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Strategies To Prepare and Use Functionalized Organometallic Reagents

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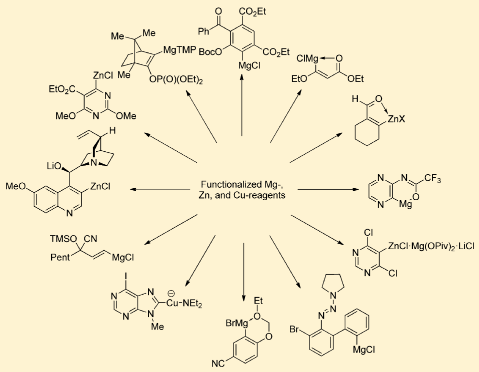

ABSTRACT: Polyfunctional zinc and magnesium organometallic reagents occupy a central position in organic synthesis. Most organic functional groups are tolerated by zinc organometallic reagents, and Csp^2-centered magnesium organometallic reagents are compatible with important functional groups, such as the ester, aryl ketone, nitro, cyano, and amide functions. This excellent chemoselectivity gives zinc— and magnesium—organometallic reagents a central position in modern organic synthesis. Efficient and general preparations of these organometallic reagents, as well as their most practical and useful reactions, are presented in this Perspective. As starting materials, a broad range of organic halides (iodides, bromides, and also to some extent chlorides) can be used for the direct insertion of magnesium or zinc powder; the presence of LiCl very efficiently promotes such insertions. Alternatively, aromatic or heterocyclic bromides also undergo a smooth bromine—magnesium exchange when treated with *i*-PrMgCl·LiCl. Alternative precursors of zinc and magnesium reagents are polyfunctionalized aryl and heteroaryl molecules, which undergo directed metalations with sterically hindered TMP bases (TMP = 2,2,6,6-tetramethylpiperide) of magnesium and zinc. This powerful C—H functionalization method gives access to polyfunctional heterocyclic zinc and magnesium reagents, which undergo efficient reactions with numerous electrophiles. The compatibility of the strong TMP-bases with BF$_3$·OEt$_2$ (formation of frustrated Lewis pairs) dramatically increases the scope of these metalations, giving for example, a practical access to magnesiated pyridines and pyrazines, which can be used as convenient building blocks for the preparation of biologically active molecules.

1. INTRODUCTION

The formation of new carbon—carbon bonds is central to organic synthesis. Whereas a broad range of electrophilic reaction partners are available for organic synthesis, the choice of polyfunctional nucleophiles is more difficult, and organometallic reagents have proven to be excellent nucleophilic intermediates for the formation of new carbon—carbon bonds. The availability of highly functionalized organometallic reagents is of special interest because it allows the formation of complex organic target molecules without the need for wasteful protection/deprotection steps. Although, recently, a variety of polyfunctional transition-metal intermediates of Pd,[1] Rh,[2] and Ru[3] have been generated in catalytic processes, this Perspective describes methods involving the stoichiometric synthesis of highly functionalized organometallic reagents of magnesium and zinc. Despite the use of stoichiometric quantities, we will demonstrate the exceptional synthetic utility of such organometallic species. The low toxicity of zinc and magnesium, as well their low price, are essential characteristics of these two metals, which have allowed us to fully exploit the exceptional compatibility of these organometallic species. Furthermore, in the presence of catalysts and appropriate reaction conditions (solvent, temperature, concentration), carbon—carbon bonds can be made with great efficiency. We will also demonstrate that zinc and magnesium organometallic reagents are compatible with strong Lewis acid catalysts (formation of frustrated Lewis pairs),[4] which considerably expand the synthetic scope of these reactive intermediates. Finally, the high sensitivity of zinc and magnesium organometallic reagents toward oxygen and water has been addressed since such properties make synthetic applications in academic and industrial laboratories more difficult. At the end of this Perspective, we will describe the preparation of solid zinc organometallic reagents with highly improved air and water stability.

Over the last 20 years, we have found a range of simple preparative methods of polyfunctional zinc— and magnesium—organometallic compounds.[5] As substrates, it is possible to use readily available organic halides,[6] as well as molecules bearing relatively acidic C—H bonds such as ketones, esters,[7] nitriles,[8] alkynes, or aromatic and heterocyclic scaffolds bearing H—C(sp^2) bonds.[9] Thus, three preparative methods will be described in detail: (1) the LiCl-promoted insertion of magnesium or zinc to various organic halides, (2) the bromine/magnesium-exchange reaction triggered by *i*-PrMgCl·LiCl, and (3) the directed metalation of numerous aromatic and heterocyclic substrates using sterically hindered TMP-bases of magnesium and Zn. We will also show that the resulting polyfunctional zinc and magnesium reagents readily form new carbon—carbon bonds with various electrophiles,

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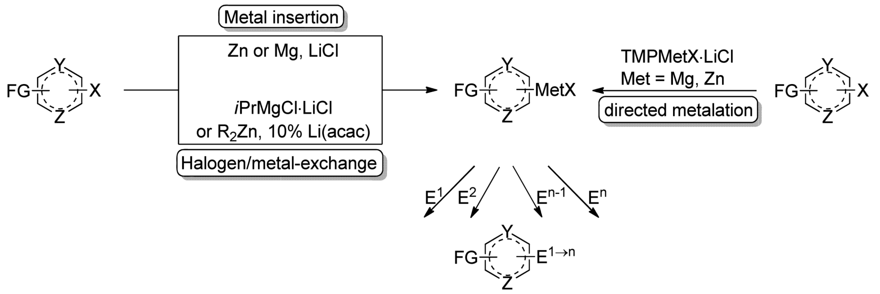
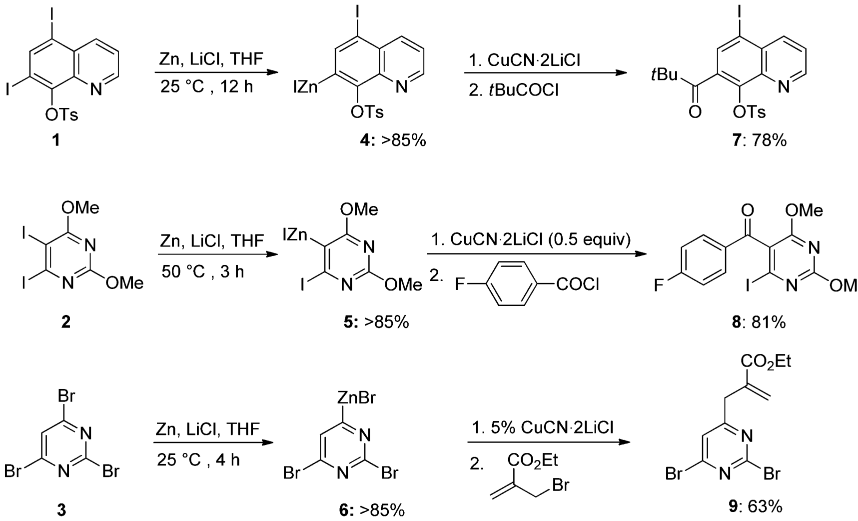
Scheme 1. General Methods for the Preparation of Polyfunctional Zinc and Magnesium Organometallic Reagents



Scheme 2. Site-Selective Zinc Insertion in the Presence of LiCl

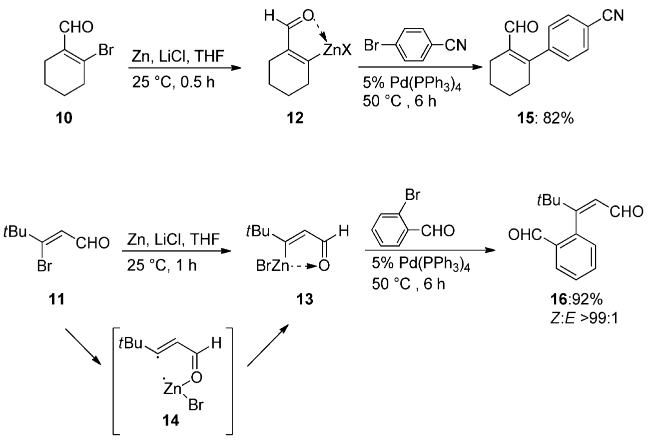


leading to a broad range of polyfunctional organic molecules (Scheme 1).

2. PREPARATION OF POLYFUNCTIONAL ZINC AND MAGNESIUM ORGANOMETALLIC RREAGENTS

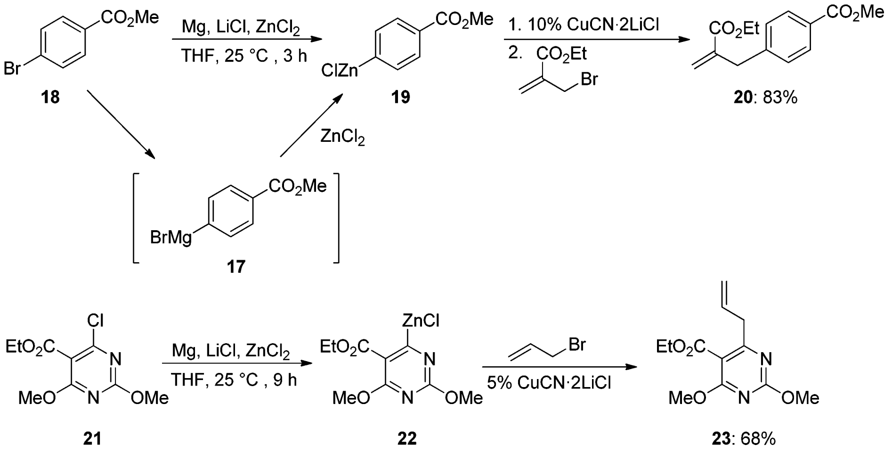
a. Selective Insertions of Magnesium and Zinc into Organic Halides. Zinc powder is a moderately good reducing reagent and reacts readily only with alkyl iodides[10] and benzylic halides.[11] Aryl iodides undergo the insertion of zinc only in polar solvents, such as DMA.[12] The use of the highly activated zinc introduced by Rieke[13] significantly improves the zinc insertion rate but requires the generation of highly active zinc powder. We have found that the presence of LiCl considerably facilitates the rates of zinc metal insertion in aryl iodides and electron-poor aryl or heteroaryl bromides.[14] The roles of LiCl may be multiple, but notably this salt has an exceptional ability to solubilize organometallic reagents and metal salts in common organic solvents, such as THF. Early on, Li_2CuCl_4 (Kochi catalyst)[15] and CuCN·2LiCl[16] were found to be very valuable sources of copper(I) for numerous carbon−carbon bond-forming reactions. Similarly, numerous salts can dissolve in THF with the aid of LiCl by forming adducts such as $MnCl_2$·2LiCl[17] or $ZnCl_2$·2LiCl.[18] Thus, the role of LiCl for accelerating the insertion of magnesium or zinc may be to remove the newly generated organometallic species from the metal magnesium or zinc surface and, therefore, regenerate the active metal sites at the surface. This activation is quite general and has been used for other metals such as indium,[19] manganese,[20] and aluminum.[19b,21] Thus, a highly site selective room-temperature zinc insertion is achieved by treating heterocyclic diiodides **1** and **2** and tribromide **3** with zinc powder in the presence of LiCl, providing functionalized zincated building blocks **4**−**6**[22,23] in high yields. The titration of polyfunctional zinc reagents is readily performed by iodometry.[24] Quenching the organocuprate with an acid chloride or an allylic halide in the presence of CuCN·2LiCl provides the expected heterocycles **7**−**9** in 63−81% yield (Scheme 2).

Scheme 3. Site and Stereoselective Insertion of Zinc to *α*,*β*-Unsaturated Aldehydes

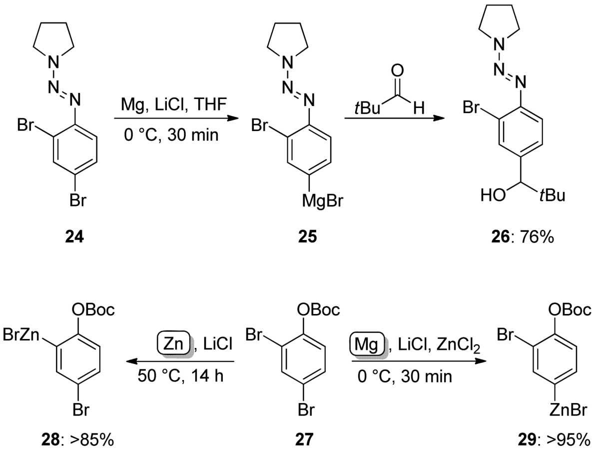


The exceptionally mild conditions allow the insertion in *α*,*β*-unsaturated aldehydes, such as **10** or **11**, leading to zinc species **12** and **13**. Although the zinc insertion is a radical reaction,[25] only *Z*-alkenylzinc bromide **13** is obtained, indicating that

Scheme 4. Magnesium Insertions in the Presence of $ZnCl_2$ and LiCl



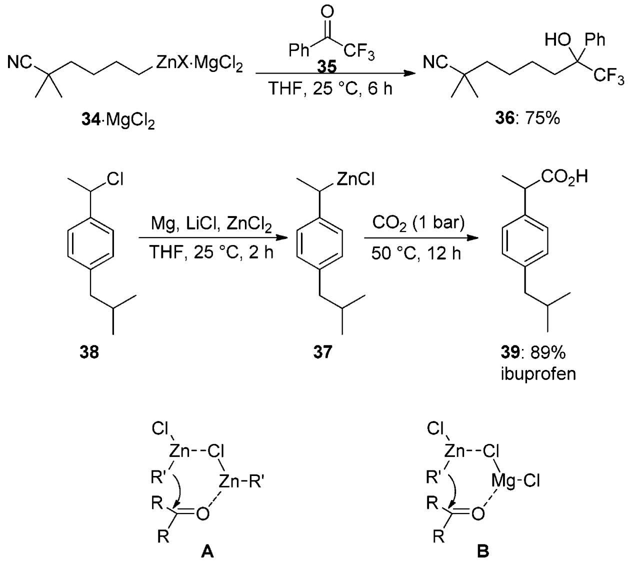
Scheme 5. Site-Selective Insertions of Zinc and Magnesium to Dibromo Aromatic Compounds



complexion of the zinc atom with the aldehyde oxygen is already present in the intermediate (**14**). Pd-catalyzed cross-couplings afford the expected unsaturated aldehydes **15** and **16** in 82–92% yield with retention of the double-bond configuration (Scheme 3).[25,26] Pd-catalyzed cross-couplings using functionalized organozinc reagents (Negishi reactions) are usually rapid.[10f,27] Related Ni-catalyzed cross-couplings are also very efficient.[10d,g,28] It should be noted that some Fe- or Co-catalyzed reactions with polyfunctional magnesium or zinc organometallic reagents have been reported.[6,11a,29]

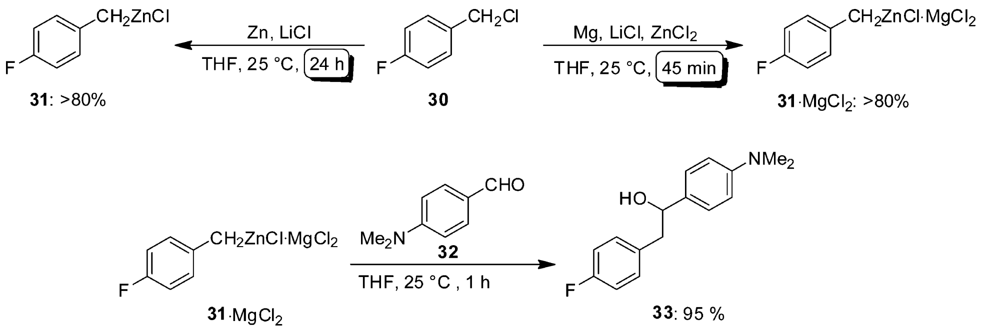
Since the moderate reducing power of zinc metal precludes insertions into electron-rich aryl bromides, we have replaced

Scheme 7. $MgCl_2$–Accelerated Additions of Zinc Organometallic Reagents to Carbonyl Derivatives

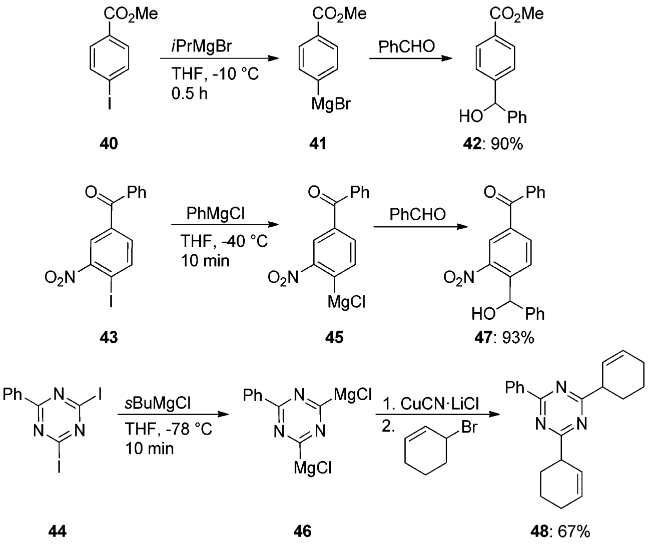


zinc by a stronger reducing metal: magnesium.[30] The presence of $ZnCl_2$ and LiCl led to a synergistic activation of the metal and immediately converts the intermediate arylmagnesium derivative (for example **17** resulting from a magnesium insertion to the bromobenzoate **18**) into the corresponding zinc reagent **19**. This insertion reaction can be performed at room temperature in THF and is complete within 3 h. Copper(I)-catalyzed allylation of **20** converts this zinc reagent

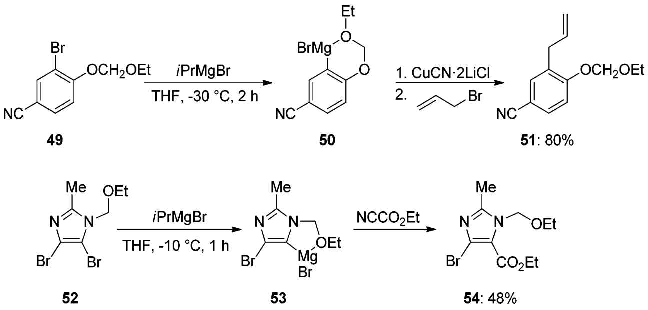
Scheme 6. Insertions of Zinc or Mg, $ZnCl_2$ to Benzylic Chlorides in the Presence of LiCl



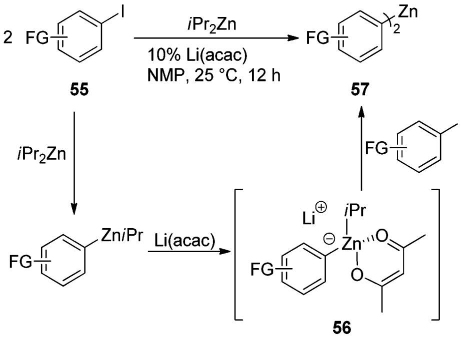
Scheme 8. Iodine−Magnesium Exchange on Functionalized Aromatic and Heterocyclic Compounds



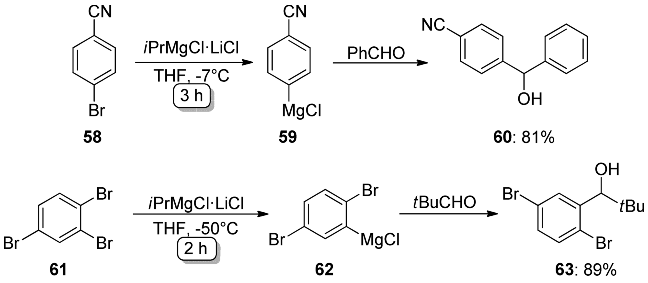
Scheme 9. Bromine−Magnesium Exchange an Activated Bromides



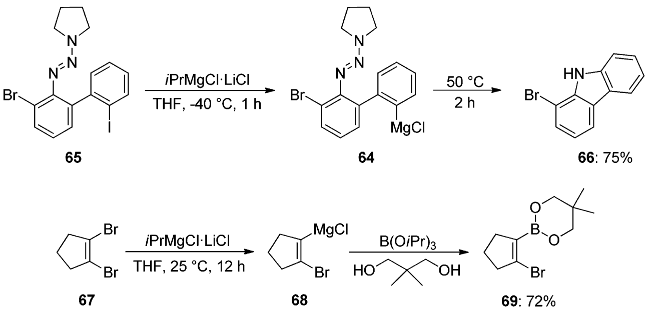
Scheme 10. Li(acac)-Catalyzed Iodine−Zinc Exchange



Scheme 11. LiCl-Accelerated Bromine−Magnesium Exchange



Scheme 12. Preparation of Highly Functionalized Magnesium Reagents Using *i*-PrMgCl·LiCl



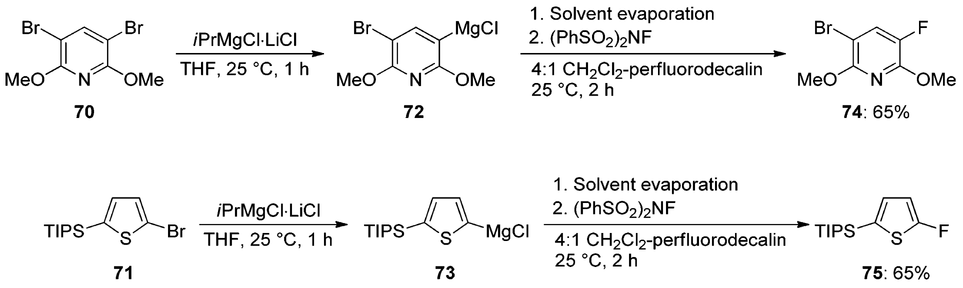
into allylated product **20** in 83% yield. This method now allows the conversion of electron-deficient heterocyclic chlorides, such as uracil derivative **21**, to the corresponding zinc reagent **22**. After allylation, uracil derivative **23** is obtained in 68% yield (Scheme 4).[31] The use of LiCl also allows the direct insertion of indium,[10i,32] manganese, and aluminum[33] to aryl iodides, and in some cases to aryl bromides.

With these insertion protocols in hand, a number of functionalized substrates undergo smooth and site-selective insertion of magnesium or zinc. Thus, dibromotriazine **24** is readily converted into 4-magnesiated species **25**,[11b] which upon trapping with pivalaldehyde, furnishes alcohol **26** in 76% yield (Scheme 5). The site selectivity of polyhalogenated substrates depends on the metal used for performing the insertion. Thus, the Boc-protected dibromophenol **27** inserts zinc exclusively in the *ortho*-position. The presence of LiCl is required, as is a temperature of 50 °C, leading to zinc reagent **28** in >85% yield. Alternatively, the use of magnesium leads to an insertion in the *para*-position, furnishing, (after transmetalation with $ZnCl_2$) zinc reagent **29** in >95% yield (Scheme 5).[34] The selective insertion of magnesium has been used to prepare boscalid with great efficiency.[35]

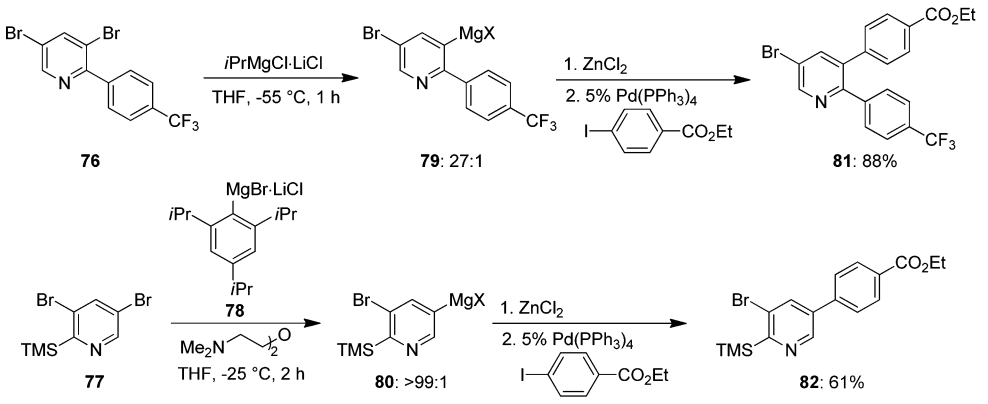
The insertion of zinc to benzylic chlorides has a broad scope and represents a unique method for preparing polyfunctional benzylic organometallic reagents.[36] Furthermore, the use of Mg, in conjunction with $ZnCl_2$ and LiCl for performing this insertion, considerably shortens the reaction time.[37] Thus, 4-fluorobenzyl chloride **30** requires ca. 24 h at room temperature for complete zinc insertion, leading to the zinc reagent **31** in >80% yield. By using Mg, $ZnCl_2$, and LiCl, the magnesium insertion occurs quickly, and the intermediate Grignard reagent is rapidly transmetalated to zinc. Overall, the zinc reagent is prepared within 45 min at the same temperature. Furthermore, the resulting benzylic zinc reagent **31** is complexed by $MgCl_2$. This Lewis acid enhances the reactivity of this benzylic zinc reagent, and the addition of **31**·$MgCl_2$ to an aldehyde, such as **32**, is complete within 1 h at 25 °C to produce alcohol **33**, whereas in the absence of $MgCl_2$, a conversion of only 23% is obtained with **31** after 20 h at 25 °C (Scheme 6).[38] It has also been shown that $LaCl_3 \cdot LiCl$ is a very powerful Lewis acid.[39] Allylic zinc reagents display an even higher reactivity toward various electrophiles due to the polar character of the carbon−zinc bond.[40]

The $MgCl_2$ catalysis is quite general and dramatically increases the reactivity of aryl, alkyl, and benzylic zinc reagents toward an addition to carbonyl groups. Thus, the functionalized alkylzinc reagent **34** adds readily to trifluoromethyl ketone **35**, furnishing tertiary alcohol **36** within 6 h at 25 °C. Also, the secondary benzylic zinc reagent **37** prepared by zinc insertion

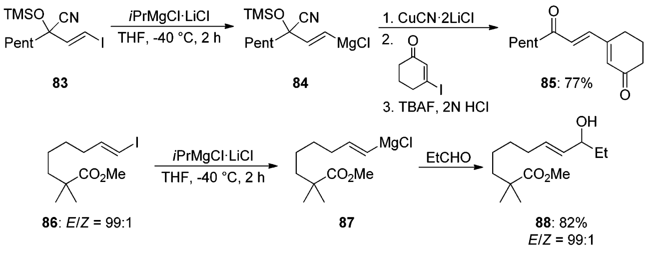
Scheme 13. Fluorination of Functionalized Magnesium Reagents Obtained by a Bromine–Magnesium Exchange



Scheme 14. Site-Selective Bromine–Magnesium Exchange on Dibromopyridines



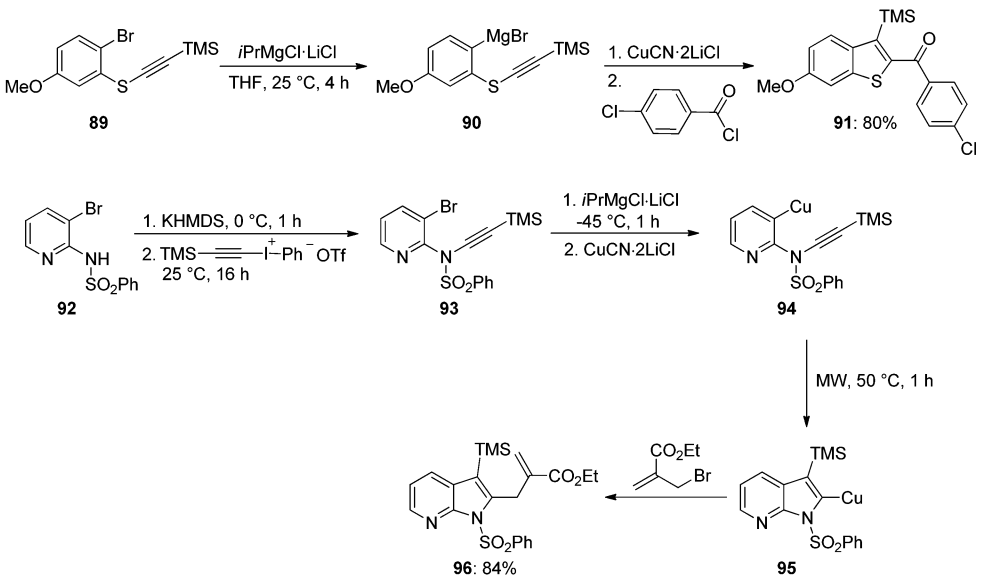
Scheme 15. Iodine–Magnesium Exchange Reactions Using *i*-PrMgCl·LiCl



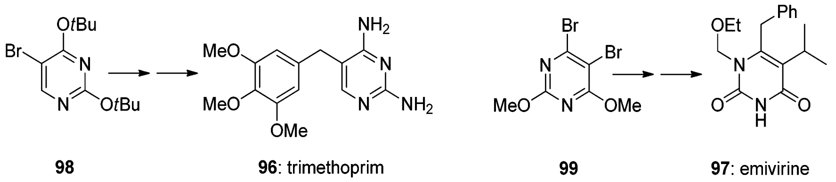
to the secondary benzylic chloride **38** adds readily to CO_2 at 50 °C within 12 h, leading to ibuprofen (**39**) in 89% yield. The catalytic effect of $MgCl_2$ may be explained by comparing the putative transition states (TS): (A) the addition of zinc organometallic reagents to a carbonyl compound via the TS and (B) proceeding in the presence of $MgCl_2$. The Lewis acid is able to electrophilically activate the carbonyl function much more effectively than an organozinc halide (Scheme 7).

b. Preparation of Magnesium or Zinc Organometallic Reagents via Halogen–Magnesium Exchange. Iodine–magnesium exchange is an excellent method for converting aryl iodides to the corresponding magnesium species.[10c,41] For

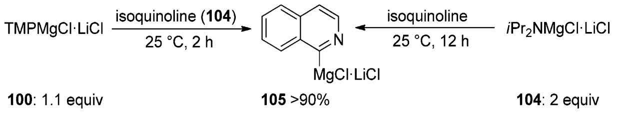
Scheme 16. Synthesis of Functionalized Benzothiophenes and Azaindoles via Intramolecular Carbocupration



Scheme 17. Preparation of Biologically Active Molecules Using a Bromine−Magnesium Exchange



Scheme 18. Relative Kinetic Basicity of TMPMgCl·LiCl (100) and *i*-Pr$_2$NMgCl·LiCl (103)



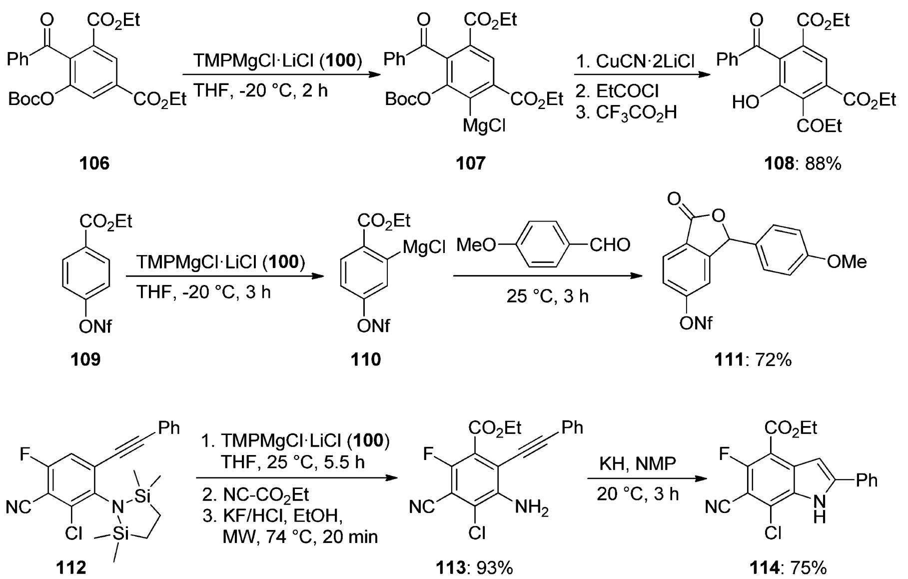
example, methyl 4-iodobenzoate **40** reacts with *i*-PrMgBr in THF at −10 °C and leads, after a reaction time of 30 min, to the Grignard reagent **41** in >95% yield.[42] After a reaction with benzaldehyde, arylmagnesium bromide **41** affords the benzylic alcohol **42** in 90% yield. Unfortunately, the iodine−magnesium exchange is usually a slow reaction. The presence of electron-withdrawing substituents on the aromatic ring such as **43**[43] or the use of electron-poor heterocycles **44**[20a] facilitates the exchange reaction, and both **43** and **44** are converted to magnesium derivatives **45** and **46** in good yields. Quenching the organometallic reagents with various standard electrophiles provides the expected products **47** and **48** (Scheme 8). Interestingly, iodine−copper exchange also gives a useful entry to polyfunctional copper reagents; however, aryl or heteroaryl *iodides* are always required as precursors for this exchange.[10a,b,44]

Bromine−magnesium exchange is much more sluggish and proceeds readily only if coordinating groups in the *ortho* position assist the bromine−magnesium exchange reaction. Thus, aryl bromide **49**, bearing an ethoxymethoxy group in the *ortho* position, reacts already with *i*-PrMgBr at −30 °C, providing complexed Grignard reagent **50**. Allylation of **50** leads to benzonitrile derivative **51** in 80% yield (Scheme 9).[45] Similarly, dibromoimidazole **52** undergoes a selective bromine−magnesium exchange with the bromine atom closest to the ethoxymethoxy substituent, affording magnesiated imidazole derivative **53**. After acylation using Mander's reagent (NC−CO$_2$Et), imidazole **54** is obtained in 48% yield (Scheme 9).[46]

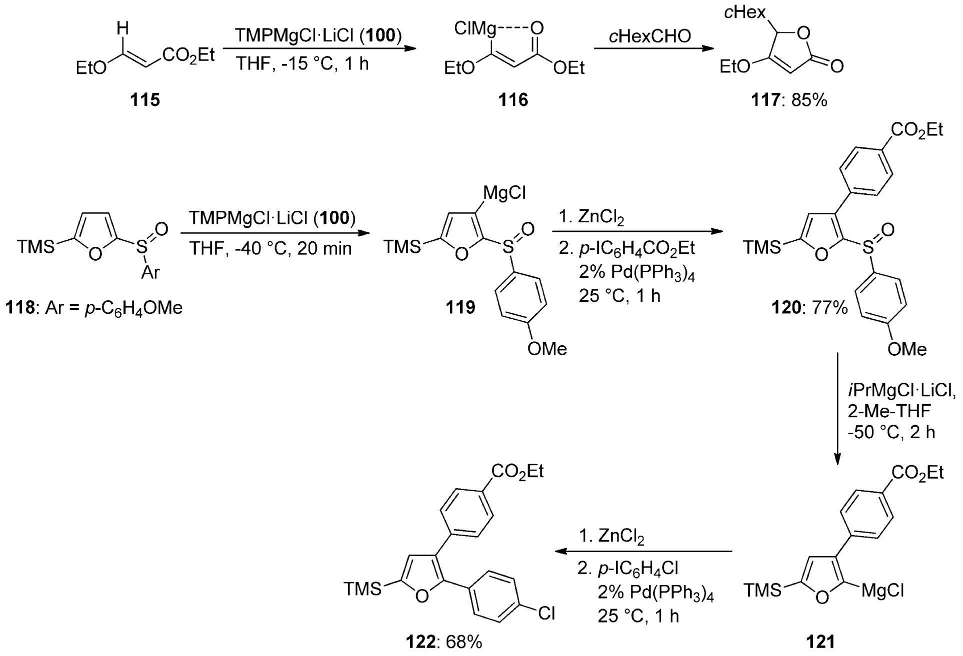
This reduced scope of the bromine−magnesium exchange reaction led us to explore catalysis of a halogen-metal exchange. Thus, in the search for improving the iodine−zinc exchange reaction on aromatic iodides **55**, we found that the addition of Li(acac) to *i*-Pr$_2$Zn considerably accelerates the iodine−zinc exchange, tentatively via zincate **56** in which a nucleophilic isopropyl group is present. This additional nucleophilicity accelerates the second iodine−zinc exchange, furnishing diarylzinc compound **57** (Scheme 10).[47]

This catalysis could be extended to the bromine−magnesium exchange using LiCl as the promoter instead of Li(acac). Thus, the use of *i*-PrMgCl·LiCl leads to a dramatic rate acceleration of the bromine−magnesium exchange and allows now the performance of such exchange reactions under especially mild reaction conditions. Thus, 4-bromobenzonitrile **58** reacts with *i*-PrMgCl·LiCl at −7 °C to provide magnesium reagent **59**, which after quenching with benzaldehyde gives alcohol **60** in 81% yield (Scheme 11). Similarly, the highly site selective bromine−magnesium exchange is observed with tribromide **61**. The exchange reaction with *i*-PrMgCl·LiCl proceeds at −50 °C and leads to Grignard reagent **62**, which after quenching with pivaldehyde furnishes alcohol **63** in 89% yield (Scheme 11).[48] The use of LiCl favors the formation of the magnesiated intermediate *i*-PrMgCl$_2^-$ Li$^+$, which should display a higher nucleophilicity compared to *i*-PrMgCl. This exchange procedure has a broad scope and has found many applications.[49] The

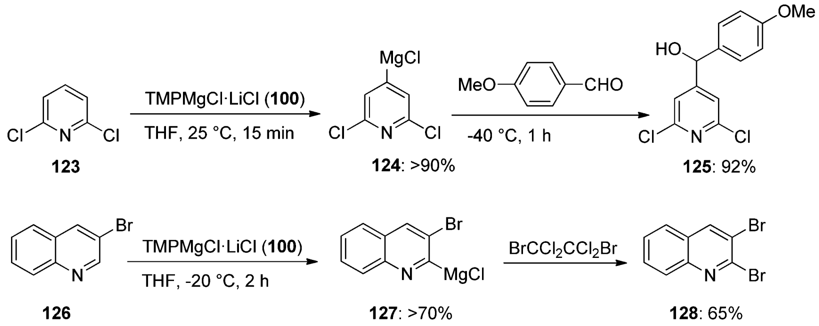
Scheme 19. Selective Magnesiations with TMPMgCl·LiCl (100)



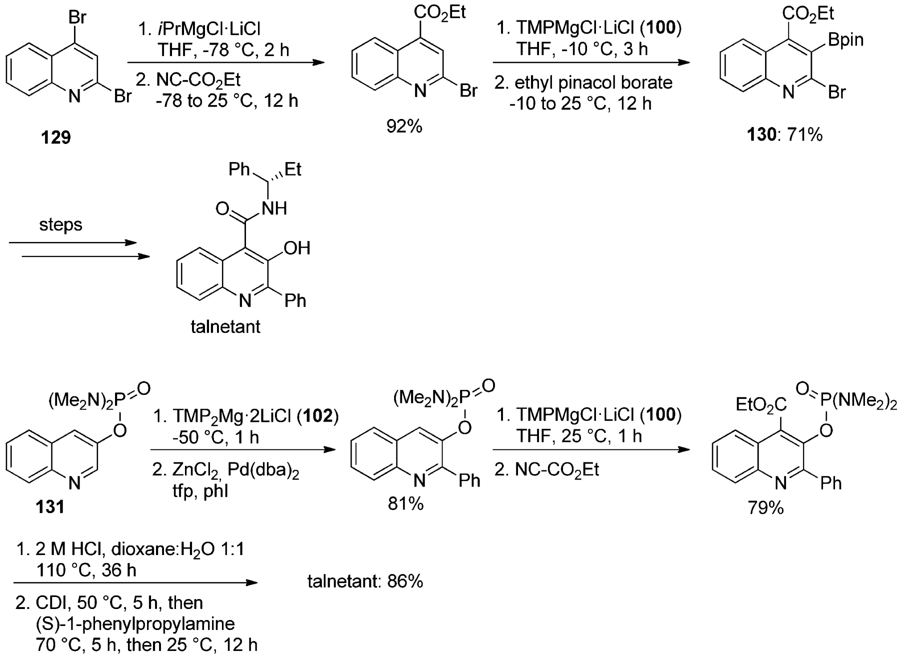
Scheme 20. Directed Magnesiation with TMPMgCl·LiCl (100)



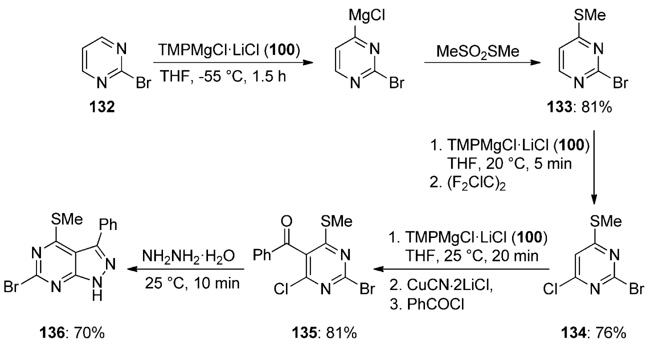
Scheme 21. Magnesiation of N-Heterocycles with TMPMgCl·LiCl (100)



Scheme 22. Comparison of Talnetant Syntheses



Scheme 23. Full Functionalization of the Pyrimidine Skeleton Using TMPMgCl·LiCl (100)



kinetics of a bromine−magnesium exchange have been carefully studied.[12,50]

Thus, LiCl-assisted bromine−magnesium exchange is compatible with a range of functional groups and therefore allows the preparation of highly functionalized Grignard reagents, such as **64**, starting from the bromotriazine **65**. Magnesium reagent **64** undergoes a ring closure, leading to carbazole **66** in 75% yield (Scheme 12).[51] Also, 1,2-dibromocyclopentene (**67**) is smoothly converted into the corresponding magnesium derivative **68**, which is readily transmetalated to boronic ester **69** in 72% yield (Scheme 12).[52]

Bromine−magnesium exchange is also an excellent method for preparing heterocyclic fluorides starting from the corresponding bromides, such as **70** or **71**. The intermediate magnesium species **72** and **73** react in approimately a 4:1 mixture of CH_2Cl_2:perfluorodecalin[53,54] with $(PhSO_2)_2N-F$, leading to the fluorinated derivatives **74** and **75** (Scheme 13).

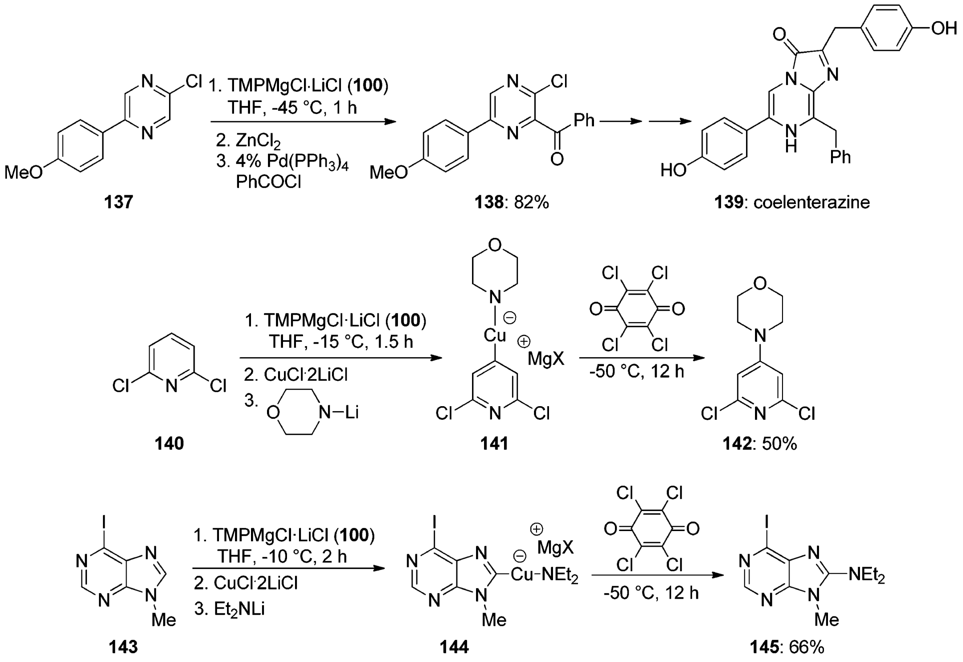
Highly site selective exchange reactions can be performed using *i*-PrMgCl·LiCl or related reagents. Thus, dibromopyridines **76** and **77** react selectively with *i*-PrMgCl·LiCl or the more sterically hindered arylmagnesium reagent **78**, providing magnesiated pyridines **79** and **80**. The site selectivity is directed by the nature of the *α*-substituent (electron-withdrawing or electron−donating), leading, after Negishi cross-couplings, to arylated pyridines **81** and **82** (Scheme 14).

The high reactivity of *i*-PrMgCl·LiCl allows halogen−magnesium exchange reactions with iodoalkenes to take place.[55,56] Silylated cyanohydrins are also well-tolerated in bromine−magnesium exchange reactions. Thus, at −40 °C, alkenyl iodide **83** is converted into the corresponding magnesium reagent **84** within 2 h. Copper-mediated substitution on 3-iodocyclohexanane produces diketone **85** in 77% yield after TBAF deprotection.[56a] The configuration of the alkene is retained in the iodine−magnesium exchange. Thus, treatment of *E*-alkenyl iodide **86** with *i*-PrMgCl·LiCl produces magnesium reagent **87**. Treatment of reagent **87** with propionaldehyde affords allylic alcohol **88** with complete retention of the double bond geometry (Scheme 15).[57]

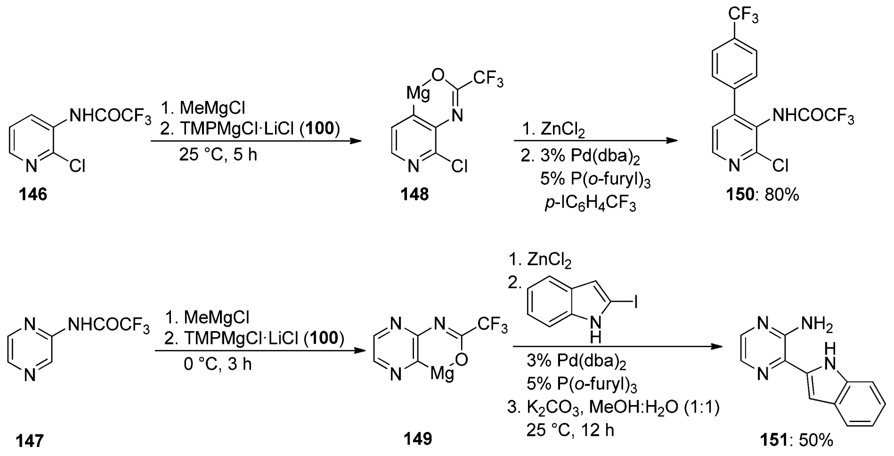
Also, a range of new heterocycles can be constructed using a bromine−magnesium exchange as a key step. Thus, treatment of alkynyl thioether **89** with *i*-PrMgCl·LiCl leads to the corresponding Grignard reagent **90**, which undergoes an intramolecular carbocupration in the presence of CuCN·2LiCl. Quenching of the resulting organocuprate with an acid chloride provides substituted benzothiophene **91** in 80% yield (Scheme 16).[58] Similarly, a range of indoles and more importantly 7-, 6-, 5-, or 4-azaindoles can be prepared using *i*-PrMgCl. Thus, after the conversion of readily available aminopyridine **92** to the alkynylamine **93**, bromine−magnesium exchange and transmetalation to copper reagent **94** leads to intramolecular *anti*-carbocupration under microwave irradiation at 50 °C for 1 h. Finally, quenching the cyclic copper intermediate **95** with an allylic bromide provides 7-azaindole **96** in 84% overall yield (Scheme 16).[59]

Finally, bromine−magnesium exchange has been applied to the synthesis of various biologically active compounds, such as the antibiotic trimethoprim **96**[60] and anti-AIDS drug emivirine **97**,[61] starting from simple uracil-derived building blocks **98** and **99** (Scheme 17).

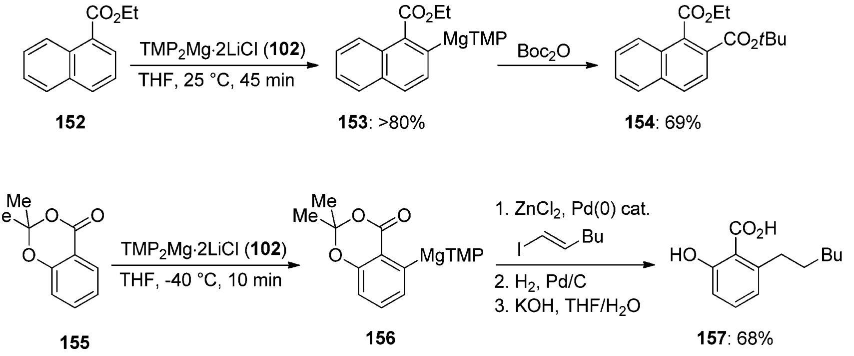
Scheme 24. Functionalization of N-Heterocycles Using TMPMgCl·LiCl (100)



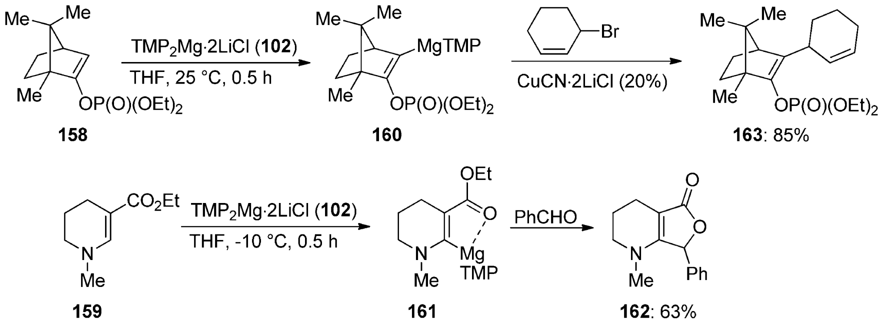
Scheme 25. Magnesiation of Amino-N-heterocycles with TMPMgCl·LiCl (100)



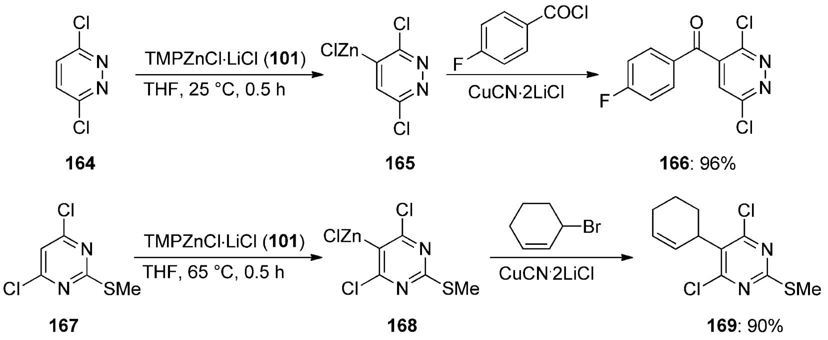
Scheme 26. TMP2Mg·2LiCl for the Magnesiation of Reluctant Substrates



Scheme 27. Functionalization of Various Alkenes Using TMPMg·2LiCl (102)

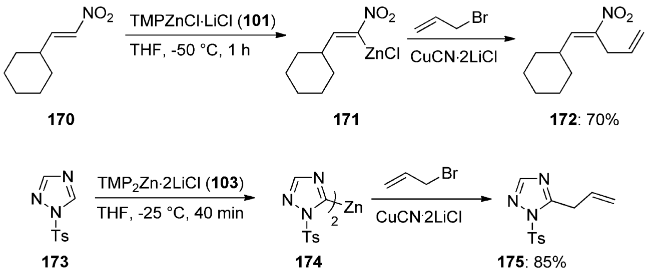


Scheme 28. Zincation of N-Heterocycles with TMPZnCl·LiCl (101)



c. Preparation of Magnesium or Zinc Organometallic Reagents via Site-Selective Deprotonation with Metallic TMP-Bases. Pioneered by Hauser,[62] the use of various metallic amides have been used to site selectively metalate unsaturated substrates.[63] The site-selective deprotonation of aromatic and heterocyclic compounds using lithium bases has been

Scheme 29. Direct Zincation of Sensitive Substrates with TMP-Zinc Bases 101 and 103



popularized by Snieckus,[64] Quéguiner,[65] and Schlosser.[66] However, the ionic character and reactivity of the carbon−lithium bond complicates the use lithium compounds with polyfunctional molecules bearing sensitive functionalities. We have developed some LiCl-solubilized metallic TMP-bases,[67] allowing a highly chemoselective and site selective metalation of a broad range of unsaturated substrates. Especially useful are TMPMgCl·LiCl (**100**),[68] TMPZnCl·LiCl (**101**),[69] TMP$_2$Mg·2LiCl (**102**), and TMP$_2$Zn·2LiCl (**103**).[70] The bulk of the TMP moiety is essential for a high kinetic selectivity of these bases. Thus, the less sterically hindered base *i*-Pr$_2$NMgCl·LiCl (**104**) is considerably less effective for deprotonations. Thus, the treatment of isoquinoline with **104** at 25 °C is sluggish and takes 24 h. Furthermore, it requires 2 equiv of **104** for a complete metalation, providing 2-magnesiated isoquinoline **105**. On the other hand, the use of TMPMgCl·LiCl (**100**) leads to a complete magnesiation within 2 h at 25 °C (Scheme 18).[68] The discrepancy between the two bases can be explained best by the higher aggregation of **104** compared to **100**.[62c,68]

d. Directed Metalation with Metallic TMP Bases. Because of this high kinetic basicity, TMPMgCl·LiCl (**100**) is able to deprotonate polyfunctional aromatics, such as highly functionalized arene **106**, under mild conditions (−20 °C, 2 h). Under these conditions, an ester, a carbonate, and an aryl ketone remain untouched during the magnesiation. The resulting magnesium reagent (**107**) can be acylated in the presence of CuCN·2LiCl,[10a] leading to pentasubstituted phenol derivative **108** in 88% yield (Scheme 19).[71] Highly electrophilic functional groups, such as a nonaflate (ONF = OSO$_2$C$_4$F$_9$),[72] are well-tolerated. Thus, the magnesiation of benzoate **109** with TMPMgCl·LiCl (**100**) proceeds readily at −20 °C, leading to Grignard reagent **110**. Addition of an aldehyde at 25 °C leads to lactone **111**.[73] Similarly, sensitive ester-substituted ferrocenes[74] can be satisfactorily magnesiated.[74] Also, the magnesiation of sensitive bis(silyl)amines, such as **112**, can be realized with TMPMgCl·LiCl (**100**) at 25 °C, leading to hexasubstituted aniline **113** in 93% yield.[75] Its cyclization using KH in NMP[76] furnishes polysubstituted indole **114** in 75% yield (Scheme 19).

TMPMgCl·LiCl (**100**) can also be used to metalate acyclic esters such as **115**. Site-selective magnesiation provides chelated magnesium derivative **116** in >90% yield. Trapping with cyclohexanecarboxaldehyde provides lactone **117** in 85% yield (Scheme 17).

The sulfoxide group is also an excellent directing group. Furthermore, it readily undergoes a sulfoxide−magnesium exchange[77] when treated with *i*-PrMgCl·LiCl. Thus, furan derivative **118** is magnesiated with TMPMgCl·LiCl (**100**) within 20 min at −40 °C, leading to magnesium reagent **119**. After a Negishi cross-coupling,[78] furan **120** is treated with *i*-PrMgCl·LiCl in 2-Me-THF at −50 °C, which leads to a sulfoxide−magnesium exchange[77,79] affording magnesium derivative **121** after 2 h. Transmetalation with ZnCl$_2$ followed by a Negishi cross-coupling[80] with an aryl iodide in the presence of (Ph$_3$P)$_4$Pd (2 mol %) leads to formation of trisubstituted furan **122** in 68% yield (Scheme 20).[80,81]

A wide range of furans,[82] thiophenes,[83] pyrroles, pyrazoles,[84] and thienothiophenes[85] can be functionalized in this way. The magnesiation of pyridines can also be achieved with TMPMgCl·LiCl (**100**), and the reaction of 2,6-dichloropyridine **123** with TMPMgCl·LiCl at 25 °C leads to 4-magnesiated pyridine **124**. Trapping the Grignard reagent with an aldehyde furnishes alcohol **125** in 92% yield.[86] The metalation of 3-bromo quinoline **126** is readily achieved with **100**, providing 2-magnesiated derivative **127**. After bromination with (BrCl$_2$C)$_2$, 2,3-dibromoquinoline (**128**) is obtained in 65% yield (Scheme 21).[87]

Using a selective bromine−magnesium exchange and a site-selective deprotonation with **100**, 2,4-dibromoquinoline (**129**) was transformed into polyfunctional quinoline **130**, which is a precursor to the pharmaceutical talnetant.[87] A shorter synthesis of talnetant was later developed by performing two sequential site selective deprotonations starting with phosphorodiamidate **131**.[88]

The full functionalization of the pyrimidine skeleton can be achieved starting with 2-bromopyridine (**132**). The first metalation at position 4 has to be performed at −55 °C. Higher magnesiation temperatures lead to the decomposition of the sensitive magnesium derivative, which is prone to add to unreacted starting material **132**.[89] After thiolation with MeSO$_2$SMe, thioether **133** is obtained in 81% yield. This pyrimidine is more electron-rich and therefore less sensitive to dimerization and oligomerization reactions. Thus, thioether **133**, can now be metalated with **100** at 20 °C. Chlorination of the magnesium intermediate with (ClF$_2$C)$_2$ provides trisubstituted pyrimidine **134** in 76% yield. Further treatment of **134** with TMPMgCl·LiCl (**100**) at 25 °C leads, after a copper-mediated benzoylation, to the fully substituted pyrimidine **135** in 81% yield. Its cyclization with hydrazine produces pyrazolopyrimidine **136** in 70% yield (Scheme 23).

Activated pyrazines, such as **137**, are metalated with TMPMgCl·LiCl (**100**)[26e] at −45 °C to provide trisubstituted pyrazines **138** after a Negishi benzoylation in 82% yield.[90] Pyrazine **138** is a key intermediate in the synthesis of coelenterazine (**139**), a chemiluminescent substance, which is responsible for the luminescence of jellyfish (Scheme 24).[91] Chlorinated heterocycles such as 2,6-dichloropyridine **140** are easily magnesiated with TMPMgCl·LiCl (**100**). After transmetalation with CuCl·2LiCl and reaction with lithium morpholide, amidocuprate **141** is produced. Treatment of amidocuprate **141** with chloranil provides aminopyridine **142** in 50% yield.[92] Similarly, iodopurine **143** is converted into amidocuprate **144**, which after oxidative coupling, furnishes aminopurine **145** in 66% yield (Scheme 24).[93,94]

The metalation of anilines and amino-N-heterocycles is especially complicated. However, the use of a trifluoroacetyl protecting group allows a smooth magnesiation of pyridine **146** and pyrazine **147**, leading to the magnesiated heterocycles **148** and **149**. Quenching by an arylation (Negishi cross-coupling) furnishes expected heterocycles **150** and **151** in 50−80% yield (Scheme 25).[95]

In some cases, TMPMgCl·LiCl (**100**) is not strong enough to ensure a fast magnesiation reaction. In theses cases, the use of $TMP_2Mg{\cdot}2LiCl$ (**102**) is required. In contrast to TMPMgCl·LiCl (**100**), bis-TMP base **102** is not stable at 25 °C and slowly opens THF. Therefore, an alternative base has been developed [*t*-Bu(*i*-Pr)N]$_2$Mg·2LiCl. This base can be readily prepared at 25 °C and is obtained in a concentration of 0.85 M in THF. These THF solutions are stable at 25 °C over months.[96]

$TMP_2Mg{\cdot}2LiCl$ (**102**) allows a room-temperature magnesiation of ethyl naphthenoate **152**, leading to magnesium derivative **153**. After acylation with Boc_2O, expected diester **154** is obtained in 69% yield (90 mmol scale reaction).[97,98] Also, salicylate acetonide **155** is smoothly magnesiated at −40 °C, leading to **156**. After Negishi alkenylation with *E*-iodohexene, hydrogenation, and saponification, salicylic acid derivative **157**, found in *Pelargonium sidoides*, is obtained in 68% yield (Scheme 26).[97]

This base is also well-suited for the magnesiation of phosphorodiamidates, formally in *meta*- and *para*-positions,[99] the aryl ring of quinolines,[87] as well as for the metalation of polyfunctional pyrazines[100,101] or uracil derivatives.[102] Interestingly, functionalized alkenyl derivatives, such as **158** and **159**, are readily magnesiated with $TMP_2Mg{\cdot}2LiCl$ (**102**). The resulting polyfunctional magnesium reagents **160**[103] and **161**[104] are readily allylated or hydroxyarylated, furnishing the expected products **162** and **163** (Scheme 27). Finally, pyrroles[105] are metalated cleanly with $TMP_2Mg{\cdot}2LiCl$ (**102**) at −30 °C.[106]

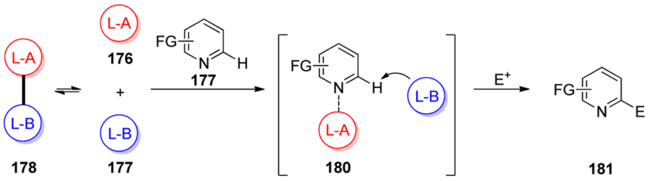
The metalation with TMP-magnesium bases produces magnesium derivatives, and it is the stability and reactivity of the newly formed carbon−magnesium bond which dictates the reaction condition for the metalation and sets the reaction conditions for the magnesiation. Therefore, it is advantageous to use a TMP-zinc base for the metalation.[107] TMPZnCl·LiCl (**101**),[69] and to a lesser extent $TMP_2Zn{\cdot}2LiCl$ (**103**),[70] proved to be highly versatile bases for the zincation of numerous aromatic and heterocyclic compounds. Since organozinc species, all of which have an excellent functional group compatibility, are produced directly, it is possible to choose a broad range of conditions for the metalation step, and an exact control of the temperature is not necessary when using TMPZnCl·LiCl (**101**).[69] This base can be used to metalate dichloropyridazine **164** at 25 °C, leading to zinc reagent **165**. Acylation of **165** with an acid chloride provides ketone **166** in almost quantitative yield.[69d] Also, such zincations can readily be performed at high temperature. Thus, pyrimidine **167** is zincated at 65 °C, leading to zinc derivative **168**. Allylation of **168** provides pyrimidine **169** in 90% yield (Scheme 28).[69d]

TMPZnCl·LiCl (**101**) also metalates nitriles and esters at the *α*-position, and the resulting zinc enolates readily undergo palladium-catalyzed cross-couplings.[7b] Trifluoromethyl ketones or nitroolefins, such as **170**, are zincated with TMPZnCl·LiCl (**101**), leading to **171**. Allylation of **171** with allyl bromide in the presence of 5% CuCN·2LiCl furnishes **172** in 70% yield.[7b] TMPZnCl·LiCl (**101**) also readily zincates purines and allows the full functionalization of this scaffold.[108] On the other hand, the use of $TMP_2Zn{\cdot}LiCl$ (**103**)[70] allows the zincation of triazoles such as **173** without fragmentation leading to **174**. Allylation of **174** furnishes triazole **175** in 85% yield (Scheme 29). $TMP_2Zn{\cdot}LiCl$ (**103**)[11c] also allows functionalization of the indazole skeleton in position 3[109] and can be used for zincations at high temperatures.[110] Other TMP-metallic bases of aluminum,[111] lanthanum,[112] manganese,[113] iron,[113,114] and zirconium[115] have been successfully prepared and used in selective metalations.

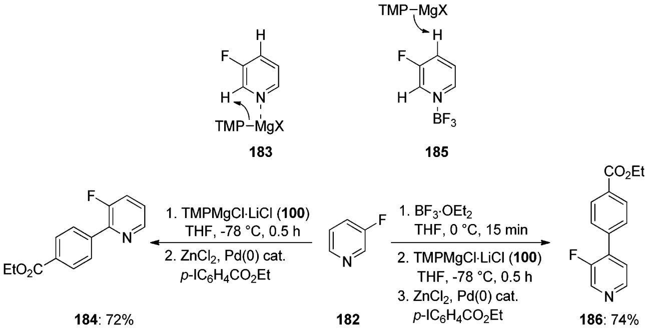
3. COMPATIBILITY OF LEWIS ACIDS AND BRØNSTED BASES: FRUSTRATED LEWIS PAIRS FOR THE METALATION OF N-HETEROCYCLES

a. Metalation of N-Heterocycles. A Lewis acid−base reaction is often a labile equilibrium, especially if the steric hindrance of both (or at least one) reaction partner is large. This phenomena, although described in the literature by Brown[116] and Wittig[117] more than 60 years ago, has received much attention only recently due to the pioneering contributions of Stefan and Erker.[118,119] Thus, the Lewis acid **176** and the Lewis base **177** may reversibly form a Lewis pair **178**, but after the addition of a N-heterocyclic derivative **179**, the Lewis acid may acidify all positions of **179** by a coordination at the heterocyclic N atom. Simultaneously, the Lewis base may play the role of a Brønsted base and abstract the kinetically more acidic proton of the complex of **179** with **176** via a transition state symbolized by **180**. The resulting metalated pyridine can then be quenched by an electrophile, providing products of type **181** (Scheme 30).[120]

Scheme 30. Frustrated Lewis Pairs for Accelerated Metalations



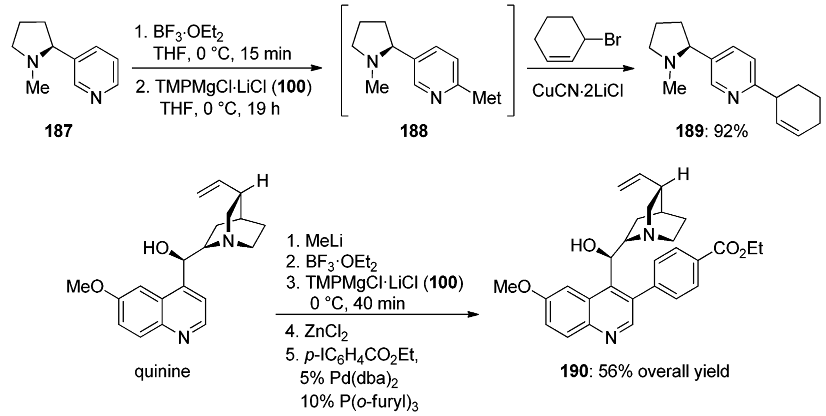
Scheme 31. Orthogonal Site-Selective Magnesiation of 3-Fluoropyridine 182



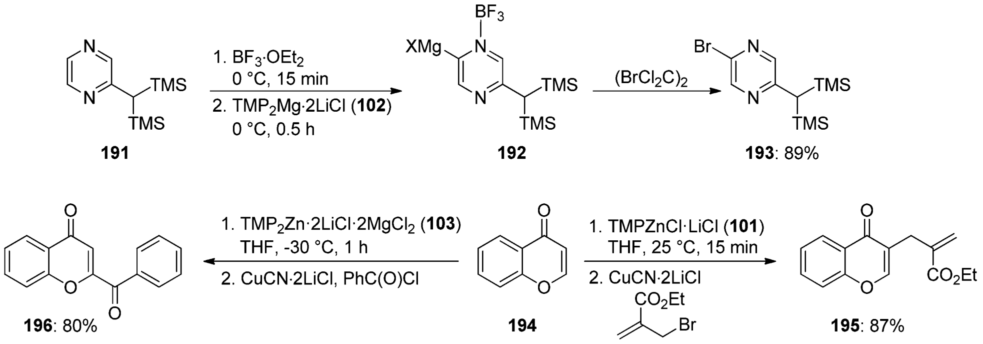
Serendipitously, we have found that the strong Lewis base TMPMgCl·LiCl (**100**) is compatible with the strong Lewis acid $BF_3{\cdot}OEt_2$ at temperatures below −20 °C.[121,122] This behavior has been exploited for performing complementary site selective functionalization of various 3-substituted pyridines, such as **182**. Thus, the magnesiation of **182** with TMPMgCl·LiCl (**100**) proceeds via the formation of a complex of type **183**, which directs the metalation in position 2, providing 2-arylated pyridine **184** after a Negishi cross-coupling in 72% yield. Alternatively, treatment of **182** with $BF_3{\cdot}OEt_2$[123] followed by TMPMgCl·LiCl (**100**) occurs via the tentative complex **185**. In this complex, the metalation at position 2 is blocked by the BF_3 moiety and the magnesiation proceeds only at position 4, leading to the 4-arylated pyridine **186** after a Negishi cross-coupling in 74% yield (Scheme 31).[121]

This behavior can be extended to a number of substituted pyridines. Thus, nicotine (**187**) is cleanly metalated in position 6 with the frustrated Lewis pair $BF_3{\cdot}$**100**, leading to the

Scheme 32. Functionalization of Natural Products by the Frustrated Pair $BF_3 \cdot 100$



Scheme 33. Metalation of Heterocycles with Frustrated Lewis Pairs



metalated species **188**. After copper-catalyzed allylation, 6-substituted nicotine derivative **189** is obtained in 92% yield (Scheme 32).[124] The identity of the atom (Mg or B) attached to carbon in the metalated species has been examined[122,124,125] and may depend on the metalated pyridine studied. Intermediates of type **188** may either be trifluoroboronates[126] or magnesium derivatives.[125] In any case, these organometallic species undergo smooth arylation reactions using standard palladium catalysts, such as $Pd(dba)_2$ and $(o\text{-furyl})_3P$.[127] Quite complex substrates, such as quinine, can be metalated under these conditions, providing 3-arylated quinine derivative **190** after Negishi cross-coupling in 56% yield (Scheme 32).[124]

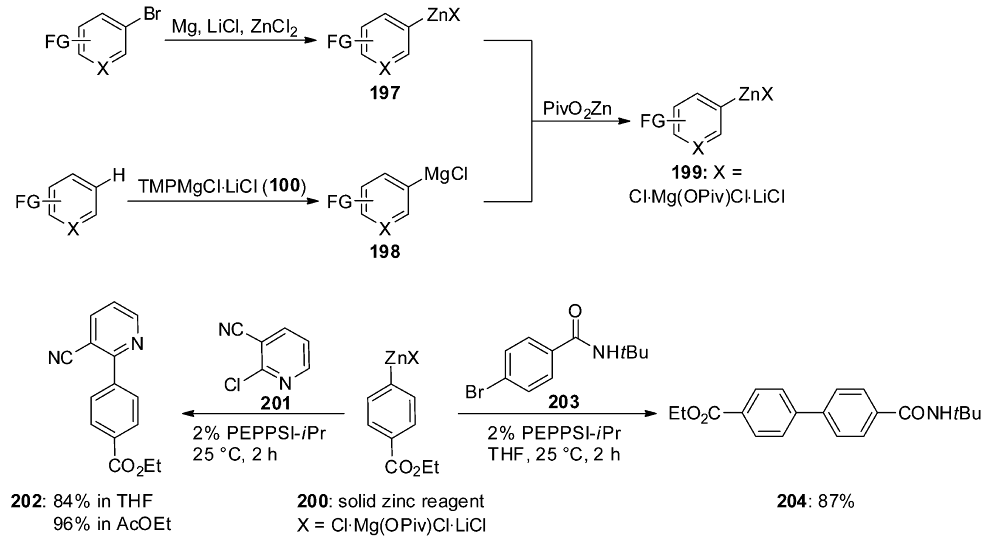
Pyrazines, such as **191**, are readily magnesiated with the Lewis pair $BF_3 \cdot OEt_2$ and $TMP_2Mg \cdot 2LiCl$ (**102**),[97,98] furnishing the site selectively metalated species **192**. Bromination of **192** furnishes heterocyclic bromide **193** in 89% yield (10 mmol scale).[128] Similarly, oxygenated heterocycles, such as chromone **194**, may be metalated either in position 2 or position 3, depending on the Lewis base used [$TMPZnCl \cdot LiCl$ (**101**) or the frustrated pair $TMP_2Zn \cdot LiCl \cdot MgCl_2$ (**103**$\cdot MgCl_2$)]. The observed site selectivity can be explained by assuming that $MgCl_2$ complexes the carbonyl oxygen, leading to metalation in position 2 (steric hindrance at position 3).[129] Thus, the zincation of **193** with $TMPZnCl \cdot LiCl$ (**101**) produces chromone **195** after a copper-catalyzed allylation in 87% yield. Alternatively, metalation of **194** with frustrated Lewis pair **103**$\cdot MgCl_2$ produces 2-acylated chromone **196** after copper-mediated benzoylation in 80% yield (Scheme 33).[129,130]

4. SOLID AIR-STABLE ORGANOZINC REAGENTS

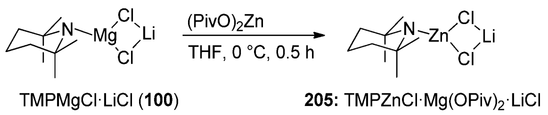
From the preceding sections, it is clear that organozinc reagents have a central importance in organic synthesis. Alterations in their structure make these reagents compatible with work in air or in wet solvents which is an important practical aspect that has been studied intensively in our laboratories. We have found that the treatment of aryl- or heteroarylzinc or -magnesium halides **197** and **198** with zinc pivalate ($[t\text{-BuCO}_2]_2Zn$) followed by the removal of the solvents leads to solid zinc reagents of type **199** that have an improved air and moisture stability (Figure 1). Most of these zinc reagents are stable for several hours in air and afterward readily undergo Negishi cross-couplings (Scheme 34).[131−133] The structure of the resulting zinc reagents **199** may be complex,[134] and the role of the zinc pivalate may be to form $Mg(OPiv)_2$, which acts as a water scavenger. These solid zinc reagents are prepared either by insertion (Mg, LiCl, $ZnCl_2$)[131] or by directed magnesiation with $TMPMgCl \cdot LiCl$ (**100**) and show excellent reactivity in Pd-catalyzed Negishi cross-couplings. Thus, the solid reagent **200** undergoes a smooth cross-coupling with chloropyridine **201**,

Figure 1. Typical appearance of a solid organozinc reagent of type **199**.

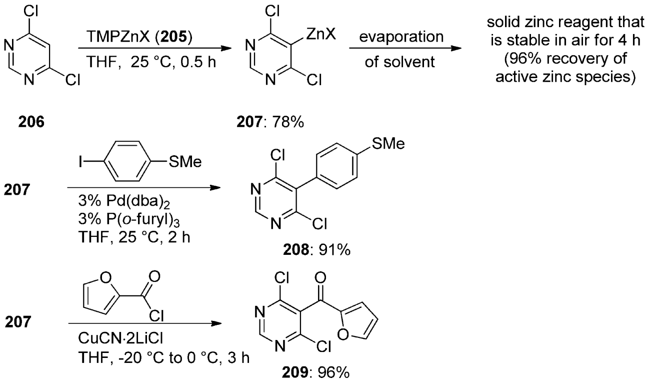
Scheme 34. Preparation of Air-Compatible Solid Organozinc Reagents



Scheme 35. Solid Zinc Organometallic Reagents Obtained by Insertion or Metalations with 100·PivO$_2$Zn or TMPZnX (205)



Scheme 36. Synthesis of Arylzinc Compounds Using Complex Base TMPZnOPiv·Mg(OPiv)Cl·LiCl



using Organ's palladium catalyst, PEPPSI-*i*-Pr.[135] An 84% yield of the desired product **202** is obtained in THF; whereas, a 96% yield is obtained in ethyl acetate, demonstrating that the choice of the solvent may be a simple way for improving the reaction yield. Also, the cross-coupling of **200** with bromoaryl amides bearing an acidic hydrogen, such as **203**, in the presence of 2 mol % of PEPPSI-*i*-Pr proceeds readily in THF within 2 h at 25 °C, leading to biphenyl **204** in 87% yield.[131] The lower basicity of zinc reagents of type **199** readily tolerate the acidic N–H bond of an amide.[136]

Complex base **205**, obtained by the reaction of TMPMgCl·LiCl (**100**) with Zn(OPiv)$_2$, directly provides solid zinc reagents after solvent evaporation. This method allows the synthesis of a broad range of polyfunctionalized solid zinc reagents, all displaying enhanced air and moisture stability (Scheme 35).

Thus, the reaction of pyrimidine **206** with TMPZnX (**205**) provides zinc reagent **207** in 78% yield as indicated by titration. Excellent yields are obtained in Pd-catalyzed cross-couplings, as well as in copper(I)-catalyzed acylations, leading to expected pyrimidines **208** and **209** in 91–96% yield (Scheme 36).

5. CONCLUSION AND PERSPECTIVES

Triggered by the excellent functional group compatibility of magnesium and zinc reagents, we have developed practical and general methods for preparing numerous zinc and magnesium organometallic reagents. We have demonstrated their excellent reactivity with various electrophiles and have shown that various magnesium or zinc reagents are also compatible with strong Lewis acids, which further extends the applications of these reagents in organic synthesis. The availability of zinc reagents with improved air and moisture stability opens additional doors. Because of the predictable and well-tuned reactivity of these reagents, we are convinced that they will find increased use in academic and industrial settings.

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Notes

The authors declare no competing financial interest.

Biography

Paul Knochel was born in 1955 in Strasbourg (France) and completed his undergraduate studies at the University of Strasbourg and his Ph.D. at the ETH Zürich with Prof. Seebach (1982). He spent 4 years with Prof. J.-F. Normant (Paris) and 1 year with Prof. M. F. Semmelhack (Princeton) as a postdoctoral researcher. After professorships at the University of Michigan (Ann Arbor) and at the Philipps-Universität (Marburg), he moved to the Ludwig-Maximilians-Universität (Munich) in 1999.

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■ REFERENCES

(1) For Pd-catalyzed C−H activation and cross-coupling reactions, as well as general reviews, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Mkhalid, I A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 824. (e) Dobereiner, G. E.; Carbtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (f) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (g) White, M. C. *Synlett* **2012**, *23*, 2746. (h) Mousseau, J. J.; Charette, A. B. *Acc. Chem. Res.* **2013**, *46*, 412.

(2) (a) Doyle, M. P. Asymmetric Addition and Insertion Reactions of Catalytically-Generated Metal Carbenes. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 191. (b) Doyle, M. P. Catalysis with Dirhodium(II) Complexes. In *Catalysis by Di- and Polynuclear Metal Cluster Complexes*; Adams, R. D., Cotton, F. A., Eds.; Wiley-VCH: New York, 2000; p 249. (c) Doyle, M. P. Chiral Dirhodium(II) Carboxamidates for Asymmetric Cyclopropanation and Carbon−Hydrogen Insertion Reactions. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 341. (d) Doyle, M. P.; Morgan, J. P.; Colyer, J. T. *J. Organomet. Chem.* **2005**, *690*, 5525. (e) Cho, C.-W.; Krische, M. J. Hydrogen-Mediated Carbon−Carbon Bond Formation Catalyzed by Rhodium. In *Handbook of Homogeneous Hydrogenation*; De Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007; Vol. 2, p 713. (f) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (g) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857. (h) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (i) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (j) Moran, J. M.; Krische, M. J. *Pure Appl. Chem.* **2012**, *84*, 1729. (k) Wang, H.; Gang, L.; Engle, K. M.; Yu, J.-Q.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6774.

(3) (a) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599. (b) Burneau, C. M.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311. (c) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225. (d) Rigaut, S.; Touchard, D.; Dixneuf, P. H. *Coordin. Chem. Rev.* **2004**, *248*, 1585. (e) Dyker, G. *Handbook of C−H Transformations*; Wiley-VCH: Weinheim, 2005. (f) *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2005. (g) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34. (h) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (i) Arockiam, P. B.; B; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (j) Li, B.; Dixneuf, P. H. Metal-Catalyzed C−H Bond Activation and C−C Bond Formation in Water. In *Metal-Catalyzed Reactions in Water*; Dixneuf, P. H., Cadierno, V., Eds.; Wiley-VCH: Weinheim, 2013; p 4. (k) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013**, *42*, 5744.

(4) (a) Rokob, T. A.; Hamza, A.; Stirling, A.; Soós, T.; Pápai, I. *Angew. Chem., Int. Ed.* **2008**, *47*, 2435. (b) Stefan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 46. (c) Erős, G.; Mehdi, G.; Pápai, I.; Rokob, T. A.; Király, P.; Tárkányi, G.; Soós, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 6559. (d) Erős, G.; Nagy, K.; Mehdi, H.; Pápai, I.; Nagy, P.; Király, P.; Tárkányi, G.; Soós, T. *Chem.—Eur. J.* **2012**, *18*, 574. (e) *Frustrated Lewis Pairs I*; Erker, G., Stephan, D. W., Eds.; Topics in Current Chemistry 332; Springer: Heidelberg, 2013. (f) *Frustrated Lewis Pairs II*; Erker, G., Stephan, D. W., Eds.; Topics in Current Chemistry 334; Springer: Heidelberg, 2013.

(5) (a) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 1039. (b) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 1043.

(6) Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5425.

(7) (a) Duez, S.; Steib, A. K.; Manolikakes, S. M.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7686. (b) Duez, S.; Bernhardt, S.; Heppekausen, J.; Fleming, F. F.; Knochel, P. *Org. Lett.* **2011**, *13*, 1690.

(8) (a) Fleming, F. F.; Zhang, Z.; Knochel, P. *Org. Lett.* **2004**, *6*, 501. (b) Fleming, F. F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200. (c) Nath, D.; Skilbeck, M. C.; Coldham, I.; Fleming, F. F. *Org. Lett.* **2014**, *16*, 62.

(9) (a) Clayden, J. In *Organolithiums: Selectivity for Synthesis*; Baldwin, J. E., Williams, R. M., Eds.; Tetrahedron Organic Chemistry Series; Pergamon: Amsterdam, 2002.; Vol. 23. (b) Tilly, D.; Chevallier, F.; Mongin, F.; Gros, P. C. *Chem. Rev.* **2014**, *114*, 1475.

(10) (a) Yeh, M. C. P.; Knochel, P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (b) Yeh, M. C. P.; Knochel, P.; Santa, L. E. *Tetrahedron Lett.* **1988**, *29*, 3887. (c) Yeh, M. C. P.; Knochel, P.; Butler, W. M.; Berk, S. C. *Tetrahedron Lett.* **1988**, *29*, 6693. (d) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 2395. (e) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799. (f) Knochel, P.; Chou, T. S.; Chen, H. G.; Yeh, M. C. P.; Rozema, M. J. *J. Org. Chem.* **1989**, *54*, 5202. (g) Majid, T. N.; Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 5069. (h) Yeh, M. C. P.; Chen, H. G.; Knochel, P. *Org. Synth.* **1992**, *70*, 195. (i) Knochel, P.; Chou, T. S.; Jubert, C.; Rajagopal, D. *J. Org. Chem.* **1993**, *58*, 588. (j) Knochel, P.; Millot, N.; Rodriguez, A.; Tucker, C. E. *Org. React.* **2001**, *58*, 417.

(11) (a) Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789. (b) Chen, H. G.; Hoechstetter, C.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4795. (c) Berk, S. C.; Yeh, M. C. P.; Jeong, N.; Knochel, P. *Organomet. Reagents* **1990**, *9*, 3053.

(12) Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413.

(13) (a) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3672. (b) Rieke, R. D. *Science* **1989**, *246*, 1260. (c) Lee, J.; Verlarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428.

(14) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.

(15) Eswein, R. P.; Howald, E. S.; Howald, R. A.; Keeton, D. P. *Inorg. Nucl. Chem.* **1967**, 437.

(16) (a) Stemmler, T.; Penner-Hahn, J. E.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 348. (b) Stemmler, T. L.; Barnhart, T. M.; Penner-Hahn, J. E.; Tucker, C. E.; Knochel, P.; Böhme, M.; Frenking, G. *J. Am. Chem. Soc.* **1995**, *117*, 12489.

(17) (a) Klement, I.; Stadtmüller, H.; Knochel, P.; Cahiez, G. *Tetrahedron Lett.* **1997**, *38*, 1927. (b) Stüdemann, T.; Ibrahim-Ouali, M.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 143. (c) Boucley, C.; Cahiez, G.; Carini, S.; Comes-Franchini, M.; Knochel, P.; Pollicino, S.; Ricci, A. *J. Organomet. Chem.* **2001**, *624*, 223. (d) Cahiez, G.; Duplais, C.; Buendia, J. *Chem. Rev.* **2009**, *109*, 1434. (e) Wunderlich, S. H.; Kienle, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7256.

(18) Dong, Z.; Clososki, G. C.; Wunderlich, S. H.; Unsinn, A.; Li, J.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 457.

(19) (a) Chen, Y.-H.; Sun, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 2236. (b) Knochel, P.; Blümke, T.; Groll, K. Chen, Y.-H. Preparation of Organoalanes for Organic Synthesis. In *Modern*

Organoaluminum Reagents; Topics in Organometallic Chemistry 41; Springer-Verlag: New York, 2013; Vol. *41*; p 173. (c) Blümke, T.; Chen, Y.-H.; Peng, Z.; Knochel, P. *Nat. Chem.* **2010**, *2*, 313.

(20) (a) Peng, Z.; Haag, B. A.; Knochel, P. *Org. Lett.* **2010**, *12*, 5398. (b) Peng, Z.; Knochel, P. *Org. Lett.* **2011**, *13*, 3198.

(21) (a) Blümke, T. D.; Klatt, T.; Koszinowski, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9926. (b) Groll, K.; Blümke, T. D.; Unsinn, A.; Haas, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 11157.

(22) Boudet, N.; Sase, S.; Sinha, P.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 12358.

(23) Soorukram, D.; Boudet, N.; Malakhov, V.; Knochel, P. *Synthesis* **2007**, 3915.

(24) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4455.

(25) Garst, J. F.; Ungváry, F. Mechanisms of Grignard Reagent Formation. In *Grignard Reagents, New Developments*; Richey, H. G., Jr., Ed.; Wiley: Chichester, 2000; p 185.

(26) (a) Lindsell, W. E. Magnesium, Calcium, Strontium and Barium, In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G., Abel, E. W., Eds., Pergamon: Oxford, 1982; Vol. *1* p 155. (b) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286. (c) Garst, J. F. *Acc. Chem. Res.* **1991**, *24*, 95. (d) Walling, C. *Acc. Chem. Res.* **1991**, *24*, 255. (e) Stadtmüller, H.; Lentz, R.; Dörner, W.; Stüdemann, T.; Tucker, C. E.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027. (f) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995. (g) Silverman, G. S.; Rakita, P. E. *Handbook of Grignard Reagents*; Heinemann, H., Ed.; Dekker: New York, 1996. (h) Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 5743. (i) Vettel, S.; Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 7473. (j) *The Chemistry of Organomagnesium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley-VCH: Weinheim, 2008.

(27) (a) Achyutha Rao, S.; Tucker, C. E.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 7575. (b) Rozema, M. J.; Knochel, P. *Tetrahedron Lett.* **1991**, *32*, 1855. (c) Knoess, H. P.; Furlong, M. T.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1991**, *56*, 5974. (d) Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 3983. (e) Rozema, M. J.; Rajagopal, D.; Tucker, C. E.; Knochel, P. *J. Organomet. Chem.* **1992**, *438*, 11.

(28) (a) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 4383. (b) Retherford, C.; Knochel, P. *Tetrahedron Lett.* **1991**, *32*, 441. (c) Janakiram Rao, C.; Knochel, P. *J. Org. Chem.* **1991**, *56*, 4593. (d) Belyk, K.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 4070. (e) Cahiez, G.; Venegas, P.; Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Chem. Soc., Chem. Commun.* **1992**, 1406.

(29) (a) Knochel, P.; Seebach, D. *Nouv. J. Chim.* **1981**, *5*, 75. (b) Knochel, P.; Seebach, D. *Synthesis* **1982**, 1017. (c) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 4427. (d) Achyutha Rao, S.; Knochel, P. 1 *J. Org. Chem.* **1991**, *56*, 4591. (e) Sidduri, A.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 7579. (f) Janikaram Rao, C.; Knochel, P. *Tetrahedron* **1993**, *49*, 29. (g) Knochel, P.; Brieden, W.; Eisenberg, C.; Rozema, M. J. *Tetrahedron Lett.* **1993**, *34*, 5881. (h) Knochel, P.; Rozema, M. J.; Tucker, C. E. Preparation of Highly Functionalized Copper Reagents. In *Chemistry—Organocopper Reagents*; Taylor, R. J. K, Ed.; Practical Approach Series; Oxford University Press: Oxford, 1993; p 348.

(30) Knochel, P. Carbometallation of Alkenes and Alkynes. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. *4*, p 865.

(31) Sämann, C.; Schade, M. A.; Yamada, S.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 9495.

(32) Retherford, C.; Yeh, M. C. P.; Schipor, I.; Chen, H.-G.; Knochel, P. *J. Org. Chem.* **1989**, *54*, 5200.

(33) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.

(34) (a) Knochel, P.; Jeong, N.; Rozema, M. J.; Yeh, M. C. P. *J. Am. Chem. Soc.* **1989**, *111*, 6474. (b) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802. (c) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192.

(35) Waas, J. R.; Sidduri, A.; Knochel, P. *Tetrahedron Lett.* **1992**, *33*, 3717.

(36) (a) Auvray, P.; Knochel, P.; Vaissermann, J.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1990**, 813. (b) Knochel, P. *Angew. Chem.* **1992**, *104*, 1486. (c) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107. (d) Metzger, A.; Schade, M. A.; Manolikakes, G.; Knochel, P. *Chem.—Asian J.* **2008**, *3*, 1678. (e) Metzger, A.; Argyo, C.; Knochel, P. *Synthesis* **2010**, 882.

(37) Metzger, A.; Piller, F. M.; Knochel, P. *Chem. Commun.* **2008**, 5824.

(38) (a) Metzger, A.; Bernhardt, S.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 4665. (b) Bernhardt, S.; Metzger, A.; Knochel, P. *Synthesis* **2010**, 3802.

(39) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 4431.

(40) (a) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 6095. (b) Knochel, P.*; Yeh, M. C. P.; Xiao, C. *Organomet. Reagents* **1989**, *8*, 2831.

(41) (a) Kai, Y.; Knochel, P.; Kwiatkowski, S.; Dunitz, J. D.; Oth, J. F. M.; Seebach, D.; Kalinowski, H. O. *Helv. Chim. Acta* **1982**, *65*, 137. (b) Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1982**, *23*, 3897. (c) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 1475. (d) Chen, H. G.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 6701. (e) Knochel, P.; Xiao, C.; Yeh, M. C. P. *Tetrahedron Lett.* **1988**, *29*, 6697.

(42) (a) 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. (b) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565. (c) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701.

(43) (a) Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1981**, *22*, 3223. (b) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1610.

(44) (a) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 5091. (b) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 5095. (c) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 5727. (d) Knochel, P.; Normant, J. F. *J. Organomet. Chem.* **1986**, *309*, 1. (e) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 4495. (f) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 4509. (g) Tucker, C. E.; Achyutha Rao, S.; Knochel, P. *J. Org. Chem.* **1990**, *55*, 5446. (h) Piazza, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3263.

(45) Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449.

(46) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618.

(47) (a) Achyutha Rao, S.; Tucker, C. E.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 7575. (b) Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 1017. (c) Gong, L.-Z.; Knochel, P. *Synlett* **2005**, 267.

(48) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

(49) Chen, H. G.; Gage, J. L.; Barrett, S. D.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 1829.

(50) (a) Chou, T.-S.; Knochel, P. *J. Org. Chem.* **1990**, *55*, 4791. (b) Sidduri, A.; Budries, N.; Laine, R. M.; Knochel, P. *Tetrahedron Lett.* **1992**, *33*, 7515.

(51) Liu, C.-Y.; Knochel, P. *Org. Lett.* **2005**, *7*, 2543.

(52) Despotopoulou, C.; Bauer, R. C.; Krasovskiy, A.; Mayer, P.; Stryker, J. M.; Knochel, P. *Chem.—Eur. J.* **2008**, *14*, 2499.

(53) Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 2215.

(54) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2219.

(55) Sämann, C.; Haag, B. A.; Knochel, P. *Chem.—Eur. J.* **2012**, *18*, 16145.

(56) (a) Liu, C.-Y.; Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2006**, *8*, 617. (b) Ren, H.; Knochel, P. *Chem. Commun.* **2006**, 726.

(57) Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215.

(58) Kunz, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 1958.

(59) Frischmuth, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 10084.

(60) Kofink, C. C.; Knochel, P. *Org. Lett.* **2006**, *8*, 4121.

(61) Boudet, N.; Knochel, P. *Org. Lett.* **2006**, *8*, 3737.

(62) (a) Meunier, L. *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758. (b) Hauser, C. R.; Walker, H. G. *J. Am. Chem. Soc.* **1947**, *69*, 295. (c) García-Álvarez, P.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; O'Hara, C. T.; Weatherstone, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 8079.

(63) (a) *Topics in Organometallic Chemistry*; Chatani, N., Ed.; Topics in Organometallic Chemistry 24; Springer: Berlin, 2007. (b) Harrison-Marchand, A.; Mongin, F. *Chem. Rev.* **2013**, *113*, 7470. (c) Mongin, F.; Harrison-Marchand, A. *Chem. Rev.* **2013**, *113*, 7563.

(64) (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Hartung, C. G.; Snieckus, V. The Directed ortho Metalation Reaction – A Point of Departure for New Synthetic Aromatic Chemistry. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; p 330. (d) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667. (e) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (f) Macklin, T.; Snieckus, V. Metalation of Arenes. Directed *ortho* and Remote Metaltion (DoM and DreM). In *Handbook of C–H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; Vol. *1*, p 106.

(65) (a) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489–4505. (b) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059–4090. (c) Chevallier, F.; Mongin, F. *Chem. Soc. Rev.* **2008**, *37*, 595.

(66) (a) Schlosser, M.; Choi, J. H.; Takagishi, S. *Tetrahedron* **1990**, *46*, 5633. (b) Schlosser, M. *Eur. J. Org. Chem.* **2001**, 3975. (c) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376. (d) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827.

(67) Haag, B. A.; Mosrin, M.; Hiriyakkanavar, I.; Malakhov, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9794.

(68) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958.

(69) (a) Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837. (b) Bresser, T.; Mosrin, M.; Monzón, G.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 4686. (c) Crestey, F.; Knochel, P. *Synthesis* **2010**, 1097. (d) Bresser, T.; Monzón, G.; Mosrin, M.; Knochel, P. *Org. Process Res. Dev.* **2010**, *14*, 1299. (e) Bresser, T.; Mosrin, M.; Monzón, G.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 4686. (f) Crestey, F.; Knochel, P. *Synthesis* **2010**, 1097. (g) Bresser, T.; Monzón, G.; Mosrin, M.; Knochel, P. *Org. Process Res. Dev.* **2010**, *14*, 1299.

(70) Wunderlich, S.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7673.

(71) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673.

(72) (a) Högermeier, J.; Reissig, H.-U.; Brüdgam, I.; Hartl, H. *Adv. Synth. Catal.* **2004**, *346*, 1868. (b) Dash, J.; Lechel, T.; Reissig, H.-U. *Org. Lett.* **2007**, *9*, 5541. (c) Högermeier, J.; Reissig, H.-U. *Adv. Synth. Catal.* **2009**, *351*, 2747.

(73) Monzón, G.; Knochel, P. *Synlett* **2010**, 304.

(74) Stoll, A. H.; Mayer, P.; Knochel, P. *Organometallic reagents* **2007**, *26*, 6694.

(75) Stoll, A. H.; Knochel, P. *Org. Lett.* **2008**, *10*, 113.

(76) (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. (b) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571.

(77) (a) Satoh, T. *Chem. Soc. Rev.* **2007**, *36*, 225. (b) Satoh, T. *Heterocycles* **2012**, *85*, 1.

(78) (a) Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597. (b) Mingxing, Q.; Negishi, E. *Tetrahedron Lett.* **2005**, *46*, 2927. (c) Metay, E.; Hu, Q.; Negishi, E. *Org. Lett.* **2006**, *8*, 5773.

(79) (a) Knochel, P.; Achyutha Rao, S. *J. Am. Chem. Soc.* **1990**, *112*, 6146. (b) Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5431. (c) Klement, I.; Lennick, K.; Tucker, C. E.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 4623.

(80) Melzig, L.; Rauhut, C. B.; Knochel, P. *Chem. Commun.* **2009**, 3536.

(81) Rauhut, C. B.; Melzig, L.; Knochel, P. *Org. Lett.* **2008**, *10*, 3891.

(82) Piller, F. M.; Knochel, P. *Synthesis* **2011**, 1751.

(83) Piller, F. M.; Knochel, P. *Org. Lett.* **2009**, *11*, 445.

(84) Despotopoulou, C.; Klier, L.; Knochel, P. *Org. Lett.* **2009**, *11*, 3326.

(85) Kunz, T.; Knochel, P. *Chem.—Eur. J.* **2011**, *17*, 866.

(86) Wunderlich, S. H.; Rohbogner, C. J.; Unsinn, A.; Knochel, P. *Org. Process Res. Dev.* **2010**, *14*, 339.

(87) Boudet, N.; Lachs, J. R.; Knochel, P. *Org. Lett.* **2007**, *9*, 5525.

(88) Rohbogner, C. J.; Wirth, S.; Knochel, P. *Org. Lett.* **2010**, *12*, 1984.

(89) (a) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497. (b) Mosrin, M.; Petrera, M.; Knochel, P. *Synthesis* **2008**, 3697. (c) Mosrin, M.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 1468.

(90) Negishi, E.-i.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181.

(91) Mosrin, M.; Bresser, T.; Knochel, P. *Org. Lett.* **2009**, *11*, 3406.

(92) Kienle, M.; Dubbaka, S. R.; del Amo, V.; Knochel, P. *Synthesis* **2007**, 1272.

(93) Dubbaka, S. R.; Kienle, M.; Mayr, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 9093.

(94) Boudet, N.; Dubbaka, S. R.; Knochel, P. *Org. Lett.* **2008**, *10*, 1715.

(95) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

(96) Rohbogner, C. J.; Wunderlich, S. H.; Clososki, G. C.; Knochel, P. *Eur. J. Org. Chem.* **2009**, 1781.

(97) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681.

(98) Wunderlich, S. H.; Rohbogner, C. J.; Unsinn, A.; Knochel, P. *Org. Process Res. Dev.* **2010**, *14*, 339.

(99) Rohbogner, C. J.; Clososki, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1503.

(100) Despotopoulou, C.; Klier, L.; Knochel, P. *Org. Lett.* **2009**, *11*, 3326.

(101) Despotopoulou, C.; Gignoux, C.; McConnell, D.; Knochel, P. *Synthesis* **2009**, 3661.

(102) Mosrin, M.; Boudet, N.; Knochel, P. *Org. Biomol. Chem.* **2008**, *6*, 3237.

(103) Piller, F. M.; Bresser, T.; Fischer, M. K. R.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 4365.

(104) Bresser, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1914.

(105) For the metalation of the oxazole scaffold, see: (a) Jubert, C.; Nowotny, S.; Kornemann, D.; Antes, I.; Tucker, C. E.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 6384. For the metalation of a thiazole scaffold, see: (b) Tucker, C. E.; Knochel, P. *J. Org. .Chem.* **1993**, *58*, 4781.

(106) Piller, F. M.; Knochel, P. *Synthesis* **2011**, 1751.

(107) (a) Rozema, M. J.; Eisenberg, C.; Lütjens, H.; Ostwald, R.; Belyk, K.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 3115. (b) Tucker, C. E.; Knochel, P. *Synthesis* **1993**, 530.

(108) Zimdars, S.; du Jourdin, X. M.; Crestey, F.; Carell, T.; Knochel, P. *Org. Lett.* **2011**, *13*, 792.

(109) Unsinn, A.; Knochel, P. *Chem. Commun.* **2012**, *48*, 2680.

(110) Wunderlich, S.; Knochel, P. *Org. Lett.* **2008**, *10*, 4705.

(111) Retherford, C.; Chou, T.-S.; Schelkun, R. M.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 1833.

(112) Tucker, C. E.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 9888.

(113) Wunderlich, S. H.; Bresser, T.; Dunst, C.; Monzon, G.; Knochel, P. *Synthesis* **2010**, 2670.

(114) Rozema, M. J.; Achyutha Rao, S.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956.

(115) Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 9717.

(116) Brown, H. C.; Schlesinger, H. I.; Cardon, S. Z. *J. Am. Chem. Soc.* **1942**, *64*, 325.

(117) Wittig, G.; Schloeder, H. *Liebigs Ann. Chem.* **1955**, *592*, 38.

(118) (a) Welch, G. C.; San Juan, R. R.; Musada, J. D.; Stephan, D. W. *Science* **2006**, *314*, 1124. (b) Welch, G. C.; Stephan, D. W. *J. Am. Chem. Soc.* **2007**, *129*, 1880.
(119) For an excellent review, see: Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 46.
(120) Knochel, P.; Karaghiosoff, K.; Manolikakes, S. Selective C−H Activations Using Frustrated Lewis Pairs. Applications in Organic Synthesis. In *Frustrated Lewis Pairs II. Topics in Current Chemistry*; Erker, G., Stephan, D. W., Eds.; Springer: Berlin, 2013; Vol. *334*, p 171.
(121) Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 5451.
(122) For pioneering work on the lithiation of BF_3-complexed pyridine with BuLi, see: (a) Kessar, S.; V. Singh, P.; Singh, K. N.; Dutt, M. *Chem. Commun.* **1991**, 570. (b) Kessar, S. V.; Singh, P.; Singh, K. N.; Bharatam, P. V.; Sharma, A. K.; Lata, S.; Kaur, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4703.
(123) For BF_3-catalysis in the presence of Grignard reagents, see: Brieden, W.; Ostwald, R.; Knochel, P. *Angew. Chem.* **1993**, *105*, 629.
(124) Jaric, M.; Haag, B. A.; Manolikakes, S.; Knochel, P. *Org. Lett.* **2011**, *13*, 2306.
(125) Manolikakes, S. M.; Jaric, M.; Karaghiosoff, K.; Knochel, P. *Chem. Commun.* **2013**, *49*, 2124.
(126) (a) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302. (b) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240.
(127) Lemaire, S.; Houpis, I. N.; Xiao, T.; Li, J.; Digard, E.; Gozlan, C.; Liu, R.; Gavryushin, A.; Diene, C.; Wang, Y.; Farina, V.; Knochel, P. *Org. Lett.* **2012**, *14*, 1480.
(128) Groll, K.; Manolikakes, S. M.; Mollat du Jourdin, X.; Jaric, M.; Bredihhin, A.; Karaghiosoff, K.; Carell, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 6776.
(129) Klier, L.; Bresser, T.; Nigst, T. A.; Karaghiosoff, K.; Knochel, P. *J. Am. Chem. Soc.* **2012**, *134*, 13584.
(130) For the use of TMPMgCl·LiCl (**100**) and Et_3Al as a selective alumination reagent, see: Unsinn, A.; Wunderlich, S. H.; Jana, A.; Karaghiosoff, K.; Knochel, P. *Chem.—Eur. J.* **2013**, *19*, 14687.
(131) Bernhardt, S.; Manolikakes, G.; Kunz, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9205.
(132) Stathakis, C. I.; Bernhardt, S.; Quint, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9428.
(133) Stathakis, C. I.; Manolikakes, S. M.; Knochel, P. *Org. Lett.* **2013**, *15*, 1302.
(134) Hernán-Gómez, A.; Herd, E.; Hevia, E.; Kennedy, A. R.; Knochel, P.; Koszinovski, K.; Manolikakes, S.; Mulvey, R. E.; Schnegelsberg, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 2706.
(135) (a) Organ, M. G.; Chass, G. A.; Fang, D.-C.; Hopkins, A. C.; Valente, C. *Synthesis* **2008**, 2776. (b) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314. (c) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314.
(136) (a) Manolikakes, G.; Munoz Hernandez, C.; Schade, M. A.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 8422. (b) Manolikakes, G.; Schade, M. A.; Munoz Hernandez, C.; Mayr, H.; Knochel, P. *Org. Lett.* **2008**, *10*, 2765. (c) Metzger, A.; Schade, M. A.; Manolikakes, G.; Knochel, P. *Chem.—Asian J.* **2008**, *3*, 1678. (d) Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 1429. (e) Dong, Z.; Manolikakes, G.; Li, J.; Knochel, P. *Synthesis* **2009**, 681. (f) Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 205. (g) Manolikakes, G.; Dong, Z.; Mayr, H.; Li, J.; Knochel, P. *Eur. J.* **2009**, *15*, 1324. (h) Dong, Z.-B.; Manolikakes, G.; Shi, L.; Knochel, P.; Mayr, H. *Chem.—Eur. J.* **2010**, *16*, 248. (i) Bernhardt, S.; Manolikakes, G.; Kunz, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9205. See also refs 28, 107, and (j) Schade, M. A.; Manolikakes, G.; Knochel, P. *Org. Lett.* **2010**, *12*, 3648. (k) Metzger, A.; Bernhardt, S.; Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 4665.