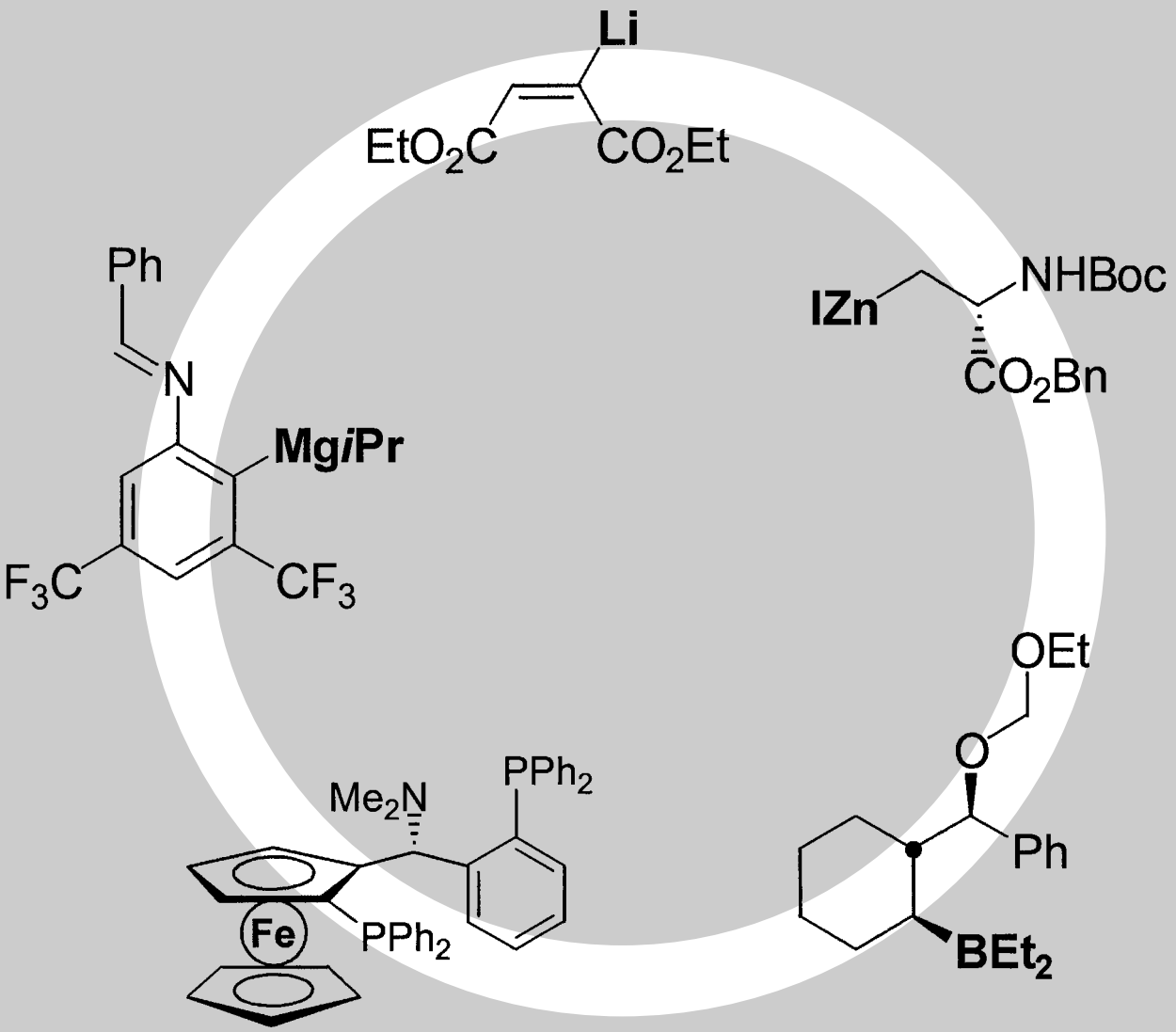
Polyfunctionalized organometallic complexes have great tolerance towards many functional groups making them particularly suitable for multistep syntheses without complicated protecting group strategies



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New Applications of Polyfunctional Organometallic Compounds in Organic Synthesis**

Andreas Boudier, Lars O. Bromm, Matthias Lotz, and Paul Knochel*

Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

In the second half of the twentieth century much effort was invested in the preparation of highly reactive polar organometallic reagents. The high reactivity of these reagents precluded the presence of many functional groups and often good chemoselectivities and stereoselectivities could only by achieved by transmetalation reactions. The synthesis of increasingly complex target molecules and the desire to avoid tedious protection–deprotection steps has led inevitably to the use of functionalized organometallic reagents in retrosynthesis. In the last fifteen years, the generation of organic derivatives of numerous metals and metalloids (Li, Mg, B, Zn, Sn) was investigated. In this review the most important preparations and applications of organometallic reagents in organic synthesis will be covered, with particular emphasis on organozinc reagents.

Keywords: asymmetric catalysis · asymmetric synthesis · C–C coupling · organometallic compounds · synthetic methods

1. Introduction

The complexity of organic target molecules is constantly increasing and novel strategies allowing the efficient formation of new carbon–carbon bonds between functionalized moieties are needed. Conventional approaches using extensive protecting-group strategies are not satisfactory[1] because of a mediocre atom economy.[2] Radical reactions are more attractive but are more difficult to tune than polar reactions.[3] On the other hand, polyfunctional organometallic complexes provide a general entry into complex molecules and extensive applications in total synthesis have been described.[4] There are two difficulties associated with organometallic reagents: 1) to tolerate the functional groups present their preparation requires mild reaction conditions; 2) their reactivity is in many cases too low so that a transition metal catalyst is required. The reactivity of an organometallic species generally increases with the increasing ionic nature of the carbon–metal bond and thus with the difference of electronegativity between the metal center and the carbon atom (Figure 1).[5]

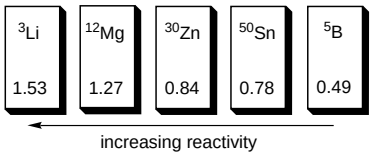

Figure 1. Metals used for the formation of polyfunctional organometallic complexes and electronegativity differences between the metal and carbon (Allred–Rochow electronegativity scale).

The polar organolithium compounds display a high reactivity toward most functional groups. The generation of polyfunctional organolithium species is only possible at low temperature or in the presence of an electrophile (Barbier reaction[6]). At the other end of the reactivity spectrum are zinc, tin, and boron which form covalent bonds with carbon. These elements show little reactivity towards many electrophilic reagents but thus, tolerate many functional groups. Decisive for the synthetic applications of these non-polar organometallic compounds is the presence of low-lying orbitals which facilitate transmetalations. This review article emphasizes the synthetic applications of the most useful classes of polyfunctional organometallic complexes, and especially the recent results with polyfunctional organozinc compounds.

2. Polyfunctional organolithium reagents

Organolithium compounds have played a central role in the development of organometallic chemistry for organic syn-

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[**] Frequently used abbreviations are defined at the end of the article.

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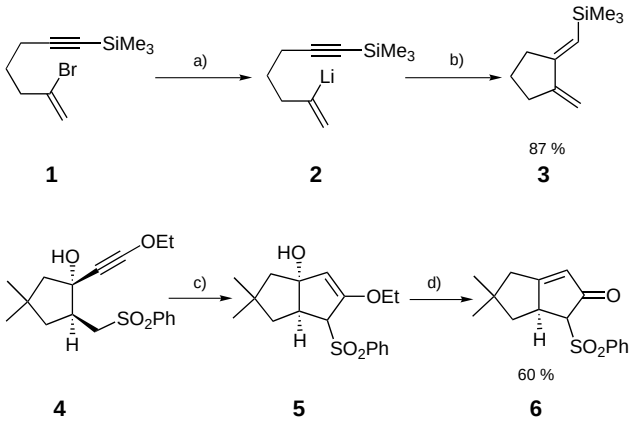
thesis.[7] These reagents have to be prepared at low temperature because they attack even moderately reactive functionalized compounds such as silylacetylene. This property has been exploited in a very useful diene synthesis: Thus, the reaction of the enyne **1** with *t*BuLi at $-100\,^{\circ}C$ affords cleanly the difunctional lithium compound **2** which undergoes a smooth cyclization at $0\,^{\circ}C$ providing the diene **3** (Scheme 1).[8] A similarly straightforward carbolithiation[9] is observed with alkoxyacetylenes. Thus, the lithiated sulfone obtained from **4** affords, after cyclization and hydrolysis via **5**, the enone **6**.[10]

The remarkable pioneer work of Parham et al.[11] has shown that various funtionalized aryl- or heteroaryllithium derivatives can be prepared by a bromine–lithium exchange. The aryllithium **7** is only stable at low temperature and has to be trapped with a highly reactive electrophile. With ketones under these conditions good yields of products such as **8** are obtained (Scheme 2). Alternatively, the unstable aryllithium can be transmetalated to the corresponding zinc reagent which is stable at $25\,^{\circ}C$ and can react with a broad variety of electrophiles in the presence of a transition metal catalyst.[12] Thus, the functionalized alkenyl iodide **9** is converted into the coresponding zinc compound **10** which, in the presence of $CuCN \cdot 2\,LiCl$,[13] smoothly adds to ethyl propiolate furnishing the unsaturated diester **11**.[14]



Scheme 1. Intramolecular carbolithiations. a) *t*BuLi (2 equiv), pentane/diethyl ether, $-100\,^{\circ}C$; b) $0\,^{\circ}C$, 1 h; c) *n*BuLi (2 equiv), $-78\,^{\circ}C \rightarrow 0\,^{\circ}C$, 0.5 h; d) H_3O^+.

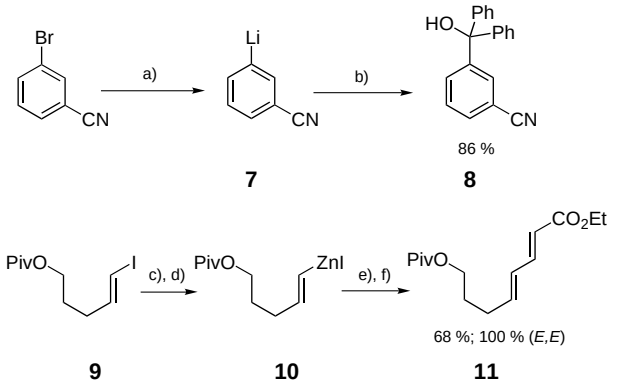
A. Boudier L. O. Bromm M. Lotz P. Knochel

Paul Knochel was born in 1955 in Strasbourg (France). He did his undergraduate studies at the University of Strasbourg and completed his Ph. D. at the ETH Zürich under the supervision of Prof. D. Seebach (1982). He spent 4 years at the CNRS at the University Pierre and Marie Curie (Paris) with Prof. J.-F. Normant and one year of post-doctoral studies at the Princeton University in the laboratory of Prof. M. F. Semmelhack. In 1987 he became assistant professor at the University of Michigan in Ann Arbor and full professor in 1991. He then accepted a C4-professor position at the Philipps-University in Marburg (Germany). In 1999, he moved to the Chemistry Department of the Ludwig-Maximilians-University (LMU) in Munich. His research interests are the development of new synthetic methods for organic chemistry using organometallic reagents, new asymmetric catalysts, and natural product synthesis.

Andreas Boudier, born 1973 in Saarlouis (Germany), passed his undergraduate studies at the University of Saarbrücken (Germany, 1992–94), Strasbourg (France, 1994–97), and Houston (USA, 1997). He started his Ph. D. in Prof. Knochel's group in 1997 at the Philipps-University in Marburg and moved with him in 1999 to the LMU Munich. His work concentrates on the preparation and reactions of chiral dialkylzinc compounds.

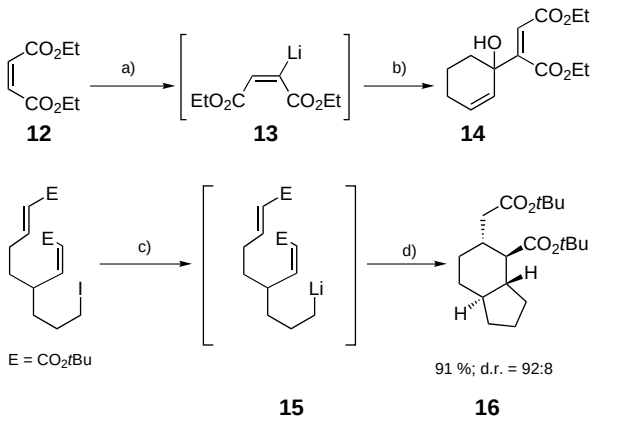
Lars Olav Bromm, born 1973 in Lich (Germany), did his undergraduate studies at the Philipps-University in Marburg (Germany) and at the University of Manchester Institute of Science and Technology (UMIST). After completing his undergraduate studies with Prof. P. Knochel on diastereoselective rearrangements of organoboranes, he moved with Prof. P. Knochel to the LMU Munich in 1999 to start a Ph. D. on the rearrangements of organoboranes and selective activation of C–H-bonds.

Matthias Lotz was born in Marburg (Germany) in 1972. He did his undergraduate studies at the Philipps-University in Marburg (1993–99). He joined the Knochel group in 1998 for his diploma thesis and started his Ph. D. at the LMU Munich in the same group in 1999. His work concentrates on the development of new ferrocenyl-type catalysts and their application in asymmetric catalysis.



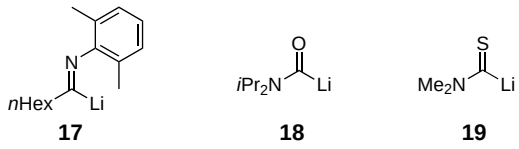
Scheme 2. Reactions of aryl and alkenyl zinc reagents. a) *n*BuLi, THF/hexane, $-100\,^{\circ}C$; b) benzophenone; c) *n*BuLi, THF/diethyl ether/hexanes, $-100\,^{\circ}C$, 4 min; d) ZnI_2, THF; e) $CuCN \cdot 2\,LiCl$, THF/Et_2S, $-20\,^{\circ}C$; f) ethyl propiolate, $-20\,^{\circ}C$, 2 h.

Under appropriate reaction conditions, the presence of an ester group is tolerated in the generation of an organolithium species. Thus, satisfactory yields of **14** are obtained by adding diethyl maleate (**12**) to a cooled solution of *N*-lithio-2,2,6,6-tetramethylpiperidine in THF and quenching immediately the short-lived intermediate **13** with an excess of an electrophile (Scheme 3).[15] A rapid iodine–lithium exchange allows the generation of a lithium compound **15** bearing two ester functions. This reagent undergoes a Michael addition furnishing with an excellent stereoselectivity the *trans*-bicyclo[4.3.0]-nonane **16** in 91 % yield.[16]

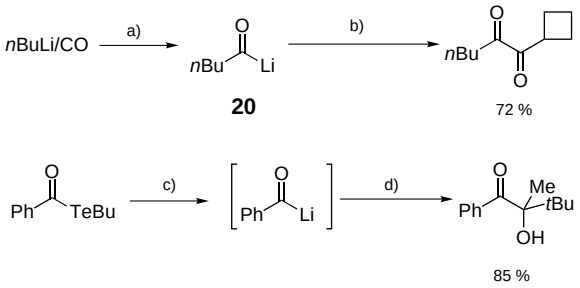


Scheme 3. Synthesis and reactions of funtionalized alkenyllithium compounds generated for ester groups. a) *N*-lithium-2,2,6,6-tetramethylpiperidine, THF, $-78\,^{\circ}C$; b) 2-cyclohexenone; c) *n*BuLi, THF, $-100\,^{\circ}C$; d) $-100\,^{\circ}C \rightarrow -30\,^{\circ}C$.

The presence of heteroatoms in close proximity to the carbon–lithium bond facilitates the formation of an organolithium species as long as the various functional groups are tolerated.[17] The direct lithiation with lithium powder in the presence of a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DBB), as popularized by Yus et al.[18], proves to be a very convenient method for preparing a broad range of polyfunctional organolithium reagents.[17–19] Thus, the difficult to prepare imidoyl (**17**), carbamoyl (**18**), or thiocarbamoyl (**19**) lithium compounds could be generated.[19,18c] The direct



preparation of acyllithium compounds such as **20**, either by a direct low-temperature route from RLi/CO[20,21] or a lithium–tellurium exchange reaction,[22] has been successfully performed. In these direct preparation methods, the acyllithium species is generated in the presence of an electrophile (Scheme 4).

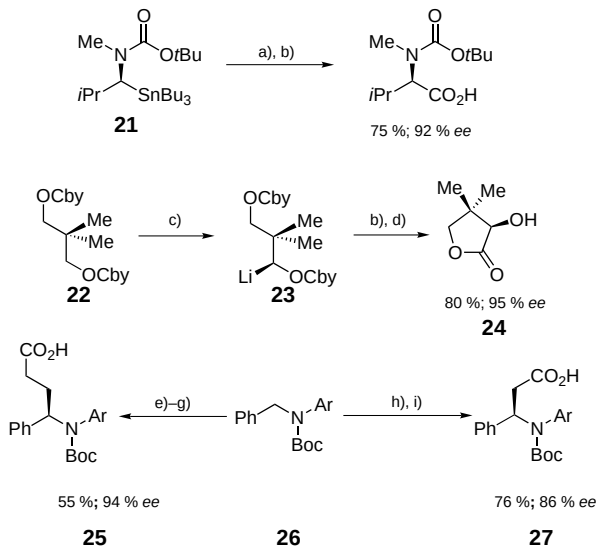


Scheme 4. Generation of acyllithium compounds. a) THF, $-100\,^{\circ}C$; b) ethyl cyclobutanecarboxylate, $-110\,^{\circ}C$; c) *n*BuLi, THF/diethyl ether, $-105\,^{\circ}C$; d) methyl-*tert*-butylketone.

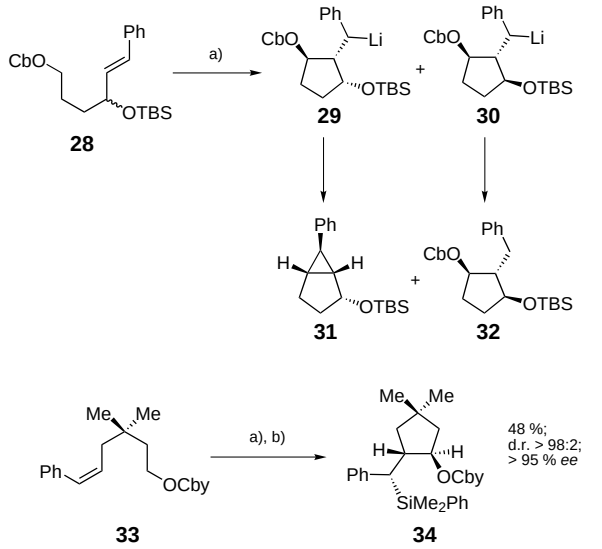
A remarkable development in the preparation of chiral functionalized organolithium reagents has led to numerous synthetic applications.[23] The chiral compounds first prepared were functionalized in the position α to oxygen.[24] Chiral organolithium reagents have also been obtained functionalized at the position α to nitrogen,[25] sulfur,[26] and, selenium.[27] Optically pure or enriched lithium compounds can be prepared from the corresponding α-substituted organostannane compounds such as **21**[28] or with the aid of the enantioselective deprotonation developed by Hoppe's group[23a] using (−)-sparteine as a chiral inductor (Scheme 5).[29]

This method has been successfully extended by Beak et al.,[30] and others, [31] to organolithium compounds functionalized at the position α to nitrogen. Thus, the enantioselective deprotonation of the 1,3-dicarbamate **22** with *s*BuLi/(−)-sparteine provides the functionalized lithium reagent **23** which is readily carbonylated affording, after acidic deprotection, (*R*)-pantolactone (**24**) in 95 % *ee*;[29] β- and γ-amino acid derivatives such as **25** and **27** are obtained from *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine (**26**) in high enantiomeric purity.[32]

Enantioselective carbometalation reactions have also been performed by using the asymmetric deprotonation assisted by (−)-sparteine. The cyclization of the racemic carbamate **28** gives a 1:1 mixture of the two compounds **31** and **32**. The intermediate **29** undergoes a fast intramolecular cyclopropane formation while the diasteriomer **30** is stable under the reaction conditions and is hydrolyzed to the diastereomerically pure cyclopentane **32** (Scheme 6).[33]



Scheme 5. Preparation and reactions of chiral organolithium compounds. a) *n*BuLi, THF, −95 °C, 10 min; b) CO_2; c) *s*BuLi, (−)-sparteine; d) HCl, Δ; e) *n*BuLi, (−)-sparteine; f) acroleine; g) CrO_3/H_2SO_4; h) *n*BuLi, (−)-sparteine, 1-bromo-3-methylbut-2-ene; i) O_3, then CrO_3. (Cby = carbamoyl group.)

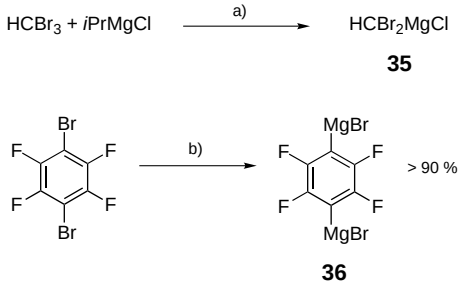


Scheme 6. Intramolecular enantioselective carbolithiation. a) *s*BuLi, (−)-sparteine, diethyl ether, −78 °C → −40 °C; b) $PhMe_2SiCl$. (Cb, Cby various carbamoyl groups.)

The stereochemistry of up to three chiral centers can be controlled in these cyclizations and the carbamate **33** undergoes a smooth cyclization providing, after silylation, the benzyl silane **34** with excellent stereoselectivity (Scheme 6).[34] The intermolecular version of this reaction is also possible and the addition of alkyllithium compounds to cinnamaldehyde and cinnamylamine also proceeds with excellent stereoselectivity.[35]

3. Polyfunctional organomagnesium reagents

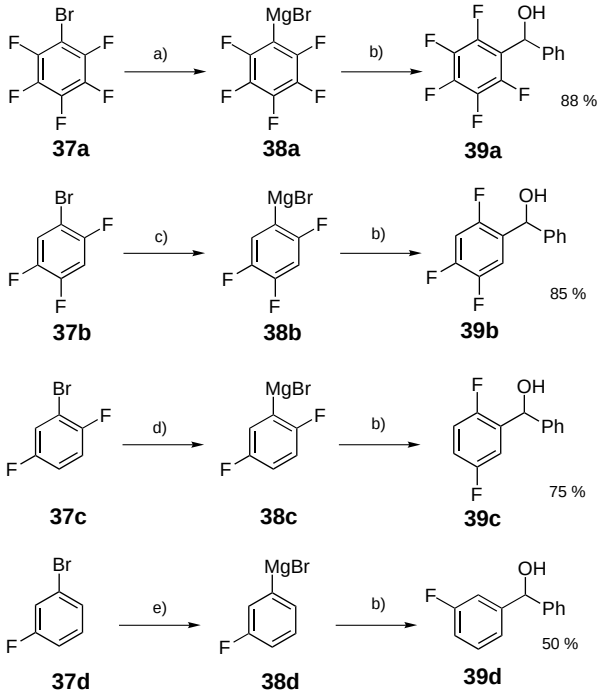
Although organomagnesium reagents bear a more covalent carbon–metal bond than organolithium reagents and thus would appear suitable for use in organic synthesis, only a few methods for generating functionalized organomagnesium species have been described.[36] The use of highly active magnesium, such as "Rieke-magnesium",[37] is not possible since the presence of electron-poor functional groups such as a carboxy or cyano group inhibits the formation of the Grignard reagent.[38] Recently, the halide–magnesium exchange reaction was employed for preparing polyfunctional aryl-, heteroaryl-, or alkenylmagnesium compounds.[39] The mild conditions required for the bromine–magnesium exchange were first discovered by Villiéras who demonstrated that highly reactive magnesium carbenoids such as **35** can be prepared at −78 °C.[40] Even dimagnesium derivatives like **36** have been prepared using the Br/Mg exchange reaction (Scheme 7).[41]



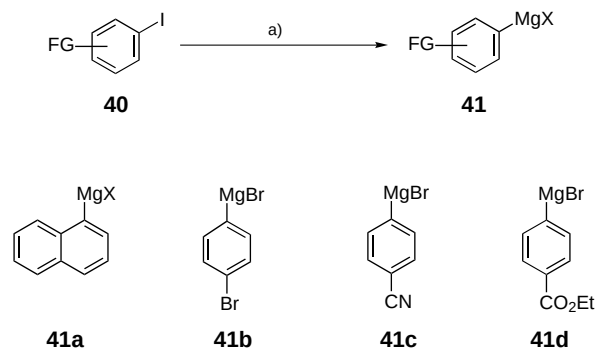
Scheme 7. Applications of the bromine–magnesium exchange. a) THF, −78 °C; b) EtMgBr (2 equiv), THF.

Both the iodine–magnesium and the bromine–magnesium exchange are accelerated by the presence of electron-withdrawing groups in the organic halide. Thus, in the fluorinated bromobenzene derivatives **37a–d** a significant difference is observed in the rates of the exchange reactions.[42,43] Whereas bromopentafluorobenzene (**37a**) reacts with *i*PrMgBr at −78 °C within 30 min giving the corresponding Grignard reagent **38a**, 1-bromo-2,4,5-trifluorobenzene (**37b**) requires a reaction temperature of −10 °C for the Br/Mg exchange reaction to **38b**. Both organomagnesium compounds react cleanly with PhCHO giving the benzyl alcohols **39a** and **39b** in 85 and 88 % yield, respectively. For the 1-bromo-2,5-difluorobenzene (**37c**), the use of the more reactive $i\text{Pr}_2\text{Mg}$ and a reaction temperature of 20 °C are required to drive the reaction to completion. The 1-bromo-3-fluorobenzene (**37d**) is converted into the corresponding magnesium reagent at 20 °C only by using an excess of $i\text{Pr}_2\text{Mg}$ (3 h). Treatment with PhCHO leads to the alcohol **39d** in only 50 % yield because of the competitive reaction of excess *i*PrMgR with the electrophile PhCHO (Scheme 8).

In contrast, the iodine–magnesium exchange is possible at lower temperatures. Thus, an unactivated aryl iodide such as 1-naphthyl iodide (**40a**) undergoes the I/Mg exchange at 25 °C within 0.5 h using 0.5 equivalents $i\text{Pr}_2\text{Mg}$. In the presence of electron-withdrawing groups such as a bromine, cyano, or ethylcarboxylate, a fast exchange reaction occurs between −25 and −40 °C leading to polyfunctional arylmagnesium compounds such as **41b–d** which are perfectly stable at these low temperatures allowing for the first time a general approach to functionalized arylmagnesium compounds (Scheme 9).[44]



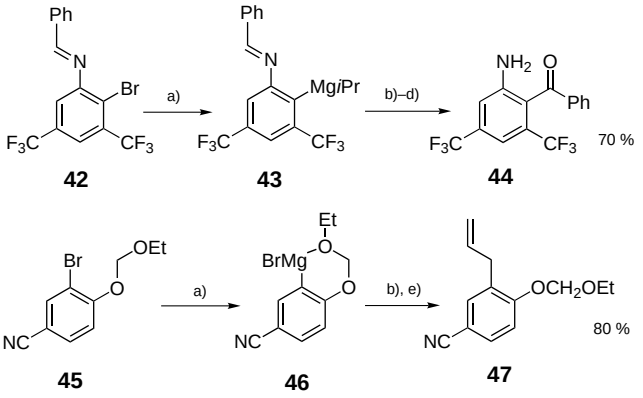
Scheme 8. Rate of the bromine–magnesium exchange depends upon the degree of fluorination of the bromoarene. a) *i*PrMgBr, THF, −78 °C, 0.5 h; b) PhCHO; c) *i*PrMgBr, THF, −10 °C, 1 h; d) *i*PrMgBr, THF, 20 °C, 2 h; e) *i*PrMgBr, THF, 20 °C, 3 h.



Scheme 9. Entry to funtionalized organomagnesium compounds by an I/Mg exchange. a) *i*PrMgBr (1.0 equiv) or iPr_2Mg (0.5 equiv), THF, −25 °C → −40 °C. (FG = functional group.)

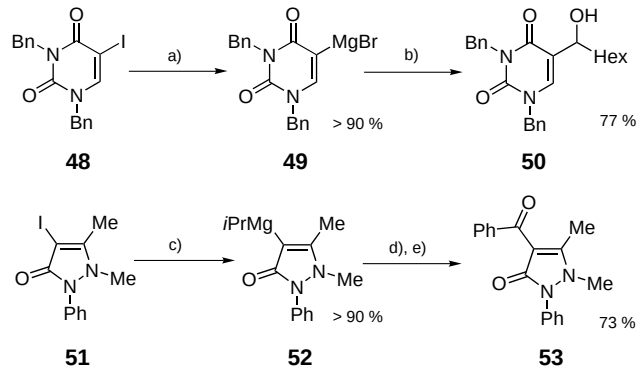
If there are sufficient electron-withdrawing groups in the molecule the bromine–magnesium exchange can also be useful in preparative chemistry. Thus, the bromobenzene derivative **42** reacts with iPr_2Mg at 0 °C and provides the imine-functionalized magnesium compound **43**. After a copper-catalyzed benzylation and acidic workup, the aniline **44** is obtained in 70% yield.[42] The presence of an *ortho*-directing group, as in **45**, considerably facilitates the exchange reaction. For example the chelate stabilized organomagnesium compound **46**, is converted by allylation into the benzonitrile **47** in 80% yield (Scheme 10).[42]

The exchange reaction can also be applied to a variety of heterocyclic iodides or bromides. Thus, the 5-iodouracil derivative **48** reacts smoothly with *i*PrMgBr in THF (−40 °C, 0.5 h) and affords the corresponding magnesium derivative **49** which displays a much higher reactivity than the



Scheme 10. Synthesis and reactions of functionalized organomagnesium derivatives. a) iPr_2Mg, THF, 0 °C, 45 min; b) CuCN (10 mol%); c) PhCOCl −30 °C → 0 °C; d) 2 M HCl; e) allyl bromide.

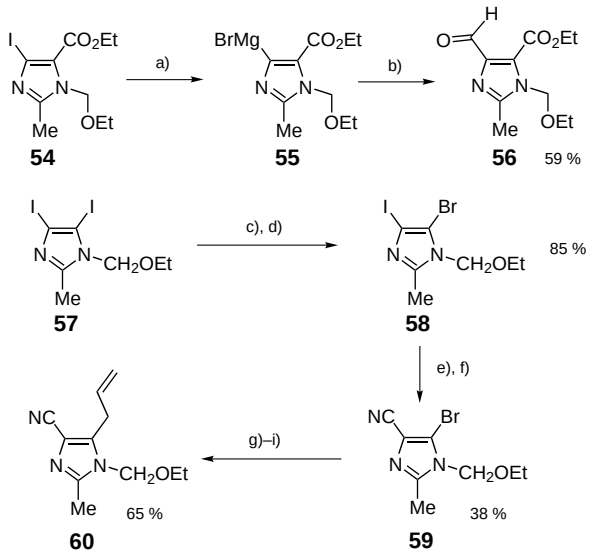
corresponding zinc derivative[45] reacting readily with, for example, aldehydes to give alcohols such as **50**. Similarly, the iodoantipyrine **51** can be converted into the corresponding heteroarylmagnesium compound **52**, which reaction with PhCOCl (after transmetalation with $CuCN \cdot 2\,LiCl$[13]) to the ketone **53** in 73% yield (Scheme 11).[46]



Scheme 11. Synthesis of heterocyclic Grignard reagents by halide–magnesium exchange and subsequent reactions. a) *i*PrMgBr, THF, −40 °C, 30 min; b) *n*HexCHO, −40 °C → rt; c) iPr_2Mg, CH_2Cl_2, −25 °C, 2 h; d) $CuCN \cdot 2\,LiCl$; e) PhCOCl, 0 °C.

Functionalized iodoimidazoles like **54** undergo an exchange reaction at −40 °C. The resulting Grignard reagent **55** reacts with DMF furnishing the aldehyde **56** in 59% yield.[46] The 4,5-diiodoimidazole (**57**) undergoes the I/Mg exchange preferentially at the 5-position. It is possible to perform a contrathermodynamic exchange at the 4-position, by converting the iodine substituent into a bromine (Scheme 12).

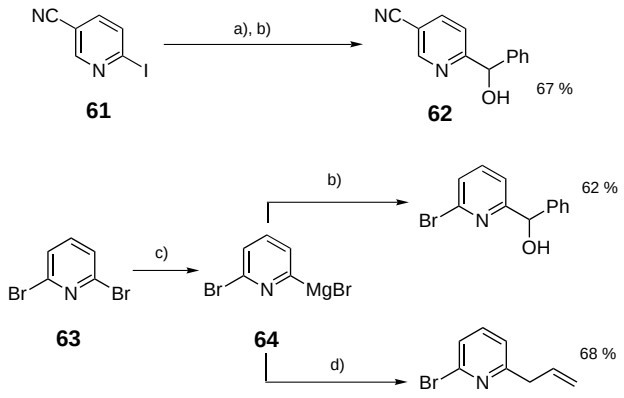
Thus, the treatment of **57** with iPr_2Mg in a mixture of THF and *N*-butylpyrrolidinone (NBP) at −35 °C leads to the incorporation of the magnesium reagent at the 5-position. Reaction with $(BrCl_2C)_2$ affords the 5-bromo-4-iodoimidazole derivative **58**. A second exchange with *i*PrMgBr gives a magnesium compound which can be cyanated by *N*-cyanobenzotriazole giving the 5-bromo-4-cyanoimidazole (**59**). This heterocyclic bromide undergoes a fast Br/Mg exchange (THF,



Scheme 12. Synthesis and reactions of functionalized magnesium imidazole derivatives. a) *i*PrMgBr, THF, −40 °C, 1 h; b) DMF; c) iPr_2Mg, THF/NBP, −35 °C, 1 h; d) $(BrCl_2C)_2$, −35 °C, 1.5 h; e) *i*PrMgBr, −50 °C, 0.5 h; f) *N*-cyanobenzotriazole, THF, −78 °C→rt, 2 h, inverse addition; g) *i*PrMgBr, THF, −50 °C, 10 min; h) CuCN·2LiCl; i) allyl bromide.

−50 °C, 10 min) leading, after copper(I)-catalyzed allylation, to the imidazole **60** (Scheme 12).[46]

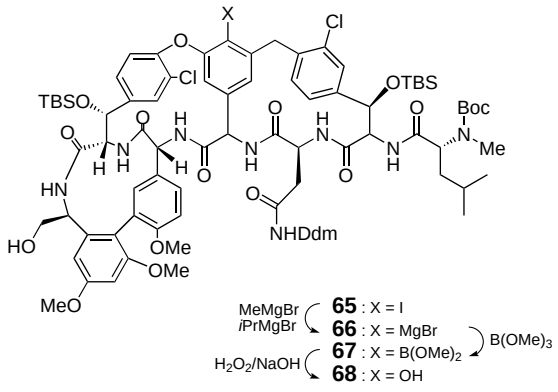
The presence of the CH_2OEt group greatly accelerates this exchange reaction. Functionalized pyridines such as **61** undergo the I/Mg exchange within a few minutes, showing again the importance of electron-withdrawing groups. After reaction with PhCHO, the expected alcohol (**62**) is obtained in 67% yield (Scheme 13).[47] Various dibromoheterocycles[43]



Scheme 13. Selective generation of pyridylmagnesium derivatives and subsequent reactions. a) *i*PrMgBr (1.1 equiv), THF, −78 °C, 2 min; b) PhCHO; c) iPr_2Mg, 20 °C, 4 h; d) allyl bromide.

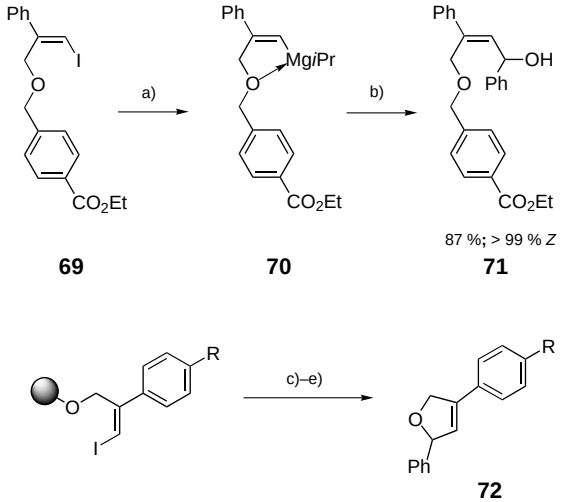
were found to undergo a chemoselective mono Mg/Br-exchange reactions. Thus, 2,6-dibromopyridine[48] (**63**) undergoes a selective exchange with iPr_2Mg (THF, 20 °C, 4 h) furnishing the magnesium derivative **64** which can be trapped by various electrophiles (Scheme 13).[42]

A Michael addition can be performed by treating the polyfunctional Grignard reagents with an enone in the presence of TMSCl (1 equiv) and CuCN·2LiCl (10 mol%).[49] In the course of the synthesis of the antibiotic Vancomycin, the iodine–magnesium exchange is used to perform a difficult oxidation reaction. The aryl iodide **65** undergoes a selective I/Mg exchange by treatment with MeMgBr and *i*PrMgBr (excess) leading to the organomagnesium derivative **66**. Reaction with $B(OMe)_3$ affords the boronic ester **67** which is oxidized to the corresponding phenol **68** with an alkaline solution of H_2O_2 (Scheme 14).[50]



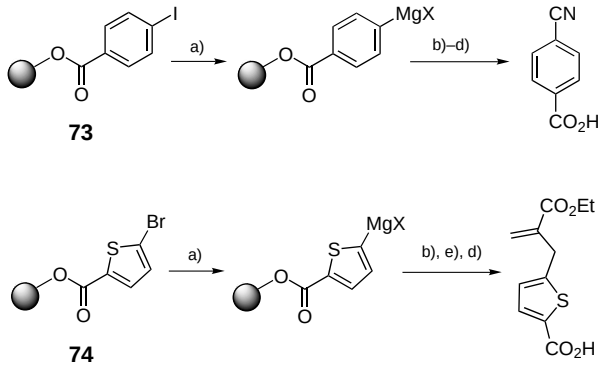
Scheme 14. Iodine–magnesium exchange in the synthesis of Vancomycin.

Besides aryl and heteroaryl iodides or bromides, alkenyl iodides also undergo an I/Mg exchange, however it is considerably slower. Thus, the reaction of (*E*)-iodooctene with iPr_2Mg requires 18 h at 25 °C for complete conversion. Again, the presence of a chelating group in the proximity of the halide helps the I/Mg exchange. Thus the allyl ether **69** undergoes an I/Mg exchange at −70 °C within 12 h giving the chelate stabilized organomagnesium derivative **70** which inturn reacts with PhCHO furnishing the (*Z*)-allyl alcohol **71** (> 99% *Z*). This reaction sequence can be efficiently performed on the solid phase and leads to dihydrofuranes of type **72**. The cleavage from the solid phase is performed under strong acidic conditions (CF_3CO_2H) which induce the cyclization reaction (Scheme 15).[51]



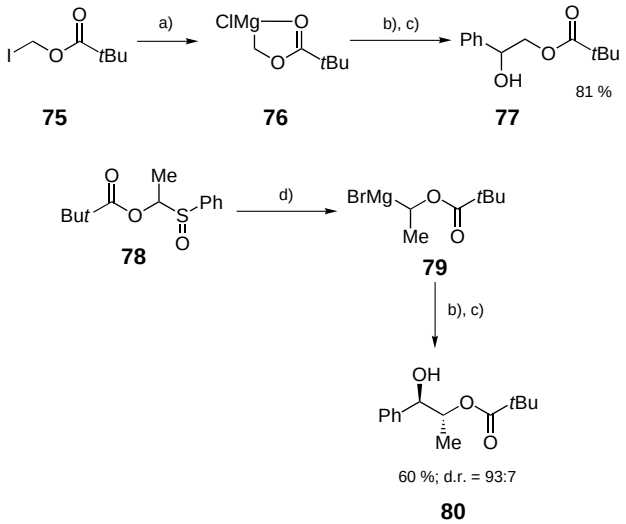
Scheme 15. Preparation and reactions of functionalized alkenylmagnesium compounds in solution and in the solid phase. (97%–98% HPLC purity). a) iPr_2Mg, THF, −70 °C, 12 h; b) PhCHO, −70 °C→rt; c) *i*PrMgBr, THF:NMP (40:1), −40 °C, 1.5 h; d) PhCHO; e) TFA:CH_2Cl_2 (1:9).

Similarly, a range of aryl iodides or heteroaryl iodides or bromides such as **73** and **74** attached to a Wang-resin are readily converted to the Grignard reagent using an excess of *i*PrMgBr (7–10 equiv). Remarkably, the ester linker is not attacked under these reaction conditions (−35 °C, 0.5–1.0 h).[44,51] This reaction constitutes one of the most general and convenient preparation methods for an organometallic species[52] on the solid phase (Scheme 16) and is ideally suited for applications in combinatorial chemistry.[53]



Scheme 16. Preparation and reactions of functionalized aryl- and heteroarylmagnesium compounds on a solid phase. (>94% HPLC purity). a) *i*PrMgBr (7 equiv), THF, −35 °C, 0.5–1 h; b) CuCN·2LiCl; c) TosCN; d) CF_3CO_2H; e) ethyl(α-bromomethyl)acrylate.

Sensitive intermediates like the functionalized carbenoid **76** could be prepared from the readily available iodomethyl pivalate (**75**). Using *i*PrMgCl, the I/Mg exchange was complete within 15 min at −78 °C. Treatment of **76** with PhCHO in the presence of TMSCl (excess) affords the 1,2-diol derivative **77** in 81%. As an extension of this reaction, the sulfoxide **78** was found to undergo a sulfoxide–magnesium exchange[54] leading to the substituted magnesium carbenoid **79** which, after reaction with PhCHO, furnishes the alcohol **80** (Scheme 17).[55]



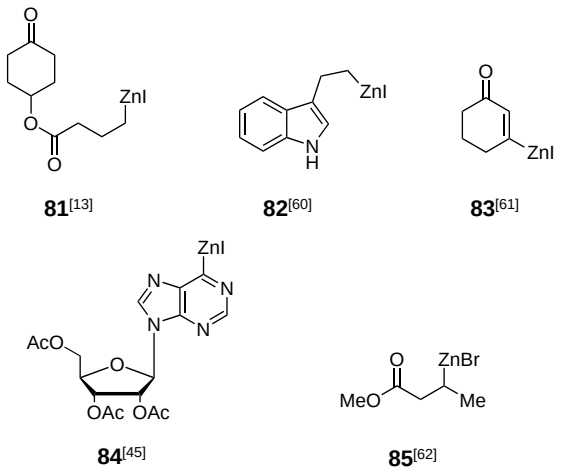
Scheme 17. Synthesis and reactions of functionalized organomagnesium carbenoids. a) *i*PrMgCl, THF/NBP, −78 °C, 15 min; b) PhCHO; c) TMSCl; d) *i*PrMgBr, THF, −78 °C, 15 min.

4. Polyfunctional organozinc reagents

Organozinc derivatives have an almost covalent carbon–metal bond and are therefore less reactive than organolithium reagents or organomagnesium compounds. This low reactivity allows for the presence of many functional groups in organozinc compounds.[12,56–58]

4.1 Preparation of organozinc reagents by halogen–zinc exchange

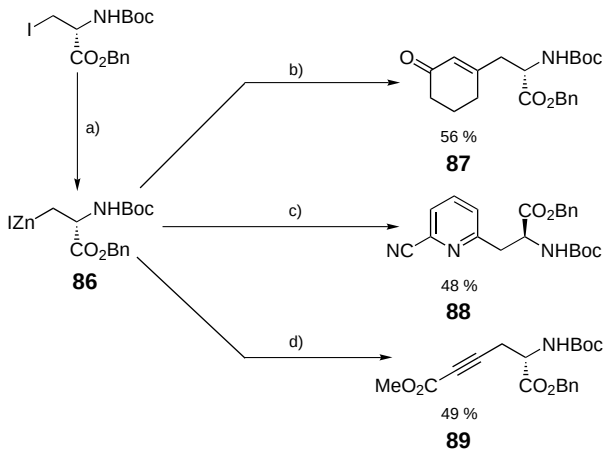
A broad range of zinc organometallics such as **81**–**84** have been prepared by the direct insertion of zinc (added in the form of zinc dust) to a polyfunctional alkyl iodide, or as for **85**, by using the reaction of highly activated "Rieke-zinc"[37,59] with an alkyl bromide. Interestingly, activated organic halides



like benzylic, allylic, or propargylic halides undergo the insertion reaction far more readily, allowing the use of the corresponding bromide, or in several cases, the corresponding chloride or phosphate.[12,63,64]

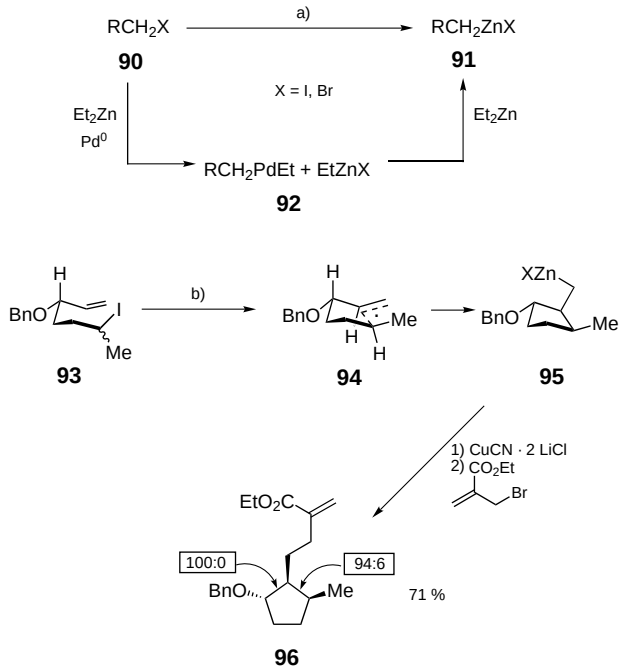
Ultrasound[65] has in some cases led to more efficient and faster zinc insertions than by conventional methods. This approach proves to be especially useful for the preparation of the zinc–serine derivative **86**. Although all these organozinc reagents are relatively unreactive they undergo fast transmetalations with most transition metal salts (except those of manganese; transmetalation is also not observed with lanthanides).

Thus, various transition metal catalysts (Pd,[66] Cu,[13] Fe,[67] Co,[67,68] Ti,[69] Ni[70]) catalyze the reaction of polyfunctional zinc compounds with functionalized electrophiles leading to a broad range of multifunctional organic molecules. Thus, the reaction of **86** with 3-iodo-2-cyclohexenone in the presence of catalytic amounts of Pd^0 provides the protected α-amino-acid **87**. Similarly the Pd^0-catalyzed reaction of **86** with 6-bromo-2-cyanopyridine furnishes the protected α-aminoacid **88**. With a copper-catalyst (CuCN·2LiCl), the addition of methyl 2-bromopropiolate[71] leads to the protected acetylene-α-aminoacid **89** (Scheme 18).



Scheme 18. Amino acid synthesis using a chiral functionalized organozinc intermediate. a) Zn, THF, 35 °C, ultrasound; b) 3-iodo-cyclohex-2-en-1-one, Pd^0; c) 2-bromo-5-cyanopyridine, Pd^0; d) $CuCN \cdot 2\,LiCl$, methyl bromopropiolate.

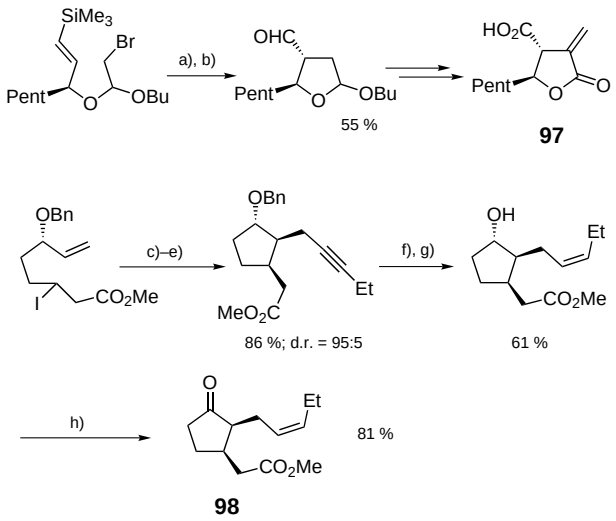
Organozinc halides of type **91** are also obtained using a palladium- or nickel-catalyzed halide–zinc exchange reaction.[70,72] The initial oxidative addition of Pd^0 to the alkyl iodide or alkyl bromide **90** proceeds by a radical mechanism (Scheme 19).[73] The palladium intermediate **92** undergoes a



Scheme 19. Radical pathway for the palladium catalyzed iodine–zinc exchange reaction. a) Et_2Zn (2 equiv), THF, Pd^0, 25 °C, 2 h; b) Et_2Zn (2 equiv), $[PdCl_2(dppf)]$ (1.5 mol %), 25 °C, 5 h.

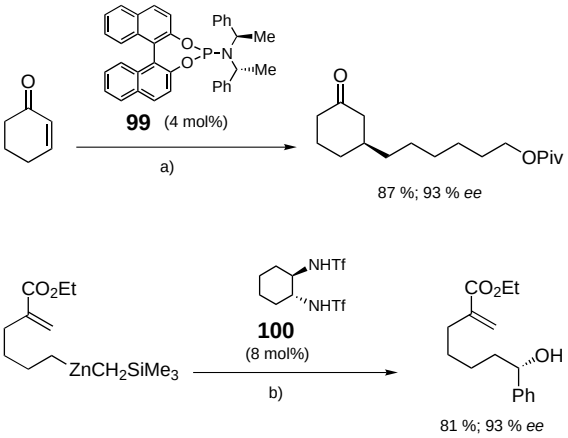
transmetalation with Et_2Zn leading to the organozinc reagent **91**. The radical nature of the halide–zinc exchange is best demonstrated by the stereoconvergent cyclization of the unsaturated alkyl iodide **93** (1:1 mixture of diastereomers) which leads to the almost diastereomerically pure compound **95** with stereocontrol of three adjacent centers.

The radical transition state **94** explains the stereoconvergence of the reaction as well as the stereochemistry of the product. After allylation with ethyl (2-bromomethyl)acrylate, the cyclopentane derivative **96** is obtained in 71 % yield.[74] This type of radical cyclization which provides an organometallic product is well suited for the preparation of polyfunctional natural products such as (−)-methylenolactocin (**97**)[75] and *cis*-methyl jasmonate (**98**)[76] (Scheme 20).



Scheme 20. Synthesis of (−)-methylenolactocin and *cis*-methyl jasmonate. a) Et_2Zn, LiI, $[Ni(acac)_2]$ cat., THF, 40 °C; b) O_2, TMSCl, THF, −5 °C; c) Et_2Zn, $[Ni(acac)_2]$ cat., THF, 25 °C; d) $CuCN \cdot 2\,LiCl$; e) 1-bromo-1-butyne, −55 °C, 48 h; f) H_2, $Pd/BaSO_4$ cat., pyridine, 92 %; g) BCl_3, CH_2Cl_2, −78 to −10 °C; h) Dess–Martin oxidation.

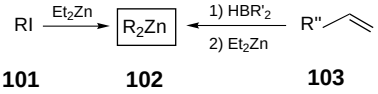
Like organozinc halides, diorganozinc compounds are an important class of organozinc reagents. The absence of halides makes these reagents especially useful in asymmetric additions (1,2- and 1,4-additions).[77,78] Thus, the use of the chiral ligand **99** (4 mol %) and $Cu(OTf)_2$ (2 mol %) allows the highly enantioselective addition of polyfunctional dialkylzinc compounds to cyclic enones (Scheme 21).[78] Also, the chiral 1,2-triflamide **100**[79] in combination with the mixed dialkyzinc compounds[80] of type $RZnCH_2SiMe_3$ allows the addition of



Scheme 21. Asymmetric catalysis with functionalized zinc complexes. a) $Zn((CH_2)_6OPiv)_2$, $Cu(OTf)_2$ (2 mol %); b) PhCHO, $Ti(OiPr)_4$, diethyl ether, −20 °C, 26 h.

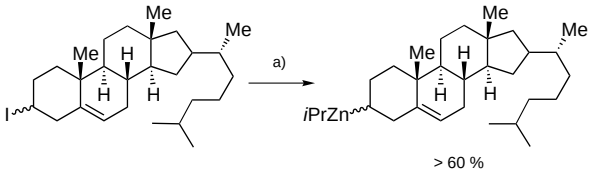
functionalized R groups to aldehydes in high enantiomeric excess (Scheme 21).[81] Furthermore, with mixed dialkylzinc compounds only the synthetically useful R group is transferred.

Several general methods are available to prepare the dialkyzinc compounds **102**, either starting from alkyl iodides **101** or more attractively from olefins **103** [Eq. (1)]. In the first



101 **102** **103** (1)

case, the functionalized alkyl iodide is treated with Et_2Zn or iPr_2Zn in THF. The presence of small amounts of Cu(I) salts like CuCN catalyzes the exchange reaction. [82,83] A mixed metal catalysis (using $MnBr_2$ and CuCl) allows the exchange reaction to be performed with alkyl bromides, however the products are alkylzinc bromides and not dialkylzinc compounds.[84] Interestingly, the iodine–zinc exchange can be strongly accelerated by irradiation, thus avoiding the use of an excess of Et_2Zn.[85] In the case of secondary alkyl iodides, which require iPr_2Zn for the exchange reaction, the use of iPr_2Zn generated in situ from *i*PrMgBr and $ZnBr_2$ (0.5 equiv) is possible. This method is very useful for the preparation of complex dialkylzinc compounds (Scheme 22).[86]



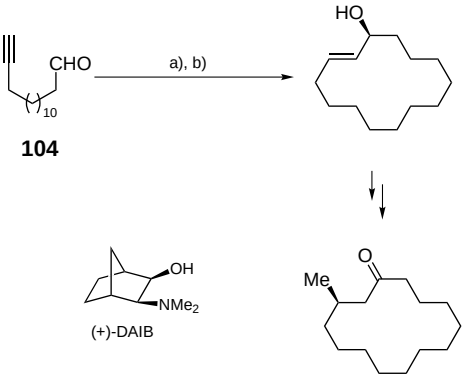
Scheme 22. An example of the iodine–magnesium exchange using iPr_2Zn prepared in situ. a) *i*PrMgBr (3.0 equiv), $ZnBr_2$ (1.5 equiv), diethyl ether, rt, 1 h.

4.2. Preparation of organozinc reagents by the boron–zinc exchange reaction

This section describes the second method of preparation for dialkylzinc compounds, the boron–zinc exchange sequence as well as two of its most important applications: the preparation of chiral dialkylzinc reagents and the diastereoselective allylic C–H activation.

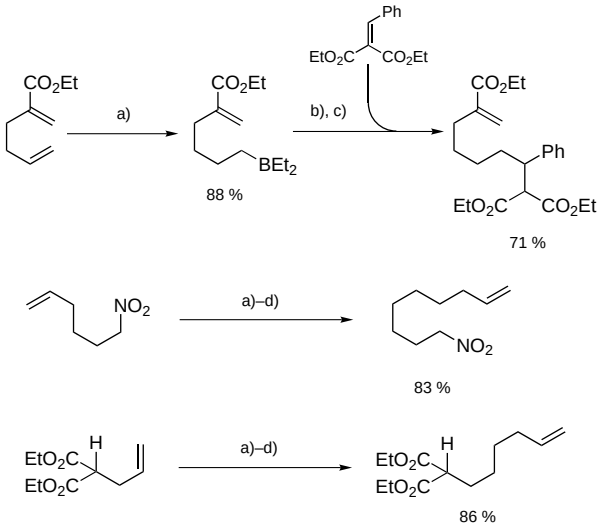
4.2.1. Scope and limitations

Organoboranes react with dialkylzinc compounds under mild conditions. The driving force of the reaction is the formation of stable dialkylzinc compounds, and in some cases, the formation of volatile organoboranes such as BMe_3 (bp = $-22\,^{\circ}C$).[87] The reaction can be used to prepare primary dialkylzinc reagents, dibenzylic organozinc compounds by using Me_2Zn or Et_2Zn, or secondary dialkylzinc reagents by using iPr_2Zn. Alkenylzinc derivatives can also be prepared, in almost quantitative yield, using Et_2Zn.[88–90] This reaction has been elegantly applied by Oppolzer et al. for an enantioselective synthesis of (*R*)-(−)-muscone (**105**) from the alkyne **104** (Scheme 23). Remarkably, the aldehyde function is not reduced by *c*Hex_2BH during the hydroboration reaction.[90,91]



Scheme 23. Enantioselective muscone synthesis. a) *c*Hex_2BH, hexane, 0 °C; b) (+)-DAIB, (1 mol %), Et_2Zn.

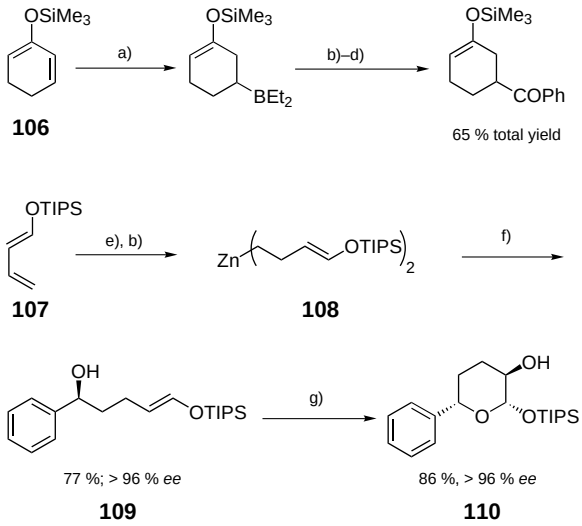
In general, the reaction conditions for the boron–zinc exchange are so mild that a number of sensitive functional groups such as acrylic ester, nitro, diethyl malonate, and enol ether are tolerated (Scheme 24).[92] The functionalized organozinc intermediates react smoothly with various electrophiles in the presence of a copper(I) catalyst, thus extending the scope of the organoborane chemistry; organoboranes themselves react only with selected electrophiles (Scheme 24).[92]



Scheme 24. Synthesis of functionalized dialkylzinc compounds by the boron–zinc exchange. a) Et_2BH, diethyl ether, 25 °C; b) Et_2Zn (neat), 0 °C; c) $CuCN \cdot 2\,LiCl$; d) allyl bromide (excess).

The hydroboration of dienic silyl enol ethers such as **106** or **107** followed by a boron–zinc exchange affords zinc complexes such as **108** which are difficult to prepare from the corresponding organic halide because of its instability and high tendency to undergo elimination reactions. The func-

tionalized organozinc reagent **108** undergoes a highly enantioselective addition to PhCHO in the presence of catalytic amounts of **100**. The resulting chiral alcohol **109** can be selectively oxidized giving the enantiomerically pure tetrahydropyrane **110** (Scheme 25).[93]



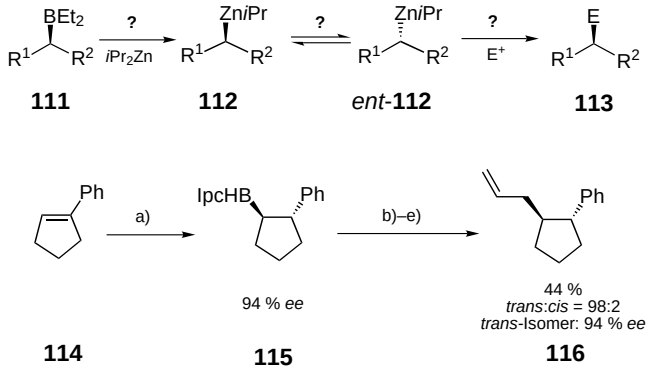
Scheme 25. Synthesis and reactions of functionalized dialkylzinc reagents by the hydroboration of 1,3-dienes. a) Et_2BH, diethyl ether, 25 °C, 12 h; b) Et_2Zn, 0 °C, c) $CuCN \cdot 2LiCl$; d) PhCOCl; e) Et_2BH, 50 °C, 4 h; f) PhCHO, **100** (8 mol %), $Ti(OiPr)_4$, toluene, −20 °C, 12 h; g) *t*BuOOH, $[VO(acac)_2]$ cat., hexane, rt, 8 h.

The boron–zinc exchange has also been applied to the preparation of 1,3-dizincapropane derivatives which are difficult to prepare by other methods.[94] Because of the high tolerance of the hydroboration reaction and the boron–zinc exchange towards functional groups, this reaction sequence represents the most versatile method for preparing polyfunctional dialkylzincs.

4.2.2. The preparation of chiral zinc complexes using the boron–zinc exchange reaction

As a result of the highly covalent character of the carbon–zinc bond, secondary organozinc derivatives should be configurationally stable. This is supported by early ^1H NMR studies which show that the activation energy required for inversion is higher than 26 kcal mol^{-1},[95] which has been confirmed by more recent measurements.[96] However, the preparation of chiral organozinc compounds such as **112** (Scheme 26) and their use for synthetic applications requires the fulfillment of several conditions: First, the boron–zinc exchange with secondary organoboranes such as **111** has to proceed stereoselectively. Second, the chiral zinc reagent formed (**112**) has to be configurationally stable under the reaction conditions used for its generation (solvent, temperature) and under the conditions used for its reactions with electrophiles. Finally, the reaction with electrophiles leading to products of type **113** has to proceed stereoselectively. Failing to fulfill any of these conditions will make the whole reaction sequence synthetically useless.

Fortunately, reaction conditions could be found to make the reaction sequence highly stereoselective.[97–100] Thus, the hydroboration of 1-phenylcyclopentene (**114**) with (−)-monoisopinocampheylborane (−)-$IpcBH_2$ (99 % *ee*)[101] provides, after recrystallization, the chiral organoborane **115**. This organoborane is first treated with Et_2BH at 50 °C for 16 h leading to a sterically less-crowded diethylorganoborane which undergoes smoothly the boron–zinc exchange within 5 h at room temperature. Stereoselective allylation of the resulting organozinc compound in the presence of $CuCN \cdot 2LiCl$ affords the expected product **116** in 44 % yield with an excellent diastereoselectivity (*cis*:*trans* = 2:98) and enantiomeric purity of 94 % *ee* (Scheme 26).[98]

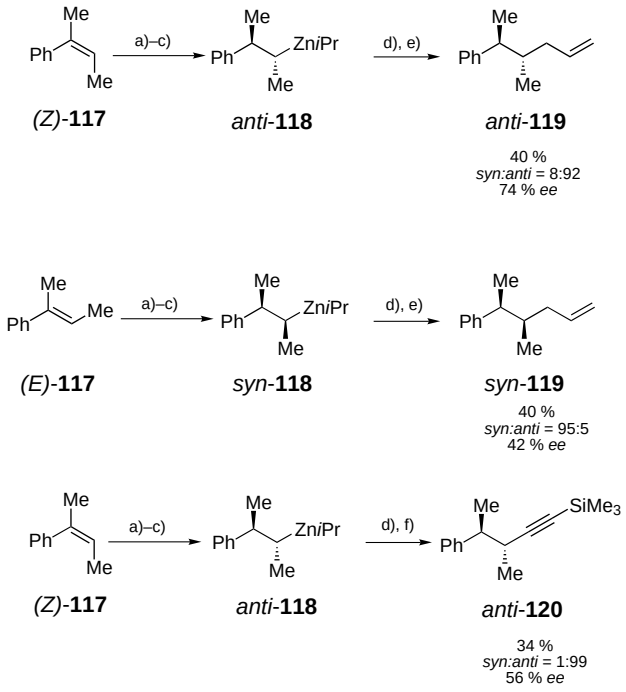


Scheme 26. Synthesis and reactions of chiral dialkylzinc compounds. a) (−)-$IpcBH_2$, diethyl ether, −35 °C; b) Et_2BH, 60 °C, 13 h; c) iPr_2Zn, rt, 4 h; d) $CuCN \cdot 2LiCl$; e) allyl bromide.

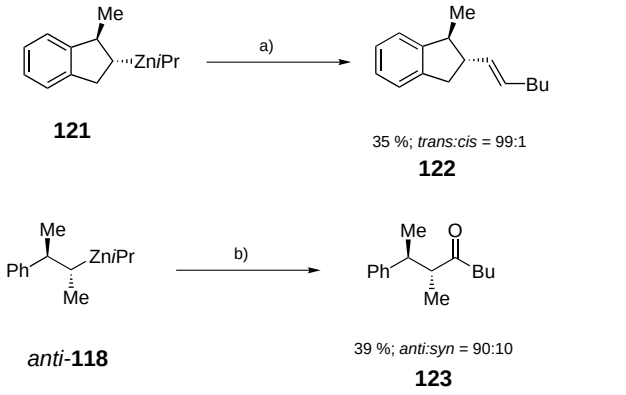
The exchange reaction can be applied to open-chain systems and allows the preparation of chiral acyclic zinc complexes with excellent diastereoselectivies. The enantioselectivity in these reactions is determined by the first asymmetric hydroboration step. Thus, starting from the styrene derivative (*Z*)-**117**, the dialkylzinc compound *anti*-**118** is obtained preferentially. Allylation leads to *anti*-**119** (*syn*:*anti* = 8:92; Scheme 27). Using the (*E*)-styrene, the same reaction sequence furnishes *syn*-**118**, and after allylation *syn*-**119** (*syn*:*anti* = 95:5).[99] The copper(I)-catalyzed cross-coupling with bromoalkynes gives especially good diastereoselectivities and provides diastereomerically pure alkynes such as **120** (Scheme 27).[99]

Palladium(0)-catalyzed reactions with electrophiles can be performed stereoselectively. The Pd^0-catalyzed cross-coupling of the organozinc complex **121** and *anti*-**118** with an alkyl iodide or an acid chloride provides the desired products **122** and **123**, respectively, with excellent diastereoselectivity (Scheme 28).[100]

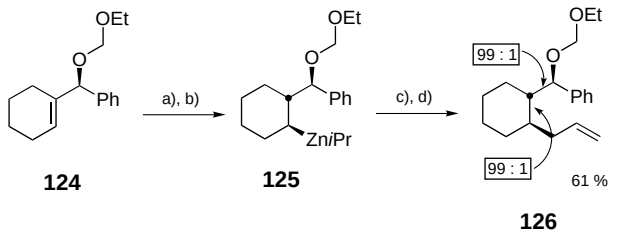
Preliminary experiments have shown that with this method the stereocontrol of three neighboring centers can be achieved. The chiral allyl ether derivative **124** undergoes a fully diastereoselective hydroboration with Et_2BH. After boron–zinc exchange (25 °C, 4 h) the zinc complex **125** is obtained. The subsequent allylation affords the expected product **126** with high diastereoselectivity (Scheme 29).[102]



Scheme 27. Synthesis and reactions of chiral open-chain dialkylzinc compounds. a) (−)-IpcBH$_2$, −35 °C, 48 h; b) Et$_2$BH, 60 °C, 16 h; c) *i*Pr$_2$Zn, 25 °C, 5 h; d) CuCN · 2 LiCl; e) allyl bromide, −78 °C; 1–2 h; f) 1-bromo-2-trimethylsilylacetylene, −78 °C; 1–2 h.



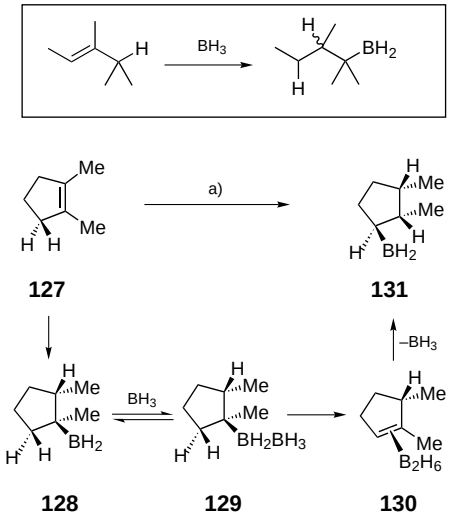
Scheme 28. Asymmetric generation of chiral dialkylzinc compounds and Pd^0-catalyzed reactions. a) [Pd(dba)$_2$] (2 mol %), P(*o*Tol)$_3$ (4 mol %), 0 °C → rt, 12 h, 1-iodohex-1-ene; b) [Pd(dba)$_2$] (2 mol %), P(*o*Tol)$_3$ (4 mol %), 0 °C → rt, 12 h, BuCOCl.



Scheme 29. Diastereoselective hydroboration and boron–zinc exchange followed by allylation. a) Et$_2$BH, 60 °C, 13 h; b) *i*Pr$_2$Zn, 25 °C, 4 h; c) CuCN · 2 LiCl cat.; d) allyl bromide.

4.2.3. Diastereoselective C–H activation

The activation of inactive C–H bonds is an important research area.[103] The hydroboration of tetrasubstituted olefins followed by a thermal rearrangement allows a formal C–H activation reaction at the allylic position. Mechanistic studies of Rickborn and Field[104] have shown that thermal rearrangement of hindered organoboranes may proceed stereoselectively. The mechanism of the thermal rearrangement is complex, but it has been reported that the presence of excess borane catalyzes the rearrangement, so that, in the case of 1,2-dimethylcyclopentene (**127**) the intermediates are the initial hydroboration product **128**, which in the presence of excess borane forms the organoborane **129** (Scheme 30). This intermediate rapidly rearranges at 50 °C via a transition state,[105] tentatively represented by **130**, giving **131** as the only diastereomer (Scheme 30).

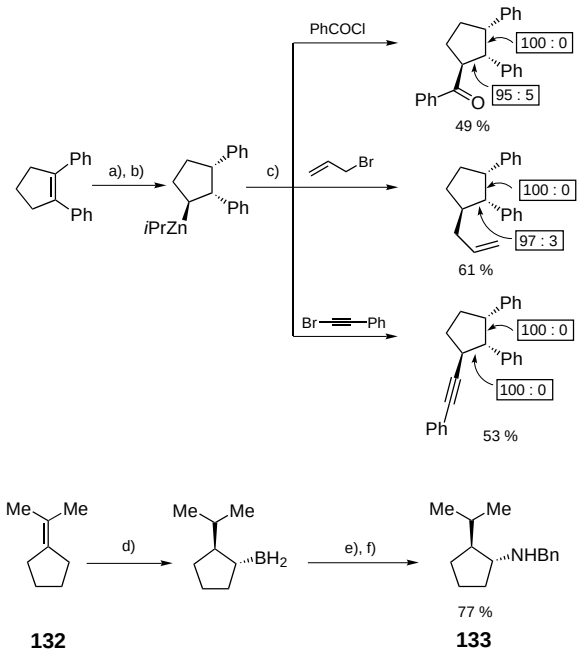


Scheme 30. The thermal rearrangement of organoboranes. a) BH$_3$ · THF, 50 °C, 3 h.

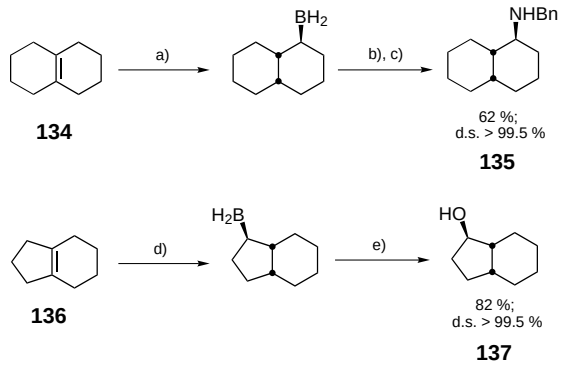
This rearrangement allows the functionalization of a range of tetrasubstituted cyclic olefins. The resulting organoborane can be transmetalated to the corresponding zinc derivative by treatment with *i*Pr$_2$Zn and reacts with several electrophiles with retention of the configuration of the stereocenter next to zinc (Scheme 31).[106] In the case of exocyclic tetrasubstituted alkenes such as **132**, the migration occurs in the ring affording, after an electrophilic amination, the *trans*-substituted benzylic amine **133** as one diastereomer (Scheme 31).[107]

For bicyclic systems, very selective migrations take place. In the case of the bicyclo[4.4.0]decene (**134**), only one diastereomer of **135** is obtained after migration and electrophilic amination.[106] Remarkably the migration in the unsymmetrical bicyclo[4.3.0]nonene (**136**), gives only **137**, derived from a migration in the five-membered ring. This may be because of the greater configurational flexibility of the five-membered ring which can therefore better accommodate the transition state required for the rearrangement (Scheme 32).

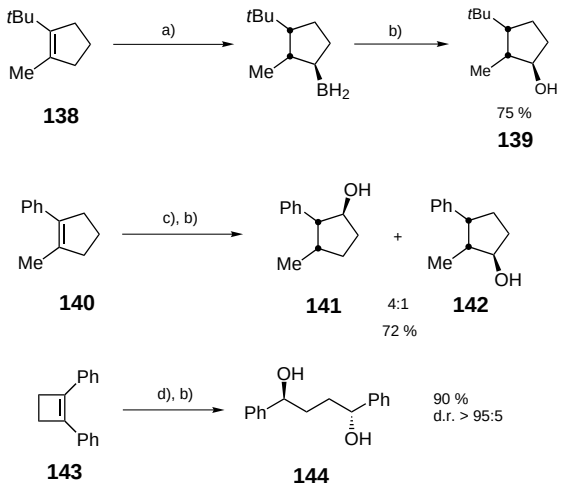
In the case of unsymmetrically substituted cyclopentenes such as **138**, only the migration to the site adjacent to the methyl substituent is observed, affording, after oxidation, the cyclopentanol **139** in 75 % as only one stereoisomer (Scheme 33). In the case of 1-phenyl-2-methylcyclopentene (**140**) the two possible tertiary organoboranes migrate with



Scheme 31. Stereoselective generation and reactions of secondary organoborane compounds. a) $BH_3 \cdot THF$, 50 °C, 3 h; b) iPr_2Zn, 25 °C, 3 h; c) $CuCN \cdot 2LiCl$; d) $BH_3 \cdot THF$, 50 °C, 8 h; e) BCl_3; f) BnN_3.



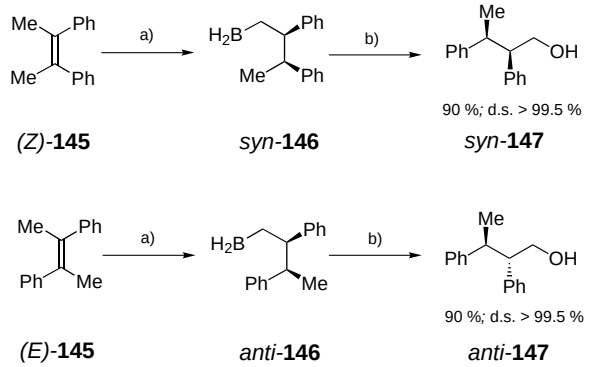
Scheme 32. Stereoselective thermal rearrangement and reactions of bicyclic organoboranes. a) $BH_3 \cdot THF$, 70 °C, 6 h; b) BCl_3; c) BnN_3; d) $BH_3 \cdot THF$, 50 °C, 3 h; e) NaOH, H_2O_2.



Scheme 33. Stereoselective rearrangements of monocyclic tertiary organoboranes. a) $BH_3 \cdot THF$, 50 °C, 3.5 h; b) NaOH, H_2O_2; c) $BH_3 \cdot THF$, 50 °C, 18 h; d) $BH_3 \cdot THF$, 50 °C, 5 h.

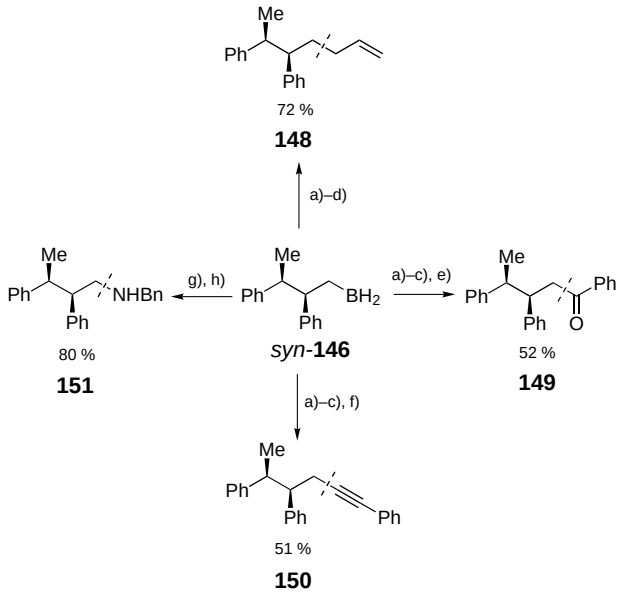
different rates. After heating to 50 °C for 18 h, the two regioisomeric alcohols **141** and **142** are obtained as a 4:1 mixture after oxidative workup.[108] Interestingly, for cyclobutene derivatives such as **143**, a ring-opening reaction is observed leading to the *meso*-diol **144** with good stereoselectivity (Scheme 33).[106]

Remarkably, highly diastereoselective rearrangements are also observed with open-chain tetrasubstituted olefins. Thus, after oxidation, the olefin (*Z*)-**145** produces only the alcohol (*syn*)-**147**, whereas the (*E*)-**145** furnishes the corresponding *anti*-alcohol (*anti*)-**147** (Scheme 34).[107]



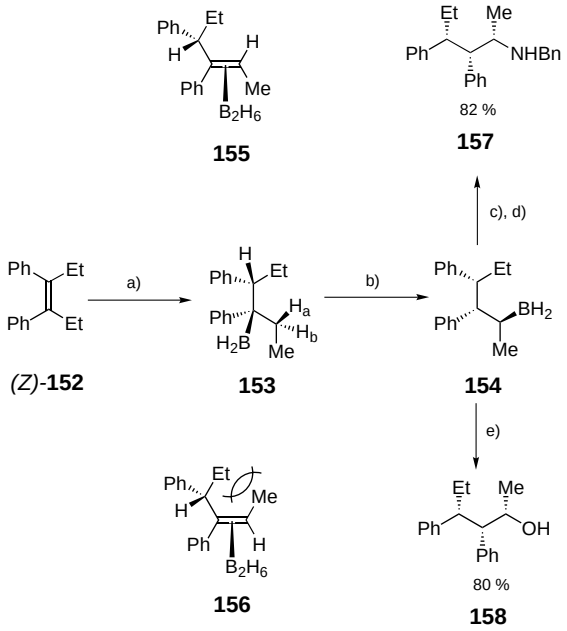
Scheme 34. Rearrangement of acyclic tertiary organoboranes. a) $BH_3 \cdot THF$, 70 °C, 12 h; b) NaOH, H_2O_2.

Bubbling ethylene through a solution of *syn*-**146** leads to the formation of the corresponding diethylborane derivative. Subsequent transmetalation of the organoborane by reaction with Et_2Zn produces the corresponding organozinc derivative which reacts with a range of carbon electrophiles leading to various products such as **148**–**150**. The direct electrophilic amination of *syn*-**146** furnishes the diastereomerically pure amine **151** (Scheme 35).[107]



Scheme 35. Stereoselective reactions of *syn*-**146**. a) ethylene; b) Et_2Zn; c) $CuCN \cdot 2LiCl$; d) allyl bromide; e) PhCOCl; f) 1-bromo-2-phenylethyne; g) BCl_3; h) BnN_3.

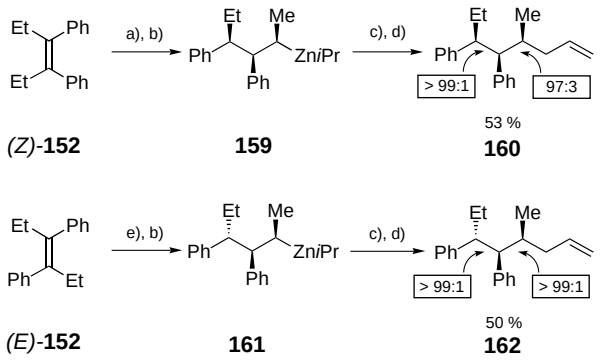
An extension of the reaction is possible by using substrates with two diastereotopic hydrogen atoms at the α position. Thus, (*Z*)-3,4-diphenylhexene (*Z*)-**152**, after hydroboration gives the tertiary organoborane **153** bearing two diastereotopic hydrogen atoms (H_a and H_b) at the α-position. Remarkably, after heating the reaction mixture to 70 °C for 12 h only one diastereomeric organoborane **154** is obtained. This is best explained by assuming that the resulting diborane–olefin complexes are intermediates of the rearrangement (see Scheme 30). By abstraction of H_a, the diborane–olefin complex **155** is formed, whereas by abstraction of H_b, the diborane–olefin complex **156** is formed. The high steric hindrance between the methyl substituent and the *cis*-1-phenylpropyl substituent precludes the formation of **156** and only an intermediate, such as **155**, may form in the course of the reaction. After oxidation or amination of **154** the two expected products **157** and **158** are isolated. The stereochemistry of the products has been confirmed by X-ray analysis (Scheme 36).[109]



Scheme 36. Diastereoselective rearrangement allowing the stereocontrol of three adjacent carbon centers. a) $BH_3 \cdot THF$; b) 70 °C, 6 h; c) BCl_3; d) BnN_3; e) NaOH, H_2O_2.

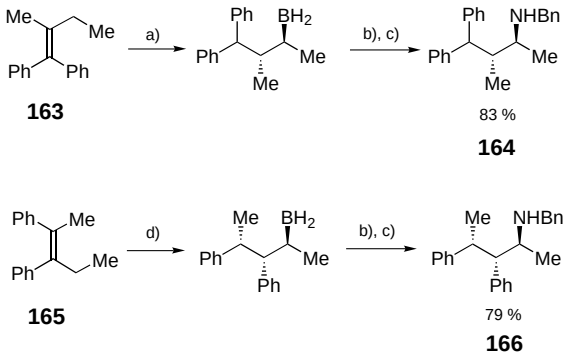
In combination with the boron–zinc exchange, the thermal rearrangement of organoboranes allows the control of the stereochemistry of three adjacent carbon centers.[109] Thus, the hydroboration and boron–zinc exchange of (*E*)- and (*Z*)-**152** produces two epimeric organozinc reagents **159** and **161**, which after a copper(I)-catalyzed allylation, lead to the diastereomerically almost pure products **160** and **162** (Scheme 37).[109]

Interestingly, by using unsymmetrically substituted acyclic olefins only one migration direction is observed. Thus, 1,1-diphenyl-2-methyl-1-butene (**163**) furnishes only the product from rearrangement in the direction of the ethyl group, no migration in the direction of the methyl group is observed. After electrophilic amination the benzylic amine **164** is



Scheme 37. Diastereoselective allylation of diastereomerically pure secondary dialkylzinc compounds. a) $BH_3 \cdot THF$, 65 °C, 12 h; b) iPr_2Zn, rt, 2 h; c) $CuCN \cdot 2\,LiCl$ (20 mol%); d) allyl bromide, −78 °C, 1–2 h; e) $BH_3 \cdot THF$, 50 °C, 6 h.

formed as one diastereomer. Similarly, (*Z*)-2,3-diphenyl-2-pentene (**165**) affords, after thermal rearrangement and amination, the benzylic amine **166** as one diastereomer (Scheme 38).[109]

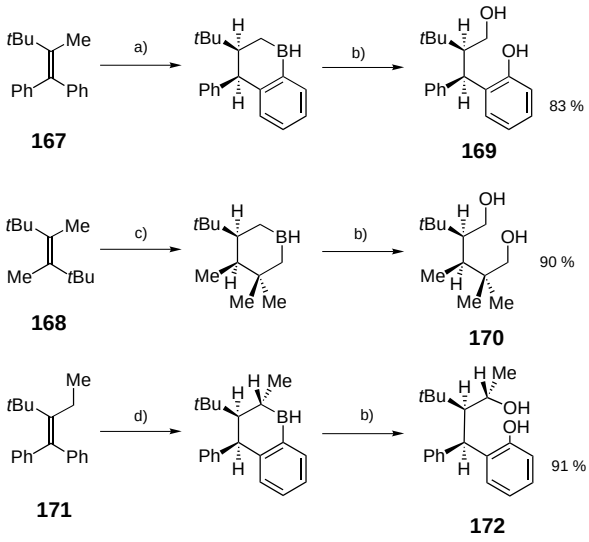


Scheme 38. Stereoselective and regioselective thermal rearrangement: a) $BH_3 \cdot THF$, 50 °C, 4 h; b) BCl_3; c) BnN_3; d) $BH_3 \cdot THF$, 65 °C, 12 h.

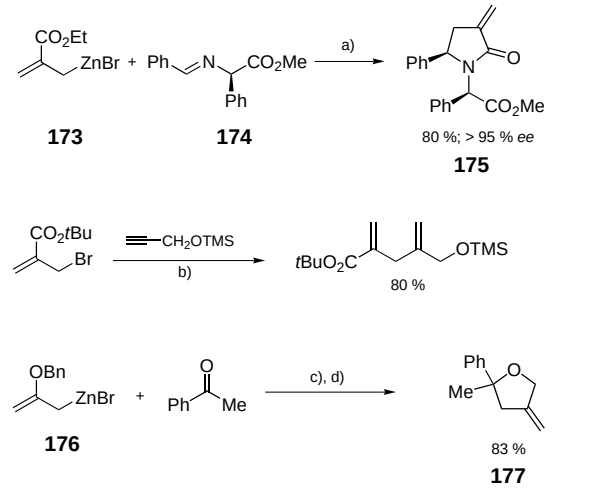
Remote C–H activations are possible and after hydroboration and rearrangement the olefins **167** and **168** undergo a remote C–H activation, subsequent oxidation produces in both cases only one diastereoisomer (**169** and **170**, respectively). By using the ethyl substituted precursor **171** control of the stereochemistry of three adjacent centers is possible leading to the hydroxyphenol **172** in 91% yield (Scheme 39).[107,110]

4.3. Functionalized allylzinc reagents

Allylzinc compounds are highly reactive and react with most functionalized organic electrophiles.[111] Some functionalized allylzinc compounds can be prepared by the direct insertion of zinc added in powder form. Thus, Villiéras et al. showed that the reaction of ethyl (2-bromomethyl)acrylate with zinc powder in THF produces the functionalized zinc reagent **173** in excellent yield.[112] Its reaction with chiral imines such as **174** furnishes α,β-unsaturated lactams[113] such as **175** (Scheme 40) with excellent diastereoselectivity. The allylzinc reagent **173** can also be prepared in situ[114] and added to alkynes. The functionalized allylzinc compound **176**



Scheme 39. Diastereoselective remote C–H activation. a) $BH_3 \cdot THF$; 50 °C, 12 h; b) NaOH, H_2O_2; c) $BH_3 \cdot THF$; 40 °C, 72 h; d) $BH_3 \cdot THF$; 50 °C, 4 h.

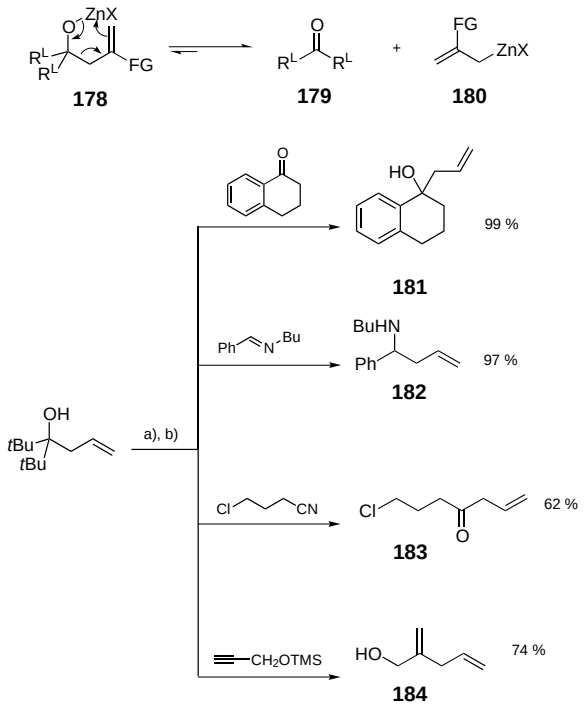


Scheme 40. Reaction of functionalized allylic organozinc reagents. a) THF, 25 °C; b) Zn, THF, 45 °C, 0.5 h; c) THF, rt; d) $[Pd(PPh_3)_4]$ cat., 65 °C, 16 h.

has been used to perform several new types of cyclization leading to, for example, 3-exo-methylene tetrahydrofurans like **177** (Scheme 40).[115]

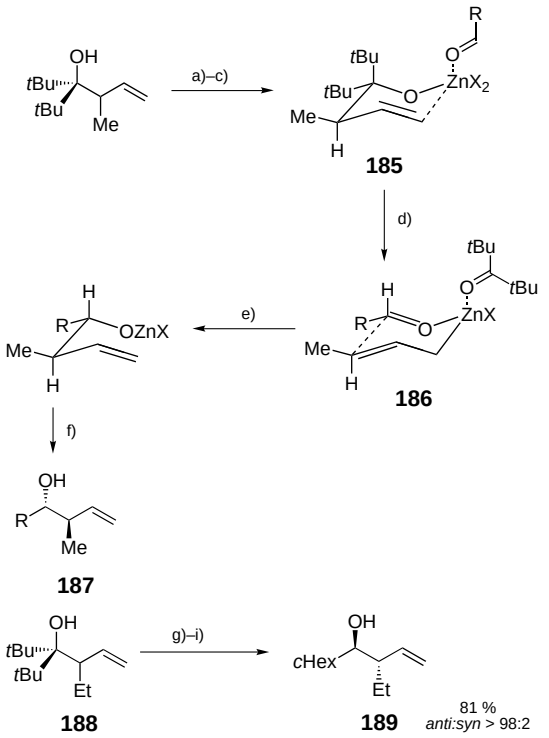
A new method for preparing the functionalized allylzinc reagents **180** uses the corresponding homoallylzinc alcoholates **178** as masked allylzinc reagents.[116, 117] The driving force for the fragmentation is the reduction of steric hindrance in **178** and the formation of the ketone **179** (R^L = large substituent such as *t*Bu).[118] If this fragmentation is performed in the presence of an organic electrophile, an allylation reaction takes place leading to products such as **181**–**184** (Scheme 41).

Interestingly, substituted homoallyl alcoholates undergo stereoselective additions to aldehydes whereas the corresponding substituted allylic organozinc compounds generated by conventional methods (insertion of zinc metal) display no stereoselectivity on addition to aldehydes. This behavior can be best explained by assuming that the homoallylzinc alcoholate **185** coordinates the aldehyde before fragmentation. The



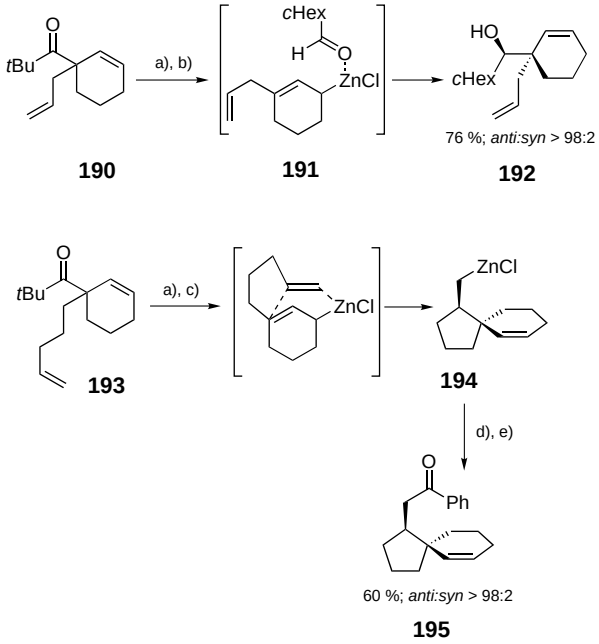
Scheme 41. Generation of allylzinc, by the fragmentation of sterically hindered homoallylzinc alcoholates, and subsequent reaction. a) *n*BuLi; b) $ZnCl_2$. (FG = functional group.)

crotylzinc reagent formed (**186**) immediately reacts with the aldehyde providing the homoallylic alcohol **187**. Especially high stereoselectivities are obtained with secondary aldehydes (Scheme 42).[116] The fragmentation of **188** provides after reaction with cyclohexanecarbaldehyde the homoallylic alcohol **189**.



Scheme 42. Diastereoselective addition reactions of substituted allylzinc compounds generated by fragmentation. a) *t*BuLi; b) RCHO; c) ZnX_2; d) fragmentation; e) allylic rearrangement, f) H_2O; g) *n*BuLi, –78 °C; h) *c*HexCHO, i) $ZnCl_2$, –78 °C.

The method can be applied to generate highly substituted allylzinc reagents such as **191**. Its reaction with *c*HexCHO furnishes the secondary alcohol **192** bearing a quaternary carbon center at the α-position. The zinc alcoholate is best generated by the direct addition of *n*BuLi to the ketone **190** at $-78\,^{\circ}C$.[119] The method can also be used for metallo–ene reactions.[120] Thus, the addition of *n*BuLi to the ketone **193** initiates the fragmentation reaction and addition to the double bond of the zinc reagent **194** which is benzoylated in the presence of $CuCN\cdot 2\,LiCl$ giving the ketone as only one diastereomer (Scheme 43).

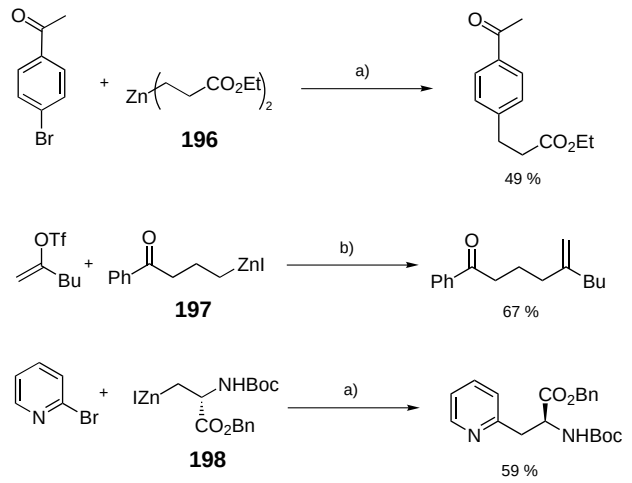


Scheme 43. Zinc–ene reaction and diastereoselective reaction of highly substituted organozinc reagents. a) *n*BuLi, $-78\,^{\circ}C$; b) *c*HexCHO, $ZnCl_2$, $-78\,^{\circ}C \rightarrow$rt, 4 h; c) $ZnCl_2$; d) $CuCN\cdot 2\,LiCl$; e) PhCOCl, rt.

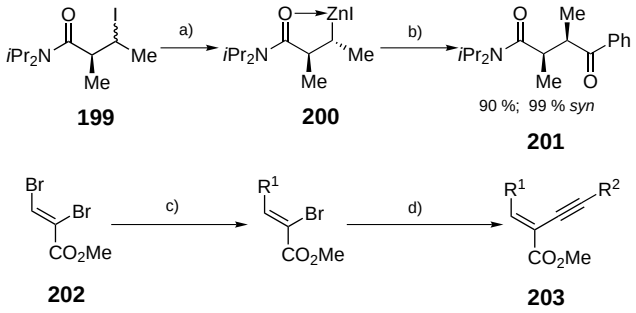
4.4. Cross-coupling reactions with polyfunctionalized organozinc compounds

Polyfunctional organozinc compounds have been extensively used in cross-coupling reactions.[121, 122] Only examples of the method pioneered by Negishi,[66, 121] the Pd^0-catalyzed cross-coupling of fuctionalized alkyl or arylzinc reagents with aryl or alkyl iodides, bromides or triflates are given. Various palladium complexes have been used as catalysts and $P(o\text{Tol})_3$ has been an especially useful ligand. Thus, ester- and keto-functionalized zinc reagents such as **196**,[123] and **197**,[124] respectively, or the zinc–serine derivative **198**[125] undergo selective coupling with aryl bromides or triflates in satisfactory yields (Scheme 44).

Interestingly, a stereoconvergent insertion of zinc into *syn*- or *anti*-iodoamide **199** furnishes the same organozinc reagent **200** which undergoes a Pd^0-catalyzed cross-coupling with benzyl chloride leading only to the *syn*-product **201** (Scheme 45).[126] A chemoselective cross-coupling can be performed with the 2,3-dibromoacrylate (**202**). Two successive

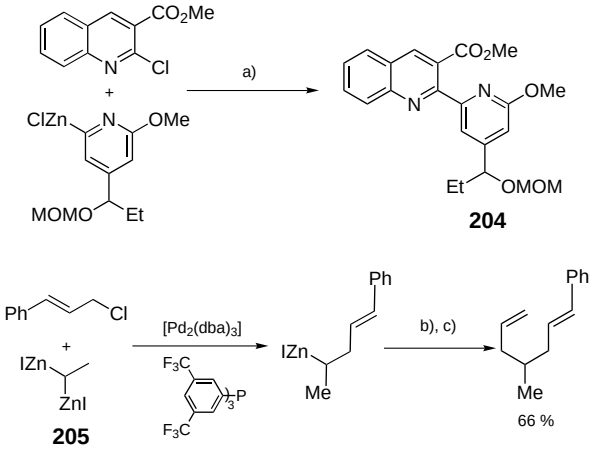


Scheme 44. Negishi cross-coupling reactions of functionalized organozinc reagents. a) $[PdCl_2\{P(o\text{Tol})_3\}_2]$ cat., THF, rt; b) $[Pd(PPh_3)_4]$ cat., THF, rt.



Scheme 45. Pd^0-catalyzed cross-coupling reaction of a chiral secondary zinc reagent and regioselective alkylation of 2,3-dibromoacrylates. a) Zn; b) PhCOCl, Pd^0; c) R^1ZnCl, $[Pd(PPh_3)_4]$ THF, rt, d) $R^2C{=}CZnCl$, $[Pd(PPh_3)_4]$.

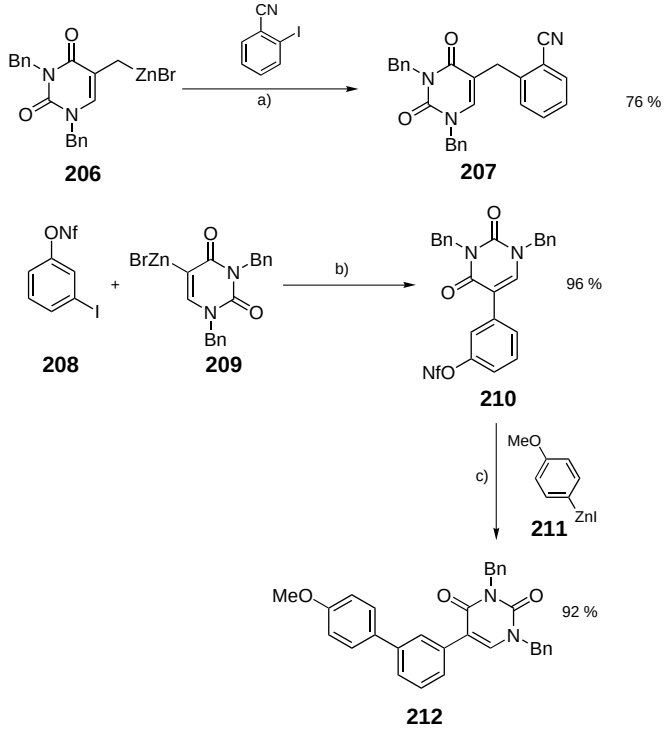
cross-coupling reactions with organozinc reagents furnished highly functionalized enynes of type **203** (Scheme 45).[127] This cross-coupling can be readily performed with heterocyclic building blocks[128] leading to precursors such as **204** which can be converted to camphothecin (Scheme 46). A novel application of dimetallic reagents has been described by Utimoto



Scheme 46. Pd^0-catalyzed cross-couplings. a) Pd^0 cat., THF, reflux; b) CuCN; c) allyl bromide.

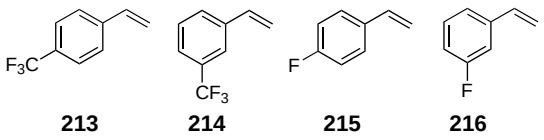
and Matsubara and co-workers using 1,1-bis(iodozinc)ethane (**205**) for the sequential coupling with two different electrophiles.[129]

An alternative catalytic system is $[Pd(dba)_2]$ and P(2-furyl)$_3$ (tfp) recently introduced by Farina et al.[130] Under these conditions, heterocyclic benzylzinc complexes such as **206** undergo smooth cross-coupling with various aryl iodides leading to 5-substituted uracil compounds of type **207**.[131] Especially suited for cross-coupling reactions with organic zinc derivatives are iodo-aryl nonaflates such as **208** (nonaflate (ONf) = nonafluorobutanesulfonate). The reaction of the zinc-uracil derivative **209** with **208** affords **210**. This nonaflate undergoes a smooth cross-coupling with the arylzinc derivative **211** providing the functionalized diphenyl **212** in high yield (Scheme 47).[132]



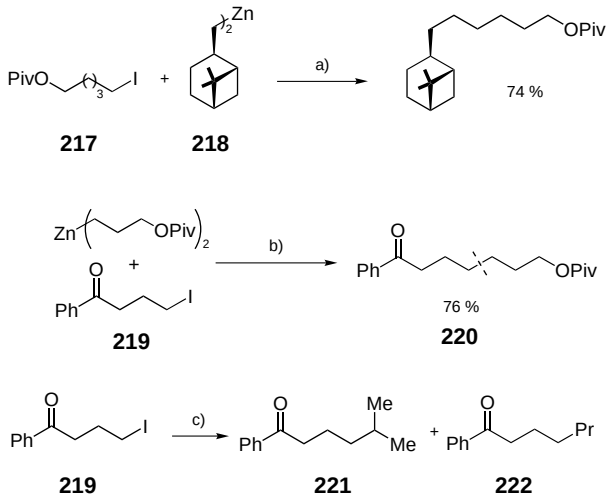
Scheme 47. Synthesis of uracil- and thymine-derivatives by a Pd^0-catalyzed cross-coupling. a) $[Pd(dba)_2]$ (2.5 mol%), tfp (5 mol%), 25 °C, 12 h; b) $[Pd(dba)_2]$, (0.5 mol%), tfp (1 mol%), 25 °C, 1 h; c) $[Pd(dba)_2]$ (2 mol%), dppf (2 mol%), 55 °C, 36 h.

Whereas Pd-catalysis is well suited for C_{sp^2}-C_{sp^2} cross-couplings, Ni-catalysis is advantageous for C_{sp^3}-C_{sp^3} cross-couplings. Very few transition metal catalyzed reactions allow the selective cross-couplings between C_{sp^3}-centers. Copper(I) has been successfully used, however often stoichiometric amounts of copper salts are necessary.[133, 134] The Pd^0-catalyzed cross-coupling between C_{sp^3}-centers is not efficient because of the slow reductive–elimination step of the intermediate $[(L_n)(R^1)Pd(R^2)]$, leading to the desired product R^1–R^2. Since this reductive elimination is too slow, exchange of the ligands can compete leading to the formation of $[(L_n)(R^1)Pd(R^1)]$ and $[(L_n)(R^2)Pd(R^2)]$, which after reductive elimination, provide homocoupling products R^1–R^1 and R^2–R^2 as side products. The use of a nickel(0) catalyst in conjunction with a promoter ligand such as *p*- or *m*-trifluoromethylstyrene (**213** and **214**) or *p*- or *m*-fluorostyrene (**215** and **216**) allows efficient cross-coupling reactions between functionalized alkyl iodides (such as **217**) and dialkylzinc compounds such as **218**.[135, 136] In the case of activated alkyl iodides like **219**, acetophenone can also be used as a



213 **214** **215** **216**

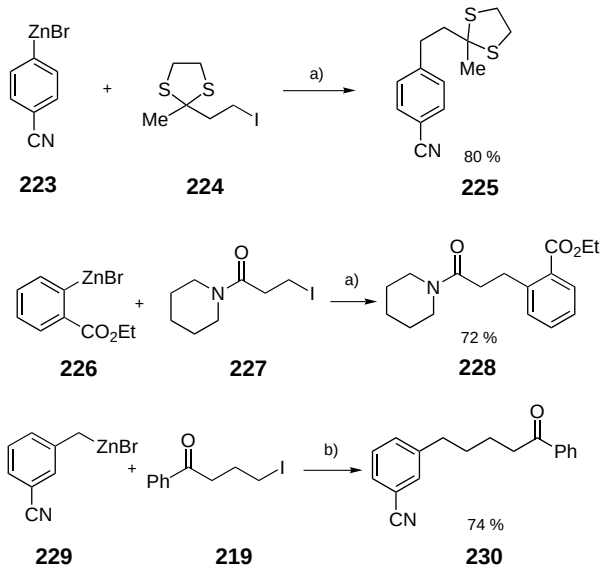
promoter affording the polyfunctional product **220**. Interestingly, in the case of the cross-coupling with secondary dialkylzinc compounds such as *i*Pr$_2$Zn, the presence of a promoter such as acetophenone improves the yield of the desired cross-coupling product **221** and reduces the amount of the coupling product **222** that results from a β-hydrogen migration and readdition (Scheme 48).[136]



Scheme 48. Ni^0-catalyzed cross-coupling reactions between primary and secondary dialkylzinc compounds and primary alkyl iodides. a) $[Ni(acac)_2]$ (10 mol%), THF:NMP (2:1), **214** (1.0 equiv); b) $[Ni(acac)_2]$ (10 mol%), THF:NMP (2:1), −35 °C, 10 h; c) *i*Pr$_2$Zn, $[Ni(acac)_2]$ (10 mol%), PhC(O)Me (0.5 equiv), THF:NMP (2:1). Without PhC(O)Me: 51% **221** and 17% **222**. With PhC(O)Me: 62% **221** and 3% **222**.

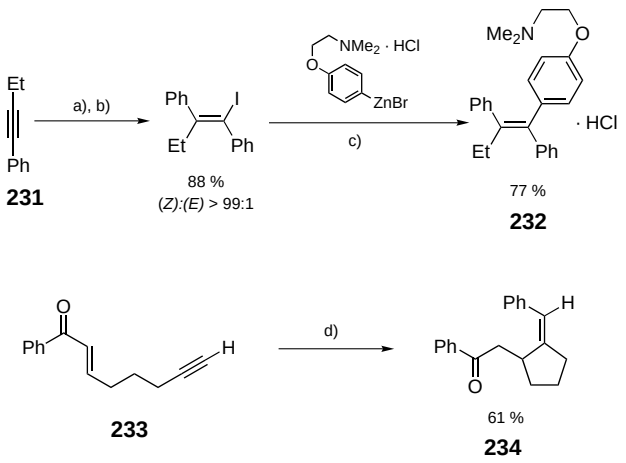
This cross-coupling can be extended to the reaction between arylzinc halides and alkyl iodides, a reaction rarely described in the literature. Thus, the arylzinc bromide **223** reacts with the functionalized alkyl iodide **224** in the presence of the promoter **213** affording the product **225** in 80% yield. The organozinc reagent **223** was obtained from the corresponding organolithium reagent and the organozinc compound **226** from the corresponding organomagnesium compound. The cross-coupling of **226** with the alkyl iodide **227** gives the benzoic acid derivative **228** in 72% yield (Scheme 49).[137] Benzylzinc bromides such as **229** were found to be unreactive towards cross-coupling with various alkyl iodides, however the addition of tetrabutylammonium iodide (3 equiv)[138] considerably facilitates this reaction leading, in the case of coupling with **219** in presence of *p*-fluorostyrene

(**215**) as promoter, to the desired product **230** in 74 % yield (Scheme 49).[139]



Scheme 49. Ni^0-catalyzed cross-coupling between arylzinc reagents and functionalized primary alkyl iodides. a) $[Ni(acac)_2]$ (10 mol %), THF:NMP (2:1), **213** (1.0 equiv), −20 °C, 4 h, b) $[Ni(acac)_2]$ (10 mol %), Bu_4NI (3 equiv), 0 °C to rt, 4–16 h, **215** (20 mol %), THF/NMP.

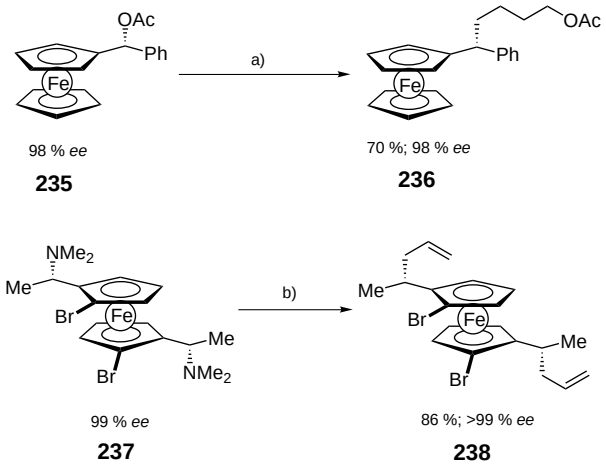
The complex $[Ni(acac)_2]$ catalyzes the carbozincation of alkynes. The reaction proceeds with excellent regio- and stereoselectivity in many cases and allows, among other things, the stereoselective preparation of tetrasubstituted olefins. The procedure has been used to prepare the anticancer drug (*Z*)-Tamoxifen (**232**) from 1-phenyl-1-butyne (**231**).[140] A range of analogues of **232** can be prepared by this method.[141] In the presence of a catalytic amount of $[Ni(cod)_2]$ organozinc halides add to alkynes such as **233** and subsequently undergo a ring closure by the intramolecular addition to an enone affording the *exo*-alkylidene cyclopentane **234** (Scheme 50).[142]



Scheme 50. Ni^0-catalyzed carbozincations of alkynes; synthesis of (*Z*)-Tamoxifen (**232**) a) Ph_2Zn, $[Ni(acac)_2]$ (25 mol %), THF/NMP, −35 °C, 3 h; b) I_2; c) $[Pd(dba)_2]$ (4 mol %), tfp (16 mol %), THF, 50 °C, 3 h; d) Ph_2Zn/PhZnCl, $[Ni(cod)_2]$ (5 mol %).

4.5. Use of organozincs for the preparation of chiral ferrocenyl ligands

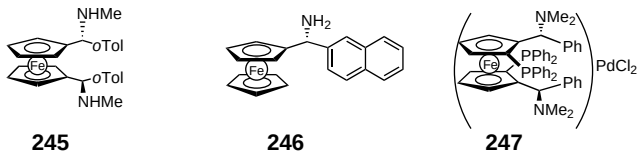
The preparation of new chiral ligands has been one of the most researched fields in the nineties and considerable progress has been made.[143] The use of zinc complexes has allowed the development of new ferrocenyl ligands.[144] It was found that chiral ferrocenyl acetates[145] of type **235** react, with almost complete retention of configuration, in the presence of $BF_3 \cdot OEt_2$ with various organozinc derivatives leading to interesting products of type **236**.[146] This reaction has been extended to the more stable (α-aminoalkyl)ferrocene derivatives such as **237**. Performing the reaction in the presence of acetyl chloride leads to the desired ferrocenes of type **238** with retention of configuration (Scheme 51).[147]



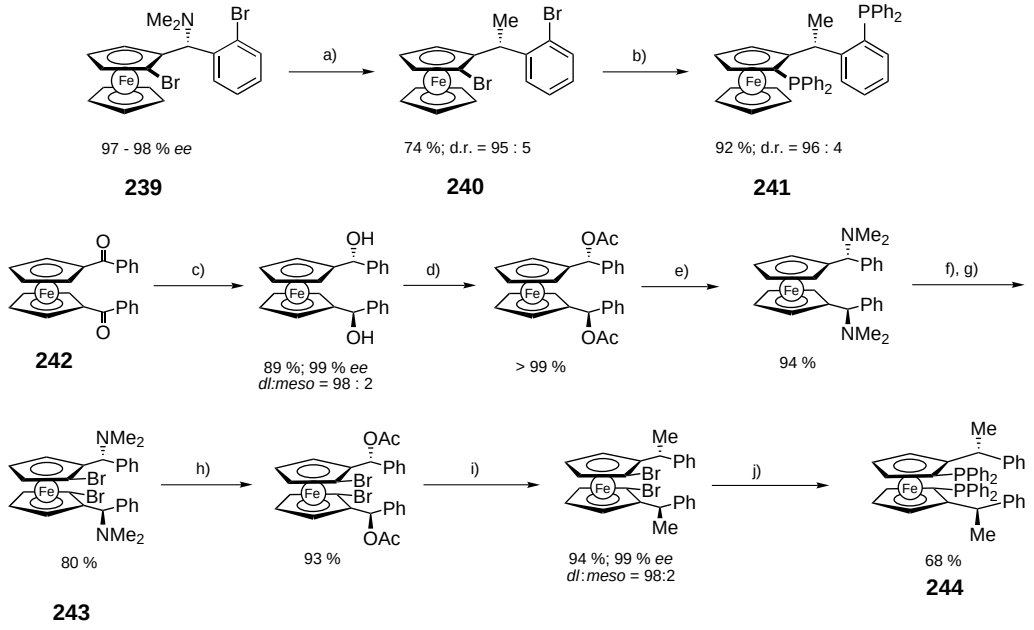
Scheme 51. Synthesis of chiral ferrocene derivatives. a) bis(4-acetoxybutylate)zinc, $BF_3 \cdot OEt_2$. b) allylzinc bromide (3 equiv), AcCl (2.4 equiv), THF, −30 °C.

More recently, a novel class of 1,5-diphosphanes such as **241** has been prepared by a substitution reaction. Monoaminoferrocenyl derivatives **239** are converted in one step into the chiral ferrocene **240**.[148] Using the methods developed in our laboratory[144] the synthesis of the C_2-symmetrical ligands of type **244** (Ferriphos) were obtained from the ferrocenyl diketone **242** via the key intermediate **243** (Scheme 52).[147, 149]

All these ferrocenyl ligands proved to be excellent ligands for various metal-catalyzed asymmetric reactions. Thus, the C_2-symmetrical aminoferrocenyl derivative **245** catalyze the transfer hydrogenation of aromatic ketones.[150] The mono-

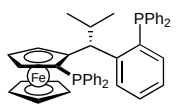


ferrocenyl compound **246** proves to be excellent for the asymmetric alkylation of allyl chlorides.[151] The palladium complex **247** gives excellent results for the cross-coupling between chiral benzylmagnesium reagents and alkenyl bromides (Scheme 53).[144]



Scheme 52. Preparation of new chiral ferrocenyl ligands. a) Me_2Zn (4 equiv), AcCl (2 equiv); b) BuLi (2.2 equiv), $ClPPh_2$ (2.3 equiv); c) $BH_3 \cdot SMe_2$ cat.; d) Ac_2O, pyridine, rt, 15 h; e) Me_2NH, THF/H_2O, rt, 15 h; f) *t*BuLi, diethyl ether, 0 °C, 0.5 h; g) $(CCl_2Br)_2$, THF, 0 °C; h) Ac_2O, 100 °C, 2.5 h; i) Me_2Zn, $BF_3 \cdot OEt_2$, THF, −78 °C→rt, 1.5 h; j) BuLi, THF, −70 °C, 0.25 h, $ClPPh_2$.

Remarkable enantioselectivities were obtained in the reduction of α-acetamidoacrylates and 1,3-dicarbonyl compounds by using the Ferriphos ligands such as **244**[147, 149] and the ligands **241** and **248**. Interestingly these two last ligands these two last ligands provide reduction products with the opposite configuration (Scheme 54).[148]

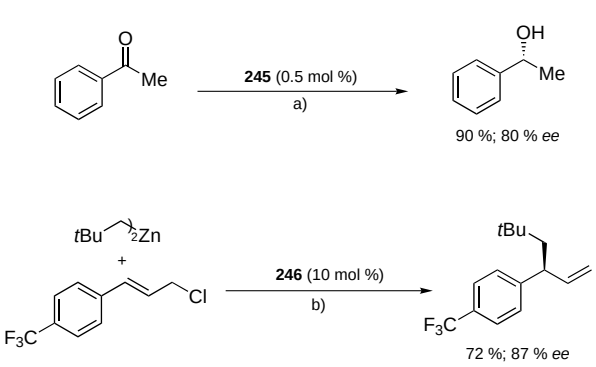


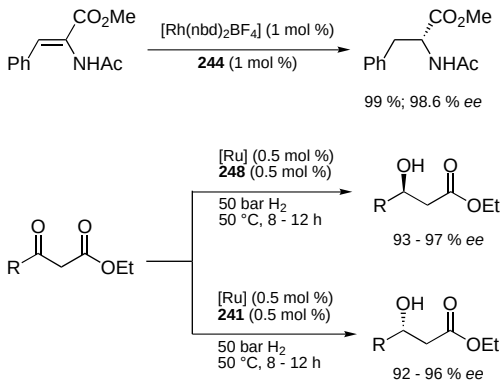
248

The discovery of these new ligands was a consequence of the development of new synthetic methods for the stereoselective manipulation of ferrocene derivatives.[144–148] The umpolung of the ferrocene reactivity, through chiral α ferrocenylalkyllithium derivatives such as **249**, opens up new synthetic possibilities for the development of new chiral ferrocenyl ligands such as **250** (Scheme 55).[152]

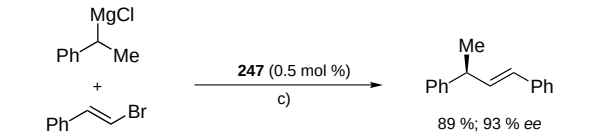
5. Conclusion and perspectives

Functionalized organometallic complexes have become key intermediates for retrosynthetic analysis and numerous applications have been described in the literature. Organozinc compounds have played a central role in the development of these reagents but other classes of compounds such as organoboranes may also play a large role in the future. Transition metal catalysis was essential for the development of many new reactions of organozinc compounds and further studies in this direction should expand further the broad field of application of functionalized organometallics.

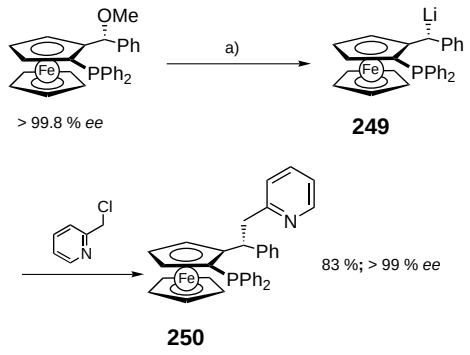




Scheme 54. Asymmetric reactions using ferrocenyl ligands.



Scheme 53. Asymmetric catalysis using ferrocenyl ligands. a) [{Ru(*p*-cumene)Cl_2}$_2$] (0.5 mol %), *i*PrOH, KOH, 22 °C, 1.5 h; b) $CuBr \cdot Me_2S$ (1 mol %), THF, −90 °C, 18 h; c) diethyl ether, 0 °C.



Scheme 55. Preparation of a new P,N-ligand via a chiral α-lithiated ferrocene. a) Lithium naphthalenide, −78 °C.

Abbreviations

Ac	acetyl
acac	acetylacetonato
Bn	benzyl
Boc	*tert*-butoxycarbonyl
cod	cycloocta-1,5-diene
dba	dibenzylidenacetone
Ddm	4,4′-dimethoxydiphenylmethyl
dppf	1,1′-bis(diphenylphosphanyl)ferrocene
MOM	methoxymethyl
nbd	norbornadiene
NBP	*N*-butylpyrrolidinone
NMP	*N*-methylpyrrolidinone
*o*Tol	2-tolyl
Piv	pivaloyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
tfp	tri(2-furyl)phosphane
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Tos	toluene-4-sulfonyl

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