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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, $TMP_2Mg·2LiCl$, TMPZnCl·LiCl and $TMP_2Zn·2LiCl$, are outstanding reagents for the metalation of functionalized aromatics and heterocycles. In the presence of Lewis acids, such as $BF_3·OEt_2$ or $MgCl_2$, 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 Cy_2NLi, are also compatible with various Lewis acids, such as $MgCl_2·2LiCl$, $ZnCl_2·2LiCl$ 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 zincations using mixed lithium-magnesium- or lithium-zinc-bases such as TMPMgCl·LiCl (**1**),[5] $TMP_2Mg·2LiCl$ (**2**),[6] TMPZnCl·LiCl (**3**)[7] or $TMP_2Zn·2LiCl$ (**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 $BF_3·OEt_2$.[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 azolyllithiums in batch.[13] Although Li-reagents 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. BF_3-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 **6** 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 $BF_3·OEt_2$ 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 $ZnCl_2$,

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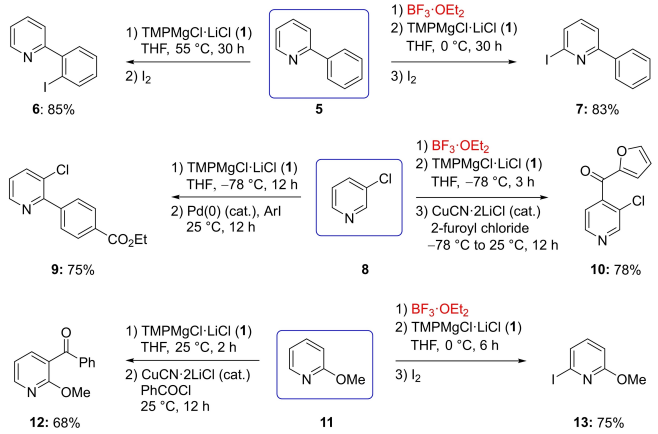
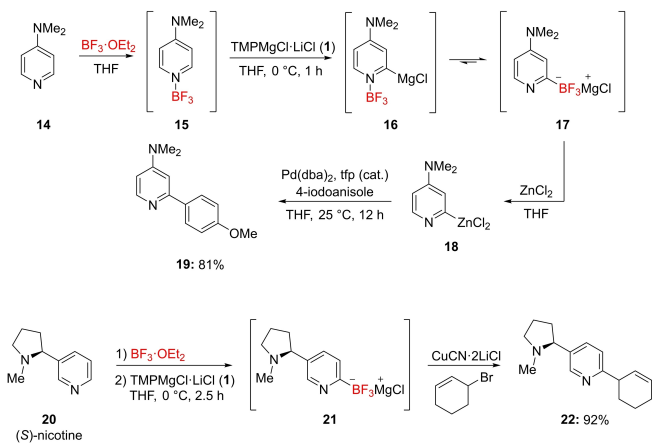
followed by Negishi cross-coupling, the 2-arylated pyridine **9** in 75% yield. However, complexation with $BF_3 \cdot OEt_2$ prior to magnesiation with **1** furnished, after transmetalation with CuCN·2LiCl[17], the 4-benzoylated pyridine **10** in 78% yield. Furthermore, the electron-rich pyridine **11** was magnesiated at position 3 with **1** within 2 h at 25 °C, giving, after transmetalation with CuCN·2LiCl[17] and benzoylation with PhCOCl, the 2,3-disubstituted pyridine **12** in 68% yield. Alternatively, a complexation with $BF_3 \cdot OEt_2$ 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 $BF_3 \cdot OEt_2$ 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



Scheme 1. $BF_3 \cdot OEt_2$ triggered magnesiations of pyridines with TMPMgCl·LiCl (**1**).



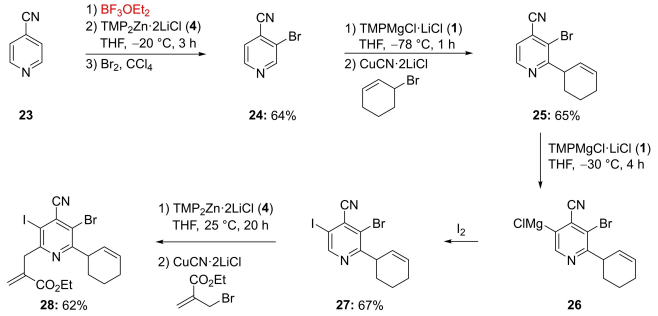
Scheme 2. BF_3-mediated metalation of aminated pyridines with TMPMgCl·LiCl (**1**).

(*S*)-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]

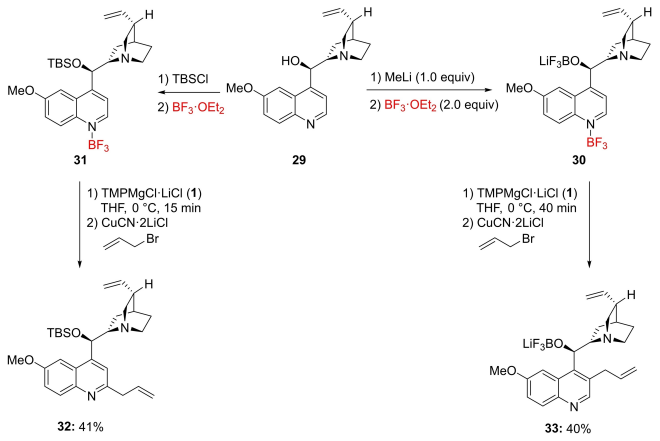
This method permitted a full functionalization of the pyridine scaffold. Thus, treatment of 4-cyanopyridine (**23**) with $BF_3 \cdot OEt_2$ followed by a zincation with $TMP_2Zn \cdot 2LiCl$ (**4**)[8] and subsequent bromination produced regioselectively the 3,4-disubstituted pyridine (**24**) in 64% yield. Further magnesiation of **24** with TMPMgCl·LiCl (**1**)[5] 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 zincation of **27** with **4** gave, after Cu-catalyzed allylation, the fully substituted pyridine **28** in 62% yield (Scheme 3).[18]

The functionalization of quinine derivatives recently received renewed attention and both nucleophilic and radical additions have been successful.[19] 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 TBS-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 TMPZnCl·LiCl (**3**)[7] 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



Scheme 3. Full functionalization of 4-cyanopyridine (**23**) using Zn- and Mg-bases with or without $BF_3 \cdot OEt_2$.



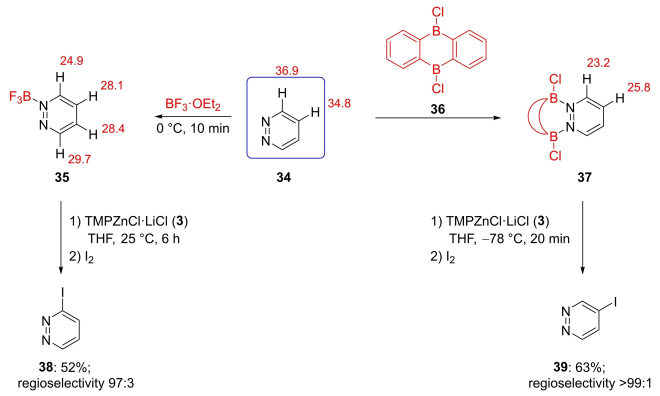
Scheme 4. Regioselective functionalization of quinine (**29**) using various protecting groups as well as the frustrated Lewis pair TMPMgCl·LiCl (**1**) and $BF_3 \cdot OEt_2$.

effect) outcome.[16] The effect of $BF_3 \cdot OEt_2$ 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 $BF_3 \cdot OEt_2$ 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 metalation occurred only at the less acidic C(4)-position. After iodolysis, the expected iodopyridazines **38** (52% yield, regiomeric ratio = 97:3) and **39** (63% yield, regiomeric ratio = > 99:1) were obtained with high regioselectivity (Scheme 5).[20]

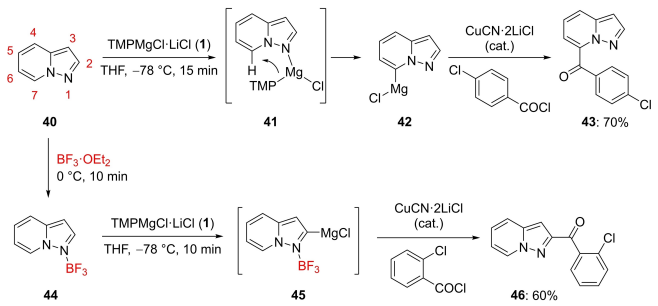
Also, less common heterocycles were metalated showing a regioselectivity switch in the presence of $BF_3 \cdot OEt_2$ as in the case of pyrazolo[1,5-a]pyridine (**40**).[21] This scaffold was found in various pharmaceutical targets and a regioselective functionalization at the C(2)-position was especially 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 $BF_3 \cdot OEt_2$ 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 $BF_3 \cdot OEt_2$ allowed a metalation at the C(2)-position. Transmetalation 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 $BF_3 \cdot OEt_2$. A first magnesiation with TMPMgCl·LiCl (**1**)[5] or $TMP_2Mg \cdot 2LiCl$ (**2**)[6] provided the heteroarylmagnesium amide **47a** which reacted with various electrophiles. Transmetalation with $ZnCl_2$ followed by Negishi cross-coupling with 4-iodoanisole produced the 4-arylnaphthyridine **48** in 75% yield. This arylated naphthyridine was then either metalated 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 $(BrCl_2C)_2$ gave the 4,8-disubstituted naphthyridine **51** in 60% yield. However, addition of $BF_3 \cdot OEt_2$ to **48** led to the Lewis pair **52**, strongly acidifying the 2-position furnishing, after treatment with **1**, the magnesium reagent **53**, which was transmetalated using CuCN·2LiCl and acylated, furnishing the ketone **54** in 70% yield (Scheme 7).[23]

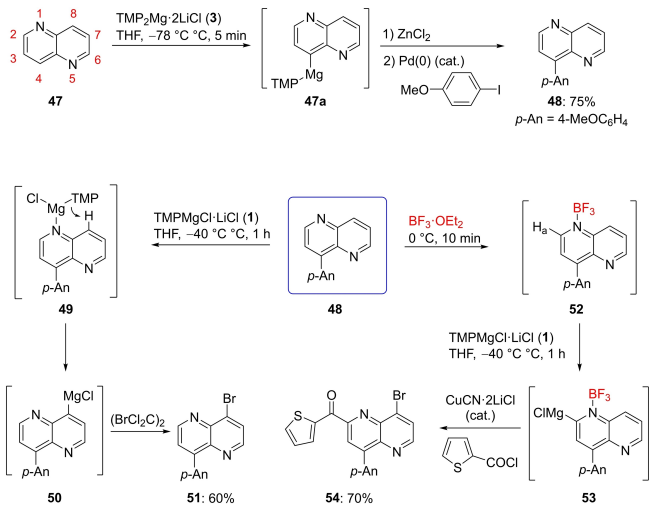
The power of the magnesium TMP-bases may best be demonstrated in two applications of the metalations of 1,5-naphthyridine (**47**) in the pharmaceutical and material science fields (Scheme 8). Thus, **47** underwent a double magnesiation when treated with an excess of TMPMgCl·LiCl (**1**; 3.0 equiv) at −20 °C affording the bis-magnesiated species **55**, which after bromination with $(BrCl_2C)_2$ 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 $TMP_2Mg \cdot 2LiCl$ (**2**) followed by transmetalation with $ZnCl_2$ and a Negishi cross-coupling with 4-*tert*-butylphenyl iodide gave the naphthyridine derivative **57** in 88% yield. Lithiation 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]



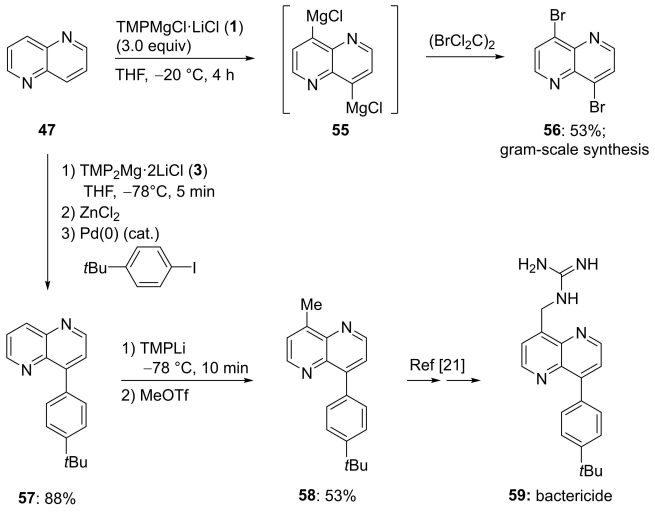
Scheme 5. $BF_3 \cdot OEt_2$ and bis-Lewis acid **36**-mediated regioselective zincations of pyridazine (**34**).



Scheme 6. Selective magnesiations of pyrazolo[1,5-a]pyridine (**40**) using TMPMgCl·LiCl (**1**) with or without $BF_3 \cdot OEt_2$.



Scheme 7. Regioselective functionalization of 4-arylated naphthyridine (**48**) by magnesiation with TMPMgCl·LiCl (**1**) in the presence or absence of $BF_3·OEt_2$.



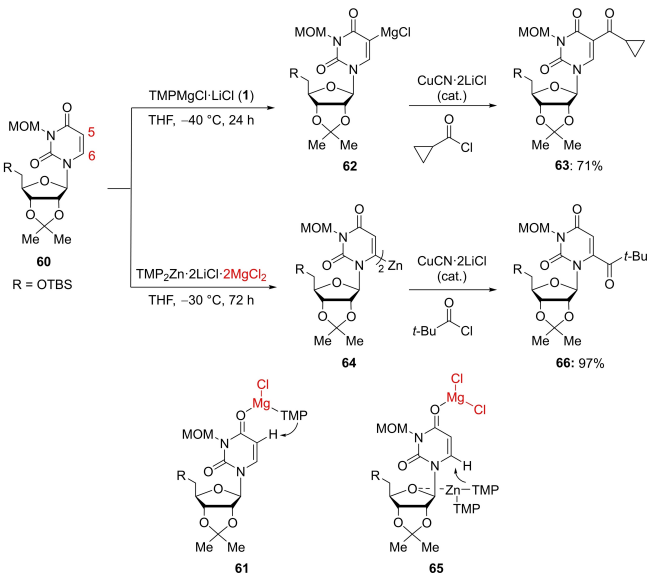
Scheme 8. Synthesis of key intermediate naphthyridines **55** and **58** for biological and material science application.

2.2. Magnesium salts as Lewis acid for regioselective metalations

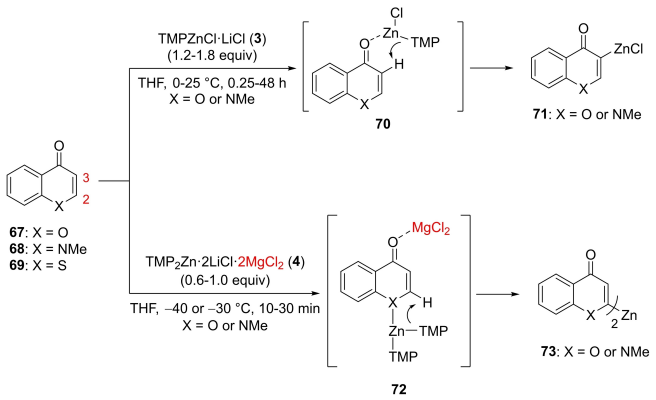
Although $BF_3·OEt_2$ was forming frustrated Lewis pairs with various Mg- or Zn-organometallics, its propensity to react with magnesium organometallics (ArMgX) provided the more stable trifluoroborate $ArBF_3^-MgX^+$ complicated further reactions with electrophiles.[10,18,26] Therefore, the use of Mg-salts 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.[27] Treatment of **60** with TMPMgCl·LiCl (**1**) led to the complex **61**, which by a proximity effect[16] 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. In strong contrast, treatment of **60** with $TMP_2Zn·2LiCl$ $2MgCl_2$ afforded the diheteroarylzinc reagent **64** via intermediate **65**, in which $MgCl_2$ complexed the uridine oxygen, whereas the TMP_2Zn base complexed the sugar-oxygen atom leading to a C(6)-deprotonation. After a similar CuCN·2LiCl mediated acylation with pivaloyl chloride, the 6-acylated uridine **66** was obtained in 95% yield (Scheme 9).[27a]

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**)[7] led to a complex of type **70**, which gave zinc organometallics of type **71** (X=O or NMe). However, using $TMP_2Zn·2LiCl$ (**4**)[8] 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).[28] The Zn-organometallics **71** and **73** were trapped by various electrophiles including allylic halides, acid chlorides, aryl iodides and bromides providing a range of functionalized flavones and isoflavones.

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.[28] This method was further applied to the preparation of the flavone chrysin (**76**)[29] as well as the isoflavone biochanin A (**77**).[30] 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-



Scheme 9. $MgCl_2$-triggered regioselective metalations of uridines using Zn- or Mg-TMP bases.

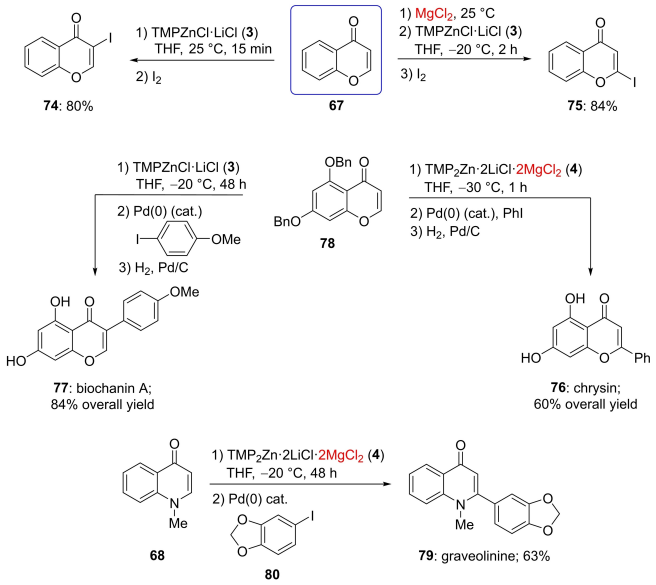


Scheme 10. Regioselective zincations of chromone **67** or quinolone **68** with TMPZn-bases **3** or **4** in the presence or absence of $MgCl_2$.

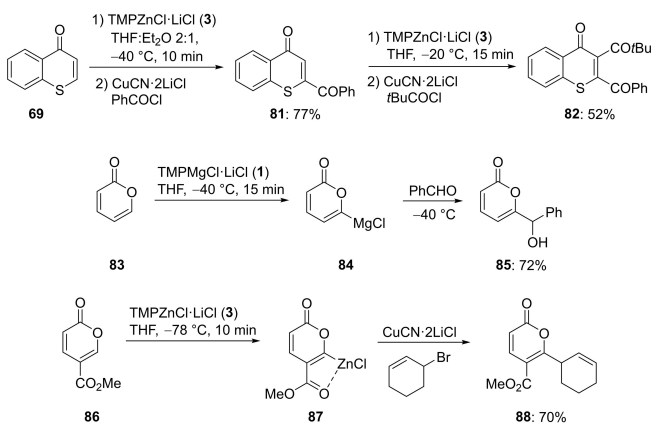
catalyzed hydrogenation, chrysin **76** in 60% overall yield. Alternatively, the reaction of **78** with an excess of TMPZnCl·LiCl (**3**) followed by a Negishi cross-coupling with 4-iodoanisole gave, after hydrogenation, biochanin A (**77**) in 84% overall yield. Furthermore, the quinolone graveolinine (**79**)[28] 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.[31]

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 Et_2O, a selective zincation at position 2 was achieved at −40 °C. Copper-mediated benzoylation 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.[32] 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-pyrone **86** was smoothly zincated with TMPZnCl·LiCl (**3**) at −78 °C perfectly tolerating the methyl ester and providing again the C(6)-metalated product **87** furnishing after a Cu-catalyzed allylation with 2-cyclohexenebromide, the pyrone **88** in 70% yield (Scheme 12).

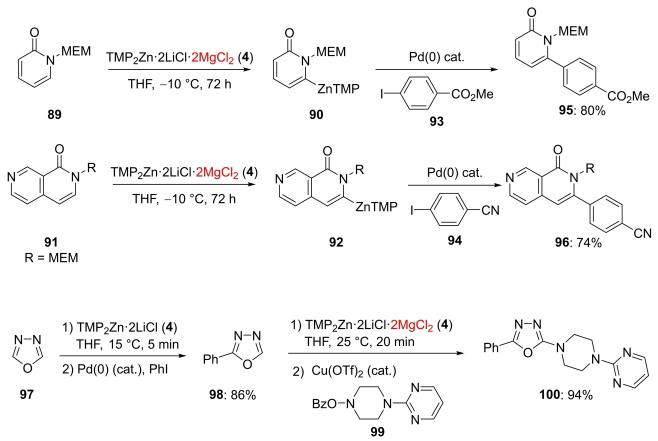
The functionalization of 2-pyridones and 2,7-naphthyridones was of special interest for their pharmaceutical properties and TMP-bases such as $TMP_2Zn \cdot 2LiCl_2$ (**4**) in the presence of $MgCl_2$ proved to be very efficient. Thus, the MEM-protected 2-pyridone **89** was zincated with **4** at −10 °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.[33] The presence of $MgCl_2$ facilitated also the zincation and amination of 1,3,4-oxadiazoles.[34] Thus, the treatment of 1,3,4-oxadiazole (**97**) with $TMP_2Zn \cdot 2LiCl$ (**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 $MgCl_2$ 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.[35]



Scheme 11. Preparation of a natural flavone, isoflavones and quinolone by regioselective metalations.



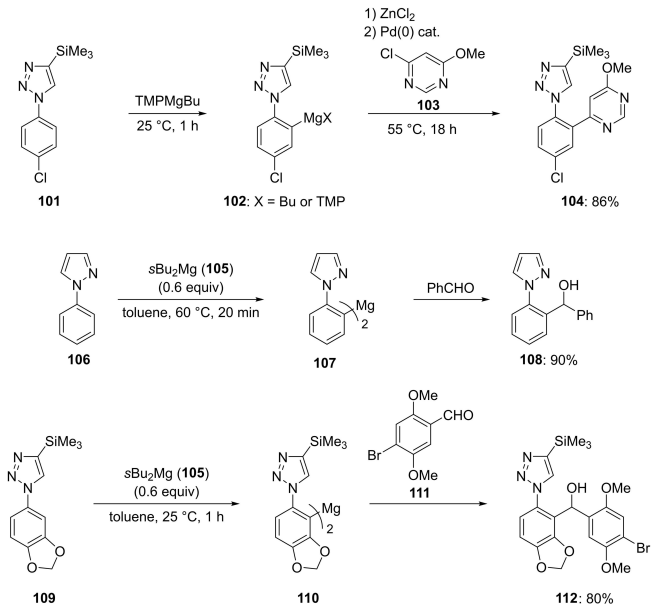
Scheme 12. Regioselective metalation of thiochromone **69** and 2-pyrones **83** and **86** using TMP-bases **1** and **3**.



Scheme 13. Regioselective metalations of various N-heterocycles with TMP-bases.

3. Regioselective magnesiations in apolar solvents

In several cases, less polar solvents and less basic ethers have improved metalation regioselectivities. Since the bases **1**–**4** showed only moderate solubilities in toluene or hydrocarbons, new bases have been designed.[36] Thus, the regioselective metalation of aryl azoles present in numerous pharmaceutical targets (such as celecoxib,[37] apixaban,[38] zibotentan,[39] and nesapidil[40]) was investigated. Whereas the magnesiation of aryl-1*H*-1,2,3-triazole **101** in THF with bases such as TMPMgCl·LiCl (**1**) or $TMP_2Mg·2LiCl$ (**2**) proved to be non-regioselective, leading to mixtures of the desired metalation 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 TMP_2Zn gave low conversion rates. The new base TMPMgBu prepared by mixing TMP–H with commercial Bu_2Mg in hexane (25 °C, 48 h)[36a] gave greatly improved results, providing the magnesiated intermediate **102**, which after transmetalation with $ZnCl_2$ 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 *s*Bu_2Mg (**105**; 0.45 M in toluene). This TMP-free base was prepared by treating *s*BuMgCl in ether with *s*BuLi (25 °C, 2 h). After solvent evaporation and redissolving in toluene, *s*$Bu_2Mg·0.5Et_2O$ was obtained which was abbreviated *s*Bu_2Mg (**105**) for the sake of clarity.[36b] With this toluene soluble base in hand, an optimum magnesiation of *N*-phenyl pyrazole (**106**) was realized providing the dipyrazolmagnesium derivative **107** which, after addition to furfural, gave the alcohol **108** in 90% yield. Electron-rich 1-aryl-2*H*-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).

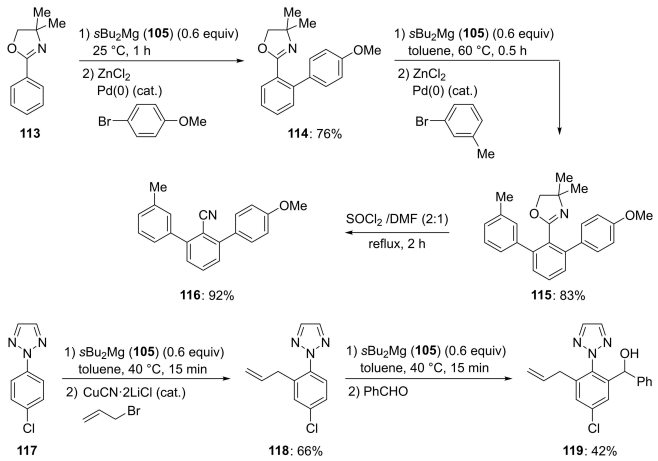


Scheme 14. Regioselective magnesiations of *N*-aryl azoles with TMPMgBu and *s*Bu_2Mg (**105**).

Standard C–H activations often fail to achieve selective mono *ortho*-functionalizations and symmetric *ortho*, *ortho*′-derivatives are obtained.[41] This limitation was avoided using magnesiations with *s*Bu_2Mg (**105**). Thus, treating oxazoline **113** with *s*Bu_2Mg (**105**) in toluene and subsequent transmetalation with $ZnCl_2$ and Negishi cross-coupling furnished the mono *ortho*-arylated oxazoline **114**. A second magnesiation of **114** with **105** (60 °C, 0.5 h) gave, after transmetalation and Negishi cross-coupling with a different aryl halide, the unsymmetric *ortho*, *ortho*′-oxazoline **115** in 83% yield. Eventually, the oxazoline directing group was converted into the corresponding aryl benzonitrile **116** in 92% yield with $SOCl_2$ in DMF (in situ generation of the Vilsmeier-reagent). Similarly, 2-(4-chlorophenyl)-2*H*-1,2,3-triazole (**117**) was magnesiated with **105** at 40 °C within 15 min providing, after a copper-catalyzed allylation, the triazole **118** in 66% yield. A subsequent second magnesiation with **105** and addition of benzaldehyde gave the *ortho*, *ortho*′-trisubstituted aryl-2*H*-1,2,3-triazole **119** in 42% yield. (Scheme 15).[36b]

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

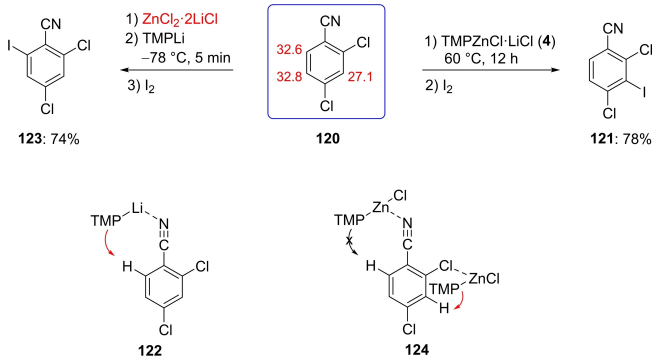
By careful choice of reaction conditions, the compatibility of magnesium and zinc amides with various Lewis acids may be extended to more reactive lithium amides like TMPLi.[42] This powerful lithiation reagent of aromatics may be used in combination with various metallic salts to achieve regioselective metalations. 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,



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

treatment of **120** with TMPZnCl·LiCl (**3**) for 12 h at 60 °C and subsequent iodolysis provided the 3-iodobenzonitrile **121** in 78% yield. On the other hand, mixing **120** with the THF soluble salt $ZnCl_2 \cdot 2LiCl$ at −78 °C and then adding TMPLi to this mixture led to a complete metalation at position C(6) within 5 min, triggered by the intermediate complex **122** affording **123** in 74% yield. The base TMPZnCl·LiCl (**3**) is able to interact with the nitrile function of **120**, providing co-complexation adduct **124**, however, the low polarity of the Zn–N bond did not permit deprotonation *ortho* to the CN group. Instead, a weaker complexation of **3** to the substrate's chlorine substituent eventually promoted metallation to result in **121**, albeit at slightly elevated conditions (Scheme 16).[43]

The presence of $ZnCl_2 \cdot 2LiCl$ in the metalation of **120** with TMPLi was essential, since in its absence only decomposition products were isolated due to the high reactivity of the resulting aryllithium species. Further investigations showed that this in situ trapping reaction conditions were also compatible with other metal salts such as $MgCl_2 \cdot 2LiCl$ or CuCN·2LiCl and were extended to other substrates including heterocyclic system such as ethyl 2-thienylcarboxylate (**125**). A similar

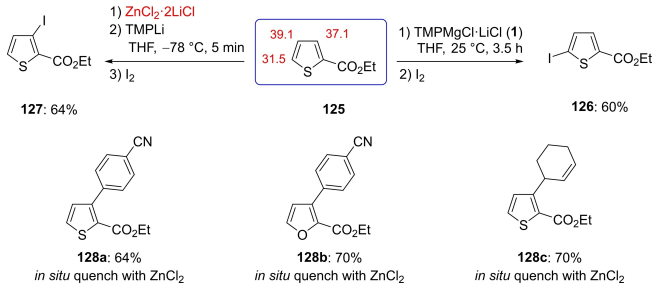


Scheme 16. Regioselective metalation via an in situ trapping metalation using $ZnCl_2 \cdot 2LiCl$ and TMPLi.

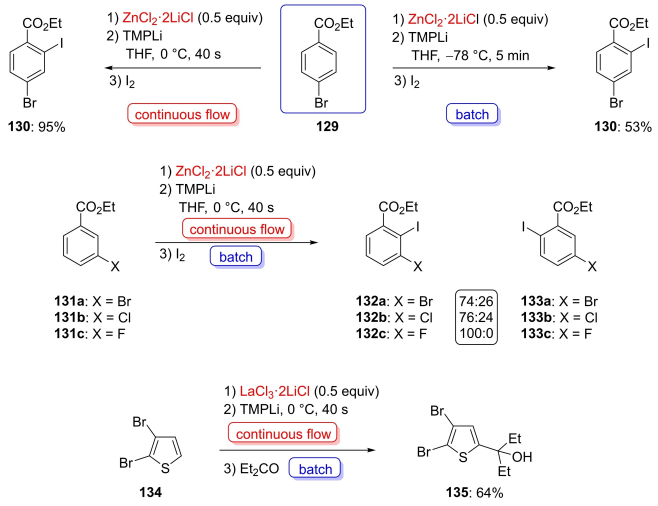
regioselectivity switch between a metalation with TMPMgCl·LiCl (**1**) which gave the 5-iodothiophene derivative **126** and the in situ trapping conditions with $ZnCl_2$ and TMPLi which gave preferentially the 3-iodothiophene derivative **127** was observed. Using other electrophiles instead of iodine 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 °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 $ZnCl_2 \cdot 2LiCl$ (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 °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, allylations, acylations and additions to aldehydes. Also, a range of heterocyclic substrates such as pyridines, furans and thiophenes were successfully functionalized.[44] Scale-up of these flow reactions did not require any further optimizations and some unusual regioselectivities were observed. Thus, both ethyl 3-bromobenzoate (**131a**) and ethyl 3-chlorobenzoate (**131b**) produced besides the expected regioisomeric 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-fluorobenzoate (**131c**) an exclusive metalation at the thermodynamically most favored position was observed.[45] Such in situ lithiations have also been performed in the presence of the THF soluble salt $LaCl_3 \cdot 2LiCl$[46] allowing additions to enolizable ketones such as Et_2CO. Thus, the reaction of dibromothiophene **134** with TMPLi in the presence of $LaCl_3 \cdot 2LiCl$ (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_2NLi). This base allowed the performance of the

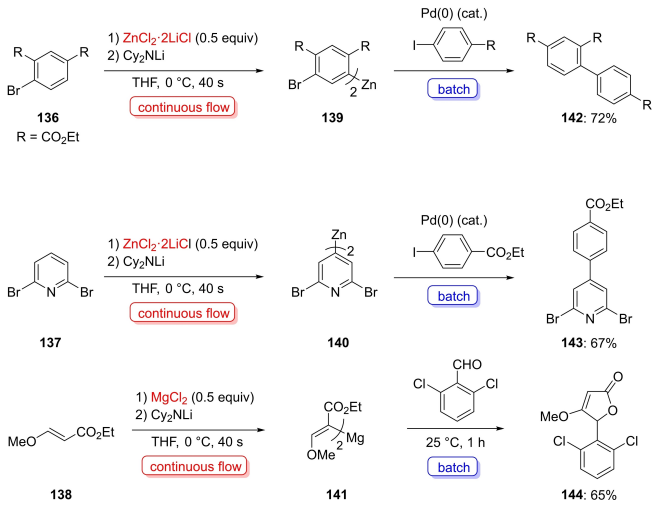


Scheme 17. Regioselective functionalizations of thiophene **125** using an in situ trapping with TMPLi and $ZnCl_2 \cdot 2LiCl$.



Scheme 18. *In situ* trapping metalations of aromatics **129**, **131 a-c** and heterocycle **134** with TMPLi in the presence of Lewis acids like $ZnCl_2 \cdot 2LiCl$ or $LaCl_3 \cdot 2LiCl$.

lithiation of highly functionalized aromatics such as **136** and heterocycles such as **137** at 0 °C. Also, acrylic esters such as **138** proved to be excellent substrates. The intermediate zinc or magnesium reagents **139**–**141** reacted with common electrophiles leading to **142**–**144** in good yields (Scheme 19).[47] These in situ trapping lithiations performed in the presence of metallic salts in continuous flow were also applied to the preparation of unsymmetrical azobenzenes.[48] Furthermore, lithiations of formamides in the presence of various electrophiles were conveniently realized in continuous flow showing the high potential of this method.



Scheme 19. *In situ* trapping metalations in continuous flow with Cy_2NLi in the presence of zinc and magnesium halides at 0 °C and batch quenching with various electrophiles.

5. Conclusion

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 $BF_3 \cdot OEt_2$ or $MgCl_2$ and THF soluble $MgCl_2 \cdot 2LiCl$ or $ZnCl_2 \cdot 2LiCl_2$, 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.

Keywords: frustrated Lewis pairs · magnesium · metalation reactions · regioselectivity · zinc

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