz, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 3.41 (br s, 1H).

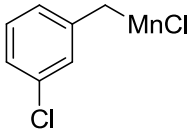
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.8, 162.6, 152.2 (d, *J* = 246.0 Hz), 146.8 (d, *J* = 10.7 Hz), 134.9 (d, *J* = 5.3 Hz), 133.2, 121.1 (d, *J* = 3.7 Hz), 120.4, 113.6 (d, *J* = 19.6 Hz), 113.1 (d, *J* = 2.2 Hz), 75.9 (d, *J* = 3.0 Hz), 56.3, 55.5, 54.7.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3328 (W), 2958 (VW), 1560 (M), 1535 (S), 1442 (M), 1362 (S), 1274 (S), 1207 (M), 1109 (M), 1010 (VS), 795 (M), 754 (W).

MS (EI, 70 eV): m/z (%) = 419 (M^+, 71), 415 (11), 401 (10), 388 (17), 294 (17), 292 (100), 274 (52), 260 (35), 217 (12), 152 (31), 138 (10), 127 (15), 112 (14).

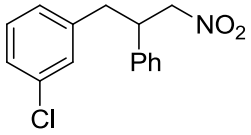
HRMS (EI): Calcd. for $[C_{14}H_{14}FIN_2O_4]^+$: 419.9982; found: 419.9975.

Preparation of (3-chlorobenzyl)manganese(II) chloride (103a).



According to **TP2**, 1-chloro-3-(chloromethyl)benzene (**102a**, 644 mg, 4 mmol) reacted with manganese powder (660 mg, 12 mmol), $InCl_3$ (22 mg, 2.5 mol %) and $PbCl_2$ (28 mg, 2.5 mol %) in THF (20 mL) within 14 h at 25 °C affording the corresponding benzylic manganese reagent **103a** in 75% yield.

Synthesis of 1-chloro-3-(3-nitro-2-phenylpropyl)benzene (104a).



Nitrostyrene (**100j**, 208 mg, 1.4 mmol), CuI (26 mg, 10 mol%) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (3-chlorobenzyl)manganese(II) chloride (**103a**, 10 mL) dropwise at -78 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 24 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 10:1) afforded **104a** (308 mg, 80%) as pale yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.39-7.25 (m, 3H), 7.24-7.12 (m, 5H), 6.99-6.91 (m, 1H), 4.63 (dd, *J* = 7.7 Hz, *J* = 2.2 Hz, 2H), 3.84-3.71 (m, 1H), 2.99 (d, *J* = 7.5 Hz, 2H).

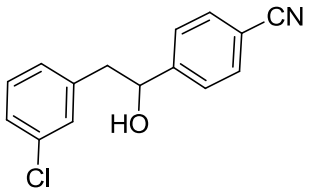
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 139.9, 138.5, 134.3, 129.8, 129.2, 128.9, 127.9, 127.5, 127.3, 127.0, 79.5, 45.8, 39.5.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3031 (VW), 2922 (VW), 1548 (VS), 1428 (M), 1377 (M), 1207 (W), 1078 (W), 908 (W), 776 (M), 697 (S), 682 (M).

MS (EI, 70 eV): m/z (%) = 275 (M^+, 5), 245 (4), 228 (12), 227 (22), 226 (27), 213 (46), 193 (23), 179 (13), 165 (6), 126 (41), 125 (11), 124 (89), 115 (10), 104 (100), 77 (10).

HRMS (EI): Calcd. for $[C_{15}H_{14}ClNO_2]^+$: 275.0713; found: 275.0710.

Synthesis of 4-(2-(3-chlorophenyl)-1-hydroxyethyl)benzonitrile (104b).



4-Formylbenzonitrile (**100h**, 183 mg, 1.4 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (3-chlorobenzyl)manganese(II) chloride (**103a**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 4:1) afforded **104b** (264 mg, 73%) as a white solid.

m. p. = 95.2 – 96.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.63 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.28-7.16 (m, 3H), 7.07-6.99 (m, 1H), 4.96 (dd, *J* = 7.6 Hz, *J* = 5.4 Hz, 1H), 3.05-2.89 (m, 2H), 2.29 (br s, 1H).

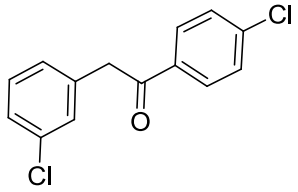
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 148.7, 139.1, 134.3, 132.2, 129.7, 129.5, 127.7, 127.0, 126.5, 118.7, 111.3, 74.2, 45.4..

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3477 (S), 2924 (VW), 2233 (M), 1666 (W), 1599 (M), 1476 (W), 1402 (M), 1228 (M), 1068 (S), 817 (M), 786 (S), 682 (M).

MS (EI, 70 eV): m/z (%) = 257 (M^+, 1), 239 (2), 204 (3), 203 (3), 202 (1), 190 (1), 176 (1), 132 (100), 128 (23), 104 (39), 91 (19), 76 (15).

HRMS (EI): Calcd. for $[C_{15}H_{12}ClNO]^+$: 257.0607; found: 257.0586.

Synthesis of 2-(3-chlorophenyl)-1-(4-chlorophenyl)ethanone (104c).



4-Chlorobenzoyl chloride (**100d**, 245 mg, 1.4 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (3-chlorobenzyl)manganese(II) chloride (**103a**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 20:1) afforded **104c** (281 mg, 75%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.95 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.30-7.26 (m, 3H), 7.17-1.13 (m, 1H), 4.25 (s, 2H).

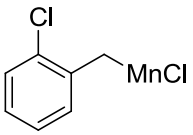
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 195.5, 139.9, 135.9, 134.6, 130.9, 129.9, 129.6, 129.0, 128.7, 127.6, 127.3, 44.8.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 2958 (VW), 2359 (VW), 1716 (S), 1689 (S), 1588 (S), 1476 (M), 1398 (M), 1269 (VS), 1090 (VS), 990 (S), 817 (M), 759 (S).

MS (EI, 70 eV): m/z (%) = 265 (0.2), 191 (3), 175 (5), 164 (2), 157 (3), 156 (2), 155 (7), 138 (100), 111 (24).

HRMS (EI): Calcd. for ($[C_{14}H_{10}Cl_2O]^+$ + H): 265.0187; found: 265.0191 ($[C_{14}H_{10}Cl_2O]^+$ + H).

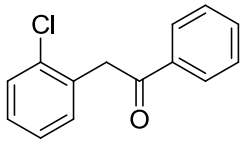
Preparation of (2-chlorobenzyl)manganese(II) chloride (103b).



According to **TP2**, 1-chloro-2-(chloromethyl)benzene (**102b**, 322 mg, 2 mmol)

reacted with manganese powder (330 mg, 6 mmol), $InCl_3$ (11 mg, 2.5 mol %) and $PbCl_2$ (14 mg, 2.5 mol %) in THF (10 mL) within 16 h at 25 °C affording the corresponding benzylic manganese reagent **103b** in 72% yield.

Synthesis of 2-(2-chlorophenyl)-1-phenylethanone (104d).



Benzoyl chloride (**100k**, 196 mg, 1.4 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (2-chlorobenzyl)manganese(II) chloride (**103b**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 16 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 20:1) afforded **104d** (284 mg, 88%) as a pale yellow solid.

m. p. = 54.8 – 56.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.15-8.07 (m, 2H), 7.66-7.43 (m, 4H), 7.32-7.24 (m, 3H), 4.47 (s, 2H),.

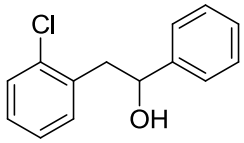
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 196.3, 136.7, 134.5, 133.3, 133.2, 131.8, 129.5, 128.7, 128.6, 128.4, 126.9, 43.3.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3026 (VW), 2908 (VW), 1715 (M), 1690 (S), 1446 (M), 1330 (M), 1272 (S), 1198 (M), 1116 (W), 989 (M), 750 (S), 684 (S), 656 (M).

MS (EI, 70 eV): m/z (%) = 231 (M^+, 11), 196 (7), 195 (46), 194 (2), 165 (10), 152 (2), 139 (2), 127 (7), 125 (21), 105 (100), 77 (62).

HRMS (EI): Calcd. for $[C_{14}H_{11}ClO]^+$: 230.0498; found: 230.0490.

Synthesis of 2-(2-chlorophenyl)-1-phenylethanol (104e).



Benzaldehyde (**100l**, 148 mg, 1.4 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (2-chlorobenzyl)manganese(II) chloride (**103b**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 9:1) afforded **104e** (241 mg, 74%) as a white solid.

m. p. = 72.7 – 74.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.43-7.26 (m, 6H), 7.23-7.14 (m, 3H), 5.03 (dd, *J* = 8.8 Hz, *J* = 4.4 Hz, 1H), 3.25-3.04 (m, 2H), 2.02 (br s. 1H).

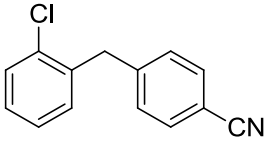
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 143.9, 135.9, 134.3, 131.9, 129.5, 128.4, 128.1, 127.6, 126.7, 125.7, 73.4, 43.8.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3278 (M), 3188 (M), 3030 (W), 2892 (W), 1945 (W), 1444 (M), 1203 (W), 1039 (S), 993 (M), 910 (W), 747 (VS), 695 (S), 681 (M).

MS (EI, 70 eV): m/z (%) = 232 (M^+, 1), 214 (2), 195 (3), 181 (3), 180 (2), 179 (9), 165 (4), 127 (4), 126 (44), 107 (100), 77 (28).

HRMS (EI): Calcd. for $[C_{14}H_{13}ClO]^+$: 232.0655; found: 232.0654.

Synthesis of 4-(2-chlorobenzyl)benzonitrile (104f).



4-Bromobenzonitrile (**100m**, 255 mg, 1.4 mmol), $Pd(PPh_3)_4$ (162 mg, 10 mol%) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (2-chlorobenzyl)manganese(II) chloride (**103b**, 10 mL) dropwise at 0 °C. The

reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 5:1) afforded **104f** (266 mg, 84%) as a white solid.

m. p. = 61.8 – 63.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.56 (d, *J* = 8.2 Hz, 2H), 7.41-7.37 (m, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.26-7.15 (m, 3H), 4.15 (s, 2H).

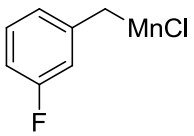
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 145.1, 136.9, 134.2, 132.2, 131.1, 129.8, 129.5, 128.3, 127.1, 118.9, 110.1, 39.3.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3402 (VW), 3069 (VW), 2225 (M), 1920 (W), 1607 (W), 1471 (M), 1433 (M), 1413 (M), 1102 (W), 1048 (M), 915 (W), 805 (M), 758 (S), 741 (VS), 673 (M), 648 (W).

MS (EI, 70 eV): m/z (%) = 227 (M^+, 43), 205 (28), 192 (100), 191 (27), 190 (43), 179 (14), 165 (38), 125 (9), 95 (10).

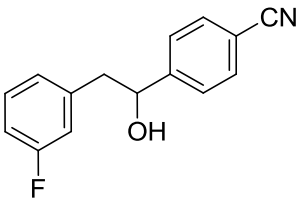
HRMS (EI): Calcd. for $[C_{14}H_{10}ClN]^+$: 227.0502; found: 227.0505.

Preparation of (3-fluorobenzyl)manganese(II) chloride (103c).



According to **TP2**, 1-(chloromethyl)-3-fluorobenzene (**102c**, 289 mg, 2 mmol) reacted with manganese powder (330 mg, 6 mmol), $InCl_3$ (11 mg, 2.5 mol %) and $PbCl_2$ (14 mg, 2.5 mol %) in THF (10 mL) within 16 h at 25 °C affording the corresponding benzylic manganese reagent **103c** in 68% yield.

Synthesis of 4-(2-(3-fluorophenyl)-1-hydroxyethyl)benzonitrile (104g).



4-Formylbenzonitrile (**100h**, 183 mg, 1.4 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (3-fluorobenzyl)manganese(II) chloride (**103c**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 2:1) afforded **104g** (254 mg, 75%) as a white solid.

m. p. = 84.9 – 86.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.64 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.32-7.23 (m, 1H), 7.01-6.87 (m, 3H), 4.98 (dd, *J* = 7.9 Hz, *J* = 5.4 Hz, 1H), 3.08-2.93 (m, 2H), 2.23 (br s, 1H).

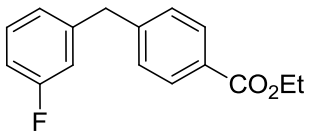
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 162.8 (d, *J* = 246.2 Hz), 148.8, 139.5 (d, *J* = 7.3 Hz), 132.3, 130.1 (d, *J* = 8.1 Hz), 126.6, 125.2 (d, *J* = 3.1 Hz), 118.8, 116.4 (d, *J* = 21.3 Hz), 113.9 (d, *J* = 21.0 Hz), 111.4, 74.3, 45.6 (d, *J* = 1.7 Hz).

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3461 (S), 2926 (VW), 2232 (M), 1606 (M), 1598 (S), 1484 (M), 1446 (M), 1403 (M), 1247 (S), 1138 (M), 1065 (VS), 1010 (W), 846 (S), 781 (S), 685 (S).

MS (EI, 70 eV): m/z (%) = 223 (8), 222 (17), 221 (14), 202 (5), 201 (4), 194 (4), 132 (100), 130 (91), 110 (93), 104 (52), 77 (24).

HRMS (EI): Calcd. for $[C_{15}H_{12}FNO]^+$: 241.0903; found: 241.0890.

Synthesis of ethyl 4-(3-fluorobenzyl)benzoate (104h).



Ethyl 4-iodobenzoate (**100a**, 386 mg, 1.4 mmol), $Pd(PPh_3)_4$ (162 mg, 10 mol%) and

THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (3-fluorobenzyl)manganese(II) chloride (**103c**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 2:1) afforded **104h** (292 mg, 80%) as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.02 (d, *J* = 8.6 Hz, 2H), 7.32-7.22 (m, 3H), 7.01-6.85 (m, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 4.04 (s, 2H), 1.41 (t, *J* = 7.2 Hz, 3H).

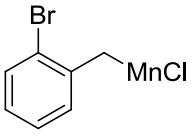
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.4, 162.9 (d, *J* = 246.0 Hz), 145.4, 142.6 (d, *J* = 7.3 Hz), 129.9 (d, *J* = 8.1 Hz), 129.8, 128.8, 128.7, 124.5 (d, *J* = 2.8 Hz), 115.7 (d, *J* = 21.8 Hz), 113.2 (d, *J* = 21.0 Hz), 60.8, 41.5 (d, *J* = 1.7 Hz), 14.3.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 2984 (VW), 2255 (VW), 1710 (S), 1609 (W), 1449 (W), 1275 (S), 1103 (M), 906 (S), 774 (W), 726 (VS), 648 (W).

MS (EI, 70 eV): m/z (%) = 258 (M^+, 51), 244 (2), 230 (18), 214 (14), 213 (100), 186 (7), 185 (39), 184 (8), 183 (27), 165 (26), 123 (5), 106 (3).

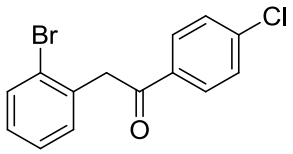
HRMS (EI): Calcd. for $[C_{16}H_{15}FO_2]^+$: 258.1056; found: 258.1051.

Preparation of (2-bromobenzyl)manganese(II) chloride (103d).



According to **TP2**, 1-bromo-2-(chloromethyl)benzene (**102d**, 411 mg, 2 mmol) reacted with manganese powder (330 mg, 6 mmol), $InCl_3$ (11 mg, 2.5 mol %) and $PbCl_2$ (14 mg, 2.5 mol %) in THF (10 mL) within 13 h at 25 °C affording the corresponding benzylic manganese reagent **103d** in 70% yield.

Synthesis of 2-(2-bromophenyl)-1-(4-chlorophenyl)ethanone (104i).



4-Chlorobenzoyl chloride (**100d**, 245 mg, 1.4 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (2-bromobenzyl)manganese(II) chloride (**103d**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 20:1) afforded **104i** (290 mg, 67%) as a white solid.

m. p. = 91.7 – 93.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.01 (d, *J* = 8.8 Hz, 2H), 7.62 (dd, *J* = 8.0 Hz, 1.1 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.51-7.14 (m, 3H), 4.44 (s, 2H).

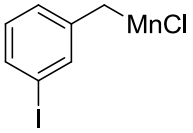
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 195.1, 139.7, 134.9, 134.6, 132.8, 131.6, 129.7, 128.9, 128.8, 127.5, 124.9, 45.7.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 2942 (W), 1718 (M), 1688 (S), 1590 (M), 1399 (M), 1321 (M), 1271 (S), 1216 (M), 1085 (S), 987 (S), 814 (S), 756 (VS), 730 (M), 654 (W).

MS (EI, 70 eV): m/z (%) = 308 (6), 232 (1), 231 (4), 230 (2), 229 (11), 170 (3), 168 (3), 165 (5), 140 (27), 139 (6), 138 (100), 111 (17).

HRMS (EI): Calcd. for $[C_{14}H_{10}BrClO + H]^+$: 308.9682; found: 308.9670 ($[C_{14}H_{10}BrClO + H]^+$).

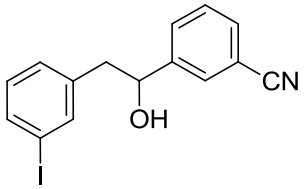
Preparation of (3-iodobenzyl)manganese(II) chloride (103e).



According to **TP2**, 1-(chloromethyl)-3-iodobenzene (**102e**, 252 mg, 1 mmol) reacted with manganese powder (165 mg, 3 mmol), $InCl_3$ (6 mg, 2.5 mol %) and $PbCl_2$ (7 mg,

2.5 mol %) in THF (5 mL) within 16 h at 25 °C affording the corresponding benzylic manganese reagent **103e** in 68% yield.

Synthesis of 3-(1-hydroxy-2-(3-iodophenyl)ethyl)benzonitrile (104j).



3-Formylbenzonitrile (**100c**, 93 mg, 0.7 mmol) and THF (1 mL) were placed in an argon-flushed flask. To this mixture was added (3-iodobenzyl)manganese(II) chloride (**103e**, 5 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 2:1) afforded **104j** (166 mg, 66%) as a white solid.

m. p. = 98.7 – 100.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.69-7.43 (m, 6H), 7.16-7.01 (m, 2H), 4.93 (dd, *J* = 8.0 Hz, *J* = 5.4 Hz, 1H), 3.01-2.85 (m, 2H), 2.24 (br s, 1H).

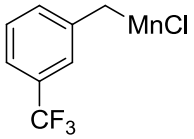
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 144.9, 139.5, 138.4, 135.9, 131.3, 130.3, 130.2, 129.5, 129.2, 128.8, 118.7, 112.4, 94.5, 73.9, 45.4.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 3546 (W), 2223 (W), 1726 (W), 1585 (W), 1430 (W), 1050 (M), 845 (W), 797 (M), 687 (S), 659 (W).

MS (EI, 70 eV): m/z (%) = 348 (M^+, 1), 330 (1), 219 (5), 218 (100), 217 (8), 203 (2), 177 (1), 132 (72), 104 (22), 91 (17), 77 (8).

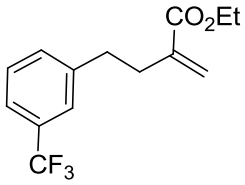
HRMS (EI): Calcd. for $[C_{15}H_{12}INO]^+$: 348.9964; found: 348.9950.

Preparation of (3-(trifluoromethyl)benzyl)manganese(II) chloride (103f).



According to **TP2**, 1-(chloromethyl)-3-(trifluoromethyl)benzene (**102f**, 389 mg, 2 mmol) reacted with manganese powder (330 mg, 6 mmol), $InCl_3$ (11 mg, 2.5 mol %) and $PbCl_2$ (14 mg, 2.5 mol %) in THF (10 mL) within 24 h at 25 °C affording the corresponding benzylic manganese reagent **103f** in 71% yield.

Synthesis of ethyl 2-methylene-4-(3-(trifluoromethyl)phenyl)butanoate (104k).



Ethyl 2-(bromomethyl)acrylate (**100b**, 270 mg, 1.4 mmol) and THF (1.5 mL) were placed in an argon-flushed flask. To this mixture was added (3-(trifluoromethyl)benzyl)manganese(II) chloride (**103f**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 20:1) afforded **120k** (267 mg, 70%) as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.52-7.36 (m, 4H), 6.19 (d, *J* = 1.4 Hz, 1H), 5.52 (q, *J* = 1.2 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.92-2.85 (m, 2H), 2.69-2.62 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H).

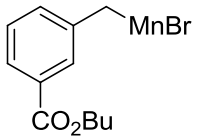
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.9, 142.3, 139.7, 131.9 (q, *J* = 1.4 Hz), 130.6 (q, *J* = 31.9 Hz), 128.7, 125.5, 124.2 (q, *J* = 272.3 Hz), 125.2 (q, *J* = 3.7 Hz), 122.9 (q, *J* = 3.9 Hz), 60.7, 34.8, 33.7, 14.2.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 2985 (W), 1713 (S), 1631 (W), 1449 (W), 1327 (VS), 1160 (S), 1118 (VS), 1072 (S), 1028 (W), 945 (W), 799 (M), 701 (M), 658 (W).

MS (EI, 70 eV): m/z (%) = 227 (M^+, 16), 226 (36), 197 (16), 177 (8), 160 (9), 159 (100), 157 (12), 129 (13), 127 (8), 109 (11).

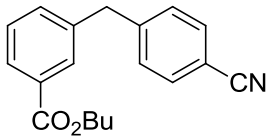
HRMS (EI): Calcd. for $[C_{14}H_{15}F_3O_2]^+$: 272.1024; found: 272.1016.

Preparation of (3-(butoxycarbonyl)benzyl)manganese(II) bromide (103g).



According to **TP2**, butyl 3-(bromomethyl)benzoate (**102g**, 271 mg, 1 mmol) reacted with manganese powder (165 mg, 6 mmol), $InCl_3$ (6 mg, 2.5 mol %) and $PbCl_2$ (7 mg, 2.5 mol %) in THF (10 mL) within 17 h at 25 °C affording the corresponding benzylic manganese reagent **103g** in 65% yield.

Synthesis of butyl 3-(4-cyanobenzyl)benzoate (104l).



4-Bromobenzonitrile (**100m**, 111 mg, 0.6 mmol), Pd-PEPPSI-*i*Pr (20 mg, 5 mol%) and THF (1 mL) were placed in an argon-flushed flask. To this mixture was added (3-(butoxycarbonyl)benzyl)manganese(II) bromide (**103g**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 5:1) afforded **104l** (125 mg, 71%) as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.97-7.91 (m, 1H), 7.90-7.86 (m, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.45-7.26 (m, 4H), 4.33 (t, *J* = 6.7 Hz, 2H), 4.10 (s, 2H), 1.82-1.70 (m, 2H), 1.56-1.41 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.4, 145.9, 139.6, 133.3, 132.4, 131.0, 129.9, 129.6, 128.8, 127.9, 118.8, 110.3, 64.9, 41.7, 30.7, 19.2, 13.7.

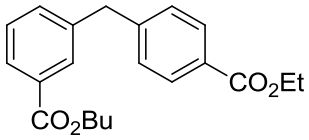
IR (Diamond-ATR, neat): ν (cm^{-1}) = 2961 (VW), 2229 (VW), 1712 (S), 1606 (W), 1281 (S), 1187 (M), 1107 (M), 907 (VS), 728 (VS), 648 (W).

MS (EI, 70 eV): m/z (%) = 293 (M^+, 12), 278 (9), 251 (14), 238 (52), 237 (90), 221 (15), 220 (100), 219 (13), 193 (24), 192 (42), 191 (22), 190 (38), 165 (31), 116 (12),

89 (6), 71 (7).

HRMS (EI): Calcd. for $[C_{19}H_{19}NO_2]^+$: 293.1416; found: 293.1403.

Synthesis of butyl 3-(4-(ethoxycarbonyl)benzyl)benzoate (104m).



Ethyl 4-iodobenzoate (**100a**, 166 mg, 0.6 mmol), Pd-PEPPSI-*i*Pr (20 mg, 5 mol%) and THF (1 mL) were placed in an argon-flushed flask. To this mixture was added (3-(butoxycarbonyl)benzyl)manganese(II) bromide (**103g**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 5:1) afforded **104m** (137 mg, 67%) as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.99 (d, *J* = 8.2 Hz, 2H), 7.94-7.89 (m, 2H), 7.42-7.34 (m, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.33 (t, *J* = 6.6 Hz, 2H), 4.10 (s, 2H), 1.81-1.71 (m, 2H), 1.55-1.44 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H).

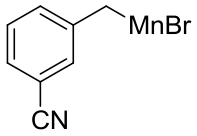
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.6, 166.5, 145.7, 140.5, 133.3, 130.9, 129.9, 129.8, 128.9, 128.7, 128.6, 127.6, 64.9, 60.8, 41.7, 30.8, 19.3, 14.3, 13.7.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 2958 (W), 1712 (VS), 1607 (W), 1443 (W), 1272 (VS), 1177 (M), 1101 (S), 1020 (W), 746 (M), 710 (W).

MS (EI, 70 eV): m/z (%) = 340 (M^+, 24), 295 (50), 285 (17), 284 (75), 267 (88), 256 (57), 239 (100), 212 (23), 211 (49), 194 (17), 166 (34), 152 (21), 111 (21), 82 (14).

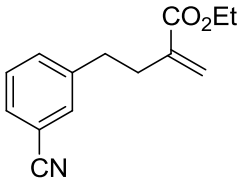
HRMS (EI): Calcd. for $[C_{21}H_{24}O_4]^+$: 340.1675; found: 340.1670.

Preparation of (3-cyanobenzyl)manganese(II) bromide (103h).



According to **TP2**, 3-(bromomethyl)benzonitrile (**102h**, 196 mg, 1 mmol) reacted with manganese powder (165 mg, 6 mmol), $InCl_3$ (6 mg, 2.5 mol %) and $PbCl_2$ (7 mg, 2.5 mol %) in THF (10 mL) within 17 h at 25 °C affording the corresponding benzylic manganese reagent **103h** in 52% yield.

Synthesis of ethyl 4-(3-cyanophenyl)-2-methylenebutanoate (104n).



Ethyl 2-(bromomethyl)acrylate (**100b**, 115 mg, 0.6 mmol) and THF (1 mL) were placed in an argon-flushed flask. To this mixture was added (3-cyanobenzyl)manganese(II) bromide (**103h**, 10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and continuously stirred for 14 h followed by quenching with brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 4:1) afforded **104n** (62 mg, 45%) as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.53-7.36 (m, 4H), 6.18 (d, *J* = 1.3 Hz, 1H), 5.49 (q, *J* = 1.2 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 2.89-2.82 (m, 2H), 2.66-2.59 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) =166.8, 142.8, 139.3, 133.1, 132.0, 129.8, 129.1, 125.7, 118.9, 112.4, 60.8, 34.5, 33.6, 14.2.

IR (Diamond-ATR, neat): ν (cm^{-1}) = 2980 (VW), 2931 (VW), 2228 (W), 1709 (VS), 1630 (W), 1482 (W), 1368 (W), 1299 (M), 1185 (S), 1094 (S), 1027 (M), 945 (M), 796 (S), 689 (S).

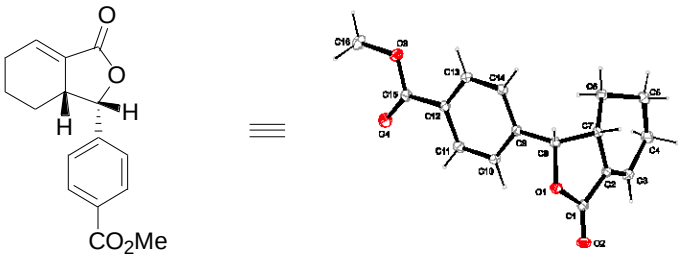
MS (EI, 70 eV): m/z (%) = 229 (M^+, 6), 184 (19), 183 (53), 155 (32), 129 (10), 116 (100), 97 (9), 89 (25), 71 (28).

HRMS (EI): Calcd. for $[C_{14}H_{15}NO_2]^+$: 229.1103; found: 229.1093

D. Appendix

1. X-Ray Structures

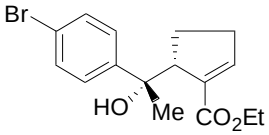
1.1 Molecular structure of 87f



net formula	$C_{16}H_{16}O_4$
M_r/g mol^{-1}	272.296
crystal size/mm	0.50 × 0.22 × 0.11
T/K	200(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	P1bar
a/Å	7.7033(6)
b/Å	8.0736(5)
c/Å	11.7722(7)
α/°	77.329(5)
β/°	89.943(5)
γ/°	70.781(6)
V/Å^3	672.49(8)
Z	2
calc. density/g cm^{-3}	1.34475(16)
μ/mm^{-1}	0.096
absorption correction	'multi-scan'
transmission factor range	0.98615–1.00000
refls. measured	4440
R_{int}	0.0149
mean σ(I)/I	0.0389
θ range	4.36–26.34
observed refls.	1953
x, y (weighting scheme)	0.0492, 0
hydrogen refinement	constr
refls in refinement	2725
parameters	182

restraints	0
$R(F_{obs})$	0.0356
$R_w(F^2)$	0.0881
S	0.958
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.186
min electron density/e Å^{-3}	−0.160

1.2 Molecular structure of 87j



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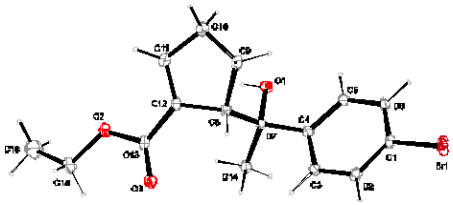
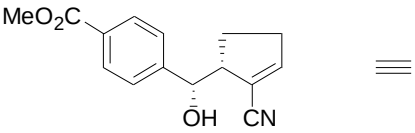
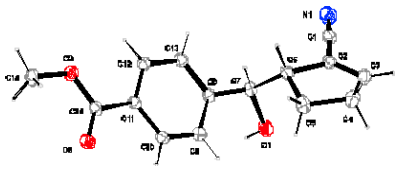


net formula	$C_{16}H_{19}BrO_3$
M_r/g mol^{-1}	339.224
crystal size/mm	0.33 × 0.18 × 0.14
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1/c$
a/Å	13.2712(9)
b/Å	12.3323(12)
c/Å	9.6115(8)
α/°	90
β/°	99.919(7)
γ/°	90
V/Å^3	1549.5(2)
Z	4
calc. density/g cm^{-3}	1.45415(19)
μ/mm^{-1}	2.657
absorption correction	'multi-scan'
transmission factor range	0.86896–1.00000
refls. measured	6200
R_{int}	0.0252
mean σ(I)/I	0.0661
θ range	4.32–26.43
observed refls.	1969
x, y (weighting scheme)	0.0278, 0
hydrogen refinement	constr
refls in refinement	3128

parameters	184
restraints	0
$R(F_{obs})$	0.0309
$R_w(F^2)$	0.0614
S	0.853
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.619
min electron density/e Å^{-3}	−0.398

1.3 Molecular structure of 87s

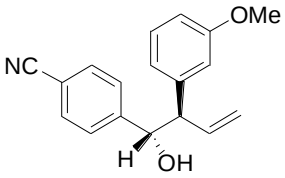


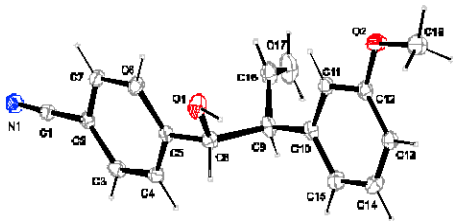


net formula	$C_{15}H_{15}NO_3$
M_r/g mol^{-1}	257.285
crystal size/mm	0.26 × 0.19 × 0.13
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic
space group	$P2_1/c$
a/Å	14.1750(6)
b/Å	7.0899(2)
c/Å	14.2253(5)
α/°	90
β/°	114.1439(19)
γ/°	90
V/Å^3	1304.57(8)
Z	4
calc. density/g cm^{-3}	1.30997(8)
μ/mm^{-1}	0.092
absorption correction	none
refls. measured	9030
R_{int}	0.0342
mean σ(I)/I	0.0315
θ range	3.14–26.03
observed refls.	1979
x, y (weighting scheme)	0.0484, 0.3295
hydrogen refinement	constr
refls in refinement	2568
parameters	174

restraints	0
$R(F_{obs})$	0.0408
$R_w(F^2)$	0.1106
S	1.048
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.194
min electron density/e Å^{-3}	−0.183

1.4 Molecular structure of 87n



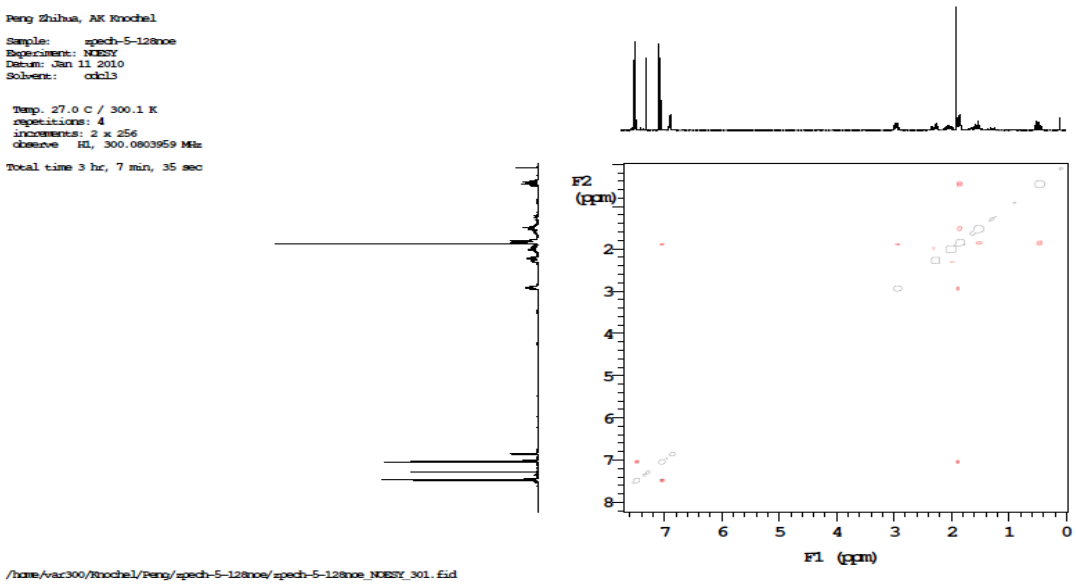


net formula	$C_{18}H_{17}NO_2$
M_r/g mol^{-1}	279.333
crystal size/mm	0.42 × 0.32 × 0.25
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	$Pna2_1$
a/Å	14.4612(7)
b/Å	10.1206(5)
c/Å	10.2612(5)
α/°	90
β/°	90
γ/°	90
V/Å^3	1501.79(13)
Z	4
calc. density/g cm^{-3}	1.23546(11)
μ/mm^{-1}	0.080
absorption correction	'multi-scan'
transmission factor range	0.97689–1.00000
refls. measured	3930
R_{int}	0.0389
mean σ(I)/I	0.0474
θ range	4.27–26.32
observed refls.	1204
x, y (weighting scheme)	0.0943, 0
hydrogen refinement	mixed

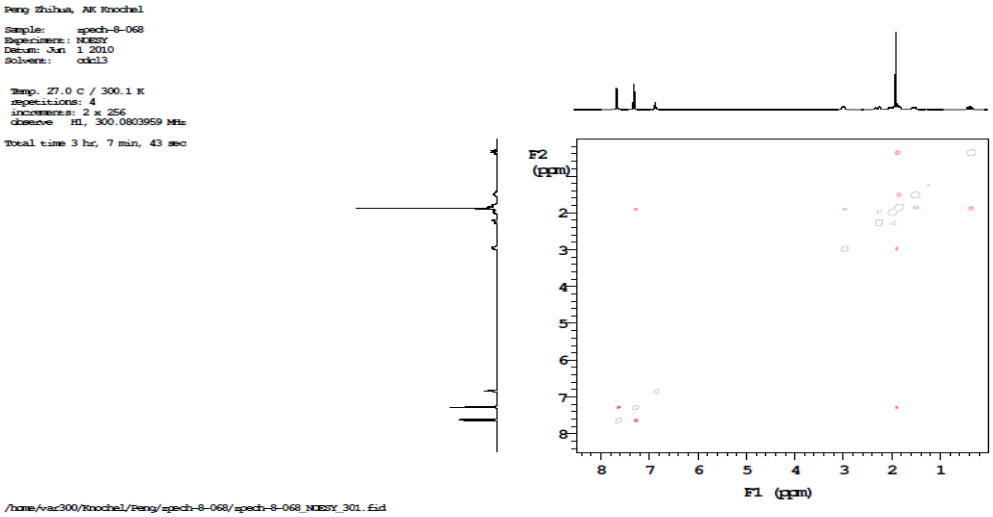
Flack parameter	−1(3)
refls in refinement	1600
parameters	195
restraints	1
$R(F_{obs})$	0.0506
$R_w(F^2)$	0.1409
S	0.976
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.600
min electron density/e Å^{-3}	−0.173

2. NOE Analysis

2.1 NOE Analysis of 87e



2.2 NOE Analysis of 87h


Peng Zhihua, AK Knochel
Sample: spech-8-068
Experiment: NOESY
Datum: Jun 1 2010
Solvent: cdcl3
Temp. 27.0 C / 300.1 K
Repetitions: 4
Increments: 2 x 256
Observe H1, 300.0803959 MHz
Total time 3 hr, 7 min, 43 sec
F2 (ppm)
F1 (ppm)
/home/vac300/Knochel/Peng/spech-8-068/spech-8-068_NOESY_301.fid

3 Curriculum Vitae

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Education

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Publications

1. Zhihua Peng, Tobias D. Blümke, Peter Mayer, and Paul Knochel*, Diastereoselective Synthesis of Homoallylic Alcohols with Adjacent Tertiary and Quaternary Centers by Using Functionalized Allylic Aluminum Reagents, *Angew. Chem. Int. Ed.* **2010,** *49*, 8516 –8519.
2. Zhihua Peng, Benjamin A. Haag, and Paul Knochel*, Preparation of 2-Magnesiated 1,3,5-Triazines via an Iodine-Magnesium Exchange, *Org. Lett.* **2010**, *12*, 5398-5401.
3. Zhihua Peng, and Paul Knochel*, Preparation of Functionalized

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4. Benjamin Haag, Zhihua Peng, and Paul Knochel*, Preparation of Polyfunctional Indazoles and Heteroarylazo Compounds Using Highly Functionalized Zinc Reagents, *Org. Lett.* **2009**, *11*, 4270-4273.
5. Tobias Blümke, Yi-Hung Chen, Zhihua Peng and Paul Knochel*, Preparation of functionalized organoaluminiums by direct insertion of aluminium to unsaturated halides, *Nat. Chem.* **2010**, *2*, 313-318.
6. Shengming Ma*, Shichao Yu and Zhihua Peng, Sc(OTf)3-catalyzed efficient synthesis of b,b-bis(indolyl) ketones by the double indolylation of acetic acid 2-methylene-3-oxobutyl ester, *Org. Biomol. Chem.* **2005**, *3*, 1933-1936.
7. Shengming Ma*, Shichao Yu, Zhihua Peng**,** and Hao Guo, Palladium-Catalyzed Functionalization of Indoles with 2-Acetoxymethyl-Substituted Electron-Deficient Alkenes, *J. Org. Chem.* **2006,** *71*, 9865-9868.