Synthetic Methods

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Regio- and Chemoselective Metalation of Arenes and Heteroarenes Using Hindered Metal Amide Bases

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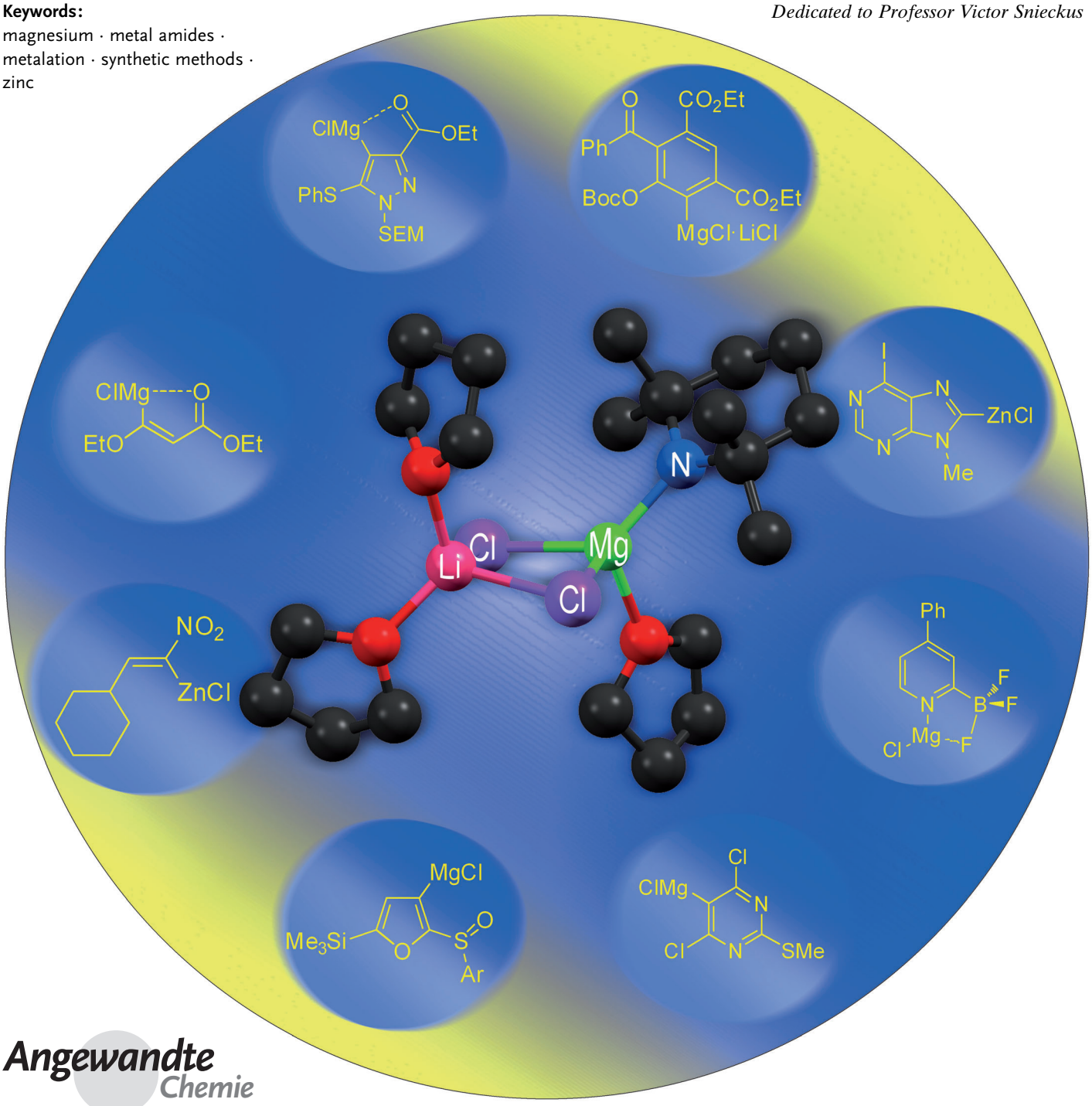
Keywords:
magnesium · metal amides · metalation · synthetic methods · zinc

Dedicated to Professor Victor Snieckus



The preparation of highly functionalized organometallic compounds can be achieved by direct C–H activation of a broad range of unsaturated substrates using lithium chloride solubilized 2,2,6,6-tetramethylpiperidide bases (TMP_nMX_m·p LiCl). These are excellent reagents for converting a wide range of aromatic and heterocyclic substrates into valuable organometallic reagents with broad applications in organic synthesis.

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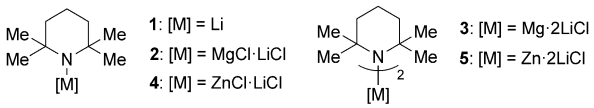
1. Introduction

1.1. General

The regioselective and chemoselective functionalization of arenes and heterocycles is an important synthetic approach to compounds with interesting biological properties[1] or physical properties.[2] The direct functionalization of unsaturated substrates can be performed either by using stoichiometric amounts of a metal base or by designing catalytic processes.[3] Whereas this last approach may allow a high atom economy,[4] the stoichiometric version provides intermediate organometallic reagents which may be trapped under appropriate conditions with a range of electrophiles and lead to various classes of products. Although such metalations using lithium reagents are well known in the chemical literature,[5–9] the high reactivity of lithium bases has precluded the use of many functionalized substrates. The resulting highly reactive aryllithium compounds obtained after metalation are usually only stable at low temperature and react with important functional groups such as esters or unhindered amides even under these mild conditions.[10]

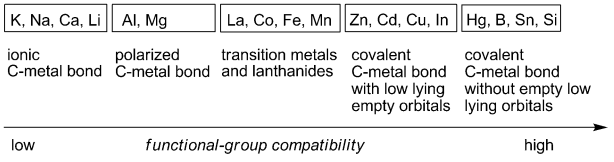
The scope of this Review deals with new chemoselective bases, mostly LiCl-solubilized 2,2,6,6-tetramethylpiperidyl (TMP) metal amides, which now allow the preparation of polyfunctional aryl and heteroaryl organometallic species containing sensitive functional groups, such as an ester, a nitrile, a ketone, an azide, a nitro group, or an aldehyde. However, some important aspects of previous metalations with hindered lithium or magnesium amides will also be described. Whereas TMPLi (**1**) has found numerous applications, new activated TMP bases—such as TMPMgCl·LiCl (**2**), TMP_2Mg·2 LiCl (**3**), TMPZnCl·LiCl (**4**), and TMP_2Zn·2 LiCl (**5**)—have considerably expanded the scope of metalations of unsaturated organic molecules, and the scope of their applications will be especially emphasized (Scheme 1). Furthermore, the factors controlling the chemoselectivity and regioselectivity of the metalation will be discussed. The conditions for achieving a compatibility of carbon–metal bonds with important functional groups present in aromatic compounds and most important classes of heterocycles will be illustrated.



Scheme 1. LiCl-solubilized TMP bases for metalation reactions.

1.2. The Chemoselectivity Issue

The compatibility of functional groups in organometallic compounds strongly depends on the nature of the metal. In general, the reactivity of a carbon–metal bond increases with the ionic character of this bond.[11] Thus, aryllithium compounds react with most functional groups at temperatures above −20 °C.[12] They are compatible with a nitrile or a nitro group only at very low temperatures (−80 to −100 °C) and usually react with an ester even at −100 °C.[10,13] On the other hand, arylmagnesium reagents, which possess a more covalent carbon–magnesium bond, are more tolerant toward various organic functionalities, and very low temperatures are not required for preparing polyfunctional aryl- or heteroarylmagnesium reagents.[14] It is possible to set up an approximative chemoselectivity scale based on experimental results from the literature (Scheme 2).[11,15] From this scale it becomes apparent, that despite their fundamental importance, the generation of K, Na, and Ca compounds may lead to limited applications in organic chemistry.[16] Lithium compounds are the only class of reagents of these polar organometallic reagents that display a broad field of application.[5] Aryllithium compounds bearing a nitrile such as **6** have been prepared in pioneering studies by Parham and Bradsher[17] by using a Br/Li exchange reaction. The presence of a sensitive



Scheme 2. Compatibility scale of organometallic compounds with functional groups.

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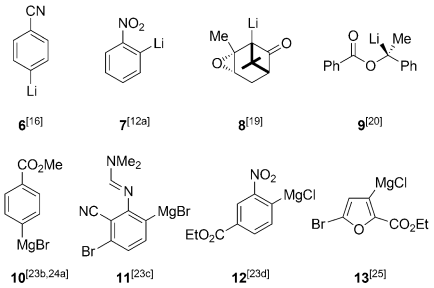
nitro group such as in **7** can be achieved using an I/Li exchange.[13a] A subsequent transmetalation with $ZnCl_2$ provides a stable and easy to handle organozinc reagent.[13] The use of microreactors may avoid low temperatures for the generation of functionalized lithium reagents.[18] Also, Barbier conditions may in some cases result in compatibility with an ester function and provides a convenient method for generating functionalized boronic esters.[19] The synthesis of a lithium reagent bearing a hindered ketone such as in **8** has been demonstrated[20] by using a Br/Li exchange. As pioneered by Hoppe and co-workers,[21] remarkable enantioselective deprotonations performed in the presence of (−)-sparteine provide an elegant entry to chiral lithium reagents bearing an ester group, such as **9**.

The next group of organometallic compounds includes Al[22] and Mg compounds.[14,23] Both of these classes of reagents possess a relatively polarized carbon–metal bond. They display a remarkable functional-group compatibility, which only became apparent in recent years, and all the polyfunctional magnesium reagents **10**–**13** can be generated by halogen–magnesium exchange,[24] direct magnesium insertion,[25] or directed magnesiation (Scheme 3).[26] A new LiCl-



Scheme 3. Functionalized organolithium and organomagnesium reagents.

mediated and $PbCl_2$-catalyzed direct insertion of Al powder into aryl iodides or bromides provides a direct entry to polyfunctional (hetero)arylaluminum reagents, such as **14** and **15**, which after transmetalation with $Zn(OAc)_2$ show a good reactivity toward aryl bromides and palladium-catalyzed cross-coupling in the presence of a Pd-PEPPSI-IPr[27] catalyst system (Scheme 4).[28]

The next group of organometallic compounds includes lanthanide and transition-metal derivatives of metals such as La, Fe, and Mn, which possess an excellent functional-group

Paul Knochel was born in 1955 in Strasbourg (France). He studied at the University of Strasbourg and completed his PhD at the ETH Zürich with Prof. D. Seebach (1982). He spent four years with Prof. J.-F. Normant (Paris) and one 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. His research interests include the development of new synthetic methods with organometallic reagents, new asymmetric catalysts, and natural product synthesis.

Benjamin Haag was born in Heidelberg (Germany) in 1981. He studied chemistry at the Ruprecht-Karls-Universität Heidelberg (Germany) and at the Universitet i Bergen (Norway). He completed his diploma with Prof. P. Comba (Heidelberg) in 2006, and in 2010 he completed his PhD in Prof. P. Knochel's group at the Ludwig-Maximilians-Universität (Munich). His work focused on frustrated Lewis pairs as well as the synthesis and functionalization of heterocycles using organometallic reagents. In 2011, he started postdoctoral research with Prof. F. D. Toste at the University of California (Berkeley).

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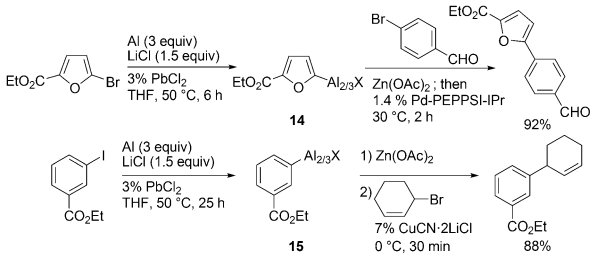
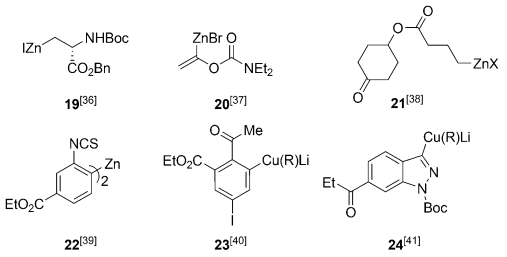
Vladimir Malakhov was born in Moscow (Russia) in 1965. He completed his undergraduate studies in pharmacy at the I. M. Sechenov Moscow Medical Academy (1985–1990). In 1997, he joined Prof. P. Knochel's group at the Philipps-Universität in Marburg (Germany) and moved in 1999 with him to the Ludwig-Maximilians-Universität (Munich). In 2010, he completed his PhD, which focused on organozinc reagents.

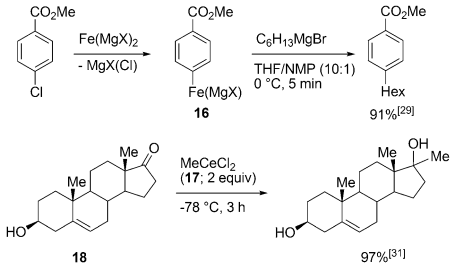


Scheme 4. Functionalized organoaluminum reagents.



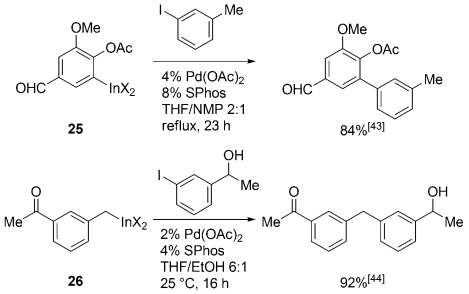
Scheme 6. Functionalized organozinc, organoindium, and organocopper reagents.[36–42]

tolerance. The synthetic utility of such transition-metal reagents is enhanced due to the presence of low-lying d orbitals, which allow an additional activation mode of organic substrates.[29] Thus, iron organometallic compounds such as **16** undergo smooth cross-coupling reactions,[30,31] and organolanthanide reagents (**17**) efficiently add to carbonyl groups in the presence of a free hydroxy function (as in the case of **18**; Scheme 5).[32,33] Directed metalations are especially well-suited for the generation of such organometallic reagents, since iodine–transition-metal exchanges proved to be difficult due to competitive cross-coupling reactions.[34] Similarly, the direct insertion of transition metals into a carbon–halogen bond is usually hampered by the high lattice energy of the metal as well as difficulties associated with activation of the metal surface.[35]



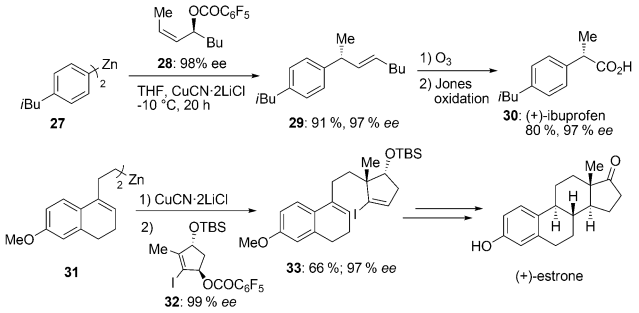
Scheme 5. Reactions of functionalized organoiron and organocerium reagents. NMP = *N*-methylpyrrolidine.

The next group, which again includes "main-group organometallic compounds" derived from Zn, Cd, Cu, and In, is of very high synthetic utility since these carbon–metal bonds have essentially covalent character (Scheme 2). Remarkably, such metal reagents are compatible with most functional groups encountered in organic synthesis, as shown for the functionalized organometallic compounds **19**–**24** (Scheme 6).[36–44] Thus, the chiral organozinc reagent **19** prepared by Jackson et al. allows an expeditive preparation of numerous chiral α-amino acids.[37] Low-temperature lithiation followed by a transmetalation with $ZnBr_2$ provides vinylic carbenoid **20** that is stable at room temperature, as shown by Snieckus and co-workers.[38] A direct insertion of zinc dust into a polyfunctional alkyl iodide bearing a ketone and an ester (25 °C, 6 h) affords the zinc reagent **21** in > 85 % yield.[39] Very unusual functional groups, such as an isothiocyanate, are tolerated in a Li(acac)-mediated (acac = acetylacetonate) I/Zn exchange, with in situ generated iPr_2Zn providing the diarylzinc reagent **22**.[40] This Li(acac)-accelerated reaction is the first example of a catalyzed halogen/metal exchange and has opened the way for elaborating LiCl-catalyzed Br/Mg exchange reactions.[43] The use of LiCl-mediated direct metal insertion is valuable for the preparation of functionalized aryl and benzylic indium reagents such as **25** and **26**.[44,45] Thus, the arylindium derivative **25** bearing an aldehyde is directly obtained by the insertion of indium powder in the presence of LiCl.[44] The benzylic reagent **26** containing a methyl ketone is also readily prepared by the insertion of indium powder in the presence of LiCl (40 °C, 6 h; Scheme 7).[45] These indium organometallic reagents readily undergo cross-coupling reactions with various aryl iodides in the presence of the Pd/SPhos catalyst system.[46]



Scheme 7. Palladium-catalyzed cross-coupling of organoindium reagents with electrophiles bearing acidic protons.

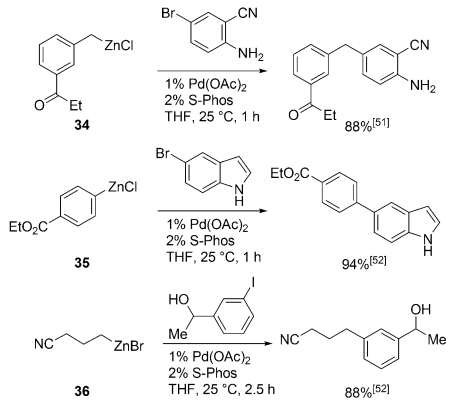
Highly functionalized copper reagents are conveniently obtained by an I/Cu exchange,[47] although a direct insertion of a Rieke copper complex has also been demonstrated.[48] The I/Cu exchange[49] using $(PhMe_2CCH_2)_2CuLi$ or $(Me_3CCH_2)_2CuLi$ readily furnishes the polyfunctional copper species **23** and **24** (Scheme 6). The availability of empty p orbitals facilitates transmetalation reactions and thus efficient carbon–carbon coupling reactions (Scheme 8).[11] Thus, a transmetalation of diarylzinc **27** with CuCN·2 LiCl leads to a highly selective *anti*-S_N2' substitution[50] on **28**, thereby providing the chiral allylic substitution product **29** (91 % yield). A subsequent ozonolysis gives (+)-ibuprofen (**30**) in 80 % yield (97 % *ee*).[50] This method has also been applied to generate the carbon skeleton of (+)-estrone. Thus,



Scheme 8. Selective copper-mediated reactions of organozinc reagents with electrophiles.[50,51] TBS = *tert*-butyldimethylsilyl.

after transmetalation with CuCN·2 LiCl,[39] the zinc reagent **31**, obtained by a boron–zinc exchange,[51] reacts with the polyfunctional pentafluorobenzoate **32** with almost complete transfer of chirality to provide the *anti*-S_N2' substitution[50] product **33** in 66 % yield (Scheme 8). The use of Lewis acids may be required to enhance the reactivity of these metal reagents.[52]

It should be emphasized that aryl- and heteroarylzinc, -copper, and -indium reagents are also compatible with acidic protons. This tolerance of OH and NH groups has been especially well studied for organozinc reagents.[53,54] Thus, the use of an appropriate Pd catalyst system allows cross-coupling reactions of the zinc organometallic compounds **34–36** with various aryl bromides or iodides bearing NH_2 groups, RNH groups, or a secondary alcohol function.[52,53] In the last case, the zinc reagent **36** is best added within 90 min to a mixture of the secondary alcohol and the catalytic system (Scheme 9).

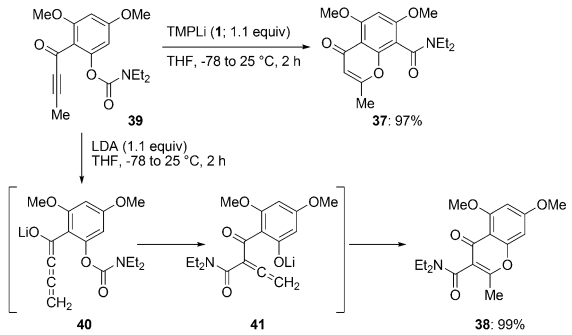


Scheme 9. Palladium-catalyzed cross-coupling of organozinc reagents with electrophiles bearing acidic protons.

2. Metalations with Hindered Metal Amides

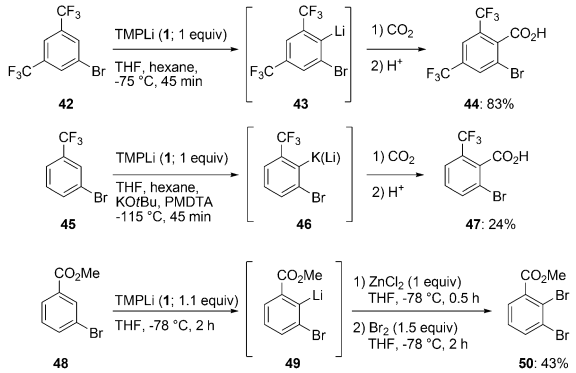
2.1. Lithiation with Lithium Amides

Since the pioneering work by the research groups of Gilman,[55] Wittig,[56] and Snieckus,[57] directed *ortho*-metalation (D*o*M) has been widely used for the regioselective functionalization of substituted aromatic and heteroaromatic compounds. Numerous substitutents such as a carbamate, amide, methoxy, or cyano group proved to direct the metalation with strong lithium bases in such reactions. The most frequently used bases for lithiations are organolithium reagents, such as BuLi or *s*BuLi, as well as sterically demanding non-nucleophilic lithium amides such as lithium diisopropylamide (LDA) or lithium 2,2,6,6-tetramethylpiperidide (TMPLi, **1**). These bases are commercially available and possess good solubility in ethereal or alkane solutions. Snieckus and co-workers have recently reported the regioselective preparation of polysubstituted chromenone carboxamides **37** and **38** through a directed *ortho*-lithiation starting from aryl carbamates such as **39** (Scheme 10).[57] Treatment of **39** with the sterically hindered TMPLi (**1**; 1.1 equiv) provided the chromenone carboxamide **37** in 97 % yield, after directed metalation, subsequent carbamoyl translocation in an aromatic *ortho*-Fries rearrangement, and an intramolecular Michael addition (Scheme 10).



Scheme 10. Preparation of chromenone carboxamides **37** and **38**.

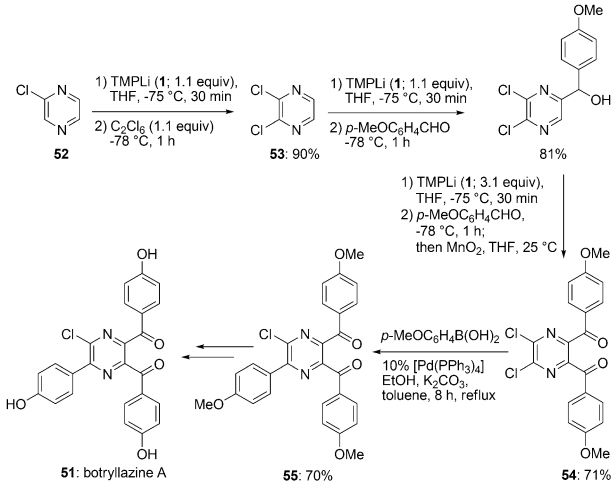
Remarkably, lithiation with LDA (1.1 equiv) instead afforded the isomeric chromenone carboxamide **38**. Initial deprotonation of the acetylenic methyl group of **39** generated a kinetic cumulene enolate **40**. Transfer of a carbamoyl group led to the phenolate **41**, which after an intramolecular Michael addition produced the product **38** in 99 % yield (Scheme 10).[57] A recent study by Schlosser et al. showed that the trifluoromethyl group can act as both an emitter and transmitter of steric pressure in metalation reactions.[58–61] Schlosser and co-workers also demonstrated the importance of buttressing effects on halogenated arenes in deprotonations.[62] For electron-poor substrates such as **42**, the metalation with TMPLi (**1**) occurs in position 2 to furnish the aryllithium **43**, which after carboxylation provides the carboxylic acid **44** in 83 % yield.[61] However, less-reactive substrates such as **45** require the use of a more active base combination, for example, "Faiglmix",[63] which is a mixture of TMPLi (**1**), PMDTA (*N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine), and KO*t*Bu. In this way, 3-bromo-1-trifluoromethylbenzene (**45**) was metalated in position 2. Quenching of the organometallic intermediate **46** with carbon dioxide furnished the corresponding benzoic acid **47** in 24 % yield (Scheme 11).[61] Remarkably, the methyl benzoate **48** is



Scheme 11. Lithiation of substituted trifluoromethylbenzenes with TMPLi (**1**) and subsequent quenching with electrophiles.

readily deprotonated with TMPLi (**1**) at −78 °C to provide a lithium reagent **49**, which after transmetalation with $ZnCl_2$ reacts directly with bromine to give the 1,2-dibromoarene **50** in 43 % yield.[64]

In 2005, Turck, Quéguiner, and co-workers[65] described a seven-step synthesis of the antitumor alkaloid botryllazine A (**51**). This synthesis involved successive regioselective lithiations starting from commercially available 2-chloropyrazine (**52**; Scheme 12). Thus, the metalation of **52** using TMPLi (**1**;



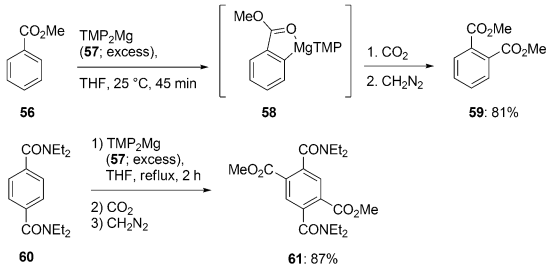
Scheme 12. Total synthesis of botryllazine A (**51**).

1.1 equiv, −75 °C) followed by chlorination with C_2Cl_6 provided 2,3-dichloropyrazine (**53**) in 90 % yield. Two successive lithiation sequences with TMPLi (**1**) and subsequent addition to *p*-methoxybenzaldehyde followed by a MnO_2 oxidation afforded the diketone **54**. Thereafter, a Suzuki cross-coupling reaction with 4-methoxyphenylboronic acid provided the tetrasubstituted pyrazine **55** in 70 % yield. After two further steps, botryllazine A (**51**) was obtained in an overall yield of 25 % (Scheme 12).

Although lithium amide bases are currently still used most frequently for lithiations, these highly reactive bases suffer from several drawbacks. Their high reactivity and strong nucleophilicity often result in undesired side reactions, for example, the Chichibabin addition.[66] During the directed *ortho*-lithiation of ester-substituted aromatic compounds using TMPLi (**1**), Upton and Beak observed the addition of the lithiated arene to the ester group of another not yet lithiated arene.[67] However, side reactions of this type can be avoided by in situ trapping of the lithiated aromatic compounds with electrophiles, as long as they contain bulky ester groups.[68,69] Furthermore, the deprotonation of arenes and heteroaromatic compounds by lithium bases often requires low temperatures (−78 to −100 °C). In some cases, an excess of base is mandatory, but this is impractical with respect to scaling-up.

2.2. Early Magnesiations with Magnesium Amides

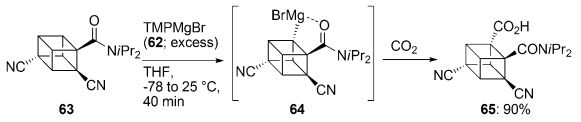
In 1947, Hauser and Walker reported magnesium amide bases of the general formula R_2NMgX and $(R_2N)_2Mg$, (Hauser bases).[70] These magnesium amide bases have gathered new interest.[71] Eaton et al. demonstrated the potential of Hauser bases for the directed *ortho*-magnesiation of aromatic compounds. Thus, the metalation of methyl benzoate (**56**) was performed at 25 °C with an excess of TMP_2Mg (**57**) in THF to furnish the magnesium reagent **58**. Subsequent trapping with carbon dioxide and diazomethane afforded the dimethyl phthalate **59** in 81 % yield (Scheme 13).[72] Treatment of *N*,*N*,*N*′,*N*′-tetraethylbenzene-



Scheme 13. Metalation of aromatic benzoates with TMP_2Mg (**57**), followed by carboxylation.

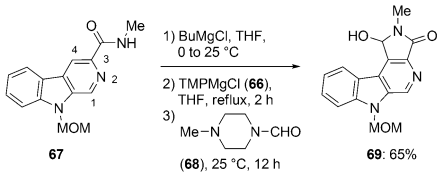
1,4-dicarboxamide (**60**) with TMP_2Mg (**57**; excess, THF, reflux, 2 h) followed by carboxylation and esterification gives the terephthalate **61** in 87 % yield (Scheme 13).[72] Hereby, Eaton et al. demonstrated the activation and directing properties of amide substitutents for *ortho*-magnesiation reactions. The magnesiation of cyclopropyl and cyclobutyl carboxamides with TMPMgBr (**62**) and TMP_2Mg (**57**) afforded various substituted cycloalkyl derivatives.[72,73] Thus, TMPMgBr (**62**) magnesiated the amido-substituted cubane **63** to give β-amidocubylmagnesium intermediate **64**. Carboxylation with carbon dioxide furnished the polyfunctional cubane **65** in 90 % yield (Scheme 14).[72]

In 1995, Mulzer and co-workers reported the regioselective functionalization of pyridine carboxamides and carbamates by using TMPMgCl (**66**) as the metalating reagent.[74] A



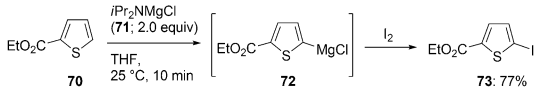
Scheme 14. Magnesiation of functionalized cubane **63** with TMPMgBr (**62**), followed by carboxylation.

regioselective *ortho*-magnesiation of the β-carboline-3-carboxamide **67** could be achieved exclusively at the C4-position (Scheme 15). Subsequent quenching of the Mg intermediate



Scheme 15. Magnesiation of **67** using TMPMgCl (**66**) followed by trapping with **68**.

with *N*-formyl-*N*′-methylpiperazine (**68**) gave the 3,4-substituted β-carboline **69**, a precursor for physiologically active compounds, in 65% yield (Scheme 15).[75] Kondo et al. further extended this method to the regio- and chemoselective functionalization of heterocycles such as indoles,[76] thiophene carboxylates, and thiazoles.[77] Thus, 2-carbethoxythiophene (**70**) was metalated at the C5-position by using an excess of iPr$_2$NMgCl (**71**; 2 equiv). The magnesiated intermediate **72** was then treated with iodine to give the functionalized iodothiophene **73** in 77% yield (Scheme 16).[77]



Scheme 16. Magnesiation of heterocycles using iPr$_2$NMgCl (**71**), followed by iodolysis.

Despite pioneering and extensive studies by Eaton et al., Mulzer and co-workers, and others on the directed magnesiation of arenes and heteroarenes, Hauser bases still suffer from several limitations. One major drawback is their low solubility in commonly used organic solvents. In general, a large excess of magnesium amide (2–12 equiv) is necessary to achieve high conversions and high reaction rates.[74] Thus, subsequent reactions with electrophiles (up to 8–10 equiv) are complicated.[78] Moreover, the magnesium diamides such as (iPr$_2$N)$_2$Mg act as reducing agents in nonsolvating media. Therefore, carbonyl, nitro, and azo substituents are often reduced during such metalation reactions.[79] In comparison to their lithium counterparts, magnesium amide bases possess an inherent weaker metalation ability.

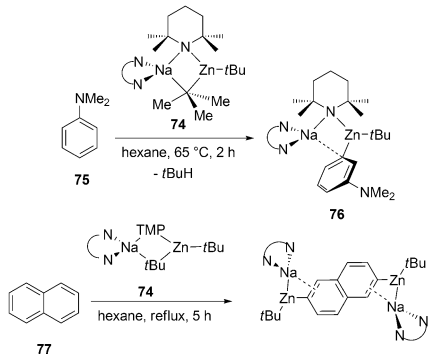
3. Metalations with Mixed Metal "ate" TMP Amides

3.1. General

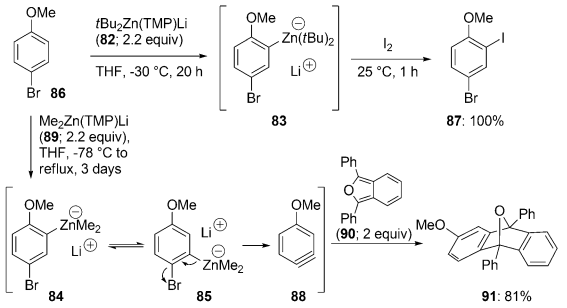
A new class of multimetallic complexes, so-called "ate" bases, has emerged in recent years to extend the functional-group tolerance of lithium bases.[5–9,80] Important contributions by Kondo, Uchiyama, Mulvey, and Mongin have been recently reported.[9] Schlosser et al. and Lochmann initiated the "superbase" approach and the "symbiotic action" of mixed-metal reagents. The BuLi/KOtBu complex (LiC-KOR; Lochmann–Schlosser reagent) displays an enhanced reactivity compared to BuLi.[81] This new combination readily deprotonates weakly or non-activated benzene derivatives, while exhibiting exceptional regioselectivity.[81] A series of homometallic superbases was introduced by Caubère that complemented this mixed-metal LiC-KOR superbase.[82] One of the most commonly and frequently used base is BuLi/Me$_2$N(CH$_2$)$_2$OLi (Caubère's base).[82] Gros and Fort used this reagent for the successful metalation of pyridines.[83] The structural mechanism of "superbasicity" was investigated in a systematic study of the mixed-metal approach.[9] Hereby, Mulvey introduced the term "avant-garde complex metalators" to address a series of "ate" species.[9]

In particular, "ate" bases of the general formula R$_n$R′$_m$MLi (or Na) were explored in detail (M = Mg, Zn, Al, Mn, Cu, etc. but M ≠ alkali metal; R, R′ = alkyl, amino, halogen, etc.). The alkali metal, Li or Na, is an essential component of this class of metalators. Mulvey also introduced the term "alkali metal mediated metalation" to emphasize the synergetic effect of the "ate" bases. The exceptional reactivity of "ate" bases cannot be obtained by the homometallic reagent itself.[9] The TMP anion embedded in these complexes has a particularly strong influence on the reactivity of the mixed-metal "ate" reagents. Consequently, recent investigations have focused in particular on TMP-derived bimetallic bases, for example, magnesiates,[84–88] zincates,[89,90] aluminates,[91,92] cadmates,[93] chromates,[94] manganates,[95] and ferrates.[94] In these reagents, the TMP anion is invariably the sole or at least the most active base ligand that enables metalation of the substrate. The predominant driving force is the elimination of TMP-H out of the assembly. Thus, combining organometallic compounds of soft metals with alkali or alkaline-earth metal additives, led to mixed-metal "ate" bases with great potential, such as R$_2$Zn(TMP)Li or R$_2$Zn(TMP)Li/Na-TMEDA.[89,90,96]

The highly active aluminum base iBu$_3$Al(TMP)Li was reported by Uchiyama, Mulvey, and Wheatley.[91,97] Whereas conventional bases such as alkyllithium compounds or lithium amides generally metalate laterally or at the *ortho* position, bases such as [(tmeda)Na(tmp)Zn(tBu)$_2$] (**74**) allow metalations of *N*,*N*-dimethylaniline (**75**) at the *meta* position (Scheme 17).[98] A crystal-structure analysis of the metalated species **76** fully supports this surprising regioselectivity.[99] Similarly, naphthalene (**77**) was zincated by the mixed Na/Zn-ate base **74** in positions 2 and 6 (Scheme 17).[99] Remarkably, [(tmeda)Na(tmp)(Bu)Mg(tmp)] metalates toluene at the *meta* position.[100]



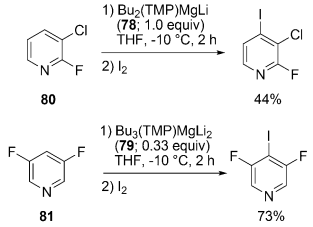
Scheme 17. Unusual metalations using TMP-zincate **74**.



Scheme 19. Zincation of 4-bromoanisole with tBu$_2$Zn(TMP)Li (**82**) and Me$_2$Zn(TMP)Li (**89**).

3.2. TMP-Magnesiate Bases

Since the first preparation of the organomagnesiate Ph$_3$MgLi by Wittig et al.,[101] several structural and synthetic studies on lithium trialkyl magnesiates have been described. Castaldi and Borsotti reported that trifluoromethylbenzene was successfully metalated with Bu$_3$MgLi.[102] Quéguiner, Mongin, and co-workers have used Bu$_2$Mg(TMP)Li (**78**) and Bu$_3$Mg(TMP)Li$_2$ (**79**) for the regioselective metalation of substituted chloro- and fluoropyridines (**80** and **81**; Scheme 18).[103] In comparison to BuLi, these metalations were performed at more convenient temperatures (−10 °C instead of −78 °C). In 1999, Mulvey and co-workers reported various preparations as well as characterizations of multimetal magnesium amides for the selective deprotonation of arenes, such as toluene,[98,100] benzene,[104] furan,[105] ferrocene,[106] ruthenocene,[106] osmocene,[106] and bis(arene)-chromium.[107]



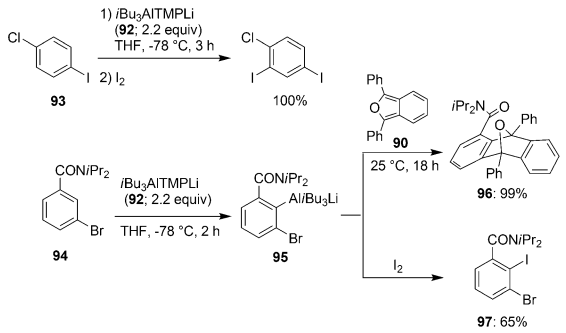
Scheme 18. Metalation and functionalization of substituted pyridines with Bu$_2$Mg(TMP)Li (**78**) and Bu$_3$Mg(TMP)Li$_2$ (**79**).

3.3. TMP-Zincate Bases

Kondo, Uchiyama, and co-workers have reported the highly chemoselective zincation of functionalized aromatic compounds[89,90,96] and heterocycles[108] by using zincates such as tBu$_2$Zn(TMP)Li (**82**) prepared from tBu$_2$Zn and TMPLi (**1**). This metalating agent proved to be compatible with aromatic substrates bearing sensitive functions such as ester or cyano groups. The nature of the alkyl ligands in zincates dramatically influences the reactivity of the resulting arylzincates **83**–**85**. Thus, treatment of 4-bromoanisole (**86**) with tBu$_2$Zn(TMP)Li (**82**; 2.2 equiv) furnished 2-iodo-4-bromoanisole **87** in quantitative yield after iodolysis (Scheme 19).[96c] Remarkably, formation of benzyne **88** was only observed when using Me$_2$Zn(TMP)Li (**89**) instead of tBu$_2$Zn(TMP)Li (**82**).[96c] A subsequent reaction with the isobenzofuran **90** gave the adduct **91** in 81% yield (Scheme 19). Aromatic compounds such as benzene,[109] naphthalene,[110] ferrocene,[111] diisopropylbenzamide,[112] anisole,[113] *N*,*N*-dimethylaniline,[114] toluene,[115] benzonitrile,[116] and pyridines[117] were successfully zincated by lithium and sodium amidozincates in the presence of the solubilizing additive *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). Crystalline complexes of such metalated species were isolated and structurally characterized.[9,115,117] Furthermore, detailed mechanistic investigations revealed that both Na-TMP zincates such as **74** (Scheme 17) and Li-TMP zincates such as tBu$_2$Zn(TMP)Li (**82**) exhibit amido basicity.[118] However, in the case of sodium zincate (**74**), the alkyl ligand subsequently deprotonates TMP-H, thereby eliminating an alkane and reintegrating the amido ligand in the organometallic complex.

3.4. TMP-Aluminate Bases

Organoaluminum compounds[119] have already been widely used as Lewis acids[22,120] or synthetic building blocks.[121] Originally, Yamamoto and co-workers reported the use of Et$_2$Al(TMP) for the regioselective deprotonation of epoxides[122] and as a catalyst in the Fischer indole synthesis.[123] However, tricoordinated aluminum reagents such as Et$_2$Al(TMP) proved to be ineffective for the direct alumination of functionalized aromatic compounds. In contrast, Uchiyama and co-workers developed the highly chemoselective lithium aluminate base, iBu$_3$Al(TMP)Li (**92**).[92,124,125] This reagent displays high regioselectivity and tolerance towards various functionalities, such as methoxy, ester, and cyano groups. Interestingly, aryl iodides could be deprotonated by iBu$_3$Al(TMP)Li (**92**), thereby avoiding halogen–metal exchange reactions.[92] In contrast to Li-TMP-zincates (see Scheme 19), the generation of a benzyne intermediate could be suppressed by using **92** and decreasing the reaction temperature. Thus, 4-chloroiodobenzene (**93**) was metalated by iBu$_3$Al(TMP)Li (**92**; 2.2 equiv, −78 °C, 3 h). Iodolysis furnished 4-chloro-1,3-diiodobenzene in quantitative yield (Scheme 20).[125] Similarly, the alumination of the benzamide derivative **94** with the aluminate base **92** (2.2 equiv, −78 °C,

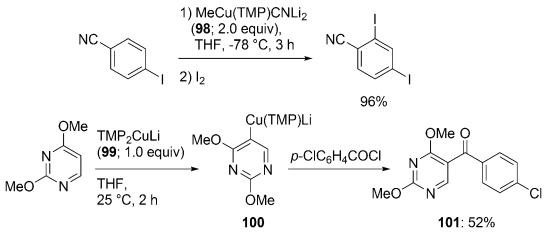


Scheme 20. Alumination with iBu$_3$Al(TMP)Li (**92**) and subsequent trapping with electrophiles.

2 h) generated the corresponding aluminum reagent **95**. A cycloaddition with the isobenzofuran **90** led to the adduct **96** in 99% yield. Alternatively, iodolysis of **95** provided 3-bromo-2-iodobenzamide (**97**) in 65% yield (Scheme 20).[92]

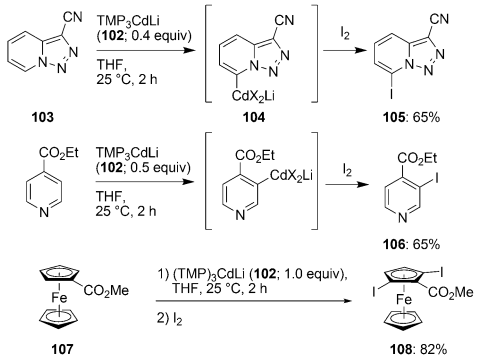
3.5. TMP-Cuprate and -Cadmate Bases

Uchiyama and co-workers reported a highly regio- and chemoselective cupration of functionalized aromatic and heteroaromatic compounds.[126] A variety of functional groups, such as nitriles and amides as well as sensitive heteroaromatic compounds, are tolerated well. Thus, treatment of 4-iodobenzonitrile with MeCu(TMP)(CN)Li$_2$ (**98**; 2.0 equiv, −78 °C, 3 h) gave, after iodolysis, 2,4-diiodobenzonitrile in 96% yield (Scheme 21). In addition, Mongin and co-workers also found that cupration of heterocycles, such as thiophene, furan, 2-halopyridines, and 2,4-dimethoxypyrimidine, occurred when using lithium amido cuprates.[127] Thus, 2,4-dimethoxypyrimidine was selectively metalated (25 °C, 2 h) with TMP$_2$CuLi (**99**). Benzoylation of the resulting pyrimidyl cuprate **100** with 4-chlorobenzoyl chloride afforded the functionalized ketone **101** in 52% yield (Scheme 21).[127]



Scheme 21. Cupration of aromatic compounds and heterocycles with MeCu(TMP)CNLi$_2$ (**98**) and TMP$_2$CuLi (**99**).

Mongin, Uchiyama, and co-workers reported the preparation of the new base TMP$_3$CdLi (**102**), which was prepared from CdCl$_2$·TMEDA and TMPLi (**1**).[93] Substituted arenes and heteroarenes bearing sensitive functions, such as ester, cyano, or keto groups, are regioselectively metalated.[93,128] Thus, by using cadmium base **102**, a substituted triazolopyridines such as **103** produces the cadmium reagent **104** (25 °C, 2 h).[129] Subsequent iodolysis furnished the iodotriazolopyridine **105** in 65% yield (Scheme 22).[93,128,130] Ethyl isonicotinate is regioselectively cadmated using TMP$_3$CdLi (**102**; 25 °C, 2 h) to furnish, after iodolysis, the substituted nicotinate **106** in 65% yield.[130]



Scheme 22. Cadmation of N-heterocycles and ferrocene derivatives with TMP$_3$CdLi (**102**), followed by iodolysis.

Detailed NMR spectroscopic investigations and DFT calculations confirmed the structure of TMP$_3$CdLi (**102**) as an intrinsic metalating reagent.[128,131] Furthermore, the use of TMEDA-solvated TMP$_3$CdLi (**102**) improves and simplifies the reaction protocol, since CdCl$_2$·TMEDA is less hygroscopic than CdCl$_2$.[129,131] Remarkably, a range of substituted ferrocenes are converted into organocadmium species by TMP$_3$CdLi (**102**). Thus, the ferrocene **107** leads, after cadmation with **102** (1 equiv, 25 °C, 2 h) and subsequent iodolysis, to the diiodoferrocene **108** in 82% yield (Scheme 22).[132] The toxicity of cadmium compounds may limit the use of these highly efficient reagents.

4. LiCl-Activated TMP Bases

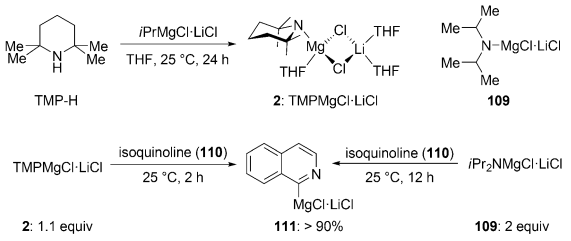
4.1. General

The combination of sterically hindered (non-nucleophilic) metallic amides with LiCl produces kinetically highly reactive and THF-soluble bases. Remarkably, these metallic amides generally require stoichiometric amounts of the base and produce organometallic intermediates that can directly react with various electrophiles. The most important of these hindered bases are lithium chloride solubilized bases of magnesium and zinc (TMPMgCl·LiCl (**2**), TMP$_2$Mg·2 LiCl (**3**), TMPZnCl·LiCl (**4**), and TMP$_2$Zn·2 LiCl (**5**)). As a consequence of the practical importance of these bases, their reactivity will be described in detail.

4.2. TMPMgCl·LiCl and Related Magnesium Bases

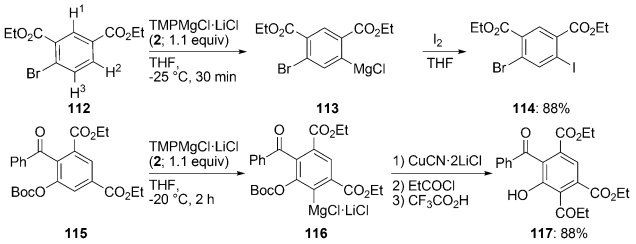
Since Hauser's pioneering studies,[70a] a range of magnesium bases have been used in organic synthesis.[70,72–74] However, all these bases displayed low solubility in THF as

a result of aggregation of the magnesium amide R_2NMgX. In consequence, an aromatic substrate may require up to 10 equivalents of base to achieve complete deprotonation. Moreover, the low solubility of these magnesium amides result in slow metalation rates, since the kinetic rate of a metalation is proportional to the concentration of the substrate and to the concentration of the base employed. Veith et al. had recognized that monomeric structures are favored for bulky metal amides.[80f] It was also well known in organometallic synthesis that numerous metallic salts may be solubilized by LiCl.[133,25,43] These facts led to the design of TMPMgCl·LiCl (**2**), which was prepared by treating TMP-H with *i*PrMgCl·LiCl[43a] in THF at 25 °C for 24 h.[84] This method allows the preparation of **2** in quantitative yield as a 1.2 M solution in THF.[84] The particularly high solubility of **2** suggests this magnesium amide has a monomeric structure. This was later confirmed by Mulvey and co-workers,[70c] who by solving its crystal structure found that two chlorine atoms bridge the two metals Mg and Li (Scheme 23).



Scheme 23. Preparation of TMPMgCl·LiCl (**2**) and evidence for its high kinetic basicity.

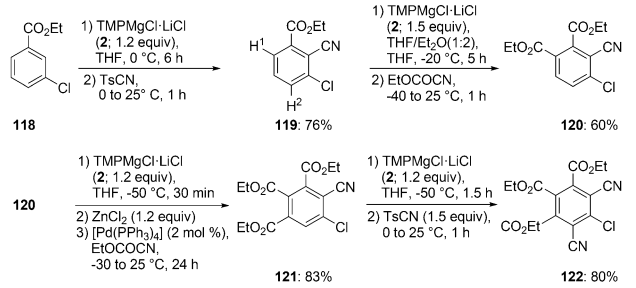
Interestingly, the magnesium amide $iPr_2NMgCl{\cdot}LiCl$ (**109**) has a much lower solubility (0.6 M in THF) and consequently a reduced reactivity. Both of these properties support a stronger aggregation of **2** compared to $iPr_2NMgCl{\cdot}LiCl$ (**109**). Thus, the magnesiation of isoquinoline (**110**) requires 2 equivalents of $iPr_2NMgCl{\cdot}LiCl$ (**109**) and a reaction time of 12 h at 25 °C, whereas the same metalation is complete within 2 h at 25 °C using TMPMgCl·LiCl (**2**) and requires only 1.1 equivalents of the base. Both reactions lead to the 2-quinolylmagnesium chloride (**111**) in greater than 90 % yield (Scheme 23).[84] Since a carbon–magnesium bond is much less ionic than a carbon–lithium bond, sensitive functional groups are more readily tolerated.[134] For example, the preparation of ester-substituted aryllithium compounds in THF is difficult, even when using a sterically hindered ester, such as a *tert*-butyl ester, at low temperature. However, various ester groups are tolerated under the mild magnesiation conditions when TMPMgCl·LiCl (**2**) is used. Thus, treatment of the diethyl bromoisophthalate **112** with TMPMgCl·LiCl (**2**; 1.1 equiv) at −25 °C for 30 min produces the functionalized magnesium derivative **113** in greater than 90 % yield. Iodolysis of **113** furnishes the polyfunctional iodobenzene **114** in 88 % yield.[84] The high kinetic basicity of **2** allows mild metalation conditions to be used and leads to a highly selective magnesiation reaction. The proton H^1 of the diester **112** (Scheme 24) is sterically hindered and the bulky



Scheme 24. Regio- and chemoselective magnesiation of highly functionalized aromatic compounds.

TMP base **2** abstracts only proton H^2 of **112**. This example shows the importance of a precoordination to the ester group, as emphasized by Snieckus, Beak, and co-workers.[80b] The resulting magnesium species **113** is perfectly stable at −25 °C. In particular, the two ester functions of **113** are compatible with an arylmagnesium derivative up to +10 °C. Similar substrates, such as the tetrasubstituted benzene **115**, which bears four sensitive groups—two esters, a *tert*-butoxycarbonyloxy group (BocO), and a benzoyl function (PhCO)—react smoothly with TMPMgCl·LiCl (**2**; 1.1 equiv) at −20 °C to result in complete deprotonation within 2 h. This affords the highly functionalized magnesium reagent **116**, which was readily acylated with propionyl chloride in the presence of $CuCN{\cdot}2\,LiCl$[135] to give, after removal of the Boc group using CF_3CO_2H, the pentasubstituted phenol **117** in 88 % yield (Scheme 24).[85,136]

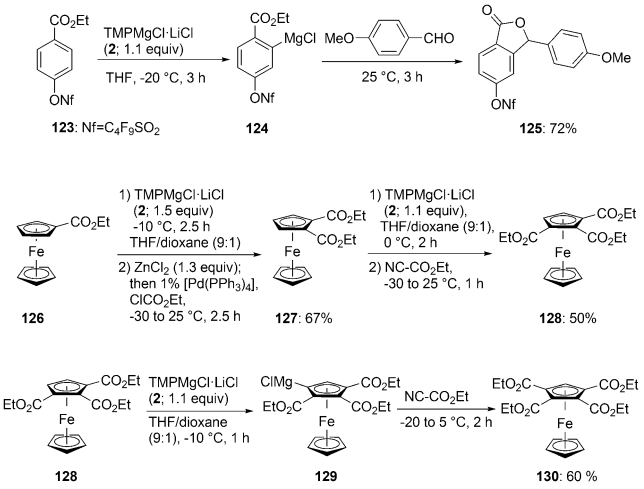
The magnesiation with TMPMgCl·LiCl (**2**) allows the metalation of all the available positions of a benzene ring. Thus, starting with ethyl 3-chlorobenzoate (**118**), a fourfold consecutive metalation with TMPMgCl·LiCl (**2**) via the intermediates **119**–**121** leads to the hexasubstituted benzene **122** in approximately 30 % overall yield (Scheme 25).[136] Interestingly, the metalation of **119** with TMPMgCl·LiCl (**2**) is only partially regioselective in THF because of a competitive deprotonation of proton H^2 in a ratio of about 90:10. This ratio could be improved in favor of the deprotonation of H^1 by switching to a less-polar solvent mixture of THF/Et_2O (1:2), which led to a ratio of 98.5:1.5 (Scheme 25).



Scheme 25. Preparation of a hexasubstituted benzene derivative by a quadruple consecutive magnesiation with TMPMgCl·LiCl (**2**).

TMPMgCl·LiCl (**2**) allows the magnesiation of a range of functionalized aromatic compounds. For example, a highly

electrophilic functionality, such as a nonaflate,[137] is compatible with such mild metalation conditions. Thus, the aromatic nonaflate **123** is magnesiated with TMPMgCl·LiCl (**2**; −20 °C, 3 h) to provide the Grignard reagent **124**. Addition of an aromatic aldehyde provides the expected lactone **125** in 72 % yield (Scheme 26).[138] Highly functionalized ferrocenes can

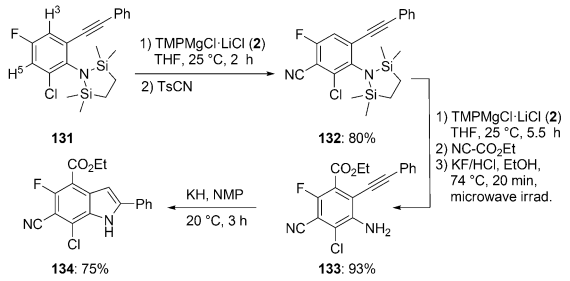


Scheme 26. Preparation of highly functionalized aromatic compounds and ferrocenes by using TMPMgCl·LiCl (**2**).

be prepared by successive magnesiation of carboethoxyferrocene **126**. Thus, its magnesiation with TMPMgCl·LiCl (**2**) in a 9:1 mixture of THF/dioxane (25 °C, 2.5 h) followed by a transmetalation with $ZnCl_2$ and palladium-catalyzed cross-coupling with $ClCO_2Et$[139] leads to the disubstituted ferrocene **127** in 67 % yield.[140] A second magnesiation with **2** and quenching with $NCCO_2Et$ furnishes the trisubstituted ferrocene **128** in 50 % yield. Interestingly, ferrocene **128** and related polyfunctionalized derivatives proved to be more sensitive, despite the fact that the Fe−C bond lengths remain standard for the ferrocene motif (2.03–2.04 Å), thus indicating no weakening of the η^5 binding. Further magnesiation of **128** with TMPMgCl·LiCl (**2**; −10 °C, 1 h) leads to **129**, quenching of which with ethyl cyanoformate produces the tetrasubstituted ferrocene **130** in 60 % yield (Scheme 26).[140]

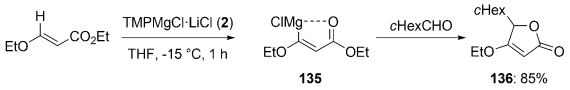
The preparation of polyfunctional indoles is possible by multiple magnesiations with TMPMgCl·LiCl (**2**) on readily available protected aniline derivatives.[141] Thus, the reaction of the tetrasubstituted protected aniline **131** with **2** (25 °C, 2 h) furnishes an intermediate Grignard reagent by selective magnesiation in position 5. Quenching with TsCN produces the corresponding benzonitrile **132** in 80 % yield. Treatment of **132** with an additional equivalent of **2** (25 °C, 5.5 h) followed by a reaction with $NC\text{-}CO_2Et$ furnishes, after desilylation with KF/HCl in ethanol, the hexasubstituted aniline **133** in 93 % yield.[141] Treatment of **133** with KH (2.0–3.6 equiv) in NMP smoothly provides the highly substituted indole derivative **134**[141] in 75 % yield (Scheme 27).[142]

Similarly, TMPMgCl·LiCl (**2**) results in a smooth magnesiation of various aromatic sulfones.[143,144] TMPMgCl·LiCl (**2**) also enables the deprotonation of functionalized cyclic and



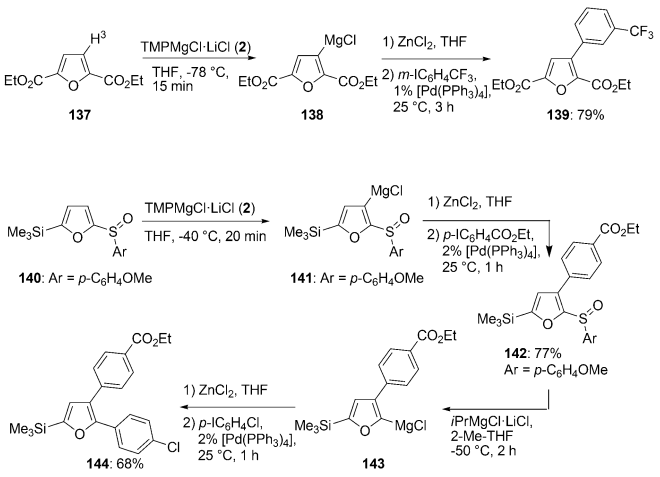
Scheme 27. Successive magnesiation of anilines of type **131** with TMPMgCl·LiCl (**2**), which lead to the highly functionalized indole **134**. Ts = toluene-4-sulfonyl.

acyclic compounds.[145,146] Thus, ethyl 2-ethoxyacrylate reacts with TMPMgCl·LiCl (**2**; 1.1 equiv, −15 °C, 1 h) to afford the β-magnesiated acrylate **135** regioselectively. Chelation with the ester function greatly facilitates the metalation and stabilizes the resulting magnesium species **135**. Reaction of **135** with acid chlorides, allylic bromide, or aldehydes proceeds smoothly. For example, the addition of **135** to *c*HexCHO furnishes the unsaturated lactone **136** in 85 % yield (Scheme 28).[146]



Scheme 28. Magnesiation of ethyl 2-ethoxyacrylate with TMPMgCl·LiCl (2). *c*Hex = cyclohexyl.

TMPMgCl·LiCl (**2**) also proves to be very useful for the selective magnesiation of a wide range of heterocycles, for example, the thiophene scaffold,[147] and allows their full functionalization. Both electron-rich and electron-poor heteroaromatic compounds are readily metalated by **2**. The presence of electron-withdrawing substituents considerably facilitates the magnesiation. Thus, a furan, such as **137**, which bears two ethoxycarbonyl groups in position 2 and 5, is smoothly magnesiated at position 3 with **2** within 15 min at −78 °C. Usually deprotonations with **2** are conveniently realized between −30 °C and 25 °C.[148] However, the deprotonation reaction requires a low temperature, since the intermediate magnesium reagent **138** undergoes decomposition at higher temperatures (possibly by a β-elimination reaction involving a ring opening). The transmetalation of **138** with $ZnCl_2$ leads to a zinc reagent which is stable indefinitely at 25 °C. Cross-coupling of this zinc species with an aryl iodide in the presence of 1 % $[Pd(PPh_3)_4]$ proceeds at 25 °C and furnishes furan **139** (Scheme 29).[148] The presence of a sulfoxide group in position 2, as for furan **140**, stabilizes the intermediate magnesium species **141** and prevents fragmentation. Moreover, the ring metalation can be performed at −40 °C and is complete within 20 min. A subsequent Negishi cross-coupling with ethyl 4-iodobenzoate (2 % $[Pd(PPh_3)_4]$, 25 °C, 1 h) gives the trisubstituted furan **142** in 77 % yield.[149] The sulfoxide moiety, which played the role of an efficient

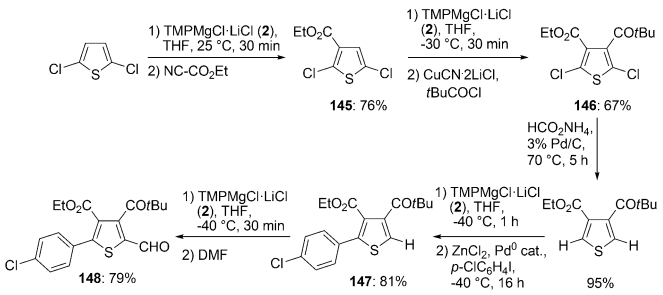


Scheme 29. Preparation of substituted furans by magnesiation with TMPMgCl·LiCl (**2**).

directing group, can be removed in the next step through a sulfoxide–magnesium exchange.[143,144,150] Thus, the treatment of **142** with *i*PrMgCl·LiCl[43a] in 2-methyltetrahydrofuran (−50 °C, 2 h) furnishes the expected magnesium species **143**. A subsequent palladium-catalyzed cross-coupling with 4-chloro-iodobenzene (25 °C, 1 h) leads to the trisubstituted furan **144** in 68 % yield (Scheme 29).[149]

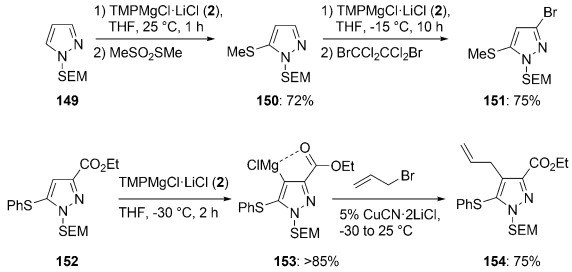
Sulfur-containing heterocycles have found several applications in the preparation of new materials.[151] Thiophenes are also important as pharmaceuticals. Five out of the 100 top-selling drugs in USA in 2007 contain a thiophene subunit.[152] Similarly, TMPMgCl·LiCl (**2**) allows a functionalization of all four thiophene positions starting from 2,5-dichlorothiophene.[148] In contrast to furan, thiophenes magnesiated in position 3 generally do not undergo ring opening. Thus, the reaction of 2,5-dichlorothiophene with **2** (1.1 equiv, 25 °C, 30 min) leads, after a reaction with ethyl cyanoformate, to the ester-substituted thiophene **145** in 76 % yield. A second magnesiation of **145** was performed at −30 °C and led, after a copper-mediated acylation with pivaloyl chloride, to the thiophene derivative **146** in 67 % yield.[147] The two chlorine substituents of 2,5-dichlorothiophene, whose role was to avoid the deprotonation at the more acidic 2- and 5-positions and to sufficiently acidify positions 3 and 4, was removed by a palladium-catalyzed reduction[153,154] with HCO_2NH_4 in ethanol at 70 °C by using microwave irradiation.[147] The reduction is usually complete within 5–6 h and is compatible with chloroaryl substituents.[147] The third magnesiation is completely regioselective, and the ester group directs the base **2** to the adjacent position, thereby providing, after a Negishi cross-coupling reaction with 4-chloroiodobenzene, thiophene derivative **147** in 81 % yield. The fourth magnesiation with **2** followed by quenching with *N*,*N*-dimethylformamide (DMF) leads to the tetrasubstituted thiophene **148** in 79 % yield and approximately 31 % overall yield starting from 2,5-dichlorothiophene (Scheme 30).[147]

TMPMgCl·LiCl (**2**) readily metalates pyrazoles at position 5. In contrast, a metalation at position 4 can only be achieved by using the *ortho*-directing effect of an ester



Scheme 30. Preparation of tetrasubstituted thiophene **148** by successive magnesiation with TMPMgCl·LiCl (**2**).

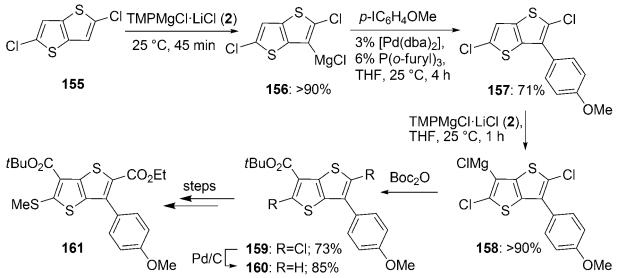
substituent in position 3. Thus, the reaction of SEM-protected pyrazole **149** with **2** is complete within 1 h at 25 °C. Quenching with $MeSO_2SMe$ furnishes pyrazole **150** in 72 % yield. Successive metalation with **2** at position 3 proceeds at −15 °C and is complete within 10 h. Bromination of the intermediate Grignard compound with $BrCCl_2CCl_2Br$ affords the 3,5-disubstituted pyrazole **151** in 75 % yield. The ester-substituted pyrazole **152** is magnesiated with **2** at −30 °C within 2 h and leads to the chelate-stabilized heteroarylmagnesium species **153**. A copper-catalyzed allylation with allyl bromide leads to the trisubstituted pyrazole **154** in 75 % yield (Scheme 31).[155]



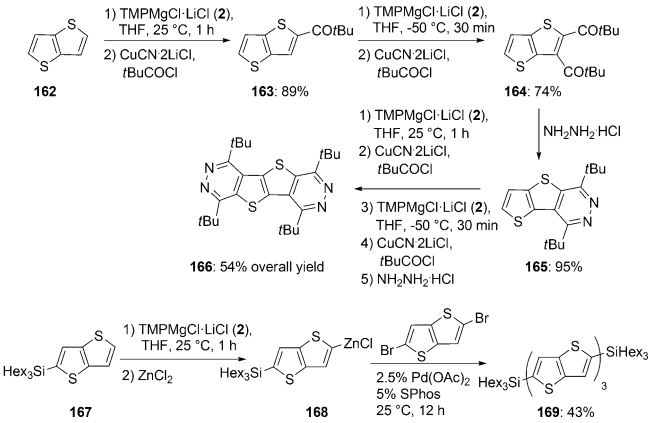
Scheme 31. Magnesiation of pyrazoles with TMPMgCl·LiCl (**2**). SEM = [2-(trimethylsilyl)ethoxy]methyl.

The thieno[3,2-*b*]thiophene system has attracted much attention for the development of new materials for organic photovoltaic and related applications.[156] Starting from 2,5-dichlorothieno[3,2-*b*]thiophene (**155**),[157] a full functionalization of this condensed heterocycle was readily achieved. The magnesiation of **155** with **2** at 25 °C produces the fully magnesiated thienothiophene **156** within 45 min. Transmetalation with $ZnCl_2$ followed by a Negishi cross-coupling reaction with 4-iodoanisole furnishes the substituted thienothiophene **157** in 71 % yield. A second equivalent of **2** leads under the same reaction conditions (25 °C, 1 h) to a quantitative second deprotonation that affords the Grignard species **158**. Treatment with Boc_2O provides the corresponding *tert*-butyl ester **159** in 73 % yield. Schlosser reduction[154,155] with HCO_2NH_4 in ethanol at 120 °C for 4–6 h leads to thienothiophene **160** in 85 % yield (Scheme 32).[156]

The C–H bond in position 2 of **160** and related thienothiophenes can also be magnesiated with TMPMgCl·LiCl (**2**;



Scheme 32. Preparation of polysubstituted thieno[3,2-*b*]thiophenes by using TMPMgCl·LiCl (**2**). Boc = *tert*-butoxycarbonyl.



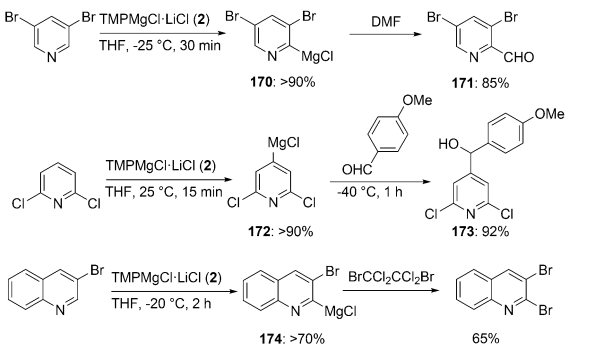
Scheme 33. Preparation of new condensed or oligomeric thienothiophenes by magnesiation with TMPMgCl·LiCl (**2**).

−20 °C, 40 min). In these cases, the low temperatures avoid any side reaction with the ester function present in the thienothiophene **160**. Tetrasubstituted thienothiophenes such as **161** have been prepared by using this iterative magnesiation procedure (Scheme 32).[156]

The direct magnesiation of the unsubstituted thieno[3,2-*b*]thiophene (**162**) was also achieved (25 °C, 1 h) and provided, after a copper-mediated acylation with pivaloyl chloride, the *tert*-butyl ketone **163** in 89 % yield. The carbonyl substitutent of **163** acts as an efficient directing group[6] for the subsequent magnesiation step with TMPMgCl·LiCl (**2**; −50 °C, 30 min). Remarkably, no competitive magnesiation occurs at position 2′. A second acylation with pivaloyl chloride produces the diketone **164** (74 % yield), which affords the new condensed pyridazine **165** in quantitative yield in the presence of hydrazine hydrate in ethanol. Repeating both magnesiation steps with **2** again and performing a second pyridazine ring closure with hydrazine hydrate generates the new tetracyclic heterocyclic system **166** in 54 % yield.[156]

Especially relevant for applications in material science is the preparation of linear thienothiophene oligomers. The difficulty in such syntheses is usually the low solubility of these heterocyclic oligomers. Therefore, the thieno[3,2-*b*]thiophene **167** was chosen as the starting material, the Hex_3Si substituent of which enhances the solubility of the resulting short oligomer. The magnesiation of **167** with TMPMgCl·LiCl (**2**) produces, after transmetalation with $ZnCl_2$, the zincated thienothiophene **168**. This undergoes a smooth palladium-catalyzed cross-coupling with 2,5-dibromothieno[3,2-*b*]thiophene in the presence of Buchwald's catalyst system[46] (2.5 % $Pd(OAc)_2$, 5 % SPhos; Scheme 33) to produce trimeric thieno[3,2-*b*]thienophene **169** in 43 % yield.[156] This study has shown that the sensitivity of trimers, such as **169**, to light strongly depends on the substituents attached to the thienothiophene moiety.

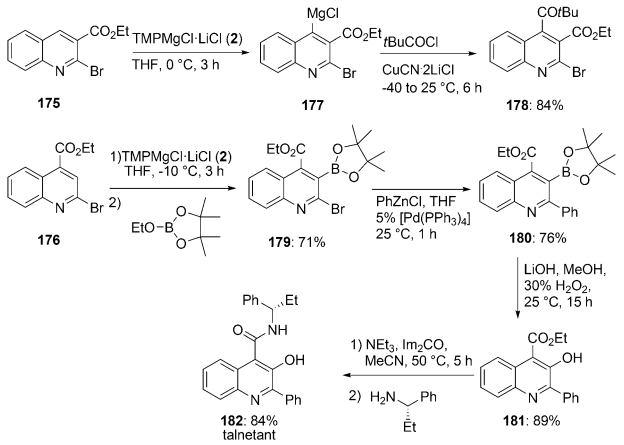
The metalation of pyridines and quinolines is especially important, since such electron-deficient heterocycles are found in numerous pharmaceuticals. TMPMgCl·LiCl (**2**) and related TMP bases (see the following section) allow the regioselective functionalization of a broad range of substituted pyridines. The range of possible bases and reaction parameters (e.g. temperature, cosolvent, and Lewis acid additives) has resulted in a unique synthetic arsenal becoming available to synthetic organic chemists. In general, pyridines and related heterocycles are electron deficient and additional nitrogen atoms in the ring further increase this electrophilicity. This property dramatically modifies the stability of resulting metalated N-heterocycles, thereby making them prone to dimerize through an addition reaction (Chichibabin reactions).[66] In consequence, lithiated pyridines are only convenient reaction intermediates if the ring bears electron-donating substituents, such as methoxy- or dimethylamino groups, which decrease the acceptor character of these heterocycles. The more covalent carbon–magnesium bond in magnesiated pyridines make them better intermediates. Halogen-dance rearrangements are usually not observed.[158] Therefore, **2** is a practical base for achieving a range of such metalations. Thus, treatment of 3,5-dibromopyridine with **2** leads to a smooth deprotonation at −25 °C to provide the 2-magnesiated pyridine **170** regioselectively. Addition of **170** to DMF leads to the corresponding pyridyl aldehyde **171** in 85 % yield (Scheme 34).[84]



Scheme 34. Regioselective metalation of halopyridines and quinolines by using TMPMgCl·LiCl (**2**).

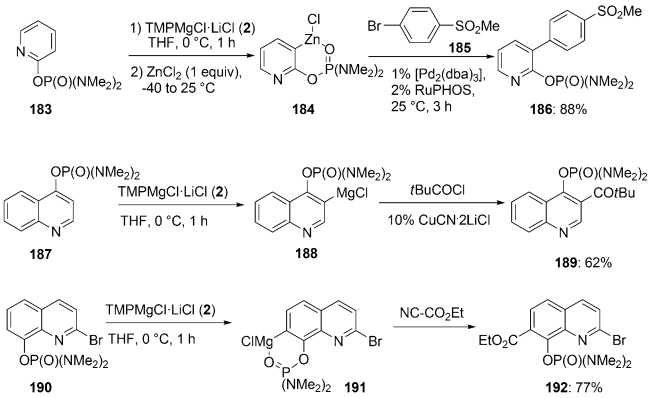
The kinetic acidity of the C–H bond in position 4 of 2,6-dichloropyridine is so high that an almost exclusive magnesiation occurs at position 4 and provides the Grignard reagent **172** in 90 % yield. Addition of **172** to 4-methoxybenzaldehyde

readily produces the alcohol **173** in 92% yield.[159] This magnesiation with TMPMgCl·LiCl (**2**; 1.1 equiv, 25 °C, 10 min) was performed on a 100 mmol scale, and equimolar amounts of the aldehyde were used. 3-Bromoquinoline proved to be sensitive toward an addition at position 2. However, its reaction with **2** produces the magnesiated quinoline **174** within 2 h at −20 °C. Quenching with $BrCCl_2CCl_2Br$ gives 2,3-dibromoquinoline in 65% yield (Scheme 34).[160] Functionalized quinolines bearing an ester, such as **175** and **176**, are smoothly magnesiated with TMPMgCl·LiCl between 0 and −10 °C.[160] The intermediate Grignard reagent **177** is acylated with pivalolyl chloride to afford the 2,3,4-trisubstituted quinoline **178** in 84% yield.[160] The magnesiation product derived from **176** was treated with ethyl pinacol borate,[161] which led to the boronic ester **179** in 71% yield. A Negishi cross-coupling of bromide **179** with PhZnCl led to the cross-coupling product **180** in 76% yield.[160] The hydroxyester **181** was obtained in 89% yield after oxidation of the boronic ester **180** with aqueous 30% H_2O_2. Amidification of **181** with (*S*)-1-phenylpropylamine provides the NK3 receptor antagonist talnetant (**182**) developed by GlaxoSmithKline (84% yield, Scheme 35).[162]



Scheme 35. Synthesis of polyfunctional quinolines with TMPMgCl·LiCl (**2**). Im = imidazolyl.

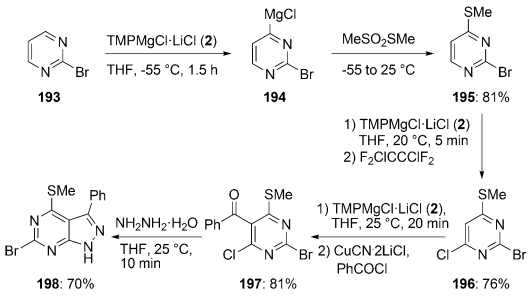
The *N*,*N*,*N*′,*N*′-tetramethyldiaminophosphorodiamidate group[162] is a very strong directing group because of the exceptional polarity of the P=O bond. The linkage of this functionality to various N-heterocycles bearing a hydroxy function leads to a smooth magnesiation. Thus, the phosphorodiamidate **183** derived from 2-hydroxypyridine reacts with TMPMgCl·LiCl (**2**; 1.5 equiv, 0 °C, 1 h) to afford, after transmetalation with $ZnCl_2$, the zinc reagent **184**. A Pd^0-catalyzed cross-coupling of aryl bromide **185** using 1% $[Pd_2(dba)_3]$ and 2% RuPHOS[163] as the catalytic system furnishes the 1,2-difunctionalized pyridine **186** in 88% yield.[164] Similarly, various hydroxyquinolines were readily magnesiated as phosphorodiamidate derivatives. Thus, the 4-substituted substrate **187** was selectively metalated in position 3 with **2** (1.5 equiv, 0 °C, 1 h) to generate the Grignard reagent **188**. The addition of 10% CuCN·2 LiCl and pivaloyl chloride affords the expected 3-ketoquinoline **189** in 62% yield.[164] Remarkably, the strongly directing phosphorodiamidate group attached at position 8 of the bromoquinoline **190** effectively activates position 7 of the benzene ring, while no deprotonation occurs at positions 3 or 4 of the pyridine ring of **190**. A magnesiation at position 7 occurs within 1 h at 0 °C to give the magnesium derivative **191**. After its quenching with NC-CO_2Et (25 °C, 3 h), the carbethoxy-substituted quinoline **192** is obtained in 77% yield (Scheme 36).[164] In



Scheme 36. Magnesiation of phosphorodiamidate-substituted N-heterocycles with TMPMgCl·LiCl (**2**). dba = *trans*,*trans*-dibenzylideneacetone.

contrast to phosphorodiamidates attached to aromatic rings, the corresponding derivatives of electron-deficient N-heterocycles are readily cleaved with 2 M HCl in dioxane/water (1:1). In several cases, this cleavage occurs at room temperature.[165]

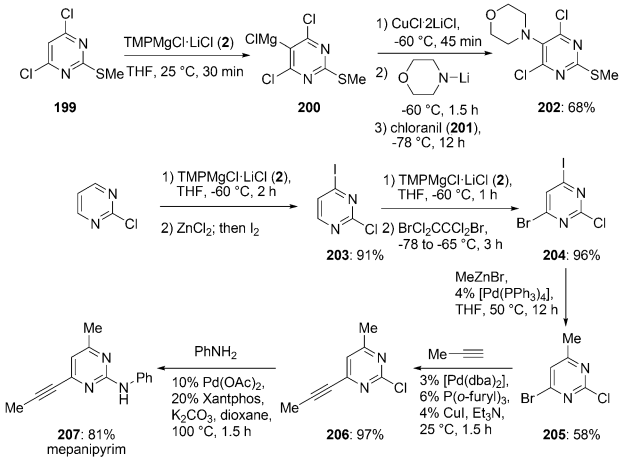
The introduction of an additional heteroatom in the pyridine ring acidifies all the positions and facilitates metalation reactions. However, addition reactions of the metalated species to such electron-deficient heterocycles are especially facile.[166] The use of TMPMgCl·LiCl (**2**) allows the selective functionalization of all the positions of 2-bromopyrimidine (**193**; Scheme 37). Thus, the reaction of **193** with **2** provides within 1.5 h at −55 °C the 4-magnesiated pyrimidine **194** in 90% yield. Its quenching with $MeSO_2SMe$ furnishes the thiomethyl ether **195** in 81% yield.[167] A second magnesiation with **2** at 20 °C occurs within 5 min, and a subsequent reaction with $F_2ClCCClF_2$ leads to the trisubstituted pyrimidine **196** in



Scheme 37. Full functionalization of 2-bromopyridine (**193**) by successive magnesiation with TMPMgCl·LiCl (**2**).

76% yield. The presence of a thiomethyl substituent increases the electron density of **195** and considerably diminishes its tendency to undergo nucleophilic additions, which conveniently allows the second magnesiation to be performed at 20°C. A third metalation with **2** in THF (25°C, 30 min) allows the full functionalization of the ring. Acylation with benzoyl chloride gives the fully substituted pyrimidine **197** in 81% yield. This N-heterocycle is readily converted with $NH_2NH_2{\cdot}H_2O$ in THF (25°C, 10 min) into the pyrazolopyrimidine **198** in 70% yield (Scheme 37).[167]

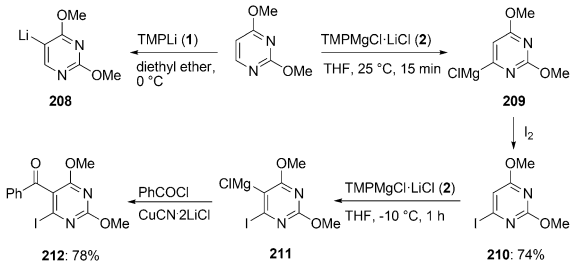
Furthermore, magnesiated pyrimidines can also be oxidatively aminated with chloranil.[168] Thus, the reaction of dichloropyrimidine **199** with TMPMgCl·LiCl (**2**) for 30 min at 25°C provides the Grignard species **200**, which is converted into the corresponding copper species. Addition of N-lithiated morpholine affords an amidocuprate, which on treatment with chloranil (**201**) at −78°C for 12 h leads to the aminated product **202** in 68% yield (Scheme 38).[169]



Scheme 38. Magnesiation of pyrimidines with TMPMgCl·LiCl (**2**) for the preparation of biologically active pyrimidines.

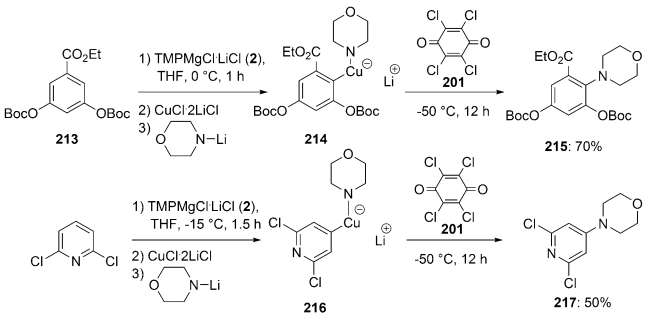
Successive magnesiations of 2-chloropyrimidine with **2** (−60°C, 2 h) followed by transmetalation with $ZnCl_2$ and iodolysis provides the dihalogenated pyrimidine **203** in 91% yield. Further treatment with **2** at −60°C for 1 h leads to magnesiation at position 6. Quenching with $BrCl_2CCCl_2Br$ gives pyrimidine **204** in 96% yield. A Negishi cross-coupling of **204** with MeZnBr produces the expected pyrimidine **205** in 58% yield. Sonogashira cross-coupling of **205** with propyne furnishes the alkynyl derivative **206** in 97% yield. Finally, amination of **206** with aniline under Buchwald–Hartwig amination conditions[170–173] produces the fungicide mepanipyrim **207**[174,175] in 81% yield (Scheme 38).[169]

The metalation of the uracil scaffold can be achieved by selective deprotonation of 2,4-dimethoxypyrimidine. Such functionalization is of particular importance because of the antiviral properties of such molecules. The research groups of Wada[176] and Quéguiner[177] reported the regioselective lithiation of 2,4-dimethoxypyrimidine at position 5 with TMPLi (**1**) in diethyl ether at 0°C to give the lithiated pyrimidine **208**. The use of TMPMgCl·LiCl (**2**) in THF at 25°C allows a complementary metalation at position 6 and affords the Grignard species **209** (Scheme 39).[178] The iodouracil derivative **210** is produced in 74% yield after iodolysis. The magnesiation of **210** proceeds smoothly with **2** (−10°C, 1 h) and furnishes the magnesium reagent **211**, which is stable toward elimination and undergoes a copper-mediated benzoylation to give the pyrimidine **212** in 78% yield (Scheme 39).



Scheme 39. Regioselective metalation of uracil derivatives with TMPMgCl·LiCl (**2**) and TMPLi (**1**).

The amination of aromatic compounds and heterocycles is of great synthetic interest. As pioneered by Buchwald and coworkers[170,179,180] and Hartwig,[171,172,181] transition-metal-catalyzed aminations have been especially successful. Amination procedures involving an oxidative process have been reported,[182] and TMPMgCl·LiCl (**2**) allows a useful extension of this approach.[183] Thus, the reaction of the ethyl benzoate derivative **213** with **2** (0°C, 1 h) followed by addition of CuCl·2LiCl furnishes an organocopper reagent. Its subsequent reaction with lithiated morpholine produces the intermediate lithium amidocuprate **214**, which in the presence of chloranil (**201**; 1.2 equiv, −50°C, 12 h) undergoes an oxidative amination,[184–186] thereby leading to the tertiary aromatic amine **215** in 70% yield (Scheme 40).[168] Various

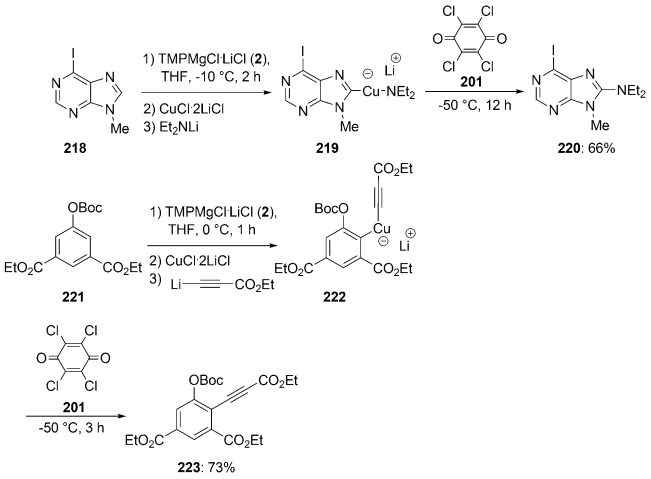


Scheme 40. Amination of benzoic acid and pyridine derivatives by magnesiation with TMPMgCl·LiCl (**2**), transformation to the amidocuprates, and subsequent oxidative coupling with chloranil (**201**).

heterocycles are oxidatively aminated with this procedure. 2,6-Dichloropyridine is regioselectively magnesiated in position 4 (ratio > 97:3) with **2** (−10°C, 1.5 h). Treatment of the resulting pyridylcopper derivative with *N*-lithiomorpholine affords the intermediate cuprate **216**. A subsequent oxidative

coupling with chloranil (**201**) then furnishes the aminated pyridine **217** in 50% yield (Scheme 40).[187]

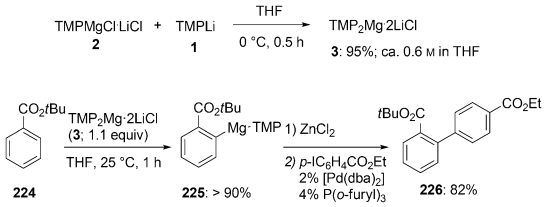
The amination of purines often requires harsh conditions and precludes the presence of reactive substituents such as an iodide. In contrast, the iodopurine derivative **218** is smoothly magnesiated (−10 °C, 2 h), transmetalated with CuCl·2 LiCl, and treated with Et_2NLi. Oxidative coupling of the resulting amidocuprate **219** with chloranil (**201**) furnishes the aminated purine **220** in 66% yield.[188] Interestingly, this oxidative coupling procedure was also used to form new carbon–carbon bonds. The magnesium reagent derived from **221** was transmetalated with CuCl·2 LiCl to afford a copper intermediate. Addition of ethyl 1-lithiopropiolate[189] furnishes at −78 °C the mixed lithium cuprate **222**. Its reaction with chloranil (**201**) at −50 °C induces an oxidative C–C bond formation to give the phenylacetylene **223** in 73% yield (Scheme 41).[190,191]



Scheme 41. Oxidative coupling of organometallic intermediates obtained by magnesiation with TMPMgCl·LiCl (**2**).

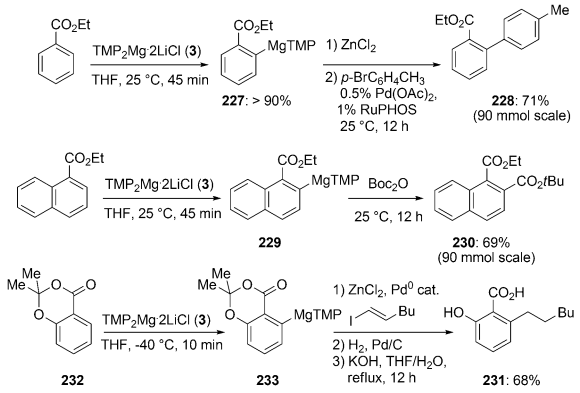
4.3. Bis-TMP-Magnesium and Related Magnesium Bases

Aromatic substrates bearing electron-donating substituents or weakly electron-accepting substituents are difficult to magnesiate with TMPMgCl·LiCl (**2**) at low temperatures. Long reaction times are required and competitive side reactions are observed. Thus, the metalation of *tert*-butyl benzoate (**224**) with **2** is incomplete at 25 °C and produces only 10% of the corresponding magnesiated species. Longer reaction times did not improve this conversion and led to progressive decomposition. The use of a stronger base $TMP_2Mg·2\,LiCl$ (**3**) solves this problem. This magnesium base was prepared in over 95% yield as a 0.6 M solution by treating **2** with TMPLi (**1**)[192,193] at 0 °C for 30 min in THF. Its reaction with *tert*-butyl benzoate (**224**) provides more than 90% of the magnesiated reagent **225**. Transmetalation with $ZnCl_2$ and cross-coupling with ethyl 4-iodobenzoate in the presence of 2% $[Pd(dba)_2]$ and 4% P(*o*-furyl)$_3$ produces the cross-coupling product **226** in 82% yield (Scheme 42).[86] The high reactivity of **3** requires its storage at low temperature, since a cleavage of the THF ring is observed at 25 °C. Ethyl benzoate is readily metalated at 25 °C within 45 min. After a



Scheme 42. Preparation and magnesiation reaction with $TMP_2Mg·2\,LiCl$ (**3**).

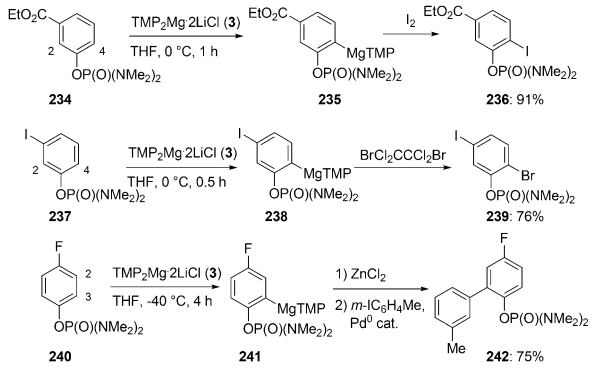
transmetalation of the intermediate arylmagnesium amide **227** with $ZnCl_2$, a palladium-catalyzed cross-coupling with 4-bromobenzonitrile in the presence of 0.5% $Pd(OAc)_2$ and 1% RuPHOS[163] furnishes the expected cross-coupling product **228** in 71% yield on a 90 mmol scale.[159] Similarly, ethyl 1-naphthoate is magnesiated smoothly with $TMP_2Mg·2\,LiCl$ (25 °C, 45 min) to provide the magnesium species **229**. A subsequent reaction with Boc_2O (25 °C, 2 h) gives the diester **230** in 69% yield (Scheme 43).[159] This metalation procedure was the key step in the synthesis of 6-



Scheme 43. Magnesiation with $TMP_2Mg·2\,LiCl$ (**3**).

hexylsalicylic acid (**231**), which is found in the essential oil of *Pelargonium sidoides* DC. Magnesiation of salicylic acid derivative **232** with $TMP_2Mg·2\,LiCl$ (**3**) was complete within 10 min at −40 °C and afforded **233**. Transmetalation with $ZnCl_2$, followed by a palladium-catalyzed cross-coupling ($ZnCl_2$ (1.1 equiv), 5% $[Pd(PPh_3)_4]$, 25 °C, 12 h) with (*E*)-1-iodo-1-hexene provides a lactone, which was readily converted in two steps into the salicylic acid **231** in 68% yield (Scheme 43).[194]

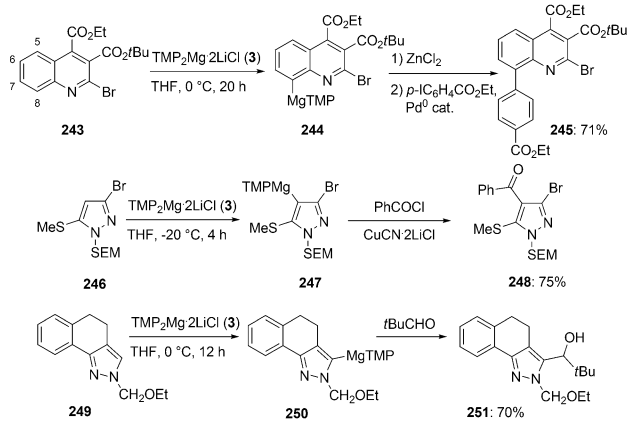
The high basicity of $TMP_2Mg·2\,LiCl$ (**3**) allows the magnesiation of various functionalized aromatic rings bearing a phosphorodiamidate group ($(Me_2N)_2P(O)O$-) as a directing group.[195] Thus, benzoate **234** is regioselectively metalated at position 4 (0 °C, 1 h) to give magnesium derivative **235**. After iodolysis, the expected 4-iodobenzoate **236** is obtained as a single product (Scheme 44).[194] This magnesiation procedure allows functionalization in the position *para* to the carboethoxy function. Steric hindrance hampers a magnesiation at position 2 of **234**. Similarly, the aromatic iodide **237** is magnesiated with **3** at position 4 (0 °C, 30 min), thereby



Scheme 44. Magnesiation of phosphorodiamidate-substituted aromatic compounds in positions *meta* und *para* to a second functional group.

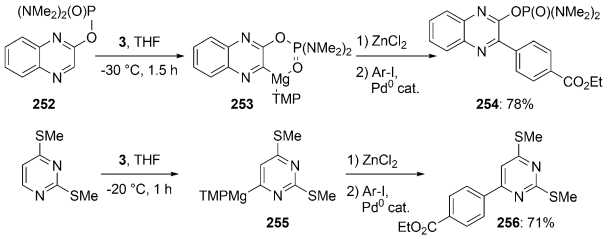
leading to **238**. Under these reaction conditions, no magnesiation is observed at position 2. Bromination with $BrCl_2CCCl_2Br$ provides the 2,5-difunctionalyzed phenol derivative **239** in 76% yield. The presence of a phosphorodiamidate group in position 4 allows a functionalization at the position *meta* to the fluoro substituent. Thus, the 1,4-disubstituted arene **240** undergoes a regioselective magnesiation with **3** to furnish the 3-magnesiated benzene derivative **241** as a single regioisomer (−40 °C, 4 h). A Negishi cross-coupling (2% $[Pd(dba)_2]$, 4% P(2-furyl)$_3$, 25 °C, 12 h) with 3-iodotoluene gives the biphenyl derivative **242** in 75% yield (Scheme 44).[195]

Remarkably, $TMP_2Mg{\cdot}2\,LiCl$ (**3**) also allows the magnesiation of various heterocycles at positions which are difficult to access otherwise. Thus, the quinoline derivative **243** bearing a bromide, a keto, and an ester group is smoothly magnesiated with **3** at position 8 of the quinoline ring to afford the magnesium reagent **244**. Cross-coupling of **244** with ethyl 4-iodobenzoate leads to the tetrasubstituted quinoline **245** in 71% yield (Scheme 45).[188] The pyrazole **246** is also functionalized in position 4 with **3**, thereby leading to the magnesium reagent **247** (−20 °C, 4 h). A copper(I)-mediated benzoylation then gives the trisubstituted pyrazole **248** in 75% yield (Scheme 45).[155] Annelated pyrazoles such as 4,5-dihydrobenzo[*g*]indazole (**249**) is readily magnesiated with **3** in position 5 to afford the magnesium reagent **250**. Addition of pivaldehyde gives the corresponding alcohol **251** in 70% yield (Scheme 45).[196]



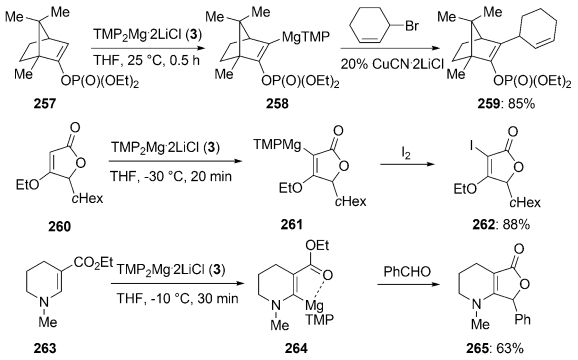
Scheme 45. Magnesiation of functionalized heterocycles with $TMP_2Mg{\cdot}2\,LiCl$ (**3**).

The use of a phosphorodiamidate directing group proves to also be valuable for the functionalization of quinoxalines. Thus, the quinoxaline **252** was readily deprotonated with $TMP_2Mg{\cdot}2\,LiCl$ (**3**) to provide the magnesium intermediate **253** (−30 °C, 1.5 h). The palladium-catalyzed cross-coupling of **253** (5% $[Pd(dba)_2]$, 10% P(2-furyl)$_3$) with ethyl 4-iodobenzoate furnishes the expected cross-coupling product **254** in 78% yield (Scheme 46).[164] Whereas 2,4-dimethoxypyrimidine is readily deprotonated by TMPMgCl·LiCl (**1**), the deprotonation of 2,4-bis(methylthio)pyrimidine to give the 6-magnesiated derivative **255** regioselectively proceeds smoothly with **3** (−20 °C, 1 h). A palladium-catalyzed cross-coupling with ethyl 4-iodobenzoate gives the dimethylthiouracil **256** in 71% yield (Scheme 46).[178]



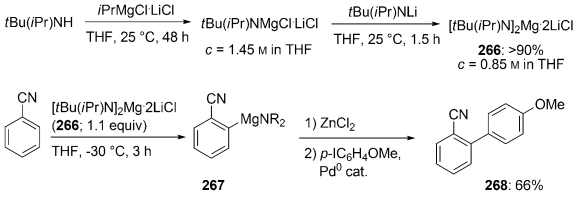
Scheme 46. Regioselective magnesiation of quinoxaline and uracil derivatives with $TMP_2Mg{\cdot}2\,LiCl$ (**3**).

Functionalized non-aromatic substrates are also smoothly magnesiated with the powerful base $TMP_2Mg{\cdot}2\,LiCl$ (**3**). Thus, the camphor-derived enol phosphate **257** is converted into the magnesium derivative **258** on reaction with **3** for 30 min at 25 °C. A copper-catalyzed allylation with 3-bromocyclohexene leads to the alkenyl phosphate **259** in 85% yield (Scheme 47).[145] The lactone **260** was also converted into the corresponding magnesium reagent **261**, which after iodolysis provided the iodolactone **262** in 88% yield (Scheme 47).[146] Treatment of the unsaturated piperidine derivative **263** with **3** at −10 °C led to the corresponding magnesium reagent **264**



Scheme 47. Magnesiation of non-aromatic cyclic molecules by using $TMP_2Mg{\cdot}2\,LiCl$ (**3**).

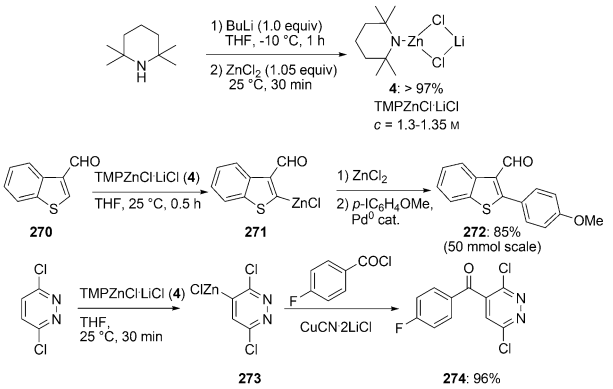
within 30 min. Its addition to benzaldehyde affords the bicyclic lactone **265** in 63% yield (Scheme 47).[146] $TMP_2Mg{\cdot}2\,LiCl$ (**3**) has a very high kinetic basicity, and this base is only stable for 24 h at 25 °C without a significant decrease in activity. Alternatively, the related base $[t\text{Bu}(i\text{Pr})\text{N}]_2Mg{\cdot}2\,LiCl$ (**266**) has an enhanced stability in THF. It can be stored at 4 °C for at least 21 days without losing its activity. The kinetic basicity of **266** is similar to that of **3**. However, the lower steric hindrance of **266** is not compatible with substrates bearing an ethoxycarbonyl group, since the corresponding amides are formed as side products in these cases. Nevertheless, the magnesiation of benzonitrile is complete within 3 h at −30 °C and affords intermediate magnesium amide **267**. A subsequent Pd^0-catalyzed cross-coupling with 4-iodoanisole produces the biphenyl **268** in 66% yield (Scheme 48).[87,197]



Scheme 48. Preparation and magnesiation of benzonitrile with $[t\text{Bu}(i\text{Pr})\text{N}]_2Mg{\cdot}2\,LiCl$ (**266**).

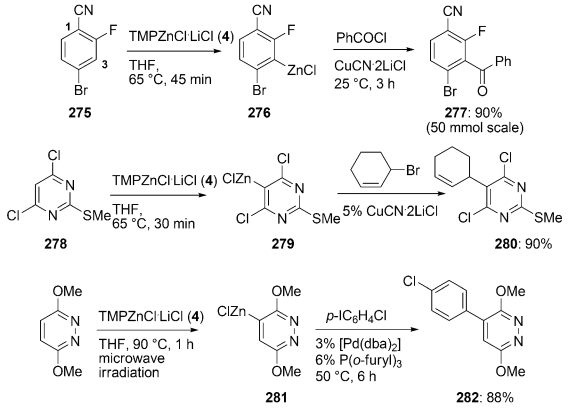
4.4. Zincations Using TMPZnCl·LiCl

Whereas the TMP-magnesium bases such as TMPMgCl·LiCl (**2**) display a high tolerance toward nitriles, esters, and aryl ketones, there are still a number of important functional groups, such as nitro, aldehyde, methyl ketone, or electron-poor N-heterocycles, that are not compatible with the use of a magnesium base. Therefore, there was a need to develop other metal-TMP bases. The use of zinc as the cation is especially appropriate, since it can be anticipated that the resulting aryl or heteroaryl zinc reagents are compatible with sensitive functional groups.[198] Treatment of TMPLi with $ZnCl_2$ at −10 °C for 30 min in THF produces the LiCl-solubilized base TMPZnCl·LiCl (**4**) in quantitative yield as a 1.3 M solution in THF.[199] This base is stable indefinitely at room temperature in the absence of air. It is highly convenient to use, since zincations with this reagent rarely require low temperatures and can be used for zincations at elevated temperatures.[200,201] Thus, the reaction of 3-formylbenzothiophene (**270**) with **4** in THF at 25 °C for 30 min provides the zinc reagent **271** in high yield. A palladium-catalyzed cross-coupling with 4-iodo-anisole in the presence of 2% $[Pd(dba)_2]$ and 4% P(*o*-furyl)$_3$[202] (25 °C, 2 h) produces the desired 2,3-disubstituted benzothiophene **272** in 85% yield.[203] This reaction was performed on a 50 mmol scale, which demonstrated that these zincations can readily be scaled up.[203] The sensitive heterocycle 3,6-dichloropyridazine can only be metalated at low temperature[204] and in moderate yields.[205,206] However, the use of **4** enables such a zincation to be performed at 25 °C within 30 min, with the zincated pyridazine **273** produced in almost quantitative yield. In the presence of a soluble copper salt, such as CuCN·2 LiCl, a smooth acylation reaction proceeds with 4-fluorobenzoyl chloride to provide the polyfunctional ketone **274** in 96% yield (Scheme 49).[199]



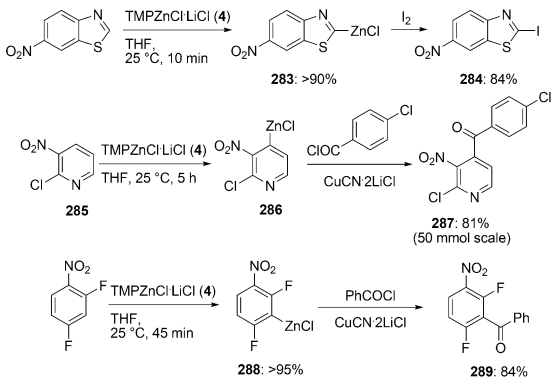
Scheme 49. Preparation and reactions of TMPZnCl·LiCl (**4**).

As mentioned above, zincations mediated by TMPZnCl·LiCl (**4**) are possible over a broad temperature range. The use of elevated reaction temperatures up to 100 °C are feasible. Thus, the benzonitrile **275** is zincated in the position *meta* to the cyano group at 65 °C within 45 min to give the polyfunctional zinc reagent **276** in quantitative yield. A copper(I)-mediated benzoylation provides the benzophenone derivative **277** in 90% yield on a 50 mmol scale (Scheme 50).[203] Similarly, the dichloropyrimidine **278** is selectively metalated in position 5 to afford the zinc reagent **279**. A copper(I)-catalyzed allylation with cyclohexenyl bromide leads to the fully substituted pyrimidine **280** in 90% yield (Scheme 50).[200] Electron-donating substituents usually diminish the metalation rate. Thus, 3,6-dimethoxypyridazine requires microwave irradiation (90 °C, 1 h) for complete zincation and generation of the zinc reagent **281**. A subsequent Negishi cross-coupling using 3% $[Pd(dba)_2]$, 6% P(*o*-furyl)$_3$, and 4-chloro-1-iodobenzene leads to the pyridazine **282** in 88% yield (Scheme 50).[200]



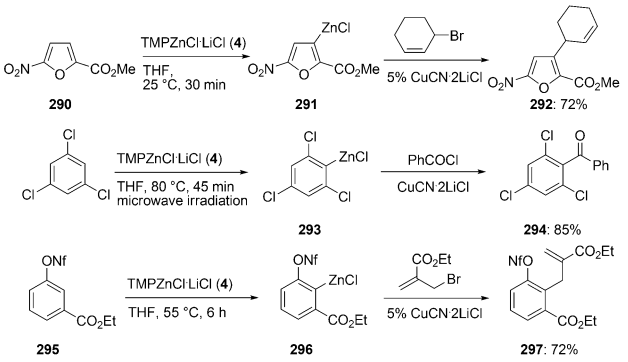
Scheme 50. High-temperature zincation with TMPZnCl·LiCl (**4**).

The preparation of organometallic compounds bearing a nitro group is highly challenging, and magnesiations of nitrobenzenes can only be achieved in a general way by using an I/Mg exchange reaction.[207] However, in several cases, TMPZnCl·LiCl (**4**) allows a direct zincation of aromatic compounds or heterocycles bearing a nitro group. The reaction of 6-nitrobenzothiazole with **4** is complete within 10 min at 25 °C and leads to the 2-*z*incated benzothiazole **283**. A subsequent iodolysis then affords the 2-iodobenzothiazole **284** in 84 % yield (Scheme 51).[199] The 3-nitropyridine **285** is zincated with **4** at position 4 within 5 h at 25 °C to give **286**, which was readily benzoylated on a 50 mmol scale in the presence of CuCN·2 LiCl to afford pyridine **287** in 81 % yield.[199,203] Interestingly, 2,4-difluoronitrobenzene is metalated at the position *meta* to the nitro group, as a consequence of the strong activation effect of the two fluorine substituents, thereby leading regioselectively to the zinc reagent **288** in greater than 95 % yield. A copper-mediated benzoylation of **288** furnishes the benzophenone derivative **289** in 84 % yield (Scheme 51).[199]



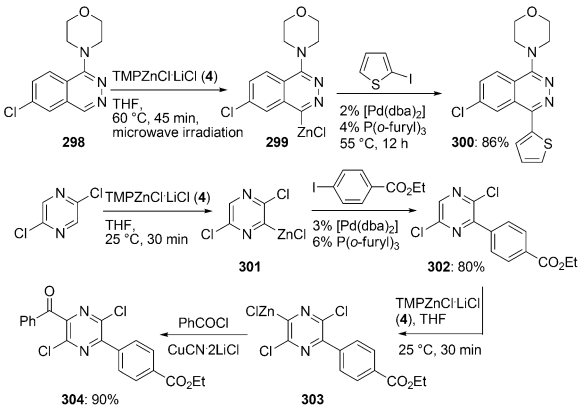
Scheme 51. Zincation of nitro-substituted substrates with TMPZnCl·LiCl (**4**).

Remarkably, exceptional regioselectivity can be achieved by using TMPZnCl·LiCl (**4**) without performing the metalations at low temperatures. Thus, disubstituted furan **290** is readily zincated with **4** at 25 °C within 30 min. The nitro group strongly activates position 4 of the furan ring through an inductive effect. Although the carbomethoxy group in position 2 is less electronegative than the nitro group, its coordination to zinc base **4** is decisive for the regioselectivity that leads to the zinc reagent **291**. A copper(I)-catalyzed allylation provides the substituted furan **292** in 72 % yield (Scheme 52).[199] Remarkably, 1,3,5-trichlorobenzene is also zincated efficiently with **4**, without formation of benzyne-derived by-products. Despite the relatively high temperature (80 °C, 45 min), the metalation leads to the zinc reagent **293**, which after a copper(I)-mediated benzoylation provides the ketone **294** in 85 % yield (Scheme 52).[200] The use of **4** also allows the zincation of substrates bearing highly electrophilic functional groups such as a nonaflate. Thus, the benzoate **295** was zincated with **4** (55 °C, 6 h) to provide the zinc reagent **296**, which was allylated to form the aryl nonaflate **297** in 72 % yield (Scheme 52).[138]



Scheme 52. Metalation of sensitive unsaturated substrates with TMPZnCl·LiCl (**4**).

Functionalized heterocycles, such as the chlorophthalazine derivative **298**, are readily zincated with TMPZnCl·LiCl (**4**) at 60 °C by using microwave irradiation (45 min). The resulting zinc reagent **299** undergoes a smooth Negishi cross-coupling with 2-iodothiophene (2 % [Pd(dba)$_2$], 4 % P(*o*-furyl)$_3$, 55 °C, 12 h) to generate the heterocycle **300** in 86 % yield.[208] It should be noted that the metalation of **298** is sluggish at 25 °C and incomplete after 48 h (Scheme 53).[208]

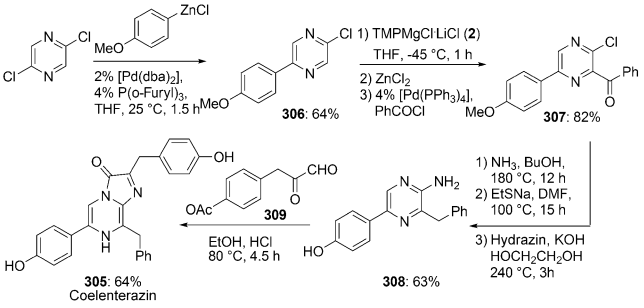


Scheme 53. Functionalization of diazines with TMPZnCl·LiCl (**4**).

The directed zincation of electron-deficient pyrazines is of particular interest, because of their importance as biologically active compounds. TMPZnCl·LiCl (**4**) allows the zincation of a range of dichloropyrazines at 25 °C. Treatment of 2,5-dichloropyrazine with **4** at 25 °C produces the zincated pyrazine **301** in almost quantitative yield within 30 min. A palladium-catalyzed cross-coupling of **301** with ethyl 4-iodobenzoate furnishes the arylated pyrazine **302** in 80 % yield. Subsequent treatment of **302** with an additional equivalent of **4** for 30 min at 25 °C allows a second zincation that leads to the zinc reagent **303**. Benzoylation of the zinc species **303** with PhCOCl in the presence of CuCN·2 LiCl furnishes the fully substituted pyrazine **304** in 90 % yield (Scheme 53).[209]

This method has been applied in the total synthesis of coelenterazine (**305**), a natural bioluminescent compound,

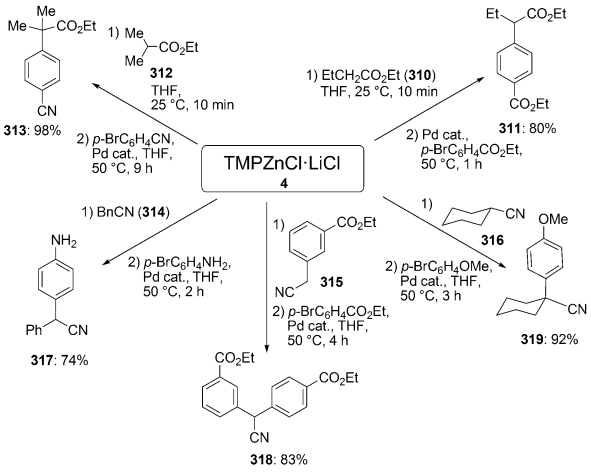
isolated from the jellyfish *Aequorea victoria*. It has found use in new optical techniques to study the behavior of cancer cells.[210] Thus, the palladium-catalyzed cross-coupling of 2,5-dichloropyrazine with anisylzinc chloride (25 °C, 1 h) affords pyrazine **306** in 64 % yield. Magnesiation of **306** with TMPMgCl·LiCl (**2**) at −45 °C is complete within 1 h and provides, after a palladium-catalyzed acylation, the trisubstituted pyrazine **307** in 82 % yield. Substitution of the activated chlorine substituent of **307** with NH_3 in BuOH, followed by deprotection of the phenol hydroxy group and Wolff–Kishner reduction produces the aminopyrazine **308** in 63 % yield. Treatment of **308** with readily prepared 1,2-ketoaldehyde **309** in ethanol leads to coelenterazine **305** in 64 % yield (Scheme 54).[209]



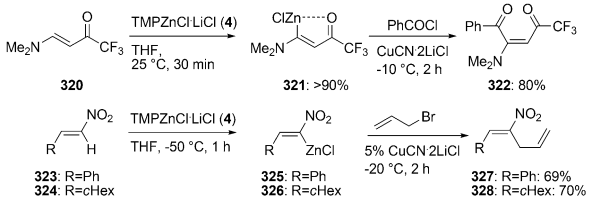
Scheme 54. Synthesis of coelenterazine (**305**).

The generation of metal enolates is of key importance for the electrophilic functionalization of carbonyl derivatives.[211] TMPZnCl·LiCl (**4**) is an excellent base for the generation of a range of zinc enolates. Ethyl butyrate (**310**) is readily converted into the intermediate zinc enolate (25 °C, 10 min), which in the presence of 2 % SPhos and 2 % $[Pd(dba)_2]$ undergoes an α-arylation with ethyl 4-bromobenzoate (50 °C, 1 h) to provide aryl acetate **311** in 80 % yield.[212] Similarly, ethyl isobutyrate (**312**) is arylated with 4-bromobenzonitrile (50 °C, 9 h) to afford benzonitrile **313** in 98 % yield (Scheme 55). The zincation of various nitriles such as **314**–**316** also proceeds smoothly under the same reaction conditions. The resulting zincated nitriles are arylated with aryl bromides (50 °C, 2–4 h) in the presence of the $Pd(OAc)_2$/SPhos[46] catalyst system. A bisarylation may also occur in the cases of nitriles **314** or **315**. However, only the monoarylated products **317** and **318** are obtained. A free aromatic amino function is also tolerated in a palladium-catalyzed cross-coupling with 4-bromoaniline. The arylated nitriles **317**–**319** are obtained in 74–92 % yield (Scheme 55).[212]

Remarkably, the TMP base **4** is kinetically sufficiently active to metalate non-aromatic substrates under very mild conditions. Thus, the trifluoromethyl ketone **320** is readily converted into the corresponding zinc reagent **321** (30 min, 25 °C) and is acylated with benzoyl chloride in the presence of CuCN·2 LiCl to generate the 1,4-diketone **322** in 80 % yield (Scheme 56).[146] Nitroolefins are highly electrophilic alkenes,[213] which are very sensitive to addition reactions with nucleophiles.[214] However, the metalation of either nitrostyrene (**323**) or 2-cyclohexylnitroethylene (**324**) with



Scheme 55. Generation of zinc enolates from nitriles and esters by using TMPZnCl·LiCl (**4**). Conditions for enolate generation: 25 °C, 10 min; Pd cat.: 2 % $Pd(OAc)_2$, 4 % SPhos.



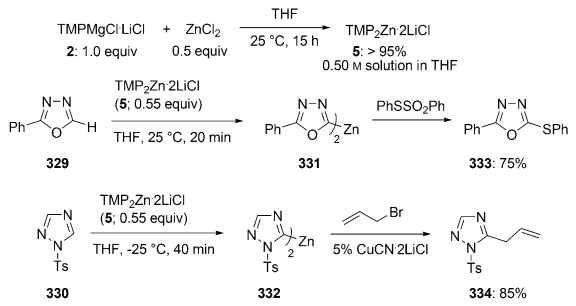
Scheme 56. Zincation of sensitive unsaturated ketones and nitro derivatives with TMPZnCl·LiCl (**4**).

TMPZnCl·LiCl (**4**) at −50 °C provides the sensitive α-zincated derivatives **325** and **326**. Their copper-catalyzed allylations with allyl bromide produces the expected alternating 1,4-dienes **327** and **328** in 69 and 70 % yield, respectively (Scheme 56).[212]

4.5. Zincations Using TMP_2Zn·2 LiCl

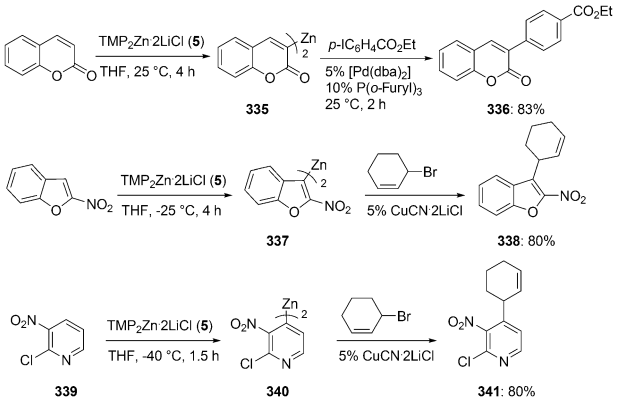
Whereas TMPZnCl·LiCl (**4**) is able to zincate a broad range of aromatic and heterocyclic substrates, there is a need for a more powerful zinc base that is able to zincate relatively unreactive unsaturated substrates. Such a zinc base was readily prepared by combining TMPMgCl·LiCl (**2**) with $ZnCl_2$ (0.5 equiv, 25 °C, 15 h), which resulted in the quantitative formation of TMP_2Zn·2$MgCl_2$·2 LiCl (**5**) as a 0.55 M solution in THF.[215] The two equivalents of LiCl ensure a good solubility of the base, whereas the additional presence of $MgCl_2$ (2 equiv) considerably enhances its kinetic basicity.[216] This new base has been especially useful for the zincation[89,96a,108,217] of sensitive heterocycles such as the 1,3,4-oxadiazole **329** and the 1,2,4-triazole **330**, which are prone to undergo fragmentation during the metalation process.[218,219] Thus, treatment of **329** and **330** with **5** affords the bis(heteroaryl)zinc reagents **331** and **332** within 20 min at 25 °C and −25 °C, respectively. Quenching of these compounds with $PhSSO_2Ph$ or allyl bromide provides the substituted hetero-

cycles **333** and **334** in 75 and 85% yield, respectively (Scheme 57).[215] As expected, both TMP moieties undergo effective deprotonations to give the corresponding diorganozinc reagents.



Scheme 57. Preparation and reactions of $TMP_2Zn{\cdot}2\,LiCl$ (**5**).

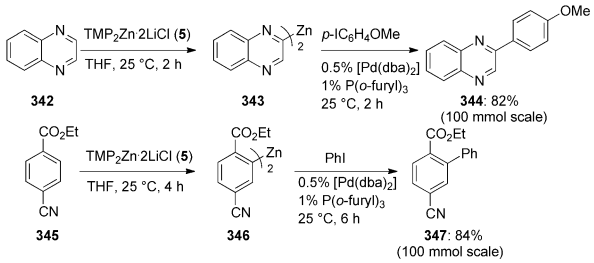
The zincation of coumarin is readily achieved with $TMP_2Zn{\cdot}2\,LiCl$ (**5**) at 25 °C within 4 h and affords the diorganozinc reagent **335** in high yield. A Negishi cross-coupling of **335** with ethyl 4-iodobenzoate (5% $[Pd(dba)_2]$, 10% P(*o*-furyl)$_3$, 25 °C, 2 h) gives the substituted coumarin **336** in 83% yield (Scheme 58). Sensitive functional groups,



Scheme 58. Zincation of sensitive heterocycles with $TMP_2Zn{\cdot}2\,LiCl$ (**5**).

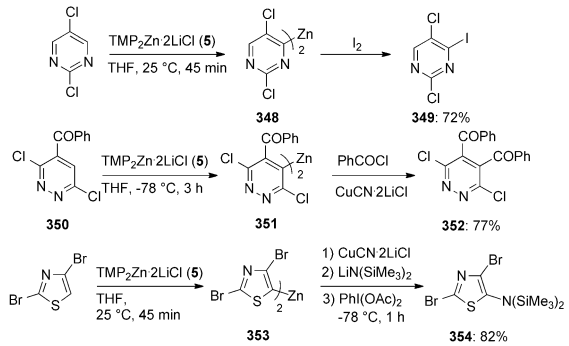
such as a nitro group, are tolerated in several types of functionalized heterocycles. Thus, 2-nitrobenzofuran is zincated at −25 °C within 1.5 h to give the zinc reagent **337**. The copper(I)-catalyzed allylation of **337** with 3-bromocyclohexene provides the benzofuran **338** in 80% yield. Similarly, the nitro-substituted pyridine **339** is zincated with **5** (0.55 equiv, −40 °C, 1.5 h) to afford the zinc organometallic **340**, which is converted into the trisubstituted pyridine **341** in 80% yield (Scheme 58).[215] Such reactions can be readily performed on a large scale (100 mmol).

Quinoxaline **342** is zincated at 25 °C within 2 h to generate the diquinoxalylzinc reagent **343**, which undergoes a subsequent palladium-catalyzed cross-coupling with 4-iodoanisole in the presence of 0.5% $[Pd(dba)_2]$ and 1% P(*o*-furyl)$_3$. The conversion is complete within 2 h at 25 °C, and affords the substituted quinoxaline **344** in 82% yield.[159] An in situ generation of $TMP_2Zn{\cdot}2\,LiCl$ (**5**) from $TMP_2Mg{\cdot}2\,LiCl$ (**3**) allows further functionalization of the quinoxaline scaffold.[220] Activated aromatic substrates bearing two electron-withdrawing substituents, such as **345**, are readily converted into the corresponding diarylzinc **346**. The cross-coupling of **346** with PhI on a 100 mmol scale in the presence of 0.5% $[Pd(dba)_2]$ and 1% P(*o*-furyl)$_3$ gives the biphenyl **347** in 84% yield (Scheme 59).[159]



Scheme 59. Large-scale zincations with $TMP_2Zn{\cdot}2\,LiCl$ (**5**).

2,5-Dichloropyrimidine can be readily metalated with $TMP_2Zn{\cdot}2\,LiCl$ (**5**) to give the zinc reagent **348** at 25 °C; a subsequent iodolysis affords **349** in 72% yield.[169] On the other hand, 3,6-dichloropyridazines requires low temperatures for efficient metalation.[194] For example, the pyridazine **350** is converted into the bis(heteroaryl)zinc **351** (−78 °C, 3 h), and is further benzoylated with PhCOCl to afford the symmetrical pyridazine **352** in 77% yield (Scheme 60).[204]

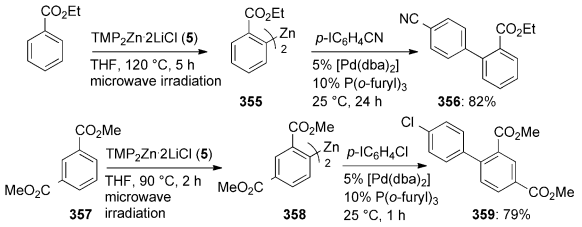


Scheme 60. Zincation of N-heterocycles with $TMP_2Zn{\cdot}2\,LiCl$ (**5**).

$TMP_2Zn{\cdot}2\,LiCl$ (**5**) proves to be especially useful for preparing bis(heteroaryl)zinc reagents which undergo oxidative aminations in high yields.[221] Thus, 2,4-dibromothiazole is converted with **5** into the diorganozinc species **353** in 45 min at 25 °C, and subsequently transmetalated to the corresponding copper derivative with $CuCl{\cdot}2\,LiCl$ (−50 °C, 30 min). The addition of $LiN(SiMe_3)_2$ (−50 °C, 1 h) furnishes a zinc amidocuprate,[221] which undergoes an oxidative amination when treated with $PhI(OAc)_2$ and leads to the 5-aminated thiazole **354** in 82% yield (Scheme 60).[222]

A major advantage of $TMP_2Zn{\cdot}2\,LiCl$ (**5**) is, similar to TMPZnCl·LiCl (**4**), the possibility of performing zincation at

elevated temperatures. This is especially valuable in the case of substrates with moderate reactivity: Thus, treatment of ethyl benzoate with **5** (0.6 equiv) at 120 °C for 5 h with microwave irradiation allows the generation of the corresponding zinc reagent **355** in over 90 % yield. A palladium-catalyzed cross-coupling with 4-iodobenzonitrile provides the functionalized biphenyl **356** in 82 % yield (Scheme 61).[223]

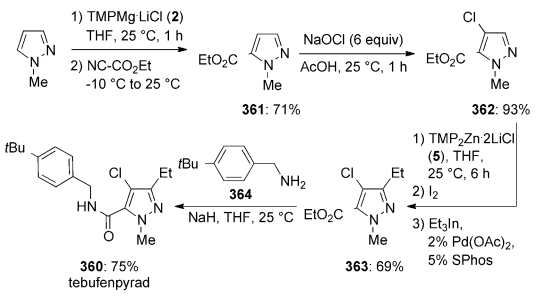


Scheme 61. Microwave-assisted high-temperature zincation with $TMP_2Zn{\cdot}2\,LiCl$ (**5**).

Even sensitive esters such as methyl esters are compatible with the zinc base at elevated temperatures. Thus, the bis(methyl ester) **357** is zincated with **5** (0.6 equiv) at 90 °C within 2 h (microwave irradiation). A subsequent Negishi cross-coupling of the resulting diarylzinc reagent **358** with 4-iodo-1-chlorobenzene furnishes the polyfunctional biphenyl **359** in 79 % yield (Scheme 61).[223]

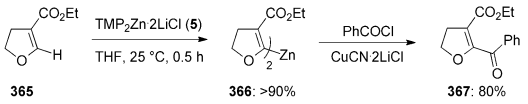
Combining the use of TMPMgCl·LiCl (**2**) with $TMP_2Zn{\cdot}2\,LiCl$ (**5**) allows a short synthesis of the acaricide tebufenpyrad (**360**).[155,224,225] Thus, magnesiation of *N*-methylpyrazole with **2** (25 °C, 1 h) followed by an acylation with NC-CO_2Et (−10 to 25 °C) generates the ethyl ester **361**. An electrophilic chlorination of **361** with NaOCl in acetic acid[224,225] gives the chloropyrazine **362** in 93 % yield. This heterocycle was zincated with **5** in THF (25 °C, 6 h) and treated with iodine. The intermediate 3-iodo-4-chloropyrazole underwent a smooth palladium-catalyzed cross-coupling with Et_3In (25 °C, 8 h),[226,227] which led to the desired pyrazole **363** in 69 % yield. Interestingly, replacing Et_3In by Et_2Zn led to extensive by-products arising from I/Zn exchange. Amidation by reaction of **363** with a benzylamine derivative **364** provides the acaricide **360** in 75 % yield (Scheme 62).

Interestingly, $TMP_2Zn{\cdot}2\,LiCl$ (**5**) also allows the zincation of non-aromatic cyclic structures such as dihydrofuran **365**.



Scheme 62. Synthesis of the acaricide tebufenpyrad (**360**) by using TMPMgCl·LiCl (**2**) and $TMP_2Zn{\cdot}2\,LiCl$ (**5**).

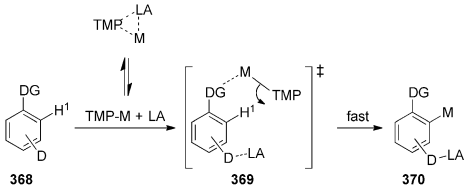
The reaction of **365** with **5** (0.6 equiv) at 25 °C for 30 min yields the unsaturated zinc reagent **366** in greater than 90 % yield. A subsequent copper(I)-mediated benzoylation then affords the ketoester **367** in 80 % yield (Scheme 63).[146]



Scheme 63. Zincation of dihydrofuran **365** with $TMP_2Zn{\cdot}2\,LiCl$ (**5**).

4.6. Lewis Acid Activated TMP Bases

The metalation rate of aromatic compounds depends on the thermodynamic acidity of the acidic hydrogen atom H^1 of the unsaturated substrate, as well as on the geometry of the metalation transition state, which results from a complexation of the base with the directing group (DG). Over the years, it has become clear that every metal Lewis base also possesses Lewis acidic properties (usually the metal center) which dictate the transition-state geometry. The presence of additional Lewis acids offers the opportunity for further electrophilic activation of substrate **368** and new possible architectures for transition states. In contrast to Brønsted acids, Lewis acids are compatible with Lewis bases that have sterical hindrance. The reversibility of Lewis acid/base pairs is a general phenomenon, which has numerous consequences on the structure and reactivity.[228] A rate acceleration of the metalation triggered by coordination of a Lewis acid (LA), as observed with several TMP bases, is depicted in Scheme 64.

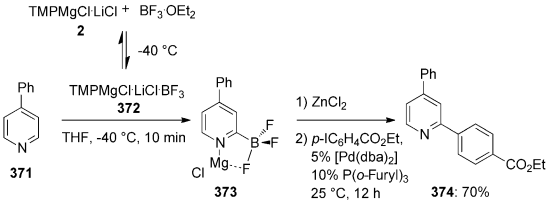


Scheme 64. Synergetic Lewis acid activation for metalation with TMP bases.

The large steric hindrance of the TMP unit facilitates the dissociation of the complexes formed between the Lewis acid (LA) and the TMP base (TMP-M). Substrate **368** is then electrophilically activated further by the Lewis acid (LA), which coordinates to the donor function (D), and also by the metal (M), which coordinates to the directing group (DG; see transition state **369**). These synergetic effects result in a fast metalation reaction that produces the metalated product **370** (Scheme 64).

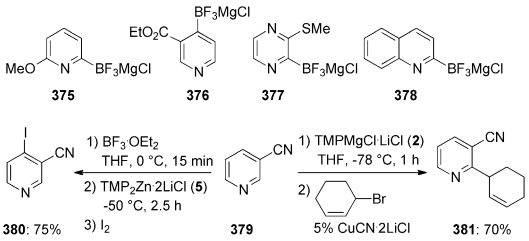
Thus, it was noticed that the preparation of $TMP_2Zn{\cdot}2\,LiCl$ (**5**) from TMPLi (**1**) and $ZnCl_2$, instead of TMPMgCl·LiCl (**2**) and $ZnCl_2$, results in a much reduced reactivity of base **5**.[215] This was due to the absence of $MgCl_2$, which has been shown in related reactions to be a powerful Lewis acid.[229] Recently, it was also found that the powerful Lewis acid BF_3 is compatible with various TMP bases such as

2,[230] **5**,[230] as well as TMP_4Zr.[231] The rate acceleration of metalation is especially effective for various N-heterocycles. Kessar et al. has shown that BF_3 in the presence of BuLi considerably facilitates the lithiation of pyridine.[232–235] Recently, it was found that the metalation of 4-phenylpyridine (**371**) is greatly accelerated with TMPMgCl·LiCl·BF_3 (**372**), which is readily prepared by mixing **2** with $BF_3{\cdot}OEt_2$ at −40 °C for 10 min. Instead of a magnesium reagent, which might be expected, a magnesium pyridyltrifluoroborate **373** was obtained, as proved by ^{13}C NMR spectroscopy.[230] The addition of $ZnCl_2$ (1 equiv) and a Pd catalyst allows a smooth cross-coupling (25 °C, 12 h) to be performed with ethyl 4-iodobenzoate to provide the 2-arylated pyridine **374** in 70 % yield (Scheme 65).[232]



Scheme 65. Metalation of 4-phenylpyridine (**371**) with TMPMgCl·LiCl·BF_3 (**372**).

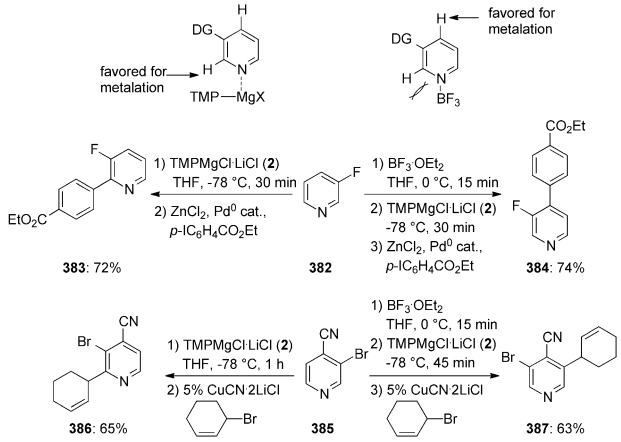
This procedure can be extended to the preparation of various magnesium *N*-heteroaryltrifluoroborates, such as **375**–**378** (Scheme 66).[230] These boron intermediates have



Scheme 66. Preparation of the (N-heteroaryl)trifuoroborates. Complementarity of metalation with and without $BF_3{\cdot}OEt_2$.

found numerous applications in organic synthesis.[236] As an alternative, the magnesium pyridyltrifluoroborates can also be prepared by the stepwise addition of $BF_3{\cdot}OEt_2$ and the TMP base. Thus, the reaction of 3-cyanopyridine (**379**) with $BF_3{\cdot}OEt_2$ at 0 °C (15 min) followed by $TMP_2Zn{\cdot}2\,LiCl$ (**5**) furnishes a 4-metalated pyridine, which after iodolysis gave the iodopyridine **380** in 75 % yield. Interestingly, treatment of **379** with TMPMgCl·LiCl (**2**) in the absence of $BF_3{\cdot}OEt_2$ at −78 °C for 1 h allows a complementary metalation at position 2 to be carried out to form, after a copper(I)-catalyzed allylation, the 2,3-disubstituted pyridine **381** in 70 % yield (Scheme 66).[230]

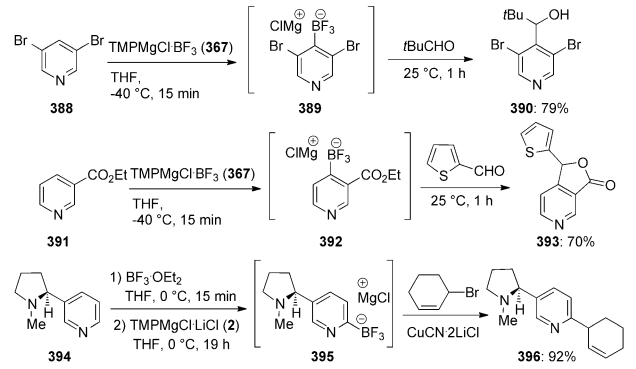
This behavior seems to be somewhat general. Several pyridines bearing a directing group (DG) in position 3 were regioselectively metalated in a complementary manner in the presence or absence of $BF_3{\cdot}OEt_2$. The coordination of BF_3 to the heterocyclic nitrogen atom disfavors the magnesiation at position 2 for steric reasons, and only a metalation at position 4 is observed. On the other hand, direct metalation with TMPMgCl·LiCl (**2**) furnishes only the 2-magnesiated pyridine (Scheme 67). Thus, treatment of 3-fluoropyridine



Scheme 67. Complementary regioselective metalation of pyridines with TMP bases in the presence or absence of $BF_3{\cdot}OEt_2$.

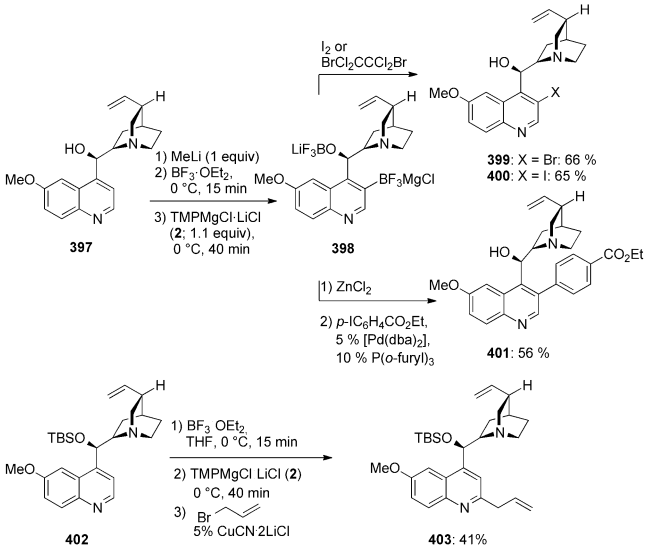
(**382**) with TMPMgCl·LiCl (**2**) leads to magnesiation at position 2. After a transmetalation with $ZnCl_2$, a palladium-catalyzed cross-coupling with ethyl 4-iodobenzoate provides the 2,3-disubstituted pyridine **383** in 72 % yield. Alternatively, complexation with $BF_3{\cdot}OEt_2$ (0 °C, 15 min) followed by metalation with **2** provides the 4-magnesiated intermediate, which in the presence of $ZnCl_2$ undergoes a smooth Negishi cross-coupling to give the 3,4-disubstituted pyridine **384** in 74 % yield. Similarly, the 3,4-disubstituted pyridine **385** undergoes regioselective metalations and allylations with 3-bromocyclohexene either at position 2 using **2** (−78 °C, 1 h), which leads to the trisubstituted pyridine **386** in 65 % yield, or in position 5 using TMPZnCl·LiCl (**4**) in the presence of $BF_3{\cdot}OEt_2$ (−78 °C, 45 min), which leads after allylation to the pyridine **387** in 63 % yield (Scheme 67).[230]

Interestingly, the use of BF_3-modified TMP bases allows the addition reactions to be performed in several cases without the use of a Rh catalyst.[237,238] Thus, 3,5-dibromopyridine (**388**) is magnesiated in position 4 with TMPMgCl·BF_3[230] (−40 °C, 15 min) to afford the organoborate **389**. Addition of pivaldehyde gives the desired alcohol **390** in 79 % yield.[238] Similarly, the reaction of ethyl nicotinate (**391**) with TMPMgCl·BF_3[230] (−40 °C, 15 min) leads to the trifluoroborate **392**. A subsequent addition of thiophene-2-carbaldehyde yields the lactone **393** in 70 % yield (Scheme 68).[238] Pyridines bearing nitrogen substituents are similarly functionalized. Thus, the reaction of (*S*)-nicotine (**394**) with $BF_3{\cdot}OEt_2$ followed by the addition of TMPMgCl·LiCl (**2**) at 0 °C provides the 6-metalated nicotine **395** selectively after 19 h.[239,240] A subsequent copper(I)-catalyzed allylation with 3-bromocyclohexene furnishes the desired adduct **396** in 92 % yield (Scheme 68).[238]



Scheme 68. Regioselective BF_3-mediated metalation of pyridine derivatives.

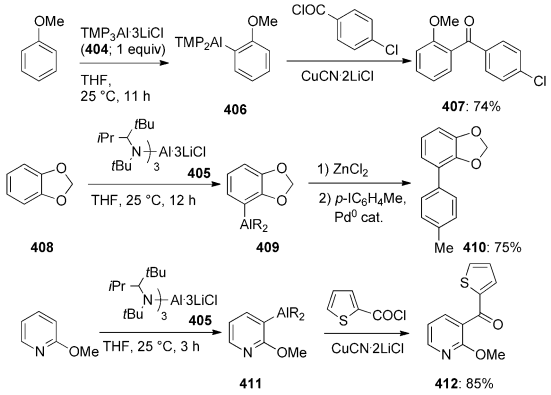
Interestingly, more complex molecules such as quinine **397**[241] can be regioselectively metalated with a BF_3/TMPMgCl·LiCl combination. Thus, treatment of **397** with MeLi followed by $BF_3{\cdot}OEt_2$ (2 equiv) and TMPMgCl·LiCl (**2**) at 0 °C for 40 min produces the intermediate **398**, which can be either iodolyzed or brominated with $Br_2Cl_4C_2$ to afford the 3-substituted quinines **399** and **400** in 65 % yield.[238] Alternatively, the reaction of **398** with $ZnCl_2$ followed by a Negishi cross-coupling reaction provides the 3-arylated quinine **401** in 56 % yield.[238] A functionalization in position 2 can be achieved using the TBS-protected quinine **402**. Treatment of **402** with $BF_3{\cdot}OEt_2$ followed by **2** at 0 °C for 15 h furnishes, after a copper(I)-catalyzed allylation, the 2-substituted quinine **403** in 41 % yield (Scheme 69).[238]



Scheme 69. Functionalization of quinine derivatives in position 2 or 3 with $BF_3{\cdot}OEt_2$/TMPMgCl·LiCl (**2**).

4.7. Other TMP-Metal Amide Bases

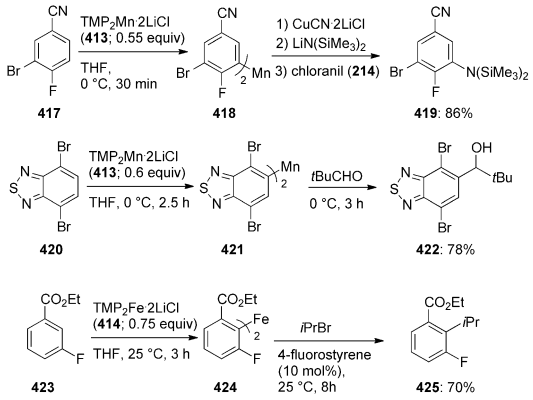
Although TMP-derived magnesium and zinc bases have found the most applications by far, it is possible to prepare a range of other useful TMP bases from TMPLi (**1**) and TMPMgCl·LiCl (**2**). Thus, the metalation of electron-rich aromatic compounds or heterocycles with **2** is usually sluggish. However, such substrates are readily aluminated at 25 °C with $TMP_3Al{\cdot}3\,LiCl$ (**404**) or the related base [*t*Bu(*i*Pr)CH-(*t*Bu)N]$_3$Al·3 LiCl (**405**).[124,242] Thus, anisole reacts with $TMP_3Al{\cdot}3\,LiCl$ (**404**) at 25 °C within 11 h to produce the corresponding aluminum reagent **406**. A subsequent copper(I)-mediated acylation then produces benzophenone **407** in 74 % yield.[242] Cyclic ethers behave in a similar way and the benzo[1,3]dioxole (**408**) is readily aluminated with **405** to provide the intermediate aluminum reagent **409**, which after a transmetalation with $ZnCl_2$ and a Pd^0-catalyzed arylation gives the expected biphenyl derivative **410** (Scheme 70).[243]



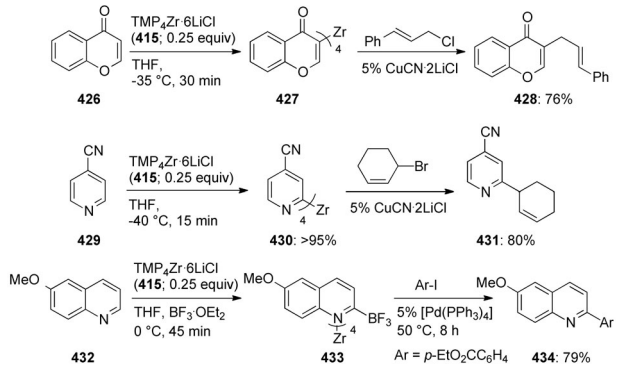
Scheme 70. Regioselective alumination with $TMP_3Al{\cdot}3\,LiCl$ (**404**) and the related base [*t*Bu(*i*Pr)CH(*t*Bu)N]$_3$Al·3 LiCl (**405**).

Interestingly, TMP-aluminum bases such as $TMP_3Al{\cdot}3\,LiCl$ (**404**) and [*t*Bu(*i*Pr)CH(*t*Bu)N]$_3$Al·3 LiCl (**405**) slowly decompose in THF at 25 °C. No decomposition occurs at 25 °C in the presence of an oxygen-containing substrate, and smooth metalations are observed. Electron-rich pyridines such as 2-methoxypyridine are readily aluminated in position 3 to give **411**, which after a copper(I)-mediated acylation affords the 2,3-disubstituted pyridine **412** in 85 % yield (Scheme 70).[242]

A range of transition-metal TMP bases have also been prepared. Especially interesting are the bases $TMP_2Mn{\cdot}2\,LiCl$ (**413**),[244] $TMP_2Fe{\cdot}4\,LiCl$ (**414**),[245] $TMP_4Zr{\cdot}6\,LiCl$ (**415**),[231] and $TMP_3La{\cdot}5\,LiCl$ (**416**).[246] All these bases are prepared in high yield by transmetalation with TMPMgCl·LiCl (**2**) and can readily be used for large-scale metalations.[194] The base **413** provides a unique pathway to functionalized arylmanganese derivatives. Thus, the benzonitrile **417** reacts with **413** (0.55 equiv, 0 °C, 30 min) to generate the 5-manganated reagent **418**. Transformation of the corresponding amido cuprate by reaction with CuCN·2 LiCl, LiHMDS and a subsequent oxidation with chloranil (**201**; −50 °C, 30 min) provides the aniline derivative **419** in 86 % yield (Scheme 71).[244] Remarkably, some sensitive heterocycles such as 3,6-dibromobenzothiadiazole (**420**) are readily manganated with $TMP_2Mn{\cdot}2\,LiCl$ (**413**) to provide the manganese derivative **421**, which after addition of pivaldehyde furnishes



Scheme 71. Manganation and ferration with $TMP_2Mn{\cdot}2\,LiCl$ (**413**) and $TMP_2Fe{\cdot}4\,LiCl$ (**414**).

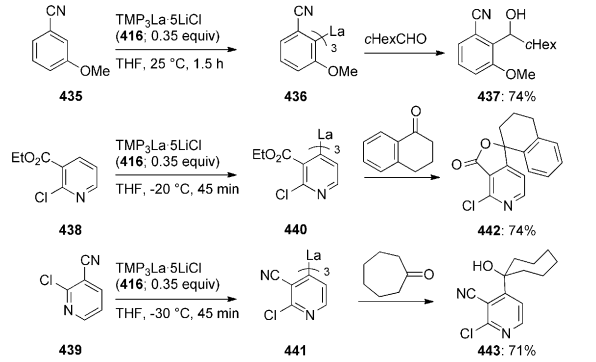


Scheme 72. Regioselective metalation with $TMP_4Zr{\cdot}6\,LiCl$ (**415**).

the alcohol **422** in 78% yield (Scheme 71).[244] The use of $TMP_2Fe{\cdot}4\,LiCl$ (**414**) provides a new entry to diaryliron(II) reagents which are stable enough to undergo nickel-catalyzed cross-coupling reactions with primary or secondary alkyl bromides or iodides. Thus, the benzoate **423** is readily converted (25 °C, 2 h) into the corresponding diaryliron derivative **424**, which in the presence of 10% 4-fluorostyrene undergoes at 25 °C a smooth cross-coupling with *i*PrBr within 8 h to afford the benzoate **425** in 70% yield (Scheme 71).[245]

$TMP_4Zr{\cdot}6\,LiCl$ (**415**) represents an economical metal base, since only 0.25 equivalent of Zr is required for a zirconation; all four TMP moieties are active in the metalation reaction. Thus, treatment of chromone **426** with **415** (0.25 equiv, −35 °C, 30 min) provides the zirconium species **427**, which after an allylation with cinnamyl chloride in the presence of 5% $CuCN{\cdot}2\,LiCl$ furnishes the allylated chromone derivatives **428** in 76% yield. 4-Cyanopyridine (**429**) is zirconated at position 2 with **415** (0.25 equiv, −40 °C, 15 min) to give the tetrapyridylzirconium **430** in greater than 95% yield. A copper-catalyzed allylation of **430** leads to the 2,4-disubstituted pyridine **431** in 80% yield. Remarkably, the zirconium base **415** is also compatible with $BF_3{\cdot}OEt_2$. Thus, the reaction of quinoline **432** with $BF_3{\cdot}OEt_2$ and **415** at 0 °C for 45 min leads to complete metalation, thereby affording the quinolyl trifluoroborate **433**. A subsequent palladium-catalyzed cross-coupling with ethyl 4-iodobenzoate at 50 °C for 8 h using 5% $[Pd(PPh_3)_4]$ as catalyst that gives the 2-arylated quinoline **434** in 79% yield (Scheme 72).[231]

Finally, the lanthanation of various aromatic compounds and heterocycles can be readily achieved with $TMP_3La{\cdot}5\,LiCl$ (**416**). All three TMP groups of this base are also available to perform the deprotonations. The reaction of the resulting unsaturated lanthanide reagents with aldehydes, ketones, as well as the direct palladium-catalyzed cross-coupling aryl iodides are especially attractive.[194,246] Thus, the reaction of the benzonitrile **435** with **416** (0.35 equiv 25 °C, 1.5 h) furnishes the lanthanum reagent **436**, which reacts smoothly with cyclohexanecarboxaldehyde to give the corresponding alcohol **437** in 74% yield. Pyridine derivatives such as **438** or **439** are metalated between −30 and −20 °C within 45 min to afford the expected lanthanide reagents **440** and **441**. Their reaction with ketones such as α-tetralone and cycloheptanone furnishes the addition products **442** and **443** in 71 and 74% yield, respectively (Scheme 73).[194,246]



Scheme 73. Lanthanation of aromatic compounds and heterocycles with $TMP_3La{\cdot}5\,LiCl$ (**416**).

5. Conclusion

The described LiCl-solubilized TMP bases considerably expand the scope of the metalation or C–H activation of unsaturated substrates. The reactions proceed under mild conditions and the resulting organometallic reagents are readily functionalized with various electrophiles in the presence of the appropriate Pd or Cu catalysts. The high kinetic basicity of the TMP bases, their high functional-group tolerance, and the practical metalation conditions are especially remarkable. Many metalations can be performed between −10 °C and 20 °C and are complete within a few hours. These bases also offer direct access to new (hetero)-aromatic transition-metal derivatives, which are valuable intermediates, not only for synthetic applications, but also for mechanistic investigations.

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