Review

Regioselective Functionalization of Pyridines using a Directed Metalation or a Halogen/Metal Exchange

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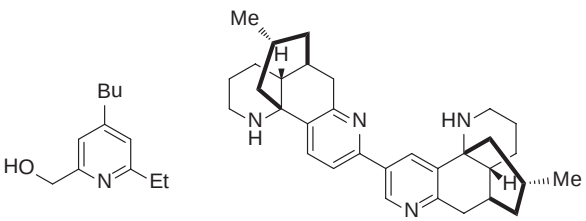
Dedicated to Professor Heinrich Nöth on the occasion of his 85th birthday

This review describes the various ways of functionalizing the pyridine scaffold using either directed metalation or halogen/metal exchange. Deprotonation can be accomplished with different lithium amides or alkyllithium reagents at low temperature. Milder conditions and higher functional group tolerance can be achieved by using ate-bases with different metals (Cd, Mg, Zn) or TMP (2,2,6,6-tetramethylpiperidyl) metal reagents (metal = Mg, Zn, Zr). With alkyllithium reagents it is also possible, by carefully adjusting the reaction conditions, to perform bromine/lithium exchange reactions. Organomagnesium reagents, like *i*PrMgX (X = Br, Cl·LiCl), may be used for exchanging more sensitive iodinated or brominated pyridines.

Key words: Pyridines, C-H Activation, Halogen/Metal Exchange

Table of Contents

1. Introduction
2. The Directed Metalation of Substituted Pyridines
2.1 The Directed Lithiation of Pyridines
2.2 The Directed Metalation Using TMP ate- and Metal-Bases (Metal = Cd, Mg, Zn, Zr)
3. Regioselective Functionalization of Pyridines *via* a Halogen/Metal Exchange
4. Summary and Conclusion



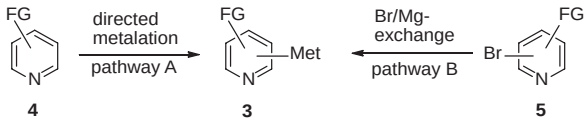
heterotaxin (**1**) (+)-complanadine A (**2**)

Fig. 1. Biologically active pyridine derivatives.

Introduction

Pyridines are an important class of *N*-heterocycles and many polysubstituted pyridines display important biological activity. Thus, pyridine derivatives such as heterotaxin (**1**) [1] or the more complex dimeric pyridine (+)-complanadine A (**2**) [2] have been the targets of total syntheses (Fig. 1). Although transition metal-catalyzed [2 + 2 + 2]-cyclotrimerizations have often been used to build up complex pyridines [3 – 6], methodologies involving main-group metal intermediates have been proven to be especially useful and of general application. Especially the directed metalation plays an important role in the regioselective introduction of substituents on the pyridine scaffold [7 – 12].

Also, the performance of regioselective bromine- or iodine/magnesium exchange reactions [13 – 15] has become an essential tool for practical applications. In this short review, we summarize recent methods allowing the preparation of functionalized pyridyl



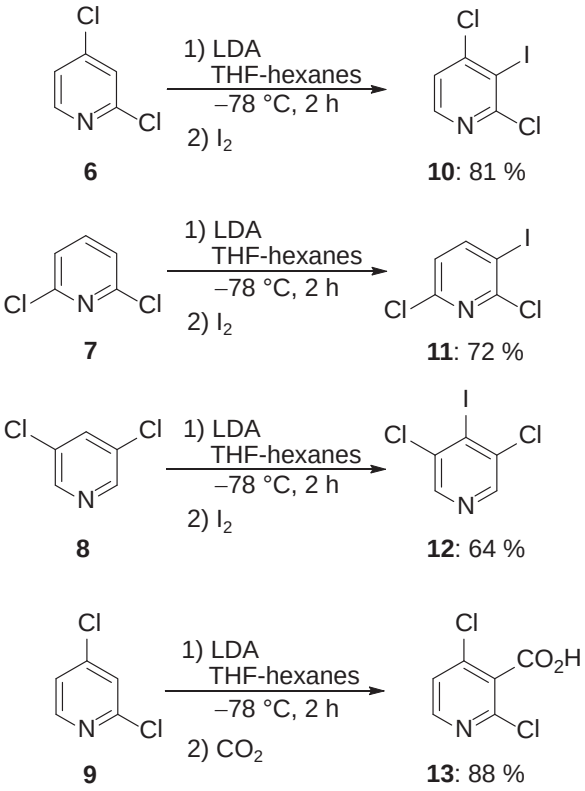
Scheme 1.

organometallics of type **3**, obtained either by a directed metalation of functionalized pyridines of type **4** (Scheme 1, pathway A) or bromine/magnesium exchange starting from bromopyridines of type **5** (Scheme 1, pathway B; FG = functional group).

The Directed Metalation of Substituted Pyridines

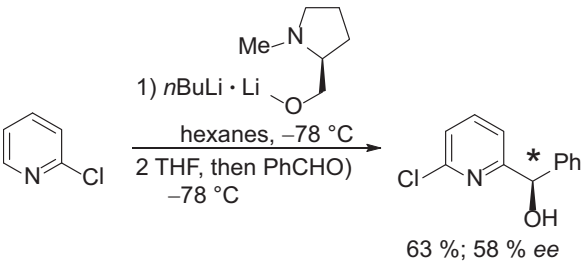
The directed lithiation of pyridines

Substituted pyridines react with a variety of metallic bases leading to metalated intermediates. Since these *N*-heterocycles are electron-deficient, the resulting metalated species may add to still non-metalated substrate leading to dimerization or to oligomeric side-products. These side-reactions occur especially with pyridines bearing electron-withdrawing substituents or when ionic bases such as lithium base are used for performing the directed metalation [7 – 12]. Nevertheless, using a proper set of reaction conditions and the appropriate lithium base allows to perform a wide range of selective metalations. The nature of the substituents attached to the pyridine scaffold deeply influences the regioselectivity and the rate of the metalation. Thus, whereas the direct lithiation of pyridine with a 1 : 1 mixture of BuLi and *t*BuOK (Schlosser base) in THF-hexanes at −100 °C leads to a mixture of regioisomeric lithiated pyridines [16, 17], the metalation of various dichloropyridines **6–9** with LDA (lithium diisopropylamide) leads regioselectively to various lithiated pyridines which can be iodolyzed or carbonylated affording the desired products **10–13** in good yields (Scheme 2) [18].



Scheme 2.

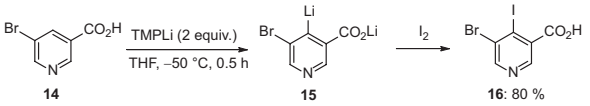
The use of mixed aggregates of *n*BuLi with aminoalkoxides such as lithium 2-dimethylaminoethanolate (LiDMAE) [19, 20] allows highly regioselective lithiations. The use of a chiral lithium alkoxide allows the performance of a regio- and enantioselective metalation (Scheme 3) [21].



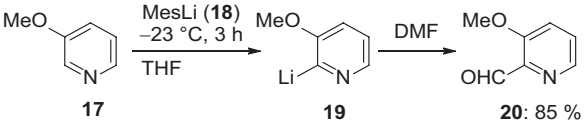
Scheme 3.

Lithium 2,2,6,6-tetramethylpiperidide (TMPLi) is a powerful base [22 – 25], and the deprotonation of pyridine carboxylic acids such as **14** proceeds smoothly leading to the lithiated intermediate **15** which, after iodolysis, furnishes the expected product **16** in 80 % yield (Scheme 4) [26].

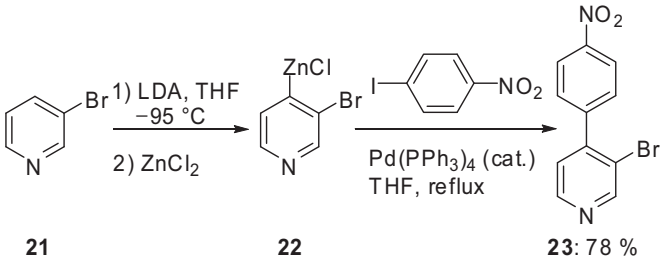
The use of lithium amides such as LDA can lead to reversible lithiations in the case of electron-rich pyridines such as 3-methoxypyridine **17**. The use of a sterically hindered aryllithium like mesityllithium **18** on the other hand leads to an irreversible deprotonation leading to a regioselective lithiation with the formation of the 2-lithiated pyridine **19**. After treatment



Scheme 4.



Scheme 5.



Scheme 6.

with DMF, the expected aldehyde **20** is obtained in 85 % yield (Scheme 5) [27].

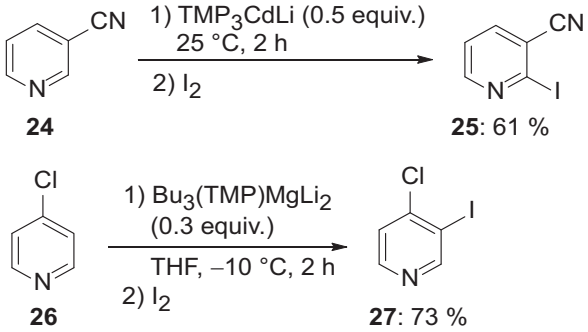
Multiple functionalization can be achieved by combining the lithiation step with a subsequent transmetalation. Thus, the reaction of the 3-bromopyridine (**21**) with LDA at −95 °C leads to a regioselective lithiation in position 4. After transmetalation with $ZnCl_2$, the corresponding zinc reagent **22** is obtained. Negishi cross-coupling of **22** with aryl halides such as 4-nitrophenyl iodide produces the 4-arylated pyridine **23** in 78 % yield. The remaining bromide in pyridine **23** can be used for the performance of a subsequent Suzuki cross-coupling reaction (Scheme 6) [28, 29].

The directed metalation using TMP ate- and metal-bases (metal = Cd, Mg, Zn, Zr)

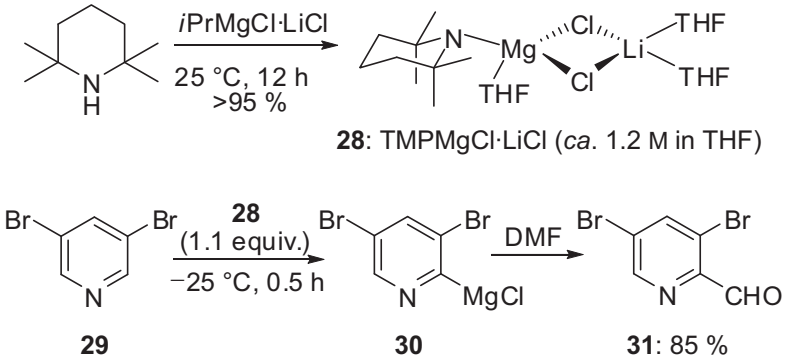
The reactivity of lithium bases can be strongly tuned by forming ate-bases with various metals [30 – 32]. Thus, the use of the lithium zincate base $TMPZnnBu_2Li$ allows to metalate pyridine in position 2 under mild conditions (25 °C). After iodolysis, 2-iodopyridine is obtained in 76 % yield [33]. The use of the related lithium cadmiate base TMP_3CdLi allows a smooth metalation of 3-cyanopyridine (**24**). After iodolysis, the iodopyridine **25** is obtained in 61 % yield (Scheme 7) [34, 35].

Compared to lithium bases, the mild reaction conditions used with ate-bases make them a versatile tool in C-H activation. Moreover, in many cases the use of an excess of ate-base can be avoided. Thus, 0.3 equivalents of the magnesium-ate base $(TMP)Bu_3MgLi_2$ is sufficient for the metalation of 4-chloropyridine **26**. Remarkably, this metalation can be performed at −10 °C. After iodolysis, the 3-iodopyridine **27** is obtained in 73 % yield (Scheme 7) [36].

Metal amides using less electropositive metals than lithium are of great interest, since the organometallics produced after metalation bear a much more covalent carbon-metal bond allowing a higher tolerance towards more sensitive functional groups. This functional group compatibility is essential, since polyfunctional pyridines are common building blocks in pharmaceutical and material sciences. Therefore, the use of magnesium amides derived from sterically hindered bases such as 2,2,6,6-tetramethylpiperidine (TMP-H) proves to be of great synthetic utility. Moreover, the addition of one equivalent of lithium chloride leads to a higher solubility of such bases in THF, allowing the performance of fast and highly chemoselective



Scheme 7.

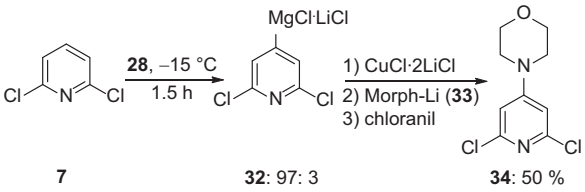


Scheme 8.

metalations. Thus, TMPMgCl·LiCl (**28**) is readily prepared by treating TMP-H with *i*PrMgCl·LiCl [13–15] in THF leading to a *ca.* 1.2 M solution. The X-ray structure of **28** has been determined by Mulvey [37] and shows clearly the role of the chloride anions for bridging the magnesium and lithium atoms. This base proves to be kinetically highly active and smoothly deprotonates a wide range of pyridines. Thus, 3,5-dibromopyridine (**29**) reacts with TMPMgCl·LiCl (**28**, 1.1 equiv.) at −25 °C within 0.5 h to give the 2-magnesiated pyridine **30**. After addition of DMF, the corresponding aldehyde **31** is obtained in 85% yield (Scheme 8) [38].

Remarkably, the use of TMPMgCl·LiCl (**28**) allows to reach unusual regioselectivities. Thus, the magnesiation of 2,6-dichloropyridine (**7**) proceeds with 97 : 3 regioselectivity in position 4 and provides the magnesium reagent **32** under mild conditions (−15 °C, 1.5 h). After transmetalation to copper with CuCN·2LiCl (1.2 equiv.) and addition of *N*-lithiomorpholine (**33**), an oxidative coupling can be accomplished by addition of chloranil leading to the aminopyridine **34** in 50% yield (Scheme 9) [39].

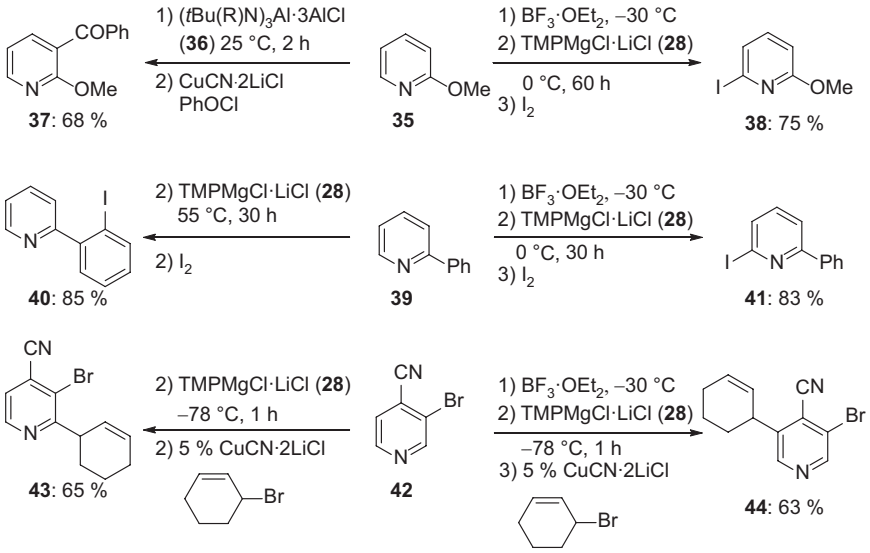
The pyridine ring can be further activated towards metalation by adding a strong Lewis acid such as $BF_3{\cdot}OEt_2$. It turns out that the sterically hindered base TMPMgCl·LiCl (**28**) reacts reversibly with $BF_3{\cdot}OEt_2$ at temperatures below −20 °C leading to the frustrated Lewis pair [40] TMPMgCl·BF_3. This adduct decomposes only at temperatures above −10 °C [41]. Through a coordination of the BF_3 group at the *N*-heterocyclic nitrogen the acidity of the pyridyl hydrogens increases, and the deprotonation of even electron-rich pyridines such as 2-methoxypyridine (**35**) proceeds readily. Interestingly, the addition of $BF_3{\cdot}OEt_2$



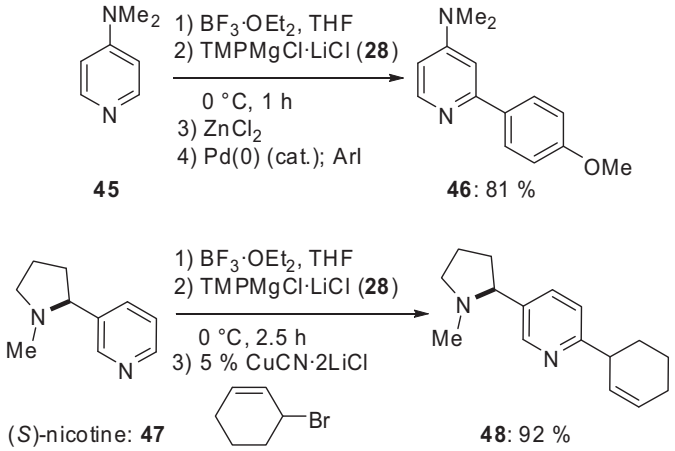
Scheme 9.

may also dramatically change the direction of the deprotonation [42]. Thus, in the absence of this Lewis acid, the metalation of **35** with the aluminum base $(t\text{Bu(R)N})_3\text{Al}{\cdot}3\text{LiCl}$ (**36**; R = *t*Bu(*i*Pr)CH) [42] proceeds in position 3 leading to the ketone **37** in 68% yield after a copper-catalyzed acylation. On the other hand, in the presence of $BF_3{\cdot}OEt_2$ (1.1 equiv.), the coordination of TMPMgCl·LiCl (**28**) at the oxygen-center of the methoxy group is hampered because of steric and inductive effects (Scheme 10).

The TMP-base is therefore metalating position 6 of the pyridine ring which is more readily accessible and clearly the most acidic position. After iodolysis, the 6-iodopyridine **38** is obtained in 75% yield (Scheme 10). This behavior is general and other substituted pyridines react in a similar way. Thus, when TMPMgCl·LiCl (**28**) is used without Lewis acid, 2-phenylpyridine (**39**) is magnesiated at the phenyl ring. In the presence of $BF_3{\cdot}OEt_2$, however, a smooth metalation occurs at position 6 of the pyridine ring. After iodolysis, the two regioisomeric iodides **40** and **41** are obtained in 83–85% yield. Also, the disubstituted 4-cyanopyridine **42** is magnesiated with TMPMgCl·LiCl in position 2 providing the 2-allylated pyridine **43** in 65% yield after copper-catalyzed allylation. In the presence of $BF_3{\cdot}OEt_2$, a complete switch of regio-



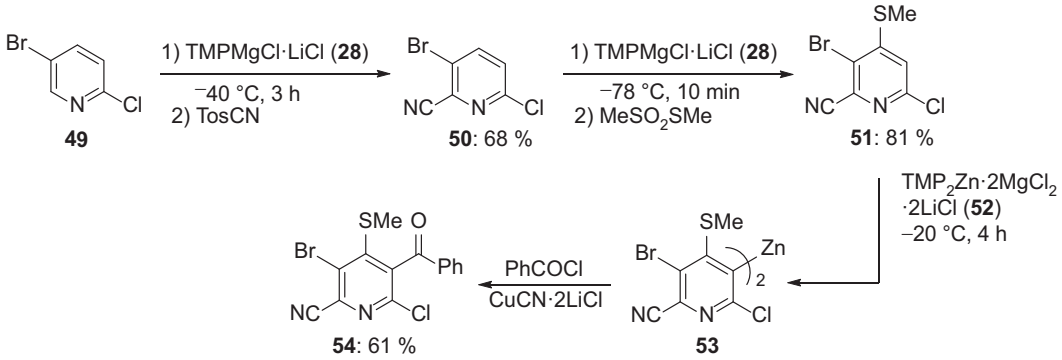
Scheme 10.



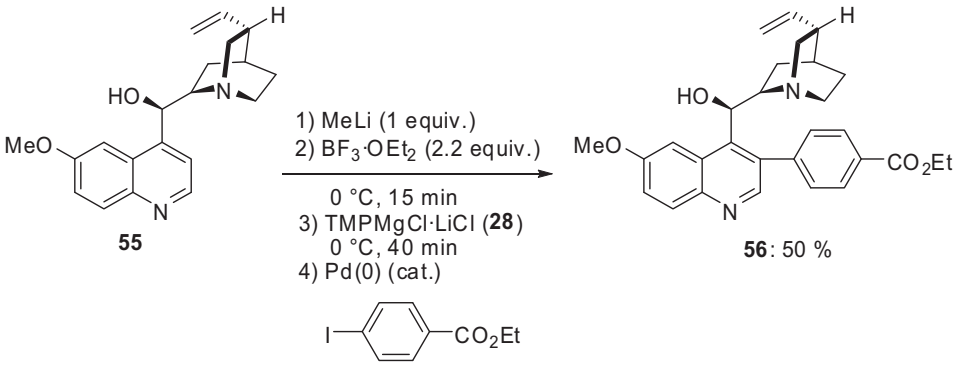
Scheme 11.

selectivity is observed, and after a copper(I)-catalyzed allylation, the 3,4,5-substituted pyridine **44** is obtained in 63 % yield (Scheme 10). Nitrogen substituents are also well tolerated in such metalation reactions. Thus, 4-dimethylaminopyridine (DMAP, **45**) is conveniently metalated with the system BF_3·OEt_2-TMPMgCl·LiCl (**28**) leading to the 2-arylated pyridine **46** in 81 % yield after Pd-catalyzed cross-coupling [43]. Similarly, the metalation of (*S*)-nicotine (**47**) proceeds selectively in position 6 providing the 3,6-disubstituted pyridine **48** in 92 % yield after a copper-catalyzed allylation (Scheme 11).

The reaction of 5-bromo-2-chloropyridine (**49**) with TMPMgCl·LiCl (**28**) allows a regioselective magnesiation in position 6. A subsequent addition of tosyl cyanide (TosCN) leads to the cyanopyridine **50** in 68 % yield. The reaction of **50** with a second equivalent of TMPMgCl·LiCl (**28**) for 10 min at −78 °C affords an intermediate magnesium derivative which, after quenching with $MeSO_2SMe$, leads to the thioether **51** in 81 % yield. The last ring position is best metalated by using TMP_2Zn·$2MgCl_2$·2LiCl (**52**) which is best prepared by reacting TMPMgCl·LiCl with $ZnCl_2$ (0.5 equiv.) [44–47]. Thus, with the base **52** the zin-



Scheme 12.



Scheme 13.

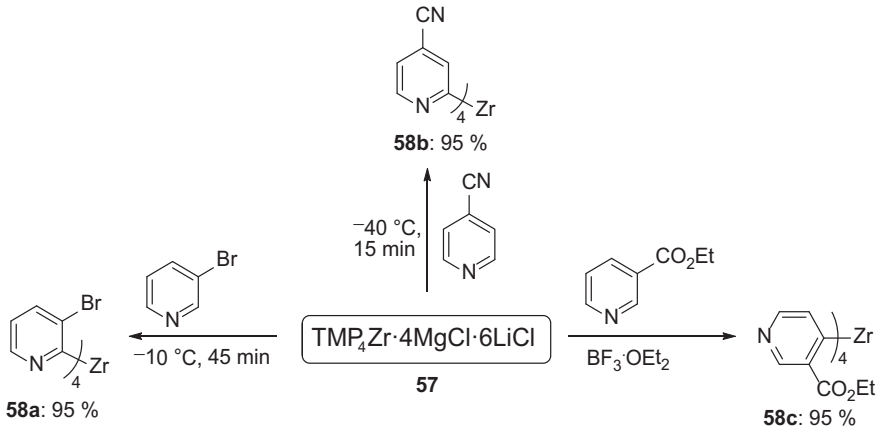
cation of **51** is achieved within 4 h at −20 °C leading to the zinc reagent **53**. Copper(I)-mediated acylation of **53** with PhCOCl provides the ketone **54** in 61 % yield (Scheme 12) [43].

The use of $BF_3{\cdot}OEt_2$ also allows the functionalization of complex pyridines or quinolines such as quinine (**55**). A regioselective metalation occurs at position 3 furnishing the arylated quinine **56** in 50 % overall yield after a Pd-catalyzed cross-coupling (Scheme 13) [43].

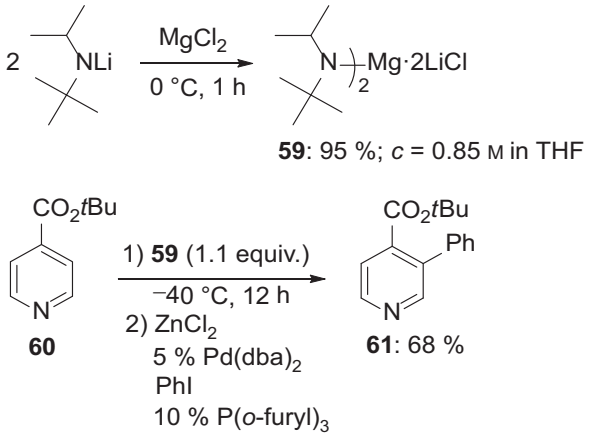
Besides TMP-Mg or -Zn bases, the use of $TMP_4Zr{\cdot}4MgCl_2{\cdot}6LiCl$ (**57**) is especially atom-economical, since 4 zirconations can be performed with base **57** affording tetraorganozirconium derivatives of type **58** [48]. Thus, the reaction of 3-bromopyridine, 4-cyanopyridine and 3-carbethoxypyridine regioselectively provides the tetrapyridylzirconium derivatives **58a–c** in 95 % yield. These zirconium derivatives react smoothly with allylic bromides or aryl halides in the presence of the appropriate copper or palladium catalysts (Scheme 14) [48].

Metalation of pyridines bearing hydrogens with moderate acidity can be achieved by using magnesium bis-amides. Whereas $TMP_2Mg{\cdot}2LiCl$ is not stable at room temperature over a longer time [49, 50], the mixed bis-amidic magnesium base **59** is perfectly stable at 25 °C for several days (>20 days). The magnesiation of the pyridine **60** with the magnesium amide **59** furnishes, after a Pd(0)-catalyzed cross-coupling, the phenylated pyridine **61** in 68 % yield (Scheme 15) [51].

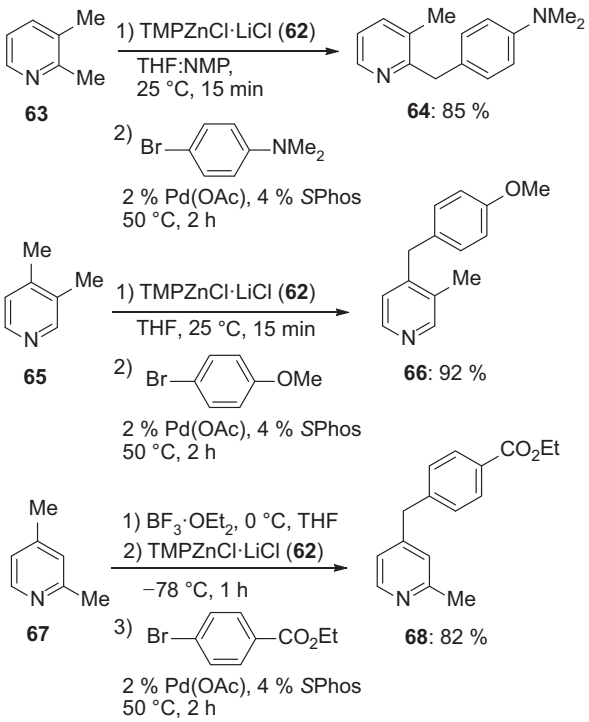
The lateral metalation of picolines and lutidines is of great synthetic interest. A highly regioselective zincation of various lutidines can be achieved under mild conditions using TMPZnCl·LiCl (**62**) [52–56]. Thus, 2,3-dimethylpyridine (**63**) is regioselectively deprotonated in THF : NEP (10 : 1); (NEP = *N*-ethylpyrrolidone) leading to the benzylated pyridine **64** after Pd-catalyzed arylation. Also, 3,4-dimethylpyridine (**65**) provides, after a fast zincation with **62** and Pd-catalyzed arylation, the 4-benzylated product **66** in 92 % yield (Scheme 16). Whereas the



Scheme 14.



Scheme 15.

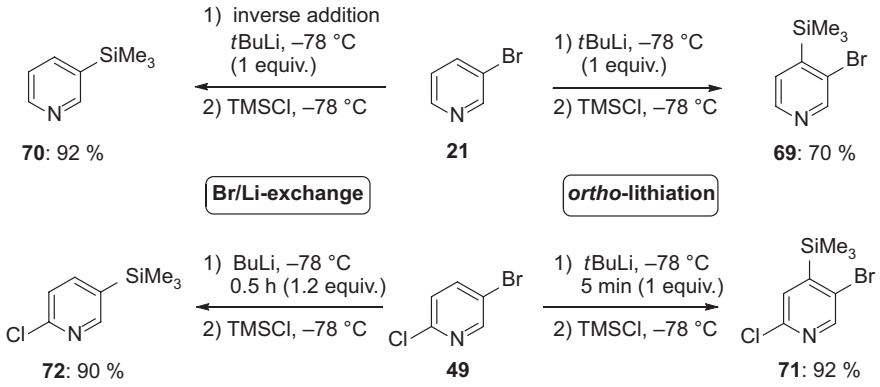


Scheme 16.

direct zincation of 2,4-dimethylpyridine (**67**) using TMPZnCl·LiCl (**62**) produces a mixture of regioisomers, the addition of $BF_3{\cdot}OEt_2$ considerably improves the regioselectivity of the metalation and leads only to the 4-benzylated pyridine **68** in 82% yield after Pd-catalyzed cross coupling (Scheme 16) [56].

Regioselective Functionalization of Pyridines *via* a Halogen/Metal Exchange

The presence of a bromo or an iodo substituent attached to the pyridine ring allows the performance of halogen/metal exchange reactions. The use of alkyllithium reagents leads to fast exchange reactions. However, the reaction conditions used are of special importance, since lithiation of the pyridine ring may be a competitive process. Thus, the addition of 1 equivalent of *t*BuLi to a solution of 3-bromopyridine (**21**) (THF, −78 °C, 5 min), followed by the addition of Me_3SiCl, furnishes the 4-silylated pyridine **69**, indicating a lithiation at position 4. By inverting the addition order (*i. e.* adding a solution of **21** to *t*BuLi), now the desired Br/Li-exchange occurs



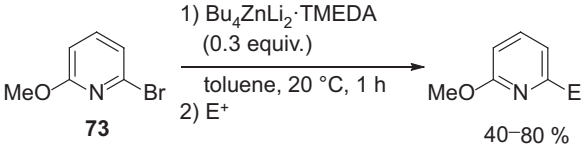
Scheme 17.

within 5 min (at −78 °C) affording the 3-silylated pyridine **70** in 92% yield after silylation. Interestingly, the nature of the lithium reagent can also change the course of the reaction. Thus, when dihalopyridine **49** is treated with *t*BuLi, the lithium reagent plays the role of a base rather than an exchange reagent, leading selectively to the trisubstituted product **71** in 92% yield after addition of Me_3SiCl (Scheme 17) [57]. In contrast, *n*BuLi selectively exchanges the bromine of **49** furnishing, after addition of Me_3SiCl, 2-chloro-5-(trimethylsilyl)pyridine (**72**) in 90% yield (Scheme 17).

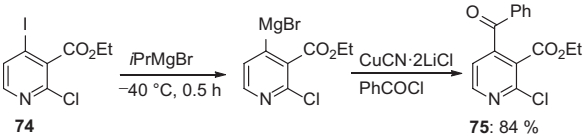
Due to these complications and in order to avoid the use of low temperatures, homoleptic zincates have been used for such exchange reactions. tBu_4ZnLi_2 has been shown to be highly selective for the performance of iodine or bromine exchanges [58, 59]. Additionally, the use of tBu_4ZnLi_2·TMEDA allows to carry out the metalations at room temperature. The use of 0.3 equivalents of the reagent may be sufficient for the exchange. Thus, the treatment of 6-bromo-2-methoxypyridine (**73**) with tBu_4ZnLi_2·TMEDA provides the desired 2,6-functionalized products in satisfactory yields after reaction with various electrophiles (Scheme 18) [60].

In many cases, the use of magnesium reagents allows to achieve iodine/magnesium exchanges in good yields. Thus, the highly functionalized iodopyridine **74** undergoes smoothly the exchange at −40 °C within 0.5 h using *i*PrMgBr. After a copper-catalyzed acylation with PhCOCl, the desired ketone **75** is obtained in 84% yield (Scheme 19) [61, 62].

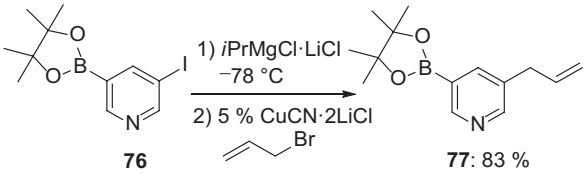
Also the iodopyridine **76**, bearing a boronic ester, undergoes readily a I/Mg-exchange reaction using



Scheme 18.



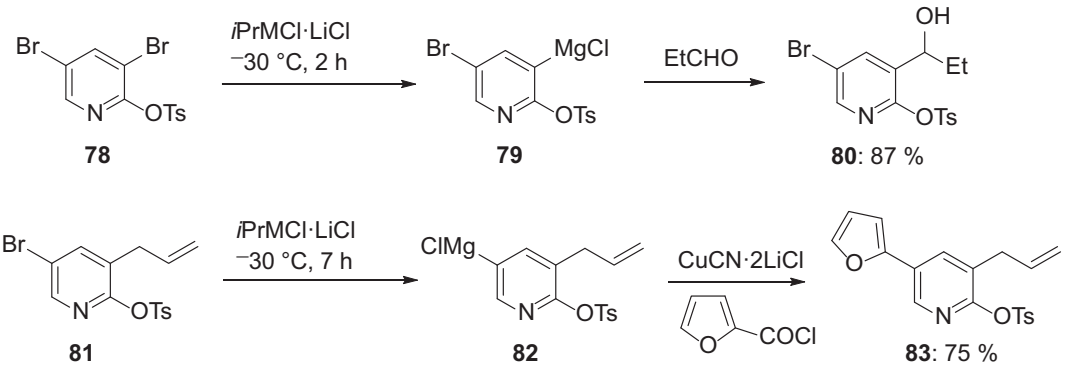
Scheme 19.



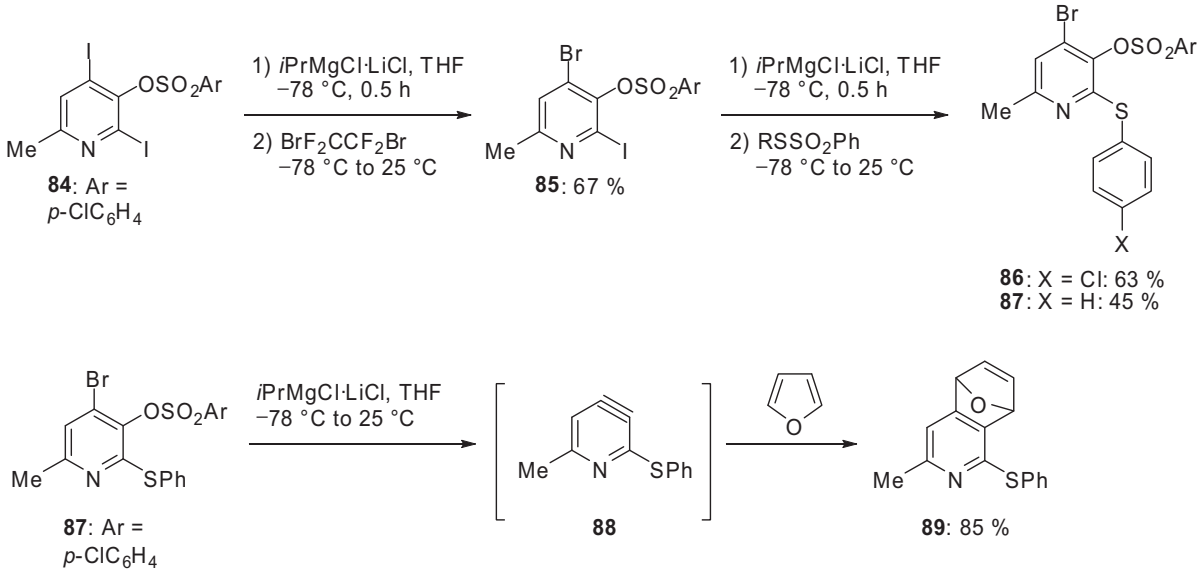
Scheme 20.

*i*PrMgCl·LiCl. Thus, after copper-catalyzed allylation, the allylated boronic ester **77** is obtained in 83% yield (Scheme 20) [63].

*i*PrMgCl·LiCl can also be applied to perform Br/Mg-exchange under mild conditions. Thus, the dibromopyridine **78** undergoes a quantitative Br/Mg-exchange using *i*PrMgCl·LiCl at −30 °C within 2 h leading to the magnesium reagent **79**, which can be trapped with numerous electrophiles. For example, its reaction with propionaldehyde provides the corresponding alcohol **80**



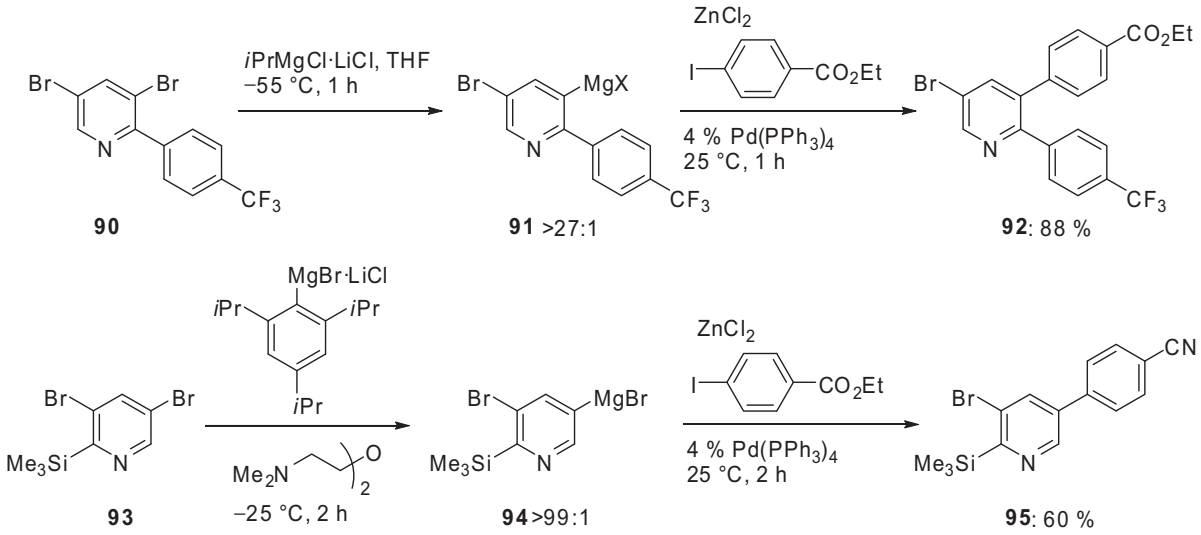
Scheme 21.



Scheme 22.

in 87% yield. Similarly, the pyridyl bromide **81** is converted at −30 °C within 7 h to the magnesiated pyridine **82**. A copper-catalyzed allylation furnishes the polyfunctional ketone **83** in 75% yield (Scheme 21) [64].

These exchange reactions can also be extended to quinolines and allow their multiple regioselective functionalization including a total synthesis of the biologically active molecule talnetant in less than six steps starting with a commercially available quinoline derivative [65]. Also, the regioselective I/Mg-exchange of diiodopyridines such as **84** can be realized under mild conditions. Using *i*PrMgCl·LiCl at −78 °C followed by quenching with $(BrF_2C)_2$ gives selectively the bromopyridine **85** in 67% overall yield. Subsequent I/Mg-exchange with *i*PrMgCl·LiCl at −78 °C provides, after reaction with $RSSO_2Ph$ (R = Ph, 4-ClC_6H_4), the thioethers **86** and **87** in 45% – 63% yield. Interestingly, the 4-chlorophenylsulfonate can be used as a leaving group in the absence of any added electrophile. Thus, the treatment of **87** with *i*PrMgCl·LiCl at −78 °C and heating of the reaction mixture to 25 °C for 1 h produces an intermediate pyridyne **88** which, after trapping with an excess of furan, produces the bicyclic product **89** in 85% yield (Scheme 22) [66].



Scheme 23.

The homogeneous nature of the Br/Mg-exchange allows to tune the reaction by changing various parameters, and impressive regioselectivities can be achieved for the functionalization of various 3,5-dibromopyridines [67]. Thus, the reaction of the dibromopyridine **90** with *i*PrMgCl·LiCl at −55 °C is complete within 1 h leading to the pyridylmagnesium reagent **91** with a regioselectivity better than 27 : 1. A transmetalation with $ZnCl_2$ followed by a Pd-catalyzed cross-coupling with ethyl 4-iodobenzoate produces the bis-arylated pyridine **92** in 88 % yield (Scheme 23). This remarkable regioselectivity is a consequence of the difference of electronegativity of the substituents at positions 2 and 6 of the pyridine ring. The aryl ring at position 2 leads to an inductive effect stabilizing eventually the resulting Grignard reagent formed after the exchange reaction. The opposite regioselectivity can be reached by having an electron-donating substituent such as a trimethylsilyl group at position 2 (pyridine **93**). This electron-donating substituent disfavors the resulting Grignard reaction by an α-effect and hampers the Br/Mg-exchange owing to steric hindrance. This steric hindrance is further increased by using a bulky arylmagnesium reagent such as mesitylmagnesium bromide. After 2 h of reaction time at −25 °C, the exchange is complete and the resulting Grignard reagent **94** is obtained. Transmetalation with $ZnCl_2$ followed by Pd-catalyzed cross-coupling with 4-iodobenzonitrile produces the pyridine **95** in 60 % isolated yield (Scheme 23) [67].

Summary and Conclusion

This review summarizes the organometallic approaches to functionalize the pyridine scaffold by either directed metalation or by halogen/metal exchange. In both cases, lithium species play a major role. Amide bases like LDA or TMPLi as well as organolithium reagents such as *t*BuLi or MesLi can be used for selective C-H activation. Interestingly, alkyllithium species either deprotonate the pyridine scaffold or allow a bromine exchange, depending on the reaction conditions. The use of lithium organometallics, however, requires in most cases low temperatures (−78 °C) and only a limited number of functionalities can be tolerated. This drawback can be overcome by switching to less electropositive metals. For directed metalations, ate-bases with metals such as cadmium, magnesium or zinc, as well as TMP metal bases (metal = Mg, Zn, Zr) allow less stringent conditions and a higher functional group tolerance. The TMP derived bases are compatible with Lewis acids like $BF_3{\cdot}OEt_2$ at low temperature, allowing to functionalize even electron-rich and complex systems like quinine, (*S*)-nicotine or DMAP. For the halogen/metal exchange, the formation of homoleptic zincates or organomagnesium reagents, like *i*PrMgX (X = Br, Cl·LiCl) makes it possible to work

under mild conditions with high functional group tolerance, allowing in certain cases to distinguish between two bromine or iodine atoms attached to the pyridine ring.

This review emphasizes the important role of organometallic chemistry in the synthesis and funtionalization of pyridines, which is of major concerns due to the biological activity of this class of substances.

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