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

Br/Mg-Exchange on 1,2-Dibromocyclopentene Derivatives and Regio- and Chemoselective Functionalizations of Pyrazoles and Related Heterocycles

von

Christina Despotopoulou

aus

Athen, Griechenland

München 2009

Erklärung

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

Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig, und ohne unerlaubte Hilfe erarbeitet.

München, am 18.06.09

Christina Despotopoulou

Dissertation eingereicht am 18.06.2009

1. Gutachter: Prof. Dr. Paul Knochel

2. Gutachter: Prof. Dr. Manfred Heuschmann

Mündliche Prüfung am 15.07.2009

This work was carried out from May 2006 to June 2009 under the guidance of Prof. Knochel at the Fakultät für Chemie und Pharmazie der Ludwig-Maximilians-Universität, Munich.

I would like to thank Prof. Dr. Paul Knochel, for giving me the opportunity to do my Ph.D. in his group, for his invaluable support and guidance throughout this time.

I am also very grateful to Prof. Dr. Manfred Heuschmann for agreeing to be my "Zweitgutachter", as well as Prof. Dr. Konstantin Karaghiosoff, Prof. Dr. Heinz Langhals, Prof. Dr. Hans Rudolf Pfaendler and Prof. Dr. Rudolf Knorr for the interest they showed in this manuscript by accepting to be referees.

For the careful correction of this manuscript I thank Dr. Andrei Gavryushin, Dr. Francois Crestey, Andreas Wagner, Tobias Blümke and Marc Mosrin.

I would also like to thank Boehringer Ingelheim GmbH, and especially Dr. Ioannis Sapountzis for the opportunity to spend three months in his R&D laboratory in Vienna as well as for all his invaluable support and friendship throughout my studies. I am also very thankful to Dr. Darryl McConnell, and Dr. Matthias Treu for the fruitful collaborations and stimulating discussions.

Special thanks also to Dr. Rick Bauer and Camille Gignoux for the fruitful collaborations and their friendship. Many thanks also to Albrecht Metzger and Laurin Melzig for the collaboration in the field of cross-couplings.

Furthermore I thank all the past and present members I met in the Knochel group, for their support and the great times we had, especially my labmates Marc Mosrin, Matthias Schade, Christoph Rohbogner, Tomke Bresser, Benoit Blanc, Benjamin Haag, Dr. Darunee Soorukram, Dr. Christiane Kofink, Dr. Nina Gommermann and Dr. Tobias Korn for the great atmosphere! A big thank you also to all the people at Boehringer Ingelheim in Vienna for 3 fantastic months! Special thanks as well to Dr. Darunee Soorukram, Dr. Murthy Cheemala, Dr. Ludwig Kaspar, Dr. Arkady Krasovskiy, Milica Jaric, Florian Achrainer, Nadine Götz and Theresa Soltner for all their help and friendship and to Dr. Andrei Gavryushin for the innumerable tipps and suggestions!

I would like to thank especially my lab neighbour Marc Mosrin for his constant support and motivation, and for all the fun we had in the lab, in Sausalitos and of course in Tunesia!

I would also like to thank Vladimir Malakhov, Beatrix Cammelade, Simon Matthe, Yulia Tsvik, Raimund Berchthold and Christine Schliski for their help in organizing everyday life in the lab as well as the analytical team of the LMU, especially Dr. David Stephenson, Claudia Dubler and Sonja Kosak for their invaluable help.

Furthermore I thank my students Lydia Klier and Katharina Böck for their contributions to this thesis and Timotheus Hohl for his help in the lab.

Finaly very special thanks go to my whole family, my parents, my grandparents, my sister Alexia and Klif for their constant love and support throughout my Ph.D.

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

1) C. Despotopoulou, R. C. Bauer; A. Krasovskiy; P. Mayer; J. M. Stryker; P. Knochel „ Selective Mono- and 1,2-Difunctionalisation of Cyclopentene Derivatives *via* Mg and Cu Intermediates" *Chem. Eur. J.* **2008**, *14*, 2499-506.

2) C. Despotopoulou, C. Gignoux, D. McConnel, P. Knochel „ Metallation of 4,5-Dihydrobenzo[*g*]indazoles", *Synthesis*, **2009**, *manuscript in press.*

3) C. Despotopoulou, L. Klier, P. Knochel, „ Total Functionalization of Pyrazole Derivatives by Selective Magnesiations", *Org. Lett.* **2009**, *manuscript in press.*

4) A. Metzger, L. Melzig, C. Despotopoulou, P. Knochel „ Pd-catalyzed Cross-Coupling of Functionalized Organozinc Reagents with Thiomethyl-Substituted Heterocycles", *manuscript submitted.*

Στην οικογένεια μου

Table of Contents

Table of Contents

Abbreviations

A: General Introduction 1
1. Overview 2
2. The Halogen-Metal Interconversion 3
3. Hydrogen-Metal Interconversion 9
4. Objectives 14

B: Results and Discussion 16
1. Functionalization of 1,2-Dibromocyclopentenyl Systems 17
   1.1 Introduction 17
   1.2 Selective mono-and 1,2-difunctionalization of cyclopentene derivatives 18
      1.2.1 Monofunctionalization using Br/Mg-exchange 18
      1.2.2 Difunctionalization via Cu-intermediates 21
      1.2.3 Mechanistic studies 24
   1.3 Difunctionalization of cyclohexene derivatives 28
2. Functionalization of 4,5-Dihydrobenzo[g]indazoles using Mg- and Zn- Heterocyclic Intermediates 32
   2.1 Introduction 32
   2.2 I/Mg-exchange on 4,5-Dihydro[g]indazoles 33
   2.3 Regioselective metallations on 4,5-dihydro[g]indazoles 39
3. Synthesis of Fully Substituted Pyrazoles via Regio- and Chemoselective Metallations 44
   3.1 Introduction 44
   3.2 Choosing the protecting group 46
      3.2.1 Starting material synthesis 46
      3.2.2 Metallations of the differently protected pyrazoles 47
   3.3 Functionalization at the C5-position 49
      3.3.1 Deprotonation at the C5- position 49
      3.3.2 Direct cross coupling reaction of the S-Me moiety of the pyrazole 51
   3.4 Selective C3- metallation of pyrazole derivatives 52
   3.5 Selective C4-metallation of pyrazole derivatives 54
   3.6 Synthesis of the acaricide Tebufenpyrad via successive functionalizations of the pyrazole core. 57
4. Summary and Outlook 60
   4.1 Functionalization of 1,2-dibromocyclopentenes 60
   4.2 Functionalization of 4,5-Dihydrobenzo[*g*]indazoles using Mg- and Zn-Heterocyclic Intermediates 62
   4.3 Synthesis of fully substituted pyrazoles via regio- and chemoselective metallations 64

C: Experimental Section 66
1. General Considerations 67
2. Typical Procedures (TP) 71
   2.1 Typical procedure for the Br/Mg-exchange reaction using *i*PrMgCl·LiCl (6) of 1,2-dibromocyclopentene (TP1) 71

2.2 Typical procedure for the 1,2-difunctionalization of 1,2-dibromocyclopentene derivatives (TP2) ... 71
2.3 Typical procedure for the 1,2-difunctionalization of 1,2 dibromocyclopentene derivatives and subsequent acylation (TP3) ... 72
2.4 Typical procedure for the I/Mg-exchange reaction on 1-benzyl-3-iodo-4,5-dihydro-1*H*-benzo[g]indazole (61) (TP4) ... 72
2.5 Typical procedure for the I/Mg-exchange reaction on 2-benzyl-3-iodo-4,5-2*H*-benzo[g]indazole (62) (TP5) ... 73
2.6 Typical procedure for the deprotonation of 1-ethoxymethyl-4,5-dihydro-1*H*-benzo[g]indazole (67) using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (14) (TP6) ... 73
2.7 Typical procedure for the deprotonation of 1-ethoxymethyl-4,5-dihydro-1*H*-benzo[g]indazole (67) using TMPMgCl·LiCl (10a) (TP7) ... 74
2.8 Typical procedure for the deprotonation of 2-ethoxymethyl-4,5-dihydro-2*H*-benzo[g]indazole (68) using $TMP_2Mg{\cdot}2LiCl$ (12) (TP8) ... 75
2.9 Typical procedure for the deprotonation reaction at the C5 position of the pyrazole ring (TP9) ... 75
2.10 Typical procedure for the deprotonation reaction at the C3 position of the pyrazole ring (TP10) ... 76
2.11 Typical procedure for the deprotonation reaction at the C4 position of the pyrazole ring (TP11) ... 76
2.12 Typical procedure for the cross-coupling of thioethers (TP12) ... 77
3. Selective Mono- and 1,2-Difunctionalization of Cyclopentene and Cyclohexene Derivatives via Mg and Cu intermediates ... 78
3.1 Starting Materials ... 78
3.2 Monofunctionalization of 1,2-dibromocyclopentene ... 80
3.3 Difunctionalization of cyclopentene derivatives ... 83
3.4 Difunctionalization of Cyclohexene Derivatives ... 88
4. Functionalization of 4,5-Dihydrobenzo[*g*]indazoles using Mg or Zn intermediates ... 95
4.1 Starting materials ... 95
4.2 Preparation of functionalized 4,5-dihydrobenzo[*g*]indazoles ... 102
4.2.1 Functionalization through I/Mg-exchange ... 102
4.2.2 Functionalization through deprotonation reactions ... 111
5. Synthesis of Fully Substituted Pyrazoles via Regio- and Chemoselective Metallations 119
5.1 Starting materials ... 119
5.2 Preparation of C5-substituted pyrazoles ... 121
5.3 Preparation of C3-substituted pyrazoles ... 129
5.4 Preparation of C4-substituted pyrazoles ... 137
5.5 Preparation of the acaricide Tebufenpyrad ... 143
D: Appendix ... 147
1. Data of the X-ray Analysis ... 148
2. Curriculum Vitae ... 149

ABBREVIATIONS

Ac	acetyl
acac	acetyl acetonate
AcOH	acetic acid
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br.	broad
Bu	butyl
*c*Pent	cyclopentyl
d	doublett
dba	*trans*,*trans*-dibenzylideneacetone
DMA	dimethylacetal
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMGs	directing metalation groups
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DoM	directed *ortho* metallation
dppp	1,3-bis(diphenylphosphino)propane
E	electrophile
Eq.	equation
equiv	equivalent
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
Hal	halogen
HRMS	high resolution mass spectroscopy
*i*Pr	isopropyl
IR	infra-red
J	coupling constant (NMR)
LDA	lithium diisopropylamide
LG	leaving group
M	molarity
m	meta
m	multiplet
Me	methyl
Met	metal
min	minute
mol.	mole

mp.	melting point
MS	mass spectroscopy
MW	microwaves
NCS	*N*-chlorosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NSAID	Nonsteroidal anti-inflammatory drugs
Nu	nucleophile
o	ortho
p	para
PEG	polyethylene glycol
PG	protecting group
Ph	phenyl
prim	primary
q	quartet
rt	room temperature
s	singulet
sat	saturated
*s*Bu	*sec*-Bu
sec	secondary
SEM	[2-(trimethylsilyl)ethoxy]methyl
S-PHOS	2-dicyclohexylphosphino-2´,6´-dimethoxybiphenyl
t	triplet
*t*Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
tfp	*tri*-(2-furyl)phosphine
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
TMP	2,2,6,6-tetramethylpiperidyl
TP	typical procedure
Ts	4-toluenesulfonyl

A: General Introduction

1. Overview

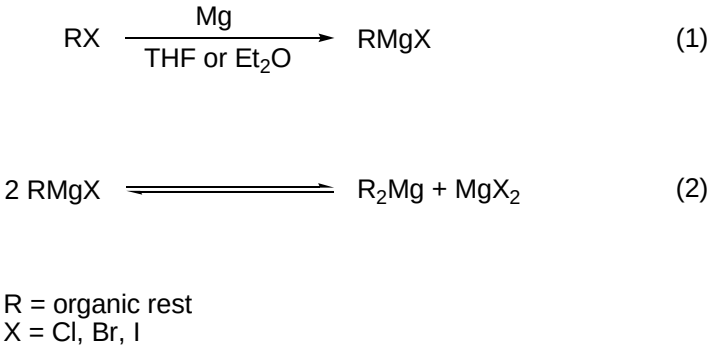
Organometallic chemistry is a central part of modern organic chemistry.[1] Two methods should be highlighted for the generation of organometallic compounds: the hydrogen-metal and halogen-metal interconversion.[2] The pioneering works of *Frankland*[3] and *Grignard*[4] have opened up new perspectives in the synthetic chemistry and have served as an inspiration to many chemists who followed in their footsteps. The recent advances in these fields show the versatility of the developed metallic reagents, confirming them as important tools, which give access to a vast number of functionalized molecules.

The reactivity and selectivity of the organometallic reagent can be tuned by transmetallation. A very polar carbon-metal bond, as in the case of organolithium species, is an indication of high reactivity but reduced tolerance towards sensitive functional groups. Organomagnesium and organozinc reagents represent an alternative, though the latter often require transition metal catalysis to promote a reaction with electrophiles.[5] In addition, inductive electron withdrawal, metal coordination and steric hindrance are some further factors that if exploited accordingly, can lead the reaction to the desired direction.[2]

[1] Wothers, P.; Greeves, N.; Warren, S.; Clayden, J. in *Organic Chemistry*; Oxford University Press, New York, **2001**.
[2] Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376.
[3] a) Frankland, E. *Liebigs Ann. Chem.* **1848-49**, *71*, 171; b) Frankland, E. *J. Chem. Soc.* **1848-49**, *2*, 263.
[4] a) Grignard, V. *Compt. Rend. Acad. Sci. Paris.* **1900**, *130*, 1322; b) Grignard, V. *Ann. Chim.* **1901**, *24*, 433.
[5] For a general overview see: a) Knochel, P.; Leuser, H.; Gong, L. -Z.; Perrone, S.; Kneisel, F. F. in *Handbook of Functionalized Organometallics*; P. Knochel, Ed.; Wiley-VCH, Weinheim **2005**: 251; b) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. in *Organic Reactions*; L. E. Overman, Ed.; Wiley & Sons Inc., New York **2001**.

2. The Halogen-Metal Interconversion

In 1912, the Nobel Prize for chemistry was awarded to *Victor Grignard*. The importance of Mg-reagents was so high that at the time of his death in 1935, there were over 6000 references in the literature.[6] The oxidative addition of magnesium to a halogen-carbon bond in etheral solvents (*V. Grignard's* discovery) is still nowdays an important method for preparing these reagents (Scheme 1, Eq. 1).[7]



Scheme 1: Synthesis of *Grignard* reagents by oxidative addition (Eq. 1) and Schlenk-equilibrium (Eq. 2).

The mechanism of the *Grignard* reaction is not yet fully clarified, though it is assumed to proceed through a single electron transfer.[8] In solution *Grignard* reagents are in equilibrium with R_2Mg and MgX_2 (Schlenk equilibrium) (Scheme 1, Eq. 2).[9] The position of this equilibrium is influenced by solvent, temperature and the anion X^-. Organomagnesium halides in solution can also form dimers or higher oligomers, depending on the concentration.[10]

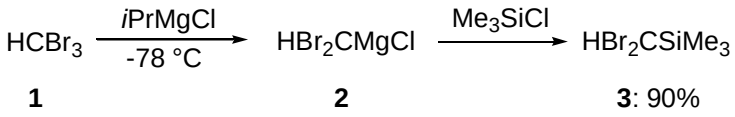
Although the direct reaction of magnesium metal with organic halides is the most commonly used method for generating organomagnesium compounds, it lacks good functional group tolerance. The often required activation of the magnesium surface by additives[11] and the

---

[6] From *Nobel Lectures, Chemistry 1901-1921*, Elsevier Publishing Company, Amsterdam, **1966**.
[7] a) Thayer, J. S. *Adv. Organomet. Chem.* **1975**, *12*, 1; b) Quadbeck-Seeger, H.-J.; Faust, R.; Knaus, G.; Siemeling, U. in *Chemie Rekorde*, Wiley-VCH, Weinheim, **1997**.
[8] a) Rogers, H. R.; Hill, C. L.; Fujiwara, Y.; Rogers, R. J.; Mitchell, H. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 217; b) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286; c) Hamdouchi, C.; Walborsky, H. M. in *Handbook of Grignard Reagents*; Silverman, G. S.; Rakita, P. E. Eds.; Marcel Dekker, New York, **1996**, pp 145-218; d) Garst, J. F. *Acc. Chem. Res.* **1991**, *24*, 95; e) Kharasch, M. S.; Reinmuth, O. in *Grignard Reactions of Nonmetallic Substances,* Prentice Hall, New York, **1954**; f) Oshima, K. in *Main Group Metals in Organic Synthesis*, Yamamoto, H.; Oshima, K. Eds.; Wiley-VCH, Weinheim, **2004**.
[9] Schlenk, W.; Schlenk Jr., W. *Chem. Ber.* **1929**, *62*, 920.
[10] Holm, T.; Crossland, I. in *Grignard Reagents-New Developments*; Richey Jr, H. G. Ed.; Wiley, New York, **2000**, 5.
[11] a) Rieke, R. D. *Science* **1989**, *246*, 1260; b) Burns, T. B.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674; c) Lee, J.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428; d) Rieke, R. D.;

exothermic conditions of the insertion are counted among the limitations of this protocol.[12] Therefore, the halogen-magnesium exchange is the method of choice for the preparation of new functionalized *Grignard* reagents.[13]

In 1967, *Jean Villiéras* showed that magnesium carbenoids can be generated in good yields via a bromine-magnesium exchange and trapped with electrophiles as illustrated by the reaction of bromoform (**1**) with *i*PrMgCl. The magnesium carbenoid **2** can be trapped with TMSCl to afford the silane **3** in 90% yield (Scheme 2).[14]



Scheme 2: Br/Mg-exchange of bromoform.

The halogen-magnesium exchange leads to the formation of the more stable organomagnesium compound (sp > sp^2(vinyl) > sp^2(aryl) >sp^3(prim) > sp^3(sec)). The mechanism is supposed to proceed through a concerted 4-centered mechanism.[15, 16] Furthermore, the formation rate of the new organomagnesium reagent is also influenced by the electronic properties of the substrate as well as by the nature of the halogen.[17] Hence electron deficient substrates enhance the exchange reaction rate. The main advantage of the halogen-magnesium exchange reaction (especially in the case of I/Mg-exchange) is that it enables the preparation of *Grignard* reagents bearing sensitive functionalities. A number of functionalized *Grignard* reagents of type **4** are now available (Scheme 3).[13, 18]

Sell, M. S.; Klein, W. R.; Chen, T.; Brown, J. D.; Hansan, M. V. in *Active Metals*, Fuerstner, A., Ed.; Wiley-VCH, Weinheim, **1995**; e) Rieke, R. D.; Sell, M. S.; Xiong, H. *J. Am. Chem. Soc.* **1995**, *117*, 5429.

[12] Bush, F. R.; De Antonis, D. M. in *Grignard Reagents-New Developments*; Richey, H. G. Jr., Ed.; Wiley, New York, **2000**, pp 165-183.

[13] For a review see: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.

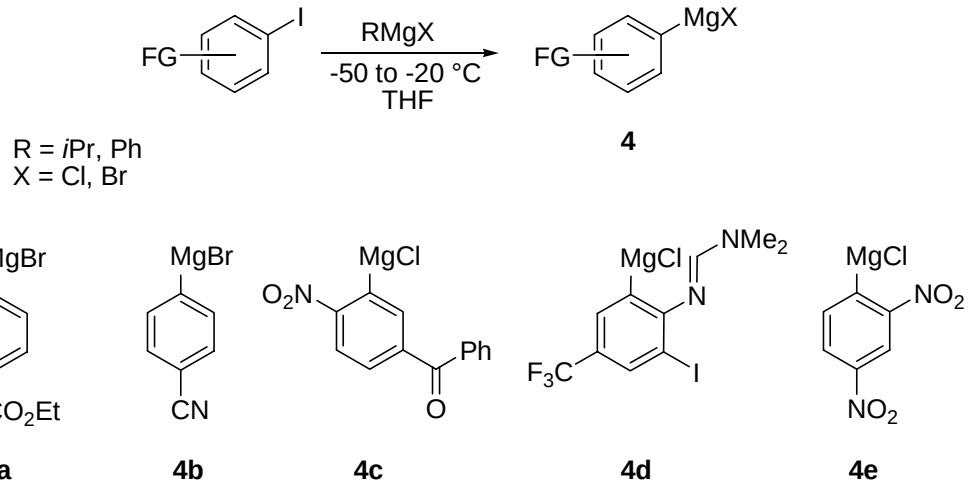
[14] Villiéras, J. *Bull. Soc. Chim. Fr.* **1967**, 1520.

[15] a) Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1; b) Reich, H. J.; Phillips, N. H.; Reich, I. L. *J. Am. Chem. Soc.* **1985**, *107*, 4101; c) Farnham, W. B.; Calabrese, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2449.

[16] Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 159.

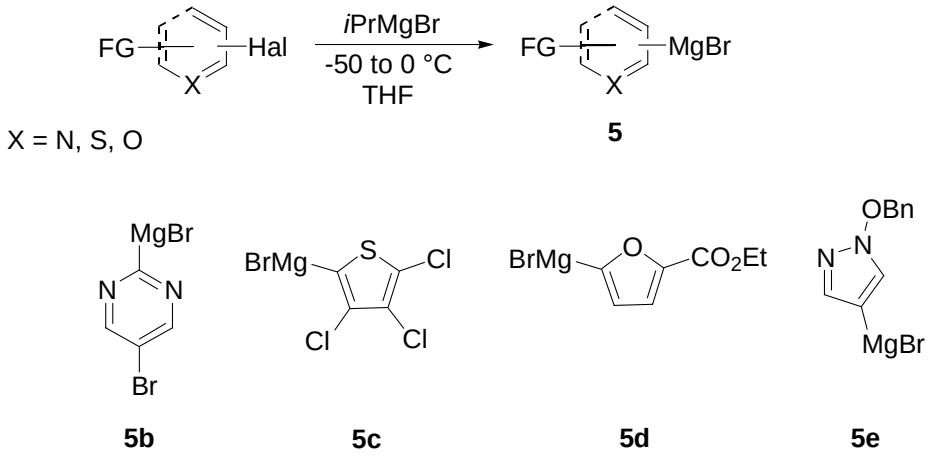
[17] Tamborski, C.; Moore, G. J. *J. Organomet. Chem.* **1971**, *26*, 153.

[18] a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; b) Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Knochel, P. *Synlett* **2001**, 477; c) Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 1610; d) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.



Scheme 3: Synthesis of functionalized arylmagnesium halides.

Similarly, using the above mentioned method, various magnesiated functionalized heterocycles of type **5** could be prepared (Scheme 4).[19]

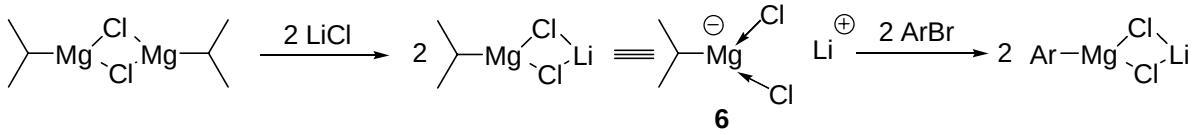


Scheme 4: Synthesis of functionalized heteroarylmagnesium halides.

Although activated aryl- and heteroaryl bromides and in particular cases even chlorides react with *i*PrMgBr to give the magnesiated species, less active bromides are reluctant to undergo the exchange reaction. In some cases, the use of trialkyl magnesiate reagents of type R_3MgLi

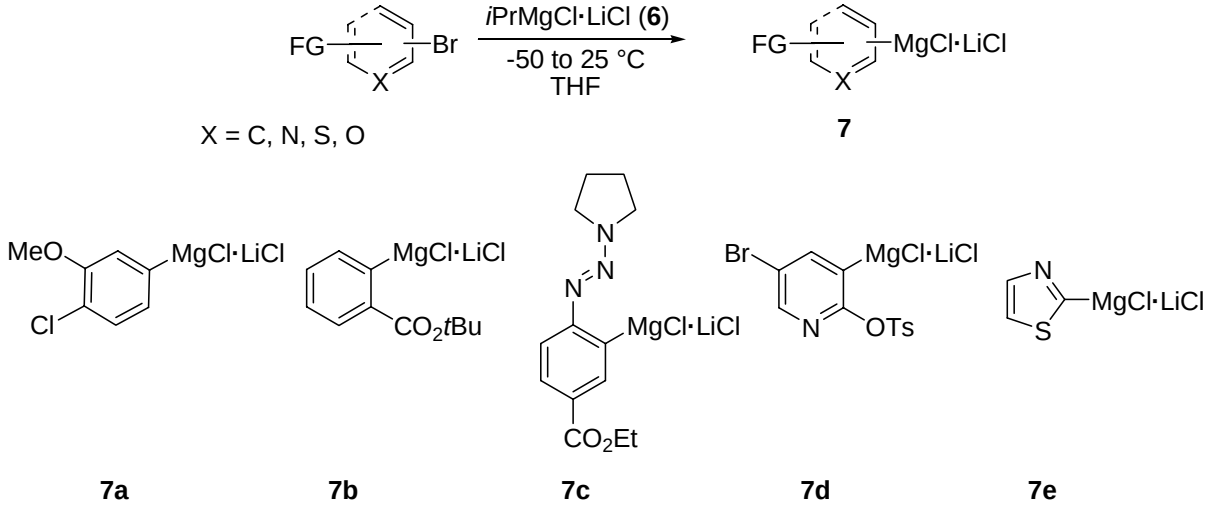
[19] a) Bérillon, L.; Lepretre, A.; Turck, A.; Plé, N.; Quéguiner, G.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 1359; b) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618; c) Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449; d) Abarbri, M.; Knochel, P. *Synlett* **1999**, 1577; e) Dehmel, F.; Abarbri, M.; Knochel, P. *Synlett* **2000**, 345; Hiriyakkanavar, I.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583.

can circumvent this drawback as is shown in the work of *Oshima.*[20] Recently it was found that the addition of LiCl catalyzes the Br/Mg-exchange, expanding thereby significantly the spectrum of applications of this method.[21] Apart from accelerating the exchange reaction, the presence of LiCl enhances also the reactivity of the resulting organomagnesium reagents. The supposed mechanism postulates that LiCl breaks the aggregates of *i*PrMgCl forming an ate-like intermediate of type **6** (Scheme 5).[15] This mechanism also explains the stoichiometric amount of LiCl needed.



Scheme 5: Proposed mechanism of the LiCl catalyzed Br/Mg-exchange.

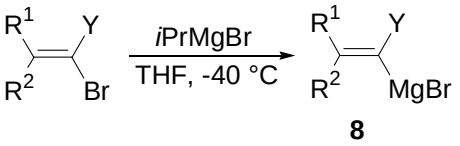
The use of the more reactive *i*PrMgCl·LiCl (**6**) enables a fast Br/Mg-exchange even at inactivated bromides, that was not possible before. This improvement in the organometallic chemistry has found many applications, since it allows the use of the cheaper and more stable bromides, leading to a broad spectrum of magnesiated and functionalized arenes and heteroarenes of type **7** (Scheme 6). [22]



Scheme 6: LiCl-catalyzed Br/Mg-exchange on aryl- and heteroaryl bromides.

[20] a) Oshima, K.; *J. Organomet. Chem.* **1999**, 575; b) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2481; c) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333.
[21] Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[22] a) Ren, H.; Knochel, P. *Chem. Commun.* **2006**, 726; b) Liu, C.-Y.; Knochel, P. *Org. Lett.* **2005**, *7*, 2543; c) Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215.

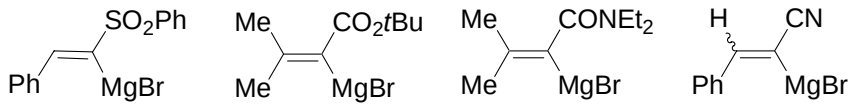
Another challenge that can be overcome by the use of the reactive *i*PrMgCl·LiCl is the metallation of olefinic systems. Without LiCl halogen-magnesium exchange reactions on alkenyl halides proceed very slowly and require higher temperatures, therefore precluding the presence of functionalities.[23] However, chelating heteroatoms or electron withdrawing groups directly linked to the double bond could facilitate an I/Mg- or even a Br/Mg-exchange affording organomagnesium alkenes of type **8**, though not always stereoselectively (Scheme 7).[24]



8

Y = CN, CO_2tBu, SO_2Ph, $CONEt_2$

.

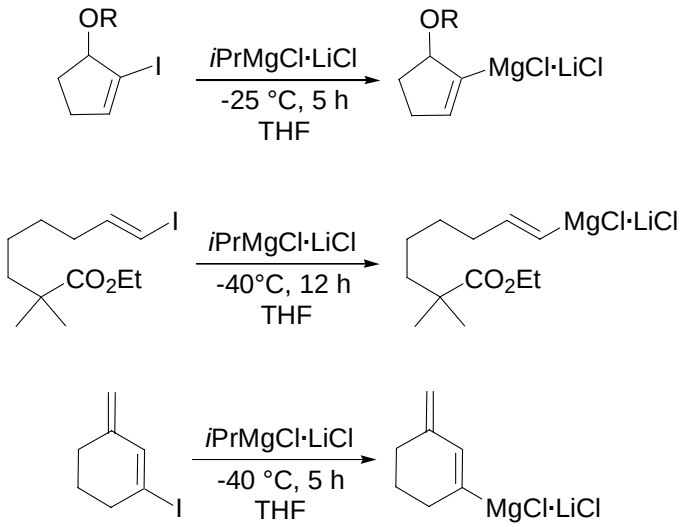


8a **8b** **8c** **8d**

Scheme 7: Br/Mg-exchange on functionalized alkenyl bromides bearing an electron withdrawing group at the *α* position.

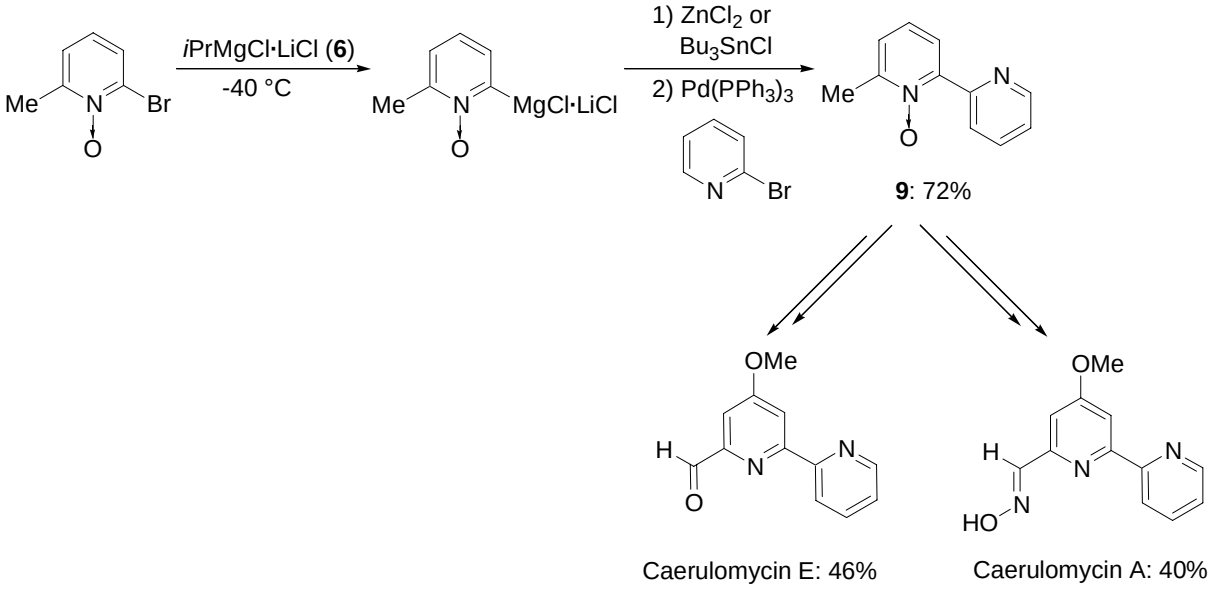
Employing the more reactive *i*PrMgCl·LiCl (**6**), alkenyl iodides with no chelating groups at the α position could undergo an I/Mg-exchange even at lower temperatures (Scheme 8).[22c, 25]

[23] Rottländer, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080.
[24] a) Thibonnet, J.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 3319; b) Krause, N. *Tetrahedron Lett.* **1989**, *30*, 5219; c) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *41*, 351; d) Fleming, F. F.; Gudipati, V.; Steward, O. W. *Org. Lett.* **2002**, *4*, 659.
[25] Ren, H.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2005**, 543.



Scheme 8: LiCl-catalyzed I/Mg-exchange on alkenyl iodides with no chelating group at α position.

The halogen-magnesium exchange has been applied in the field of natural product synthesis. A recently reported total synthesis of Caerulomycins E and A, that display antibiotic activity, employs a Br/Mg-exchange reaction using *i*PrMgCl·LiCl to furnish the key intermediate **9** (Scheme 9).[26]



Scheme 9: Br/Mg-exchange in the total synthesis of Caerulomycins E and A.

[26] Duan, X.-F.; Ma, Z.-Q.; Zhang, F.; Zhang, Z.-B. *J. Org. Chem*. **2009**, *74*, 939.

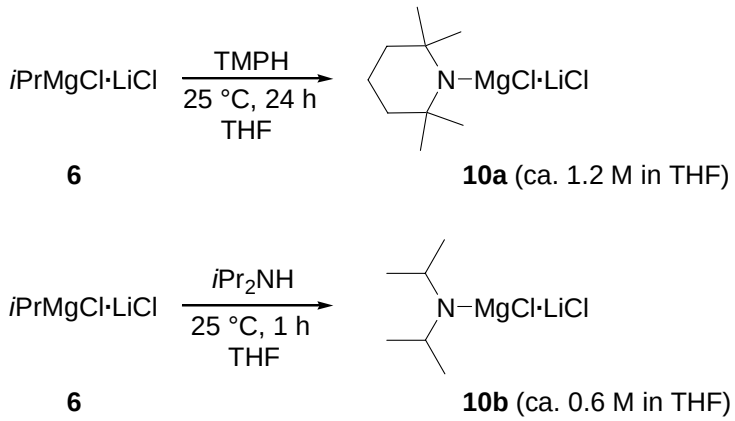
3. Hydrogen-Metal Interconversion

The second very prominent method to generate organometallic compounds is the direct deprotonation. Since the pioneering work by *Gilman*[27] and *Wittig*,[28] the directed *ortho* metallation (DoM) reaction has been widely used as a powerful and efficient method for regioselective functionalization of aromatic compounds.[2, 29] Organolithium bases had dominated this field so far, especially due to their ability to coordinate to a heteroatom-containing DMG (directing metallation group) leading to an *ortho*-lithiation.[30] However, the high reactivity of the resulting Li-compounds is, as in the case of the halogen-magnesium exchange, associated with undesired side reactions and limited functional group tolerance. In that respect, an improvement was achieved with the works of *Hauser*[31] and *Eaton*[32]. Amide bases of type R_2NMgBr or $(R_2N)_2Mg$ proved to be more stable than their corresponding Li-analogues, compromising nevertheless the solubility and kinetic basicity.[33]

The real breakthrough for the regioselective deprotonation came in 2006 when it was reported for the first time a highly soluble and inexpensive base of the type $R_2NMgCl{\cdot}LiCl$ (**10)** that displayed a high kinetic activity (Scheme 10).[34]

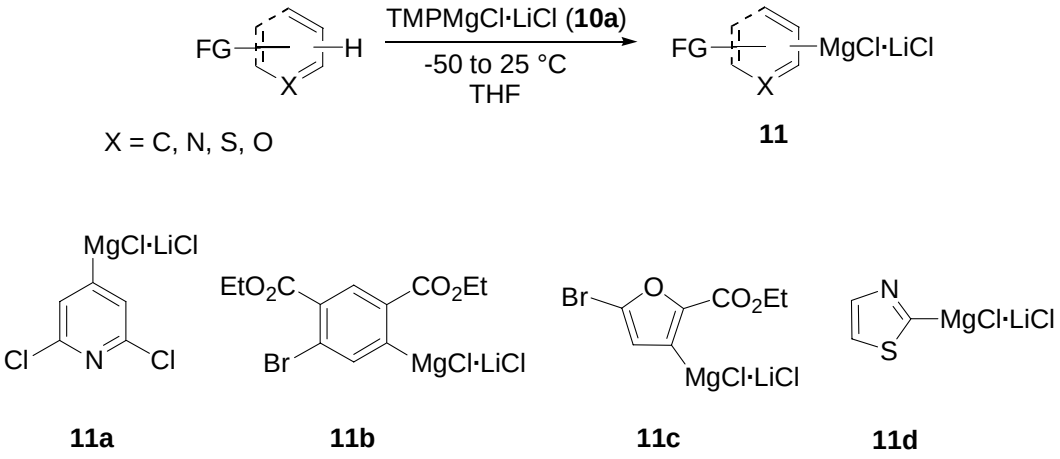
---

[27] Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109.
[28] Wittig, G.; Fuhrmann, G. *Ber. Dtsch. Chem. Ges.* **1940**, *73*, 1197.
[29] a) Gschwend, H. W.; Rodriguez, H. R. *Org. React*. **1979**, *26*, 1; b) Beak, P.; Snieckus, V. *Acc. Chem. Res*. **1982**, *15*, 306; c) Snieckus, V. *Chem. Rev*. **1990**, *90*, 879; d) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297; e) Clayden, J.; Stimson, C. C.; Keenan, M. *Chem. Commun*. **2006**, 1393; f) Henderson, K. W.; Kerr, W. J. *Chem. -Eur. J*. **2001**, 3431; g) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489; h) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059; i) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev*. **2005**, *105*, 827; j) Kauch, M.; Hoppe, D. *Synthesis* **2006**, 1578; k) Clegg, W.; Dale, S. H.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem. Int. Ed*. **2006**, *45*, 2371; l) Hodgson, D. M.; Miles, S. M. *Angew. Chem. Int. Ed*. **2006**, *45*, 93; m) Yus, M.; Foubelo, F. in *Handbook of Functionalized Organometallics*; Knochel, P. Ed.; Wiley-VCH: Weinheim, Germany, **2005**; Vol. 1, p 7.
[30] a) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed*. **2004**, *43*, 2206; b) Schlosser, M. in *Struktur und Reaktivität Polar Organometalle*, Springer Verlag; Berlin, **1973**; c) Wakefield, B. J. in *The Chemistry of Organolithium Compounds*, Pergamon; Oxford, **1974**; d) Wardell, J. L. in *Comprehensive Organometallic Chemistry*; Wilkinson, E.; Stone, F. G. A.; Abel, E.; Eds.; Pergamon; Oxford **1982**, Vol 1, Chapter 1; e) Bates, R. B.; Ogle, C. A. in *Carbanion Chemistry*; Springer Verlag; Berlin, **1983**.
[31] a) Hauser, C. R.; Walker, H. G. *J. Am. Chem. Soc*. **1947**, *69*, 295; b) Hauser, C. R.; Frostick, F. C. *J. Am. Chem. Soc*. **1949**, *71*, 1350.
[32] a) Eaton, P. E.; Lee, C. H.; Xiong, Y. *J. Am. Chem. Soc*. **1989**, *111*, 8016; b) Eaton, P. E.; Martin, R. M. *J. Org. Chem*. **1988**, *53*, 2728; c) Eaton, P. E.; Lukin, K. A. *J. Am. Chem. Soc*. **1993**, *115*, 11370; d) Zhang, M. -X.; Eaton, P. E. *Angew. Chem. Int. Ed*. **2002**, *41*, 2169.
[33] a) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem. Int. Ed*. **2007**, *46*, 3802; b) Westerhausen, M. *Dalton Trans*. **2006**, 4768; c) Kondo, Y.; Akihiro, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans.1* **1996**, *1*, 2331.
[34] a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed*. **2006**, *45*, 2958; b) Lin, W.; Baron, O.; Knochel, P. *Org. Lett*. **2006**, *8*, 5673; c) Mosrin, M.; Knochel, P. *Org. Lett*. **2008**, *10*, 2497: d) Mosrin, M.; Boudet, N.; Knochel, P. *Org. Biomol. Chem*. **2008**, *6*, 3237.



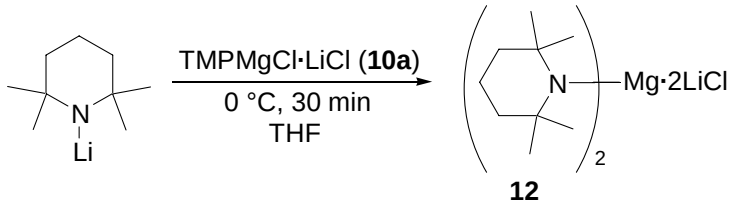
Scheme 10: Preparation of the mixed Mg/Li amides of type **10**.

Similarly to the halogen-magnesium exchange, the accelerating effect induced by LiCl is attributed to the breaking of the oligomeric aggregates of the magnesium amides.[33a] In addition, these amide bases display an excellent thermal stability and can be stored as THF solutions at 25 °C for over 6 months with no decrease in concentration. Using TMPMgCl·LiCl (**10a**) for the regioselective metallation of arenes and heteroarenes, a wide range of new magnesium species of type **11** can be obtained, which would not be available otherwise (Scheme 11).[34]

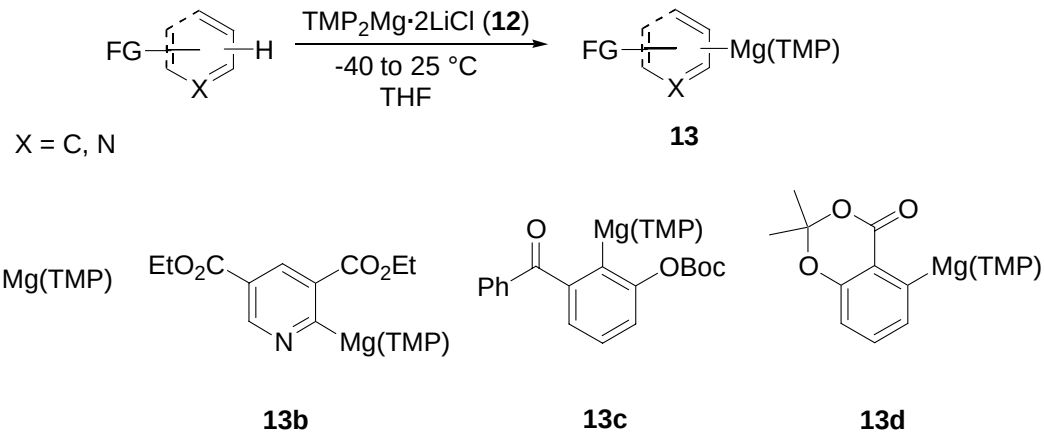


Scheme 11: Magnesiation of functionalized aromatic systems using TMPMgCl·LiCl (**10a**).

A more reactive magnesium bisamide base complexed with LiCl of the general type $(R_2N)_2Mg{\cdot}2LiCl$ proved to be more powerful than TMPMgCl·LiCl (**10a**).[35] The new base $TMP_2Mg{\cdot}2LiCl$ (**12**) was able to efficiently deprotonate even moderately activated arenes that could not be metallated using the monoamide base **10a** (Scheme 12). Thus a number of metallated species of type **13** could be obtained (Scheme 13).[35]



Scheme 12: Preparation of the magnesium bisamide base $TMP_2Mg{\cdot}2LiCl$ (**12**).

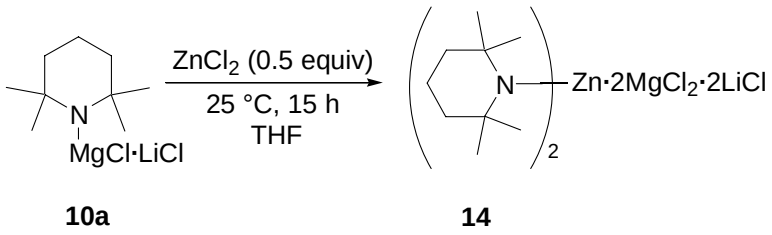


Scheme 13: Regio- and chemoselective directed magnesiation using $TMP_2Mg{\cdot}2LiCl$ (**12**).

The new magnesium amide bases, along with their excellent stability and reactivity proved also to be compatible with a number of sensitive functional groups such as esters, nitriles and aryl ketones. However, in the case of sensitive heterocycles or in the presence of nitro groups or aldehydes, the magnesium bases were too reactive to allow a selective metallation. The need for a milder yet efficient metallating agent became therefore apparent. Based mainly upon the works of *Kondo*,[36] *Wunderlich* and *Knochel* explored the preparation of a milder

[35] a) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem. Int. Ed*. **2007**, *46*, 7681; b) Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem. Int. Ed*. **2008**, *47*, 1503; c) Rohbogner, C. J.; Wunderlich, S. H.; Clososki, G. C.; Knochel, P. *Eur. J. Org. Chem*. **2009**, 1781.

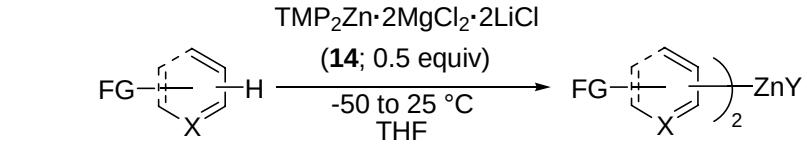
zincate base. Hence, treatment of TMPMgCl·LiCl (**10a**) with $ZnCl_2$ resulted in the mixed Zn/Mg/Li base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**14**) (Scheme 14).[34c, 37]



10a **14**

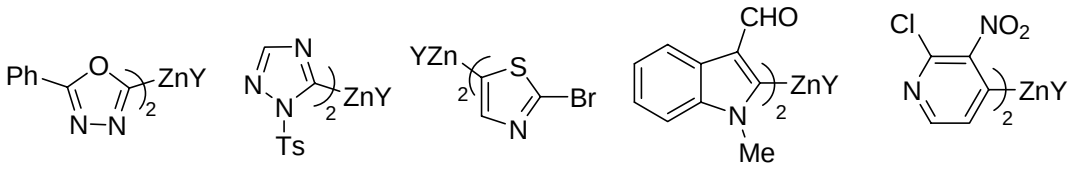
Scheme 14: Preparation of the zincate base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**14**).

This novel base **14** displays a high activity for the zincation of sensitive heterocycles that are prone to decomposition when treated with the more reactive Mg- or Li-bases.[36] Furthermore using **14**, zincation was possible even in the presence of nitro groups or aldehydes to produce metallated compounds of type **15** (Scheme 15).



X = C, N, S, O
Y = $2MgCl_2{\cdot}2LiCl$

15



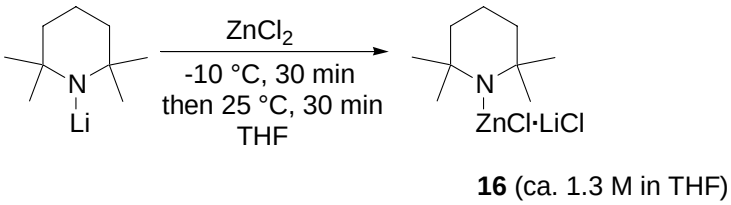
15a **15b** **15c** **15d** **15e**

Scheme 15: Zincation of sensitive heterocycles even bearing an aldehyde or a nitro group using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**14**).

[36] a) Kondo, Y.; Shilai, H.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc*. **1999**, *121*, 3539; b) Imahori, T.; Uchiyama, M.; Kondo, Y. *Chem. Commun*. **2001**, 2450; c) Schwab, P. F. H.; Fleischer, F.; Michl, J. *J. Org. Chem*. **2002**, *67*, 443; d) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otami, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc*. **2002**, *124*, 8514; e) Uchiyama, M.; Matsumoto, Y.; Nobuto, D-; Furuyama, T.; Yamaguchi, K.; Morokuma, K. *J. Am. Chem. Soc*. **2006**, *128*, 8748; f) Armstrong, D. R.; Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem. Int. Ed*. **2006**, *45*, 2374; g) Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatly, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc*. **2007**, *129*, 1921.

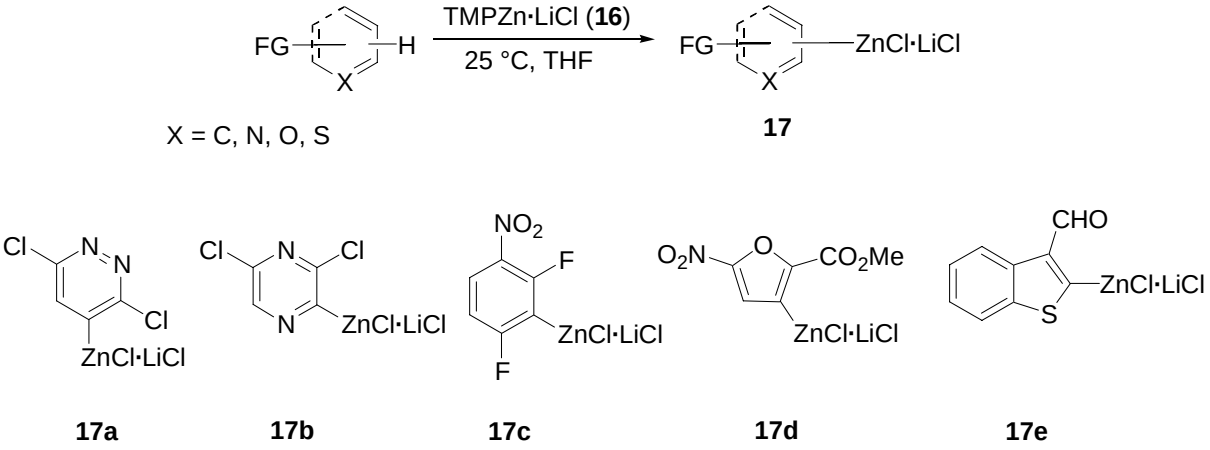
[37] a) Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed*. **2007**, *46*, 7685; b) Wunderlich, S. H.; Knochel, P. *Chem. Commun*. **2008**, 6387; c) Wunderlich, S. H.; Knochel, P. *Org. Lett*. **2008**, *10*, 4705.

Interestingly, by omitting the magnesium salt, *Mosrin* and *Knochel* managed to produce an even milder base that could perform metallations of sensitive substrates at 25 °C.[38] This new mixed Zn/Li base TMPZnCl·LiCl (**16**) displays an excellent thermal stability and can be stored at 25 °C for more than one month (Scheme 16).



Scheme 16: Preparation of the base TMPZnCl·LiCl (**16**).

Contrary to $TMP_2Zn·2MgCl_2·2LiCl$ (**14**), this new complex base TMPZnCl·LiCl (**16**) proved to be very good for chemoselective zincations of sensitive aromatics and heteroaromatics at 25 °C yielding organozinc compounds of type **17** (Scheme 17). The very mild conditions under which the zincation proceeds, are of great importance especially for industrial applications and convenient reaction upscaling.



Scheme 17: Zincation of sensitive arenes and heteroarenes at 25 °C using TMPZnCl·LiCl (**16**).

Overall, the amide bases described above represent very useful tools that can be applied to different molecular systems complementary, to achieve high yield metallations.

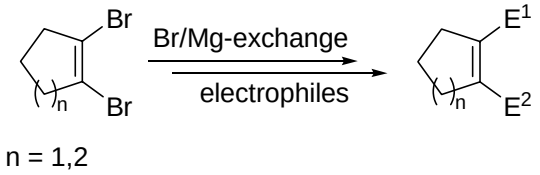
[38] Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837.

4. Objectives

After the development of powerful organomagnesium reagents for performing a Br/Mg-exchange reaction, the field of the metallation of olefinic systems still remained to be explored.

In a first project, the Br/Mg-exchange has been applied to the 1,2-difunctionalization of dibromocycloalkenes. The objectives were:

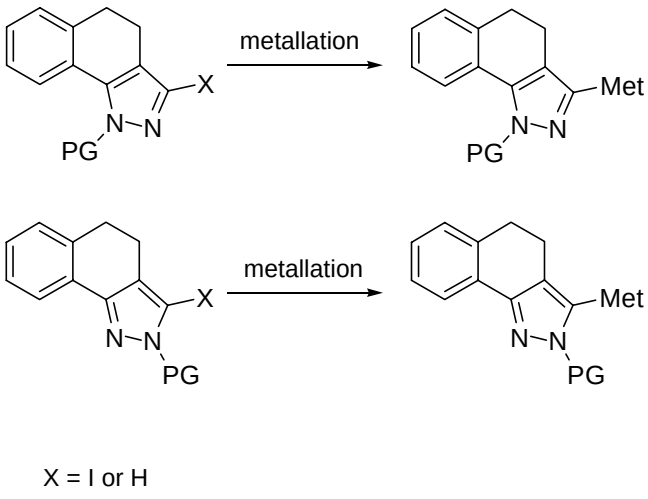
- 1,2-difunctionalization of dibromocyclopentene derivatives,
- extension of this methodology to dibromocyclohexene derivatives.



Scheme 18: Difunctionalization of cycloalkenylic systems.

The second project was a cooperation with Boehringer Ingelheim GmbH Austria and involved the functionalization of 4,5-dihydrobenzo[g]indazoles, a very important scaffold in the pharmaceutical industry. The aim of this work was:

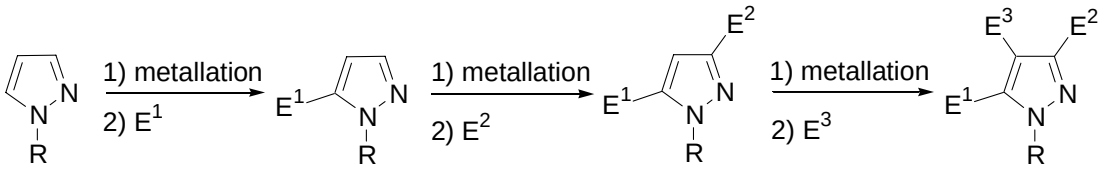
- application of the I/Mg-exchange on the two isomeric 4,5-dihydrobenzo[g]indazole heterocycles,
- direct metallation using the developed amide-bases on the two isomeric 4,5-dihydrobenzo[g]indazole heterocycles.



Scheme 19: Metallation of the isomeric 4,5-dihydrobenzo[*g*]indazoles.

The third project was devoted to the full functionalization of the pyrazole ring through successive regioselective metallations. Following goals needed to be achieved:

- development of a general procedure for the synthesis of fully substituted pyrazoles with complete regiocontrol, starting from readily available unsubstituted pyrazoles,
- application to the synthesis of the acaricide Tebufenpyrad.



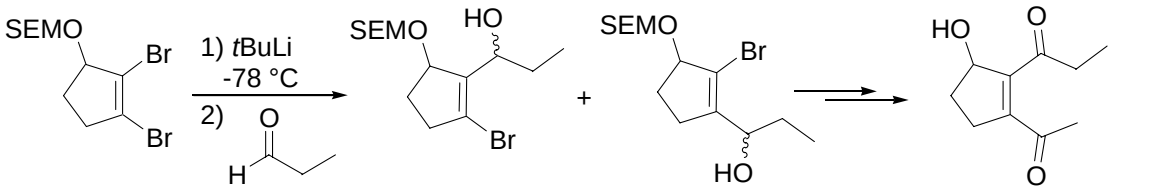
Scheme 20: Proposed full functionalization of the pyrazole core.

B: Results and Discussion

1. Functionalization of 1,2-Dibromocyclopentene Systems

1.1 Introduction

The cycloalkenylic system is a significant scaffold, present in many natural products. For example, cyclopentene derivatives have been isolated from the mushroom species *Tricholoma columbetta*. In fact, the total synthesis of the cyclopentenol derivative Columbetdione (**18**), reported in 2003 by *Vidari* involves a Br/Li-exchange. The exchange however proceeds at -78 °C and results in a mixture of diastereomers (Scheme 21).[39]



Columbetdione (**18**)

Scheme 21: Total synthesis of Columbetdione through a Br/Li-exchange.

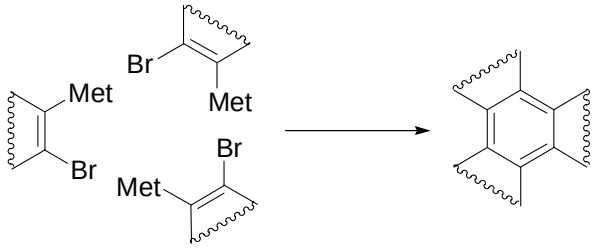
Furthermore, 1,2-difunctionalized cyclopentene derivatives are also interesting for the pharmaceutical industry as potential nonsteroidal anti-inflammatory drugs (NSAIDs).[40] 1,2-Diarylcyclopentenes have been reported as very potent and orally active cyclooxygenase inhibitors.[40]

Nevertheless, cycloalkenes are most prominent in the field of supramolecular chemistry.[41] Trisannelated benzenes of polycyclic structures have attracted considerable interest in the past years, due to their unusual electronic features and geometries that make them suitable for applications in nanotechnology,[42] in the field of liquid crystals[43] and as linear polymers with

---

[39] Vadalá, A.; Finzi, P. V.; Zanoni, G.; Vidari, G. *Eur. J. Org. Chem.* **2003**, 642.
[40] Reitz, D. B.; Li, J. J.; Norton, M. B.; Reinhard, E. J.; Collins, J. T.; Anderson, G. D.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1994**, *37*, 3878.
[41] a) Hunter, C. A. *Chem. Soc. Rev*. **1994**, 101; b) Ma, J. C.; Dougherty, D. A. *Chem. Rev*. **1997**, *97*, 1303; c) Lehn, J. -M. *Supramolecular Chemistry*, VCH, Weinheim, **1995**; Diderich, F. *Cyclophanes*, The Royal Society of Chemistry, Cambridge, **1994**.
[42] Balzani, V.; Credi, A.; Venturi, M. *Chem. -Eur. J*. **2002**, *8*, 5524.
[43] a) Felder, D.; Heinrich, B.; Guillon, D.; Nicoud, J. -F.; Nierengarten, J. -F. *Chem. -Eur. J*. **2000**, *6*, 3501; b) Cooke, G.; Kaushal, N.; Boden, N.; Bushby, R. J.; Lu, Z.; Lozman, O. *Tetrahedron Lett*. **2000**, *41*, 7955; c) Holder, S. J.; Elemans, J. A. A.; Donners, J. J. J. M.; Boeraskker, M. J.; de Gelder, R.; Barberá, J.; Rowan, A. E.; Nolte, R. J. M. *J. Org. Chem*. **2001**, *66*, 391.

π-conjugated carbon scaffolds.[44] These interesting structures are mainly obtained through cyclotrimerization reactions of 1,2-dihalocycloalkenes. A halogen/lithium or a halogen/tin exchange furnishes the metallated intermediates **19** that can subsequently undergo a Pd- or Cu-catalyzed coupling (Scheme 22).[45] The Li-intermediates are, however, unstable and eliminate to form the very reactive alkynes, resulting thus in a mixture of products. *De Lucchi* manages in his work, by using trimethyltin substituted alkenes, to circumvent the rapid elimination with a compromise in the toxicity.[46] Therefore, there exists a need for a simple generation of stable organometallic species of type **19** with a halogen at the *β* position.



19

Met = Li, SnR_3

Scheme 22: Cyclotrimerization reaction of cycloalkenylic bromides of type **19**.

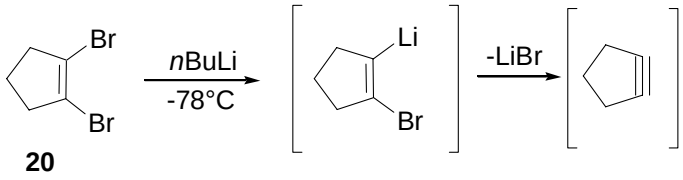
1.2 Selective mono-and 1,2-difunctionalization of cyclopentene derivatives

1.2.1 Monofunctionalization using Br/Mg-exchange

Recently, we have shown that an I/Mg-exchange using *i*PrMgCl·LiCl (**6**) allows a stereoselective preparation of alkenylmagnesium reagents starting from polyfunctional alkenyl iodides.[22c, 25] Whereas this exchange proceeds at low temperatures, alkenyl bromides do not react with *i*PrMgCl·LiCl (**6**) even at 40-50 °C.[25] Of special interest would be the preparation of magnesium derivatives of 1,2-dibromocycloalkenes, since the corresponding

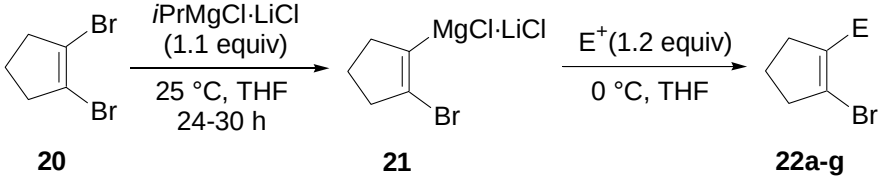
[44] Kosinski, C.; Hirsch, A.; Heinemann, F. W.; Hampel, F. *Eur. J. Org. Chem*. **2001**, 3879.
[45] a) Gassman, P.; Gennick, I. *J. Am. Chem. Soc*. **1980**, *102*, 6863; b) Singh, S. B.; Hart, H. *J. Org. Chem*. **1990**, *55*, 3412; c) Komatsu, K.; Aonuma, S.; Jinbu, Y.; Tsuji, R.; Hirosawa, C.; Takeuchi, K. *J. Org. Chem*. **1991**, *56*, 195; d) Durr, R.; Cossu, S.; Lucchini, V.; De Lucchi, O. *Angew. Chem. Int. Ed*. **1997**, *36*, 2805.
[46] a) Cossu, S.; De Lucchi, O.; Paulon, A.; Peluso, P.; Zonta, C. *Tetrahedron Lett*. **2001**, *42*, 3515; b) Cossu, S.; Cimenti, C.; Peluso, P.; Paulon, A.; De Lucchi, O. *Angew. Chem. Int. Ed*. **2001**, *40*, 4086; c) Peluso, P.; De Lucchi, O.; Cossu, S. *Eur. J. Org. Chem*. **2002**, 4032; d) Paulon, A.; Cossu, S.; De Lucchi, O.; Zonta, C. *Chem. Commun*. **2000**, 1837; e) Zonta, C.; Cossu, S.; De Lucchi, O. *Eur. J. Org. Chem*. **2000**, 1965; f) Dastan, A.; Uzundumlu, E.; Balci, M.; Fabris, F.; De Lucchi, O. *Eur. J. Org. Chem*. **2004**, 183.

lithium organometallics [47] are elusive intermediates. Thus, a Br/Li-exchange on 2,3-dibromobicyclo[2.2.1]hept-2-ene and 1,2-dibromocyclopentene (**20**) using *n*BuLi at -78 °C leads to unstable organolithium compounds, which decompose at room temperature within 18 h (Scheme 23).[48]



Scheme 23: Br/Li-exchange on **20**, resulting in the formation of cyclopentyne.

The reaction of 1,2-dibromocyclopentene (**20**) with *i*PrMgCl·LiCl (**6**; 1.1 equiv, 25 °C, 24-30 h) provides the corresponding magnesium reagent **21** bearing a *β*-bromine (Scheme 24).



Scheme 24: Br/Mg-exchange on 1,2-dibromocyclopentene (**20**) and subsequent trapping with electrophiles.

Remarkably, this new magnesium species shows no tendency to eliminate MgClBr at room temperature and can be stored for more than a month at 25 °C as a 1 M solution in THF under argon with a minimal decrease in activity. Reactions of the magnesium reagent **21** with various electrophiles produced the functionalized cyclopentenyl bromides **22a-g** in 65-82% yield (Table 1).

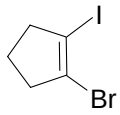
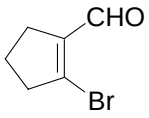
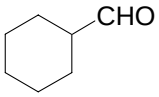
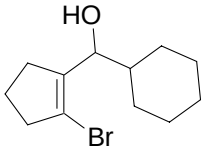
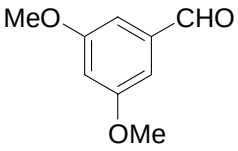
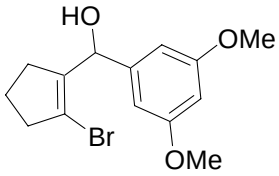
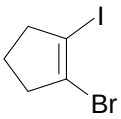
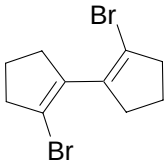
Treatment of the magnesium reagent **21** with iodine provides the unsymmetrical 1-bromo-2-iodocyclopentene (**22a**) in 82% yield (entry 1 of Table 1). Quenching of **21** with DMF gave

[47] a) Luparia, M.; Vadalá, A.; Zanoni, G.; Vidari, G. *Org. Lett.* **2006**, *8*, 2147; b) Tranmer, G. K.; Yip, C.; Handerson, S.; Jordan, R. W.; Tam, W. *Can. J. Chem.* **2000**, *78*, 527; c) Dastan, A.; Uzundumlu, E.; Balci, M.; Fabris, F.; De Lucchi, O. *Eur. J. Org. Chem.* **2004**, 183; d) Paquette, L. A.; Doyon, J. *J. Am. Chem. Soc.* **1995**, *117*, 6799. e) Gassman, P. G.; Gennick, I. *J. Am. Chem. Soc.* **1980**, *102*, 6863; f) Foubelo, F.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 459.

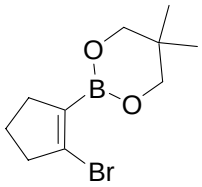
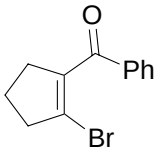
[48] a) Wittig, G.; Krebs, A. *Chem. Ber.* **1961**, *94*, 3260; b) Wittig, G.; Pohlke, R. *Chem. Ber.* **1961**, *94*, 3276; c) Wittig, G. *Rev. Chim.* **1962**, *7*, 1393; d) Wittig, G.; Weinlich, J.; Wilson, E. R. *Chem. Ber.* **1965**, *98*, 458; e) Wittig, G.; Heyn, J. *Liebigs Ann. Chem.* **1969**, *726*, 57; f) Wittig, G.; Heyn, J. *Liebigs Ann. Chem.* **1972**, *756*, 1; g) Gilbert, J. C.; Hou, D. -R.; Grimme, J. W. *J. Org. Chem.* **1999**, *64*, 1529.

the *β*-bromo-unsaturated aldehyde **22b** (82%, entry 2). Reactions with aliphatic and aromatic aldehydes afford the allylic alcohols **22c** and **22d** in 77–80% yield (entries 3 and 4). Dimerization of **21**, leading to **22e** (entry 5), was best performed via a palladium-catalyzed *Negishi* cross-coupling[49] in 80% yield. The reaction with $(i\text{PrO})_3\text{B}$, followed by the addition of 2,2-dimethylpropane-1,3-diol, yielded the cycloalkenyl boronic ester **22f** in 72% yield (entry 6). Benzoylation of **21** after transmetallation with $ZnCl_2$ and addition of CuCN·2LiCl (20 mol%) provided the ketone **22g** in 65% yield (entry 7).[50]

Table 1. Reactions of β-bromoalkenylmagnesium chloride (**21**) with various electrophiles.

Entry	Electrophile	Product	Yield [%][a]
1	I_2	**22a** 	82
2	DMF	**22b** 	82
3		**22c** 	80[b]
4		**22d** 	77[b]
5		**22e** 	80[c]

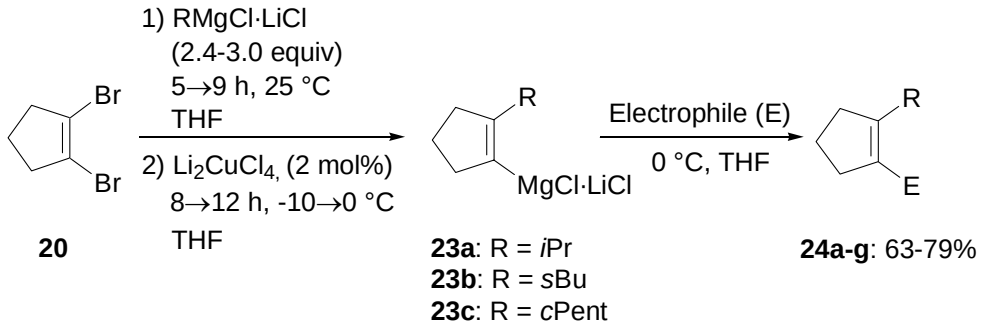
[49] *Negishi*, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.
[50] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

6	1) $(i\text{PrO})_3\text{B}$ 2) 	**22f** 	72
7	PhCOCl	**22g** 	65[d]

[a] Yield of analytically pure product. [b] These experiments were performed by *Dr. R. Bauer* and are given here for the sake of completeness. [c] **21** was transmetallated with $ZnCl_2$ (1 equiv), followed by the addition of $Pd(dba)_2$ (5 mol%) and tfp (7 mol%). [d] At -20 °C, **21** was transmetallated with $ZnCl_2$ (1 equiv), then CuCN·2LiCl (20 mol%).

1.2.2 Difunctionalization via Cu-intermediates

In the presence of an excess of *i*PrMgCl·LiCl (**6**; 2.4 equiv) and a catalytic amount of Li_2CuCl_4 (2 mol%, 0 °C, 8–12 h), the *β*-bromine of the intermediate *Grignard* reagent **21** is substituted by an isopropyl group, furnishing the *Grignard* reagent **23a** (Scheme 25).

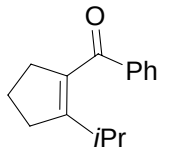
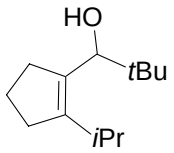
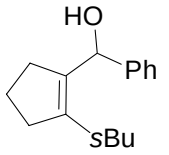
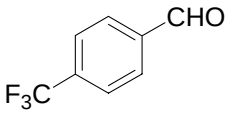
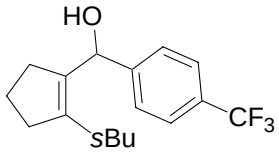
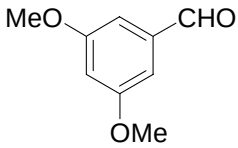
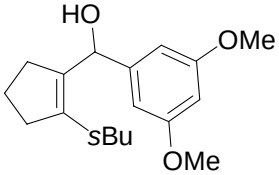
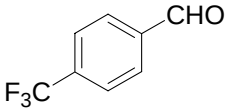
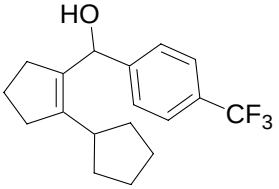


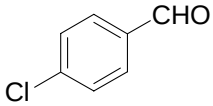
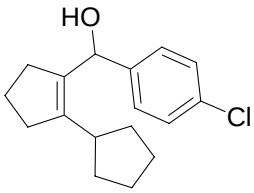
Scheme 25: Preparation of alkenylmagnesium reagents **23** via a Cu-catalyzed coupling and subsequent reaction with electrophiles.

After transmetallation with $ZnCl_2$, a copper-catalyzed acylation[50] yielded the unsaturated ketone **24a** (entry 1 of Table 2). Quenching with aldehydes provided the allylic and benzylic alcohols **24b-g** in 63-79% yield over 3 steps in a one-pot procedure (entries 2-7). An excess of alkylmagnesium reagent was necessary to overcome undesired homocoupling reactions; this was most prevalent when *c*-C_5H_9MgCl·LiCl was used, requiring 3 equivalents of the reagent to complete both the exchange and coupling steps. Expanding the scope of the

reaction beyond secondary alkylmagnesium reagents proved to be unsuccessful. With *n*BuMgCl, *n*BuLi, *t*BuMgCl, PhMgCl, and PhLi, coupling between alkenylmagnesium species (of both types **21** and **23**) was a major side-reaction. Preliminary experiments also showed the same difficulties when allyl- and benzylorganomagnesium reagents were used.

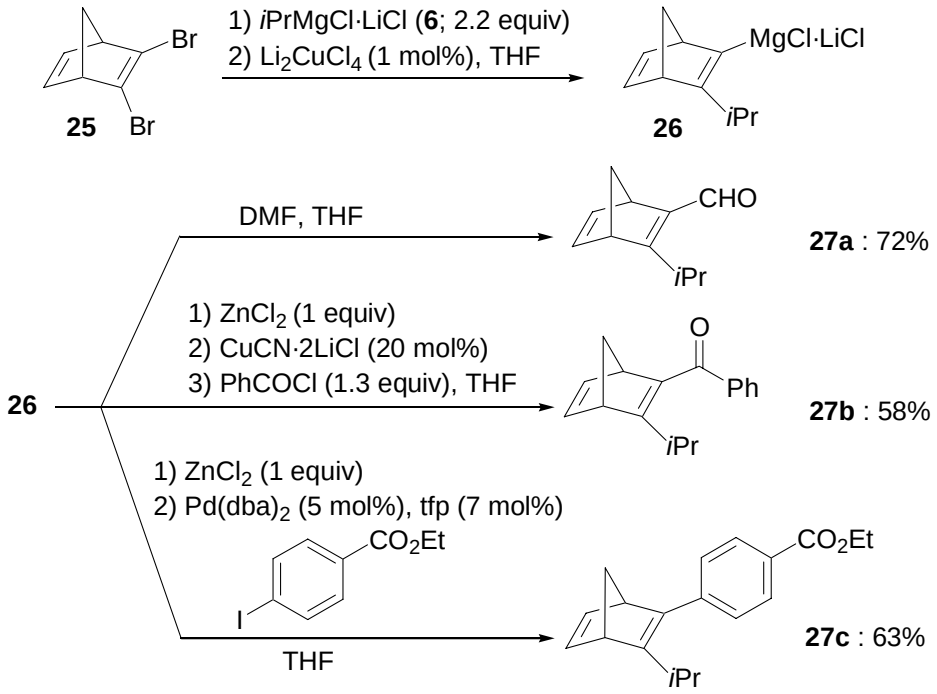
Table 2. Products of type **24** obtained via a Cu-catalyzed coupling.[a]

Entry	RMgCl·LiCl	Electrophile	Product	Yield [%][b]
1	*i*PrMgCl·LiCl (2.4 equiv)	PhCOCl (1.5 equiv)	**24a** 	66[c]
2	*i*PrMgCl·LiCl (2.4 equiv)	*t*BuCHO (1.5 equiv)	**24b** 	74
3	*s*BuMgCl·LiCl (2.8 equiv)	PhCHO (1.6 equiv)	**24c** 	68
4	*s*BuMgCl·LiCl (2.8 equiv)	 (1.6 equiv)	**24d** 	79
5	*s*BuMgCl·LiCl (2.8 equiv)	 (1.6 equiv)	**24e** 	63
6	*c*PentMgCl·LiCl (3.0 equiv)	 (1.7 equiv)	**24f** 	73

7	*c*PentMgCl·LiCl (3.0 equiv)	 (1.7 equiv)	**24g** 	65

[a] These experiments were performed by *Dr. R. Bauer* and are given here for the sake of completeness. [b]Isolated, analytically pure product. [c]At -20 °C, **23a** was transmetallated with $ZnCl_2$ (1 equiv), then CuCN·2LiCl (20 mol%).

Extension of this reactivity pattern to the norbornadiene framework [51] was effective, as shown in Scheme 26. Compared to 1,2-dibromocyclopentene (**20**), the Br/Mg-exchange on 1,2-dibromonorbornadiene (**25**) proceeded at a similar rate (25 °C, 7 h) and coupling with *i*PrMgCl was accomplished using Li_2CuCl_4 (1 mol%) (Scheme 26).



Scheme 26: Preparation and reactions of norbornadienylmagnesium reagent (**26**).

The reaction of **26** with DMF produced the unsaturated aldehyde **27a** in 72% yield. Transmetallation of **26** to the corresponding zinc reagent, followed by copper-catalyzed[50]

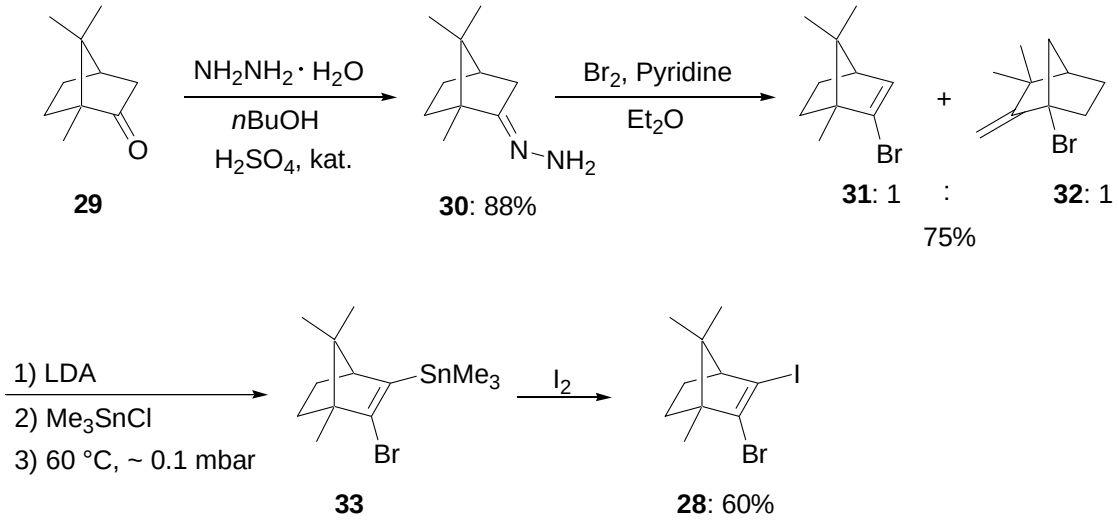
[51] a) Tranmer, G. K.; Tam, W. *Synthesis* **2002**, 1675; b) Yoo, W. -J.; Tsui, G. C.; Tam, W. *Eur. J. Org. Chem.* **2005**, 1044.

benzoylation, afforded the unsaturated ketone **27b**. *Negishi*[49] cross-coupling with ethyl 4-iodobenzoate gave the arylated norbornadiene **27c** in 63% yield (Scheme 26).

1.2.3 Mechanistic studies

The mechanism of this copper-catalyzed bromine-substitution reaction was investigated. Under our standard conditions, the *Grignard* reagent **21** did not appear to eliminate MgClBr to provide cyclopentyne. No trapping of this highly reactive intermediate could be achieved by the addition of furan, 2,3,4,5-tetraphenylcyclopentadienone or dihydropyran.[52] We therefore prepared the unsymmetrical bicyclo[2.2.1]alkenyl-2,3-dihalide **28** in order to determine the regioselectivity of the cross-coupling. The synthesis of the 2-bromo-3-iodocamphor derivative **28** was accomplished regioselectively starting from D-camphor **29** over 4 steps in 40% overall yield. Reaction of the D-camphor **29** with hydrazine furnished hydrazone **30** in 88% yield that was then subjected to a Shapiro reaction, yielding according to the published procedure[53] a 1:1 mixture of the desired bromide **31** and the Meerwein rearrangement product **32**. Deprotonation at the vinylic position with LDA occurred only in **31**. *In situ* trapping with trimethyltin chloride as described by *De Lucchi*[54] afforded the tin derivative **33**. The last step was an Sn/I-exchange reaction on the cycloalkenyltin derivative **33**, yielding the iodide **28** in 60% (Scheme 27).[54]

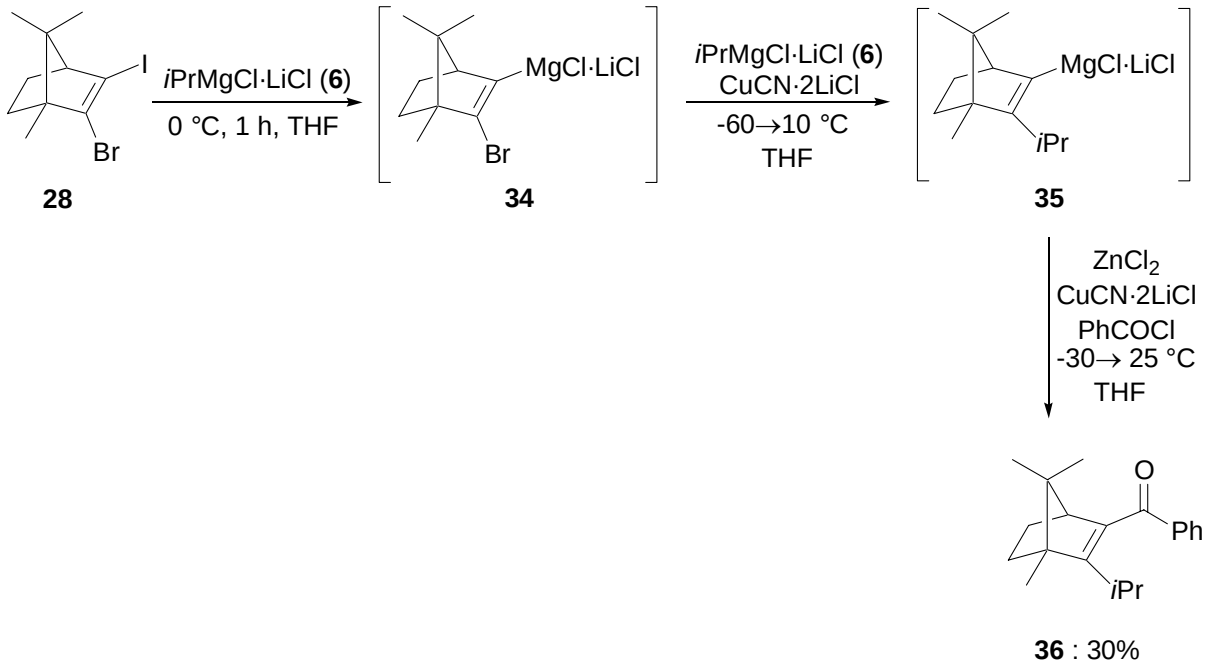
[52] a) Gilbert, J. C.; McKinley, E. G.; Hou, D. -R. *Tetrahedron* **1997**, *53*, 9891; b) Gilbert, J. C.; Hou, D. -R.; Grimme, J. W. *J. Org. Chem.* **1999**, *64*, 1529; c) Gilbert, J. C.; Hou, D. -R. *J. Org. Chem.* **2003**, *68*, 10067.
[53] a) Cremlyn, R.; Bartlet, M.; Lloyd, J. *Phosphorus, Sulfur, and Silicon and the related elements* **1988**, *40*, 91. b) Pross, A.; Sternhell, S. *Aust. J. Chem.* **1971**, *24*, 1437.
[54] Fabris, F.; Zambrini, L.; Rosso, E.; De Lucchi, O. *Eur. J. Org. Chem.* **2004**, 3313.



Scheme 27: Synthesis of (*R*)-2-bromo-3-iodo-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (**33**).

An I/Mg-exchange on the dihalide **28** with *i*PrMgCl·LiCl (**6**; 1.1 equiv) proceeded at 0 °C within 1 h. The *Grignard* reagent **34** proved to be significantly less reactive than the corresponding norbornadiene derivative **26**. Best results for the copper-catalyzed coupling of **34** with *i*PrMgCl were obtained by using a stoichiometric amount of CuCN·2LiCl. The *Grignard* reagent **35**, after transmetallation to zinc and copper-catalyzed acylation[50] with benzoyl chloride yielded the unsaturated ketone **36** in 30% overall yield from **28** (Scheme 28).[55]

[55] A small amount of the other regioisomer of **35** was observed by GC/MS analysis (major:minor 92:8) but was not isolated.



Scheme 28:. Regioselective Cu-catalyzed cross-coupling of alkenyl- and alkylmagnesium species.

Characterization by 1D and 2D NMR experiments, as well as by X-ray crystallographic analysis, confirmed the structure of **36**, proving that the new carbon-carbon bond with *i*Pr is formed at the carbon atom that initially bore the bromine atom (Figure 1).[56]

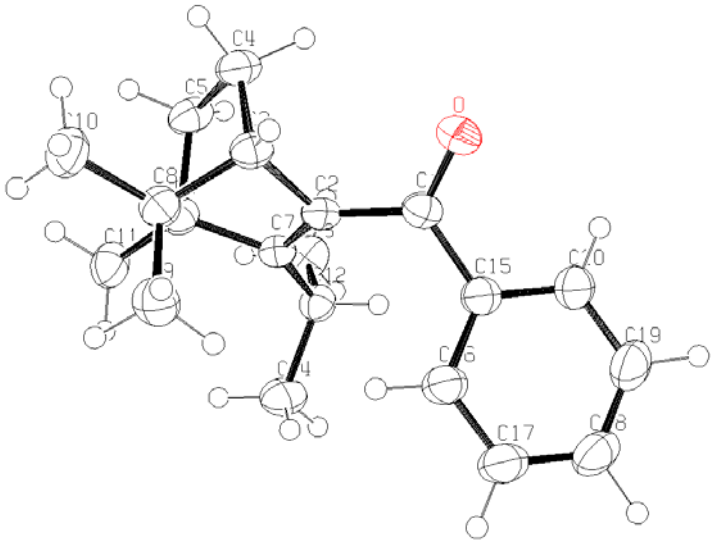
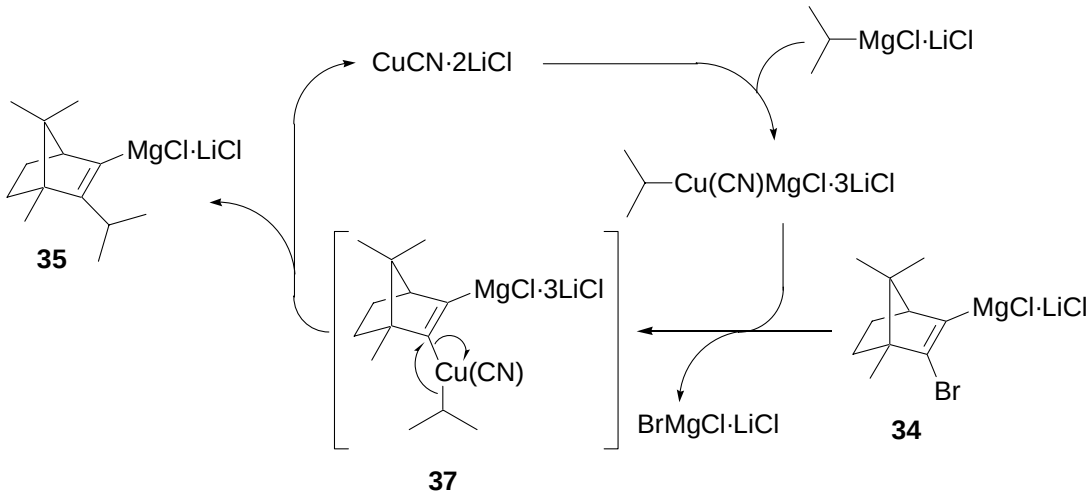


Figure 1: X-ray-structure of compound **36**.

[56] Full details about atomic coordinates, bond lengths and bond angles can be obtained from **The Cambridge Crystallographic Data Centre (CCDC 650282)** via www.ccdc.cam.ac.uk/data-request/cif.

Therefore, we propose the following mechanism for the copper-catalyzed coupling (Scheme 29). Transmetallation of *i*PrMgCl to *i*PrCu(CN)Li, followed by oxidative addition of the carbon-bromine bond in **34** tentatively generates intermediate **37**. Reductive elimination gives intermediate **35**, which is acylated with benzoyl chloride upon transmetallation with CuCN·2LiCl (1 equiv). Alternatively, the reaction may proceed through a cuprio(III)-cyclopropane intermediate,[57] which produces the alkenylmagnesium reagent **35** via a β-elimination assisted by the polymetallic components of the organocuprate.



Scheme 29: Tentative mechanism for the regioselective Cu(I) catalyzed cross-coupling reaction.

The presence of a carbon-magnesium bond in *β*-position to the carbon-bromine bond as found in compound **34** may have an accelerating effect for such cross-couplings. This rate increase is also found with a related alkenyl bromide bearing a carbon-tin bond in *β*-position, as was proved by a kinetic measurement experiment. 1-Bromocyclopentene[58] (1.0 equiv) and 1-(trimethylstannyl)-2-bromocyclopentene[59] (1.0 equiv) were cooled to -65 °C. *i*PrMgCl·LiCl (2.0 equiv) as well as CuCN·2LiCl (4 mol%) were added, and the reaction mixture was allowed to slowly warm up to 5 °C over 5 h. The progress of the reaction was monitored by GC analysis of hydrolyzed reaction aliquots, taken every 30 min. It was observed that 1-(trimethylstannyl)-2-bromocyclopentene ($t_{1/2}$ = 60 min) reacted much faster with

[57] For a more detailed description of the mechanism of the substitution reaction on an sp^2 carbon see: Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 12264.
[58] Roman, U.; Ruhdorfer, J.; Knorr, R. *Synthesis* **1993**, *10*, 985.
[59] Corey, E. J.; Estreicher, H. *Tetrahedron Lett.* **1980**, *21*, 1113.

*i*PrMgCl·LiCl and catalytic CuCN·2LiCl compared to 1-bromocyclopentene ($t_{1/2}$ = 135 min). 1-(Trimethylstannyl)-2-bromocyclopentene was fully consumed within 150 min. The results are summarized in Figure 2**.**

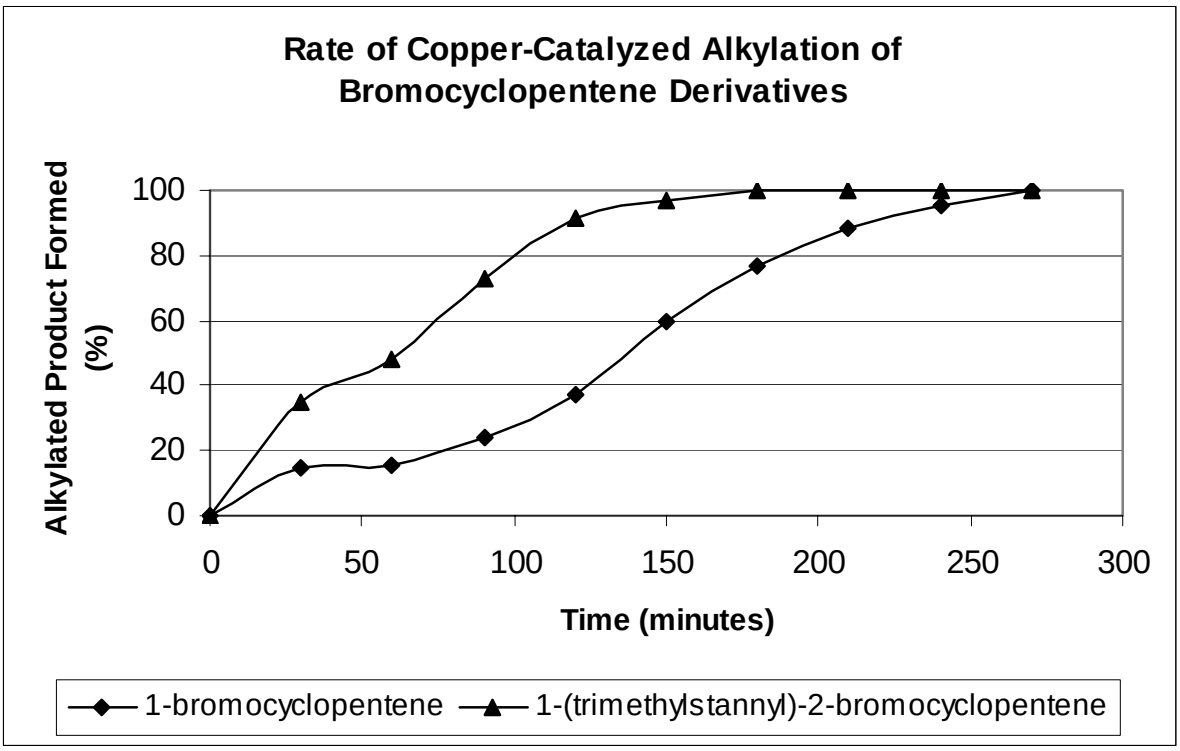
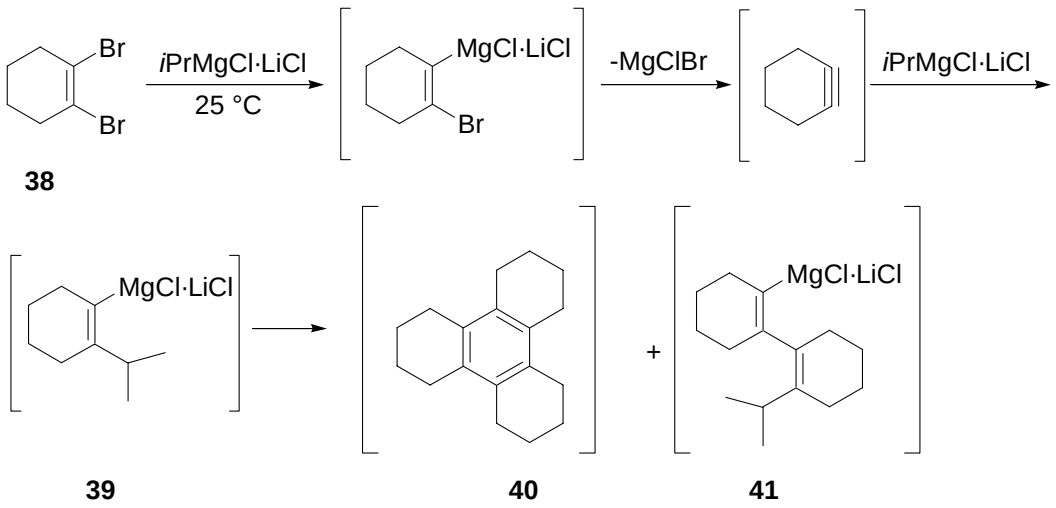


Figure 2: Rate of copper-catalyzed alkylation of two bromocyclopentene derivatives.

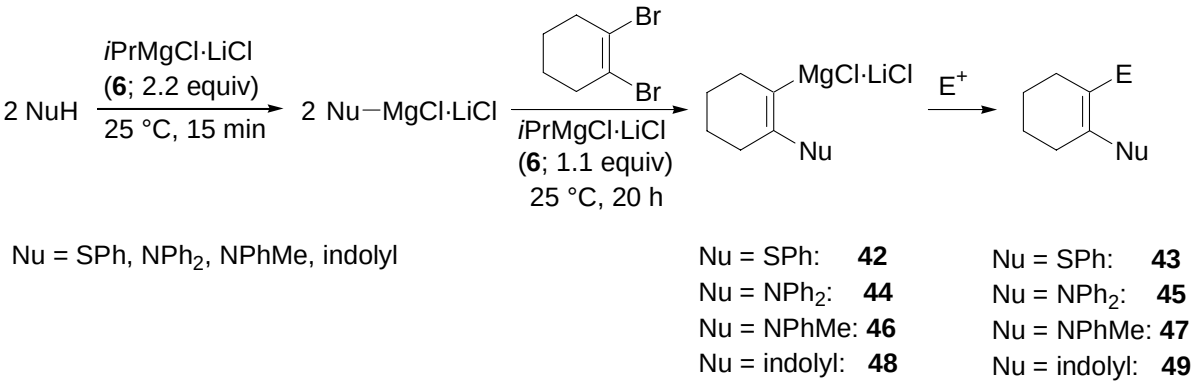
1.3 Difunctionalization of cyclohexene derivatives

Extending this work to the cyclohexene system proved more difficult. Starting from the 1,2 dibromocyclohexene (**38**) selective Br/Mg-exchange could not be achieved. Fast MgBrCl elimination under formation of cyclohexyne led always to byproducts of type **39-41** (Scheme 30).



Scheme 30: Attempt of a Br/Mg-exchange on dibromocyclohexene **38**.

Contrary to the cyclopentene system, the less strained cyclohexene ring was more prone to form a triple bond, so that all attempts to prohibit the elimination step failed.
Interestingly, a 1,2-difunctionalization of the dibromocyclohexene **38** could be achieved when the Br/Mg-exchange is performed in the presence of an excess of a strong nucleophile (Scheme 31).

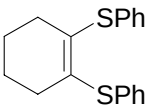
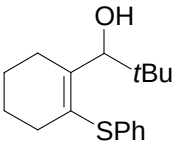
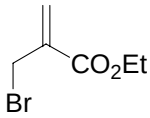
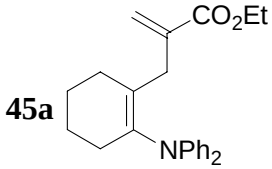
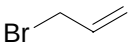
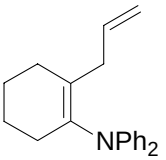
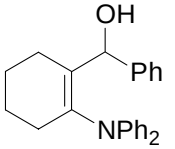


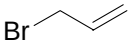
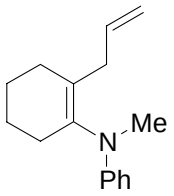
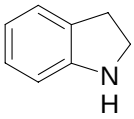
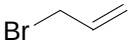
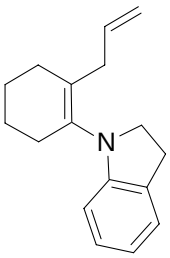
Scheme 31: 1,2-Difunctionalization of dibromocyclohexene **38**.

Hence, a number of different difunctionalized cyclohexenes could be prepared (Table 3). Performing the Br/Mg-exchange of dibromocyclohexene **38** in the presence of magnesiated thiophenol generated the new organomagnesium compound **42** that was subsequently trapped with $PhSSO_2Ph$ or pivaldehyde to furnish the expected products **43a** and **43b** in 56% and 63% yields respectively (Table 3, entries 1 and 2). Similarly, reaction with the magnesiated diphenyl amine gave organomagnesium reagent **44**, which could be allylated in the presence

of CuCN·2LiCl affording the cyclohexene derivatives **45a** and **45b** in 50-61% yield (entries 3 and 4). Trapping of **44** with benzaldehyde produced the corresponding alcohol **45c** in 49% yield (entry 5). Apart from diphenylamine, other secondary amines could also be employed. Thus, in the presence of *N*-methylaniline or indoline, cyclohexenylmagnesium reagents **46** and **48** were obtained respectively. Their Cu(I) catalyzed allylation afforded the difunctionalized cyclohexenes **47** and **49** in 50-52% yield (entries 6 and 7).

Table 3. Products obtained from a one-pot difunctionalization of cyclohexene.

Entry	Nucleophile (NuH)	Electrophile	Product	Yield [%][a]
1	PhSH	$PhSSO_2Ph$	**43a** 	56
2	PhSH	*t*-BuCHO	**43b** 	63
3	Ph_2NH		**45a** 	50[b]
4	Ph_2NH		**45b** 	61[b]
5	Ph_2NH	PhCHO	**45c** 	49

6	MeNHPh		**47** 	52[b]
7			**49** 	50[b]

[a] Isolated, analytically pure product. [b] Catalyzed with 20 mol% CuCN·2LiCl.

A one pot difunctionalization, similarly to the cyclopentene difunctionalization, can thus be achieved. However, this reaction proceeds in poor yields and is limited to the use of amines or thiols as nucleophiles. Performing the reaction in the presence of aryl or alkyl *Grignard* reagents resulted in complex mixtures of dimeric and trimeric structures of type **39-41**.

2. Functionalization of 4,5-Dihydrobenzo[g]indazoles using Mg- and Zn-Heterocyclic Intermediates

2.1 Introduction

Fused pyrazoles and their derivatives are known to possess a wide range of biological activities.[60] For example, pyrazoles fused to a steroid A-ring have been reported to enhance anti-inflammatory activity.[61] Other tricyclic pyrazoles show antimicrobial, antiallergic and non-estrogenic contraceptive activities.[62] Since steroid based pharmaceuticals often have side effects in living organisms, these non-steroidal pyrazole derivatives may deserve attention as potential steroid-analogues.[63] It is therefore, of great interest, especially for the pharmaceutical industry to develop a general method to obtain functionalized 4,5-dihydrobenzo[*g*]indazoles. The metallation procedures developed in our group[64] enable the introduction of different substituents to a heterocycle, giving thus an easy access to various analogs. This approach may find huge application in the industry, since it allows a fast generation of molecular libraries just by modifying an already existing heterocyclic core.

4,5-Dihydrobenzo[*g*]indazole derivatives occur in two isomeric forms, namely of type **50** and **51**. In order to study the metallation of these heterocycles, both isomers were prepared and

---

[60] a) Shenone, S.; Bruno, O.; Ranise, A.; Brullo, C.; Bondavalli, F.; Filippelli, W.; Mazzeo, F.; Capuano, A. Falcone, G. *Il Farmaco* **2003**, *58*, 845; b) Pinna, G. A.; Pirisi, M. A.; Grella, G. E.; Gherardini, L.; Mussinu, J. M.; Paglietti, G.; Ferrari, A. M.; Rastelli, G. *Arch. Pharm. Med. Chem.* **2001**, *334*, 337.

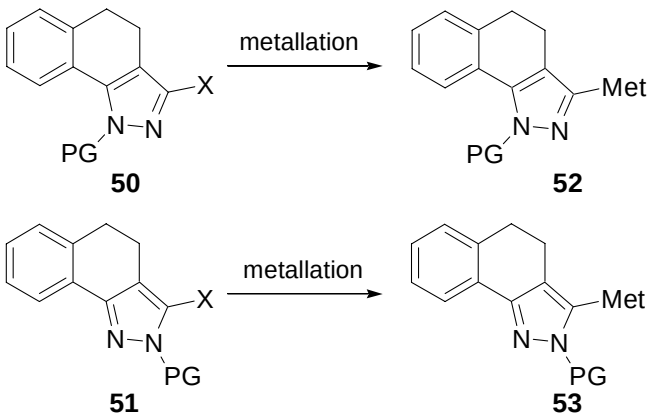
[61] a) Hamilton, R. W. *J. Heterocyclic Chem.* **1976**, *13*, 545; b) Hirschmann, R.; Buchschacher, P.; Steinberg, N. G.; Fried, J. H.; Ellis, R.; Kent, G. J.; Tischler, M. *J. Am. Chem. Soc.* **1964**, *86*, 1520.

[62] a) Sivaprasad, G.; Sridhar, R.; Perumal, P. T. *J. Heterocyclic Chem.* **2006**, *43*, 389; b) Habeck, D. A.; Houlihan, W. J. *Chem. Abstr.* **1977**, *84*, 121821; c) Coombs, R. V.; Houlihan, W. J. *Chem. Abstr.* **1974**, *82*, 57687; d) Coombs, R. V.; Houlihan, W. J. *Chem. Abstr.* **1974**, *82*, 57684; e) Habeck, D. A.; Houlihan, W. J. *Chem. Abstr.* **1974**, *81*, 25661; f) Arnold, L. D.; Xu, Y.; Barlozzari, T. *Chem. Abstr.* **1999**, *130*, 282067; g) Di Parsia, M. T.; Suarez, C.; Vitolo, M. J.; Marquez, V. E.; Beyer, B.; Urbina, C.; Hurtado, I. *J. Med. Chem.* **1981**, *24*, 117; h) Bondavalli, F.; Longobardi, M.; Schenone, P. *Farmaco, Ed. Sci.* **1975**, *30*, 391; i) Ramalingam, K.; Wong, L. F.; Berlin, K. D.; Brown, R. A.; Fischer, R.; Blunk, J.; Durham, N. N. *J. Med. Chem.* **1977**, *20*, 664; j) Hashem, M. M.; Berlin, K. D.; Chesnut, R. W.; Durham, N. N. *J. Carbohydr., Nucleosides, Nucleotides* **1975,** *2*, 357; k) Hashem, M. M.; Berlin, K. D.; Chesnut, R. W.; Durham, N. N. *J. Med. Chem.* **1976**, *19*, 229; l) Chesnut, R. W.; Haslam, D. F.; Durham, N. N.; Berlin, K. D. *Can. J. Biochem.* **1972**, *50*, 516; m) Morgan, J. G.; Berlin, K. D.; Durham, N. N.; Chsnut, R. W. *J. Heterocycl. Chem.* **1971**, *8*, 61; n) Hartmann, R. W.; Waechter, G. A.; Sergejew, T.; Wuertz, R.; Dueerkop, J. *Arch. Pharm.(Weinheim, Germany)* **1995**, *328*, 573; o) Deeb, A.; Bayoumy, B.; Hataba, A.; Fikry, R. *Heterocycles* **1991**, *32*, 901; p) Allen, M. S.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1992**, *35*, 368.

[63] a) Vazquez Lopez, E. A.; Klimova, E. I.; Klimova, T.; Toledano, C. A.; Ramirez, L. R.; Toscano, R. A.; Garcia, M. M. *Synthesis* **2004**, 2471; b) Schvekhgeimer M. G. A. *Russ. Chem. Rev.* **1996**, *65*, 80.

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

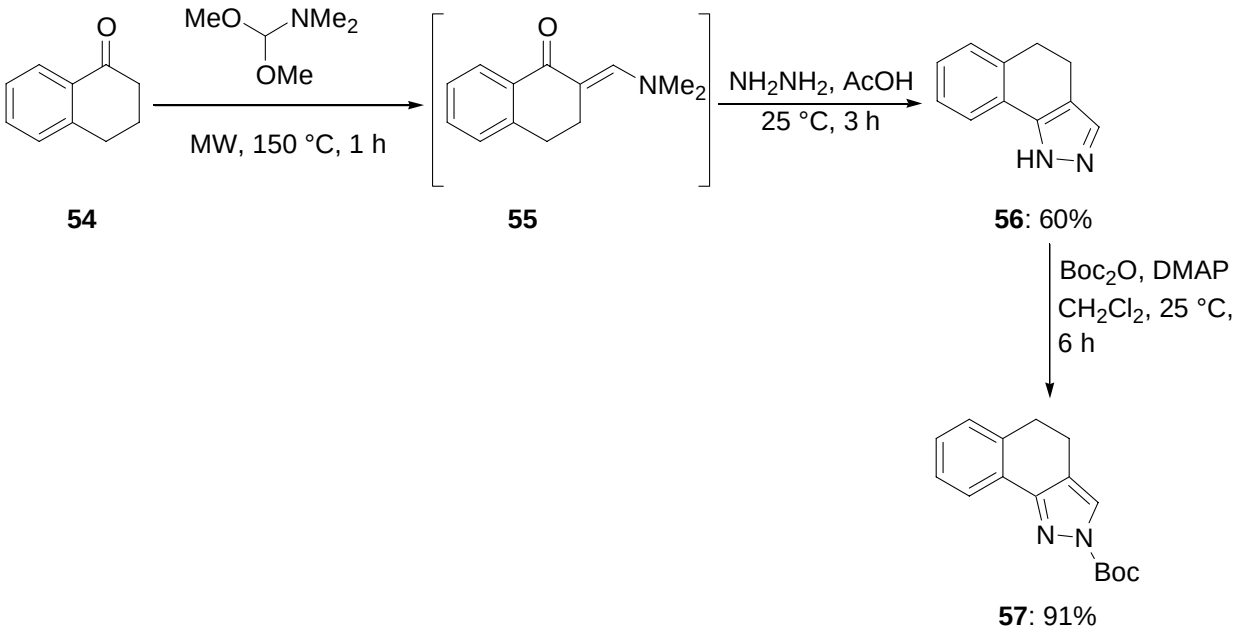
subjected to I/Mg-exchange or deprotonation reactions leading to the organometallic reagents **52** and **53** respectively (Scheme 32).



Scheme 32. Metallation of the dihydrobenzo[*g*]indazoles of type **50** and **51**.

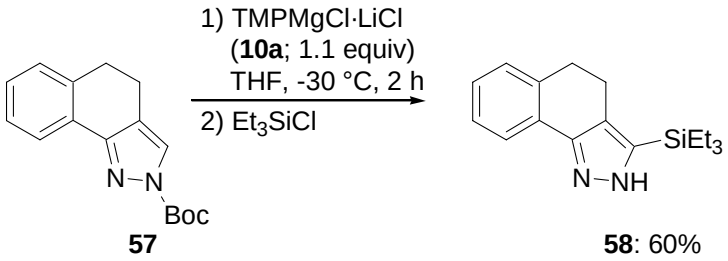
2.2 I/Mg-exchange on 4,5-Dihydro[g]indazoles

The required 4,5-dihydrobenzo[*g*]indazoles of type **50** and **51** were readily prepared from commercially available materials. The reaction of *α*-tetralone (**54**) with dimethylformamide dimethylacetal under microwave irradiation (150 °C, 1 h) gave the alkylidene ketone **55**. Subsequent addition of hydrazine in acetic acid (25 °C, 3 h) furnished the desired 4,5-dihydrobenzo[*g*]indazole **56** in 60% yield. Protection of the pyrazole moiety with Boc_2O gave *tert*-butyl-4,5-dihydro-benzo[*g*]indazole-2-carboxylate (**57**) as a single isomer in 91% yield (Scheme 33).



Scheme 33: Preparation of *tert*-butyl-4,5-dihydro-benzo[*g*]indazole-2-carboxylate (**57**).

Using commercially available TMPMgCl·LiCl (**10a**) base,[65] we were able to deprotonate **57** selectively at the C3 position of the pyrazole ring at -30 °C within 2 h (Scheme 34). Reaction of the resulting magnesiated intermediate with Et_3SiCl furnished the 3-triethylsilanyl-4,5-dihydrobenzo[*g*]indazole (**58**) in 60% yield. The Boc-protecting group, known in this kind of systems to be very labile, was cleaved during the workup.

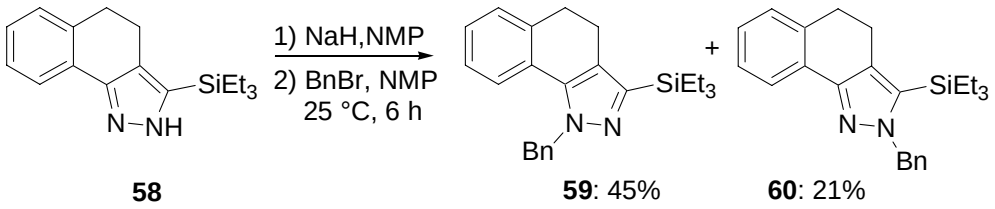


Scheme 34: Deprotonation of *tert*-butyl-4,5-dihydrobenzo[*g*]indazole-2-carboxylate (**57**) at C3 and reaction with Et_3SiCl.

The silylated benzo[*g*]indazole **58** was then benzylated ((i)NaH, NMP; (ii) BnBr, NMP, 25 °C, 5 h) providing a mixture of the 1-benzyl-3-triethylsilanyl-4,5-dihydro-1*H*-

[65] TMPMgCl·LiCl is available from Chemetall (Frankfurt) and Aldrich.

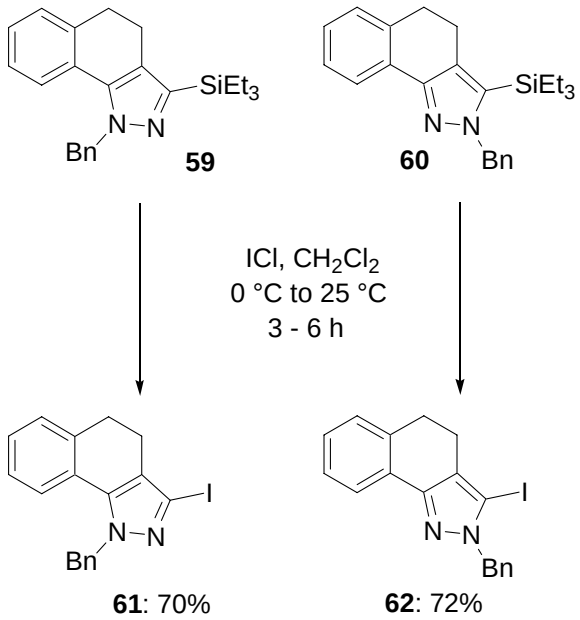
benzo[*g*]indazole (**59**) and the 2-benzyl-3-triethylsilanyl-4,5-dihydro-2*H*-benzo[*g*]indazole (**60**) which could be separated by column chromatography and isolated in 45% and 21% yields respectively (Scheme 35).



58 **59**: 45% **60**: 21%

Scheme 35: Benzylation of 4,5-dihydrobenzo[*g*]indazole **58**.

The silyl group of the benzo[*g*]indazoles **59** and **60** was readily converted to the corresponding heterocyclic iodides **61** and **62** by the reaction with ICl in CH_2Cl_2 (25 °C, 3-6 h) in 70-72% yields (Scheme 36).

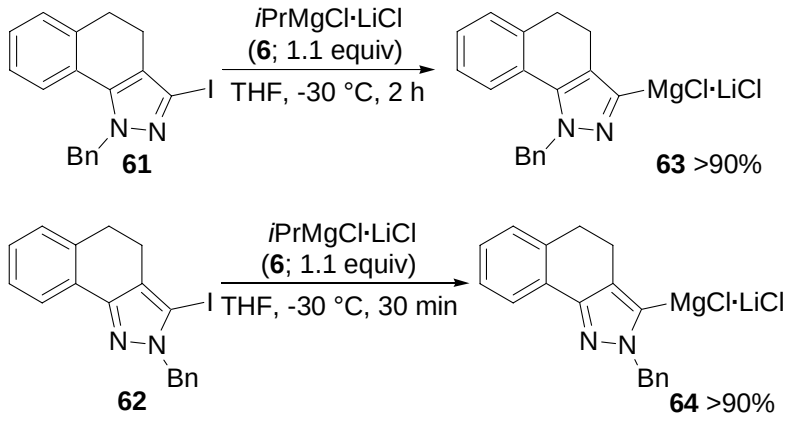


61: 70% **62**: 72%

Scheme 36: Iodination of benzo[*g*]indazoles **59** and **60** with ICl.

The iodinated derivatives **61** and **62** were then magnesiated by using an I/Mg-exchange. In both cases, a full conversion to the corresponding organomagnesium reagents could be achieved using commercially available *i*PrMgCl·LiCl (**6**) at -30 °C, leading to the corresponding organomagnesium species **63** and **64** (Scheme 37). Interestingly, the I/Mg-

exchange rate of **61** was ca. 4 times slower than for the isomer **62**, which may be indicative for the enhanced stability of **63** compared to **64**.

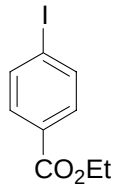
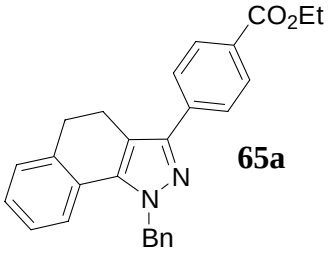
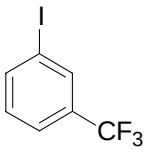
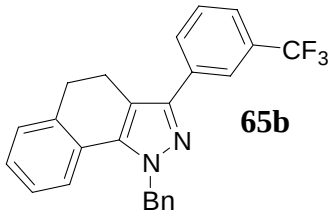
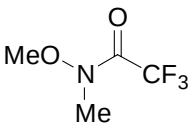
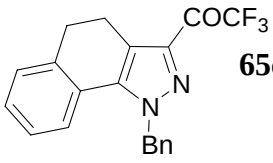
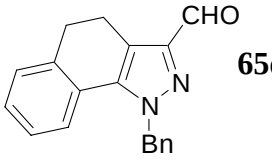
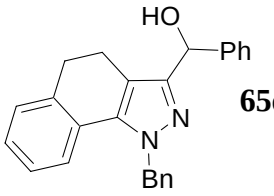
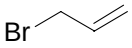
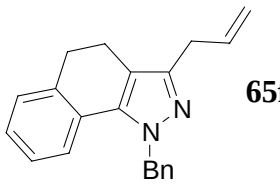


Scheme 37: I/Mg-exchange on the isomeric benzo[*g*]indazoles **61** and **62**.

Trapping the magnesiated species **63** and **64** with various electrophiles furnished a range of C3-substituted benzo[*g*]indazoles **65a-f** and **66a-d** as summarized in Tables 4 and 5. Thus, after a transmetallation of the magnesium reagent **63** with $ZnCl_2$, *Negishi*[49] cross-coupling reactions with aryl iodides could be carried out furnishing **65a** and **65b** in 68% and 59% yields respectively (Table 4, entries 1 and 2). Reacting **63** with *N*-methoxy-*N*-methyltrifluoro-acetamide provided the ketone **65c** in 73% yield (entry 3). Trapping **63** with DMF or benzaldehyde resulted in the formation of aldehyde **65d** and alcohol **65e** in 63% and 61% yields, respectively (entries 4 and 5). Transmetallation with CuCN·2LiCl enabled the allylation of **63** with allyl bromide, furnishing **65f** in 75% yield (entry 6).

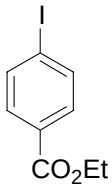
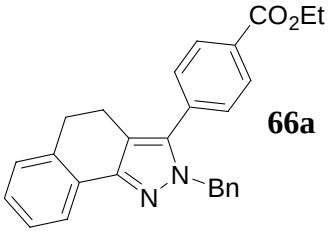
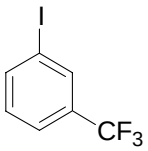
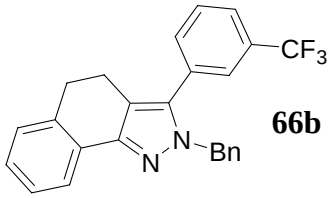
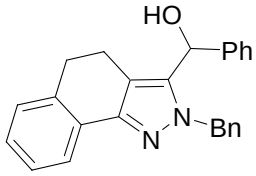
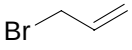
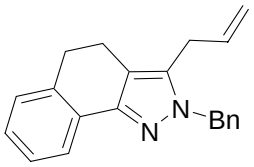
Similarly, the 3-magnesiated heterocycle **64** also undergoes *Negishi*[49] cross-coupling reactions (after transmetallation with $ZnCl_2$) affording benzo[*g*]indazoles **66a** and **66b** in 65% and 67% yields respectively (Table 5, entries 1 and 2). Alcohol **66c** was obtained in 68% yield after subsequent trapping of **64** with benzaldehyde (entry 3). Allylation of **64** with allyl bromide afforded (after transmetallation with CuCN·2LiCl) **66d** in 74% yield (entry 4).

Table 4. Reactions of the 3-magnesiated heterocycle **63** with electrophiles leading to products **65a-f.**

Entry	Electrophile	Product of type **65**	Yield [%][a]
1		 **65a**	68[b]
2		 **65b**	59[b]
3		 **65c**	73
4	DMF	 **65d**	63
5	PhCHO	 **65e**	61
6		 **65f**	75[c]

[a] Isolated, analytically pure product. [b] Obtained after transmetallation with $ZnCl_2$ (1.0 equiv) by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol%) and tfp (10 mol%). [c]Transmetallation with CuCN·2LiCl (1.0 equiv).

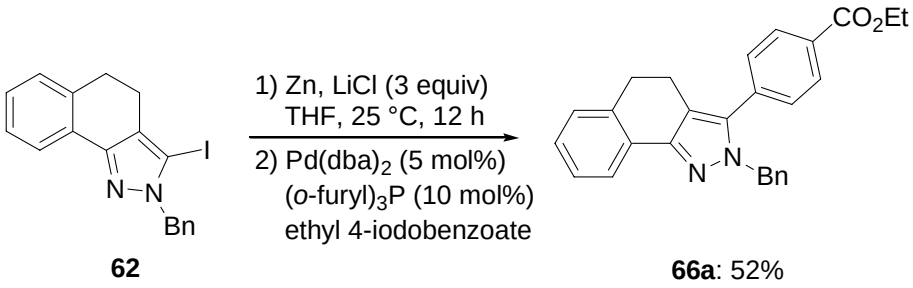
Table 5. Reactions of the 3-magnesiated heterocycle **64** with electrophiles leading to products **66a-d.**

Entry	Electrophile	Product of type **66**	Yield [%][a]
1		 **66a**	67[b]
2		 **66b**	65[b]
3	PhCHO	 **66c**	68
4		 **66d**	74[c]

[a] Isolated, analytically pure product. [b] Obtained after transmetallation with $ZnCl_2$ (1.0 equiv) by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol%) and tfp (10 mol%). [c]Transmetallation with CuCN·2LiCl (1.0 equiv).

The reactivity difference of the two isomeric iodides **61** and **62** becomes more apparent when performing a zinc insertion.[66] In the case of **62**, the insertion in the presence of LiCl was complete within 12 h at 25 °C, leading to the corresponding zinc reagent which undergoes a *Negishi*[49] cross-coupling furnishing **66a** in 52% yield (Scheme 38). However, benzo[*g*]-indazole **61** proved to be inert towards zinc insertion, even at higher temperatures.

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

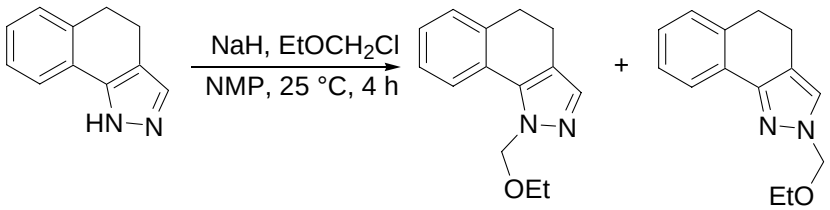


62 **66a**: 52%

Scheme 38: Zn-insertion in compound **62** and cross-coupling with ethyl 4-iodobenzoate.

2.3 Regioselective metallations on 4,5-dihydro[g]indazoles

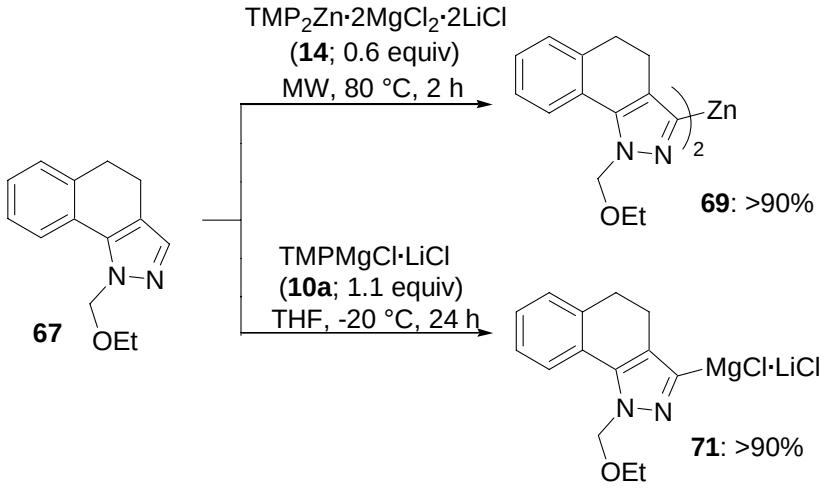
Next, we examined the metallation of benzo[*g*]indazoles of type **50** and **51** by performing deprotonation reactions using the new mixed Mg/Li- and Zn/Mg/Li-amide bases of type **10a**, **12** and **14**. However, deprotonation in the presence of the benzyl protecting group occurred solely at the benzylic position of the protecting group. Therefore we changed to the ethoxymethyl as a protecting group. Thus, treatment of **56** at 25 °C with NaH and subsequent trapping with $EtOCH_2Cl$ yielded 10% of 1-ethoxymethyl-4,5-dihydro-1*H*-benzo[*g*]indazole (**67**) and 50% of 2-ethoxymethyl-4,5-dihydro-2*H*-benzo[*g*]indazole (**68**) which could be readily separated by column chromatography (Scheme 39).



56 **67**: 10% **68**: 50%

Scheme 39: Protection of **56** with (chloromethoxy)ethane.

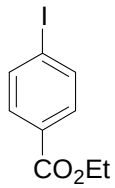
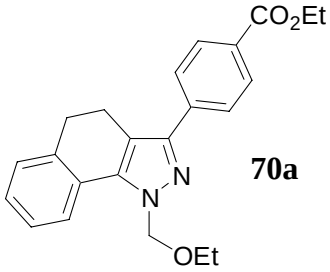
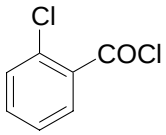
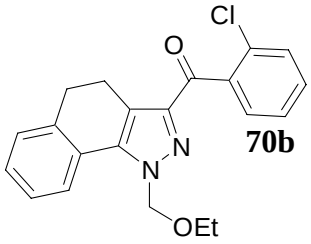
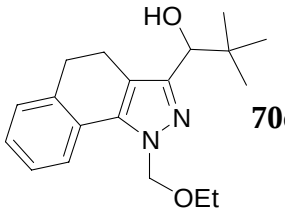
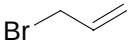
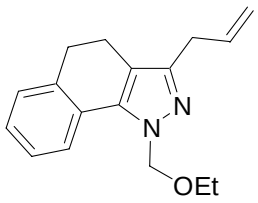
The heterocycles **67** and **68** proved to be well suited for several directed metallations. Thus, protected benzo[*g*]indazole **67** was deprotonated using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**14**) under microwave irradiation, leading to the zinc organometallic **69** (Scheme 40).



Scheme 40: Selective deprotonation of **67** at C3 using $TMP_2Mg{\cdot}2MgCl_2{\cdot}2LiCl$ (**14**) and TMPMgCl·LiCl (**10a**).

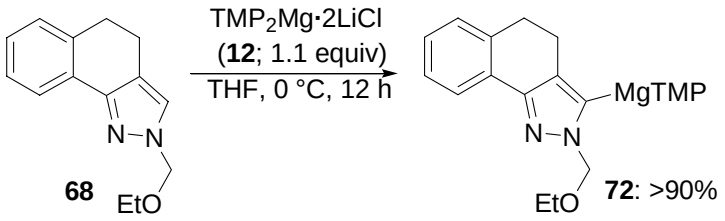
This zinc reagent readily undergoes a *Negishi*[49] cross-coupling with ethyl 4-iodobenzoate using $Pd(dba)_2$ (5 mol%) and $(o\text{-furyl})_3P$ (10 mol%) as catalyst providing the expected product **70a** in 62% yield (Table 6, entry 1). The reaction of **69**, after transmetallation with CuCN·2LiCl[50], with an acyl chloride afforded the expected product **70b** in 55% yield (entry 2). Magnesiation of the benzo[*g*]indazole **67** could also be performed using base TMPMgCl·LiCl (**10a**) at -20 °C (Scheme 41). The magnesiated species **71** was successfully added to pivaldehyde leading to the corresponding alcohol **70c** in 60% yield (entry 3). After transmetallation with CuCN·2LiCl, the organomagnesium reagent **71** reacted with allyl bromide to furnish the allylated product **70d** in 68% (entry 4).

Table 6. Reactions of the metallated species **69** and **71** with electrophiles leading to products **70a-d.**

Entry	Mg- orZn-reagent	Electrophile	Product of type **70**	Yield [%][a]
1	**69**		 **70a**	62[b]
2	**69**		 **70b**	55[c]
3	**71**	*t*BuCHO	 **70c**	60
4	**71**		 **70d**	68[c]

[a] Isolated, analytically pure product. [b] Obtained after transmetallation with $ZnCl_2$ (1.0 equiv) by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol%) and tfp (10 mol%). [c]Transmetallation with CuCN·2LiCl (1.0 equiv).

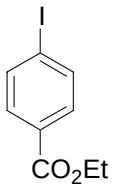
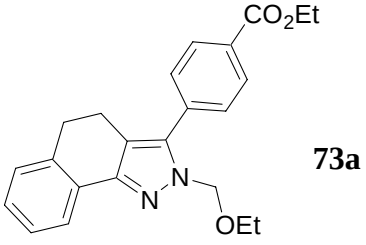
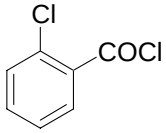
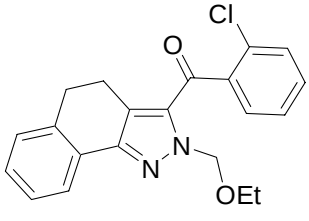
Benzo[*g*]indazole **68**, proved to be more difficult to deprotonate at the C3 position. Treatment of **68** with TMPMgCl·LiCl (**10a**) gave only a conversion of 80% after stirring for 48 h at 25 °C. However, by using the stronger base $TMP_2Mg·2LiCl$ (**12**), a full conversion to the magnesiated species **72** could be obtained within 12 h at 0 °C (Scheme 41).

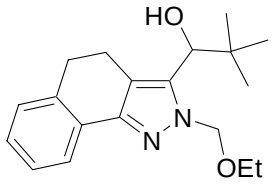
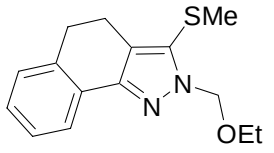


Scheme 41: Deprotonation of **68** at C3 using $TMP_2Mg·2LiCl$ (**12**).

The organomagnesium reagent **72** undergoes after transmetallation with $ZnCl_2$ a *Negishi*[49] cross-coupling reaction furnishing **73a** in 93% yield (Table 7, entry 1). Transmetallation of **72** with CuCN·2LiCl[52] enabled an acylation reaction with 2-chlorobenzoyl chloride and gave the ketone **73b** in 60% yield (entry 2). Reaction of **72** with pivaldehyde furnished the C3-substituted benzo[*g*]indazole **73c** in 70% yield (entry 3). Finally, the reaction of **72** with methanethiosulfonic acid *S*-methyl ester gave the expected product **73d** in 83% yield (entry 4).

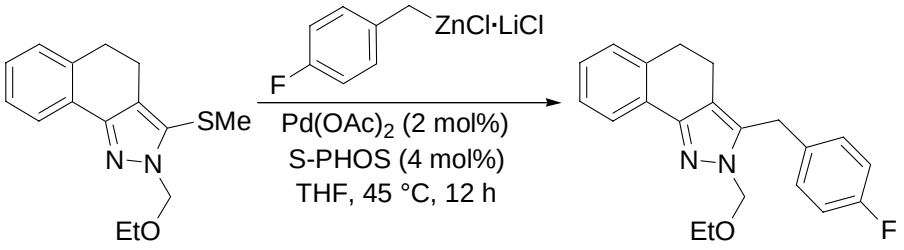
Table 7. Reactions of the 3-magnesiated species **72** with electrophiles leading to products **73a-d.**

Entry	Electrophile	Product of type **73**	Yield [%][a]
1		 **73a**	93[b]
2		 **73b**	60[c]

3	*t*BuCHO		**73c**	70
4	$MeSSO_2Me$		**73d**	83

[a] Isolated, analytically pure product. [b] Obtained after transmetallation with $ZnCl_2$ (1.0 equiv) by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol%) and tfp (10 mol%). [c]Transmetallation with CuCN·2LiCl (1.0 equiv).

Interestingly, the SMe-moiety of benzo[*g*]indazole **73d** could undergo, under Pd-catalysis, a cross coupling reaction with a zinc reagent to furnish **73e** in in 62% yield (Scheme 42). This reaction is similar to the *Liebeskind-Srogl* reaction.[67]



73d **73e**: 62%

Scheme 43: Cross coupling reaction with the SMe-moiety of **73d** furnishing the benzyl derivative **73e**.

[67] For an excellent review see: Prokopcová, H.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2009**, *48*, 2276.

3. Synthesis of Fully Substituted Pyrazoles via Regio- and Chemoselective Metallations

3.1 Introduction

Pyrazole derivatives display a broad spectrum of biological activities and are used as cholesterol lowering,[68] anti-inflammatory,[69] anticancer,[70] antidepressant and anti-psychotic[71] agents. They are therefore attractive building blocks for pharmaceutical research and pyrazoles are present in leading pharmaceuticals as for example Celebrex®[69] and Viagra®[72]. These heterocycles have also found applications in the agrochemical industry (e.g. Fipronil®)[73] and recently also in the field of photoprotectors, ultraviolet stabilizers and energetic materials (Scheme 43).[74]

As a result, there is a constant strive to develop new methods for the synthesis of highly substituted pyrazoles. So far, the main access to fully functionalized pyrazoles involves condensation reactions between hydrazines and 1,3-dicarbonyl compounds and their derivatives[75] or 1,3-dipolar cycloadditions.[76] However, some limitations of these methods are

---

[69] Sliskovic, D. R.; Roth, B. D.; Wilson, M. W.; Hoefle, M. L.; Newton, R. S. *J. Med. Chem.* **1990**, *33*, 31.

[70] Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P.C. *J. Med. Chem.* **1997**, *40*, 1347.

[71] Stauffer, S. R.; Katzenellenbogen, J. A. *J. Comb. Chem.* **2000**, *2*, 318.

[72] Moore, K. W.; Bonner, K.; Jones, E. A.; Emms, F.; Leeson, P. D.; Marwood, R.; Patel, S.; Rowley, M.; Thomas, S.; Carling, R. W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1285.

[73] Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1819.

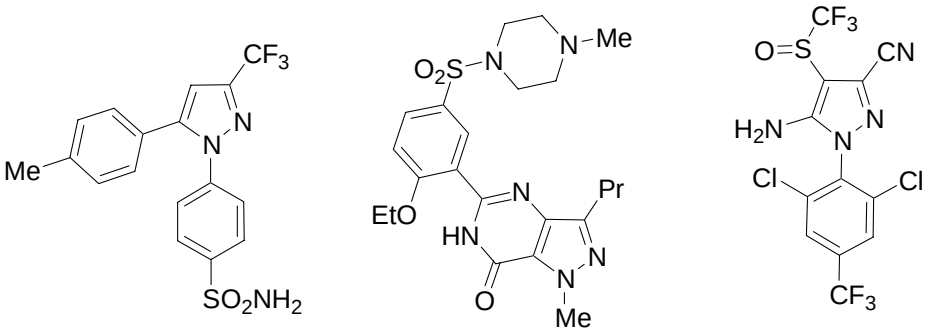
[73] a) Tomlin, C. D. S., Ed.; *The Pesticide Manual*, 12th ed.; British Crop Protection Council: Farnham, UK, **2000**; pp 413-415; b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 2nd ed.; Wiley & Sons: New York, **2004**; pp 179-184.

[75] a) Elguero, J. in *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: New York, **1984**; Vol.5, pp 291-297; b) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*, Shinkai, I., Ed.; Elsevier: Oxford, **1996**; Vol. 3, pp 3-75; c) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Targets Heterocycl. Syst*. **2002**, *6*, 52; d) Gribble, G.; Joule, J. *Progress in Heterocyclic Chemistry, 18*; Elsevier: Oxford, **2007**; e) Cavero, E.; Uriel, S.; Romero, P.; Serrano, J. L.; Gimenez, R. *J. Am. Chem. Soc.* **2007**, *129*, 11608; f) Catalán, J.; Fabero, F.; Guijano, M. S.; Claramunt, R. M.; Maria, M. D. S.; Foces-Foces, M. C.; Cano, F. H.; Elguero, J.; Sastre, R. *J. Am. Chem. Soc.* **1990**, *112*, 747; g) Catalán, J.; Fabero, F.; Claramunt, R. M.; Maria, M. D. S.; Foces-Foces, M. C.; Cano, F. H.; Martinez-Ripoll, M.; Elguero, J.; Sastre, R. *J. Am. Chem. Soc.* **1992**, *114*, 5039; h) Ye, C.; Gard, G. L.; Winter, R. W.;Syvret, R. G.; Twamley, B.; Shreeve, J. M. *Org. Lett.* **2007**, *9*, 3841.

[76] a) Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1996**, *6*, 347; b) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675; c) Zefirov, N. S.; Kozhushkov, S. I.; Kuznetsova, T. S. *Tetrahedron* **1982**, *38*, 1693; d) Kokoreva, O. V.; Averina, E. B.; Ivanova, O. A.; Kozhushkov, S. I.; Kuznetsova, T. S. *Chem. Heterocycl. Comp.* **2001**, *37*, 834; e) Ahmed, M. S.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487; f) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Org. Lett.* **2008**, *10*, 2377.

[77] a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons; New York, **1984**; Vol I; b) Martin, R.; Rodriguez Rivero, M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 7079 ; c) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381.

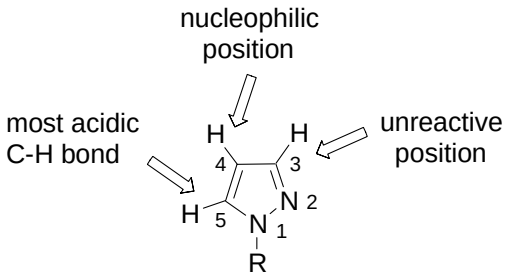
the poor regioselectivity, multistep synthesis of the starting materials and the harsh conditions required.[77]



Celebrex Viagra Fipronil

Scheme 43: Pharmaceutical active pyrazoles.

Deprotonation reactions on the pyrazole ring were until now, limited to lithiations at very low temperatures on the most acidic C5 position.[78] Functionalization at the C3 position of the pyrazole core was only possible through a protecting group switch, while the C4 position was accessed through electrophilic substitutions (Scheme 44).[79]



Scheme 44: Reactivity properties of the pyrazole ring.

[78] a) Aggarwal, V. K.; De Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381; b) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006** *8*, 2675; c) Deng, X.; Mani, N. S. *Org. Lett.* **2008** *10*, 1307.

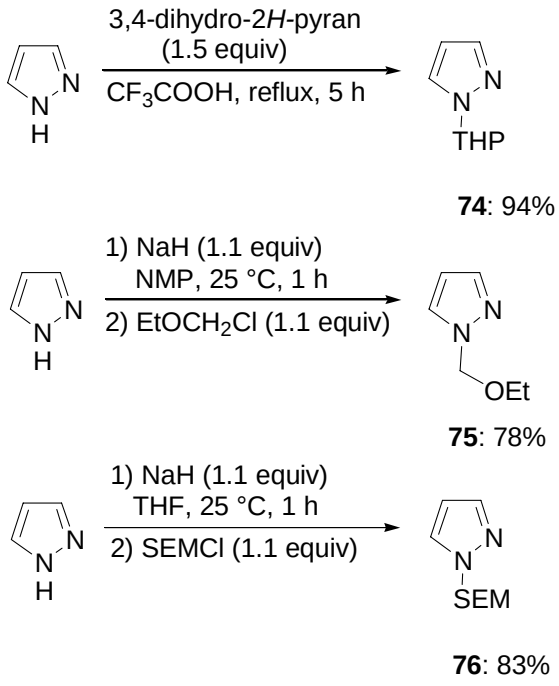
[79] a) *Science of Synthesis*; Stanovnik, B., Svete, J. D., Eds.; Thieme: Stuttgart, **2002**; Vol. 12, pp 173-203; b) Gupta, R. R.; Kumar, M.; Gupra, V. *Heterocyclic Chemistry*; Springer: Berlin, **1998**; p452; c) Behr, L. C.; Fusco, R.; Jarboe, C. H. Pyrazoles, Pyrazolines, pyrazolidines, indazoles and condensed rings. In *The Chemistry of Heterocyclic Compounds*; Wiley, R. H., Ed.; Interscience Publishers: New York, **1967**; Vol. 22 pp 107-109; d) L´Helgoual´ch, J. -M.; Seggio, A.; Chevallier, F.; Yonehara, M.; Jeanneau, E.; Uchiyama, M.; Mongin, F. *J. Org. Chem.* **2008**, *73*, 177; e) Schlosser, M.; Volle, J. -N.; Leroux, F.; Schenk, K. *Eur. J. Org. Chem.* **2002**, 2913; f) Gérard, A. -L.; Bouillon, A.; Mahatsekake, C.; Collot, V.; Rault, S. *Tetrahedron Lett.* **2006**, *47*, 4665; g) Balle, T.; Vedsø, P.; Begtrup, M. *J. Org Chem.* **1999**, *64*, 5366; h) Alley, P. W.; Shirley, D. A. *J. Am. Chem. Soc.* **1958**, *80*, 6271; i) Subramanyam, C. *Synth. Comm.* **1995**, *25*, 761.

[80] a) McLaughlin, M.; Marcantonio, K.; Chen, C.-Y.; Davies, I. W. *J. Org. Chem.* **2008**, *73*, 4309; b) Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042.

3.2 Choosing the protecting group

3.2.1 Starting material synthesis

First for the metallation of the pyrazole ring, the most suitable protecting group had to be selected. For this purpose the differently protected *N*-1-pyrazoles **74**,[80] **75**[81] and **76**[82] were synthesized (Scheme 45).



Scheme 45: Protection of pyrazole leading to 1-(tetrahydropyran-2-yl)- (**74**), 1-ethoxymethyl- (**75**) and 1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazole (**76**).

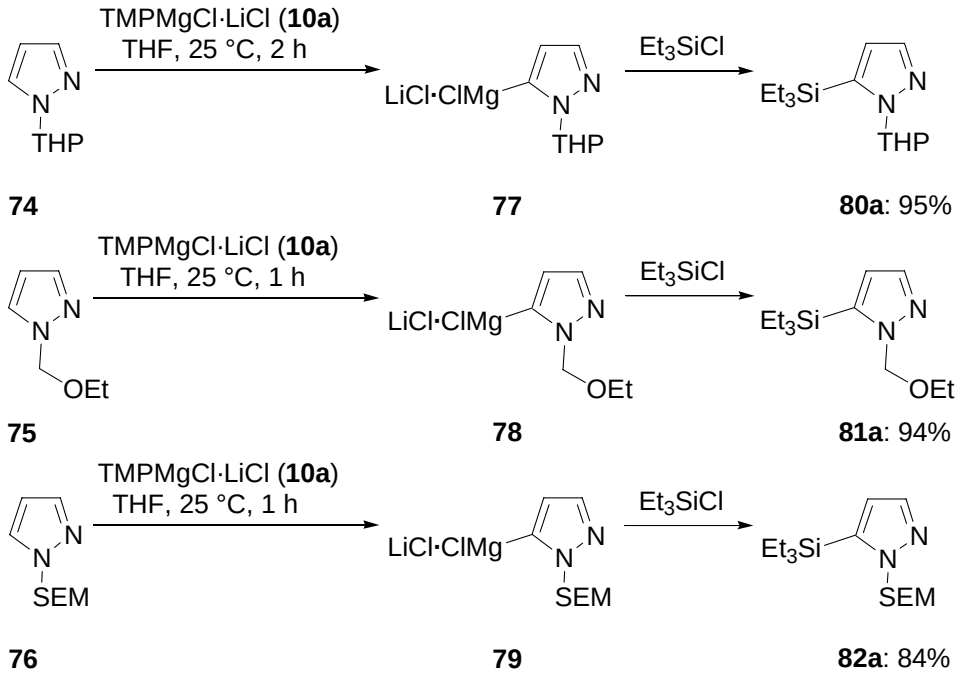
These protecting groups were chosen due to their stability under basic conditions and their easy cleavage under acidic conditions.

---

[80] Young, M. B.; Barrow, J. C.; Glass, K. L.; Lundell, G. F.; Newton, C. L.; Pellicore, J. M.; Rittle, K. E.; Selnick, H. G.; Stauffer, K. J.; Vacca, J. P.; Williams, P. D.; Bohn, D.; Clayton, F. C.; Cook, J. J.; Krueger, J. A.; Kuo, L. C.; Lewis, S. D.; Lucas, B. J.; McMasters, D. R.; Miller-Stein, C.; Pietrak, B. L.; Wallace, A. A.; White, R. B.; Wong, B.; Yan, Y.; Nantermet, P. G. *J. Med. Chem.* **2004**, *47*, 2995.
[81] Fray, M. J.; Allen, P.; Bradley, P. R.; Challenger, C. E.; Closier, M.; Evans, T. J.; Lewis, M. L.; Mathias, J. P.; Nichols, C. L.; Po-Ba, Y. M.; Snow, H.; Stefaniak, M. H.; Vuong, H. V. *Heterocycles* **2006**, *67*, 489.
[82] Fugina, N.; Holzer, W.; Wasicky, M. *Heterocycles* **1992**, *34*, 303.

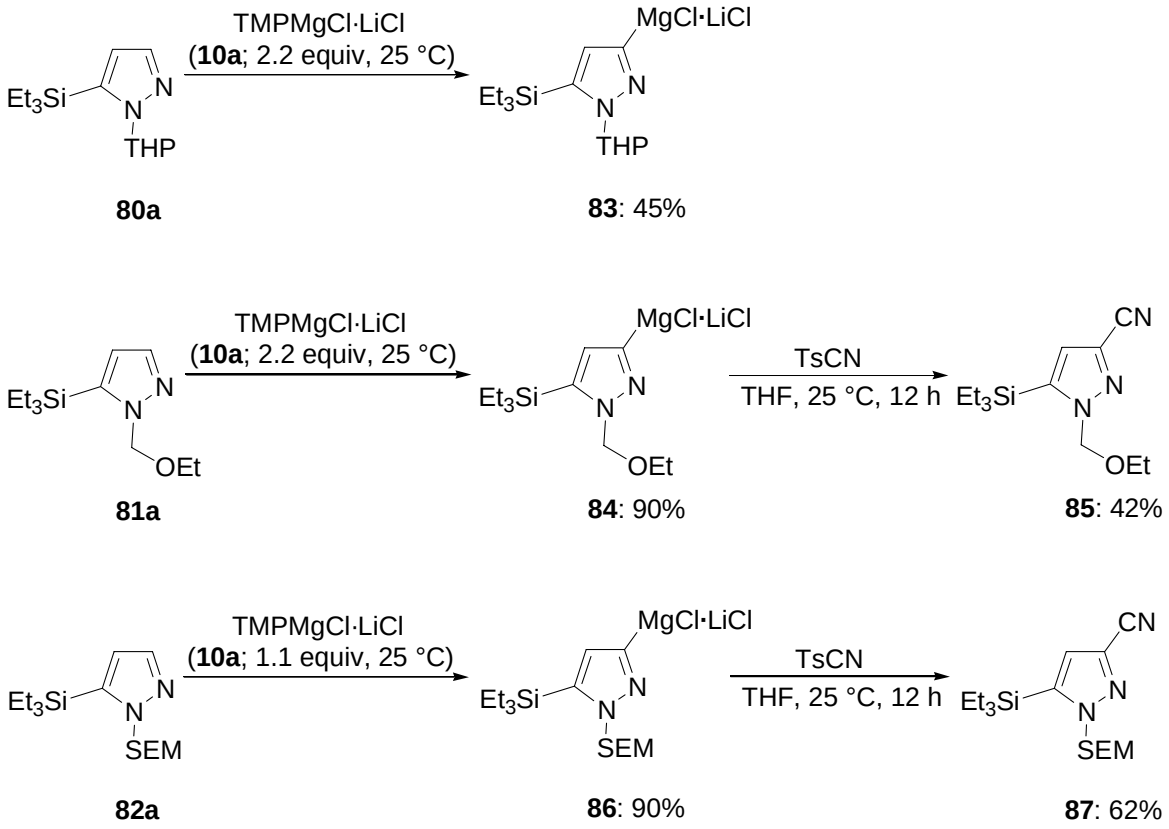
3.2.2 Metallations of the differently protected pyrazoles

Starting from the protected pyrazoles **74**, **75** and **76**, magnesiation of the C5 position could be achieved using TMPMgCl·LiCl (**10a**; 1.1 equiv, 25 °C, 1 h). The resulting magnesiated pyrazoles **77**, **78** and **79** could be trapped with triethylsilyl chloride furnishing the silylated products **80a**, **81a** and **82a** in 84-95% yields (Scheme 46).



Scheme 46: Deprotonation at the C5 position using TMPMgCl·LiCl and subsequent trapping with Et_3SiCl.

The isolated pyrazoles **80a**, **81a** and **82a** were treated for a second time with TMPMgCl·LiCl (**10a**) to achieve metallation at the C3 position (Scheme 47).



Scheme 47: Metallation at the C5-position.

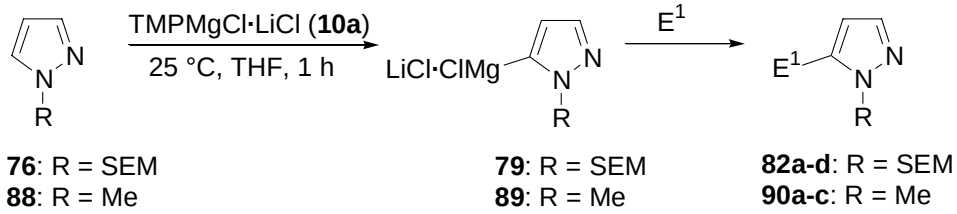
After treatment with 1.1 equivalents of **10a,** only in the case of **82a** could a 90% conversion to the magnesiated species **86** be achieved. Trapping **86** with TsCN furnished nitrile **87** in 62% yield. However, pyrazole **81a** needed 2 equivalents of the base **10a** to reach a 90% conversion to the metallated species **84**. Subsequent reaction with TsCN afforded **85** in 42% yield. In the case of **80a** even with 2 equivalents of **10a** a maximum conversion of 45% to **83** could only be obtained. Employing the stronger base $TMP_2Mg·2LiCl$ (**12**) resulted mainly in decomposition of **83**.

On account of these results all further research was focused on the SEM-protected pyrazole (**76**). Furthermore, since the *N*-methylpyrazole moiety is present in many biologically active compounds, we decided to investigate the metallation of *N*-methylpyrazole (**88**) as well.

3.3 Functionalization at the C5-position

3.3.1 Deprotonation at the C5- position

Starting from the SEM-protected pyrazole **76** or the commercially available 1-methyl-1*H*-pyrazole (**88**), magnesiation of the C5 position could be achieved using TMPMgCl·LiCl (**10a**) under the conditions already mentioned (1.1 equiv, 25 °C, 1 h) (Scheme 48).



76: R = SEM
88: R = Me

79: R = SEM
89: R = Me

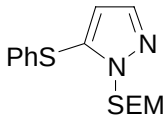
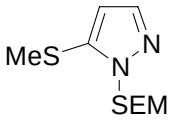
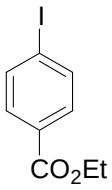
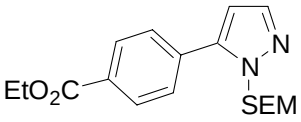
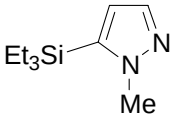
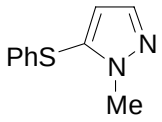
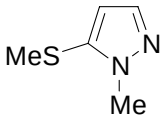
82a-d: R = SEM
90a-c: R = Me

Scheme 48: Magnesiation of pyrazole derivatives **76** and **88** at the C5 position using TMPMgCl·LiCl (**10a**).

Trapping of the resulting magnesiated pyrazole **79** with various electrophiles such as Et_3SiCl, $PhSO_2SPh$ and $MeSSO_2Me$ gave the corresponding 5-substituted pyrazoles **82a-c** in 72-84% yield (Table 8, entries 1-3). Organomagnesium reagent **79** successfully underwent, after transmetallation with $ZnCl_2$, a *Negishi*[49] cross-coupling furnishing the expected product **82d** in 91% yield (entry 4). Similarly, the 5-magnesiated *N*-methylpyrazole (**88**) provided after reaction with Et_3SiCl, $PhSSO_2Ph$ and $MeSSO_2Me$ the new substituted pyrazole derivatives **90a-c** in 77-83% yields (entries 5-7).

Table 8: C5-substituted pyrazoles of type **82** and **90**.

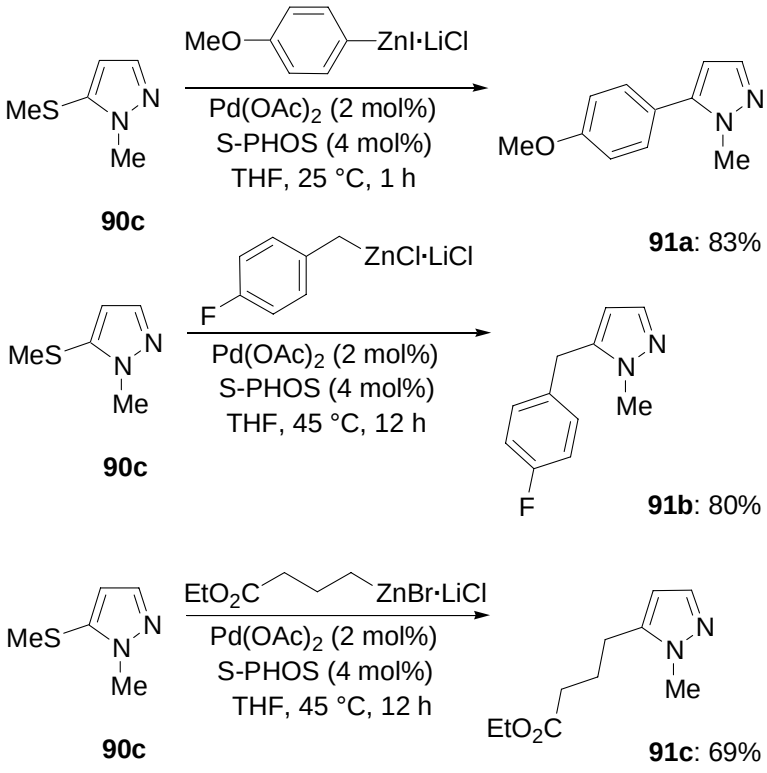
Entry	Mg-reagent	Electrophile	Product	Yield [%][a]
1	**82**	Et_3SiCl	 **82a**	84

2	**82**	$PhSSO_2Ph$		**82b**	82
3	**82**	$MeSSO_2Me$		**82c**	72
4	**82**			**82d**	91[b]
5	**89**	Et_3SiCl		**90a**	80
6	**89**	$PhSSO_2Ph$		**90b**	83
7	**89**	$MeSSO_2Me$		**90c**	79

[a] Isolated, analytically pure product. [b] Obtained after transmetallation with $ZnCl_2$ (1.0 equiv) by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol%) and tfp (10 mol%).

3.3.2 Direct cross coupling reaction of the S-Me moiety of the pyrazole

1-Methyl-5-methylsulfanyl-1*H*-pyrazole (**90c**) could be subjected to a cross coupling reaction, similar to the *Liebeskind-Srogl* reaction.[67, 83] However, in this case zinc reagents were used as coupling partners instead of the organoboron compounds, mostly employed for the coupling of thioesters (Scheme 49).



Scheme 49: Cross coupling reaction with the S-Me moiety of the pyrazole leading to products of type **91**.

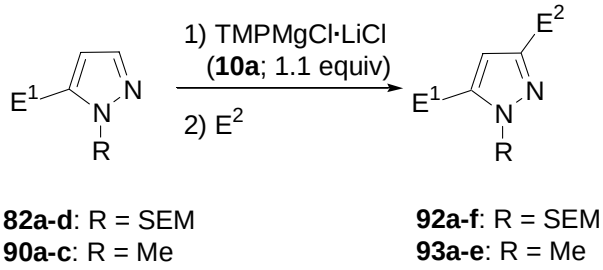
Ila and *Junjappa* have already reported cross coupling reactions between the methylthio functionality of a pyrazole derivative and *Grignard* reagents.[84] In their case, the reaction proceeds in the presence of 30 mol% $NiCl_2$(dppp) and has to be heated at 90 °C for 12 h to reach full conversion. Using zinc reagents in the presence of LiCl, the reaction could be performed under milder conditions.[85]

---

[83] Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979.
[84] Peruncheralathan, S.; Khan, T. A.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 10030.
[85] For the LiCl mediated preparation of the zinc compounds, see: a) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107; c) Metzger, A.; Piller, F. M.; Knochel, P. *Chem. Commun.* **2008**, 5824; d) Metzger, A.; Schade,

3.4 Selective C3- metallation of pyrazole derivatives

A subsequent deprotonation at position C3 was readily achieved by adding TMPMgCl·LiCl (**10a**; 1.1 equiv) to various 5-substituted pyrazoles of type **82** and **90** (Scheme 50).



82a-d: R = SEM
90a-c: R = Me

92a-f: R = SEM
93a-e: R = Me

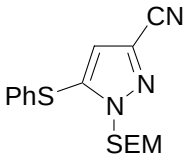
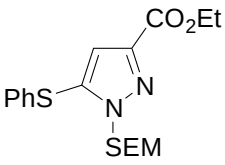
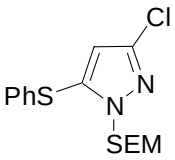
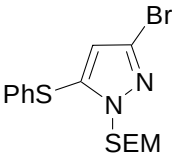
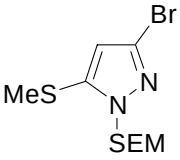
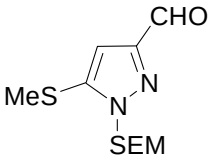
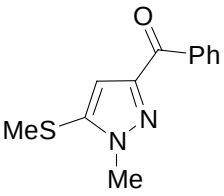
Scheme 50: Selective deprotonation at the C3 position of the pyrazole ring.

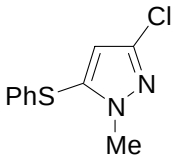
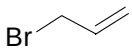
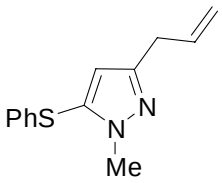
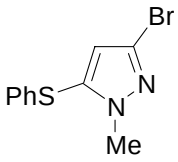
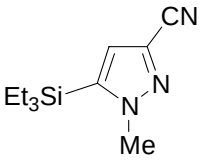
Thus, treatment of the SEM-protected pyrazoles **82b** and **82c** with TMPMgCl·LiCl (**10a**; 1.1 equiv, -15 °C, 10 h) and subsequent quenching with TsCN, $NCCO_2Et$, FCl_2CCClF_2,[86] $(BrCl_2C)_2$ and DMF furnished the 3,5-disubstituted pyrazoles **92a-f** in 65-76% yield (Table 9, entries 1-6). Similarly, the *N*-methylated pyrazoles **90b** and **90c** were magnesiated under the same conditions. Metallation of **90c** using TMPMgCl·LiCl (**10a**; 1.1 equiv, -15 °C, 10 h) followed by the transmetallation with CuCN·2LiCl[50] and addition of benzoyl chloride gave the expected ketone **93a** in 78% yield (entry 7). Magnesiation of the pyrazole **90b** (**10a**; 1.1 equiv, -15 °C, 10 h) gave after chlorination with FCl_2CCClF_2[86] (-15 °C to 25 °C, 5 h) the chloro derivative **93b** in 69% yield (entry 8) and in the presence of CuCN·2LiCl allylation with allyl bromide furnished the pyrazole **93c** in 78% yield (entry 9). Quenching of the magnesiated **90b** with $(BrCl_2C)_2$ furnished bromopyrazole **93d** in 70% yield (entry 10). The 5-silylated pyrazole **90a** was deprotonated using TMPMgCl·LiCl (**10a**; 1.1 equiv, 25 °C, 2 h). Subsequent reaction with TsCN afforded the corresponding nitrile **93d** in 61% yield (entry 11).

M. A.; Manolikakes, G.; Knochel, P. *Chem. Asian J.* **2008**, *3*, 1678; e) Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 7380.

[86] Marzi, E.; Bobbio, C.; Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2005**, *10*, 2116.

Table 9. Disubstituted pyrazoles of type **92** and **93** obtained by regioselective magnesiation of pyrazoles of type **82** and **90** with TMPMgCl·LiCl (**10a**) and subsequent quenching with electrophiles.

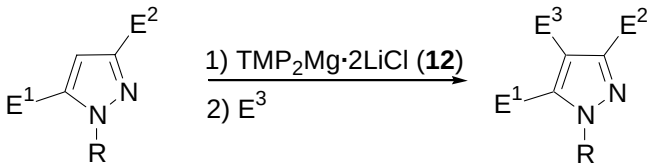
Entry	Substrate	Electrophile	Product		Yield [%][a]
1	**82b**	TsCN		**92a**	68
2	**82b**	$NCCO_2Et$		**92b**	71
3	**82b**	Cl_2FCCF_2Cl		**92c**	65
4	**82b**	$(BrCl_2C)_2$		**92d**	73
5	**82c**	$(BrCl_2C)_2$		**92e**	75
6	**82c**	DMF		**92f**	76
7	**90c**	PhCOCl		**93a**	78[b]

8	**90b**	Cl_2FCCF_2Cl		**93b**	69
9	**90b**			**93c**	78[c]
10	**90b**	$(BrCl_2C)_2$		**93d**	70
11	**90a**	TsCN		**93e**	61

[a] Isolated, analytically pure product. [b] Transmetallation with 1.1 equiv of CuCN·2LiCl. [c] Catalyzed with 5 mol % of CuCN·2LiCl.

3.5 Selective C4-metallation of pyrazole derivatives

The remaining position 4 of the pyrazole core was smoothly magnesiated using the stronger base $TMP_2Mg·2LiCl$ (**12**; 1.1 equiv, -20 °C, 4 h) (Scheme 51).



92a-e: R = SEM
93a-d: R = Me

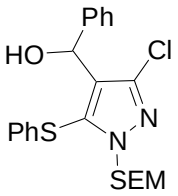
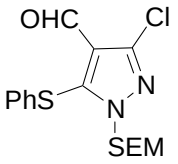
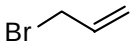
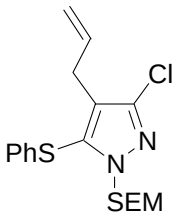
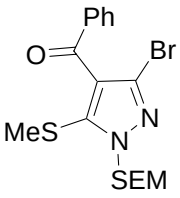
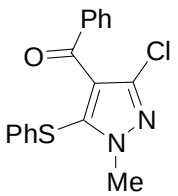
94a-d: R = SEM
95a-b: R = Me

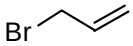
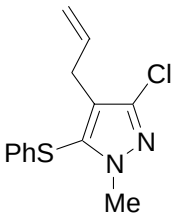
Scheme 52: Selective deprotonation at the C4 position of the pyrazole ring.

Thus, the disubstituted pyrazole **92c** was deprotonated at position 4 and reacted with benzaldehyde or DMF giving the corresponding alcohol **94a** in 71% yield or aldehyde **94b** in

67% yield (Table 10, entries 1 and 2). In the presence of CuCN·2LiCl, the magnesiated **92c** reacted with allyl bromide to give **94c** in 74% yield (entry 3). The deprotonation of **92d** under the same conditions gave after transmetallation with CuCN·2LiCl the expected ketone **94d** in 75% yield (entry 4). Similarly, *N*-methylpyrazole **93b** was magnesiated and transmetallated with CuCN·2LiCl, leading after reaction with benzoyl chloride and allyl bromide to the trisubstituted pyrazoles **95a** and **95b** in 70-76% yield (entries 5 and 6).

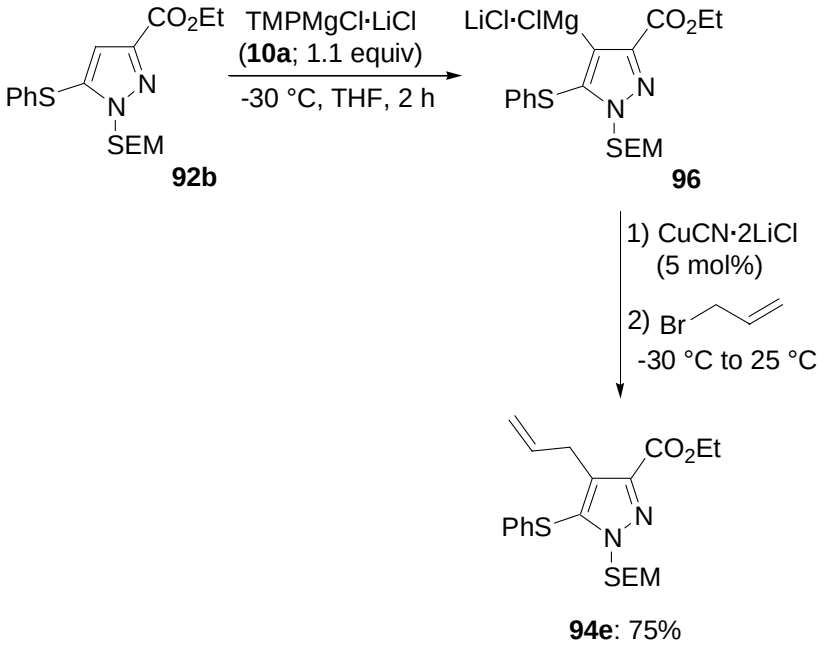
Table 10. Trisubstituted pyrazoles of type **94** and **95** obtained by regioselective magnesiation of pyrazoles of type **92** and **93** with $TMP_2Mg·2LiCl$ (**12**) and quenching with electrophiles.

Entry	Substrate	Electrophile	Product	Yield [%][a]
1	**92c**	PhCOH	 **94a**	71
2	**92c**	DMF	 **94b**	67
3	**92c**		 **94c**	74
4	**92d**	PhCOCl	 **94d**	75[b]
5	**93b**	PhCOCl	 **95a**	76[b]

6	**93b**			**95b**	70[c]

[a] Isolated, analytically pure product. [b] Transmetallation with 1.1 equiv of CuCN·2LiCl. [c] Catalyzed with 5 mol % of CuCN·2LiCl.

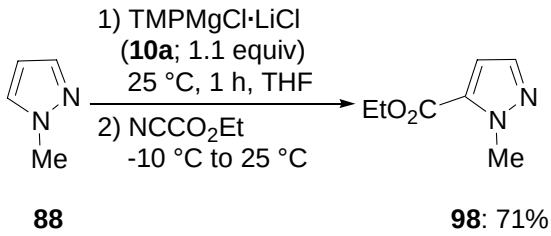
Interestingly, pyrazole **92b** bearing an ester moiety at the C3 position could be deprotonated with the milder base TMPMgCl·LiCl (**10a**; 1.1 equiv, -30 °C, 2 h). Quenching of the resulting magnesium reagent **96** in the presence of CuCN·2LiCl with allyl bromide afforded the allylated pyrazole **94e** in 75% yield (Scheme 52).



Scheme 52: Magnesiation of pyrazole **92b** at position C4 using TMPMgCl·LiCl (**10a**).

3.6 Synthesis of the acaricide Tebufenpyrad via successive functionalizations of the pyrazole core.

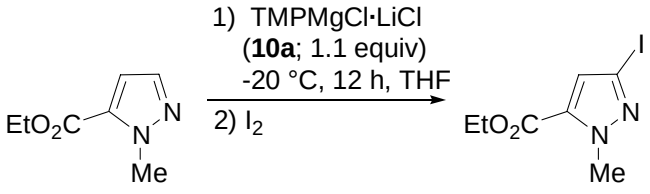
This functionalization of the pyrazole core was applied to the synthesis of the acaricide Tebufenpyrad (**97**).[87] *N*-methylpyrazole **88** was treated with TMPMgCl·LiCl (**10a**; 1.1 equiv, 25 °C, 1 h) and quenched with $NCCO_2Et$ providing the expected ester **98** (Scheme 53).



88 **98**: 71%

Scheme 53: Synthesis of ethyl-2-methyl-2*H*-pyrazole-3-carboxylate (**98**).

Pyrazole **98** was then magnesiated at position C3 using TMPMgCl·LiCl (**10a**; 1.1 equiv, -20 °C, 12 h). Reaction with I_2 furnished the iodo compound **99** in 56% yield (Scheme 54).

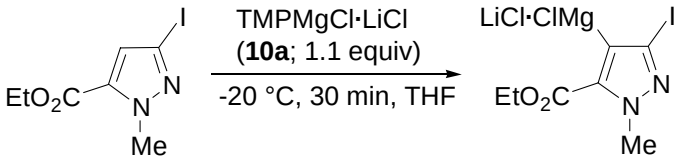


98 **99**: 56%

Scheme 54: Magnesiation of **98** using TMPMgCl·LiCl (**10a**) and subsequent iodination leading to **99**.

To achieve the chlorination at the C4 position, **99** was treated with TMPMgCl·LiCl (**10a**) at -20 °C. After stirring for 30 min complete conversion to the magnesiated species **100** was observed (Scheme 55).

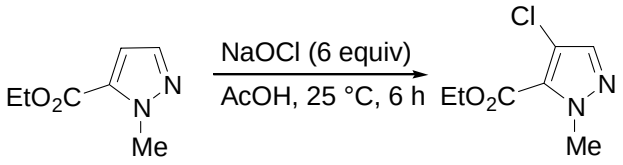
[87] a) Marcic, D. *Exp. Appl. Acarol* **2005**, *36*, 177, and references cited therein; b) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Cunat, A. C.; Villanova, S.; Murguía, M. *J. Org. Chem.* **2008**, *73*, 3523; c) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Bueno, J. C.; Villanova, S. *J. Org. Chem.* **2008**, *73*, 8545.



99 **100**

Scheme 55: Magnesiation of pyrazole **98** using TMPMgCl·LiCl (**10a**).

However, all attempts to trap **100** with a chlorinating electrophile failed due to the instability of the organomagnesium reagent **100** at temperatures higher than -20 °C. The electrophiles tried (Cl_2FCCF_2Cl, NCS) were not reactive enough to chlorinate the substrate at -20 °C. Knowing that position C4 is also very nucleophilic, we tried to chlorinate pyrazole **98** via an electrophilic substitution reaction, by treating it directly with NaOCl in acetic acid.[87b,c] The *in situ* generated chlorine reacted with **98** forming the disubstituted pyrazole **101** in 93% yield (Scheme 56).

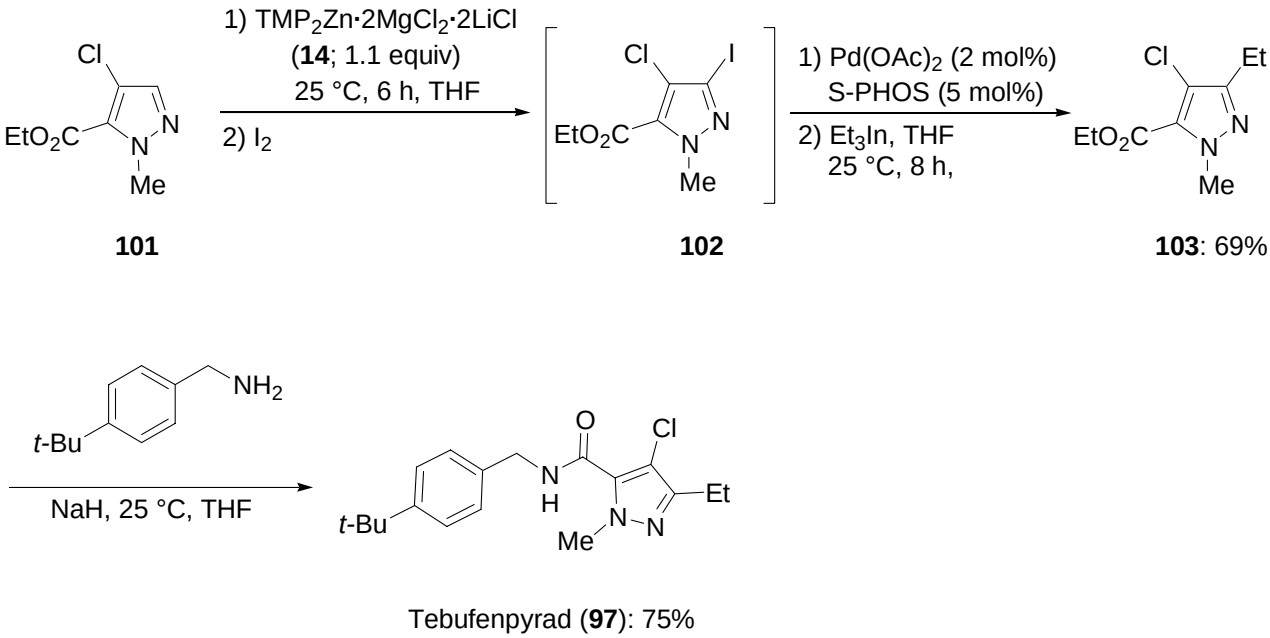


98 **101**: 93%

Scheme 56: Chlorination of **98** with *in situ* generated Cl_2.

Pyrazole **101** was deprotonated using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**14**; 1.1 equiv, 25 °C, 6 h) and subsequent addition of I_2 furnished the iodopyrazole **102**. Attempts to perform a *Negishi* cross coupling were unsuccessfull. A major side reaction was the I/Zn- exchange at the iodide of **102**. We could circumvent this side reaction however, by transmetallation to indium. Thus, iodide **102** undergoes a one-pot cross-coupling reaction with Et_3In generated by the reaction of EtMgCl (1.5 equiv) with $InCl_3$ (0.5 equiv)[88] affording the Tebufenpyrad precursor **103** in 69% yield. Subsequent reaction of **103** with 4-*tert*-butyl-benzylamine afforded Tebufenpyrad (**97**) in 75% yield (Scheme 57).

[88] a) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *Synthesis* **2005**, 485; b) Pérez, I.; Pérez-Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155.



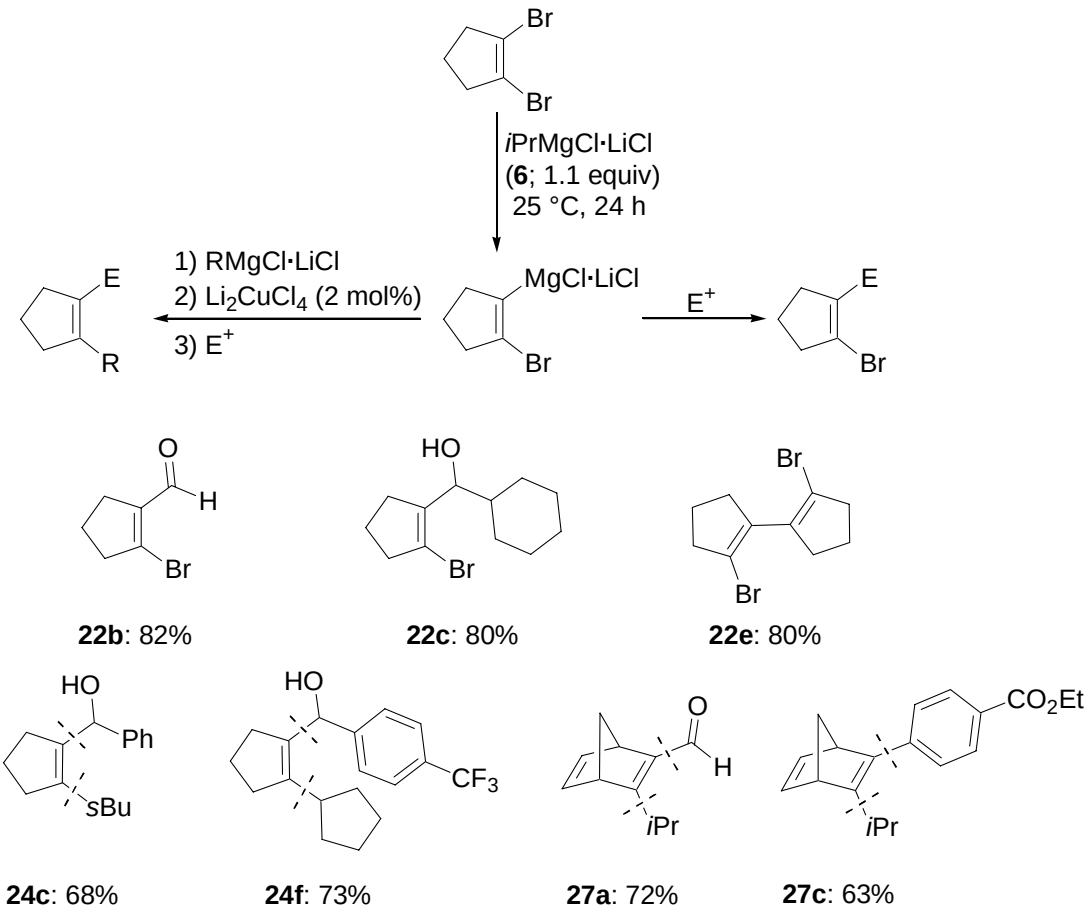
Scheme 57: Synthesis of the acaricide Tebufenpyrad (**97**).

4. Summary and Outlook

This work was focused on the functionalization of cyclic dibromoalkenes and heterocycles containing the pyrazole scaffold through metallation reactions. Furthermore, the developed procedures were applied to the synthesis of the acaricide Tebufenpyrad.

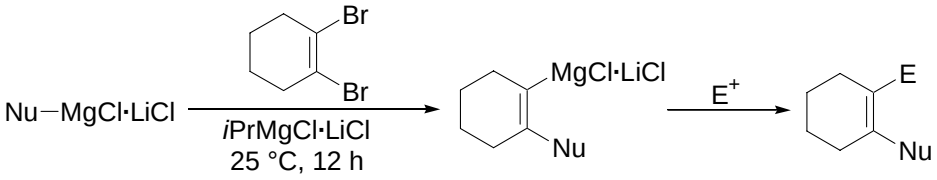
4.1 Functionalization of 1,2-dibromocyclopentenes

In summary, the use of *i*PrMgCl·LiCl (**6**) allowed a simple, high-yielding preparation of previously unknown cyclic *β*-bromo-substituted alkenylmagnesium reagents. Furthermore, a copper-catalysed heterocoupling reaction was performed, permitting the regioselective formation of new *β*-alkylated cycloalkenylmagnesium compounds that could be further reacted with a range of electrophiles. This sequence constituted an effective one-pot cascade difunctionalisation of cycloalkenes (Scheme 58).

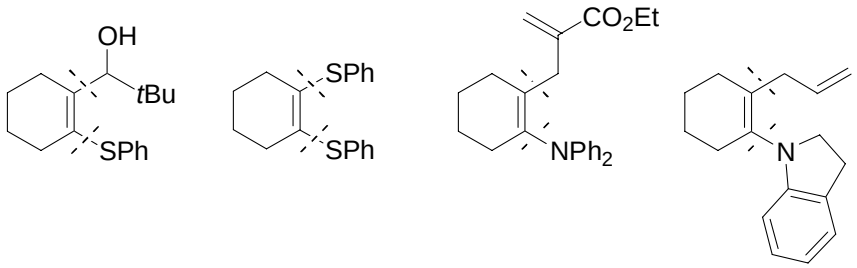


Scheme 58: Mono- and difunctionalization of cyclopentene derivatives.

Extending this method to the dibromocyclohexene system, we were able to obtain difunctionalized cyclohexene derivatives in 49-63% yields (Scheme 59). The reaction on the six-membered rings proceeds however, through a different mechanistic pathway than the one proposed for the five-membered rings.



Nu: secondary amines, or thiols



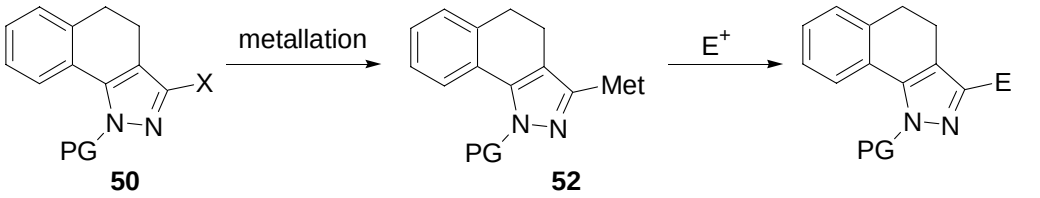
43b: 63% **43a**: 56% **45a**: 50% **49**: 50%

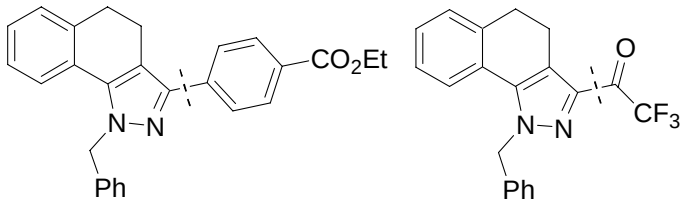
Scheme 59: Difunctionalization of cyclohexene derivatives.

Application of these methods to the synthesis of trisannelated benzenes or π-conjugated carbon frameworks could be of great interest in the field of supramolecular chemistry.[43, 44, 46]

4.2 Functionalization of 4,5-Dihydrobenzo[*g*]indazoles using Mg- and Zn-Heterocyclic Intermediates

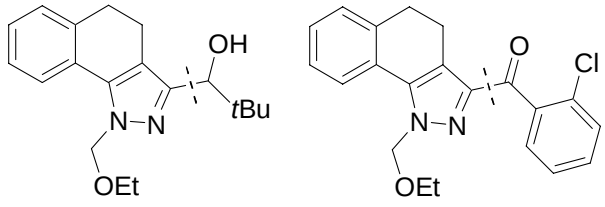
We studied the various metallation procedures on the dihydrobenzo[*g*]indazoles of type **50** and **51** at the C3 position of the pyrazole moiety. The use of an I/Mg-exchange or direct metallations using TMPMgCl·LiCl (**10a**), $TMP_2Mg·2LiCl$ (**12**) or $TMP_2Zn·2MgCl_2·2LiCl$ (**14**) proved to be complementary. Dihydrobenzo[*g*]indazoles of type **50** could be successfully metallated using an I/Mg-exchange reaction in the presence of the benzyl protecting group. Direct deprotonations could be achieved using both TMPMgCl·LiCl (**10a**) or the milder base $TMP_2Zn·2MgCl_2·2LiCl$ (**14**) (Scheme 60).





65a: 68%
(**6**; 1.1 equiv, -30 °C, 2 h)

65c: 73%
(**6**; 1.1 equiv, -30 °C, 2 h)

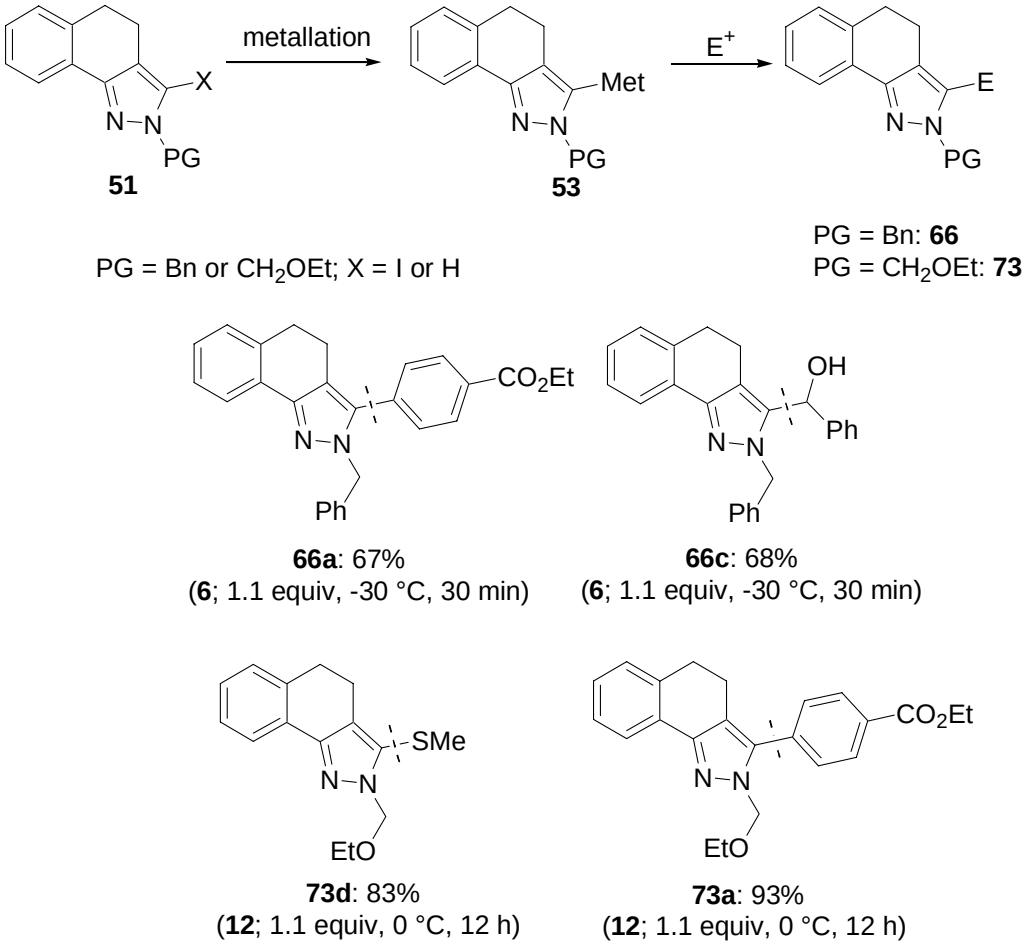


70c: 60%
(**10a**; 1.1 equiv,
-20 °C, 24 h)

70b: 55%
(**14**; 0.6 equiv,
MW, 80 °C, 2 h)

Scheme 60: Metallation of 4,5-dihydrobenzo[*g*]indazole of type **50**.

Similarly, dihydrobenzo[*g*]indazole of type **51** containing a benzyl protecting group could be metallated through an I/Mg-exchange reaction. Direct metallation by using $TMP_2Mg{\cdot}2LiCl$ (**12**) was possible, when the benzyl- was replaced with the ethoxymethyl- protecting group (Scheme 61).

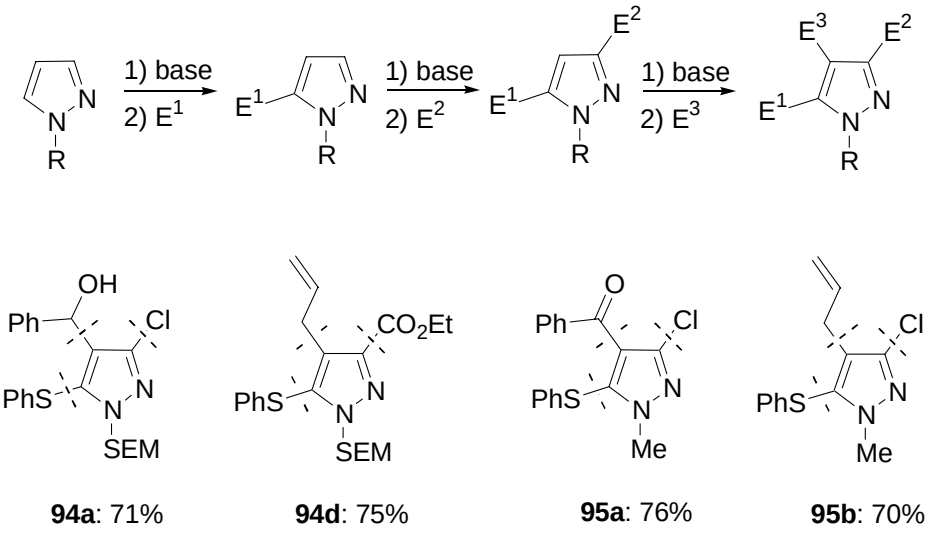


Scheme 61: Metallation of 4,5-dihydrobenzo[*g*]indazole of type **51**.

As this method enables the fast generation of molecular libraries, a large number of substituted polycyclic heterocycles can thus be prepared. Further applications of this interesting substance class in the pharmaceutical industry are being explored by Boehringer Ingelheim.

4.3 Synthesis of fully substituted pyrazoles via regio- and chemoselective metallations

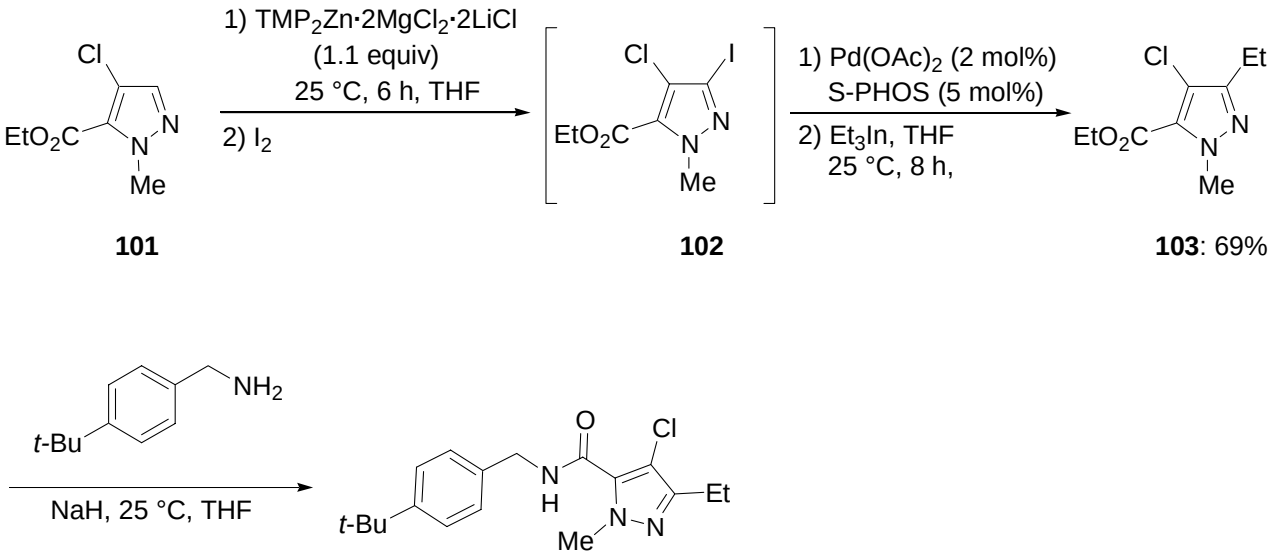
We developed a new chemo- and regioselective method of functionalization of pyrazoles through successive metallations using TMPMgCl·LiCl (**10a**) and $TMP_2Mg·2LiCl$ (**12**) starting from readily available *N*-substituted pyrazoles. This method has the advantage of avoiding the generation of undesired regioisomers. Thus, a number of trisubstituted pyrazoles, including the acaricide Tebufenpyrad (**97**) could be prepared (Scheme 62).



94a: 71% **94d**: 75% **95a**: 76% **95b**: 70%

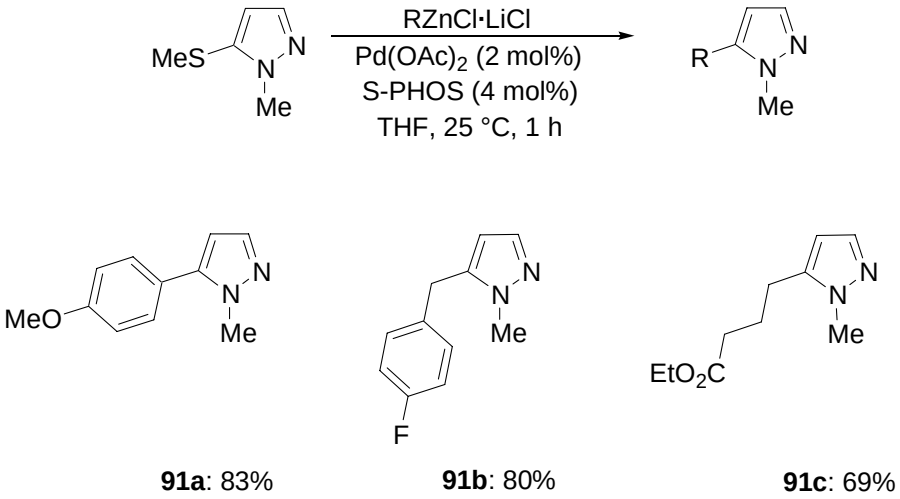
Scheme 62: Full functionalization of pyrazole derivatives through successive metallations.

We could develop a rapid route to fully substituted pyrazoles with complete regiocontrol of all substituents. An application to the synthesis of the acaricide Tebufenpyrad was also reported (Scheme 63).



Scheme 63: Synthesis of Tebufenpyrad (**97**).

Furthermore, the thioether functionality could undergo cross-coupling reactions with zinc reagents, yielding C5-arylated, alkylated or benzylated pyrazole derivatives (Scheme 64).



Scheme 64: Cross-coupling reactions with the thioether moiety of the pyrazole ring.

Since the pyrazole scaffold plays a significant role in this field, this work can be extended to the preparation of more complex pyrazoles and can find important applications in the pharmaceutical and agrochemical industry.

C: Experimental Section

1. General Considerations

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

Solvents

Solvents were dried according to standard methods by distillation from drying agents as stated below and were stored under argon.

CH_2Cl_2 and **toluene** were predried over $CaCl_{2(s)}$ and distilled from $CaH_{2(s)}$.

Diethyl ether and **THF** were continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

Dimethylformamide (DMF) was heated to reflux for 14 h over $CaH_{2(s)}$ and distilled from $CaH_{2(s)}$.

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

Methanol was treated with magnesium turnings (20g/L) and sodium, heated to reflux for 6 h and distilled.

Triethylamine was dried over $KOH_{(s)}$ and distilled from $KOH_{(s)}$.

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

Reagents: metal salt solutions

CuCN·2LiCl solution (1.0 M/THF) was prepared by drying CuCN (869 mg, 10 mmol) and LiCl (848 mg, 20 mmol) in a Schlenk flask under vacuum for 5 h at 140 °C. After cooling to 25 °C, dry THF (10 mL) was added and stirred continuously until the salts were dissolved.

$ZnCl_2$ solution (1.0 M/THF) was prepared by drying $ZnCl_2$ (20.45 g, 150 mmol) under vacuum for 5 h at 150 °C. After cooling to 25 °C, dry THF (150 mmol) was added and stirred continuously until the salts were dissolved.

Lithium reagents

***n*-Butyllithium** was used as a 1.5 M solution in hexane purchased by Chemetall.

***t*-Butyllithium** was used as a 1.5 M solution in pentane purchased by Chemetall.

Magnesium reagents

***i*PrMgCl·LiCl** was used as a 1.2 M solution in THF purchased by Chemetall.

TMPMgCl·LiCl (10a): was prepared according to the literature procedure.[34a]

TMP_2Mg·2LiCl (12): was prepared according to the literature procedure.[35a]

TMP_2Zn·2$MgCl_2$·2LiCl (14): was prepared according to the literature procedure.[37a]

The content of organometallic reagents was determined either by the method of *Paquette* (organolithium or –magnesium reagents)[89] or the method of *Knochel* (organomagnesium or -zinc reagents)[90] prior to use.

Other reagents

The following reagents were prepared according to literature procedures: Palladium(II)bis(dibenzylideneacetone),[91] tri-(2-furyl)phosphine[92], ethyl 2-(bromomethyl)-acrylate,[93] *S*-phenyl benzenesulfonothioate[94] and 2,3-dibromo-bicyclo[2.2.1]hepta-2,5-diene[95] .

[89] Lin, H. -S. Paquette, A. *Synth. Commun.* **1994**, *24*, 2503.
[90] Krasovskiy, A. ; Knochel, P. *Synthesis* **2006**, *5*, 890.
[91] Takahashi, Y.; Ito, T.; Sakai, S. *Chem. Commun.* **1970**, 1065.
[92] Allen, D. W.; Hutley, B. G.; Mellor, M. T. J. *J. Chem. Soc. Perkin Trans. II* **1972**, 63.
[93] Villieras, J.; Rambaud, M. *Org. Synth*. **1988**, *66*, 220.
[94] Fujiki, K.; Tanifuji, N.; Sasaki, Y.; Yokoyama, T. *Synthesis*, **2002**, 343.
[95] Tranmer, G. K.; Yip, C.; Handerson, S.; Jordan, R. W.; Tam, W. *Can. J. Chem.* **2000**, *78*, 527.

Chromatography

Thin layer chromatography (TLC) was performed using aluminium plates coated with SiO_2 (Merck 60, F-254). The spots were visualized by UV light and/or by staining of the TLC plate with the solution below followed, if necessary, by heating with a heat gun:

- $KMnO_4$ (0.3 g), K_2CO_3 (20 g), KOH (0.3 g) in water (300 mL)
- Neat iodine absorbed on silica gel
- Phosphor molybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g), conc. H_2SO_4(12.0 mL) in water (230 mL).

Flash column chromatography was performed using SiO_2 60 (0.04-0.063 mm, 230-400 mesh ASTM) from Merck or aluminium oxide 90 active neutral (0.063-0.200 mm, 70-230 mesh ASTM), grade III,[96] from Merck.

The column diameters and the amount of silica gel were calculated according to the recommendation of W. C. Still.[97]

Analytical Data

NMR spectra were recorded on *Bruker* ARX 200, AC 300, WH 400 or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the deuterated solvent peak: $CDCl_3$ (δ 3 H = 7.25; δ C (ppm) = 77.0), C_6D_6 (δ H = 7.15; δ C(ppm) = 128.0).
For the characterization of the observed signal multiplicities, the following abbreviations were used: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), td (doublet of triplets), quint (quintet), sext (sextet), sept (septet), br (broad), m (multiplet). If not otherwise noted, the coupling constants given are C-H coupling constants.

Melting points are uncorrected and were measured on a *Büchi* B.540 apparatus.

Infrared spectra were recorded from 4000-400 cm^{-1} on a *Nicolet* 510 FT-IR or a *Perkin-Elmer* 281 IR spectrometer. Samples were measured either as film between potassium

[96] Brockmann, H.; Schodder, H. *Ber. Deut. Chem. Ges*. **1941**, *74*, 73.
[97] Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

bromide plates (film), as potassium bromide tablets (KBr), or neat (*Smiths Detection* DuraSampl *IR* II Diamond ATR).
The absorption bands are reported in wavenumbers (cm^{-1}). For the band characterization, the following abbreviations were used: br (broad), vs (very strong), s (strong), m (medium), w (weak).

Gas chromatography (GC) was performed with instruments of the type *Hewlett-Packard* 6890 or 5890 Series II, using a column of the type HP 5 (*Hewlett-Packard*, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm; film thickness: 0.25 μm). The detection was accomplished using a flame ionization detector. Depending on the retention time of the substrate, decane or tetradecane were used as internal standards.
Mass spectra were recorded on a *Finnigan* MAT 95Q or *Finnigan* MAT90 instrument for electron impact ionization (EI). High resolution mass spectra (HRMS) were recorded on the same instrument.
For the combination of gas chromatography with mass spectroscopic detection, a GC-MS of the type *Hewlett-Packard* 6890 / MSD 5793 networking was used (column: HP 5-MS, *Hewlett-Packard*; 5% phenylmethylpolysiloxane; length: 15 m, diameter 0.25 mm; film thickness: 0.25 μm).

2. Typical Procedures (TP)

2.1 Typical procedure for the Br/Mg-exchange reaction using *i*PrMgCl·LiCl (6) of 1,2-dibromocyclopentene (TP1)

Dibromide **20** (1.00 equiv) was added to a flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum. *i*PrMgCl·LiCl (**6**; 1.10 equiv in THF) was added at 25 °C while stirring. Upon completion of the exchange (determined by GC analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution, 24-30 h), the reaction mixture was cooled to 0 °C with an ice bath. The electrophile was slowly added and the solution was allowed to warm up to 25 °C. After stirring for 2 h at 25 °C, a sat. NH_4Cl solution was added and the aq. layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. Removal of the solvent *in vacuo* and purification by flash chromatography (SiO_2, initially neutralized with 3% Et_3N) afforded the desired product.

2.2 Typical procedure for the 1,2-difunctionalization of 1,2-dibromocyclopentene derivatives (TP2)

Dibromide **20** or **25** respectively (1.00 equiv) was added to a flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum. *i*PrMgCl·LiCl (**6**; 2.20-3.00 equiv in THF) was added at 25 °C while stirring. Upon completion of the exchange (determined by GC analysis of hydrolyzed reaction aliquots, 6 h), the solution was cooled to -10 °C. Li_2CuCl_4 (0.10 M solution in THF, 2 mol%) was added dropwise and the solution was slowly allowed to warm to 0 °C. Upon completion of the coupling (determined by GC analysis of hydrolyzed reaction aliquots, 9 h), the electrophile (1.30-1.70 equiv) was slowly added and the solution was warmed to 25 °C. After 2 h stirring at 25 °C, the reaction mixture was quenched with a sat. NH_4Cl solution and the aq. layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. Removal of the solvent *in vacuo* and purification by flash chromatography (SiO_2, initially neutralized with 3% Et_3N) afforded the desired product.

2.3 Typical procedure for the 1,2-difunctionalization of 1,2 dibromocyclopentene derivatives and subsequent acylation (TP3)

Dibromide **20** or **25** respectively (1.00 equiv) was added to a flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum. *i*PrMgCl·LiCl (**6**; 2.20-2.40 equiv) was added at 25 °C while stirring. Upon completion of the exchange (determined by GC analysis of hydrolyzed reaction aliquots, 6 h), the solution was cooled to -10 °C. Li_2CuCl_4 (0.10 M in THF, 2 mol%) was added dropwise and the solution was slowly warmed to 0 °C. Upon completion of the coupling (determined by GC analysis of hydrolyzed reaction aliquots, 9 h), the solution was cooled to -30 °C and $ZnCl_2$ solution (1.00 M in THF, 1.00 equiv) was added. After stirring for 30 min, the solution was warmed to -20 °C and a CuCN·2LiCl solution (1.00 M in THF, 20 mol%) was added. After stirring for 5 min, an acid chloride (1.20-1.50 equiv) was added and the solution was warmed to 25 °C. The reaction mixture was stirred at 25 °C for 2 h, and then quenched with sat. NH_4Cl solution. The aq. layer was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Removal of the solvent *in vacuo* and purification by flash chromatography (SiO_2, initially neutralized with 3% Et_3N) afforded the desired product.

2.4 Typical procedure for the I/Mg-exchange reaction on 1-benzyl-3-iodo-4,5-dihydro-1*H*-benzo[g]indazole (61) (TP4)

A flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with 1-benzyl-3-iodo-4,5-dihydro-1*H*-benzo[g]indazole (**61**; 386 mg, 1.00 mmol), dissolved in THF (1.0 mL). *i*PrMgCl·LiCl (**6**; 1.00 mL, 1.10 M in THF, 1.10 mmol) was added slowly at -30 °C and the resulting mixture was stirred for 2 h. The completion of the exchange reaction was checked by GC-analysis of hydrolyzed reaction aliquots. The freshly prepared organomagnesium reagent **63** was either transmetallated with $ZnCl_2$ (1.00 mL, 1.00 M, 1.00 mmol) and used in a *Negishi* cross-coupling with the corresponding iodides, or transmetallated with CuCN·2LiCl (1.00 mL, 1.00 M in THF, 1.00 mmol) for subsequent allylation or acylation. When used directly, the corresponding electrophile was added at -30 °C and the reaction mixture was slowly allowed to warm up to 25 °C. The consumption of the magnesium reagent was checked by GC analysis of hydrolyzed reaction aliquots, using

tetradecane as internal standard. After complete conversion, the mixture was quenched with sat. NH_4Cl solution (in the presence of copper a 25% aq. NH_3 solution was also added to the mixture) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography afforded the desired C3-functionalized 4,5-dihydro-1*H*-benzo[g]indazoles (**65a-f**).

2.5 Typical procedure for the I/Mg-exchange reaction on 2-benzyl-3-iodo-4,5-2*H*-benzo[g]indazole (62) (TP5)

A flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with 2-benzyl-3-iodo-4,5-dihydro-2*H*-benzo[g]indazole (**62**; 386 mg, 1.00 mmol), dissolved in THF (1.0 mL). *i*PrMgCl·LiCl (**6**; 1.00 mL, 1.10 M in THF, 1.10 mmol) was added slowly at -30 °C and the resulting mixture was stirred for 30 min. The completion of the exchange reaction was checked by GC-analysis of hydrolyzed reaction aliquots. The freshly prepared organomagnesium reagent **64** was either transmetallated with $ZnCl_2$ (1.00 mL, 1.00 M in THF, 1.00 mmol) and used in a *Negishi* cross-coupling with the corresponding iodides, or transmetallated with CuCN·2LiCl (1.00 mL, 1.00 M in THF, 1.00 mmol) for subsequent allylation or acylation. When used directly, the corresponding electrophile was added at -30 °C and the reaction mixture was slowly allowed to warm up to 25 °C. The consumption of the magnesium reagent was checked by GC analysis of hydrolyzed reaction aliquots, using tetradecane as internal standard. After complete conversion, the mixture was quenched with sat. NH_4Cl solution (in the presence of copper a 25% aq. NH_3 solution was also added to the mixture) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography afforded the desired C3-functionalized 4,5-dihydro-2H-benzo[g]indazoles (**66a-d**).

2.6 Typical procedure for the deprotonation of 1-ethoxymethyl-4,5-dihydro-1*H*-benzo[g]indazole (67) using $TMP_2Zn·2MgCl_2·2LiCl$ (14) (TP6)

A dry and argon flushed 10 mL pressurized vial, equipped with a magnetic stirring bar, was charged with 1-ethoxymethyl-4,5-dihydro-1*H*-benzo[g]indazole (**67**; 228 mg, 1.00 mmol)

dissolved in THF (1.0 mL). The $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ base (**14**; 1.50 mL, 0.40 M in THF, 0.60 mmol) was added and the reaction mixture was heated using a Discover BenchMate® Microwave system at 80 °C and 200 W for 2 h. The completion of the metallation was checked by GC-analysis of reaction aliquots quenched with I_2 in dry THF. After complete metallation and cooling to 25 °C the organozinc reagent **69** was either used directly in a *Negishi* cross-coupling reaction or was cooled to -20 °C and transmetallated with CuCN·2LiCl (1.00 mL, 1.00 M in THF, 1.00 mmol) for a subsequent reaction with an acyl chloride. The consumption of the zinc reagent was checked by GC analysis of hydrolyzed reaction aliquots, using tetradecane as internal standard. After complete conversion, the mixture was quenched with sat. NH_4Cl solution (in the presence of copper a 25% aq. NH_3 solution was also added to the mixture) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography afforded the desired C3-functionalized 4,5-dihydro-1*H*-benzo[g]indazoles (**70a-b**).

2.7 Typical procedure for the deprotonation of 1-ethoxymethyl-4,5-dihydro-1*H*-benzo[g]indazole (67) using TMPMgCl·LiCl (10a) (TP7)

A flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with 1-ethoxymethyl-4,5-dihydro-1*H*-benzo[g]indazole (**67**; 228 mg, 1.00 mmol), dissolved in THF (1.0 mL). TMPMgCl·LiCl (**10a**; 1.00 mL, 1.10 M in THF, 1.10 mmol) was added slowly at -20 °C and the mixture was stirred for 24 h. The completion of the exchange reaction was checked by GC-analysis of reaction aliquots quenched with I_2 in dry THF. After complete metallation the organomagnesium reagent **71** was either reacted directly with electrophiles, or transmetallated with CuCN·2LiCl (1.00 mL, 1.00 M in THF, 1.00 mmol) to undergo a subsequent allylation or acylation. The consumption of the magnesium reagent was checked by GC analysis of hydrolyzed reaction aliquots, using tetradecane as internal standard. After completion of the reaction the mixture was quenched with sat. NH_4Cl solution (in the presence of copper a 25% aq. NH_3 solution was also added to the mixture) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography afforded the desired C3-functionalized 4,5-dihydro-1*H*-benzo[g]indazoles (**70c-d**).

2.8 Typical procedure for the deprotonation of 2-ethoxymethyl-4,5-dihydro-2*H*-benzo[g]indazole (68) using $TMP_2Mg{\cdot}2LiCl$ (12) (TP8)

A flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with 2-ethoxymethyl-4,5-dihydro-2*H*-benzo[g]indazole (**68**; 228 mg, 1.00 mmol), dissolved in THF (1.0 mL). $TMP_2Mg{\cdot}2LiCl$ (**12**; 1.80 mL, 0.60 M in THF, 1.10 mmol) was added slowly at 0 °C and the mixture was stirred for 12 h. The completion of the exchange reaction was checked by GC-analysis of reaction aliquots quenched with I_2 in dry THF. After complete metallation the organomagnesium reagent **72** was either reacted directly with electrophiles, or transmetallated with CuCN·2LiCl (1.00 mL, 1.00 M in THF, 1.00 mmol) to undergo a subsequent allylation or acylation. Transmetallation with $ZnCl_2$ (1.00 mL, 1.00 M in THF, 1.00 mmol) was necessary before performing a *Negishi* cross-coupling. The consumption of the magnesium reagent was checked by GC analysis of hydrolyzed reaction aliquots, using tetradecane as internal standard. After complete conversion, the mixture was quenched with sat. NH_4Cl solution (in the presence of copper a 25% aq. NH_3 solution was also added to the mixture) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography afforded the desired C3-functionalized 4,5-dihydro-2*H*-benzo[g]indazoles (**73a-d**).

2.9 Typical procedure for the deprotonation reaction at the C5 position of the pyrazole ring (TP9)

A dry and argon flushed flask equipped with a magnetic stirring bar and a septum, was charged with the pyrazole (1.00 mmol) and THF (1.0 mL). TMPMgCl·LiCl (**10a**; 1.00 mL, 1.10 M in THF, 1.10 mmol) was added dropwise at 25 °C and the reaction mixture was stirred for 2 h. The completion of the deprotonation was checked by GC analysis of reaction aliquots quenched with I_2. After complete conversion, the electrophile (1.20 mmol) was added at 0 °C and the mixture was allowed to slowly warm up to 25 °C. The consumption of the organomagnesium reagent was checked by GC-analysis of hydrolyzed reaction aliquots and the reaction mixture was quenched with brine and extracted with EtOAc (3 x 50 mL). The

organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography furnished the desired products.

2.10 Typical procedure for the deprotonation reaction at the C3 position of the pyrazole ring (TP10)

A dry and argon flushed flask equipped with a magnetic stirring bar and a septum, was charged with the pyrazole (1.00 mmol) and THF (1.0 mL). The reaction mixture was cooled to -15 °C and TMPMgCl·LiCl (**10a**; 1.00 mL, 1.10 M in THF, 1.10 mmol) was added dropwise. The reaction mixture was stirred for 8 h. The completion of the deprotonation was checked by GC analysis of reaction aliquots quenched with I_2. After complete conversion, the electrophile (1.20 mmol) was added at -20 °C and the mixture was allowed to slowly warm up to 25 °C. The consumption of the organomagnesium reagent was checked by GC-analysis of hydrolyzed reaction aliquots and the reaction mixture was quenched with brine and extracted with EtOAc (3 x 50 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography furnished the desired products.

2.11 Typical procedure for the deprotonation reaction at the C4 position of the pyrazole ring (TP11)

A dry and argon flushed flask equipped with a magnetic stirring bar and a septum, was charged with the pyrazole (1.00 mmol) and THF (1.0 mL). The reaction mixture was cooled to -20 °C and TMP_2Mg·2LiCl (**12**; 2.00 mL, 0.56 M in THF, 1.10 mmol) was added dropwise. The reaction mixture was stirred for 4 h at -20 °C. The completion of the deprotonation was checked by GC analysis of reaction aliquots quenched with I_2. After complete conversion the electrophile (1.20 mmol) was added at -20 °C and the mixture was allowed to slowly warm up to 25 °C. The consumption of the organomagnesium reagent was checked by GC-analysis of hydrolyzed reaction aliquots and the reaction mixture was quenched with brine and extracted with EtOAc (3 x 50 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography furnished the desired products.

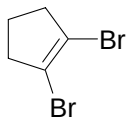
2.12 Typical procedure for the cross-coupling of thioethers (TP12)

A flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with the corresponding thioether (1.00 mmol) dissolved in THF (1.0 mL). To this solution was added 2 mol% $Pd(OAc)_2$ (4.50 mg, 0.02 mmol) and 4 mol% SPhos (16.5 mg, 0.04 mmol). The zinc reagent was added dropwise and the mixture was warmed to the desired temperature and stirred for the appropriate amount of time. The completion of the reaction was checked by GC-analysis of hydrolyzed reaction aliquots. The mixture was quenched with sat. aq. Na_2CO_3 solution and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography afforded the desired products.

3. Selective Mono- and 1,2-Difunctionalization of Cyclopentene and Cyclohexene Derivatives via Mg and Cu intermediates

3.1 Starting Materials

Synthesis of 1,2-dibromocyclopentene (20) [98]



To a dry and nitrogen flushed 2L 3-neck flask equipped with a thermometer, a dropping funnel and a magnetic stirring bar containing a suspension of PCl_5 (215 g, 1.03 mol) in benzene (250 mL), cyclopentanone (91.6 mL, 1.04 mol) was added dropwise, keeping the temperature below 35 °C. After addition of the ketone the reaction mixture was stirred for 40 min at 25 °C and the formed HCl was removed in a N_2 flow. The yellow solution was cooled to -20 °C and Br_2 (30 mL, 0.60 mol) was added dropwise within 40 min. After completion of the reaction the solution was poured onto ice and extracted with pentane. The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was added to a 3-neck flask equipped with a dropping funnel and a magnetic stirring bar, dissolved in pentane (150 mL) and cooled to -25 °C. A suspension of *t*BuOK (120 g, 1.07 mol) in THF (500 mL) was added dropwise within 1 h. After completion of the addition the reaction mixture was poured onto ice and extracted with pentane. The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The brown oil was purified by distillation (10 mbar, 60 °C) yielding 1,2-dibromo cyclopentene as a colourless oil (46.3 g, 21%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.60 (t, $^3J_{H\text{-}H}$ = 7.5 Hz, 4 H), 2.09-1.99 (m, 2 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 121.9, 39.0, 22.4.

MS (70 eV, EI), *m/z* (%): 226 (53), 224 (M^+, 50) 145 (48), 119 (6), 65 (100).

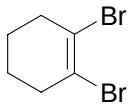
IR (film): 2954 (w), 2853 (w), 1724 (w), 1622 (m), 1442 (w), 1309 (w), 1200 (w), 1106 (s), 1059 (m), 935 (vw), 839 (vs).

HRMS (EI) calcd. for $C_5H_6{}^{79}Br_2$: 223.8836, found: 223.8846.

---

[98] K. Voigt, P. von Zezschwitz, K. Rosauer, A. Lansky, A. Adams, O. Reiser, A. de Meijere, *Eur. J. Org. Chem.* **1998**, 1521.

Synthesis of 1,2-dibromocyclohexene (38)



To a dry and nitrogen flushed 2L 3-neck flask equipped with a thermometer, a dropping funnel and a magnetic stirring bar, containing a suspension of PCl_5 (108.3 g, 0.52 mol) in chloroform (270 mL), cyclohexanone (49.1 g, 0.50 mol) dissolved in chloroform (160 mL) was added dropwise at 0 °C within 1 h. After addition of the ketone the reaction mixture was stirred for 1 h at 25 °C and then refluxed for 2 h. The yellow solution was poured onto ice and treated with $NaHCO_3$ until neutral pH was obtained. The organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was added to a 3-neck flask equipped with a dropping funnel and a magnetic stirring bar, dissolved in CH_2Cl_2 (30 mL) and cooled to -10 °C. A solution of Br_2 (32.0 g, 0.20 mol) in CH_2Cl_2 (12 mL) was added dropwise over a period of 1 h to the reaction mixture. After completion of the addition the mixture was poured onto ice and extracted with pentane. The organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The yellow residue was dissolved in pentane (75 mL) and cooled to -25 °C. A suspension of *t*BuOK (56.0 g, 0.50 mol) in THF (250 mL) was added dropwise to the solution. After completion of the reaction the mixture was poured onto ice and extracted with pentane. The organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, pentane) and recrystallized from methanol. 1,2 Dibromocyclohexene was isolated as colourless crystals (90 g, 75%).

m.p.: 45.8-47.2 °C

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.57-2.54 (m, 4 H), 1.76-1.72 (m, 4 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 122.9, 37.2, 24.0.

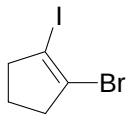
IR (Diamond ATR): 2944 (m), 2927 (m), 1718 (w), 1634 (m), 1447 (m), 1429 (m), 1322 (m), 1262 (w), 1170 (w), 1140 (w), 1114 (w), 1073 (w), 989 (s), 962 (s), 852 (m), 816 (m), 748 (s).

MS (70 eV, EI), *m/z* (%): 242 (28), 240 (49), 238 (M^+, 25), 161 (35), 159 (37), 133 (12), 131 (15), 91 (20), 80 (26), 79 (100), 78 (11), 77 (39), 57 (13), 55 (14), 52 (13), 51 (23), 50 (12), 44 (36), 43 (16), 41 (11).

HRMS (EI) calcd. for $C_6H_8{}^{79}Br_2$: 237.8993, found: 237.8993.

3.2 Monofunctionalization of 1,2-dibromocyclopentene

Synthesis of 1-bromo-2-iodocyclopentene (22a)



Dibromide **20** (1.00 mmol, 226 mg) was reacted according to **TP1** with *i*PrMgCl·LiCl (**6**; 0.89 mL, 1.24 M in THF, 1.10 mmol). After completion of the exchange, the organomagnesium reagent **21** was quenched with iodine (305 mg, 1.20 mmol) in THF (2.00 mL) at -20 °C. Purification by flash chromatography was done according to **TP1**, (SiO_2, pentane) yielding 1-bromo-2-iodocyclopentene (**22a**), as a pale yellow oil (223 mg, 82%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.67-2.59 (m, 4 H), 2.05 (quint, $^3J_{H-H}$ = 7.5 Hz, 2 H).

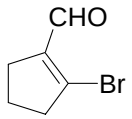
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 130.2, 97.2, 43.5, 39.6, 24.1.

IR (film): 2951 (m), 2848 (m), 1604 (m), 1440 (m), 1382 (w), 1306 (m), 1287 (w), 1199 (w), 1132 (w), 1091 (s), 1042 (w), 1028 (w), 903 (w), 824 (s), 747 (w), 692 (w).

MS (EI, 70 eV), *m/z* (%): 272 (M^+, 100), 206 (2), 193 (17), 145 (21), 127 (13), 65 (63).

HRMS (EI): calcd. for $C_5H_6{}^{79}BrI$: 271.8698, found: 271.8686.

Synthesis of 2-bromocyclopent-1-enecarbaldehyde (22b)



According to **TP1**, *i*PrMgCl·LiCl (**6**; 1.65 mL, 1.06 M in THF, 1.75 mmol) was added to **20** (359 mg, 1.59 mmol). The alkenylmagnesium species **21** was quenched with DMF (0.15 mL, 1.91 mmol). Following work-up, the obtained oil was purified by flash chromatography (SiO_2, pentane:CH_2Cl_2/1:1) to give the product **22b** as a pale yellow oil (228 mg, 82%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.89 (s, 1 H), 2.92-2.87 (m, 2 H), 2.55-2.50 (m, 2 H), 2.01 (quint, $^3J_{H-H}$ = 7.5 Hz, 2 H).

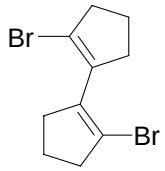
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 189.5, 141.6, 140.3, 42.8, 29.5, 21.6.

IR (film): 2925 (w), 1662 (s), 1599 (s), 1329 (w), 1240 (w), 1195 (w), 1074 (m), 909 (m), 720 (s).

MS (EI, 70 eV), *m/z* (%): 174 (M^+, 100), 145 (10), 95 (45), 94 (12), 67 (90), 66 (41), 65 (73), 41 (20).

HRMS (EI): calcd. for $C_6H_7{}^{79}BrO$: 173.9680, found: 173.9681.

Synthesis of 2,2'-dibromobicyclopentyl-1,1'-diene (22e)



According to **TP1**, *i*PrMgCl·LiCl (**6**; 4.50 mL, 1.22 M in THF, 5.50 mmol) was added to **20** (1.13 g, 5.00 mmol). The alkenylmagnesium species **21** was transmetallated with $ZnCl_2$ (1.00 M in THF solution, 2.75 mL) at -20 °C and the solution was stirred for 15 min. 1-Bromo-2-iodocyclopentene (**22a**;1.36 g, 5.00 mmol) was then added to the reaction mixture at -20 °C followed by $Pd(dba)_2$ (144 mg, 5 mol%) and (*o*-furyl)$_3$P (81 mg, 7 mol%). After the work-up, the obtained oil was purified by flash chromatography (SiO_2, pentane) to give the product **22e** as a colourless oil (1.16 g, 77%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.71-2.53 (m, 8 H), 1.96 (quint, $^3J_{H\text{-}H}$ = 7.6 Hz, 4 H).

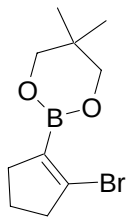
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 136.9, 119.0, 41.4, 35.0, 22.8.

IR (film): 4329 (w), 4250 (w), 2966 (m), 2946 (m), 2893 (m), 2846 (s), 1668 (w), 1615 (w), 1435 (m), 1308 (m), 1283 (m), 1202 (w), 1134 (w), 1118 (w), 1082 (m), 1033 (s), 998 (w), 922 (m), 907 (m), 876 (w), 784 (s).

MS (EI, 70 eV), *m/z* (%): 292 (M^+, 100), 290 (47), 213 (32), 211 (32), 132 (58), 131 (61), 129 (10), 117 (28), 116 (11), 115 (14), 104 (16), 103 (14), 91 (30), 77 (17), 65 (23), 64 (25), 63 (10), 51 (16).

HRMS (EI): calcd. for $C_{10}H_{12}{}^{79}Br_2$: 289.9306, found: 289.9316.

Synthesis of 2-(2-bromocyclopent-1-enyl)-5,5-dimethyl[1,3,2]dioxaborinane (22f)



According to **TP1**, *i*PrMgCl·LiCl (**6**; 0.90 mL, 1.22 M in THF, 1.10 mmol) was added to **20** (226 mg, 1.00 mmol) at 25 °C. The alkenylmagnesium species **21** was reacted with (*i*-PrO)$_3$B (0.28 mL, 1.20 mmol) at -20 °C and the reaction mixture was slowly warmed up to 25 °C. 2,2-Dimethylpropane-1,3-diol (156 mg, 1.50 mmol) was then added neat to the solution. After the work-up, the obtained oil was purified by flash chromatography (SiO_2, pentane:ether/7:3) to give the product **22f** as a brown oil (185 mg, 72%).

^{1}H-NMR (C_6D_6, 300 MHz): δ = 3.34 (s, 4 H), 2.61-2.53 (m, 4 H), 1.58 (quint, $^3J_{H\text{-}H}$ = 7.6 Hz, 2 H), 0.57 (s, 6 H).

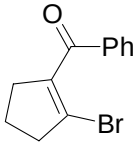
^{13}C-NMR (C_6D_6, 75 MHz): δ = 132.2, 71.9, 44.0, 36.3, 31.3, 23.4, 21.5 (olefinic C attached to B not observed due to quadrupolar coupling).

IR (film): 2958 (m), 2926 (m), 1731 (m), 1616 (m), 1476 (m), 14181318 (s), 1253 (s), 1118 (s), 1073 (w), 840 (w), 696 (m), 672 (w).

MS (EI, 70 eV), *m/z* (%): 258 (M^+, 100), 180 (40), 179 (63), 135 (46), 93 (62), 79 (28).

HRMS (EI): calcd. for $C_{10}H_{16}B^{79}BrO_2$: 258.0427, found: 258.0433.

Synthesis of (2-bromocyclopent-1-enyl)-phenylmethanone (22g)



According to **TP1**, *i*PrMgCl·LiCl (**6**; 0.85 mL, 1.30 M in THF, 1.10 mmol) was added to **20** (226 mg, 1.00 mmol). After the exchange was complete, the solution was cooled to -30 °C and $ZnCl_2$ solution (1.00 mL, 1.0 M in THF, 1.00 mmol) was added. After stirring for 30 min, the solution was warmed to -20 °C and CuCN·2LiCl solution (1.00 mL, 1.00 M in THF, 1.00 mmol) was added. After stirring for 5 min, benzoyl chloride (0.14 mL, 1.20 mmol) was added and the solution was warmed to 25 °C. After stirring 2 h at 25 °C, a sat. NH_4Cl solution (5

mL) was added and the aq. layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Removal of solvent *in vacuo* and purification by flash chromatography (SiO_2, pentane:ether/9:1) afforded the product **22g** as a pale yellow oil (162 mg, 65%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.92 (d, $^3J_{H-H}$ = 7.0 Hz, 2 H), 7.20-7.12 (m, 3 H), 2.49-2.40 (m, 4 H), 1.50 (quint, $^3J_{H-H}$ = 7.6 Hz, 2 H).

^{13}C-NMR (C_6D_6, 75 MHz): δ = 194.0, 140.7, 136.7, 133.0, 129.6, 128.6, 123.4, 41.9, 35.5, 22.1.

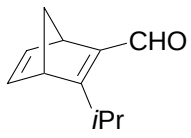
IR (film): 1653 (s), 1616 (m), 1595 (m), 1451 (m), 1321 (s), 1283 (s), 1072 (m), 955 (m), 840 (m), 792 (m), 713 (s), 687 (s), 675 (s).

MS (EI, 70 eV), *m/z* (%): 252 (64), 251 (17), 250 (M^+, 66), 175 (23), 173 (23), 172 (13), 171 (100), 170 (11), 143 (32), 128 (15), 105 (47), 77 (22).

HRMS (EI): calcd. for $C_{12}H_{11}{}^{79}BrO$: 249.9993, found: 249.9992.

3.3 Difunctionalization of cyclopentene derivatives

Synthesis of 3-isopropylbicyclo[2.2.1]hepta-2,5-diene-2-carbaldehyde (27a)



According to **TP2**, *i*PrMgCl·LiCl (**6**; 1.80 mL, 1.22 M in THF, 2.20 mmol) was added to **25** (250 mg, 1.00 mmol). After the exchange was complete, Li_2CuCl_4 was added (0.1 mL, 0.10 M in THF, 0.01 mmol). The newly formed alkenylmagnesium species **26** was quenched with DMF (0.12 mL, 1.50 mmol). After the work-up, the resultant oil was purified by flash chromatography (SiO_2, pentane:ethyl acetate/9:1) to give the product **27a** as a yellow oil (116 mg, 72%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.87 (s, 1 H), 6.65-6.63 (m, 1 H), 6.38-6.36 (m, 1 H), 4.09 (s, 1 H), 3.22 (s, 1 H), 2.93 (sept, $^3J_{H-H}$ = 6.8 Hz, 1 H), 1.77 (d, $^3J_{H-H}$ = 6.7 Hz, 1 H), 1.63 (d, $^3J_{H-H}$ = 6.7 Hz, 1 H), 0.81 (d, $^3J_{H-H}$ = 6.8 Hz, 3 H), 0.63 (d, $^3J_{H-H}$ = 6.8 Hz, 3 H).

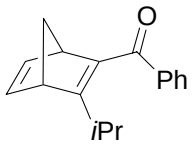
^{13}C-NMR (C_6D_6, 75 MHz): δ = 183.5, 182.5, 147.0, 143.7, 141.0, 70.0, 51.8, 47.7, 27.0, 19.0.

IR (film): 3437 (w), 2966 (s), 1659 (s), 1465 (m), 1332 (w), 1291 (m), 701 (w), 664 (w).

MS (EI, 70 eV), *m/z* (%): 162 (M^+, 45), 147 (16), 133 (10), 129 (12), 119 (21), 105 (17), 96 (10), 92 (12), 91 (52), 77 (14), 67 (10), 66 (100), 65 (13), 41 (13).

HRMS (EI): calcd. for $C_{11}H_{14}O$: 162.1045, found: 162.1035.

Synthesis of (3-isopropylbicyclo[2.2.1]hepta-2,5-dien-2-yl)phenylmethanone (27b)



According to **TP3**, *i*PrMgCl·LiCl (**6**; 1.80 mL, 1.22 M in THF, 2.20 mmol) was added to **25** (250 mg, 1.00 mmol). After the exchange was complete, Li_2CuCl_4 was added (0.10 mL, 0.10 M in THF, 0.01 mmol). The newly formed alkenylmagnesium species **26** was transmetallated with $ZnCl_2$ (1.00 mL, 1.00 M in THF, 1.0 mmol) and subsequently with CuCN·2LiCl (0.20 mL, 1.00 M in THF, 0.20 mmol), and the resultant copper-zinc reagent was quenched with benzoyl chloride (0.17 mL, 1.50 mmol). After the work-up, the resultant oil was purified by flash chromatography (SiO_2, pentane:ethyl acetate/9:1) to give the product **27a** as a pale yellow solid (138 mg, 58%).

m.p.: 47.8-50.4 °C.

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.76 (d, $^3J_{H\text{-}H}$ = 6.7 Hz, 2 H), 7.14-7.07 (m, 3 H), 6.90-6.88 (m, 1 H), 6.52-6.50 (m, 1 H), 3.86 (s, 1 H), 3.38 (s, 1 H), 2.87 (sept, $^3J_{H\text{-}H}$ = 6.7 Hz, 1 H), 1.89 (d, $^3J_{H\text{-}H}$ = 6.5 Hz, 1 H), 1.85 (d, $^3J_{H\text{-}H}$ = 6.5 Hz, 1 H), 0.91 (d, $^3J_{H\text{-}H}$ = 3.3 Hz, 3 H), 0.62 (d, $^3J_{H\text{-}H}$ = 3.3 Hz, 3 H).

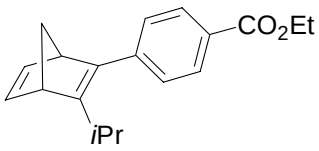
^{13}C-NMR (C_6D_6, 100 MHz): δ = 193.0, 172.3, 145.4, 143.4, 141.0, 140.4, 131.8, 128.7, 128.2, 69.6, 53.0, 51.7, 28.2, 20.4, 18.7.

IR (film): 2966 (m), 2868 (w), 1628 (s), 1334 (m), 1288 (m), 1250 (m), 999 (w), 884 (w), 808 (w), 725 (s), 696 (m), 662 (s).

MS (EI, 70 eV), *m/z* (%): 238 (M^+, 39), 223 (11), 195 (11), 173 (17), 172 (34), 115 (10), 105 (100), 91 (22), 78 (11), 77 (80), 66 (41), 65 (14), 51 (31), 43 (11), 41 (37).

HRMS (EI): calcd. for $C_{17}H_{18}O$: 238.1358, found 238.1344.

Synthesis of ethyl 4-(3-isopropylbicyclo[2.2.1]hepta-2,5-dien-2-yl)benzoate (27c)



According to **TP2**, *i*PrMgCl·LiCl (**6**; 1.80 mL, 1.22 M in THF, 2.20 mmol) was added to **25** (250 mg, 1.00 mmol). After the exchange was complete, Li_2CuCl_4 was added (0.01 mmol, 0.10 M in THF, 0.10 mL). The newly formed alkenylmagnesium species **26** was coupled with ethyl 4-iodobenzoate (414 mg, 1.50 mmol) using 5 mol% $Pd(dba)_2$ (29 mg, 0.05 mmol) and 7 mol% (*o*-furyl)$_3$P (16 mg, 0.07 mmol). After the work-up, the resultant oil was purified by flash chromatography (SiO_2, pentane:ethyl acetate/19:1) to give the product **27c** as a white solid (177 mg, 63%).

m.p.: 42.3-43.7 °C.

^{1}H-NMR (C_6D_6, 400 MHz): δ = 8.24 (d, $^3J_{H-H}$ = 8.4 Hz, 2 H), 7.21-7.19 (m, 2 H), 6.79-6.77 (m, 1 H), 6.66-6.64 (m, 1 H), 4.15 (q, $^3J_{H-H}$ = 7.0 Hz, 2 H), 3.52 (s, 1 H), 3.44 (s, 1 H), 2.93 (sept, $^3J_{H-H}$ = 6.7 Hz, 1 H), 1.93 (s, 2 H), 1.08-1.03 (m, 6 H), 0.72 (d, $^3J_{H-H}$ = 6.7 Hz, 3 H).

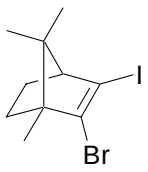
^{13}C-NMR (C_6D_6, 100 MHz): δ = 166.1, 158.4, 144.6, 142.5, 142.1, 129.9, 128.6, 126.2, 69.9, 60.5, 55.0, 51.1, 27.3, 21.4, 19.0, 14.2.

IR (film): 2960 (m), 1712 (s), 1604 (m), 1463 (w), 1365 (w), 1268 (s), 1176 (m), 1103 (s), 1022 (m), 857 (w), 808 (w), 772 (s), 724 (s), 708 (s).

MS (EI, 70 eV), *m/z* (%): 283 (20), 282 (M^+, 100), 259 (12), 235 (17), 215 (35), 214 (55), 171 (10), 167 (11), 165 (10), 143 (52), 128 (12).

HRMS (EI): calcd. for $C_{19}H_{22}O_2$: 282.1620, found: 282.1635.

Synthesis of 2-bromo-3-iodo-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (28)



(*R*)-2-Bromo-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (2.15 g, 10 mmol), obtained via a Shapiro reaction from the camphor hydrazone according to the published procedure[99] was deprotonated at the vinylic position with LDA (25 mmol, 1 M in THF) and trapped *in situ* with trimethyltin chloride (2.0 g, 10 mmol), as described by De Lucchi.[100] The product **33** was not isolated, but quenched *in situ* with iodine (2.79 g, 11.0 mmol) dissolved in THF (20 mL) to yield **28**. The reaction mixture was concentrated under high vacuum, to remove the Me_3SnI, and the product was extracted with pentane and washed with a saturated $Na_2S_2O_3$ solution and water. The resultant oil was purified by flash chromatography (SiO_2, pentane) to give the product **28** as a pale yellow oil (1.68 g, 60%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 2.34 (d, $^3J_{H\text{-}H}$ = 3.5 Hz, 1 H), 1.42-1.36 (m, 1 H), 1.23-1.18 (m, 1 H), 1.04-0.97 (m, 2 H), 0.94 (s, 3 H), 0.76 (s, 3 H), 0.47 (s, 3 H).

^{13}C-NMR (C_6D_6, 100 MHz): δ = 139.2, 99.2, 63.8, 59.5, 56.8, 31.8, 25.0, 19.6, 18.9, 13.4.

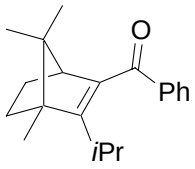
IR (film): 2958 (s), 2871 (m), 1574 (m), 1472 (w), 1441 (w), 1388 (w), 1300 (w), 1152 (w), 1111 (w), 1013 (s), 969 (m), 815 (m), 773 (m), 730 (s).

MS (EI, 70 eV), *m/z* (%): 342 (36), 340 (M^+, 41), 314 (12), 216 (12), 215 (98), 214 (12), 213 (96).

HRMS (EI): calcd. for $C_{10}H_{14}BrI$: 339.9324, found 339.9335.

[99] a) R. Cremlyn, M. Bartlet, J. Lloyd, *Phosphorus, Sulfur, and Silicon and the related elements*, **1988**, *40*, 91; b) A. Pross, S. Sternhell, *Aust. J. Chem.* **1971**, *24*, 1437.
[100] F. Fabris, L. Zambrini, E. Rosso, O. De Lucchi, *Eur. J. Org. Chem.* **2004**, 3313.

Synthesis of (3-isopropyl-4,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)(phenyl)methanone (36)



According to **TP3**, *i*PrMgCl·LiCl (**6**; 1.80 mL, 1.22 M in THF, 2.20 mmol) was added to **33** (340 mg, 1.00 mmol). After the exchange was complete (1 h, 0 °C), CuCN·2LiCl was added (1.00 mL, 1.00 mmol) at -60 °C. The newly formed alkenylmagnesium species **35** was transmetallated first to $ZnCl_2$ (1.00 mL, 1.00 M in THF, 1.00 mmol) and subsequently after 10 min with CuCN·2LiCl (1.00 mL, 1.00 M, 1.00 mmol) and then quenched with benzoyl chloride (0.17 mL, 1.50 mmol) at -30 °C. After the work-up, the resultant oil was purified by flash chromatography (SiO_2, pentane:ethyl acetate/19:1) to give the product **36,** which was recrystallized from heptane to give colourless crystals (85 mg, 30%).

m.p.: 61.7-64.5 °C.

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.97-7.95 (m, 2 H), 7.13-7.10 (m, 3 H), 2.76 (sept, $^3J_{H-H}$ = 7.0 Hz, 1 H), 2.64 (d, $^3J_{H-H}$ = 3.5 Hz, 1 H), 1.86-1.79 (m, 1 H), 1.59-1.43 (m, 2 H), 1.29-1.22 (m, 1 H), 1.03-0.95 (m, 12 H), 0.62 (s, 3 H).

^{13}C-NMR (C_6D_6, 100 MHz): δ = 195.7, 159.9, 140.6, 140.1, 132.1, 129.1, 128.4, 58.2, 56.1, 55.6, 33.1, 29.1, 26.3, 20.8, 20.5, 20.0, 19.3, 13.2.

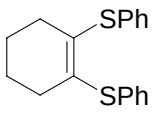
IR (film): 2962 (s), 2872 (w), 1629 (s), 1595 (m), 1446 (m), 1331 (m), 1272 (m), 1249 (m), 809 (m), 778 (w), 720 (s), 692 (s), 660 (s).

MS (EI, 70 eV), *m/z* (%): 283 (23), 282 (M^+, 100), 280 (28), 279 (18), 267 (22), 265 (20), 254 (10), 239 (25), 237 (11), 105 (35).

HRMS (EI): calcd. For $C_{20}H_{26}O$: 282.1984, found 282.1992.

3.4 Difunctionalization of Cyclohexene Derivatives

Synthesis of 1,1´-[cyclohex-1-ene-1,2-diylbis(thio)]dibenzene (43a)



In a dry and argon flushed flask equipped with a septum and a magnetic stirring bar, thiophenol (242 mg, 2.20 mmol) was dissolved in THF (1.0 mL). *i*PrMgCl·LiCl (**6**; 1.90 mL, 1.30 M in THF, 2.50 mmol) was added at 25 °C and the reaction mixture was stirred until no gas evolution occurred. 1,2-Dibromocyclohexene (**38**; 480 mg, 2.00 mmol) was added to the mixture followed by a second equivalent of *i*PrMgCl·LiCl (**6**; 1.70 mL, 1.30 M in THF, 2.20 mmol). The mixture was stirred for 12 h at 25 °C, and the completion of the reaction was checked by GC analysis of hydrolyzed reaction aliquots. After complete conversion to the organomagnesium reagent **42** was achieved, the reaction mixture was cooled to -20 °C and reacted with methanethiosulfonic acid S-methyl ester (315 mg, 2.50 mmol). The mixture was allowed to slowly warm up to 25 °C. The solution was quenched with a sat. aq. NH_4Cl solution, and extracted with ether (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3; pentane) yielded **43a** as a pale yellow oil (333 mg, 56%).

^{1}H-NMR (C_6D_6, 300 MHz): δ = 7.42-7.38 (m, 4 H), 7.05-6.92 (m, 6 H), 2.16-2.12 (m, 4 H), 1.30-1.25 (m, 4 H).

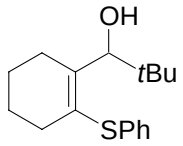
^{13}C-NMR (C_6D_6, 75 MHz): δ = 135.0, 134.3, 132.0, 129.1, 127.1, 32.6, 23.7.

IR (film): 2930 (w), 1581 (m), 1474 (m), 1438 (m), 1326 (w), 1020 (m), 914 (w), 782 (w), 736 (s), 689 (s).

MS (EI, 70 eV) ***m/z***: 300 (9), 299 (17), 298 (M^+, 100), 189 (22), 160 (10), 155 (7), 147 (41), 128 (5), 115 (4), 111 (5), 109 (6), 79 (9), 77 (9).

HRMS (EI): calcd. for $C_{18}H_{18}S_2$: 298.0850, found: 298.0844.

Synthesis of 2,2-dimethyl-1-(2-phenylsulfanylcyclohex-1-enyl) propan-1-ol (43b)



In a dry and argon flushed flask equipped with a septum and a magnetic stirring bar, thiophenol (242 mg, 2.20 mmol) was dissolved in THF (1.0 mL). *i*PrMgCl·LiCl (**6**; 1.90 mL, 1.30 M in THF, 2.50 mmol) was added at 25 °C and the reaction mixture was stirred until no gas evolution occurred. 1,2-Dibromocyclohexene (**38**; 480 mg, 2.00 mmol) was added to the mixture followed by a second equivalent of *i*PrMgCl·LiCl (**6**; 1.70 mL, 1.30 M in THF, 2.20 mmol). The mixture was stirred for 12 h at 25 °C, and the completion of the reaction was checked by GC analysis of hydrolyzed reaction aliquots. After complete conversion to the organomagnesium reagent **42** was achieved, the reaction mixture was cooled to -20 °C and reacted with pivaldehyde (215 mg, 2.50 mmol). The mixture was allowed to slowly warm up to 25 °C. The solution was quenched with a sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3; pentane) yielded **43b** as a pale yellow oil (347 mg, 63%).

^{1}H-NMR (C_6D_6, 300 MHz): δ = 7.31 (d, $^3J_{H\text{-}H}$ = 8.1 Hz, 2 H), 7.05 (t, $^3J_{H\text{-}H}$ = 7.5 Hz, 2 H), 6.94 (t, $^3J_{H\text{-}H}$ = 7.3 Hz, 1 H), 5.02 (s, 1 H), 2.58-2.45 (m, 1 H), 2.30-2.20 (m, 2 H), 2.19-2.06 (m, 1 H), 1.50-1.38 (m, 4 H), 1.04 (s, 9 H).

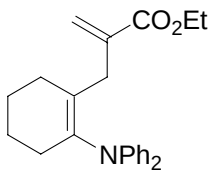
^{13}C-NMR (C_6D_6, 75 MHz): δ = 145.8, 136.6, 129.7, 129.2, 127.5, 126.1, 78.8, 36.8, 32.1, 27.5, 27.3, 24.3, 23.0.

IR (film): 2931 (s), 1583 (m), 1477 (m), 1439 (m), 1362 (w), 1192 (w), 1087 (w), 994 (s), 956 (m), 905 (w), 814 (m), 739 (s), 720 (m), 690 (s).

MS (EI, 70 eV) ***m/z***: 276 (M^+, 3), 258 (8), 243 (6), 221 (6), 220 (14), 219 (100), 217 (4), 202 (7), 201 (39), 147 (7), 141 (7), 133 (3), 127 (4), 123 (3), 115 (3), 110 (6), 109 (4), 105 (5), 97 (4), 91 (9), 83 (6), 81 (13), 79 (15), 77 (10), 69 (7), 67 (7), 57 (11), 55 (11), 41 (15).

HRMS (EI): calcd. for $C_{17}H_{24}OS$: 276.1548, found: 276.1540.

Synthesis of ethyl 2-(2-diphenylaminocyclohex-1-enylmethyl) acrylic carboxylate (45a)



In a dry and argon flushed flask equipped with a septum and a magnetic stirring bar, diphenylamine (2.20 mmol, 372 mg) was dissolved in THF (1.0 mL). *i*PrMgCl·LiCl (**6**; 1.90 mL, 1.30 м in THF, 2.50 mmol) was added at 25 °C and the reaction mixture was stirred until no gas evolution occurred. 1,2-Dibromocyclohexene (**38**; 480 mg, 2.00 mmol) was added to the mixture followed by a second equivalent of *i*PrMgCl·LiCl (**6**; 1.70 mL, 1.30 м in THF, 2.20 mmol). The mixture was stirred for 12 h at 25 °C, and the completion of the reaction was checked by GC analysis of hydrolyzed reaction aliquots. After complete conversion to the organomagnesium reagent **44** was achieved, the reaction mixture was cooled to -20 °C and transmetallated with CuCN·2LiCl (2.00 mL, 1.00 м in THF, 2.00 mmol). 2-Bromomethyl acrylic acid ethyl ester (483 mg, 2.50 mmol) was then added and the mixture was stirred for 1 h at -20 °C. The solution was quenched with a sat. aq. NH_4Cl solution followed by a 25% aq. NH_3 solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (Al_2O_3, pentane:ether/9:1) yielded **45a** as a yellow oil (357 mg, 50%).

^{1}H-NMR (C_6D_6, 600 MHz): δ = 7.19 (d, $^3J_{H\text{-}H}$ = 7.5 Hz, 4 H), 7.12 (t, $^3J_{H\text{-}H}$ = 7.9 Hz, 4 H), 6.83 (t, $^3J_{H\text{-}H}$ = 7.3 Hz, 2 H), 6.10 (s, 1 H), 5.05 (s, 1 H), 3.97 (q, $^3J_{H\text{-}H}$ = 7.1 Hz, 2 H), 3.2, (s, 2 H), 2.15-2.11 (m, 2 H), 1.99-1.96 (m, 2 H), 1.50-1.44 (m, 4 H), 0.92 (t, $^3J_{H\text{-}H}$ = 7.1 Hz, 3 H).

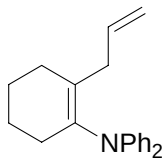
^{13}C-NMR (C_6D_6, 150 MHz): δ = 166.8, 146.8, 138.7, 137.1, 131.8, 129.4, 125.9, 121.4, 121.1, 60.5, 35.1, 28.8, 28.6, 23.8, 23.2, 14.2.

IR (film): 2930 (w), 1712 (s), 1587 (s), 1488 (s), 1294 (m), 1249 (m), 1146 (m), 1027 (m), 945 (w), 879 (w), 817 (w), 747 (s), 692 (s), 646 (w).

MS (EI, 70 eV) ***m/z***: 361 (M^+, 10), 263 (16), 262 (71), 261 (9), 260 (37), 259 (14), 258 (11), 256 (12), 249 (39), 248 (100), 247 (20), 246 (23), 244 (10), 232 (9), 219 (17), 218 (19), 217 (9), 206 (26), 204 (9), 194 (15), 180 (12), 167 (12), 91 (10), 77 (9), 44 (11).

HRMS (EI): calcd. for $C_{24}H_{27}NO_2$: 361.2042, found: 361.2039.

Synthesis of (2-allyl cyclohex-1-enyl)diphenylamine (45b)



In a dry and argon flushed flask equipped with a septum and a magnetic stirring bar, diphenylamine (372 mg, 2.20 mmol) was dissolved in THF (1.0 mL). *i*PrMgCl·LiCl (**6**; 1.90 mL, 1.30 M in THF, 2.50 mmol) was added at 25 °C and the reaction mixture was stirred until no gas evolution occurred. 1,2-Dibromocyclohexene (**38**; 480 mg, 2.00 mmol) was added to the mixture followed by a second equivalent of *i*PrMgCl·LiCl (**6**; 1.70 mL, 1.30 M in THF, 2.20 mmol). The mixture was stirred for 12 h at 25 °C, and the completion of the reaction was checked by GC analysis of hydrolyzed reaction aliquots. After complete conversion to the organomagnesium reagent **44** was achieved, the reaction mixture was cooled to -20 °C and transmetallated with CuCN·2LiCl (2.00 mL, 1.00 M in THF, 2.00 mmol). Allyl bromide (300 mg, 2.50 mmol) was then added and the mixture was stirred for 1 h at -20 °C. The solution was quenched with a sat. aq. NH_4Cl solution followed by a 25% aqueous NH_3 solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (Al_2O_3, pentane) yielded **45b** as a pale yellow oil (352 mg, 61%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.15-7.09 (m, 8 H), 6.85-6.80 (m, 2 H), 5.55-5.45 (m, 1 H), 4.89-4.81 (m, 2 H), 2.80 (d, $^3J_{H\text{-}H}$ = 7.0 Hz, 2 H), 2.12-2.05 (m, 2 H), 1.98-1.93 (m, 2 H), 1.52-1.44 (m, 4 H).

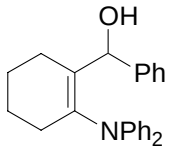
^{13}C-NMR (C_6D_6, 100 MHz): δ = 146.9, 136.2, 135.8, 133.0, 129.4, 121.3, 120.8, 116.2, 37.6, 28.7, 28.4, 23.9, 23.1.

IR (film): 2926 (w), 1586 (s), 1486 (s), 1309 (m), 1293 (m), 1247 (m), 1175 (w), 1138 (w), 995 (w), 910 (m), 746 (s), 691 (s).

MS (EI, 70 eV) ***m/z***: 290 (22), 289 (M^+, 100), 288 (37), 274 (7), 260 (15), 249 (18), 248 (99), 247 (16), 246 (20), 232 (5), 220 (6), 219 (7), 218 (10), 212 (7), 206 (15), 198 (20), 170 (7), 169 (8), 168 (8), 167 (11), 130 (7), 117 (8), 115 (6), 91 (11), 77 (18).

HRMS (EI): calcd. for $C_{21}H_{23}N$: 289.1830, found: 289.1808.

Synthesis of (2-diphenylaminocyclohex-1-enyl)phenylmethanol (45c)



In a dry and argon flushed flask equipped with a septum and a magnetic stirring bar, diphenylamine (372 mg, 2.20 mmol) was dissolved in THF (1.0 mL). *i*PrMgCl·LiCl (**6**; 1.90 mL, 1.30 M in THF, 2.50 mmol) was added at 25 °C and the reaction mixture was stirred until no gas evolution occurred. 1,2-Dibromocyclohexene (**38**; 480 mg, 2.00 mmol) was added to the mixture followed by a second equivalent of *i*PrMgCl·LiCl (**6**; 1.70 mL, 1.30 M in THF, 2.20 mmol). The mixture was stirred for 12 h at 25 °C, and the completion of the reaction was checked by GC analysis of hydrolyzed reaction aliquots. After complete conversion to the organomagnesium reagent **44** was achieved, the reaction mixture was cooled to -20 °C and reacted with benzaldehyde (265 mg, 2.50 mmol). The mixture was allowed to slowly warm up to 25 °C. The solution was quenched with a sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (Al_2O_3, pentane) yielded **45c** as a pale yellow oil (348 mg, 49%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.37-7.33 (m, 2 H), 7.23-7.18 (m, 8 H), 7.14-7.10 (m, 3 H), 6.86 (t, $^3J_{H\text{-}H}$ = 7.2 Hz, 2 H), 5.98 (s, 1 H), 2.46-2.36 (m, 1 H), 2.26-1.99 (m, 3 H), 1.47-1.32 (m, 4 H).

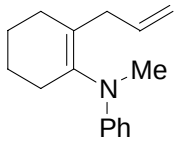
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 142.9, 138.5, 137.0, 129.6, 128.2, 127.0, 126.4, 121.7, 121.0, 118.2, 71.2, 28.6, 23.4, 23.4, 22.8.

IR (film): 3358 (w), 2934 (w), 1696 (m), 1590 (s), 1493 (s), 1448 (m), 1417 (w), 1310 (s), 1173 (w), 1143 (w), 1027 (w), 875 (w), 745 (s), 690 (s).

MS (EI, 70 eV) ***m/z***: 338 (13), 337 (44), 336 (55), 260 (10), 249 (17), 248 (80), 247 (85), 246 (31), 244 (14), 232 (10), 220 (16), 219 (68), 218 (100), 217 (37), 206 (18), 204 (14), 115 (15), 109 (14), 105 (10), 97 (17), 91 (!4), 85 (21), 83 (19), 77 (21), 71 (29), 70 (11), 69 (20), 57 (45), 56 (12), 55 (27), 43 (33).

HRMS (EI): calcd. for $C_{25}H_{25}NO$: 355.1936, found: 355.1921.

Synthesis of (2-allylcyclohex-1-enyl)-N-methylaniline (47)



In a dry and argon flushed flask equipped with a septum and a magnetic stirring bar, methyl-phenyl-amine (236 mg, 2.20 mmol) was dissolved in THF (1.0 mL). *i*PrMgCl·LiCl (**6**; 1.90 mL, 1.30 M in THF, 2.50 mmol) was added at 25 °C and the reaction mixture was stirred until no gas evolution occurred. 1,2-Dibromocyclohexene (**38**; 480 mg, 2.00 mmol) was added to the mixture followed by a second equivalent of *i*PrMgCl·LiCl (**6**; 1.70 mL, 1.30 M in THF, 2.20 mmol). The mixture was stirred for 12 h at 25 °C, and the completion of the reaction was checked by GC analysis of reaction aliquots. After complete conversion to the organomagnesium reagent **46** was achieved, the reaction mixture was cooled to -20 °C and transmetallated with CuCN·2LiCl (2.00 mL, 1.00 M in THF, 2.00 mmol). Allyl bromide (300 mg, 2.50 mmol) was then added and the mixture was stirred for 1 h at -20 °C. The solution was quenched with a sat. aq. NH_4Cl solution followed by a 25% aq. NH_3 solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (Al_2O_3, pentane) yielded **47** as a pale yellow oil (312 mg, 52%).

^{1}H-NMR (C_6D_6, 600 MHz): δ = 7.27 (t, $^3J_{H-H}$ = 8.6 Hz, 2 H), 6.80 (t, $^3J_{H-H}$ = 7.3 Hz, 1 H), 6.68 (d, $^3J_{H-H}$ = 7.9 Hz, 2 H), 5.74-5.67 (m, 1 H), 4.96 (s, 1 H), 4.94-4.93 (m, 1 H), 2.75-2.74 (m, 2 H), 2.70 (s, 3 H), 1.96-1.94 (m, 2 H), 1.90-1.88 (m, 2 H), 1.51-1.43 (m, 4 H).

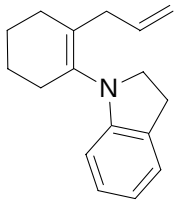
^{13}C-NMR (C_6D_6, 150 MHz): δ = 148.3, 137.7, 136.6, 132.8, 129.5, 116.8, 115.7, 112.7, 37.0, 37.0, 28.4, 25.1, 23.8, 23.1.

IR (film): 2927 (m), 1597 (s), 1574 (w), 1498 (s), 1448 (w), 1355 (m), 1329 (m), 1298 (w), 1232 (m), 1185 (w), 1117 (w), 1038 (m), 990 (m), 908 (m), 864 (m), 745 (s), 692 (s), 622 (w).

MS (EI, 70 eV) ***m/z***: 228 (14), 227 (M^+, 100), 226 (36), 212 (34), 199 (10), 198 (30), 187 (10), 186 (73), 185 (17), 170 (8), 144 (9).

HRMS (EI): calcd. for $C_{16}H_{21}N$: 227.1674, found: 227.1670.

Synthesis of 1-(2-allyl cyclohex-1-enyl)-2,3-dihydro-1H-indole (49)



In a dry and argon flushed flask equipped with a septum and a magnetic stirring bar, indoline (262 mg, 2.20 mmol) was dissolved in THF (1.0 mL). *i*PrMgCl·LiCl (**6**; 1.90 mL, 1.30 M in THF, 2.50 mmol) was added at 25 °C and the reaction mixture was stirred until no gas evolution occurred. 1,2-Dibromocyclohexene (**38**; 480 mg, 2.00 mmol) was added to the mixture followed by a second equivalent of *i*PrMgCl·LiCl (**6**; 1.70 mL, 1.30 M in THF, 2.20 mmol). The mixture was stirred for 12 h at 25 °C, and the completion of the reaction was checked by GC analysis of hydrolyzed reaction aliquots. After complete conversion to the organomagnesium reagent **48** was achieved, the reaction mixture was cooled to -20 °C and transmetallated with CuCN·2LiCl (2.00 mL, 1.00M in THF, 2.00 mmol). Allyl bromide (300 mg, 2.50 mmol) was then added and the mixture was stirred for 1 h at -20 °C. The solution was quenched with a sat. aq. NH_4Cl solution followed by a 25% aq. NH_3 solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3, pentane) yielded **49** as a pale yellow oil (240 mg, 50%).

^{1}H-NMR (C_6D_6, 600 MHz): δ = 7.10 (t, $^3J_{H-H}$ = 7.6 Hz, 1 H), 7.06 (d, $^3J_{H-H}$ = 7.1 Hz, 1 H), 6.75 (t, $^3J_{H-H}$ = 7.3 Hz, 1 H), 6.37 (d, $^3J_{H-H}$ = 7.9 Hz, 1 H), 5.83-5.76 (m, 1 H), 5.04-4.98 (m, 2 H), 3.23 (t, $^3J_{H-H}$ = 8.5 Hz, 2 H), 3.01-2.88 (s, br, 2 H), 2.74 (t, $^3J_{H-H}$ = 8.1 Hz, 2 H), 2.02-2.00 (m, 2 H), 1.92-1.85 (m, 2 H), 1.54-1.46 (m, 4 H).

^{13}C-NMR (C_6D_6, 150 MHz): δ = 151.1, 137.3, 133.5, 132.9, 129.7, 127.7, 124.7, 117.7, 115.4, 107.9, 51.5, 37.2, 28.9, 28.7, 23.8, 23.2, 23.1.

IR (film): 2925 (m), 1604 (s), 1485 (s), 1458 (m), 1373 (w), 1259 (s), 1204 (w), 994 (w), 908 (m), 741 (s), 687 (w).

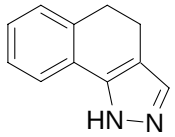
MS (EI, 70 eV) ***m/z***: 240 (20), 239 (M^+, 100), 238 (60), 224 (60), 222 (19), 212 (13), 211 (30), 210 (61), 208 (14), 198 (15), 196 (46), 194 (16), 182 (32), 181 (13), 180 (15), 168 (23), 167 (17), 130 (20), 119 (13), 118 (27), 91 (26), 79 (14), 77 (20), 44 (17), 41 (13).

HRMS (EI): calcd. for $C_{17}H_{21}N$: 239.1674, found: 239.1668.

4. Functionalization of 4,5-Dihydrobenzo[*g*]indazoles using Mg or Zn intermediates

4.1 Starting materials

Synthesis of 4,5-dihydro-2*H*-benzo[g]indazole (56)



α-Tetralone (5.4 mL, 40 mmol) and dimethylformamide dimethylacetal (10.8 mL, 80 mmol) were dissolved in DMF (50 mL) and the reaction mixture was heated under microwave irradiation at 150 °C (200 W) for 60 min. To the dark red solution was then added acetic acid (200 mL) and hydrazine hydrate (64% aq. solution, 4 mL). The reaction mixture was stirred at 25 °C for 3 h. The completion of the reaction was checked by GC analysis of hydrolyzed reaction aliquots. Most of the acetic acid was then removed by evaporation. The mixture was quenched with 50% sat. $NaHCO_3$ and then extracted with toluene. The organic phase was first washed with $NaHCO_3$ until neutral pH was obtained, then with water and was finally dried over anhydrous Na_2SO_4. After evaporation of the solvent the residue was recrystallized from heptane to yield yellow crystals (4.1 g, 60%).

m.p.: 126.0-127.8 °C.

^{1}H-NMR (C_6D_6, 300 MHz): δ = 8.05 (d, $^3J_{H\text{-}H}$ = 7.1 Hz, 1 H), 7.13-7.03 (m, 3 H), 6.98 (s, 1 H), 2.65 (t, $^3J_{H\text{-}H}$ = 7.3 Hz, 2 H), 2.45 (t, $^3J_{H\text{-}H}$ = 7.3 Hz, 2 H).

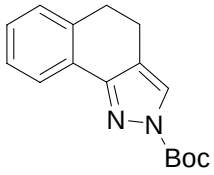
^{13}C-NMR (C_6D_6, 75 MHz): δ = 146.5, 137.0, 130.0, 130.0, 128.7, 127.6, 127.2, 122.6, 116.1, 30.1, 19.5.

IR (Diamond ATR): 3142 (m), 2927 (m), 1469 (m), 1435 (m), 1382 (w), 1320 (w), 1169 (w), 1097 (w), 1066 (m), 954 (m), 887 (w), 789 (s), 767 (s), 736 (s), 716 (s), 652 (w), 609 (m).

MS (EI, 70 eV) *m/z*, (%): 171 (9), 170 (M^+, 100), 169 (63), 155 (2), 143 (27), 142 (27), 139 (3), 115 (21), 89 (5), 70 (4).

HRMS (EI): calcd. for $C_{11}H_{10}N_2$:170.0844, found:170.0836.

Synthesis of *tert*-butyl- 4,5-dihydro-benzo[g]indazole-2-carboxylate (57)



4,5-Dihydro-2*H*-benzo[g]indazole (**56**; 4.3 g, 25 mmol) was dissolved in CH_2Cl_2 (50 mL). Di-*tert*-butyldicarbonate (7.0 g, 33 mmol) and DMAP (611 mg, 5.0 mmol) were added at 25 °C and the reaction mixture was stirred for 6 h. The completion of the reaction was checked by TLC and the excess of the unreacted di-*tert*-butyldicarbonate was removed by adding 3 drops of diethylene diamine. The reaction mixture was quenched with water and extracted with ether. The organic phase was washed with water and brine and dried over Na_2SO_4. After evaporation of the solvent the residue was purified by flash chromatography (SiO_2, pentane:ether/9:1) to give pale yellow crystals (840 mg, 91%).

m.p.: 74.7-76.0 °C

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.03-8.01 (m, 1 H), 7.79 (dd, $^4J_{H-H}$ = 1.1 Hz , 1 H), 7.28-7.19 (m, 3 H), 2.91 (t, $^3J_{H-H}$ = 7.2 Hz, 2 H), 2.76 (t, $^3J_{H-H}$ = 7.2 Hz, 2 H), 1.63 (s, 9 H).

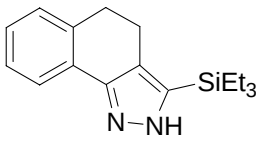
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 152.5, 148.0, 137.7, 128.8, 128.3, 128.3, 126.9, 126.5, 123.8, 119.7, 84.7, 29.1, 28.0, 19.1.

IR (Diamond ATR): 2970 (w), 2938 (w), 1737 (s), 1450 (m), 1412 (m), 1356 (s), 1251 (s), 1149 (s), 959 (s), 845 (m), 764 (m), 719 (m).

MS (EI, 70 eV) *m/z*, (%): 270 (M^+, 7), 171 (10), 170 (100), 169 (56), 143 (24), 141 (19), 115 (17), 57 (13), 41 (11).

HRMS (EI): calcd. for $C_{16}H_{18}N_2O_2$: 270.1368, found: 270.1371.

Synthesis of 3-triethylsilyl-4,5-dihydro-2*H*-benzo[g]indazole (58)



A flame dried flask was flushed with argon and charged with *tert*-butyl 4,5-dihydrobenzo[g]indazole-2-carboxylate (**57**; 1.35 g, 5.0 mmol) and THF (2.0 mL). The solution was cooled to -30 °C and TMPMgCl·LiCl (**10a**; 5.0 mL, 1.1 м in THF, 5.5 mmol)

was added dropwise. The deprotonation was followed by GC analysis of reaction aliquots previously quenched with I_2. After 2 h the deprotonation was complete and triethylsilyl chloride (904 mg, 6.0 mmol) was added at -30 °C. The reaction mixture was allowed to warm up to 25 °C. After completion of the reaction, the mixture was quenched with 50% sat. $NaHCO_3$ and was extracted with ether. The organic phase was washed with water and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography (SiO_2, pentane:ether/1:1) to give a white solid (815 mg, 60%).

m.p.: 124.6 °C-126.2 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.90 (d, $^3J_{H-H}$ = 7.6 Hz, 1 H), 7.29-7.19 (m, 3 H), 2.96 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H), 2.84 (t, $^3J_{H-H}$ = 7.2 Hz, 2 H), 1.01 (t, $^3J_{H-H}$ = 8.1 Hz, 9 H), 0.88 (q, $^3J_{H-H}$ = 7.8 Hz, 6 H).

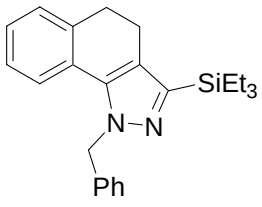
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 148.7, 136.6, 135.3, 130.0, 128.1, 127.2, 126.7, 124.2, 122.5, 30.0, 20.5, 7.3, 3.3.

IR (Diamond ATR): 2952 (w), 1738 (s), 1436 (w), 1377 (w), 1216 (m), 1064 (m), 995 (m), 891 (w), 769 (m), 723 (s).

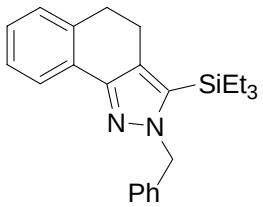
MS (EI, 70 eV) *m/z*, (%): 286 (4), 285 (16), 284 (M^+, 73), 256 (15), 255 (50), 228 (17), 227 (100), 199 (41), 170 (10), 128 (3), 114 (8), 100 (10), 59 (7).

HRMS (EI): calcd. for $C_{17}H_{24}N_2Si$: 284.1709, found: 284.1704.

Synthesis of 1-benzyl-3-triethylsilyl-4,5-dihydro-1*H*-benzo[g]indazole (59) and 2-benzyl-3-triethylsilyl-4,5-dihydro-2*H*-benzo[g]indazole (60)



59



60

A flame dried flask was flushed with argon and charged with 3-(triethylsilyl)-4,5-dihydro-2*H*-benzo[g]indazole (**58**; 3.12 g, 11 mmol) and NMP (20 mL). At 25 °C NaH 60% in oil (480 mg, 12 mmol) was added and the mixture was stirred until no gas emission occured. After 2 h, benzyl bromide (2.2 g, 13 mmol) was added and the reaction mixture was stirred for 6 h. The completion of the reaction was checked by GC analysis, which showed that the 2 regioisomers were formed in a ratio of 2:1 (**59**:**60**). The crude mixture was quenched with

water and extracted with ether. The organic phase was washed with water and brine and dried over Na_2SO_4. After evaporation of the solvent the two regioisomers were separated by flash chromatography (SiO_2, pentane:ether/8:2). In the first fraction benzo[g]indazole **59** was isolated as a pale yellow oil in 44% yield (1.8 g) whereas **60** was isolated as a pale yellow oil in the second fraction in 21% yield (860 mg).

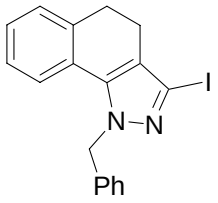
1-Benzyl-3-triethylsilyl-4,5-dihydro-1*H*-benzo[g]indazole (59):

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.38-7.36 (m, 1 H), 7.32-7.29 (m, 2 H), 7.26-7.23 (m, 2 H), 7.12-7.08 (m, 4 H), 5.70 (s, 2 H), 2.88 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H), 2.77 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H), 1.03 (t, $^3J_{H-H}$ = 7.9 Hz, 9 H), 0.89 (q, $^3J_{H-H}$ = 7.9 Hz, 6 H).
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 145.7, 138.0, 137.7, 137.5, 128.7, 128.5, 127.4, 127.2, 126.9, 126.7, 126.2, 126.1, 122.2, 54.6, 31.2, 21.1, 7.5, 3.8.
IR (Diamond ATR): 2952 (w), 2873, 1739 (s), 1454 (w), 1334 (m), 1276 (m), 1253 (m), 1154 (m), 1002 (m), 974 (w), 864 (w), 763 (m), 725 (s), 694 (s).
MS (EI, 70 eV) *m/z*, (%): 375 (26), 374 (M^+, 79), 373 (10), 347 (18), 346 (64), 345 (62), 318 (17), 317 (56), 290 (12), 289 (44), 287 (12), 284 (20), 283 (78), 256 (19), 255 (79), 253 (11), 228 (13), 227 (55), 226 (14), 225 (17), 199 (15), 198 (18), 197 (22), 195 (9), 170 (20), 169 (11), 167 (12), 143 (8), 115 (20), 110 (8), 92 (8), 91 (100), 87 (14), 59 (18).
HRMS (ESI): calcd. for $C_{24}H_{30}N_2Si$: 374.2178, found: 375.2253 $[M+H]^+$.

2-Benzyl-3-triethylsilyl-4,5-dihydro-2*H*-benzo[g]indazole (60):

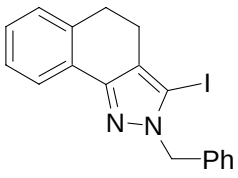
^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.88 (d, $^3J_{H-H}$ = 7.7 Hz, 1 H), 7.27-7.18 (m, 6 H), 6.96 (d, $^3J_{H-H}$ = 7.0 Hz, 2 H), 5.49 (s, 2 H), 2.96 (t, $^3J_{H-H}$ = 7.3 Hz, 2 H), 2.87 (t, $^3J_{H-H}$ = 7.6 Hz, 2 H), 0.87 (t, $^3J_{H-H}$ = 7.8 Hz, 9 H), 0.73 (q, $^3J_{H-H}$ = 7.5 Hz, 6 H).
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 147.9, 138.8, 136.2, 135.9, 130.0, 128.4, 128.0, 127.1, 127.1, 127.0, 126.8, 125.9, 122.5, 55.9, 30.0, 21.1, 7.2, 3.7.
IR (Diamond ATR): 2952 (m), 2874 (w), 1737 (s), 1454 (w), 1334 (m), 1248 (s), 1154 (s), 1001 (m), 957 (w), 892 (w), 840 (w), 723 (s), 695 (s).
MS (EI, 70 eV) *m/z*, (%): 376 (6), 375 (23), 374 (M^+, 24), 346 (30), 345 (100), 317 (6), 287 (6), 197 (6), 172 (9), 91 (31), 59 (17).
HRMS (ESI): calcd. for $C_{24}H_{30}N_2Si$: 374.2178, found: 375.2257$[M+H]^+$.

Synthesis of 1-benzyl-3-iodo-4,5-dihydro-1*H*-benzo[g]indazole (61)



A dry flask was flushed with argon and charged with 1-benzyl-3-(triethylsilyl)-4,5-dihydro-1*H*-benzo[g]indazole (**59**; 748 mg, 2.0 mmol) and CH_2Cl_2 (2.0 mL). ICl (390 mg, 2.4 mmol) was added to the solution at 0 °C. The completion of the reaction was checked by GC-analysis of hydrolyzed reaction aliquots. After 3 h, the mixture was quenched with sat. $Na_2S_2O_3$ and extracted with ether. The organic phase was washed with water and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude mixture was purified by flash chromatography (SiO_2, pentane:ether/9:1) to yield **61** as a white solid (540 mg, 70%).
m.p.: 119.1-120.8 °C.
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.36-7.26 (m, 5 H), 7.21-7.10 (m, 4 H), 5.64 (s, 2 H), 2.92 (t, $^3J_{H\text{-}H}$ = 7.4 Hz, 2 H), 2.62 (t, $^3J_{H\text{-}H}$ = 7.4 Hz, 2 H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 139.3, 137.9, 136.8, 129.0, 128.9, 128.1, 127.6, 126.9, 126.2, 126.1, 124.3, 122.5, 95.7, 55.1, 30.5, 20.9.
IR (Diamond ATR): 2932 (w), 1450 (w), 1409 (m), 1358 (w), 1307 (w), 1150 (w), 1083 (m), 907 (m), 763 (m), 726 (s), 694 (s).
MS (EI, 70 eV) *m/z*, (%): 388 (2), 387 (16), 386 (M^+, 100), 385 (29), 384 (2), 294 (4), 260 (5), 259 (24), 258 (5), 257 (4), 232 (2), 193 (3), 168 (3), 143 (3), 140 (4), 139 (6), 129 (3), 127 (2), 115 (2), 91 (63).
HRMS (EI): calcd. for $C_{18}H_{15}IN_2$: 386.0280, found: 386.0276.

Synthesis of 2-benzyl-3-iodo-4,5-dihydro-2*H*-benzo[g]indazole (62)



A dry flask was flushed with argon and charged with 2-benzyl-3-(triethylsilyl)-4,5-dihydro-2*H*-benzo[g]indazole (**60**; 380 mg, 1.0 mmol) and CH_2Cl_2 (1.0 mL). ICl (194 mg, 1.1 mmol) was added to the solution at 0 °C. The completion of the reaction was checked by GC-

analysis of hydrolyzed reaction aliquots. After 6 h, the mixture was quenched with sat. $Na_2S_2O_3$ and extracted with ether. The organic phase was washed with water and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude mixture was purified by flash chromatography (SiO_2, pentane:ether, 9:1) to yield **62** as a pale yellow solid (277 mg, 72%).

m.p.: 96.4-97.9 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.84 (d, $^3J_{H-H}$ = 7.7 Hz, 1 H), 7.32-7.30 (m, 2 H), 7.27-7.21 (m, 6 H), 5.45 (s, 2 H), 2.96 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H), 2.65 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H).

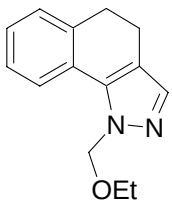
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 149.5, 136.8, 136.6, 129.3, 128.6, 128.4, 127.7, 127.7, 127.2, 126.9, 123.8, 122.1, 81.0, 55.5, 29.2, 20.6.

IR (Diamond ATR): 2913 (m), 2877 (m), 1474 (w), 1456 (w), 1373 (w), 1358 (w), 1320 (m), 1237 (m), 1068 (s), 1005 (m), 843 (m), 772 (m), 736 (s), 722 (s), 698 (s).

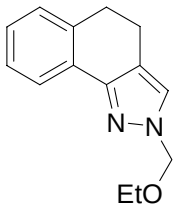
MS (EI, 70 eV) *m/z*, (%): 386 (M^+, 1), 296 (29), 295 (25), 294 (100), 293 (20), 259 (46), 230 (2), 217 (5), 203 (17), 168 (2), 140 (3), 115 (3), 91 (85), 65 (7).

HRMS (EI): calcd. for $C_{18}H_{15}IN_2$: 386.0280, found: 386.0276.

Synthesis of 1-ethoxymethyl-4,5-dihydro-1*H*-benzo[g]indazole (67) and 2-ethoxymethyl-4,5-dihydro-2*H*-benzo[g]indazole (68)



67



68

A flame dried flask was flushed with argon and charged with 4,5-dihydro-2*H*-benzo[g]indazole (**56**; 1.7 g, 10 mmol) and NMP (10 mL). At 25 °C NaH 60% in oil (450 mg, 11 mmol) was added and the mixture was stirred until no gas evolution occured. After 30 min, (chloromethoxy)ethane (1.1 g, 12 mmol) was added and the reaction mixture was stirred for 4 h at 25 °C. The completion of the reaction was checked by GC analysis, which showed that the 2 regioisomers were formed in a ratio of 1:5 (67:68). The crude mixture was quenched with water and extracted with ether. The organic phase was washed with water and brine and dried over Na_2SO_4. After evaporation of the solvent the two regioisomers were separated by flash chromatography (SiO_2, pentane:ether/9:1). In the first fraction benzo[g]indazole **67** was

isolated in 10% yield (230 mg) as yellow oil, whereas **68** was isolated in the second fraction in 50% yield (1.1 g) as a yellow oil.

1-Ethoxymethyl-4,5-dihydro-1*H*-benzo[g]indazole (67):

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.86 (d, $^{3}J_{H-H}$ = 7.8 Hz, 1 H), 7.38 (s, 1 H), 7.34-7.29 (m, 2 H), 7.24-7.21 (m, 1 H), 5.64 (s, 2 H), 3.70 (q, $^{3}J_{H-H}$ = 7.0 Hz, 2 H), 2.89 (t, $^{3}J_{H-H}$ = 7.4 Hz, 2 H), 2.71 (t, $^{3}J_{H-H}$ = 7.4 Hz, 2 H), 1.21 (t, $^{3}J_{H-H}$ = 7.0 Hz, 3 H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 138.6, 137.5, 136.2, 128.6, 127.6, 127.1, 126.9, 123.7, 119.3, 79.2, 64.2, 30.5, 19.7, 14.9.

IR (Diamond ATR): 2975 (w), 2937 (w), 1707 (w), 1514 (w), 1466 (m), 1448 (m), 1382 (m), 1303 (m), 1262 (w), 1231 (w), 1161 (w), 1089 (s), 1017 (m), 984 (m), 891 (m), 845 (m), 784 (s), 763 (s), 734 (s), 695 (s), 627 (m).

MS (EI, 70 eV) *m/z*, (%): 228 (M^+, 11), 192 (14), 184 (24), 183 (100), 169 (12), 165 (8), 143 (4), 142 (5), 128 (5), 127 (5), 115 (11), 101 (8), 83 (4), 74 (6), 69 (5), 59 (12), 57 (7), 55 (5), 45 (6), 44 (7), 43 (6), 41 (5).

HRMS (EI): calcd. for $C_{14}H_{16}N_2O$: 228.1263, found: 228.1261.

2-Ethoxymethyl-4,5-dihydro-2*H*-benzo[g]indazole (68):

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.88 (d, $^{3}J_{H-H}$ = 7.5 Hz, 1 H), 7.34 (s, 1 H), 7.27-7.19 (m, 3 H), 5.44 (s, 2 H), 3.58 (q, $^{3}J_{H-H}$ = 7.0 Hz, 2 H), 2.93 (t, $^{3}J_{H-H}$ = 7.3 Hz, 2 H), 2.77 (t, $^{3}J_{H-H}$ = 7.4 Hz, 2 H), 1.18 (t, $^{3}J_{H-H}$ = 7.0 Hz, 3 H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 148.8, 136.7, 129.6, 128.3, 127.5, 126.8, 126.3, 122.4, 117.9, 80.5, 64.6, 29.5, 19.2, 14.9.

IR (Diamond ATR): 2976 (w), 2933 (w), 1470 (m), 1439 (w), 1423 (w), 1330 (m), 1234 (m), 1141 (m), 1093 (s), 991 (m), 892 (m), 794 (m), 764 (s), 736 (m), 716 (s), 681 (w), 651 (w).

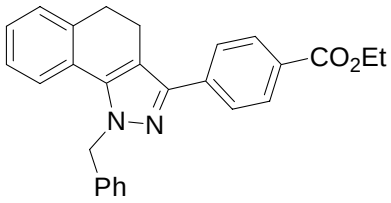
MS (EI, 70 eV) *m/z*, (%): 229 (13), 228 (M^+, 95), 184 (100), 183 (81), 181 (12), 170 (19), 169 (51), 168 (13), 143 (15), 142 (19), 140 (11), 139 (11), 128 (14), 127 (12), 116 (14), 115 (37), 59 (13).

HRMS (EI): calcd. for $C_{14}H_{16}N_2O$: 228.1263, found: 228.1261.

4.2 Preparation of functionalized 4,5-dihydrobenzo[*g*]indazoles

4.2.1 Functionalization through I/Mg-exchange

Synthesis of ethyl 4-(1-benzyl-4,5-dihydro-1*H*-benzo[g]indazol-3-yl)benzoate (65a)



According to **TP4**, the 3-magnesiated heterocycle **63** (1.00 mmol) was transmetallated with $ZnCl_2$ (1.00 mL, 1.00 M in THF, 1.00 mmol) and stirred for 30 min at -30 °C. Ethyl 4-iodobenzoate (331 mg, 1.20 mmol) was dissolved in THF (1.00 mL) and mixed with $Pd(dba)_2$ (28 mg, 0.05 mmol) and (*o*-furyl)$_3$P (23 mg, 0.10 mmol). This mixture was added to the zinc-reagent at -30 °C and the mixture was allowed to slowly warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **65a** was isolated as a white solid (277 mg, 68%).

m.p.: 117.8-119.2 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.14 (d, $^3J_{H-H}$ = 8.6 Hz, 2 H), 7.86 (d, $^3J_{H-H}$ = 8.6 Hz, 2 H), 7.35-7.26 (m, 5 H), 7.21-7.15 (m, 4 H), 5.73 (s, 2 H), 4.41 (q, $^3J_{H-H}$ = 7.2 Hz, 2 H), 2.99-2.93 (m, 4 H), 1.42 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H).

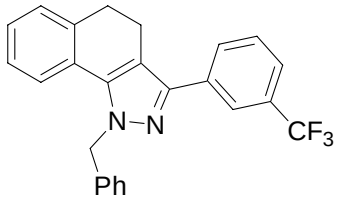
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 166.5, 146.1, 139.7, 138.1, 137.4, 137.1, 129.8, 129.1, 128.8, 128.7, 127.6, 127.5, 126.9, 126.8, 126.1, 122.3, 116.7, 60.9, 54.8, 30.9, 20.6, 14.3.

IR (Diamond ATR): 2981 (m), 1709 (s), 1611 (m), 1449 (m), 1364 (m), 1270 (s), 1099 (s), 1018 (m), 857 (m), 776 (m), 721 (s), 695 (m).

MS (EI, 70 eV) *m/z*, (%): 409 (24), 408 (M^+, 100), 407 (91), 406 (33), 393 (4), 379 (7), 363 (6), 331 (10), 317 (6), 303 (3), 289 (4), 259 (7), 244 (4), 216 (6), 215 (12), 91 (50).

HRMS (EI): calcd. for $C_{27}H_{24}N_2O_2$: 408.1838, found: 408.1826.

Synthesis of 1-benzyl-3-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-benzo[g]indazole (65b)



According to **TP4**, the 3-magnesiated heterocycle **63** (1.00 mmol) was transmetallated with $ZnCl_2$ (1.00 mL, 1.00 M in THF, 1.00 mmol) and stirred for 30 min at -30 °C. 1-Iodo-3-trifluoromethylbenzene (327 mg, 1.2 mmol) was dissolved in THF (1.00 mL) and mixed with $Pd(dba)_2$ (28 mg, 0.05 mmol) and (*o*-furyl)$_3$P (23 mg, 0.10 mmol). This mixture was added to the zinc reagent at -30 °C and the mixture was allowed to slowly warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **65b** was isolated as a white solid (238 mg, 59%).

m.p.: 80.7-82.7 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 8.07 (s, 1 H), 7.98-7.96 (m, 1 H), 7.69-7.49 (m, 3 H), 7.36-7.27 (m, 4 H), 7.23-7.17 (m, 4 H), 5.75 (s, 2 H), 2.97 (s, 4 H).

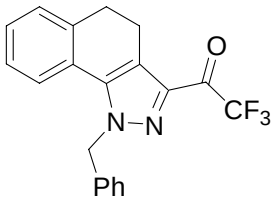
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 145.8, 139.8, 137.5, 137.1, 134.4, 130.9 (q, $J_{C\text{-}F}$ = 32.3 Hz), 130.4, 129.0, 128.9, 128.8, 127.7, 127.5, 126.9, 126.1, 126.1, 124.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.2 (q, $J_{C\text{-}F}$ = 272.3 Hz), 124.0 (q, $J_{C\text{-}F}$ = 3.7 Hz), 122.4, 118.7, 54.8, 30.9, 20.5.

IR (Diamond ATR): 1452 (m), 1325 (s), 1316 (s), 1156 (s), 1122 (s), 1073 (w), 913 (m), 807 (m), 736 (m), 727 (s), 700 (s).

MS (EI, 70 eV) *m/z*, (%): 406 (5), 405 (24), 404 (M^+, 100), 403 (80), 402 (19), 401 (5), 389 (5), 385 (4), 327 (18), 314 (4), 313 (15), 312 (3), 285 (3), 283 (6), 259 (11), 215 (3), 214 (12), 141 (4), 115 (3), 92 (6), 91 (66), 65 (6), 57 (3), 44 (19), 43 (3).

HRMS (EI): calcd. for $C_{25}H_{19}F_3N_2$: 404.1500, found: 404.1490.

Synthesis of 1-(1-benzyl-4,5-dihydro-1*H*-benzo[g]indazol-3-yl)-2,2,2-trifluoroethanone (65c)



According to **TP4**, the 3-magnesiated heterocycle **63** (1.0 mmol) was reacted with 2,2,2-trifluoro-*N*-methoxy-*N*-methylacetamide (189 mg, 1.2 mmol) at -30 °C. The mixture was slowly allowed to warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **65c** was isolated as a white solid (260 mg, 73%).

m.p.: 105.0-106.9 ° C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.39-7.30 (m, 5 H), 7.24-7.15 (m, 4 H), 5.78 (s, 2 H), 3.11 (t, $^3J_{H\text{-}H}$ = 7.6 Hz, 2 H), 2.95 (t, $^3J_{H\text{-}H}$ = 7.5 Hz, 2 H).

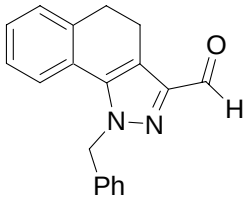
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 176.4 (q, $J_{C\text{-}F}$ = 36.1 Hz), 140.4, 140.0, 137.6, 135.5, 129.1, 128.5, 128.0, 127.0, 126.2, 125.4, 124.7, 124.7, 122.5, 116.4 (q, $J_{C\text{-}F}$ = 290.7 Hz), 56.0, 29.9, 19.7.

IR (Diamond ATR): 2981 (w), 1705 (s), 1498 (m), 1432 (m), 1320 (m), 1195 (s), 1141 (s), 1019 (m), 957 (s), 887 (s), 760 (m), 726 (s), 693 (m).

MS (EI, 70 eV) *m/z*, (%): 357 (15), 356 (M^+, 67), 355 (18), 287 (16), 279 (12), 266 (6), 265 (36), 264 (7), 259 (8), 195 (4), 168 (13), 143 (4), 139 (5), 92 (10), 91 (100), 83 (5), 71 (6), 69 (5), 65 (10), 57 (7), 44 (15), 41 (5).

HRMS (EI): calcd. for $C_{20}H_{15}F_3N_2O$: 356.1136, found: 356.1133.

Synthesis of 1-benzyl-4,5-dihydro-1*H*-benzo[g]indazole-3-carbaldehyde (65d)



According to **TP4**, the 3-magnesiated heterocycle **63** (1.0 mmol) was reacted with DMF (0.08 mL, 1.5 mmol) at -30 °C. The mixture was allowed to slowly warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **65d** was isolated as a white solid (181 mg, 63%).

m.p.: 99.3-100.5 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 10.09 (s, 1 H), 7.38-7.28 (m, 5 H), 7.23-7.14 (m, 4 H), 5.73 (s, 2 H), 3.07 (t, $^3J_{H\text{-}H}$ = 7.5 Hz, 2 H), 2.92 (t, $^3J_{H\text{-}H}$ = 7.5 Hz, 2 H).

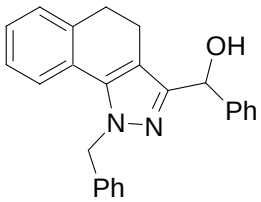
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 187.8, 146.3, 140.5, 137.9, 135.9, 129.0, 128.2, 127.9, 126.9, 126.2, 125.9, 122.3, 120.5, 55.6, 30.1, 19.3.

IR (Diamond ATR): 1738 (s), 1686 (s), 1496 (w), 1439 (m), 1365 (m), 1217 (m), 1159 (w), 1017 (m), 833 (m), 791 (s), 766 (s), 725 (s), 704 (m), 693 (m).

MS (EI, 70 eV) *m/z*, (%): 289 (18), 288 (M^+, 91), 287 (13), 260 (6), 259 (26), 211 (9), 198 (11), 197 (82), 196 (17), 170 (7), 169 (58), 142 (8), 139 (8), 115 (12), 91 (100) 89 (6), 65 (17), 43 (24).

HRMS (EI): calcd. for $C_{19}H_{16}N_2O$: 288.1263, found: 288.1258.

Synthesis of (1-benzyl-4,5-dihydro-1*H*-benzo[g]indazol-3-yl)phenylmethanol (65e)



According to **TP4**, the 3-magnesiated heterocycle **63** (1.0 mmol) was reacted with benzaldehyde (127 mg, 1.2 mmol) at -30 °C. The mixture was allowed to slowly warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/8:2) **65e** was isolated as a pale yellow oil (223 mg, 61%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.46 (d, $^3J_{H-H}$ = 7.0 Hz, 2 H), 7.36-7.31 (m, 4 H), 7.28-7.21 (m, 4 H), 7.15-7.08 (m, 4 H), 5.96 (d, $^3J_{H-H}$ = 3.8 Hz, 1 H), 5.63 (s, 2 H), 3.43 (s, br, 1 H), 2.77 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H), 2.41 (t, $^3J_{H-H}$ = 7.3 Hz, 2 H).

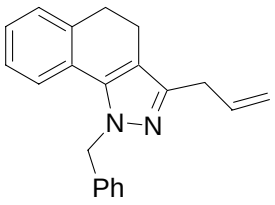
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 149.7, 142.6, 139.6, 137.6, 137.3, 137.3, 128.8, 128.7, 128.3, 127.5, 127.5, 126.8, 126.8, 126.6, 126.2, 122.2, 115.8, 70.8, 54.6, 30.6, 19.2.

IR (Diamond ATR): 2980 (m), 1496 (m), 1453 (m), 1382 (m), 1326 (m), 1261 (w), 1163 (m), 1122 (m), 764 (m), 724 (s), 695 (s).

MS (EI, 70 eV) *m/z*, (%): 367 (26), 366 (M^+, 100), 365 (8), 350 (12), 349 (14), 348 (21), 347 (31), 275 (25), 273 (10), 271 (8), 259 (22), 258 (8), 257 (25), 256 (7), 244 (7), 229 (11), 197 (7), 183 (11), 169 (19), 115 (7), 105 (21), 92 (8), 91 (98), 77 (12), 65 (7).

HRMS (EI): calcd. for $C_{25}H_{22}N_2O$: 366.1732, found: 366.1725.

Synthesis of 3-allyl-1-benzyl-4,5-dihydro-1*H*-benzo[g]indazole (65f)



According to **TP4**, the 3-magnesiated heterocycle **63** (1.0 mmol) was transmetallated with CuCN·2LiCl (1.0 mL, 1.0 м in THF, 1.0 mmol). After 15 min stirring at -30 °C, it was reacted with allyl bromide (144 mg, 1.2 mmol). The mixture was allowed to slowly warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **65f** was isolated as a pale yellow oil (225 mg, 75%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.33-7.22 (m, 5 H), 7.17-7.09 (m, 4 H), 6.08-5.98 (m, 1 H), 5.61 (s, 2 H), 5.15-5.06 (m, 2 H), 3.46 (td, $^3J_{H-H}$ = 6.2 Hz, $^4J_{H-H}$ = 1.6 Hz, 2 H), 2.89 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H), 2.64 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H).

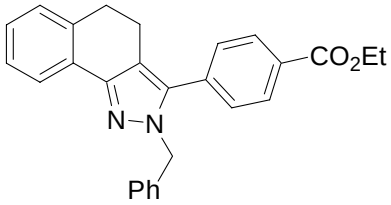
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 146.0, 138.7, 137.6, 137.6, 135.7, 128.8, 128.7, 127.3, 127.2, 127.2, 126.8, 126.1, 122.2, 117.0, 115.6, 54.3, 31.5, 30.9, 19.2.

IR (Diamond ATR): 2980 (m), 1639 (w), 1486 (m), 1453 (m), 1158 (w), 912 (m), 760 (m), 728 (s), 694 (s).

MS (EI, 70 eV) *m/z*, (%): 301 (22), 300 (M^+, 100), 299 (68), 285 (9), 271 (4), 259 (8), 257 (8), 223 (15), 210 (7), 209 (38), 207 (7), 183 (10), 181 (8), 168 (6), 165 (7), 152 (4), 127 (4), 115 (7), 91 (59), 65 (7), 44 (9).

HRMS (EI): calcd. for $C_{21}H_{20}N_2$: 300.1626, found: 300.1620.

Synthesis of ethyl 4-(2-benzyl-4,5-dihydro-2*H*-benzo[g]indazol-3-yl)benzoate (66a)



A. Through I/Mg-exchange:

According to **TP5**, the 3-magnesiated heterocycle **64** (1.00 mmol) was transmetallated with $ZnCl_2$ (1.00 mL, 1.00 M in THF, 1.00 mmol) and stirred for 30 min at -30 °C. Ethyl 4-iodobenzoate (331 mg, 1.20 mmol) was dissolved in THF (1.00 mL) and mixed with $Pd(dba)_2$ (28 mg, 0.05 mmol) and (*o*-furyl)$_3$P (23 mg, 0.10 mmol). This mixture was added to the zinc reagent at -30 °C and the mixture was allowed to slowly warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **66a** was isolated as a white solid (273 mg, 67%).

B. Through Zn-insertion:

A flame dried flask was flushed with argon and charged with LiCl (127 mg, 3.00 mmol). The salt was dried under high vacuum at 300 °C and then flushed with Ar. The process was repeated three times. The Zn-powder (196 mg, 3.00 mmol) was then added and the procedure repeated. After the mixture cooled down to 25 °C, THF (1 mL) was added and the Zn was activated by adding a few drops of 1,2-dibromoethane. The mixture was heated twice until reflux and then cooled down to 25 °C again. A few drops of trimethylsilylchloride were added and the mixture was heated to reflux again. 2-Benzyl-3-iodo-4,5-dihydro-1*H*-benzo[g]indazole (**62**) (374 mg, 1.00 mmol) was then added. After stirring at 25 °C for 14 h, GC-analysis of reaction aliquots showed complete conversion to the desired Zn-species. A second flame dried flask flushed with argon, was charged with $Pd(dba)_2$ (28.75 mg, 0.05 mmol), tfp (16.25 mg, 0.07 mmol) and THF (1 mL). After 10 min stirring ethyl 4-iodo-benzoate (415 mg, 1.5 mmol) was added, followed by the addition of the Zn-compound. The reaction mixture was stirred overnight and then quenched with sat. aq. NH_4Cl. After work up according to **TP5** and evaporation of the solvent the crude product was purified by flash chromatography (SiO_2, pentane:ether/9:1) to yield **66a** a white solid (201 mg, 52%).

m.p: 94.5-95.5 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.05 (d, $^3J_{H-H}$ = 8.3 Hz, 2 H), 7.93 (d, $^3J_{H-H}$ = 7.4 Hz, 1 H), 7.33 (d, $^3J_{H-H}$ = 8.1 Hz, 2 H), 7.30-7.20 (m, 6 H), 7.06, (d, $^3J_{H-H}$ = 7.4 Hz, 2 H), 5.37 (s, 2 H), 4.35 (q, $^3J_{H-H}$ = 7.2 Hz, 2 H), 2.96 (t, $^3J_{H-H}$ = 7.3 Hz, 2 H), 2.73 (t, $^3J_{H-H}$ = 7.3 Hz, 2 H), 1.40 (t, $^3J_{H-H}$ = 7.1 Hz, 3 H).

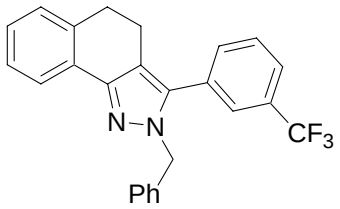
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 165.1, 147.0, 137.8, 136.7, 135.6, 133.6, 129.3, 128.8, 128.8, 128.1, 127.6, 127.3, 126.5, 126.4, 125.8, 125.7, 121.4, 115.4, 60.2, 52.5, 28.6, 18.4, 13.3.

IR (Diamond ATR): 2930 (w), 2831 (w), 1722 (s), 1612 (m), 1475 (m), 1436 (m), 1362 (m), 1310 (m), 1267 (s), 1101 (s), 1027 (m), 1008 (m), 864 (m), 770 (s), 728 (s), 701 (s).

MS (EI, 70 eV) *m/z*, (%): 409 (23), 408 (M^+, 100), 407 (48), 378 (7), 331 (8), 317 (10), 289 (6), 259 (15), 215 (12), 149 (4), 115 (4), 91 (30).

HRMS (EI): calcd. for $C_{27}H_{24}N_2O_2$: 408.1838, found: 408.1826.

Synthesis of 2-benzyl-3-(3-(trifluoromethyl)phenyl)-4,5-dihydro-2*H*-benzo[g]indazole (66b)



According to **TP5**, the 3-magnesiated heterocycle **64** (1.00 mmol) was transmetallated with $ZnCl_2$ (1.00 mL, 1.0 M in THF, 1.00 mmol) and stirred for 30 min at -30 °C. 1-Iodo-3-trifluoromethyl-benzene (327 mg, 1.20 mmol) was dissolved in THF (1.00 mL) and mixed with $Pd(dba)_2$ (28 mg, 0.05 mmol) and (*o*-furyl)$_3$P (23 mg, 0.10 mmol). This mixture was added to the zinc reagent at -30 °C and the mixture was allowed to slowly warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **66b** was isolated as a yellow oil (263 mg, 65%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.96 (d, $^3J_{H-H}$ = 7.5 Hz, 1 H), 7.65 (d, $^3J_{H-H}$ = 7.7 Hz, 1 H), 7.55-7.42 (m, 3 H), 7.33-7.22 (m, 6 H), 7.8, (d, $^3J_{H-H}$ = 7.5 Hz, 2 H), 5.35 (s, 2 H), 2.97 (t, $^3J_{H-H}$ = 7.3 Hz, 2 H), 2.72 (t, $^3J_{H-H}$ = 7.2 Hz, 2 H).

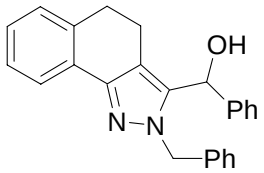
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 147.8, 138.2, 137.5, 136.5, 132.5, 131.1 (q, J_{C-F} = 32.4 Hz), 131.1, 129.7, 129.2, 128.6, 128.3, 127.6, 127.5, 126.9, 126.7, 126.1 (q, J_{C-F} = 3.8 Hz), 125.1 (q, J_{C-F} = 3.5 Hz), 123.8 (q, J_{C-F} = 272.6 Hz), 122.4, 116.4, 53.6, 29.6, 19.3.

IR (Diamond ATR): 1496 (w), 1455 (w), 1331 (s), 1319 (s), 1168 (m), 1124 (s), 1073 (m), 1025 (w), 806 (w), 775 (w), 730 (s), 701 (s).

MS (EI, 70 eV) *m/z*, (%): 406 (3), 405 (23), 404 (M^+, 100), 403 (48), 402 (5), 389 (2), 385 (3), 329 (3), 328 (12), 315 (5), 314 (16), 285 (2), 283 (3), 260 (3), 259 (15), 216 (4), 215 (10), 213 (2), 142 (3), 115 (5), 92 (5), 91 (60), 89 (2), 65 (4), 44 (2).

HRMS (EI): calcd. for $C_{25}H_{19}F_3N_2$: 404.1500, found: 404.1490.

Synthesis of (2-benzyl-4,5-dihydro-2*H*-benzo[g]indazol-3-yl)phenylmethanol (66c)



According to **TP5**, the 3-magnesiated heterocycle **64** (1.0 mmol) was reacted with benzaldehyde (127 mg, 1.2 mmol) at -30 °C. The mixture was allowed to slowly warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/8:2) **66c** was isolated as a pale yellow oil (249 mg, 68%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 8.19 (d, $^3J_{H\text{-}H}$ = 7.4 Hz, 1 H), 7.25-7.21 (m, 2 H), 7.13-6.94 (m, 11 H), 5.80 (s, 1 H), 5.21 (d, $^3J_{H\text{-}H}$ = 4.5 Hz, 2 H), 4.54 (s, br, 1 H), 2.62-2.49 (m, 2 H), 2.45-2.38 (m, 1 H), 2.25-2.15 (m, 1 H).

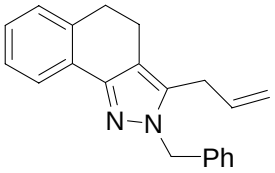
^{13}C-NMR (C_6D_6, 100 MHz): δ = 148.0, 141.7, 141.6, 140.5, 138.0, 136.7, 130.3, 128.6, 128.5, 128.5, 127.6, 127.5, 127.4, 127.0, 126.4, 122.9, 116.1, 67.0, 53.7, 29.6, 19.4.

IR (Diamond ATR): 1496 (w), 1453 (m), 1438 (m), 1290 (m), 1124 (w), 1097 (w), 1025 (m), 728 (s), 696 (s).

MS (EI, 70 eV) *m/z*, (%): 367 (22), 366 (M^+, 100), 365 (5), 364 (8), 350 (5), 349 (5), 348 (11), 347 (15), 276 (5), 275 (29), 273 (3), 271 (6), 260 (4), 259 (17), 258 (3), 257 (9), 229 (6), 228 (4), 197 (9), 169 (5), 115 (4), 105 (10), 92 (4), 91 (49), 77 (4).

HRMS (EI): calcd. for $C_{25}H_{22}N_2O$: 366.1732, found: 366.1731.

Synthesis of 3-allyl-2-benzyl-4,5-dihydro-2*H*-benzo[g]indazole (66d)



According to **TP5**, the 3-magnesiated heterocycle **64** (1.0 mmol) was transmetallated with CuCN·2LiCl (1.0 mL, 1.0 M in THF, 1.0 mmol). After 15 min stirring at -30 °C, it was reacted with allyl bromide (144 mg, 1.2 mmol). The mixture was slowly allowed to warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **66d** was isolated as a pale yellow solid (222 mg, 74%).

m.p.: 60.8-62.4 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.90 (d, $^3J_{H-H}$ = 7.6 Hz, 1 H), 7.32-7.18 (m, 6 H), 7.13-7.11 (m, 2 H), 5.81-5.71 (m, 1 H), 5.36 (s, 2 H), 5.07-4.97 (m, 2 H), 3.28 (td, $^3J_{H-H}$ = 5.8 Hz, $^4J_{H-H}$ = 1.6 Hz, 2 H), 2.95 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H), 2.68 (t, $^3J_{H-H}$ = 7.2 Hz, 2 H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 147.1, 137.5, 136.5, 135.5, 133.4, 130.1, 128.6, 128.2, 127.4, 127.1, 126.7, 126.5, 122.1, 116.5, 115.5, 53.2, 29.6, 28.6, 18.9.

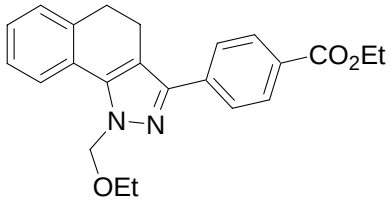
IR (Diamond ATR): 2942 (w), 1738 (s), 1640 (w), 1485 (m), 1456 (m), 1379 (m), 1319 (m), 1207 (m), 917 (m), 765 (m), 736 (s), 699 (m).

MS (EI, 70 eV) *m/z*, (%): 301 (23), 300 (M^+, 100), 299 (37), 298 (6), 285 (8), 271 (10), 259 (13), 258 (4), 257 (10), 223 (18), 210 (7), 209 (34), 207 (6), 183 (6), 181 (6), 178 (4), 168 (5), 165 (7), 152 (5), 115 (7), 92 (6), 91 (62), 83 (4), 65 (8), 44 (15).

HRMS (EI): calcd. for $C_{21}H_{20}N_2$: 300.1626, found: 300.1622.

4.2.2 Functionalization through deprotonation reactions

Synthesis of ethyl 4-(1-ethoxymethyl-4,5-dihydro-1*H*-benzo[g]indazol-3-yl)benzoate (70a)



According to **TP6**, the 3-zincated heterocycle **69** (1.00 mmol) was transmetallated with $ZnCl_2$ (1.0 mL, 1.0 M in THF, 1.0 mmol) and stirred for 10 min at 25 °C. Ethyl 4-iodobenzoate (331 mg, 1.20 mmol) was dissolved in THF (1.0 mL) and mixed with $Pd(dba)_2$ (28 mg, 0.05 mmol) and (*o*-furyl)$_3$P (23 mg, 0.10 mmol). This mixture was added to the zinc reagent **69** at 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **70a** was isolated as a white solid (233 mg, 62%).

m.p.: 114.2-115.6 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 8.11 (d, $^3J_{H-H}$ = 8.1 Hz, 2 H), 7.93 (d, $^3J_{H-H}$ = 7.7 Hz, 1 H), 7.80 (d, $^3J_{H-H}$ = 8.3 Hz, 2 H), 7.36-7.32 (m, 2 H), 7.28-7.26 (m, 1 H), 5.71 (s, 2 H), 4.40 (q, $^3J_{H-H}$ = 7.2 Hz, 2 H), 3.76 (q, $^3J_{H-H}$ = 7.0 Hz, 2 H), 2.93 (s, 4 H), 1.41 (t, $^3J_{H-H}$ = 7.1 Hz, 3 H), 1.23 (t, $^3J_{H-H}$ = 7.0 Hz, 3 H).

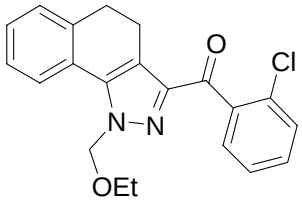
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 166.5, 146.2, 140.3, 137.9, 137.3, 129.9, 129.4, 128.5, 127.9, 127.3, 127.0, 126.9, 123.9, 117.3, 79.5, 64.4, 61.0, 30.6, 20.5, 14.9, 14.4.

IR (Diamond ATR): 1707 (s), 1611 (m), 1444 (w), 1387 (w), 1366 (w), 1277 (s), 1228 (w), 1178 (w), 1112 (m), 1085 (s), 1020 (m), 862 (m), 806 (w), 780 (m), 765 (m), 722 (s), 706 (m), 650 (w).

MS (EI, 70 eV) *m/z*, (%): 376 (M^+, 5), 332 (30), 331 (100), 303 (13), 258 (4), 216 (4), 143 (3), 115 (3).

HRMS (EI): calcd. for $C_{23}H_{24}N_2O_3$: 376.1787, found: 376.1777.

Synthesis of (2-chloro-phenyl)-(1-ethoxymethyl-4,5-dihydro-1*H*-benzo[g]indazol-3-yl)-methanone (70b)



According to **TP6**, the 3-zincated heterocycle **69** (1.0 mmol) was transmetallated with CuCN·2LiCl (1.0 mL, 1.0 м in THF, 1.0 mmol) at -20 °C. After 15 min stirring at -20 °C, it was reacted with 2-chlorobenzoyl chloride (209 mg, 1.2 mmol). The mixture was slowly allowed to warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **70b** was isolated as a pale yellow solid (219 mg, 55%).

m.p.: 131.8-133.6 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.89 (d, $^3J_{H-H}$ = 7.7 Hz, 1 H), 7.55 (d, $^3J_{H-H}$ = 7.5Hz, 1 H), 7.45-7.39 (m, 2 H), 7.36-7.32 (m, 3 H), 7.29-7.26 (m, 1 H), 5.64 (s, 2 H), 3.67 (q, $^3J_{H-H}$ = 7.0 Hz, 2 H), 3.07 (t, $^3J_{H-H}$ = 7.6 Hz, 2 H), 2.94 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H), 1.19 (t, $^3J_{H-H}$ = 7.0 Hz, 3 H).

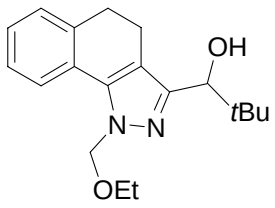
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 190.3, 145.3, 140.6, 139.0, 137.5, 131.7, 131.1, 130.0, 129.8, 128.7, 128.3, 127.2, 126.2, 126.1, 123.7, 122.5, 80.0, 64.5, 30.0, 19.8, 14.8.

IR (Diamond ATR): 2980 (w), 2931 (w), 2880 (w), 1648 (m), 1589 (w), 1435 (m), 1356 (w), 1309 (w), 1274 (w), 1193 (w), 1162 (w), 1111 (m), 1090 (s), 1057 (m), 958 (m), 892 (m), 807 (m), 757 (s), 735 (s).

MS (EI, 70 eV) *m/z*, (%): 368 (14), 367 (10), 366 (M^+, 41), 324 (19), 323 (30), 322 (55), 321 (71), 310 (9), 309 (31), 308 (17), 307 (52), 306 (9), 293 (11), 287 (21), 286 (9), 285 (25), 272 (10), 227 (8), 216 (9), 215 (20), 197 (24), 195 (15), 184 (15), 183 (96), 182 (10), 181 (34), 169 (17), 154 (9), 141 (33), 139 (100), 115 (14), 113 (11), 111 (32), 75 (10).

HRMS (EI): calcd. for $C_{21}H_{19}ClN_2O_2$: 366.1135, found: 366.1129

Synthesis of 1-(1-ethoxymethyl-4,5-dihydro-1*H*-benzo[g]indazol-3-yl)-2,2-dimethyl-propan-1-ol (70c)



According to **TP7**, the 3-magnesiated heterocycle **71** (1.0 mmol) was reacted with pivaldehyde (103 mg, 1.2 mmol) at -20 °C. The mixture was slowly allowed to warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/8:2) **71** was isolated as a white solid (161 mg, 60%).

m.p.: 93.2-94.3 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.86 (d, $^3J_{H-H}$ = 7.5 Hz, 1 H), 7.33-7.29 (m, 2 H), 7.24-7.23 (m, 1 H), 5.66-5.58 (m, 2 H), 4.45 (s, 1 H), 3.70 (q, $^3J_{H-H}$ = 7.0 Hz, 2 H), 2.87 (t, $^3J_{H-H}$ = 7.2 Hz, 2 H), 2.70-2.64 (m, 2 H), 1.21 (t, $^3J_{H-H}$ = 7.0 Hz, 3 H), 0.96 (s, 9 H).

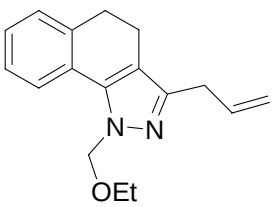
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 148.6, 139.3, 137.6, 130.1, 128.5, 127.8, 127.2, 123.9, 117.4, 79.0, 76.0, 64.2, 36.9, 30.6, 25.8, 20.2, 15.0.

IR (Diamond ATR): 3258 (m), 2923 (s), 2854 (s), 1476 (m), 1458 (m), 1447 (m), 1358 (m), 1310 (w), 1296 (w), 1260 (w), 1173 (w), 1070 (s), 1008 (s), 930 (w), 897 (w), 828 (m), 782 (m), 766 (m), 737 (m), 716 (w), 652 (w).

MS (EI, 70 eV) *m/z*, (%): 314 (12), 258 (15), 257 (19), 212 (13), 211 (100), 199 (10), 59 (61)**.**

HRMS (EI): calcd. for $C_{19}H_{26}O_2N_2$: 314.1994, found: 314.1986.

Synthesis of 3-allyl-1-ethoxymethyl-4,5-dihydro-1*H*-benzo[g]indazole (70d)



According to **TP7**, the 3-magnesiated heterocycle **71** (1.0 mmol) was transmetallated with CuCN·2LiCl (1.0 mL, 1.0 м in THF, 1.0 mmol) at -20 °C. After 15 min stirring at -20 °C, it was reacted with allyl bromide (144 mg, 1.2 mmol). The mixture was allowed to slowly warm

up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **70d** was isolated as a white solid (182 mg, 68%).

m.p.: 114.2-115.6 °C.

^{1}H-NMR (C_6D_6, 400 MHz): δ = 8.06 (d, $^3J_{H-H}$ = 7.6 Hz, 1 H), 7.14-7.12 (m, 1 H), 7.08-7.01 (m, 2 H), 6.13-6.03 (m, 1 H), 5.41 (s, 2 H), 5.14-5.03 (m, 2 H), 3.62 (t, $^3J_{H-H}$ = 7.0 Hz, 2 H), 3.44 (td, $^3J_{H-H}$ = 6.5 Hz, $^4J_{H-H}$ = 1.6 Hz, 2 H), 2.65 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H), 2.41 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H), 0.99 (t, $^3J_{H-H}$ = 7.0 Hz, 3 H).

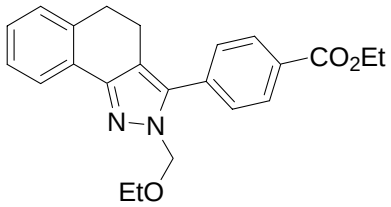
^{13}C-NMR (C_6D_6, 100 MHz): δ = 146.1, 139.3, 137.4, 136.3, 128.8, 128.0, 127.6, 127.4, 124.1, 117.7, 115.5, 79.2, 64.3, 31.8, 30.9, 19.5, 15.0.

IR (Diamond ATR): 2976 (w), 2933 (w), 2896 (w), 1483 (m), 1446 (m), 1368 (w), 1310 (m), 1263 (w), 1222 (w), 1169 (w), 1088 (s), 1017 (m), 934 (m), 912 (s), 835 (m), 759 (s), 734 (m), 700 (m).

MS (EI, 70 eV) *m/z*, (%): 268 (M^+, 7), 261 (3), 225 (3), 224 (23), 223 (100), 222 (2), 221 (7), 210 (2), 209 (4), 207 (3), 196 (4), 195 (4), 183 (3), 181 (5), 169 (3), 168 (3), 165 (3), 154 (3), 142 (2), 128 (2), 115 (4).

HRMS (EI): calcd. for $C_{17}H_{20}N_2O$: 268.1576, found: 268.1575.

Synthesis of ethyl 4-(2-ethoxymethyl-4,5-dihydro-2*H*-benzo[g]indazol-3-yl)benzoate (73a)



According to **TP8**, the 3-magnesiated heterocycle **72** (1.0 mmol) was transmetallated with $ZnCl_2$ (1.0 mL, 1.0 M in THF, 1.0 mmol) and stirred for 30 min at 0 °C. Ethyl 4-iodobenzoate (331 mg, 1.2 mmol) was dissolved in THF (1.0 mL) and mixed with $Pd(dba)_2$ (28 mg, 0.05 mmol) and (*o*-furyl)$_3$P (23 mg, 0.10 mmol). This mixture was added to the zinc reagent at 0 °C, and the mixture was allowed to slowly warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **73a** was isolated as a white solid (350 mg, 93%).

m.p.: 117.7-119.8 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 8.16 (d, $^3J_{H-H}$ = 8.1 Hz, 2 H), 7.94 (d, $^3J_{H-H}$ = 7.5Hz, 1 H), 7.65 (d, $^3J_{H-H}$ = 8.3 Hz, 2 H), 7.31-7.28 (m, 1 H), 7.24-7.23 (m, 2 H), 5.44 (s, 2 H), 4.41 (q,

$^{3}J_{H\text{-}H}$ = 7.2 Hz, 2 H), 3.73 (q, $^{3}J_{H\text{-}H}$ = 7.0 Hz, 2 H), 2.95 (t, $^{3}J_{H\text{-}H}$ = 7.2 Hz, 2 H), 2.78 (t, $^{3}J_{H\text{-}H}$ = 7.3 Hz, 2 H), 1.41 (t, $^{3}J_{H\text{-}H}$ = 7.1 Hz, 3 H), 1.21 (t, $^{3}J_{H\text{-}H}$ = 7.0 Hz, 3 H).

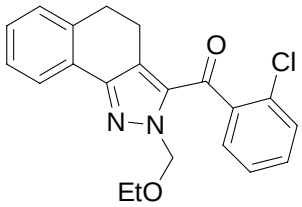
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 166.2, 148.1, 139.1, 136.8, 134.1, 130.3, 129.9, 129.3, 129.2, 128.4, 127.9, 126.9, 122.7, 117.0, 78.3, 64.7, 61.2, 29.5, 19.6, 15.0, 14.3.

IR (Diamond ATR): 2927 (m), 1718 (s), 1610 (m), 1438 (m), 1367 (w), 1304 (w), 1271 (s), 1220 (w), 1170 (w), 1099 (s), 1076 (s), 1027 (m), 995 (w), 864 (m), 831 (m), 771 (s), 732 (s), 704 (s).

MS (EI, 70 eV) *m/z*, (%): 376 (M^+, 5), 334 (5), 333 (31), 332 (100), 303 (10), 289 (2), 273 (1), 258 (4), 244 (2), 215 (6), 202 (2), 189 (1), 143 (3), 142 (2), 128 (2), 115 (3), 97 (1), 59 (1).

HRMS (EI): calcd. for $C_{23}H_{24}N_2O_3$: 376.1787, found: 376.1789.

Synthesis of (2-chloro phenyl)-(2-ethoxymethyl-4,5-dihydro-2*H*-benzo[g]indazol-3-yl)-methanone (73b)



According to **TP8**, the 3-magnesiated heterocycle **72** (1.0 mmol) was transmetallated with CuCN·2LiCl (1.0 mL, 1.0 м in THF, 1.0 mmol) at -20 °C. After 15 min stirring at -20 °C, it was reacted with 2-chlorobenzoyl chloride (209 mg, 1.2 mmol). The mixture was slowly allowed to warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/9:1) **73b** was isolated as a pale yellow solid (220 mg, 60%).

m.p.: 96.9-98.4 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.92 (d, $^{3}J_{H\text{-}H}$ = 7.7 Hz, 1 H), 7.47-7.38 (m, 4 H), 7.27 (t, $^{3}J_{H\text{-}H}$ = 7.5 Hz 1 H), 7.21 (t, $^{3}J_{H\text{-}H}$ = 7.4 Hz 1 H), 7.15 (d, $^{3}J_{H\text{-}H}$ = 7.5 Hz, 1 H), 5.93 (s, 2 H), 3.65 (q, $^{3}J_{H\text{-}H}$ = 7.0 Hz, 2 H), 2.74 (t, $^{3}J_{H\text{-}H}$ = 7.4 Hz, 2 H), 2.14 (t, $^{3}J_{H\text{-}H}$ = 7.4 Hz, 2 H), 1.19 (t, $^{3}J_{H\text{-}H}$ = 7.0 Hz, 3 H).

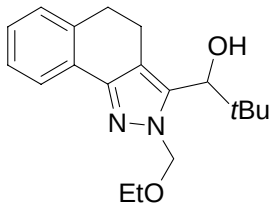
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 185.0, 148.1, 139.0, 136.0, 135.4, 131.9, 131.3, 130.3, 129.0, 128.6, 128.2, 128.1, 127.3, 127.0, 124.1, 122.6, 80.1, 64.8, 28.7, 19.9, 15.0.

IR (Diamond ATR): 1658 (s), 1590 (w), 1426 (s), 1320 (w), 1281 (m), 1235 (w), 1093 (s), 1057 (m), 1031 (m), 915 (s), 836 (m), 760 (s), 735 (s), 643 (m).

MS (EI, 70 eV) *m/z*, (%): 366 (M^+, 39), 337 (17), 323 (22), 322 (18), 321 (64), 309 (34), 308 (16), 307 (22), 293 (21), 288 (15), 287 (72), 286 (14), 285 (28), 227 (17), 215 (19), 197 (29), 183 (71), 181 (26), 169 (24), 141 (30), 139 (100), 115 (15), 111 (31), 74 (14), 59 (25).

HRMS (EI): calcd. for $C_{21}H_{19}ClN_2O_2$: 366.1135, found: 366.1129.

Synthesis of 1-(2-ethoxymethyl-4,5-dihydro-2*H*-benzo[g]indazol-3-yl)-2,2-dimethyl-propan-1-ol (73c)



According to **TP8**, the 3-magnesiated heterocycle **72** (1.0 mmol) was reacted with pivaldehyde (103 mg, 1.2 mmol) at 0 °C. The mixture was slowly allowed to warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/8:2) **73c** was isolated as a pale yellow solid (220 mg, 70%).

m.p.: 93.9-96.0 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.84 (d, $^3J_{H-H}$ = 7.3 Hz, 1 H), 7.26-7.24 (m, 1 H), 7.21-7.18 (m, 2 H), 5.68-5.66 (m, 1 H), 5.50-5.48 (m, 1 H), 4.71 (s, 1 H), 3.57-3.51 (m, 2 H), 2.89 (t, $^3J_{H-H}$ = 7.2 Hz, 2 H), 2.78-2.70 (m, 2 H), 1.12 (t, $^3J_{H-H}$ = 7.1 Hz, 3 H), 0.99 (s, 9 H).

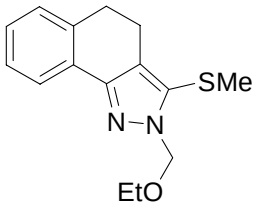
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 147.8, 139.2, 136.8, 129.6, 128.2, 127.6, 126.8, 122.4, 117.6, 80.0, 75.0, 64.6, 38.0, 29.6, 26.1, 20.8, 14.8.

IR (Diamond ATR): 3257 (w), 2948 (w), 2482 (w), 1442 (w), 1359 (w), 1296 (m), 1244 (w), 1199 (w), 1104 (s), 1088 (s), 1063 (m), 1013 (m), 896 (w), 872 (m), 760 (m), 739 (m), 715 (m).

MS (EI, 70 eV) *m/z*, (%): 314 (M^+, 3), 269 (2), 257 (7), 212 (13), 211 (100), 199 (3), 183 (4), 169 (3), 154 (1), 142 (2), 127 (1), 115 (3), 59 (5), 44 (2), 41 (2).

HRMS (EI): calcd. for $C_{19}H_{26}N_2O_2$: 314.1994, found: 314.2000.

Synthesis of 2-ethoxymethyl-3-methylsulfanyl-4,5-dihydro-2*H*-benzo[g]indazole (73d)



According to **TP8**, the 3-magnesiated heterocycle **72** (1.0 mmol) was reacted with methanethiosulfonic acid *S*-methyl ester (152 mg, 1.2 mmol) at 0 °C. The mixture was allowed to slowly warm up to 25 °C. After purification by flash chromatography (SiO_2, pentane:ether/8:2) **73d** was isolated as a yellow oil (227 mg, 83%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.88 (d, $^3J_{H-H}$ = 7.3 Hz, 1 H), 7.29-7.20 (m, 3 H), 5.64 (s, 2 H), 3.64 (t, $^3J_{H-H}$ = 7.0 Hz, 2 H), 2.96 (t, $^3J_{H-H}$ = 7.4 Hz, 2 H), 2.82-2.77 (m, 2 H), 2.34 (s, 3 H), 1.17 (t, $^3J_{H-H}$ = 7.0 Hz, 3 H).

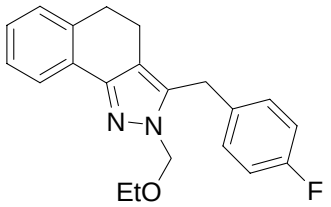
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 148.2, 136.8, 132.1, 129.1, 128.4, 128.0, 126.9, 122.7, 122.5, 67.9, 64.5, 29.2, 19.5, 19.3, 15.0.

IR (Diamond ATR): 2929 (w), 1472 (m), 1438 (m), 1296 (m), 1278 (m), 1240 (m), 1098 (s), 1068 (s), 1028 (w), 973 (w), 892 (w), 825 (m), 772 (s), 726 (s), 685 (w).

MS (EI, 70 eV) *m/z*, (%): 275 (3), 274 (M^+, 20), 231 (7), 230 (24), 229 (100), 227 (9), 216 (5), 215 (13), 197 (14), 187 (4), 184 (2), 183 (14), 182 (10), 181 (18), 171 (14), 169 (10), 168 (9), 156 (6), 154 (6), 153 (4), 152 (3), 142 (5), 141 (3), 140 (5), 139 (4), 128 (12), 127 (8), 117 (3), 116 (4), 115 (8), 89 (4), 59 (6), 43 (2).

HRMS (EI): calcd. for $C_{15}H_{18}N_2OS$: 274.1140, found: 274.1133.

Synthesis of 2-ethoxymethyl-3-(4-fluorobenzyl)-4,5-dihydro-2*H*-benzo[g]indazole (73e)



According to **TP12** benzo[g]indazole **73d** (275 mg, 1.0 mmol), dissolved in THF (1.0 mL) was reacted with 4-fluorobenzylzinc chloride (2.1 mL, 0.72 м in THF in THF, 1.5 mmol). The reaction mixture was heated to 45 °C for 12 h. Purification by flash chromatography (SiO_2, pentane:EtOAc/95:5) afforded the desired product **73e** as a pale yellow oil (208 mg, 62%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 8.33 (d, $^{3}J_{H-H}$ = 7.7 Hz, 1 H), 7.22-7.18 (m, 2 H), 7.10-7.07 (m, 2 H), 6.78 (s, 2 H), 6.76-6.75 (m, 1 H), 5.18 (s, 2 H), 3.71 (s, 2 H), 3.42 (q, $^{3}J_{H-H}$ = 7.0 Hz, 2 H), 2.68 (t, $^{3}J_{H-H}$ = 7.3 Hz, 2 H), 2.30 (t, $^{3}J_{H-H}$ = 7.3 Hz, 2 H), 0.93 (t, $^{3}J_{H-H}$ = 7.0 Hz, 3 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 162.0 (d, $^{1}J_{C-F}$ = 244.4 Hz), 147.9, 136.8, 134.0 (d, $^{3}J_{C-F}$ = 3.4 Hz), 130.9, 130.1, 130.0, 128.6, 127.7, 127.3, 123.0, 116.7, 115.5 (d, $^{2}J_{C-F}$ = 21.4 Hz), 78.8, 64.3, 29.9, 29.2, 19.3, 14.9.

IR (film): 2929 (w), 1602 (m), 1508 (s), 1483 (m), 1440 (m), 1357 (m), 1309 (m), 1284 (m), 1220 (s), 1157 (m), 1081 (s), 1016 (m), 891 (w), 834 (m), 767 (s), 733 (m).

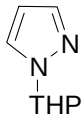
MS (EI, 70 eV) *m/z*, (%): 336 (M^+, 13), 293 (7), 292 (39), 291 (100), 290 (3), 289 (6), 277 (6), 233 (4), 197 (4), 183 (6), 181 (5), 169 (4), 115 (7), 109 (17), 97 (5), 83 (6), 71 (6), 70 (4), 69 (8), 57 (10), 56 (4), 55 (9), 40 (19), 38 (9), 37 (8).

HRMS (EI): calcd. for $C_{21}H_{21}FN_2O$: 336.1638, found: 336.1623.

5. Synthesis of Fully Substituted Pyrazoles via Regio- and Chemoselective Metallations

5.1 Starting materials

Synthesis of 1-(tetrahydropyran-2-yl)-1*H*-pyrazole (74)[101]



In a flask equipped with a magnetic stirring bar and a reflux condenser, a mixture of pyrazole (14.3 g, 210.0 mmol), 3,4-dihydro-2*H*-pyran (29 mL, 320.0 mmol), and trifluoroacetic acid (0.1 mL, 1.3 mmol) was refluxed for 5 h. Addition of sodium hydride (60% in oil; 200 mg, 8.0 mmol) and distillation (70 °C, 1.1 mbar) gave 1-tetrahydropyran-2-yl-pyrazole as a colourless oil (30.34 g, 94%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.57 (d, $^3J_{H\text{-}H}$ = 2.4 Hz, 1 H), 7.51 (d, $^3J_{H\text{-}H}$ = 0.7 Hz, 1 H), 6.25 (s, 1 H), 5.37-5.33 (m, 1 H), 4.04-3.99 (m, 1 H), 3.69-3.61 (m, 1 H), 2.17-1.98 (m, 3 H), 1.68-1.54 (m, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.4, 127.4, 105.8, 87.3, 67.6, 30.3, 24.8, 22.3.

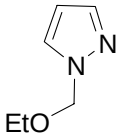
IR (Diamond ATR): 2943 (m), 2856 (w), 1382 (m), 1207 (m), 1195 (m), 1176 (m), 1082 (s), 1037 (s), 962 (s), 919 (s), 876 (s), 749 (s), 621 (s).

MS (70 eV, EI): ***m/z* (%):** 152 (M^+, 15), 124 (38), 85 (100), 84 (76), 69 (68).

HRMS (EI): calcd. for $C_8H_{12}N_2O$: 152.0950, found: 152.0945.

[101] Young, M. B.; Barrow, J. C.; Glass, K. L.; Lundell, G. F.; Newton, C. L.; Pellicore, J. M.; Rittle, K. E.; Selnick, H. G.; Stauffer, K. J.; Vacca, J. P.; Williams, P. D.; Bohn, D.; Clayton, F. C.; Cook, J. J.; Krueger, J. A.; Kuo, L. C.; Lewis, S. D.; Lucas, B. J.; McMasters, D. R.; Miller-Stein, C.; Pietrak, B. L.; Wallace, A. A.; White, R. B.; Wong, B.; Yan, Y.; Nantermet, P. G. *J. Med. Chem.* **2004**, *47*, 2995.

Synthesis of 1-ethoxymethyl-1*H*-pyrazole (75)



A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with 1*H*-pyrazole (3.4 g, 50 mmol) dissolved in THF (50 mL). At 25 °C NaH (60% in oil; 1.32 g, 55 mmol) was added and the mixture was stirred for 1 h. The reaction mixture was then cooled to 0 °C followed by addition of ethoxymethyl chloride (5.16 mL, 55 mmol). The completion of the reaction was checked by GC analysis of hydrolyzed reaction aliquots. After 2 h stirring the mixture was quenched with brine and extracted with EtOAc. The organic extracts were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude residue was purified by distillation (95 °C, 101 mbar), producing a colourless oil (4.95 g, 78 %).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.56 (d, $^3J_{H\text{-}H}$ = 2.4 Hz, 1 H), 7.54 (d, $^3J_{H\text{-}H}$ = 2.0 Hz, 1 H), 6.32 (t, $^3J_{H\text{-}H}$ = 2.0 Hz, 1 H), 5.44 (s, 2 H), 3.54-3.47 (q, $^3J_{H\text{-}H}$ = 7.1 Hz, 2 H), 1.15 (t, $^3J_{H\text{-}H}$ = 7.1 Hz, 3 H).

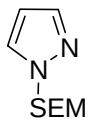
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.9, 129.4, 106.8, 80.3, 64.7, 14.8

IR (Diamond ATR): 2980 (w), 1737 (m), 1715 (m), 1517 (m), 1383 (s), 1289 (s), 1242 (m), 1100 (s), 1085 (s), 1049 (s), 1021 (s), 964 (m), 743 (s), 617 (s).

MS (70 eV, EI): ***m/z* (%):** 126 (M^+, 2), 83 (11), 82 (33), 68 (100), 59 (40).

HRMS(EI): calcd. for $C_6H_{10}N_2O$: 127.0871, found: 127.0860

Synthesis of 1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrazole (76)[102]



A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with 1*H*-pyrazole (1.9 g, 28 mmol) dissolved in THF (30 mL). At 25 °C NaH (60% in oil; 720 mg, 31 mmol) was added and the mixture was stirred for 1 h. The reaction mixture was then cooled to 0 °C followed by addition of (trimethylsilyl)-ethoxymethyl chloride (5.50 mL, 31 mmol). The completion of the reaction was checked by GC analysis of

[102] Fugina, N.; Holzer, W.; Wasicky, M. *Heterocycles* **1992**, *34*, 303.

hydrolyzed reaction aliquots. After 2 h stirring the mixture was quenched with brine and extracted with EtOAc (3 x 50 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude residue was purified by distillation (174-180 °C, 100 mbar), furnishing **76** as a colourless oil (4.6 g, 83 %)

^{1}H-NMR (C_6D_6, 300 MHz): δ = 7.53 (d, $^3J_{H-H}$ = 1.8 Hz, 1 H), 7.10 (d, $^3J_{H-H}$ = 2.3 Hz, 1 H), 6.07 (t, $^3J_{H-H}$ = 2.0 Hz, 1 H), 5.10 (s, 2 H), 3.52 (t, $^3J_{H-H}$ = 7.9 Hz, 2 H), 0.80 (t, $^3J_{H-H}$ = 7.9 Hz, 2 H), -0.10 (s, 9 H).

^{13}C-NMR (C_6D_6, 75 MHz): δ = 139.8, 129.1, 106.7, 80.1, 66.6, 17.8, -1.4.

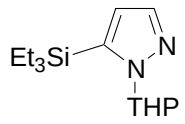
IR (Diamond ATR): 1517 (m), 1391 (m), 1377 (m), 1288 (m), 1248 (s), 1085 (s), 1024 (w), 964 (w), 916 (m), 858 (m), 832 (s), 745 (s), 693 (m), 617 (m).

MS (EI, 70 eV) ***m/z,*** (%): 198 (M^+, 1), 155 (14), 125 (100), 115 (8), 98 (12), 97 (9), 82 (49), 81 (56), 73 (46), 70 (5), 69 (4), 59 (4), 43 (5).

HRMS (EI): calcd. for $C_9H_{18}N_2OSi$: 198.1188, found: 198.1202.

5.2 Preparation of C5-substituted pyrazoles

Synthesis of 1-(tetrahydropyran-2-yl)-5-triethylsilyl-1*H*-pyrazole (80a)



According to **TP9,** pyrazole **74** (3.0 g, 20 mmol) dissolved in THF (20 mL) was treated with TMPMgCl·LiCl (**10a**; 20 mL, 1.1 M in THF, 22 mmol) at 25 °C. After stirring for 1 h, triethylsilyl chloride (3.6 mL, 22 mmol) was added to the mixture. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) afforded the product as a yellow oil (5.06 g, 95%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.58 (d, $^3J_{H-H}$ = 1.5 Hz, 1 H), 6.39 (d, $^3J_{H-H}$ = 1.7 Hz, 1 H), 5.27-5.23 (m, 1 H), 4.07-4.00 (m, 1 H), 3.64-3.56 (m, 1 H), 2.12-1.90 (m, 3 H), 1.76- 1.53 (m, 3 H), 0.99-0.93 (m, 9 H), 0.85-0.77 (m, 6 H).

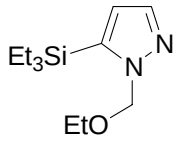
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.3, 139.3, 115.9, 87.3, 67.7, 30.2, 24.9, 22.9, 7.2, 3.7.

IR (Diamond ATR): 2953 (m), 2875 (m), 1741 (w), 1243 (m), 1084 (s), 1043.4 (s), 1000 (s), 928 (m), 914 (m), 788 (m), 733 (s), 721 (s), 702 (s).

MS (70 eV, EI): ***m/z*** **(%)**: 266 (M^+, 1), 238 (13), 237 (89).

HRMS: calcd. for $C_{14}H_{26}N_2OSi$: 266.1814, found: 266.1803.

Synthesis of 1-ethoxymethyl-5-triethylsilyl-1*H*-pyrazole (81a)



According to **TP9,** 1-ethoxymethylpyrazole (**75**; 960 mg, 7.6 mmol) dissolved in THF (7.6 mL) was treated with TMPMgCl·LiCl (**10a**; 7.6 mL, 1.1 м in THF, 8.4 mmol) at 25 °C. After stirring for 1 h, triethylsilyl chloride (1.3 mL, 9.0 mmol) was added to the mixture. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) afforded the product as a yellow oil (1.7 g, 94%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.52 (d, $^3J_{H\text{-}H}$ = 1.7 Hz, 1 H), 6.47 (d, $^3J_{H\text{-}H}$ = 1.7 Hz, 1 H), 5.47 (s, 2 H), 3.50- 3.43 (q, $^3J_{H\text{-}H}$ = 7.1 Hz, 2 H), 1.12 (t, $^3J_{H\text{-}H}$ =7.1 Hz, 3 H), 0.99-0.91 (m, 9 H), 0.88-0.80 (m, 6 H).

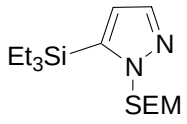
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.8, 117.3, 99.4, 80.7, 64.2, 14.8, 7.2, 3.4.

IR (Diamond ATR): 2954 (m), 2876 (m), 1458 (w), 1301 (m), 1234 (m), 1108 (s), 1080 (s), 1003 (m), 928 (m), 790 (m), 760 (s), 721 (s), 702 (s).

MS (70 eV, EI): ***m/z* (%)**: 240 (M^+, 1), 211 (57), 167 (35), 139 (100), 110 (36), 103 (32).

HRMS (EI): calcd. for $C_{12}H_{24}N_2OSi$: 240.1658, found: 240.1655.

Synthesis of 5-triethylsilyl-1-(2-trimethylsilyl-ethoxymethyl)-1*H*-pyrazole (82a)



According to **TP9**, the pyrazole (**76**; 1.9 g, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (**10a**; 10 mL, 1.1 м in THF, 11 mmol). After stirring for 1 h, triethylsilyl chloride (1.8 mL, 11 mmol) was added to the mixture. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) afforded the desired compound **82a** as a yellow oil (2.64 g, 84%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.51 (d, $^3J_{H\text{-}H}$ = 1.7 Hz, 1 H), 6.45 (d, $^3J_{H\text{-}H}$ = 1.7 Hz, 1 H), 5.46 (s, 2 H), 3.48 (t, $^3J_{H\text{-}H}$ = 8.1 Hz, 2 H), 0.97-0.79 (m, 17 H), -0.05 (s, 9 H).

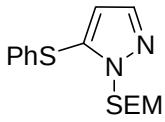
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.0, 138.7, 117.2, 80.4, 66.1, 17.8, 7.2, 3.4, -1.5.

IR (Diamond ATR): 2954 (m), 2876 (m), 1458 (w), 1417 (w), 1249 (m), 1111 (s), 1079 (s), 1002 (m), 927 (m), 858 (s), 833 (s), 790 (m), 761 (s), 734 (s), 701 (s).

MS (70 eV, EI): *m/z* (%): 312 (M^+, 1), 269 (13), 255 (14), 198 (13), 196 (23), 168 (41), 167 (12), 140 (15), 139 (16), 73 (100).

HRMS (EI): calcd. for $C_{15}H_{32}N_2OSi_2$: 312.2053, found: 312.2044.

Synthesis of 5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (82b)



According to **TP9**, 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (**76**; 1.98 g, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (**10a**;10 mL, 1.1 M in THF, 11 mmol). The resulting organomagnesium reagent **79** was added dropwise at 0 °C to a solution of *S*-phenyl benzenesulfonothioate (3.0 g, 12 mmol) in THF (10 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) afforded the desired compound **82b** as a yellow oil (2.5 g, 82%).

^{1}H-NMR (C_6D_6, 600 MHz): δ = 7.50 (d, $^3J_{H\text{-}H}$ = 1.8 Hz, 1 H), 7.05 (d, $^3J_{H\text{-}H}$ = 8.3 Hz, 2 H), 6.90 (t, $^3J_{H\text{-}H}$ = 7.6 Hz, 2 H), 6.83 (t, $^3J_{H\text{-}H}$ = 7.3 Hz, 1 H), 6.35 (d, $^3J_{H\text{-}H}$ = 1.6 Hz, 1 H), 5.40 (s, 2 H), 3.57 (t, $^3J_{H\text{-}H}$ = 7.9 Hz, 2 H), 0.75 (t, $^3J_{H\text{-}H}$ = 7.9 Hz, 2 H), -0.10 (s, 9 H).

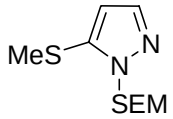
^{13}C-NMR (C_6D_6, 150 MHz): δ = 140.1, 136.4, 131.3, 129.3, 127.7, 126.4, 115.2, 77.9, 66.7, 17.8, -1.4.

IR (Diamond ATR): 1584 (m), 1479 (m), 1441 (w), 1372 (w), 1303 (w), 1285 (w), 1247 (m), 1114 (m), 1078 (s), 1024 (w), 998 (w), 920 (w), 857 (m), 833 (s), 791 (m), 738 (s), 688 (s).

MS (EI, 70 eV) *m/z*, (%): 306 (M^+, 7), 263 (22), 261 (15), 233 (24), 206 (21), 191 (12), 190 (83), 189 (52), 179 (11), 176 (19), 171 (14), 167 (9), 157 (23), 153 (11), 116 (13), 115 (7), 113 (12), 110 (8), 109 (14), 91 (22), 87 (20), 73 (100).

HRMS (EI): calcd. for $C_{15}H_{22}N_2OS$: 306.1222, found: 306.1223.

Synthesis of 5-(methylthio)-1-[(2-trimethylsilyl)ethoxy]methyl-1*H*-pyrazole (82c)



According to **TP9**, 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (**76**; 1.98 g, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (**10a**; 10 mL, 1.1 M in THF, 11 mmol). The resulting organomagnesium reagent **79** was added dropwise at 0 °C to a solution of methanethiosulfonic acid *S*-methyl ester (1.5 g, 12 mmol) in THF (10 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) afforded the desired compound **82c** as a yellow oil (1.76 g, 72%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.48 (d, $^3J_{H\text{-}H}$ = 1.8 Hz, 1 H), 6.12 (d, $^3J_{H\text{-}H}$ = 2.0 Hz, 1 H), 5.41 (s, 2 H), 3.64 (t, $^3J_{H\text{-}H}$ = 8.0 Hz, 2 H), 1.96 (s, 3 H), 0.83 (t, $^3J_{H\text{-}H}$ = 8.0 Hz, 2 H), -0.09 (s, 9 H).

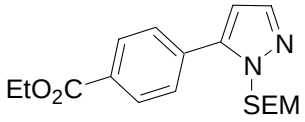
^{13}C-NMR (C_6D_6, 100 MHz): δ = 139.7, 136.9, 110.4, 77.7, 66.6, 18.9, 17.9, -1.4.

IR (Diamond ATR): 1420 (w), 1372 (w), 1287 (w), 1247 (m), 1113 (m), 1078 (s), 997 (w), 973 (w), 920 (w), 857 (s), 832 (s), 751 (s), 693 (m), 664 (w).

MS (EI, 70 eV) *m/z*, (%): 244 (M^+, 3), 201 (50), 199 (27), 186 (16), 172 (13), 171 (100), 153 (48), 144 (29), 128 (86), 127 (47), 116 (10), 114 (9), 73 (21).

HRMS (EI): calcd. for $C_{10}H_{20}N_2OSSi$: 244.1066, found: 244.1073.

Synthesis of ethyl 4-[2-(2-trimethylsilanyl-ethoxymethyl)-2*H*-pyrazol-3-yl]benzoate (82d)



According to **TP9**, 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (**76**; 198.0 mg, 1.00 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (**10a**; 1.00 mL, 1.10 M in THF, 1.10 mmol) leading to the organomagnesium reagent **5a** which was transmetallated with $ZnCl_2$ (1.00 mL, 1.00 M in THF, 1.00 mmol). Ethyl 4-iodobenzoate (331.0 mg, 1.20 mmol) dissolved in THF (1.0 mL) and mixed with 2 mol% $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and 4 mol% S-PHOS (16.5 mg, 0.04 mmol) was added at 25 °C to the zinc reagent.

Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **82d** as colourless oil (315 mg, 91%).

^{1}H-NMR (C_6D_6, 300 MHz): δ = 8.20 (d, $^3J_{H-H}$ = 8.6 Hz, 2 H), 7.65 (d, $^3J_{H-H}$ = 8.6 Hz, 2 H), 7.54 (d, $^3J_{H-H}$ = 1.8 Hz , 1 H), 6.22 (d, $^3J_{H-H}$ = 1.8 Hz, 1 H), 5.21 (s, 2 H), 4.14 (q, $^3J_{H-H}$ = 7.2 Hz, 2 H), 3.79 (t, $^3J_{H-H}$ = 8.0 Hz, 2 H), 1.03 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H), 0.87 (t, $^3J_{H-H}$ = 8.0 Hz, 2 H), -0.08 (s, 9 H).

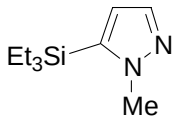
^{13}C-NMR (C_6D_6, 75 MHz): δ = 165.8, 143.3, 139.4, 134.9, 130.9, 130.3, 128.9, 107.6, 78.2, 67.0, 60.9, 18.0, 14.2, -1.4.

IR (Diamond ATR): 2953 (w), 1714 (s), 1614 (m), 1378 (m), 1271 (s), 1185 (m), 1084 (s), 1023 (m), 982 (w), 925 (w), 860 (m), 833 (s), 762 (s), 704 (m), 648 (w).

MS (EI, 70 eV) *m/z*, (%): 346 (M^+, 1), 303 (11), 301 (9), 287 (10), 273 (8), 259 (2), 245 (6), 230 (62), 229 (100), 216 (8), 201 (11), 185 (4), 171 (8), 157 (5), 114 (8), 73 (24).

HRMS (EI): calcd. for $C_{18}H_{26}N_2O_3Si$: 346.1713, found: 346.1702.

Synthesis of 1-methyl-5-(triethylsilyl)-1*H*-pyrazole (90a)



According to **TP9,** *N*-methylpyrazole (**88**; 820 mg, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (**10a**;10 mL, 1.1 M in THF, 11 mmol). The resulting organomagnesium reagent **89** was added dropwise at 0 °C to a solution of triethylsilyl chloride (1.8 g, 12 mmol) in THF (10 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **90a** as a yellow oil (1.56 g, 80%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.48 (d, $^3J_{H-H}$ = 1.9 Hz, 1 H), 6.37 (d, $^3J_{H-H}$ = 1.7 Hz 1 H), 3.94 (s, 3 H), 0.98-0.92 (m, 9 H), 0.86-0.77 (m, 6 H).

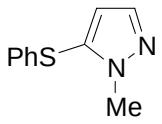
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 139.5, 138.2, 115.7, 39.7, 7.3, 3.5.

IR (Diamond ATR): 2954 (s), 1738 (s), 1370 (s), 1229 (m), 1045 (m), 929 (w), 716 (s).

MS (EI, 70 eV) *m/z*, (%): 219 (5), 196 (M^+, 7), 167 (57), 149 (2), 139 (100), 111 (59), 109 (2), 97 (2), 82 (7), 71 (3), 57 (5), 55 (3), 44 (7).

HRMS (EI): calcd. for $C_{10}H_{20}N_2Si$: 196.1396, found: 196.1383.

Synthesis of 1-methyl-5-(phenylthio)-1*H*-pyrazole (90b)



According to **TP9**, *N*-methylpyrazole (**88**; 820 mg, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (**10a**;10 mL, 1.1 M in THF, 11 mmol). The resulting organomagnesium reagent 5b was added dropwise at 0 °C to a solution of *S*-phenyl benzenesulfonothioate (3.0 g, 12 mmol) in THF (10 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **90b** as a yellow oil (1.58 g, 83%).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.57 (d, $^3J_{H-H}$ = 1.9 Hz, 1 H), 7.26-7.24 (m, 2 H), 7.18-7.15 (m, 1 H), 7.06-7.04 (m, 2 H), 6.54 (d, $^3J_{H-H}$ = 1.9 Hz, 1 H), 3.83 (s, 3 H).

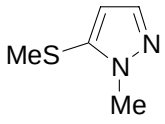
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 138.8, 135.2, 129.3, 129.3, 127.1, 126.4, 114.0, 36.7.

IR (Diamond ATR): 2970 (m), 1739 (s), 1582 (w), 1478 (m), 1440 (m), 1408 (m), 1380 (m), 1217 (m), 1081 (m), 922 (m), 782 (m), 737 (s), 688 (s), 651 (m).

MS (EI, 70 eV) *m/z*, (%): 190 (M^+, 100), 175 (11), 162 (12), 157 (4), 147 (6), 134 (3), 130 (3), 121 (8), 118 (12), 109 (3), 103 (5), 91 (4), 77 (7), 69 (3), 57 (5), 44 (23).

HRMS (EI): calcd. for $C_{10}H_{10}N_2S$: 190.0565, found: 190.0563.

Synthesis of 1-methyl-5-(methylthio)-1*H*-pyrazole (90c)



According to **TP9**, *N*-methylpyrazole (**88**; 820 mg, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (**10a**; 10 mL, 1.1 M in THF, 11 mmol). The resulting organomagnesium reagent **89** was added dropwise at 0 °C to a solution of methanethiosulfonic acid *S*-methyl ester (1.5 g, 12 mmol) in THF (10 mL). After purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5), the desired compound **90c** was isolated as a yellow oil (1.01 g, 79%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.49 (d, $^3J_{H-H}$ = 1.8 Hz, 1 H), 6.11 (d, $^3J_{H-H}$ = 1.9 Hz, 1 H), 3.46 (s, 3 H), 1.75 (s, 3 H).

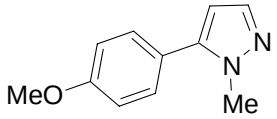
^{13}C-NMR (C_6D_6, 100 MHz): δ = 138.9, 135.3, 109.4, 36.1, 18.4.

IR (Diamond ATR): 1729 (w), 1682 (w), 1625 (w), 1412 (s), 1381 (s), 1319 (w), 1272 (m), 1192 (m), 1110 (w), 1038 (w), 992 (m), 973 (m), 924 (s), 870 (w), 778 (s), 707 (s), 650 (m).

MS (EI, 70 eV) *m/z*, (%): 130 (5), 129 (6), 128 (M^+, 100), 113 (33), 98 (4), 95 (14), 86 (9), 81 (5), 71 (7), 70 (14), 69 (11), 67 (20), 59 (3), 57 (4), 54 (5), 52 (5), 45 (10), 43 (4).

HRMS (EI): calcd. for $C_5H_8N_2S$: 128.0408, found: 128.0397.

Synthesis of 5-(4-methoxy-phenyl)-1-methyl-1*H*-pyrazole (91a)



According to **TP12** pyrazole **90c** (128 mg, 1.0 mmol), dissolved in THF (1.0 mL) was reacted with 4-methoxybenzylzinc iodide (1.4 mL, 1.09 м in THF, 1.5 mmol). The reaction mixture was stirred at 25 °C for 1 h. Purification by flash chromatography (SiO_2, pentane:EtOAc/9:1) afforded the desired product **91a** as a white solid (156 mg, 83%).

m.p.: 47.3-48.5

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.49 (d, $J_{H\text{-}H}$ = 2.2 Hz, 1 H), 7.34-7.30 (m, 2 H), 6.99-6.95 (m, 2 H), 6.24 (d, $J_{H\text{-}H}$ = 2.0 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H).

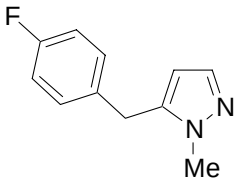
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 159.7, 143.4, 138.2, 130.0, 123.0, 114.1, 105.6, 55.3, 37.3.

IR (film): 1610 (w), 1575 (w), 1539 (w), 1464 (m), 1381 (m), 1283 (m), 1248 (s), 1180 (m), 1114 (w), 1026 (m), 980 (m), 925 (w), 836 (s), 773 (s), 604 (m).

MS (EI, 70 eV) *m/z*, (%): 189 (11), 188 (M^+, 100), 187 (2), 174 (9), 173 (58), 146 (3), 145 (13), 133 (2), 118 (7), 117 (5), 116 (2), 115 (2), 103 (2), 102 (5), 94 (4), 91 (7), 90 (2), 89 (4), 77 (4), 76 (4), 75 (2), 65 (4), 63 (4), 50 (2).

HRMS (EI): calcd. for $C_{11}H_{12}N_2O$: 188.0950, found: 188.0951.

Synthesis of 5-(4-fluoro-benzyl)-1-methyl-1*H*-pyrazole (91b)



According to **TP12** pyrazole **90c** (128 mg, 1.0 mmol), dissolved in THF (1.0 mL) was reacted with 4-fluorobenzylzinc chloride (2.1 mL, 0.72 м in THF, 1.5 mmol). The reaction mixture was

heated to 45 °C for 12 h. Purification by flash chromatography (SiO_2, pentane:EtOAc/95:5) afforded the desired product **91b** as a pale yellow oil (152 mg, 80%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.50 (d, J_{H-H} = 2.0 Hz, 1 H), 6.75-6.70 (m, 2 H), 6.66-6.63 (m, 2 H), 5.80 (d, J_{H-H} = 1.8 Hz, 1 H), 3.31 (s, 2 H), 3.17 (s, 3 H).

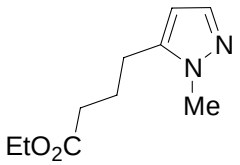
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 162.0 (d, J_{H-H} = 244.1 Hz), 138.2, 133.7 (d, J_{H-H} = 3.5 Hz), 130.1, 130.0, 115.5, (d, J_{H-H} = 21.1 Hz), 105.9, 35.9, 30.8.

IR (film): 1602 (w), 1508 (s), 1483 (m), 1440 (m), 1357 (m), 1284 (m), 1220 (s), 1157 (m), 1081 (s), 1016 (m), 891 (w), 835 (s), 767 (s), 733 (m).

MS (EI, 70 eV) ***m/z***: 191 (13), 190 (M^+, 100), 189 (40), 175 (30), 162 (12), 148 (19), 146 (17), 135 (5), 133 (9), 127 (7), 120 (6), 109 (17), 97 (6), 95 (35), 85 (8), 83 (7), 71 (10), 69 (7), 57 (17), 56 (6), 55 (10), 44 (7), 43 (12), 41 (9).

HRMS (EI): calcd. for $C_{11}H_{11}FN_2$: 190.0906, found: 190.0894.

Synthesis of ethyl 4-(2-methyl-2*H*-pyrazol-3-yl)butanoate (91c)



According to **TP12** pyrazole **90c** (128 mg, 1.0 mmol), dissolved in THF (1.0 mL) was reacted with 4-(ethylcarboxy)butylzinc bromide (4.2 mL, 0.36 м in THF, 1.5 mmol). The reaction mixture was heated to 45 °C for 12 h. Purification by flash chromatography (SiO_2, pentane:EtOAc/95:5) afforded the desired product **91c** as a pale yellow oil (135 mg, 69%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.36 (d, J_{H-H} = 1.5 Hz, 1 H), 6.02 (d, J_{H-H} = 1.5 Hz, 1 H), 4.12 (q, J_{H-H} = 7.1 Hz, 2 H), 3.79 (s, 3 H), 2.64 (t, J_{H-H} = 7.7 Hz, 2 H), 2.36 (t, J_{H-H} = 7.1 Hz, 2 H), 1.94 (quint, J_{H-H} = 7.3 Hz, 2 H), 1.24 (t, J_{H-H} = 7.1 Hz, 3 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 173.0, 141.8, 137.9, 104.4, 60.4, 36.0, 33.3, 24.8, 23.6, 14.2.

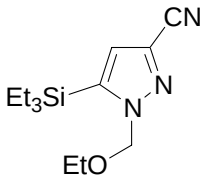
IR (film): 2940 (w), 1728 (s), 1397 (w), 1375 (w), 1178 (m), 1025 (m), 930 (m), 859 (w), 771 (m), 651 (w).

MS (EI, 70 eV) ***m/z*****, (%):** 197 (3), 196 (M^+, 26), 152 (5), 151 (58), 124 (6), 123 (11), 121 (6), 110 (7), 109 (100), 108 (31), 107 (8), 96 (37), 95 (50), 80 (4), 68 (5), 61 (4), 60 (6), 55 (5), 52 (8), 42 (8), 41 (9).

HRMS (EI): calcd. for $C_{10}H_{16}N_2O_2$: 196.1212, found: 196.1205.

5.3 Preparation of C3-substituted pyrazoles

Synthesis of 1-ethoxymethyl-5-triethylsilyl-1*H*-pyrazole-3-carbonitrile (85)



According to **TP10** pyrazole **81a** (730 mg, 3.0 mmol) dissolved in THF (3.0 ml) was treated with TMPMgCl·LiCl (**10a**; 6 mL, 1.1 M in THF, 6.6 mmol) at 25 °C. After stirring for 2 h, the obtained organomagnesium reagent **84** was reacted with TsCN (1.3 g, 7.8 mmol). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished **85** as a yellow oil (331 mg, 42%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.79 (s, 1 H), 5.47 (s, 2 H), 3.50-3.46 (q, $^3J_{H-H}$ =7.1, 2 H), 1.14 (t, $^3J_{H-H}$ = 6.9 Hz, 3 H), 0.93 (t, $^3J_{H-H}$ = 7.6, 9 H), 0.87-0.85 (m, 6 H).

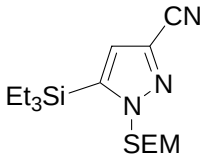
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 143.1, 124.5, 121.9, 114.2, 81.5, 65.0, 14.6, 7.1, 3.2.

IR (Diamond ATR): 2957 (m), 2877 (m), 2241 (m), 1739(m), 1457 (w), 1388(m), 1307 (m), 1237 (m), 1106 (s), 1080 (s), 1005 (s), 766 (s), 723(s), 703 (s), 610 (m).

MS (70 eV, EI): ***m/z*, (%):** 266 (M+H, 1), 236 (38), 208 (12), 192 (44), 165 (11), 164 (100), 136 (22), 103 (30).

HRMS (EI): calcd. for $C_{13}H_{23}N_3OSi$: 265.1610, found: 266.1679 $[M+H]^+$.

Synthesis of 5-triethylsilyl-1-(2-trimethylsilyl-ethoxymethyl)-1*H*-pyrazole-3-carbonitrile (87):



According to **TP10** pyrazole **82a** (312, 10.0 mmol) dissolved in THF (1.0 ml) was treated with TMPMgCl·LiCl (**10a**; 2.0 mL, 1.1 M in THF, 2.2 mmol) at 25 °C. After stirring for 2 h, the obtained organomagnesium reagent **86** was reacted with TsCN (434 mg, 2.6 mmol). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished **87** as a yellow oil (243 mg, 72%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.79 (s, 1 H), 5.46 (s, 2 H), 3.49 (t, $^3J_{H-H}$ = 8.3 Hz, 2 H), 0.95-0.83 (m, 17 H), -0.02 (s, 9 H).

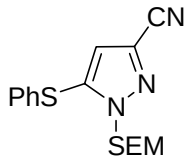
^{13}C NMR ($CDCl_3$, 150 MHz): = 143.0, 124.4, 121.9, 114.2, 81.2, 67.0, 17.7, 7.1, 3.2, -1.5.

IR (Diamond ATR): 2955 (m), 2877 (m) 2241 (w) , 1739 (w,b), 1388 (m) 1458 (w), 1417 (w), 1305 (m), 1248 (m), 1098 (s), 1080 (s), 1007 (s), 939 (m), 914 (m), 859 (s), 834 (s), 765 (s), 737 (s) 724 (s), 702 (s), 610 (m)

MS (70 eV, EI): ***m/z* (%):** 337 (M^+, 1), 294 (19), 280 (15), 221 (11), 193 (11), 164 (9), 101 (12), 73 (100).

HRMS (EI): calcd. for $C_{16}H_{31}N_3OSi_2$: 337.2006, found: 337.2000.

Synthesis of 5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carbonitrile (92a)



According to **TP10,** the pyrazole **82b** (306 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (**10a**; 1.0 mL, 1.1 M in THF, 1.1 mmol). TsCN (217 mg, 1.2 mmol), dissolved in THF (1.0 mL) was added dropwise at -15 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **92a** as a yellow oil (225 mg, 68%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.30-7.18 (m, 5 H), 6.73 (s, 1 H), 5.49 (s, 2 H), 3.50 (t, $^3J_{H\text{-}H}$ = 8.3 Hz, 2 H), 0.77 (t, $^3J_{H\text{-}H}$ = 8.3 Hz, 2 H), -0.08 (s, 9 H).

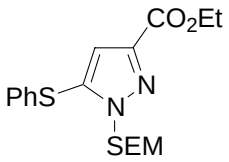
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 136.1, 132.8, 129.61, 129.56, 128.0, 125.5, 117.8, 113.3, 78.7, 67.4, 17.6, -1.5.

IR (Diamond ATR): 2970 (s), 2243 (w), 1739 (s), 1365 (m), 1217 (m), 1073 (m), 1000 (w), 834 (s), 740 (m), 688 (m), 615 (w).

MS (EI, 70 eV) *m/z*, (%): 331 (M^+, 3), 288 (23), 286 (11), 274 (14), 273 (48), 272 (42), 258 (27), 215 (33), 206 (12), 201 (6), 196 (5), 182 (5), 179 (6), 150 (6), 146 (3), 135 (3), 129 (5), 121 (3), 116 (3), 109 (8), 103 (3), 91 (25), 84 (5), 77 (5), 73 (100), 65 (3), 59 (3), 45 (6).

HRMS (EI): calcd. for $C_{16}H_{21}ClN_3OSSi$: 331.1175, found: 331.1160.

Synthesis of ethyl 5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate (92b)



According to **TP10,** the pyrazole **82b** (306 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (1.0 mL, 1.1 M in THF, 1.1 mmol). $NCCO_2Et$ (120 mg, 1.2 mmol) was added dropwise at -15 °C and the mixture was allowed to slowly warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **92b** as a yellow oil (268 mg, 71%).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.30-7.17 (m, 5 H), 6.99 (s, 1 H), 5.56 (s, 2 H), 4.40 (q, $^3J_{H-H}$ = 7.2 Hz, 2H), 3.55-3.50 (m, 2 H), 1.38 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H), 0.80-0.74 (m, 2 H), -0.07 (s, 9 H).

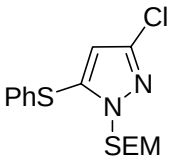
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 161.8, 143.9, 134.6, 134.1, 129.4, 128.7, 127.2, 116.5, 78.6, 67.0, 61.2, 17.7, 14.3, -1.5.

IR (Diamond ATR): 2970 (s), 1739 (s), 1365 (m), 1204 (s), 1091 (m), 834 (m), 740 (w), 688 (w).

MS (EI, 70 eV) *m/z*, (%): 378 (M^+, 1), 333 (21), 305 (29), 291 (6), 277 (100), 262 (54), 261 (33), 248 (16), 233 (29), 229 (24), 215 (9), 202 (8), 197 (4), 185 (15), 153 (4), 146 (6), 139 (4), 123 (3), 109 (9), 91 (12), 73 (36).

HRMS (EI): calcd. for $C_{18}H_{26}N_2O_3SSi$: 378.1433, found: 378.1426.

Synthesis of 3-chloro-5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (92c)



According to **TP10,** the pyrazole **82b** (306 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (**10a**; 1.0 mL, 1.1 M in THF, 1.1 mmol). The resulting organomagnesium reagent was added dropwise at -15 °C to Cl_2FCCF_2Cl (372 mg, 2.0 mmol) dissolved in THF (1.0 mL). Purification by flash chromatography (SiO_2 initially neutralized

with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **92c** as a yellow oil (221 mg, 65%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.31-7.19 (m, 5 H), 6.38 (s, 1 H), 5.43 (s, 2 H), 3.53 (t, $^3J_{H-H}$ = 8.2 Hz, 2H), 0.81 (t, J_{H-H} = 8.3 Hz, 2H), -0.05 (s, 9 H).

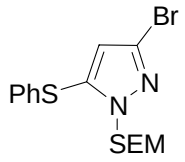
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 140.1, 135.1, 133.9, 129.4, 128.8, 127.3, 112.6, 77.8, 66.9, 17.7, -1.5.

IR (Diamond ATR): 1582 (m), 1468 (m), 1441 (m), 1362 (m), 1275 (w), 1231 (m), 1083 (s), 1022 (m), 957 (s), 740 (s), 688 (s).

MS (EI, 70 eV) *m/z*, (%): 340 (M^+, 2), 297 (33) 295 (16), 282 (20), 267 (19), 224 (67), 223 (43), 205 (23), 189 (15), 147 (38), 141 (11), 134 (10), 121 (12), 111 (14), 109 (15), 99 (14), 97 (19), 93 (14), 91 (26), 85 (47), 83 (26), 77 (12), 73 (100), 71 (57), 69 (23), 57 (70), 55 (24), 44 (52), 43 (40), 41 (17).

HRMS (EI): calcd. for $C_{15}H_{21}ClN_2OSSi$: 340.0832, found: 340.0827.

Synthesis of 3-bromo-5-phenylthio-1-(2-trimethylsilylethoxymethyl)-1*H*-pyrazole (92d)



According to **TP10,** pyrazole (**82b**) (306 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (**10a**; 1.0 mL, 1.1 M in THF, 1.1 mmol). Dibromtetrachlorethane (390 mg, 1.2 mmol), dissolved in THF (1.0 mL) was added dropwise at -15 °C. After purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5), pyrazole **92f** was isolated as a yellow oil (280 mg, 73%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.03-6.99 (m, 2 H), 6.91-6.84 (m, 3 H), 6.24 (s, 1 H), 5.20 (s, 2 H), 3.50 (t, $^3J_{H-H}$ = 7.9 Hz, 2 H), 0.71 (t, $^3J_{H-H}$ = 7.9 Hz, 2 H), -0.11 (s, 9 H).

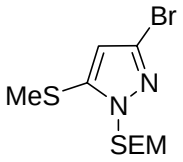
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 134.9, 134.8, 129.5, 128.8, 127.1, 127.0, 116.4, 77.9, 67.0, 17.7, -1.4.

IR (Diamond ATR): 1583 (w), 1472 (m), 1441 (w), 1357 (m), 1293 (m), 1248 (m), 1086 (s), 1024 (m), 956 (s), 913 (w), 857 (m), 832 (s), 738 (s), 688 (s), 663 (m), 612 (w).

MS (EI, 70 eV) *m/z*, (%): 384 (M^+, 2), 343 (14), 341 (25), 339 (12), 328 (9), 326 (8), 313 (8), 311 (8), 270 (21), 269 (18), 268 (21), 267 (17), 256 (6), 254 (6), 251 (11), 249 (11), 237 (8), 235 (7), 190 (9), 189 (78), 188 (14), 167 (9), 148 (42), 139 (7), 137 (7), 121 (10), 109 (10), 91 (20), 73 (100).

HRMS (EI): calcd. for $C_{15}H_{21}{}^{79}BrN_2OSSi$: 384.0327, found: 384.0320.

Synthesis of 3-bromo-5-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (92e)



According to **TP10**, the pyrazole **82c** (245 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (**10a**; 1.0 mL, 1.1 M in THF, 1.1 mmol). Dibromotetrachloroethane (390 mg, 1.2 mmol), dissolved in THF (1.0 mL) was added dropwise at -15 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **92e** as a yellow oil (242 mg, 75%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 6.29 (s, 1 H), 5.42 (s, 2 H), 3.50 (t, $^3J_{H-H}$ = 8.3 Hz, 2 H), 2.43 (s, 3 H), 0.88 (t, $^3J_{H-H}$ = 8.3 Hz, 2 H), -0.03 (s, 9 H).

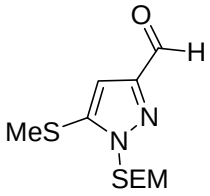
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 140.1, 126.4, 111.5, 77.7, 66.8, 18.7, 17.8, -1.5.

IR (Diamond ATR): 2952 (w), 1472 (m), 1355 (w), 1292 (m), 1248 (m), 1083 (s), 956 (m), 913 (w), 857 (s), 833 (s), 755 (s), 693 (m).

MS (EI, 70 eV) *m/z*, (%): 322 (M^+, 1), 280 (11), 279 (22), 277 (12), 266 (15), 264 (15), 251 (29), 249 (25), 233 (12), 231 (12), 213 (4), 208 (42), 207 (25), 206 (40), 205 (21), 194 (4), 192 (4), 170 (4), 139 (11), 137 (11), 127 (18), 115 (4), 105 (16), 103 (4), 86 (16), 79 (4), 74 (8), 73 (100), 61 (5), 59 (5), 45 (7).

HRMS (EI): calcd. for $C_{10}H_{19}BrN_2OSSi$: 322.0171, found: 322.0169.

Synthesis of 5-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carbaldehyde (92f)



According to **TP10**, the pyrazole **82c** (245 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (**10a**; 1.0 mL, 1.1 M in THF, 1.1 mmol). DMF (0.12 mL, 1.5 mmol), was added at -15 °C. Purification by flash chromatography (SiO_2 initially neutralized

with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **92f** as a yellow oil (207 mg, 76%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 10.08 (s, 1 H), 6.66 (s, 1 H), 5.20 (s, 2 H), 3.53 (t, $^3J_{H-H}$ = 7.9 Hz, 2 H), 1.78 (s, 3 H), 0.70 (t, $^3J_{H-H}$ = 7.9 Hz, 2 H), -0.10 (s, 9 H).

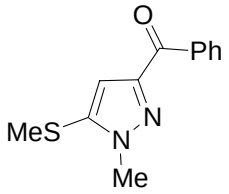
^{13}C-NMR (C_6D_6, 100 MHz): δ = 185.5, 151.9, 140.9, 107.7, 78.6, 67.0, 17.8, 17.7, -1.47.

IR (Diamond ATR): 2953 (w), 1699 (s), 1413 (w), 1306 (w), 1247 (m), 1183 (w), 1097 (m),1069 (m), 913 (w), 858 (m), 834 (s), 775 (m), 752 (s), 694 (w).

MS (EI, 70 eV) *m/z*, (%): 272 (M^+, 1), 229 (4) 227 (12), 214 (11), 201 (10), 200 (17), 199 (100), 156 (86), 155 (14), 143 (7), 127 (4), 116 (3), 109 (3), 100 (4), 85 (3), 83 (6), 78 (5), 73 (85), 69 (3), 61 (6), 59 (5), 57 (6), 43 (6), 39 (17).

HRMS (EI): calcd. for $C_{11}H_{20}N_2O_2SSi$: 272.1015, found: 272.1003.#

Synthesis of (1-methyl-5-methylthio-1*H*-pyrazol-3-yl) phenylmethanone (93a)



According to **TP10,** 1-methyl-5-(methylthio)-1*H*-pyrazole (**90b**; 128 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (**10a**; 1.0 mL, 1.1 M in THF, 1.1 mmol). The resulting organomagnesium reagent was transmetallated with CuCN·2LiCl (1.0 mL, 1.0 M in THF, 1.0 mmol) at -15 °C. Benzoyl chloride (168 mg, 1.2 mmol) was added and the reaction mixture was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **93a** as a pale yellow solid (181 mg, 78%).

m.p.: 52.8-54.2 °C.

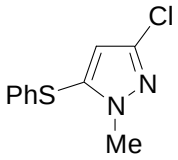
^{1}H-NMR (C_6D_6, 400 MHz): δ = 8.65-8.62 (m, 2 H), 7.21-7.19 (m, 3 H), 7.02 (s, 1 H), 3.26 (s, 3 H), 1.70 (s, 3 H).

^{13}C-NMR (C_6D_6, 100 MHz): δ = 186.3, 151.0, 138.5, 138.0, 132.5, 131.1, 128.2, 111.2, 36.6, 17.5.

IR (Diamond ATR): 1716 (w), 1645 (s), 1597 (w), 1576 (w), 1449 (m), 1395 (m), 1364 (m), 1282 (m), 1233 (s), 1175 (w), 1133 (w), 1014 (w), 966 (w), 896 (s), 781 (m), 730 (s), 698 (s), 672 (m), 640 (m).

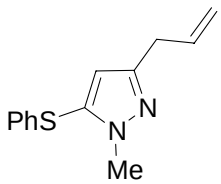
MS (EI, 70 eV) *m/z*, (%): 234 (4), 233 (12), 232 (M^+, 100), 231 (4), 217 (3), 204 (8), 191 (2), 189 (6), 185 (16), 158 (13), 157 (6), 155 (44), 144 (3), 105 (26), 80 (4), 77 (28).
HRMS (EI): calcd. for $C_{12}H_{12}N_2OS$: 232.0670, found: 232.0665.

Synthesis of 3-chloro-1-methyl-5-(phenylthio)-1*H*-pyrazole (93b)



According to **TP10**, 1-methyl-5-(phenylthio)-1*H*-pyrazole (**90b**; 190 mg, 1.0 mmol) dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (**10a**; 1.0 mL, 1.1 M in THF, 1.1 mmol). The resulting organomagnesium reagent was added dropwise at -15 °C to a solution of Cl_2FCCF_2Cl (372 mg, 2.0 mmol) in THF (1.0 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **93b** as a yellow oil (168 mg, 75%).
^{1}H-NMR (C_6D_6, 400 MHz): δ = 6.88-6.80 (m, 5 H), 6.27 (s, 1 H), 3.21 (s, 3 H).
^{13}C-NMR (C_6D_6, 100 MHz): δ = 134.9, 132.7, 129.6, 127.5, 126.7, 125.3, 115.9, 36.4.
IR (Diamond ATR): 1582 (m), 1465 (s), 1441 (m), 1363 (s), 1278 (w), 1084 (w), 1070 (w), 1024 (m), 958 (s), 754 (m), 738 (m), 722 (s), 688 (s), 637 (m), 617 (m).
MS (EI, 70 eV) *m/z*, (%): 226 (41), 225 (11), 224 (M^+, 100), 209 (12), 196 (6), 189 (10), 174 (5), 156 (6), 148 (5), 135 (7), 130 (5), 121 (8), 109 (7), 91 (7), 77 (9), 71 (6), 57 (9), 44 (22).
HRMS (EI): calcd. for $C_{10}H_9ClN_2S$: 224.0175, found: 224.0171.

Synthesis of 3-allyl-1-methyl-5-(phenylthio)-1*H*-pyrazole (93c)



According to **TP10**, the pyrazole **90b** (190 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (**10a**; 1.0 mL, 1.1 M in THF, 1.1 mmol). The resulting organomagnesium reagent was transmetallated with CuCN·2LiCl (0.1 mL, 1.0 M in THF, 0.1 mmol) at -15 °C. Allyl bromide (146 mg, 1.2 mmol) was added and the reaction mixture was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized

with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **93c** as a yellow oil (179 mg, 78%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 6.95-6.78 (m, 5 H), 6.32 (s, 1 H), 6.09-5.99 (1 H), 5.12-5.00 (m, 2 H), 3.43 (s, 2 H), 3.41 (s, 3 H).

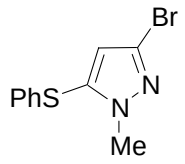
^{13}C-NMR (C_6D_6, 100 MHz): δ = 150.7, 136.4, 136.3, 129.5, 128.3, 126.8, 126.1, 115.9, 113.2, 36.1, 33.4.

IR (Diamond ATR): 2970 (m), 1739 (s), 1641 (w), 1582 (w), 1507 (m), 1478 (m), 1440 (m), 1365 (m), 1217 (m), 1075 (w), 1024 (w), 914 (m), 804 (w), 737 (s), 688 (s), 652 (w).

MS (EI, 70 eV) *m/z*, (%): 231 (13), 230 (M^+, 100), 229 (21), 215 (2), 204 (18), 197 (1), 189 (3), 121 (22), 109 (6), 105 (2), 94 (2), 80 (5), 77 (3).

HRMS (EI): calcd. for $C_{13}H_{14}N_2S$: 230.0878, found:230.0871.

Synthesis of 3-bromo-1-methyl-5-(phenylthio)-1*H*-pyrazole (93d)



According to **TP10**, 1-methyl-5-(phenylthio)-1*H*-pyrazole (**90b**) (190 mg, 1.0 mmol) dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (**10a**; 1.0 mL, 1.1 м in THF, 1.1 mmol). The resulting organomagnesium reagent was added dropwise at -15 °C to a solution of dibromtetrachlorethane (390 mg, 1.2 mmol) in THF (1.0 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) afforded pyrazole **93d** as a yellow oil (188 mg, 70%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.30-7.17 (m, 3 H), 7.11-7.08, (m, 2 H), 6.49 (s, 1 H), 3.78 (s, 3 H).

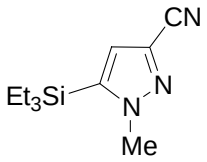
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 134.0, 133.4, 129.5, 127.8, 126.9, 124.9, 115.4, 37.0.

IR (Diamond ATR): 2970 (m), 1739 (s), 1581 (w), 1464 (m), 1362 (s), 1217 (m), 1066 (w), 1023 (w), 957 (s), 789 (w), 737 (s), 688 (s).

MS (EI, 70 eV) *m/z*, (%): 270 (100), 269 (12), 268 (M^+, 100), 255 (3), 189 (28), 174 (9), 162 (6), 156 (6), 148 (5), 146 (5), 134 (2), 130 (4), 121 (9), 118 (5), 116 (7), 109 (12), 80 (6), 68 (6).

HRMS (EI): calcd. for $C_{10}H_9{}^{79}BrN_2S$: 267.9670, found: 267.9657.

Synthesis of 1-methyl-5-(triethylsilyl)-1*H*-pyrazole-3-carbonitrile (93e)



According to **TP10,** the pyrazole **90a** (196 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (**10a**; 1.0 mL, 1.1 M in THF, 1.1 mmol) at 25 °C. After stirring for 5 h, full conversion to the organomagnesium reagent was achieved. TsCN (217 mg, 1.2 mmol), dissolved in THF (1.0 mL) was added dropwise at -15 °C and the mixture was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **93e** as a yellow oil (135 mg, 61%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 6.69 (s, 1 H), 3.95 (s, 3 H), 0.95-0.89 (m, 9 H), 0.85-0.76 (m. 6 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 142.4, 123.7, 120.9, 114.2, 40.6, 7.0, 3.1.

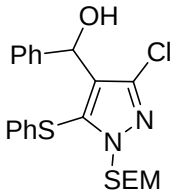
IR (Diamond ATR): 2956 (m), 2877 (m), 2239 (m), 1457 (w), 1416 (w), 1392 (m), 1288 (w), 1239 (w), 1145 (w), 1088 (m), 1012 (s), 810 (m), 723 (s), 695 (s).

MS (EI, 70 eV) *m/z*, (%): 221 (M^+, 2), 192 (67), 164 (100), 136 (40), 124 (3), 107 (2), 91 (3),

HRMS (EI): calcd. for $C_{11}H_{19}N_3Si$: 221.1348, found: 221.1341.

5.4 Preparation of C4-substituted pyrazoles

Synthesis of (3-chloro-5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)(phenyl)methanol (94a)



According to **TP11,** the pyrazole **92c** (370 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMP_2Mg·2LiCl (**12**; 1.8 mL, 0.6 M in THF, 1.1 mmol). After completion of the deprotonation, benzaldehyde (127 mg, 1.2 mmol) was added and the solution was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3%

Et_3N, pentane:EtOAc/9:1) furnished the desired compound **94a** as a pale yellow oil (317 mg, 71%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.43-7.40 (m, 2 H), 7.11-6.77 (m, 8 H), 6.02 (s, 1 H) 5.22-5.15 (m, 1H), 5.18 (s, 1 H), 3.50 (t, $^3J_{H-H}$ = 8.0 Hz, 2H), 2.01 (s, 1 H), 0.68 (t, $^3J_{H-H}$ = 8.0 Hz, 2H), -0.13 (s, 9 H).

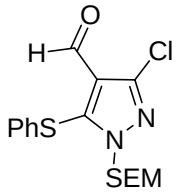
^{13}C-NMR (C_6D_6, 100 MHz): δ = 142.6, 139.3, 135.0, 131.4, 129.4, 128.4, 128.3, 127.6, 127.4, 126.7, 126.3, 78.0, 68.4, 67.1, 17.7, -1.4.

IR (Diamond ATR): 1728 (m), 1430 (w), 1378 (m), 1301 (m), 1249 (m), 1098 (s), 1019 (m), 937 (w), 923 (w), 860 (s), 835 (s), 759 (s), 737 (s), 694 (s), 687 (s).

MS (EI, 70 eV) *m/z*, (%): 446 (M^+, 7), 403 (21), 369 (16), 330 (19), 328 (11), 311 (16), 309 (10), 295 (24), 293 (29), 243 (18), 241 (12), 239 (33), 109 (12), 105 (22), 91 (35), 77 (14), 73 (100).

HRMS (EI): calcd. for $C_{22}H_{27}ClN_2O_2SSi$: 446.1251, found: 446.1245.

Synthesis of 3-chloro-5-phenylthio-1-(2-trimethylsilylethoxymethyl)-1*H*-pyrazole-4-carbaldehyde (94b)



According to **TP11**, the pyrazole **92c** (370 mg, 1.0 mmol) was treated with $TMP_2Mg{\cdot}2LiCl$ (**12**; 1.8 mL, 0.6 M in THF, 1.1 mmol). DMF (0.12 mL, 1.5 mmol) was then added and the reaction mixture was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **94b** as a pale yellow oil (239 mg, 65%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 9.89 (s, 1 H), 7.01-6.99, (m, 2 H), 6.82-6.80 (m, 3 H), 5.10 (s, 2 H), 3.48-3.43 (m, 2 H), 0.72-0.68 (m, 2 H), -0.12 (s, 9 H).

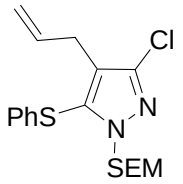
^{13}C-NMR (C_6D_6, 100 MHz): δ = 182.1, 142.0, 139.5, 133.4, 129.7, 129.4, 127.7, 121.6, 77.9, 67.6, 17.7, -1.5.

IR (Diamond ATR): 2970 (w), 2952 (w), 2900 (w), 1739 (s), 1690 (s), 1494 (m), 1412 (m), 1354 (m), 1297 (w), 1248 (m), 1217 (m), 1096 (s), 858 (s), 833 (s), 776 (s), 740 (m), 687 (m).

MS (EI, 70 eV) *m/z*, (%): 368 (M^+, 10), 327 (16), 326 (9), 325 (47), 323 (30), 312 (15), 311 (47), 310 (37), 309 (99), 303 (9), 297 (10), 295 (21), 254 (19), 253 (16), 252 (48), 251 (29), 232 (18), 229 (13), 219 (10), 217 (33), 110 (14), 109 (25), 93 (14), 91 (21), 73 (100).

HRMS (EI): calcd. for $C_{16}H_{21}ClN_2O_2SSi$: 368.0782, found: 368.0768.

Synthesis of 4-allyl-3-chloro-5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (94c)



According to **TP11,** 3-chloro-5-phenylthio-1-(2-trimethylsilylethoxymethyl)-1*H*-pyrazole (**92c**; 370 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with $TMP_2Mg{\cdot}2LiCl$ (**12**; 1.8 mL, 0.6 M in THF, 1.1 mmol). After completion of the deprotonation, CuCN·2LiCl (0.1 mL, 1.0 M in THF, 0.1 mmol) was added and the mixture was stirred for 5 min before adding allyl bromide (146 mg, 1.2 mmol). The solution was allowed to warm up to 25 °C. The crude product was purified by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) and yielded the pure product as a colourless oil (281 mg, 74%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.27-7.16 (m, 3 H), 7.08-7.06 (m, 2 H), 5.82-5.72 (m, 1 H), 5.47 (s, 2 H), 4.99-4.94 (m, 2 H), 3.58-3.54 (m, 2 H), 3.26 (dt, $^3J_{H\text{-}H}$ = 6.2 Hz, $^4J_{H\text{-}H}$ = 1.5 Hz, 2 H), 0.83-0.78 (m, 2 H), -0.03 (s, 9 H).

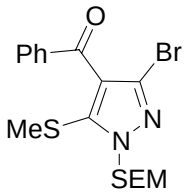
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 140.2, 134.7, 134.2, 131.2, 129.2, 127.1, 126.5, 123.3, 115.9, 77.8, 66.8, 27.9, 17.7, -1.5.

IR (Diamond ATR): 2953 (m), 1739 (s), 1375 (s), 1248 (m), 1217 (m), 1092 (s), 913 (m), 833 (s), 737 (s), 688 (s).

MS (EI, 70 eV) *m/z*, (%): 380 (M^+, 2), 337 (19), 335 (13), 307 (8), 287 (13), 271 (6), 265 (11), 264 (24), 263 (22), 250 (6), 245 (6), 241 (6), 228 (19), 213 (36), 188 (4), 177 (4), 173 (4), 167 (6), 155 (4), 123 (5), 115 (5), 110 (8), 109 (12), 105 (5), 95 (5), 93 (13), 91 (39), 73 (100).

HRMS (EI): calcd. for $C_{18}H_{25}ClN_2SSi$:380.1145, found:380.1131.

Synthesis of [3-bromo-5-methylthio-1-(2-trimethylsilylethoxymethyl)-1*H*-pyrazol-4-yl]-phenylmethanone (94d)



According to **TP11**, the pyrazole **92d** (323 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with $TMP_2Mg{\cdot}2LiCl$ (**12**; 1.8 mL, 0.6 M in THF, 1.1 mmol). After completion of the deprotonation, CuCN·2LiCl (1.0 mL, 1.0 M in THF, 1.0 mmol) was added and the mixture was stirred for 5 min before adding benzoyl chloride (169 mg, 1.2 mmol). The solution was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **94d** as a pale yellow oil (320 mg, 75%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.82-7.79 (m, 2 H), 7.62-7.56 (m, 1 H), 7.48-7.43 (m, 2 H), 5.60 (s, 2 H), 3.70 (t, $^3J_{H\text{-}H}$ = 8.3 Hz, 2 H), 2.37 (s, 3 H), 0.92 (t, $^3J_{H\text{-}H}$ = 8.2 Hz, 2H), 0.00 (s, 9 H).

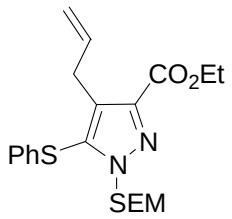
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 189.7, 140.2, 137.2, 133.5, 129.9, 128.4, 126.6, 125.6, 78.0, 67.4, 20.2, 17.9, -1.44.

IR (Diamond ATR): 1657 (s), 1598 (w), 1482 (m), 1365 (m), 1247 (s), 1230 (s), 1175 (w), 1088 (s), 1015 (W), 903 (m), 833 (s), 765 (m), 731 (m), 692 (s).

MS (EI, 70 eV) *m/z*, (%): 426 (M^+, 1), 385 (15), 383 (23), 381 (10), 369 (6), 355 (12), 353 (13), 337 (19), 335 (20), 317 (12), 312 (34), 311 (16), 310 (33), 309 (11), 293 (7), 279 (7), 256 (6), 231 (36), 139 (8), 137 (8), 105 (70), 91 (9), 77 (35), 73 (100), 43 (11).

HRMS (EI): calcd. for $C_{17}H_{23}{}^{79}BrN_2O_2SSi$: 426.0433, found: 426.0428.

Synthesis of ethyl 4-allyl-5-(phenylthio)-1-(2-trimethylsilylethoxymethyl)-1*H*-pyrazole-3-carboxylate (94e)



Ethyl 5-(phenylthio)-1-(2-trimethylsilylethoxymethyl)-1*H*-pyrazole-3-carboxylate (**92b**; 380 mg, 1.0 mmol) was dissolved in THF (1.0 mL) and added to a flame-dried flask equipped with a magnetic stirring bar, an argon inlet and a septum. The mixture was cooled to -30 °C and TMPMgCl·LiCl (**10a**; 1.0 mL, 1.1 M in THF, 1.1 mmol) was added while stirring. Upon completion of the exchange (determined by GC analysis of reaction aliquots quenched with I_2, 2 h), CuCN·2LiCl (0.1 mL, 1.0 M in THF, 0.1 mmol) was added and the reaction mixture was stirred for 5 min before adding allyl bromide (146 mg, 1.2 mmol). The solution was then allowed to slowly warm up to 25 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched according to **TP11**. Removal of the solvent *in vacuo* and purification by flash chromatography (SiO_2, initially neutralized with 3% Et_3N, pentane:EtOAc, 9:1) afforded the desired product as a yellow oil (297 mg, 71 %).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.24-7.13 (m, 3 H), 7.02-6.99 (m, 2 H), 5.91-5.78 (m, 1 H), 5.56 (s, 2 H), 4.93-4.87 (m, 2 H), 4.43 (q, $^3J_{H-H}$ = 7.2 Hz, 2 H), 3.57-3.49 (m, 4 H), 1.40 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H), 0.77-0.71 (m, 2 H), -0.08 (s, 9 H).

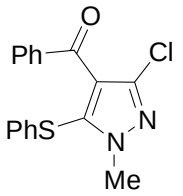
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 162.2, 141.6, 135.7, 134.9, 131.6, 130.0, 129.2, 126.9, 126.4, 115.4, 78.7, 67.0, 61.0, 28.8, 17.7, 14.4, -1.5.

IR (Diamond ATR): 2970 (s), 1718 (s), 1480 (w), 1365 (m), 1306 (w), 1247 (s), 1091 (s), 912 (w), 834 (s), 738 (m), 688 (m).

MS (EI, 70 eV) m/z, (%): 418 (M^+, 10), 373 (30), 346 (13), 345 (51), 331 (16), 318 (13), 317 (57), 315 (13), 302 (50), 301 (25), 299 (14), 288 (28), 287 (34), 256 (16), 255 (17), 242 (14), 230 (23), 229 (100), 228 (24), 213 (12), 190 (12), 111 (13), 109 (17), 97 (28), 91 (45), 85 (12), 83 (16), 81 (12), 75 (16), 73 (80), 71 (17), 69 (19), 59 (13), 57 (24), 55 (17), 44 (24).

HRMS (EI): calcd. for $C_{21}H_{30}N_2O_3SSi$:418.1746, found:418.1749.

Synthesis of (3-chloro-1-methyl-5-phenylthio-1*H*-pyrazol-4-yl)phenylmethanone (95a)



According to **TP11**, the pyrazole **93b** (225 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with $TMP_2Mg{\cdot}2LiCl$ (**12**; 1.8 mL, 0.6 M in THF, 1.1 mmol). After completion of the deprotonation $CuCN{\cdot}2LiCl$ (1.0 mL, 1.0 M in THF, 1.0 mmol) was added and the mixture was stirred for 5 min before adding benzoyl chloride (169 mg, 1.2 mmol). The solution was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **95a** as a pale yellow oil (240 mg, 73%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.80-7.78 (m, 2 H), 7.11-6.76 (m, 8 H), 3.16 (s, 3 H).

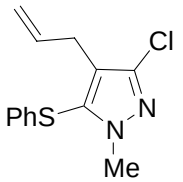
^{13}C-NMR (C_6D_6, 100 MHz): δ = 188.1, 138.7, 138.1, 135.1, 133.8, 133.1, 130.0, 129.6, 128.6, 128.5, 127.1, 124.3, 36.8.

IR (Diamond ATR): 2970 (m), 1737 (s), 1653 (s), 1580 (w), 1478 (m), 1378 (m), 1244 (s), 1078 (m), 906 (m), 812 (w), 732 (s), 688 (s).

MS (EI, 70 eV) *m/z*, (%): 330 (24), 329 (16), 328 (M^+, 66), 295 (3), 255 (34), 254 (14), 253 (100), 224 (6), 196 (4), 188 (3), 175 (3), 136 (2), 109 (5), 107 (3), 105 (32), 77 (20).

HRMS (EI): calcd. for $C_{17}H_{13}ClN_2OS$: 328.0437, found: 328.0430.

Synthesis of 4-allyl-3-chloro-1-methyl-5-(phenylthio)-1*H*-pyrazole (95b)



According to **TP11**, the pyrazole **93b** (225 mg, 1.0 mmol) dissolved in THF (1.0 mL) was treated with $TMP_2Mg{\cdot}2LiCl$ (**12**; 1.8 mL, 0.6 M in THF, 1.1 mmol). After completion of the deprotonation, $CuCN{\cdot}2LiCl$ (0.1 mL, 1.0 M in THF, 0.1 mmol) was added and the mixture was stirred for 5 min before adding allyl bromide (146 mg, 1.2 mmol). The solution was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized

with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **95b** as a colourless oil (185 mg, 70%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.29-7.12 (m, 3 H), 7.03-7.00 (m, 2 H), 5.86-5.76 (m, 1 H), 5.02-4.97 (m, 2 H), 3.80 (s, 3 H), 3.28-3.26 (m, 2 H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 138.4, 134.7, 134.5, 130.4, 129.4, 126.7, 126.4, 122.1, 115.8, 37.1, 28.1.

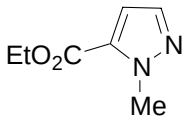
IR (Diamond ATR): 2970 (m), 1739 (s), 1582 (w), 1365 (s), 1217 (s), 1078 (m), 910 (m), 805 (w), 737 (s), 688 (s).

MS (EI, 70 eV) *m/z*, (%): 266 (30), 265 (19), 264 (M^+, 100), 263 (23), 249 (19), 237 (14), 235 (11), 230 (20), 202 (9), 201 (9), 196 (26), 189 (15), 187 (39), 185 (11), 173 (9), 161 (11), 160 (11), 155 (10), 151 (11), 120 (17), 119 (30), 115 (7), 114 (10), 113 (25), 44 (49).

HRMS (EI): calcd. for $C_{13}H_{13}ClN_2S$: 264.0488, found: 264.0480.

5.5 Preparation of the acaricide Tebufenpyrad

Synthesis of ethyl 1-methyl-1*H*-pyrazole-5-carboxylate (98)



According to **TP9,** the pyrazole **88** (820 mg, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (**10a**; 10 mL, 1.1 M in THF, 11 mmol). The resulting organomagnesium reagent was added dropwise at 0 °C to a solution of ethyl cyanoformate (990 mg, 12 mmol) in THF (10 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **98** as a yellow oil (1.19 g, 77%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.42 (d, $^3J_{H\text{-}H}$ = 2.2 Hz, 1 H), 6.80 (d, $^3J_{H\text{-}H}$ = 2.2 Hz 1 H), 4.34-4.27 (q, $^3J_{H\text{-}H}$ = 7.2 Hz, 2H), 4.15 (s, 3H), 1.34 (t, $^3J_{H\text{-}H}$ = 7.1 Hz, 3H).

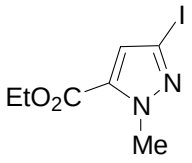
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 159.8, 137.6, 132.4, 111.1, 60.9, 39.5, 14.2.

IR (Diamond ATR): 2982 (w), 1719 (s), 1516 (m), 1472 (m), 1392 (m), 1317 (s), 1249 (s), 1113 (s), 1022 (s), 930 (m), 761 (s), 653 (m).

MS (EI, 70 eV) *m/z*, (%): 169 (6), 154 (M^+, 57), 131 (6), 126 (35), 118 (11), 109 (100), 95 (10), 81 (8), 72 (3), 69 (17), 54 (6), 44 (9).

HRMS (EI): calcd. for $C_7H_{10}N_2O_2$: 154.0742, found: 154.0745.

Synthesis of ethyl 3-iodo-1-methyl-1*H*-pyrazole-5-carboxylate (99)



According to **TP10,** pyrazole **98** (155 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (**10a**; 1.0 mL, 1.1 M in THF, 1.1 mmol). I_2 (305 mg, 1.2 mmol), dissolved in THF (1.0 mL) was added dropwise at -15 °C and the mixture was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) afforded pyrazole **99** as a yellow oil (154 mg, 55%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 6.94 (s, 1 H), 4.31 (q, $^3J_{H-H}$ = 7.1 Hz, 2H), 4.15 (s, 3 H), 1.34 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H).

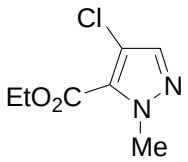
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 158.5, 134.4, 119.5, 92.5, 61.3, 39.8, 14.1.

IR (Diamond ATR): 2925 (w), 1723 (s), 1506 (w), 1467 (m), 1367 (m), 1351 (m), 1318 (m), 1300 (m), 1246 (s), 1130 (m), 1081 (m), 1029 (m), 954 (m), 816 (w), 762 (s), 721 (w).

MS (EI, 70 eV) *m/z*, (%): 281 (10), 280 (M^+, 27), 256 (46), 239 (20), 207 (12), 149 (12), 143 (11), 129 (17), 125 (11), 111 (11), 102 (37), 97 (22), 95 (14), 91 (16), 83 (26), 71 (22), 69 (32), 60 (22), 57 (35), 44 (100), 41 (43).

HRMS (EI): calcd. for $C_7H_9IN_2O_2$: 279.9709, found: 279.9702.

Synthesis of ethyl 4-chloro-2-methyl-2*H*-pyrazole-3-carboxylate (101)



A flask equipped with a magnetic stirring bar was charged with the pyrazole **98** (462 mg, 3.0 mmol) dissolved in acetic acid (10 mL). At 25 °C NaOCl (13% aq. solution; 7.0 mL, 12 mmol) was added and the reaction mixture was stirred for 6 h. Complete reaction conversion was checked by GC-analysis of hydrolyzed reaction aliquots. The mixture was quenched with water and extracted with EtOAc (3 x 50 mL). The organic extracts were dried over anhydrous Na_2SO_4 and filtered. Removal of the solvents furnished the product **101** as a white solid in (525 mg, 93%) yield.

m.p.: 33.7-34.2 °C.

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.27 (s, 1 H), 3.97 (q, $^3J_{H-H}$ = 7.1 Hz, 2 H), 3.68 (s, 3 H), 0.96 (t, $^3J_{H-H}$ = 7.1 Hz, 3 H).

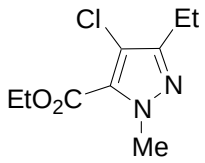
^{13}C-NMR (C_6D_6, 100 MHz): δ = 158.9, 137.5, 127.9, 115.2, 61.0, 40.6, 14.0.

IR (Diamond ATR): 2929 (w), 1718 (s), 1453 (m), 1422 (m), 1388 (m), 1266 (s), 1110 (s), 1031 (m), 991 (m), 863 (m), 840 (m), 776 (m), 748 (w), 649 (w).

MS (EI, 70 eV) *m/z*, (%): 190 (28), 188 (M^+, 100), 162 (11), 161 (13), 160 (43), 159 (36), 146 (4), 145 (22), 144 (12), 143 (86), 142 (6), 141 (12), 131 (6), 129 (19), 116 (9), 115 (11), 114 (8), 88 (10), 80 (5), 61 (5), 52 (4).

HRMS (EI): calcd. for $C_7H_9ClIN_2O_2$: 188.0353, found: 188.0350.

Synthesis of ethyl 4-chloro-5-ethyl-2-methyl-2*H*-pyrazole-3-carboxylate (103)



In a dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum, pyrazole **101** (188 mg, 1.00 mmol) was dissolved in THF (1.0 mL). At 25 °C $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**14**; 2.80 mL, 0.4 M in THF, 1.10 mmol) was added dropwise and the mixture was stirred for 30 min. Completion of the metallation was checked by GC-analysis of reaction aliquots previously quenched with I_2. After full conversion was achieved, I_2 (305.0 mg, 1.20 mmol) was added to the mixture and the consumption of the metallated reagent was checked by GC-analysis of hydrolyzed reaction aliquots. After 30 min stirring, iodide **102** was mixed with 2 mol% $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and 4 mol% S-PHOS (16.5 mg, 0.04 mmol). To this mixture, a pre-mixed solution of EtMgCl (0.53 mL, 2.80 M in THF, 1.50 mmol) and $InCl_3$ in THF (0.50 mL, 1.00 M in THF in THF, 0.50 mmol) was added dropwise. The reaction mixture was stirred for 8 h and completion of the cross-coupling was determined by GC-analysis. The mixture was quenched with water and extracted with EtOAc (3 x 20 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, pentane:EtOAc/9:1) furnished the desired compound **103** as a white solid (149 mg, 69%).

m.p.: 33.4-34.8 °C.

^{1}H-NMR (C_6D_6, 300 MHz): δ = 4.01 (q, $^3J_{H-H}$ = 7.2 Hz, 2 H), 3.73 (s, 3 H), 2.63 (q, $^3J_{H-H}$ = 7.5 Hz, 2 H), 1.25 (t, $^3J_{H-H}$ = 7.5 Hz, 3 H), 0.00 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H).

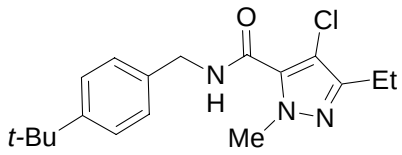
^{13}C-NMR (C_6D_6, 75 MHz): δ = 159.1, 150.2, 129.2, 113.1, 60.9, 40.3, 19.6, 14.0, 12.9.

IR (Diamond ATR): 2977 (w), 1714 (s), 1476 (m), 1449 (m), 1414 (w), 1272 (s), 1242 (m), 1117 (s), 1069 (m), 1032 (s), 872 (w), 774 (m), 626 (w).

MS (EI, 70 eV) *m/z*, (%): 219 (3), 218 (26), 217 (10), 216 (M^+, 100), 215 (9), 203 (13), 201 (40), 190 (5), 189 (11), 188 (16), 187 (35), 175 (15), 173 (60), 171 (26), 157 (9), 143 (4), 135 (3), 88 (3).

HRMS (EI): calcd. for $C_9H_{13}ClN_2O_2$: 216.0666, found: 216.0669.

Synthesis of 4-chloro-5-ethyl-2-methyl-2*H*-pyrazole-3-carboxylic acid 4-tert-butyl-benzylamide (97)



In a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum, *4-tert*-butylbenzylamine (196 mg, 1.2 mmol), dissolved in THF (1.0 mL) was deprotonated with NaH (60% in oil; 60 mg, 1.5 mmol). After gas emission had ceased, pyrazole **103** (216 mg, 1.0 mmol) dissolved in THF (1.0 mL) was added to the mixture at 25 °C. The reaction mixture was stirred for 3 h, quenched with water and extracted with EtOAc (3 x 20 mL). The organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, pentane: EtOAc/9:1) furnished Tebufenpyrad (**97**) as colourless crystals (250 mg, 75%).

m.p.: 55.7-57.4 °C.

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.26-7.24 (m, 2 H), 7.19-7.16 (m, 2 H), 6.69 (s, br, 1 H), 4.44 (d, $^3J_{H-H}$ = 5.7 Hz, 2 H), 3.96 (s, 3 H), 2.55 (q, $^3J_{H-H}$ = 7.6 Hz, 2 H), 1.23 (t, $^3J_{H-H}$ = 7.6 Hz, 3 H), 1.20 (s, 9 H).

^{13}C-NMR (C_6D_6, 100 MHz): δ = 158.3, 150.5, 149.2, 135.5, 131.5, 127.8, 125.9, 107.4, 43.2, 40.5, 34.4, 31.4, 19.5, 12.9.

IR (Diamond ATR): 3309 (w), 2966 (m), 1646 (s), 1546 (s), 1512 (m), 1449 (w), 1290 (s), 1270 (m), 1094 (w), 986 (w), 828 (w), 789 (w), 622 (m).

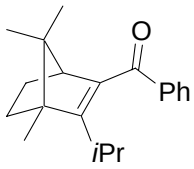
MS (EI, 70 eV) *m/z*, (%): 336 (4), 335 (22), 334 (14), 333 (M^+, 75), 321 (5), 320 (29), 319 (17), 318 (100), 298 (6), 278 (12), 277 (7), 276 (39), 173 (22), 172 (6), 171 (78), 162 (6), 159 (7), 152 (5), 147 (7), 146 (7), 145 (18), 138 (9), 137 (12), 131 (14), 117 (8).

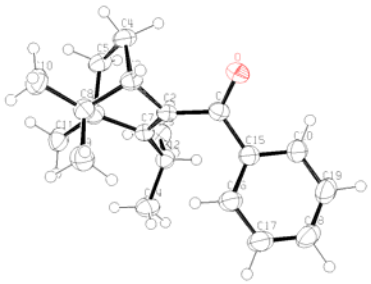
HRMS (EI): calcd. for $C_{18}H_{24}ClN_3O$: 333.1608, found: 333.1601.

D: Appendix

1. Data of the X-ray Analysis

Synthesis of (3-isopropyl-4,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)(phenyl)methanone (36)





Crystal Data

Formula:	$C_{20}H_{26}O$
Formula weight:	282.42
Crystal system:	monoclinic
Space group:	P21 (No. 4)
[a, b, c] (Å):	[10.6530(4), 7.2770(3), 10.6892(4)]
[α, β, γ] (deg):	[90.00, 98.652(2), 90.00]
V (Å^3):	819.22(5)
Z:	2
D_{calc} (g/cm^{-3}):	1.14
M(Mo_{Ka}) (mm^{-1}):	0.068
F(000):	308
Crystal size [mm]:	0.15 x 0.13 x 0.11
Temperature (K):	200
Radiation (Mo_{Ka}) (Å):	0.71073
θ_{min}, θ_{max} (deg):	3.4, 27.5
Dataset:	-13: 13; -9: 9; -13: 13
Tot., Uniq. Data, R_{int}:	7147, 3587, 0.0432
Observed data [I > 2.0 σ(I)]:	2980
N_{ref}, N_{par}:	3587, 295
R, wR^2, S:	0.0410, 0.0899, 1.054
Min. and max. resd. dens. (e. Å^{-3}):	-0.14, 0.13

CCDC 650282 contains the supplementary crystallographic data for this compound. These data can be obtained online free of charge from the Cambridge Crystallographic Data Centre.

2. Curriculum Vitae

Christina Despotopoulou

Date of birth:	25.01.1983
Place of birth:	Athens/Greece
Marital Status:	single
Nationality:	Greek

Education

1988 – 1994	BILINGUAL PRIMARY SCHOOL GRUNDSCHULE DES DEUTSCH-GRIECHISCHEN ERZIEHUNGSVEREINS
1994 – 2000	GERMAN SCHOOL OF ATHENS (GYMNASIUM) Greek high school diploma and German Abitur (Grade 1.3)
Okt. 2000 – Feb. 2006	STUDIES IN CHEMISTRY AT THE LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN Diploma thesis in the group of Prof. Dr. Paul Knochel, on "Selective Synthesis And Reactions of dienylic- und alkenylic Grignard-Reagents *via* Br/Mg-exchange" (Grade 1.0)
Since Mai 2006	PHD-THESIS AT THE LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN In the group of Prof. Dr. Paul Knochel

Languages

Greek	mother tongue
English	fluent
German	fluent

Scholarships

2001 – 2003	Scholarship of the German National Academic Foundation (Studienstiftung des Deutschen Volkes)

Work experience and internships

Since Mai 2006	LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

	Teaching Assistant for the organic lab-courses.
Jan 2007 – Mar 2007	BOEHRINGER-INGELHEIM-AUSTRIA GMBH Internship in the department of Medicinal Chemistry in Vienna (cancer research) in the research group of Dr Ioannis Sapountzis

Extracurricular activities

Oct 1998	Model United Nations in the German School of Athens (Chairman, Youth Commission)
Jun 1999	Model United Nations "Leadership Conference"In New York
Jan 2004 – Mai 2004	Choreography and stage design in the musical "A midsummer nights dream" (AGV München)
Aug 2004	Volunteer at the Olympic Games in Athens (Doping control)

Publications

1) C. Despotopoulou, L. Klier, P. Knochel, „ Total Functionalization of Pyrazole Derivatives by Selective Magnesiations", *Org. Lett.* 2009, *in press.*

2) C. Despotopoulou, C. Gignoux, D. McConnel, P. Knochel „ Metallation of 4,5-Dihydrobenzo[*g*]-indazoles", *Synthesis,* 2009, *in press.*

3) C. Despotopoulou, R. C. Bauer; A. Krasovskiy; P. Mayer; J. M. Stryker; P. Knochel " Selective Mono- and 1,2-Difunctionalisation of Cyclopentene Derivatives *via* Mg and Cu Intermediates" *Chem. Eur. J.* 2008, *14*, 2499-506.

4) I. Sapountzis, W. Lin, C. C. Kofink, C. Despotopoulou, P. Knochel, "Iron-catalyzed aryl-aryl Cross couplings with magnesium derived copper reagents" *Angew. Chem. Int. Ed.* 2005, *44*, 1654.

5) H. Emme, C. Despotopoulou, H. Huppertz," Gamma-Ce$(BO_2)_3$ Ein Neues Hochdruck-polymorph in der Reihe der Seltenerd-meta-oxoborate" *Z. Anorg. Allg. Chem.* 2004, *630*, 1717.

6) H. Emme, C. Despotopoulou, H. Huppertz, "High–Pressure Synthesis and Crystal Structure of the Structurally New Orthorhombic Rare–Earth Meta–Oxoborates gamma-RE$(BO_2)_3$ (RE = La – Nd)" *Z. Anorg. Allg. Chem.* 2004, *630*, 2450.

Oral- and Poster-Presentations

1) C. Despotopoulou “Total Functionalization of Pyrazole Derivatives by Selective Magnesiations” Poster Presentation at ISMOC February 19th to 22nd 2009 in Monastir,Tunesia (Poster award).

2) C. Despotopoulou “Total Functionalization of Pyrazole Derivatives by Selective Magnesiations” Poster Presentation at the Synthesefest March 17th to 18th 2009 in Munich at the Ludwig–Maximilians University.

3) C. Despotopoulou “Functionalization of Alkenylic Systems and 4,5- Dihydro-benzo[*g*]indazoles using Mg-Reagents” Oral Presentation at Boehringer-Ingelheim Austria GmbH, February 11th 2008 in Vienna.