Regioselective C–H Activation of Substituted Pyridines and other Azines using Mg- and Zn-TMP-Bases

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Abstract The metalation of substituted pyridines, diazines and related N-heterocycles using TMPMgCl·LiCl, TMP2Mg·2LiCl, TMPZnCl·LiCl or TMP2Zn·2LiCl·2MgCl2 (TMP = 2,2,6,6-tetramethylpiperidyl) in the presence or absence of a Lewis acid is reviewed.

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Key words azines, metalation, N-heterocycles, pyridine, TMP bases

1 Introduction

The regioselective functionalization of azines, especially pyridines, is an important synthetic challenge because of the importance of these N-heterocycles as pharmaceuticals and agrochemicals.1 The use of lithium bases for achieving regioselective lithiations has been pioneered by Snieckus,2 Schlosser,3 Quégine4 and Mongin4b–j,5 as well as Gros.6 These powerful bases produce lithiated N-heterocycles, which are often only stable at low temperature, although the performance of such metatalizations in continuous flow may avoid such low temperatures.7 Furthermore, the use of lithium magnesiate or zincate bases pioneered by Mulvey,8 Mongin,8b,9 Uchiyama8b,9a,10 Kondo8b,10a–c,11 has considerably broadened the scope of metalations for the functionalizations of pyridines and other azines. Recently, it became clear that highly reactive magnesium and zinc bases can be obtained by mixing sterically hindered magnesium and zinc bases (derived mostly from 2,2,6,6-tetramethylpiperidyl (TMP-H)) with LiCl.12 The resulting, highly THF-soluble bases13 are mostly monomeric and kinetically highly active for the magnesiation and zincation of various functionalized pyridines or sensitive azines.13 Furthermore, in such metalations, only magnesiated or zinicated heterocycles are produced, which are compatible with a range of functional groups at moderate to low temperatures. In the case of the zincation of azines, either ambient or elevated temperature (up to 120 °C)14 can be used, offering considerable potential for industrial applications. Since the metalation of azines using magnesiate or zinicate bases has already been reported extensively,8–11 this review will focus on recent advances describing the most practical and regioselective C–H activations15 of functionalized pyridines and other azines, using mostly zinc and magnesium TMP-bases.16

2 Magnesiation of Pyridines and Related Azines

2.1 Magnesiations using TMPMgCl·LiCl (1)

Usually, magnesium amides of type R2NMgX or (R2N)2Mg are aggregated and relatively slow deprotonation reagents, partially because of their moderate solubility.17 Mulzer pioneered the use of TMPMgCl for the magnesiation of an azine.18 A base with higher activity and higher solubility in THF was obtained by using TMPMgCl with LiCl (1 equiv). Thus, mixing of TMP-H with i-PrMgCl·LiCl in THF (25 °C, 24 h) provides a ca. 1.4 M soluble base TMPMgCl·LiCl (1).12,13
This base magnesiates a range of functionalized pyridines and quinolines under mild conditions. Since magnesium reagents are produced, there is no need for low temperatures as it is often the case with corresponding lithiations.\textsuperscript{19,20} Thus, the magnesiation of 2-bromoquinoline 2 with TMPMgCl-LiCl (1) at \(-20\,^\circ\text{C}\) for 2 h provides the ortho-magnesiated product 3 (Scheme 1). After bromolysis, the dibromoquinoline 4 is obtained in 65\% yield.\textsuperscript{21} Pyridines bearing less sensitive functional groups, such as 3,5-dibromopyridine (5) or 2,6-dichloropyridine (6), are magnesiated at convenient temperatures (\(-25\,^\circ\text{C}\) or 25\,^\circ\text{C}\), regioselectively providing the pyridylmagnesium derivatives 7 and 8.

Quenching with various electrophiles, such as N,N-dimethylformamide (DMF) or 4-methoxybenzaldehyde, affords the polyfunctional pyridines 9 and 10 in 85–92\% yield (Scheme 1).\textsuperscript{12}

The last reaction can be readily scaled up to a 100 mmol-scale with no yield loss.\textsuperscript{22} Aminopyridines are converted into the corresponding trifluoroacetamides such as 11. Deprotonation of the amide function with MeMgCl and ring-magnesiation with TMPMgCl-LiCl (1) furnishes the Grignard reagent 12, which, after a transmetalation with ZnCl\textsubscript{2} and Negishi cross-coupling,\textsuperscript{23,24} affords the 4-arylated pyridine 13 in 80\% yield (Scheme 2).\textsuperscript{25} The trifluoroacetamido group of 11 is an excellent directing group. Similarly, a sulfoxide function directs a magnesiation in the ortho-position with high efficiency. Thus, pyridine 14, bearing a sulfoxide function at position C4, is magnesiated at \(-30\,^\circ\text{C}\) with TMPMgCl-LiCl (1) within 20 min (Scheme 3). Addition of ZnCl\textsubscript{2} and Negishi cross-coupling with \(p\)-iodoanisole catalyzed by 5\% Pd(PPh\textsubscript{3})\textsubscript{4} (50\,^\circ\text{C}, 2 h) furnishes the tetra-substituted pyridine 15 in 68\% yield. The sulfoxide group can then be converted into a new magnesium reagent through sulfoxide–magnesium exchange\textsuperscript{26} in 2-methyl-THF\textsuperscript{27} triggered by \(i\)-PrMgCl-LiCl (\(-50\,^\circ\text{C}, 5\,\text{min}\)). Transmetalation with ZnCl\textsubscript{2} followed by a Negishi cross-coupling

\begin{center}
\textbf{Scheme 1} Regioselective magnesiation of halogenoazines using TMP-MgCl-LiCl (1)
\end{center}

\begin{center}
\begin{align*}
\text{N} & \text{Br} \quad \text{1, THF} \quad \text{–20 °C, 2 h} \\
\text{N} & \text{Br} \quad \text{MgCl} \quad \text{BrCCl}_2 \quad \text{N} & \text{Br} \\
\text{Br} & \quad \text{Br} \quad \text{N} & \text{Br} \\
\text{Br} & \quad \text{Br} \quad \text{N} & \text{Br} \quad \text{CHO} \\
\text{CHO} & \quad \text{OMe}
\end{align*}
\end{center}

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with ethyl 5-bromonicotinate (16), catalyzed by 2% Pd(PPh3)4 (50 °C, 5 h), leads to the complex bis-pyridine 17 in 82% yield (Scheme 3).28

Likewise, sulfonamides are excellent directing groups2c–d,29 and can undergo amination reactions when treated with an excess of a magnesium amide. Thus, sulfonamides 18 and 19 are magnesiated with TMPMgCl·LiCl (1; THF, 0 °C, 2 h). After iodolysis and amination at 25 °C (2 h) with piperidyl-magnesium chloride, aminoquinolines 20 and 21 are obtained in 52–59% yield over two steps (Scheme 4).30

TMPMgCl·LiCl (1) also proves to be an excellent base for the C–H activation of 3-methoxypyridine (22). Thus, treatment of 22 with 10% FeCl3 and 25% diamine (23) and an excess of TMPMgCl·LiCl (1) at 25 °C for 2 h allows facile alkylation with various alkyl bromides such as 5-bromopentene (24), providing the alkylated product 25 in 85% yield (Scheme 5).31

The N,N,N′,N′-tetramethylphosphordiamidate group (OP(O)(NMe2)2) was found to be a more powerful directing group than the methoxy group,32 which allows efficient magnesiations with TMPMgCl·LiCl (1). Thus, the 4-substituted pyridine 26 is magnesiated with I1 (1.5 equiv, 0 °C, 1 h) and subsequently thiolated by reaction with MeSSO2Me, affording the disubstituted pyridine 27 in 88% yield.

Similarly, quinoline 28 was magnesiated with TMPMgCl·LiCl (1) at 0 °C within 1 h and acylated in the presence of a copper(I)-catalyst (CuCN·2LiCl), furnishing the ketone 29 in 62% yield (Scheme 6).33 This method has been used to prepare the pyridine based COX-2 inhibitor etoricoxib 3034 starting from the phosphordiamidate substituted pyridine 31. Thus, the magnesiation of 31 with TMPMgCl·LiCl (1) in THF at 0 °C for 1 h, followed by a transmetalation with ZnCl2 and Negishi cross-coupling with aryl bromide 32 using 1%
Pd$_2$(dba)$_3$ (dba = dibenzylideneacetone) and 2% RuPhos provides the arylated pyridine 33 in 88% yield. Standard transformations and Stille cross-coupling provides the desired pharmaceutical 30 (Scheme 7).

### 2.2 Magnesiations using TMP$_2$Mg·2LiCl (34) and Related Bases

Although TMPMgCl-LiCl (1) is a very powerful magnesiation reagent, in the case of substrates bearing weakly acidic or sterically hindered protons, the magnesiation is advantageously performed using TMP$_2$Mg·2LiCl (34). Often, the presence of sensitive functional groups, such as a carbethoxy group, requires low magnesiation temperatures, since higher temperatures lead to considerable side reactions. TMP$_2$Mg·2LiCl (34), which is prepared in quantitative yield by treating TMPLi with 1, can be stored at 25 °C for several hours. A degradation after several days is however observed. This base readily magnesiates 4-carbethoxypyridine (35) at −40 °C for 12 h, leading to 36, furnishing, after iodolysis, the iodopyridine 37 in 66% yield (Scheme 8). The phosphordiamidate substituted quinoline 38 was magnesiated with 34, yielding the magnesium reagent 39 (−50 °C, 1 h). After transmetalation with ZnCl$_2$ and Negishi cross-coupling using PhI, 5% Pd(dba)$_2$ and 10% P(o-furyl)$_3$ as catalyst, the arylated quinoline 40 is obtained in 81% yield. Interestingly, the quinoline 40 can now be magnesiated with TMPMgCl-LiCl (1) at 25 °C within 1 h. The presence of the phenyl group at position 2 avoids nucleophilic additions to the quinoline ring and allows higher metalation temperatures (25 °C instead of −50 °C). Quenching with NC-CO$_2$Et produces the 2,3,4-trisubstituted quinoline 41, which is further converted into Talnetant (42), an NK$_3$ receptor antagonist, in 86% yield (Scheme 8).

An alternative base with enhanced thermal stability derived from t-butyl-isopropylamine (tBu(iPr)NH, 43) was obtained by treating TMPLi with 43 with n-BuLi, giving 44, followed by the addition of tBu(iPr)NMgCl-LiCl (45), affording the
magnesium bis-amide 46 in >90% yield (Scheme 9). The metatalation of 4-tert-butoxycarbonylpyridine (47) with 46 provides the expected pyridine 48 in 68% yield (Scheme 9).

2.3 BF₃·OEt₂-Promoted Metalations of Pyridines

A typical mono-substituted pyridine, 3-fluoropyridine (49), can be metalated in two complementary positions (position C2 or position C4) with TMPMgCl·LiCl (1), either in the absence or in the presence of the strong Lewis acid BF₃·OEt₂ (Scheme 10). Preliminary experiments showed that BF₃·OEt₂ does not react in an irreversible manner with TMPMgCl·LiCl (1) at temperatures below –30 °C. Also, the 3-fluoro substituent considerably acidifies the adjacent positions C2 and C4 of 49. The position of the metatalation is determined by the nature of the complexation with the TMP-base. Thus, by adding TMPMgCl·LiCl (1) to 49, a complexation of 1 to the heterocyclic N-atom takes place, leading to a complex of type 50, which favors metatalation at position C2. On the other hand, in the presence of BF₃·OEt₂, this strong Lewis acid forms a complex with the N-atom of the pyridine ring and the base I may, if at all, only complex the fluorine substituent.

This favors a metatalation at position C4 (see 51). Thus, the presence or absence of BF₃·OEt₂ allows the arylation of 3-fluoropyridine (49) either in position C2 or C4, leading to the expected products 52 and 53 (Scheme 10). The exact nature of the organometallic species obtained after the metatalation of 49 in the presence of BF₃·OEt₂ has been examined by 13C NMR spectroscopy. This regioselectivity switch is observed for a range of pyridines. An unexpected regioselectivity is observed in the case of 2-phenylpyridine (54). Thus, the treatment of 54 with TMPMgCl·LiCl (1) at 55 °C provides the magnesiated pyridine 55. After iodolysis, pyridine 56 is obtained in 85% yield. Alternatively, the treatment of 54 with BF₃·OEt₂, followed by TMPMgCl·LiCl (1), furnishes, after iodolysis, the 2,6-disubstituted pyridine 57 in 83% yield (Scheme 11).

This methodology also allows the functionalization of 4-dimethylaminopyridine (58) in position 2. In this case, the coordination with BF₃·OEt₂ greatly acidifies all the heterocyclic hydrogen atoms, especially those in position C2. Thus, treatment of 58 with BF₃·OEt₂ in THF, followed by TMPMgCl·LiCl (1) at 0 °C for 1 h, furnishes the magnesium derivative 59 or, after metallotropy, the trifluoroborate derivative 60. After a copper(I)-catalyzed acylation, the 2-ketopyridine 61 is obtained in 68% yield. Similarly, 2-chloro-4-dimethylaminopyridine (62) is allylated via the organometallic intermediate 63, furnishing the trisubstituted pyridine 64 in 78% yield (Scheme 12).
Furthermore a regioselective functionalization of (S)-nicotine (65) via the organometallic intermediate 66, leading to 6-functionalized nicotine derivatives, such as 67, is feasible. Similarly, the metalation of quinine (68) can be tuned depending on the reaction conditions used. Thus, the formation of the lithium alcoholate of quinine followed by the addition of BF$_3$·OEt$_2$ (2 equiv) is tentatively thought to provide intermediate 69, which leads to a complexation of 1 at the basic tertiary nitrogen atom and therefore leads to the 3-iodinated quinoline 70 in 65% yield (Scheme 13).

By tuning the protecting groups attached to quinine (68), a switch of the metalation is observed. Thus, the conversion of 68 into the TBDMS-silyl enol ether 71 followed by addition of BF$_3$·OEt$_2$ (1 equiv) now leads to the BF$_3$-adduct 72, which can be metalated with TMPMgCl·LiCl (1) exclusively at the position C2, providing, after iodolysis, the 2-iodoquine derivative 73 in 44% yield (Scheme 14).

The regioselectivity of the metalation of pyridines and quinolines is the result of steric and electronic factors, often leading to kinetically controlled products. Thus, the bis-trimethylsilylmethyl group, which is readily attached to the pyridine scaffold, directs the metalation by steric effects. Therefore, the 3-substituted pyridine 74 was activated with BF$_3$·OEt$_2$ (0 °C, 15 min) and magnesiated with TMP$_2$Mg·2LiCl (34), since the magnesiation with 1 proved to be ineffective. The BF$_3$-adduct 75 is exclusively metalated at position C6, providing, after a Negishi cross-coupling with an iodopyrimidine, the bisazine 76 in 65% yield (Scheme 15). Interestingly, 6-bromo-3-bis(trimethylsilylmethyl)pyridine (77) can be directly metalated by TMP$_2$Mg·2LiCl (34) at 0 °C for 25 h, affording the magnesium derivative 78. Due to the steric hindrance of the silyl-substituent at position C3, no magnesiation occurs at position C2, and only a magnesiation is observed at position C5. Subsequent acylation with an acid chloride, after transmetalation to copper(I) with CuCN·2LiCl, provides ketone 79 in 60% yield (Scheme 15).
3 Zincation of Pyridines and Related Azines using TMPZnCl-LiCl and TMP₂Zn-2LiCl-2MgCl₂

The availability of kinetically active zinc amides further extends the scope of directed metalations of functionalized azines. Two complementary zinc bases TMPZnCl-LiCl (80) and TMP₂Zn-2LiCl-2MgCl₂ (81) are obtained from TMPLi and ZnCl₂ or TMPMgCl-LiCl (1) and ZnCl₂ (Scheme 16).11,44,45 Since the carbon–zinc bond is much more covalent than the carbon–magnesium bond, electrophilic functional groups are much better tolerated in such zinc organometallics and the directed zincation of various functionalized pyridines such as 82 and 83 is readily achieved.14 As the carbon–zinc bond in heteroarylzinc reagents is stable up to 100 °C, directed zincations of pyridines 82–83 have been performed under microwave irradiation under elevated temperatures (60–80 °C), providing the corresponding dipyridylzinc reagents 84–85 in high yields. After quenching with electrophiles such as allylic bromides or acyl chlorides in the presence of a copper(I) catalyst, the expected products 86–87 are obtained in 68–80% yield (Scheme 16).14

Furthermore, pyridylzinc organometallics do not undergo electron-transfer reactions. Therefore, the electron-deficient nitro group is well tolerated in the zincation of nitro-substituted pyridines such as 88. In this case, the zincation proceeds at –40 °C within 1.5 h, leading to the bis-pyridylzinc 89. After a copper-catalyzed allylation with 3-bromocyclohexene, the trisubstituted pyridine 90 is obtained in 80% yield (Scheme 17).44 Alternatively, the milder zinc base TMPZnCl-LiCl (80) can be used to zincate 88 at 25 °C within 5 h and does not require low temperature metalations45,46 leading to the acylated pyridine 91 in 77% yield on 50 mmol scale (Scheme 17).46

Highly oxidized pyridines, such as pyridine N-oxides, are smoothly zincated with TMPZnCl-LiCl (80) at 25 °C and such functionalizations of pyridines are possible in large scale (20 mmol) in high yields.
Thus, a room-temperature zinication of pyridine N-oxide 92 with TMPZnCl-LiCl (80), and subsequent cross-coupling with the heteroaryl bromide 93, provides the desired cross-coupling product 94 in 95% yield. Remarkably, this reaction has been extended to diazine N-oxides such as pyridazine N-oxide 95, providing, after cross-coupling with the heterocyclic bromide 96, the complex heterocycle 97 in 66% yield (Scheme 18).

The use of TMPZnCl-LiCl (80) is compatible with electrophilic aminations as shown by Wang. Thus, TMPZnCl-LiCl (80) regioselectively zincates 3-fluoropyridine (49) at 25 °C. Addition of a Cu(II)-catalyst (5 mol% Cu(OAc)2) at 50 °C for 18 h in the presence of the electrophilic amination reagent, a benzoyloxypiperazine derivative (98), provides the amination product 99 in 53% yield at a 60 mmol scale. A related cobalt(II)-catalyzed amination can be performed under milder conditions using CoCl2·2LiCl as catalyst (2.5%). In this case, the amination proceeds at 25 °C. Thus, pyridylzinc pivalate 100 and 101, obtained by the magnesiation of the corresponding azine and diazine 102 and 103 with TMPMgCl-LiCl (1) followed by the addition of Zn(OPiv)2, are treated with N-hydroxymorpholine benzoate in THF at 25 °C for 2 h, furnishing the aminated derivatives 104 and 105 in 91–95% yield (Scheme 19).

The performance of lateral zincations of pyridines has been achieved by using TMP2Zn·2LiCl·2MgCl2 (81). Thus, the treatment of the cyanohydrine derivative 106 with TMP2Zn·2LiCl·2MgCl2 (81) at 0 °C for 1 h provides the benzylic pyridylzinc derivative 107.

This zinc reagent can be acylated with cyclopropanecarbonyl chloride in the presence of 20% CuCN·2LiCl, affording, after tetrabutylammonium fluoride (TBAF) treatment, ketone 108 in 80% yield (Scheme 20).

The scope of azine zinckations has been extended by performing a Barbier type zinckation in which the metatalation is performed with TMPLi in the presence of ZnCl2·2LiCl at low temperature. Thus, to a mixture of ZnCl2·2LiCl and the substrate pyridine 109, a THF solution of TMPLi (ca. 1.5 equiv) is added at –78 °C. Under these conditions, the directed lithiation of 109 is fast, producing the ortho-lithiated pyridine 110, which is a highly reactive intermediate, that is transmetalated in situ with the soluble ZnCl2·2LiCl, providing the stable pyridylzinc reagent 111. Quenching with an electrophile (E-X) under appropriate reaction conditions furnishes then the functionalized pyridine 112 (Scheme 21).
That such a Barbier reaction proceeds properly relies on the slow transmetalation between TMPLi and ZnCl$_2$·2LiCl at −78 °C. On the other hand, the directed lithiation and transmetalation steps are required to be fast. This reaction setup has a good reaction scope and the functionalized pyridines 113–115 are smoothly metalated under these in situ trapping conditions, using either ZnCl$_2$·2LiCl or MgCl$_2$·2LiCl as trapping salts, providing the zincated pyridine derivatives 116–118. After quenching with various electrophiles (aldehydes or aryl halides in the presence of a Pd-catalyst) the polyfunctionalized pyridines 119–121 are obtained in 79–94% yield (Scheme 22).

By using this procedure, a range of pyridines such as 122–123 are readily functionalized via the intermediate organometallics 124–125 leading to the expected products 126–127 in 80–98% yield (Scheme 24).

In some cases, this procedure may be performed by replacing TMPLi with the 100 times cheaper lithium bis-cyclohexylamide (Cy$_2$NLi). For example, the ethyl nicotinate 115 was metalated with Cy$_2$NLi (1.5 equiv) at 0 °C within 40 s and further allylated under copper(I)-catalysis in batch, leading to the pyridine 128 in 88% yield (Scheme 25).
The combined use of TMP-zinc and magnesium bases (TMPMgCl-LiCl (1), TMPZnCl-LiCl (80) and TMP2Zn-2LiCl-2MgCl2 (81)) in several cases allows a full functionalization of the pyridine scaffold. Thus, the treatment of 5-bromo-2-chloropyridine (129) with TMPMgCl-LiCl (1) in THF (–40 °C, 3 h), followed by the addition of tosyl cyanide furnishes the regioselective product 130 in 68% yield.42 Remarkably, the pyridine 130 is magnesiated at low temperature with TMPMgCl-LiCl (1), affording the 4-magnesiated pyridine 131. The regioselectivity of this magnesiation may be explained by a preferential complexation of TMPMgCl-LiCl (1) to the bromo-substituent, triggering a metalation in position C4. Quenching with MeSO2SMe provides thioether bromo-substituent, triggering a metalation in position C4.

4 Metalation of Pyridines using other TMP-Bases

It should be mentioned that related TMP-amide base derivatives from manganese, aluminum, and lanthanum have been reported. Thus, 2-chloro-5-fluoropyridine 135 can be treated with TMP2Mn-4LiCl2 (THF, 0 °C, 4 h), leading to the bis-pyridylmanganese species 136. After the addition of chloranil (1 equiv) at –40 °C for 0.5 h, the bis-pyridine 137 is obtained in 64% yield.55c The reaction of the 3-cyano-pyridine 113 with TMP2Mn-4LiCl 2 (THF, 0 °C, 0.5 h) affords an intermediate manganese-species 138, which, after transmetalation with CuCl2-LiCl, followed by the addition of Li[N(SiMe3)2], leads to 139 and oxidative amination with chloranil gives the 4-aminopyridine 140 in 75% yield (Scheme 27).55a

Aluminum-TMP amides have proven to be especially useful for the metalation of electron-rich pyridines. Thus, the treatment of TMPLi with AlCl3 provides the corresponding TMP2Al-3LiCl base (141) as a 0.3 M solution in THF. This base readily aluminates the 2-methoxypyridine 142 leading to the tris-arylaluminum 143, which provides, after transmetalation to zinc and to copper, and acylation, the expected ketone 144 in 90% yield (Scheme 28).56

The treatment of TMPMgCl-LiCl with LaCl3·2LiCl58,59 and its addition to a functionalized pyridine such as 115 leads to an organometallic intermediate best represented as 145. From recent results,59 the reagent 145 may be better represented as a magnesium reagent complexed with LaCl3, rather than a true aryllanthanum species.59 However, the reaction of 145 with the sterically hindered ketone 146 leads to the expected addition product 147 in 74% yield (Scheme 29).57
5 Magnesiation and Zincation of Diazines

Whereas the metalation of pyridines and quinolones is relatively well explored, the metalation of diazines such as pyrimidine (148), pyrazine (149), and pyridazine (150) is much less studied, and the functionalization of these N-heterocycles remains a challenge, as the predictability of the appropriate base for their metalation is still difficult (Figure 1).

Nevertheless, the TMP-based TMPMgCl·LiCl (1), TMPMg·2LiCl (34), TMPZnCl·LiCl (80) and TMPZn·2LiCl·2MgCl₂ (81) have proven to be a set of very useful metalation reagents, especially well-suited for the functionalization of diazines and annulated analogues. These bases also constitute an automated strong base screening platform, as recently shown by Boga and Christensen.⁶⁰ Some recent applications are shown below, as well as guidelines for rationalizing the metalations of various diazines. Whereas pyrimidine itself has a high propensity to add magnesium nucleophiles, substituted pyrimidines are better substrates for metalations. Thus, 2-bromopyrimidine (151) undergoes a smooth magnesiation with TMPMgCl·LiCl (1) at –55 °C within 1.5 h and produces the 4-magnesiated pyrimidine 152 in >90% yield. After thiolation of 152 with MeSO₂SMe, the corresponding thioether 153 is obtained in 81% yield.⁶¹,⁶² The methylthio substituent has a highly stabilizing effect and considerably stabilizes the pyrimidine towards unwanted nucleophilic additions. Thus, further magnesiation of 153 may now be performed at room temperature and the metalation is complete within 5 min, producing the magnesiated pyrimidine 154, which, after chlorination, provides the trisubstituted pyrimidine 155 in 76% yield. The last position of the ring is magnesiated under similar conditions furnishing, after copper(I)-mediated benzoylation, the ketone 156 in 81% yield (Scheme 30).⁶³

This methodology has been applied to the functionalization of 2-chloropyrimidine (157), providing a convenient synthesis of the fungicide mepanipyrim 158.⁶⁵ Thus, the magnesiation of 157 at –60 °C is complete within 2 h using TMPMgCl·LiCl (1). Transmetalation with ZnCl₂ and iodolysis affords the bis-halogenated pyrimidine 159 in 91% yield. Subsequent magnesiation with TMPMgCl·LiCl (1; –60 °C, 1 h) followed by a bromination with 1,2-dibromotetrachloroethane affords the tri-halogenated pyrimidine 160 in almost quantitative yield (96%). Negishi cross-coupling of the most reactive iodine-substituent at 160 using MeZnBr furnishes the pyrimidine 161 in 58% yield. Sonogashira cross-coupling with propyne gives the alkynyipyrimidine 162 in 97% yield. Finally, Pd-catalyzed amination of 162 with aniline furnishes mepanipyrim 158 in 81% yield (Scheme 31).⁶³

The amination of the pyrimidine scaffold can also be achieved using TMPMgCl·LiCl (1). Thus, the magnesiation of dichloropyrimidine 163 with 1 at 25 °C for 0.5 h produces the magnesium reagent 164. Its transmetalation with CuCl·2LiCl followed by the addition of N-lithiomorpholine (165) leads to the lithium amidocrope 166, which, after oxidative amination using chloronil, leads to the 5-amino-pyrimidine 167 in 68% yield (Scheme 32).⁶₃,⁶⁴

The regioselectivity of the metatation of uracil may be controlled by the bases used.⁶₅–⁶⁷ Thus, the deprotonation of 2,4-dimethoxypyrimidine 168 with TMPLi proceeds through precomplexation of the lithium base at oxygen and leads to an ortho-lithiation (169). On the other hand, magnesiation with TMPMgCl·LiCl (1) in THF is triggered by a
complexation of the magnesium base I at the heterocyclic N-atom and therefore leads to a magnesiation at the ortho-position to nitrogen, providing the magnesium derivative 170. After quenching with ethyl cyanoformate, the uracil 171 is obtained in 71% yield. Subsequent magnesiation leads to 172 and a copper(II)-mediated benzoylation gives ketone 173 in 78% yield (Scheme 33).67,68

The magnesiation of dichloropyrimidine 163 (25 °C, 0.5 h) with TMPMgCl·LiCl (1) provides the magnesium derivative 164 as shown in Scheme 32. Its treatment with chiral sulfamidate 174 for 1 h at 25 °C followed by acidification with trifluoroacetic acid (TFA) and heating with Et3N (4 equiv) in MeCN for 0.5 h at 80 °C leads to the chiral heterocycle 175 in 85% yield. Using the sulfamidate 176 provides tetrahydropyridopyrimidine 177, which is a precursor for various unsaturated heterocycles (Scheme 34).69

The use of magnesium intermediates in some cases leads to rearrangements,70,71 as shown by the magnesiation of indolizine 178 using TMPMgCl·LiCl (1) at 25 °C for 1 h. Under these conditions, a dynamic equilibrium between the two isomeric magnesium species 179 and 180 is observed. Whereas more reactive electrophiles such as iodine and aldehydes provide the products of type 181, less reactive electrophiles such as Cl3CCl3 or a Negishi cross-coupling provide products of type 182 (Scheme 35).70
An in situ trapping procedure in several cases avoids side-reactions and provides high yields of products. Thus, the functionalization of the quinoxaline scaffold is possible using TMPLi. The treatment of dichloroquinoxaline \( \text{183} \) with TMPLi (2.4 equiv) in the presence of an excess of TMS-Cl furnishes the bis-silyl derivative \( \text{184} \) in 74% yield. After the addition of ICl (1 equiv) the mono-iodinated quinoxaline derivative \( \text{185} \) is obtained in 63% yield. Similarly, the 2,7-naphthyridine \( \text{186} \) can be converted into silyl derivative \( \text{187} \) in 73% yield (Scheme 36).\(^{73}\)

![Scheme 36](image)

**Scheme 36** Functionalization of quinoxalines and 2,7-naphthyridines using TMPLi

The 1,5-naphthyridine scaffold \( \text{188} \) has been examined in more detail. Complexation of \( \text{TMPMgCl·LiCl} \) (\( \text{34} \)) to the nitrogen-atom N1 of \( \text{188} \) leads to a selective metalation in position C8. This magnesiation has to be performed at \(-78^\circ \text{C}\) (for 5 min) to avoid decomposition of the metalated species. The resulting magnesium species \( \text{189} \) can be functionalized with various electrophiles \( E^+\cdot X \) providing products of type \( \text{190} \). The mono-substituted naphthyridines \( \text{190} \) can be regioselectively functionalized using either \( \text{TMPLi} \) (Scheme 37) or the combination of \( \text{1} \) and \( \text{BF}_3\cdot\text{OEt}_2 \). In the first case, complexation of the base \( \text{1} \) occurs at the sterically most accessible N5, leading to a magnesiation and thus functionalization at position C4 (\( \text{191} \)).

![Scheme 37](image)

**Scheme 37** Regioselective magnesiation and functionalization of 1,5-naphthyridines using \( \text{TMPMgCl·LiCl} \) (\( \text{34} \)) and \( \text{TMPLi-lithiation at position C4} \) followed by a methylation with methyl triflate affords the disubstituted naphthyridine \( \text{200} \) in 53% yield. This naphthyridine can be converted into the antibacterial drug candidate \( \text{198} \) (Scheme 39).\(^{74,75}\)

On the other hand, the addition of \( \text{BF}_3\cdot\text{OEt}_2 \) prior to the addition of \( \text{1} \) blocks a complexation of the magnesium base at N5 and, since N1 is also inaccessible due to the substituent \( E^+\cdot X \), a complexation of \( \text{1} \) to the \( \text{BF}_3 \) unit and a deprotonation of the most acidic hydrogen at position C6. After quenching with an electrophile \( E^+\cdot X \) the disubstituted 1,5-naphthyridine \( \text{192} \) is obtained (Scheme 37).\(^{74}\) The products of type \( \text{192} \) may be further metalated, although a very strong lithium base (TMPLi) is required. Thus, the reaction of \( \text{192a} \) with TMPLi at \(-78^\circ \text{C}\) for 0.5 h provides the lithium intermediate \( \text{193} \), which is trapped with iodine, furnishing the adduct \( \text{194} \) in 70% yield. The use of TMPLi also allows a fourth functionalization and the reaction of \( \text{194} \) with TMPLi at \(-78^\circ \text{C}\) for 90 s (1) leads to an ortho-lithiation, providing the lithium reagent \( \text{195} \), which gives the more stable lithium derivative \( \text{196} \) through an intramolecular iodine–lithium exchange. After quenching with an electrophile such as an acid chloride in the presence of stoichiometric amounts of \( \text{CuCN·2LiCl} \), the corresponding ketone \( \text{197} \) is obtained in 70% yield (Scheme 38).\(^{74}\) This methodology can be applied for the synthesis of an antibacterial agent such as \( \text{198} \). Thus, the magnesiation of 1,5-naphthyridine \( \text{188} \) with \( \text{TMPMgCl·LiCl} \) (\( \text{34} \)) from –40 to –20 °C for 4 h, followed by a transmetalation with \( \text{ZnCl}_2 \) and \( \text{Pd(0)} \) catalyzed cross-coupling with 4-tert-butylphenyl iodide, provides the aryalted naphthyridine \( \text{199} \) in 88% yield. TMPLi-lithiation at position C4 followed by a methylation with methyl triflate affords the disubstituted naphthyridine \( \text{200} \) in 53% yield. This naphthyridine can be converted into the antibacterial drug candidate \( \text{198} \) (Scheme 39).\(^{74,75}\)
TMPMgCl-LiCl (1) can be used to magnesiate highly functionalized 2,7-naphthyridines such as 201. Thus, the treatment of 201 triggered by a coordination at N2, affords the magnesium derivative 202, which undergoes an intramolecular addition to the carbethoxy function, providing the alkaloid sampangine 203 in 35% yield (Scheme 40).76

Bracher has extended this strategy to a marine pyridoacridine alkaloid demethyldeoxyamphimedine (204). Thus, the magnesiation of ethyl nicotinate 205 with TMPMgCl-LiCl (1) in the presence of BF3·OEt2, followed by transmetalation with ZnCl2, furnishes the zinc reagent 206, which, after cross-coupling with 2-iodoaniline in the presence of a palladium-catalyst, furnishes the lactam 207 in 50% yield. Conversion into the corresponding bromide 208 using POBr3, followed by a second cross-coupling with the zincated ethyl nicotinate 206, produces the naphthyridine 209 in 78% yield. Cyclization of 209 with TMPMgCl-LiCl (1) furnishes the desired marine pyridoacridine alkaloid 204 in 28% yield (Scheme 41).77

The metalation of the cinnoline scaffold (210) can also be realized using TMPMg-2LiCl (34). Thus, the reaction of 210 first with BF3·OEt2, followed by the addition of TMPMg-2LiCl (34) at –78 °C for 10 min, leads to a regioselective magnesiation at C3. This regioselectivity can be explained by assuming that BF3·OEt2 complexes at the most readily available nitrogen N2 and that TMP 2Mg·2LiCl coordinates at BF3 leading to a metalation at C3 (see 211). After Pd(0)-catalyzed cross-couplings, the desired arylated products of type 212 are obtained. Alternatively, the metalation of 210 with TMPZn-2LiCl-2MgCl2 (49) in the presence of MgCl2 leads to a preferential complexation at N1 of the base and at N2 of MgCl2, favoring a zincation at C8 via a transition state of type 213. After palladium-catalyzed arylation with various aryl iodides, 8-arylated cinnolines of type 214 are obtained (Scheme 42).78
As shown above, the presence or absence of a Lewis acid such as BF$_3$·OEt$_2$ or MgCl$_2$ is essential for achieving a high regioselectivity in metalations with TMP-bases. This has been demonstrated for various heterocyclic metalations.\textsuperscript{79–81} Especially relevant in the frame of this review is the regioselective metalation of the pyrazine scaffold. Thus, the introduction of a bulky bis-trimethylsilylmethyl-substituent to the pyrazine core is readily realized by treating chloropyrazine with the magnesium reagent. The resulting silyl-substituted pyrazine proved to be difficult to magnesiate using TMP-magnesium bases such as or . However, a precomplexation with BF$_3$·OEt$_2$ sufficiently acidifies the ring hydrogen atoms, allowing a regioselective metalation at the least sterically hindered position at C5 (see Scheme 43).\textsuperscript{81}

The resulting magnesium reagent reacts with various electrophiles. Chlorination with PhSO$_2$Cl provides the chloropyrazine in 61% yield. This pyrazine is readily magnesiated in a subsequent step. Remarkably, the inductive effect of the chlorine substituent is sufficient for a magnesiation to be achieved with TMP$_2$Mg·2LiCl (34) in the absence of BF$_3$·OEt$_2$. The resulting magnesiated pyrazine can be brominated with 1,2-dibromotetrachloroethane providing the bis-halogenated pyrazine in 93% yield. Finally, the last ring hydrogen of can again be metalated with TMP$_2$Mg·2LiCl (34), leading to the magnesium species (Scheme 44).\textsuperscript{81}

The metalation of the pyrazine and the pyridazine scaffolds remains a challenge and usually quite strong bases are required for these metalations. Especially for the pyridazine scaffold, either yields are low or the electrophile scope is narrow.\textsuperscript{8f,9a} The presence of two chlorine substituents in 3,6-dichloropyrazine facilitates the metalation and now TMP$_2$Zn·MgCl$_2$·LiCl (81) leads to a zincation at –78 °C.\textsuperscript{82} Also, a more convenient zincation of pyridazine can be realized at 25 °C with TMPZnCl·LiCl (80). The resulting zinc reagent can be acylated after a transmetalation with CuCN·2LiCl, leading to the corresponding ketone (Scheme 45).\textsuperscript{45} Similarly, the corresponding dibromopyridazine is zincated with TMPZnCl·LiCl (80) under the same conditions, furnishing the zincated heterocycle
229, which is benzoated, after transmetalation with CuCN·2LiCl, leading to the ketone 230 in 86% yield (Scheme 45).84

Finally, zinc-TMP-bases are especially efficient for the zinication of 2-pyridones and 2,7-naphthyridones. Thus, treatment of functionalized 2-pyridone 231 with TMP2Zn·2LiCl (81) at –10 °C for 72 h leads to the zinctated pyridone 232, which, after iodolysis, affords the iodopyridone 233 in 80% yield. Similarly, naphthyridone 234 is zinctated regioselectively and Pd-catalyzed cross-coupling with 4-idoaniline provides the cross-coupling product 235 in 76% yield (Scheme 46).84

6 Conclusion

The functionalization of azines and diazines is an important task for pharmaceutical and agro-chemical research. Herein, we have summarized recent developments in the field of azine metatation using TMPMgCl·LiCl (1), TMP2Mg·2LiCl (34), TMPZnCl·LiCl (80), and TMP2Zn·2LiCl·2MgCl2 (81), and have shown that they are excellent bases for the functionalization of N-heterocycles. The additional use of BF3·OEt2 or MgCl2 as Lewis acids considerably expands the scope of these bases. Furthermore, the performance of such metatations not in batch, but in continuous flow, allows further tuning of the reaction conditions, so that more convenient reaction temperatures and short reaction times can be achieved. In the future, the combination of these methods will certainly facilitate the functionalization of diazines and benzo-analogues further, since this research is still in its infancy.

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References
