Regioselective Magnesiation and Zincation Reactions of Aromatics and Heterocycles Triggered by Lewis Acids

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Dedicated to Prof. Dr. Wolfgang Steglich and Prof. Dr. Herbert Mayr

Abstract: Mixed TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl), such as TMPMgCl·LiCl, TMPMg·2LiCl, TMPZnCl·LiCl and TMPZn·2LiCl, are outstanding reagents for the metalation of functionalized aromatics and heterocycles. In the presence of Lewis acids, such as BF₃·OEt₂ or MgCl₂, the metalation scope of such bases was dramatically increased, and regioselectivity switches were achieved in the presence or absence of these Lewis acids. Furthermore, highly reactive lithium bases, such as TMPLi or Cy₃NLi, are also compatible with various Lewis acids, such as MgCl₂·2LiCl, ZnCl₂·2LiCl or CuCN·2LiCl. Performing such metalations in continuous flow using commercial setups permitted practical and convenient reaction conditions.

1. Introduction

The regioselective metalation of aromatics and heterocycles has been intensively studied, since these synthetic transformations provided organometallic intermediates that, after trapping reactions with various classes of electrophiles, led to a broad range of highly functionalized scaffolds of potential interest for pharmaceutical and agrochemical industry or material science applications.[1] Although the lithiation of unsaturated molecules has been widely developed,[2] the low functional group tolerance of most aryl- or heteroaryllithium reagents hampered the preparation of highly functionalized organolithiums. A solution to this lack of compatibility was the use of continuous flow microreactors using ultra-fast reaction conditions.[3] Also, the preparation of TMP-zincate or cuprate bases and related ate-bases allowed various smooth metalations of some functionalized unsaturated molecules.[4] Additionally, magnesiations and zinccations using mixed lithium-magnesium- or lithium-zinc-bases such as TMPMgCl·LiCl (1),[5] TMPMg·2LiCl (2),[6] TMPZnCl·LiCl (3)[7] or TMPZn·2LiCl (4),[8] (TMP = 2,2,6,6-tetramethylpiperidyl), giving Mg- or Zn-organometallics bearing less ionic carbon-metal bonds, are compatible with a variety of functional groups and well suited for the construction of polyfunctional molecules.[9] Furthermore, these bases are usually more regioselective and more importantly compatible with the presence of various Lewis acids, including strong Lewis acids such as BF₃·OEt₂.[10] In situ metalations in the presence of TMSCl or boronic esters have been well described and provided a convenient approach to various functionalized aryl silanes or boronic esters.[11] Schmalz reported a useful procedure involving in situ Br/Li-exchange.[12] Furthermore, such in situ metalations proved also to be very useful for the preparation of various azoyllithiums in batch.[13] Although Li-reactants are less tolerant to strong Lewis acids, some useful applications such as the opening of epoxides have been reported.[14] Thus, the ability of organomagnesium and organozinc reagents to be compatible with various Lewis acids opened new ways to control the regioselectivity of metalations, and the use of such frustrated Lewis pairs[15] for synthetic applications is the topic of this concept mini-review.

2. Lewis-acid additives for regioselective metalations

2.1. BF₃-mediated metalations

The coordination of a Lewis acid to N-heterocycles strongly directed the metalation of these molecules. Thus, the reaction of 2-phenylpyridine (5) with TMPMgCl·LiCl (1) in THF at 55 °C for 30 h provided, after iodolysis, the aryl iodide in 85% yield. This regioselectivity was explained by coordination of the TMP-base to the heterocyclic nitrogen,[16] directing the metalation towards the ortho-position of the phenyl ring. On the other hand, treatment of 5 with BF₃·OEt₂ afforded an intermediate pyridine adduct, which prevented complexation of 1 to nitrogen. At the same time the pyridine ring protons were acidified, especially the ortho-hydrogen at C(6), leading to a magnesiation at this position. After iodolysis, 6-iodo-2-phenylpyridine (7) was obtained in 83% yield. Also, 3-chloropyridine (8) provided after metalation with 1 and subsequent transmetalation with ZnCl₂,
followed by Negishi cross-coupling, the 2-arylated pyridine 9 in 75% yield. However, complexation with BF$_3$-OEt$_2$ prior to magnesiation with 1 furnished, after transmetalation with CuCN·2LiCl [18], the 4-benzoylated pyridine 10 in 78% yield. Furthermore, the electron-rich pyridine 11 was magnesiated at position 3 with 1 within 2 h at 25°C, giving, after transmetalation with CuCN·2LiCl [18] and benzoylation with PhCOCl, the 2,3-disubstituted pyridine 12 in 68% yield. Alternatively, a complexation with BF$_3$·OEt$_2$ directed the magnesiation to position 6, giving after iodolysis 6-iodo-2-methoxypyridine (13) in 75% yield (Scheme 1). [10a,b]

This procedure also allowed the functionalization of highly electron-rich pyridines such as 4-dimethylaminopyridine (14). Complexation with BF$_3$·OEt$_2$ provided the Lewis pair 15, which after treatment with TMPMgCl·LiCl (1) produced the magnesiated pyridine 16. This intermediate isomerized to the more stable pyridyl trifluoroborate 17 as shown by NMR-analysis. After transmetalation to the corresponding zinc derivative 18 by the addition of ZnCl$_2$ and subsequent Negishi cross-coupling with 4-iodoanisole, the 2,4-disubstituted pyridine 19 was obtained in 81% yield. This reaction was also performed with (5)-nicotine (20) and allowed a regioselective functionalization in position 6. The trifluoroborate intermediate 21 was transmetalated with CuCN·2LiCl and allylation using 3-bromocyclohexene afforded the nicotine derivative 22 in 92% yield (Scheme 2). [18]

This method permitted a full functionalization of the pyridine scaffold. Thus, treatment of 4-cyanopyridine (23) with BF$_3$·OEt$_2$ followed by a zincation with TMPZn·2LiCl (4) [19] and subsequent bromination produced regioselectively the 3,4-disubstituted pyridine (24) in 64% yield. Further magnesiation of 24 with TMPMgCl·LiCl (1) [11] at −78°C, followed by copper-catalyzed allylation gave the 2,3,4-trisubstituted pyridine 25 in 65% yield. Thereby, the bromine-substituent at position 3 directed this magnesiation exclusively at the 2-position. The next magnesiation of 25 with 1 at −30°C for 4 h gave the 5-magnesiated pyridine 26, which, after iodolysis, provided the tetra-substituted pyridine 27. Further zirconation of 27 with 4 gave, after Cu-catalyzed allylation, the fully substituted pyridine 28 in 62% yield (Scheme 3). [19]

The functionalization of quinine derivatives recently received renewed attention and both nucleophilic and radical additions have been successful. [20] By performing an appropriate protection of the secondary alcohol function of quinine (29) as lithium trifluoroborate 30 or as silyl ether 31, a selective metalation of the pyridine ring was possible either at the 2- or 3-position. This result may be explained by steric effects due to the bulky TBZ-group preventing a coordination of 1 at the tertiary amine nitrogen. However, BF$_3$ acidified the pyridine ring protons in both cases and after treatment with CuCN·2LiCl and allyl bromide, 32 or 33 were obtained in 40–41% yield (Scheme 4).

From these examples, it became clear that multiple factors govern these regioselective metalations. Nevertheless, some predictive guidelines have been established with the zinc base TMPZn·LiCl (3) [11] bearing a relatively covalent N–Zn bond making this base most susceptible to thermodynamic considerations and therefore to the pKa-values of various heterocyclic ring protons. A large agreement between calculated and experimental deprotonation sites was observed (>80%). Discrepancies were only found when pKa-values were very close or when a basic oxygen or nitrogen heteroatom coordinated the base 3, favoring a CIPE-driven (complex induced proximity

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**Scheme 1.** BF$_3$·OEt$_2$ triggered magnesiations of pyridines with TMPMgCl·LiCl (1).

**Scheme 2.** BF$_3$-mediated metalation of aminated pyridines with TMPMgCl·LiCl (1).

**Scheme 3.** Full functionalization of 4-cyanopyridine (23) using Zn- and Mg-bases with or without BF$_3$·OEt$_2$. 

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effect) outcome.\(^{[24]}\) The effect of BF\(_3\)·OEt\(_2\) on the heterocyclic ring protons was well demonstrated in the case of pyridazine (34), which indicated the lowest pKa-value for position C(4). A complexation with BF\(_3\)·OEt\(_2\) afforded 35 with all positions strongly acidified, but especially the closest position at C(3). A complexation with the bis-Lewis acid 36 similarly acidified all positions, but due to steric hindrance in complex 37, a metatlation occurred only at the less acidic C(4)-position. After iodolysis, the expected iodopyridazines \(\text{38 (52 % yield, regio-meric ratio = 97:3) and 39 (63 % yield, regio-meric ratio = > 99:1) were obtained with high regioselectivity (Scheme 5).}\(^{[26]}\)

Also, less common heterocycles were metatlated showing a regioselectivity switch in the presence of BF\(_3\)·OEt\(_2\) as in the case of pyrazolo[1,5-a]pyridine (40).\(^{[21]}\) This scaffold was found in various pharmaceutical targets and a regioselective functionalization at the C(2)-position was especially challenging. The reaction of 40 with TMPMgCl·LiCl (1) proceeded via the intermediate complex 41, affording the magnesium derivative 42. Cu-mediated acylation with 4-chlorobenzoyl chloride furnished the C(7)-functionalized heterocycle 43 in 70 % yield. However, treatment of 40 with BF\(_3\)·OEt\(_2\) provided tentatively the Lewis pair 44 in which a complexation of 1 is no longer possible. Thus, the acidified ring protons caused by the presence of BF\(_3\)·OEt\(_2\) allowed a metatlation at the C(2)-position. Transmetatlation with CuCN·2LiCl and acylation with 2-chlorobenzoyl chloride gave the 2-acylated heterocycle 46 in 60 % yield (Scheme 6).\(^{[22]}\)

1,5-Naphthyridine (47) may likewise be functionalized in the presence of BF\(_3\)·OEt\(_2\). A first magnesiation with TMPMgCl·LiCl (1)\(^{[16]}\) or TMP\(_2\)Mg·2LiCl (2)\(^{[16]}\) provided the heteroaryl magnesium amide 47a which reacted with various electrophiles. Transmetatlation with ZnCl\(_2\) followed by Negishi cross-coupling with 4-idoanisole produced the 4-arylnaphthyridine 48 in 75 % yield. This arylated naphthyridine was then either metatlated in C(8)-position or in C(2)-position depending on the presence or absence of BF\(_3\). The peri-substitution of 48 with an anisyl group at the 4-position hampered a complexation with 1, so that only the adduct 49\(^{[16]}\) was formed affording the magnesium species 50, which after bromination with (BrCl)\(_2\) gave the 4,8-disubstituted naphthyridine 51 in 60 % yield. However, addition of BF\(_3\)·OEt\(_2\) to 48 led to the Lewis pair 52, strongly acidifying the 2-position furnishing, after treatment with 1, the magnesium reagent 53, which was transmetatlated using CuCN·2LiCl and acylated, furnishing the ketone 54 in 70 % yield (Scheme 7).\(^{[21]}\)

The power of the magnesium TMP-bases may best be demonstrated in two applications of the metatlations of 1,5-naphthyridine (47) in the pharmaceutical and material science fields (Scheme 8). Thus, 47 underwent a double magnesiation when treated with an excess of TMPMgCl·LiCl (1; 3.0 equiv) at \(-20 ^\circ C\) affording the bis-magnesiated species 55, which after bromination with (BrCl)\(_2\) led to the 4,8-dibromonaphthyridine 56 in 53 % yield (gram-scale preparation). The obtained dibromide is a key precursor in the synthesis of OLED materials.\(^{[24]}\) Also, the magnesiation of 47 with TMP\(_2\)Mg·2LiCl (2) followed by transmetatlation with ZnCl\(_2\) and a Negishi cross-coupling with 4-tert-butylphenyl iodide gave the naphthyridine derivative 57 in 88 % yield. Lihitation of 57 at the 8-position with TMPli and subsequent methylation with methyl triflate afforded the di-substituted naphthyridine 58 in 53 % yield, which could be converted to the antibacterial drug candidate 59 as described in the literature.\(^{[25]}\)
2.2. Magnesium salts as Lewis acid for regioselective metalations

Although BF$_3$·OEt$_2$ was forming frustrated Lewis pairs with various Mg- or Zn-organometallics, its propensity to react with magnesium organometallics (ArMgX) provided the more stable trifluoroborate ArBF$_3$MgX$^+$, complicated further reactions with electrophiles. Therefore, the use of Mg-salts as Lewis acids as well as other related metallic salts gained interest as these milder Lewis acids may also be used in combination with more polar organometallics or amides such as TMPLi. Thus, the regioselective metalation of uridines such as 60 at 5- or 6-position was achieved in the presence or absence of MgCl$_2$ as Lewis acid additive. Treatment of 60 with TMPMgCl-LiCl (1) led to the complex 61, which by a proximity effect provided the 5-magnesiated uridine 62. After a copper (I)-mediated acylation with cyclopropanecarbonyl chloride the ketone 63 was obtained in 71% yield TMP2Zn·2LiCl·2MgCl$_2$ afforded the diheteroaromatic reagent 64 via intermediate 65, in which MgCl$_2$ complexed the uridine oxygen, whereas the TMP$_2$Zn base complexed the sugar-oxygen atom leading to a (C6)-deprotonation. After a similar CuCN·2LiCl mediated acylation with pivaloyl chloride, the 6-acylated uridine 66 was obtained in 95% yield (Scheme 9).

This selectivity was extended to various heterocyclic ring systems such as chromones like 67, quinolones such as 68 or thiochromones such as 69. In the case of 67 and 68, treatment with TMPZnCl-LiCl (3) led to a complex of type 70, which gave zinc organometallics of type 71 (X=O or NMe). However, using TMP$_2$Zn-LiCl (4) in the presence of MgCl$_2$, a precomplexation of MgCl$_2$ to the carbonyl group of 67 or 68 forced the base to complex to the heteroatom X (as shown for 72) and abstracted the C(2)-proton furnishing the diorganozinc species 73 (X=O or NMe; Scheme 10).

The MgCl$_2$-effect was further demonstrated by treating chromone 67 with TMPZnCl-LiCl (3) in the presence or absence of this mild Lewis acid. We presumed that MgCl$_2$ coordinated to the ketone function (as shown in Scheme 10) avoiding a metalation at position 2. After iodolysis, either the 2- or 3-iodochromones 74 or 75 were obtained using temperatures between 20°C and 25°C. This method was further applied to the preparation of the flavone chrysfin (76) as well as the isoflavone biochanin A (77). Thus, the chromone 78 was treated with 4 (in the presence of MgCl$_2$) and submitted to a Negishi cross-coupling reaction with PhI, providing after Pd/C-
catalyzed hydrogenation, chrysin 76 in 60% overall yield. Alternatively, the reaction of 78 with an excess of TMPZnCl-LiCl (3) followed by a Negishi cross-coupling with 4-iodoanisole gave, after hydrogenation, biochanin A (77) in 84% overall yield. Furthermore, the quinolone graveolinine (79) was prepared from quinolone 68 via a zincation with 4 and Negishi cross-coupling with aryl iodide 80 (Scheme 11). These metalations were readily performed on a larger scale. 

In the case of thiochromone (69), the thermodynamically favored metalation in position 2 influenced the regioselectivity of the zincation and using TMPZnCl-LiCl (3) in THF produced a mixture of both regioisomeric zinc species. However, by switching to a less polar solvent, for example, a 2:1 mixture of THF and Et₂O, a selective zincation at position 2 was achieved at −40°C. Copper-mediated benzylation with PhCOCl furnished the diketone 81 in 77% yield. A subsequent second zincation with 3 in THF produced the triketone 82 after another copper mediated acylation in 52% yield. These zincations were extended to other related heterocycles such as 4-pyrones and 2-pyrones. For example, 83 was regioselectively magnesiated at position 6 with TMPMgCl-LiCl (1) at −40°C within 10 min giving 84. Addition of benzaldehyde gave the alcohol 85 in 72% yield. Also, the functionalized 2-pyrene 86 was smoothly zinicated with TMPZnCl-LiCl (3) at −78°C perfectly tolerating the methyl ester and providing again the C(6)-metalted product 87 furnishing after a Cu-catalyzed allylation with 2-cyclohexenecarbonyl, the pyrone 88 in 70% yield (Scheme 12).

The functionalization of 2-pyridones and 2,7-naphthyridones was of special interest for their pharmaceutical properties and TMP-bases such as TMPZn-LiCl (4) in the presence of MgCl₂ proved to be very efficient. Thus, the MEM-protected 2-pyridone 89 was zinicated with 4 at −10°C leading to the N-heteroarylzinc amide 90. The same reactivity was observed with the 2,7-naphthyridone 91 affording the zinc species 92. After a Pd-catalyzed cross-coupling with aryl iodides 93 and 94, the functionalized arylated products 95 and 96 were obtained in 74-80% yield. The presence of MgCl₂ facilitated also the zincation and amination of 1,3,4-oxadiazoles. Thus, the treatment of 1,3,4-oxadiazole (97) with TMPZn-LiCl (4) (0.55 equiv) in THF at 25°C was completed within 5 min. Pd-catalyzed cross-coupling with PhI gave 2-phenyl-1,3,4-oxadiazole (98) which was further metalated with 4 (0.55 equiv.) in the presence of MgCl₂ at 25°C for 20 min. Copper-catalyzed electrophilic amination with O-hydroxylamine benzoate 99 furnished the aminated 1,3,4-oxadiazole 100 in 94% yield (Scheme 13). In summary, Zn- and Mg-TMP-bases complexed with LiCl such as 1–4 have found numerous applications in the mild and regioselective functionalization of aromatics and N-heterocycles.
3. Regioselective magnesiations in apolar solvents

In several cases, less polar solvents and less basic ethers have improved regioselectivity results. Since the bases 1–4 showed only moderate solubilities in toluene or hydrocarbons, new bases have been designed.[16] Thus, the regioselective magnesiation of aryl azoles present in numerous pharmaceutical targets (such as celecoxib,[35] apixaban,[36] zibotentan,[39] and nesapidil[40]) was investigated. Whereas the magnesiation of ary-1H-1,2,3-triazole (25) in THF with bases such as TMPMgCl · LiCl (1) or TMPMg · 2LiCl (2) proved to be non-regioselective, leading to mixtures of the desired magnesiation product at ortho-position of the aryl system as well as at the heterocyclic ring, switching the solvent to toluene greatly improved this regioselectivity. Nevertheless, standard bases such as TMPMgCl and TMPMgBu gave low conversion rates. The new base TMPMgBu prepared by mixing TMPMgCl and commercial BuLi in hexane (25 °C, 48 h)[36e] gave greatly improved results, providing the magnesiated intermediate 102, which after transmetalation with ZnCl2 and a subsequent Negishi cross-coupling with the heteroaryl chloride 103 furnished the key active pharmaceutical ingredient (API) 104 in 86% yield. This method was further improved by the preparation of a new and cheap alternative base sBuMg (105; 0.45 M in toluene). This TMP-free base was prepared by treating sBuMgCl in ether with sBuLi (25 °C, 2 h). After solvent evaporation and redissolving in toluene, sBuMg · 0.5Et2O was obtained which was abbreviated sBuMg (105) for the sake of clarity.[36e] With this toluene soluble base in hand, an optimum magnesiation of N-phenyl pyrazole (106) was realized providing the dipyrrozolmagnesium derivative 107 which, after addition to furfural, gave the alcohol 108 in 90% yield. Electron-rich 1-aryl-2H-1,2,3-triazoles such as 109 were efficiently magnesiated with 105 (25 °C, 1 h). The resulting diorganomagnesium reagent 110 reacted with the aromatic aldehyde 111 affording the polyfunctional product 112 in 80% yield (Scheme 14).

4. Regioselective in situ trapping metallocations of functionalized arenes and heteroarenes

By careful choice of reaction conditions, the compatibility of magnesium and zinc amides with various Lewis acids may be extended to more reactive lithium amides like TMPLi.[42] This powerful lithiation reagent of aromatics may be used in combination with various metallic salts to achieve regioselective metallocations. Thus, considering 2,4-dichlorobenzonitrile (120) theoretical calculations indicate that the most acidic proton was in position C(3) between the two chlorine substituents. Indeed,
regioselectivity switch between a metalation with TMPMgCl-LiCl (1) which gave the 5-iodothiophene derivative 126 and the in situ trapping conditions with ZnCl\(_2\) and TMPLi which gave preferentially the 3-iodothiophene derivative 127 was observed. Using other electrophiles instead of iodine produced as expected the corresponding products 128a–c in satisfactory yields (Scheme 17).

Unique regioselectivities in the metalation of functionalized aromatic and heterocycles were reached by these in situ trapping metalations. Nevertheless, a low reaction temperature of \(-78^\circ\text{C}\) still had to be used and a scale-up required extensive optimizations. These drawbacks could be eliminated by performing such metalations in micro-reactors, in a continuous flow setup. Thus, the mixing of ethyl 4-bromobenzoate (129) with ZnCl\(_2\)-2LiCl (0.5 equiv) and treating it with TMPLi in a commercial continuous flow apparatus provided after iodolysis the corresponding iodide 130 in 95% yield. Performing the same reaction in batch at \(-78^\circ\text{C}\) as described above produced the iodide 130 in only 53% yield, clearly demonstrating the advantages of the continuous flow setup. Instead of an iodolysis, various reactions with electrophiles were performed including Negishi cross-couplings, alkylations, acylations and additions to aldehydes. Also, a range of heterocyclic substrates such as pyridines, furans and thiophenes were successfully functionalized.\(^\text{[44]}\) Scale-up of these flow reactions did not require any further optimizations and some unusual regioselectivities were observed. Thus, both ethyl 3-bromothiophene (131a) and ethyl 3-chlorothiophene (131b) produced besides the expected regiosomeric products 132a and 132b significant amounts of the products 133a and 133b resulting from a directed metalation at the least hindered ortho-position to the ester group. In the case of ethyl 3-fluorothiophene (131c) an exclusive metalation at the thermodynamically most favored position was observed.\(^\text{[45]}\) Such in situ lithiations have also been performed in the presence of the THF soluble salt LaCl\(_2\)-2LiCl\(^\text{[46]}\) allowing additions to enolizable ketones such as Et\(_2\)CO. Thus, the reaction of dibromothiophene 134 with TMPLi in the presence of LaCl\(_2\)-2LiCl (0.5 equiv) gave after the addition of diethyl ketone in batch the tertiary alcohol 135 in 64% yield (Scheme 18).

A further improvement may be the replacement of TMPLi by the ca. 100 times cheaper alternative lithium dicyclohexylamide (Cy\(_2\)NLi). This base allowed the performance of the

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**Scheme 15.** Selective sequential ortho, ortho'-functionalization of oxazoline 113 and 2-aryl-2H-1,2,3-triazole 117.

**Scheme 16.** Regioselective metalation via an in situ trapping metalation using ZnCl\(_2\)-2LiCl and TMPLi.

**Scheme 17.** Regioselective functionalizations of thiophene 125 using an in situ trapping with TMPLi and ZnCl\(_2\)-2LiCl.
In this concept article, TMP-bases of magnesium and zinc were demonstrated to be powerful metalating reagents of functionalized aromatics and heteroaromatics. In combination with Lewis acids, such as BF$_3$·OEt$_2$ or MgCl$_2$ and THF soluble MgCl$_2$·2LiCl or ZnCl$_2$·2LiCl, the scope of these metalations was dramatically increased. In several cases, a switch of regioselectivity was observed. Furthermore, the strong lithium base TMPLi was also compatible with various Lewis acids at low temperature. Using a continuous commercial flow setup performing these metalations in micro-reactors further made the reaction conditions more convenient and practical.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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