*n*BuLi/Lithium Aminoalkoxide Aggregates: New and Promising Lithiating Agents for Pyridine Derivatives

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*n*BuLi/lithium aminoalkoxide aggregates have proven to be useful new lithiating agents. This review covers the current status of the authors' works on the direct metallation of pyridine derivatives with these reagents, featuring the scope of their synthetic potential.

Introduction

Pyridine derivatives have become essential in many fields, such as transition metal chemistry,[1] supramolecular chemistry,[2] optoelectronic[3] or luminescent materials,[4] and pharmaceutical chemistry.[5] Consequently, the growing need for such compounds continuously drives chemists to design efficient and selective methods to introduce functionalities on the pyridine ring. Of these various methods, the use of lithiated pyridines has been the focus of many studies over the last two past decades and has resulted in numerous new substituted derivatives.[6] Although halogen-lithium exchange on bromo- or iodopyridines[7a,7b] has proven to be an efficient process,[7] hydrogen-lithium exchange represents a more straightforward route to functional derivatives. Unfortunately, the π-deficiency of pyridines has long limited the scope of this latter reaction. Indeed, treatment with alkyllithiums has usually resulted in nucleophilic attack on the azomethine bond.[8] To overcome this side-reaction and to favor lithiation, one alternative has been to turn alkyllithium species into sterically hindered non-nucleophilic lithium dialkylamides, especially LDA[9] and LTMP.[10]

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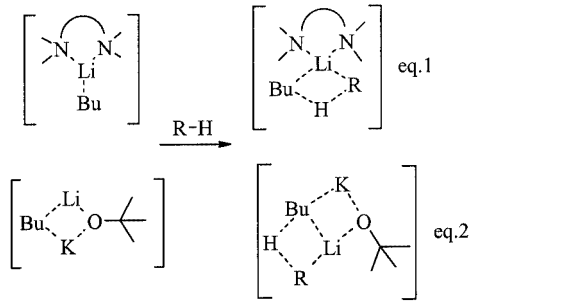
MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

Despite their lower basicities ($pK_a \approx 35-37$ for LDA and LTMP) compared to alkyllithiums ($pK_a \approx 45$), these reagents have successfully effected the metallation of main pyridines, but also display some drawbacks. They often need to be used in excess (2−4 equiv.) and their preparation needs expensive starting amines, especially in the case of LTMP. Equilibrated reactions are also observed in some cases and imply in situ trapping of lithio intermediates.[11]

The strongly basic alkyllithium thus remains of interest, and efforts have been devoted to turn nucleophilic alkyllithiums into basic reagents; that is, to increase their basicity/nucleophilicity ratio, with a particular focus on the most common and easily handled *n*BuLi.

One way to increase this ratio is to enhance the basicity through association between *n*BuLi and lithium-chelating diamines such as TMEDA.[12] The diamine here decreases the degree of aggregation of BuLi from hexamers essentially to dimers and monomers [Equation (1), Scheme 1).

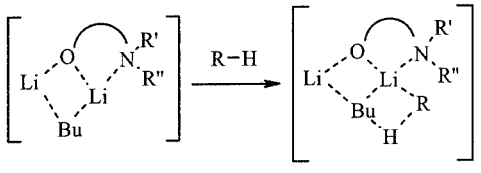


Scheme 1. Activation of *n*BuLi by chelating diamines [Equation1) and *t*BuOK [Equation2)

Another option has been to employ the superbase known as LICKOR (*n*BuLi/*t*BuOK) developed by Schlosser et al.[13] and Lochman et al.,[14] which contains potassium alkoxide as a highly electron-rich complexing agent [Scheme 1, Equation (2)]. LICKOR species, associating two different alkali cations, are also known as multimetal superbases (MSBs).[15] This family of bimetallic reagents has proven powerful in the aliphatic, aromatic, and heteroaromatic series.[15]

In contrast, unimetal superbases (USBs), developed by Lochmann[14c] (for lithium) and Caubère (for sodium),[16] with simple linear or branched alkoxides were found in our hands to be totally inefficient for metallation of pyridine derivatives.

Our aim therefore became to design a new class of lithium-containing unimetallic superbases combining a chelating amino group and an electron-rich alkoxide in the same reagent (Scheme 2). We thought that association between *n*BuLi and a lithium aminoalkoxide might enhance basicity by complexation and inhibit nucleophilicity by formation of sterically hindered aggregates.

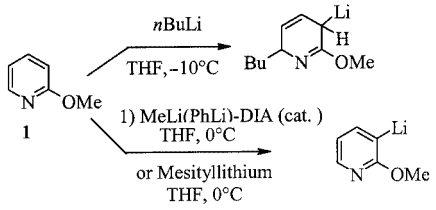


Scheme 2. Potential activation of *n*BuLi with aminoalkoxides

This review summarizes the current status of our work on the metallation of pyridine derivatives with *n*BuLi/lithium aminoalkoxide reagents, featuring both mechanistic aspects and the scope of the synthetic potential of this new methodology.

The Discovery of *n*BuLi/Aminoalkoxide Reagents

The properties of *n*BuLi/aminoalkoxide reagents were first discovered during lithiation of 2-methoxypyridine (**1**). This substrate was found to be appropriate for an investigation of the basicity/nucleophilicity ratio of a new basic reagent, as two kinds of reactions were observed depending on the metallation agent used. Thomas showed that *n*BuLi added exclusively onto the azomethine bond,[17] while Quéguiner et al.[11] and Comins et al.[9d] reported that, with LDA, lithiation occurred at C-3 as a consequence of directed *ortho*-metallation (DOM)[18] of the methoxy group. They subsequently found evidence of an equilibrated reaction when the compatible TMSCl was used as electrophile. As a consequence, new reagents combining MeLi[11] or PhLi[19]with catalytic amount of diisopropylamine were then developed, in order to avoid protonation of the lithiated pyridine in the reaction medium. Meanwhile, Comins and co-workers introduced the use of mesityllithium[18] as an efficient hindered aryllithium to promote the reaction (Scheme 3).



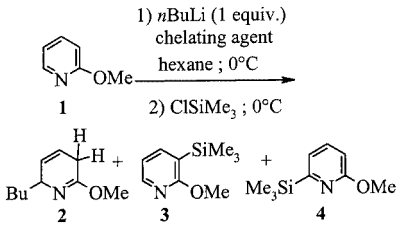
Scheme 3. Treatment of **1** with conventional lithiating agents

The *n*BuLi/ROLi reagents were prepared by mixing a solution of 1 equiv. of ROH in anhydrous hexane with 2 equiv. of *n*BuLi at 0 °C, and were subsequently allowed to react with **1**. The lithiated species formed in the reaction medium were trapped with an excess of chlorotrimethylsilane. The first experiments with various chelating agents (Table 1) rapidly revealed the atypical behavior of aminoalkoxide.[20]

While TMEDA, tertiary alkoxides, glycoxides, or monoethers of glycoxides mainly afforded the addition product **2**, lithium dimethylaminoethoxide (LiDMAE) gave the best metallation/addition ratio, providing **4** in 42% yield. Moreover, lithiation occurred exclusively at C-6 without any trace of the usually obtained 3-silyl derivative **3**.

This unprecedented result confirmed our hypothesis concerning the ability of aminoalkoxide to modify the basicity/nucleophilicity ratio of *n*BuLi. We then attempted to optimize this new reaction.

Table 1. Treatment of **1** with various *n*BuLi-chelating agent combinations



Chelating agent	**2** (%)[a]	**3** (%)[a]	**4** (%)[a]
TMEDA	31	16	–
*t*BuOLi	100	–	–
$LiO(CH_2)_2OLi$	100	–	–
$EtO(CH_2)_2OLi$	26	–	7
$Me_2N(CH_2)_2OLi$	28	–	42

[a] GC yields

The next experiments found that the yield and selectivity were dramatically dependent on base amount and reagent stoichiometry (Table 2).

Table 2. Effect of reagent stoichiometry on selectivity.

BuLi (equiv.)	LiDMAE (equiv.)	**2** (%)[a]	**3** (%)[a]	**4** (%)[a]
1	1	28	–	42
2	1	87	–	–
1	2	1	17	52
1	3	3	23	35
1	5	3	22	16
2	2	10	–	80
4	4	5	–	95

[a] GC yields.

While an increase in the *n*BuLi/LiDMAE ratio resulted in nucleophilic addition, a decrease in this ratio produced the C-3-lithiated compound in notable quantities. Also surprising was the substantial benefit obtained by increasing the amount of base, the use of 4 equiv. almost abolishing the addition product. The results as a whole revealed the outstanding importance of complexation in the lithiation process (discussed below).

The metallation solvent was also found to modify the metallation selectivity dramatically (Table 3). When chelating solvents were used instead of hexane, only addition product **2** was obtained. This indicated a probable strong aggregation between *n*BuLi/LiDMAE and **1** in apolar solvents. In THF, chelation competes with aggregation and free *n*BuLi was probably produced, resulting in classical nucleophilic addition. This is supported by the good selectivity obtained in the non-chelating toluene.

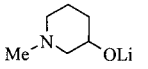
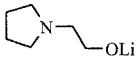
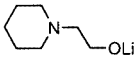
Table 3. Effect of metallation solvent on selectivity

Solvent[a]	**2** (%)[b]	**4** (%)[b]
hexane	5	95
toluene	15	85
diethyl ether	100	–
tetrahydrofuran	100	–
dioxane	100	–

[a] Reaction performed with 4 equiv. of *n*BuLi/LiDMAE. [b] GC yields.

The addition/metallation ratio was also monitored by the structure of the aminoalkoxide[21] (Table 4). To promote the C-6 lithiation in high yield, the aminoalkoxides have to possess appropriate structures involving low steric hindrance at nitrogen and unsubstituted two-carbon chains between nitrogen and alkoxide. This was probably a strong indication of the involvement of the nitrogen atom of the aminoalkoxide in the reactive aggregates.

Table 4. Effect of the aminoalkoxide structure on selectivity[a]

Aminoalkoxide	**2**(%)[b]	**4**(%)[b]
$Me_2N(CH_2)_2OLi$	5	95
i-$Pr_2N(CH_2)_2OLi$	90	-
$Me_2N(CH_2)_3OLi$	85	-
$Me_2NCH(Me)CH(Ph)OLi$	40	56
	32	64
	10	86
	27	67

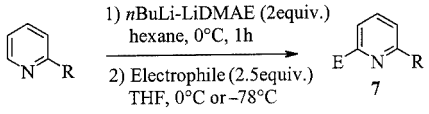
[a] Reactions performed with 4 equiv. of *n*BuLi-ROLi. [b] GC yields.

Lithiation of Pyridines Bearing a Heteroatom at C-2

The *n*BuLi/LiDMAE-induced lithiation process was not limited to **1**, and was also applied successfully to other substrates bearing a chelating heteroatom at C-2, such as 2-methylthiopyridine (**5**) and 2-dimethylaminopyridine (**6**). Treatment of a set of electrophiles gave a range of 2,6-disubstituted pyridines **7**[21,22] in good to high yields (Table 5).

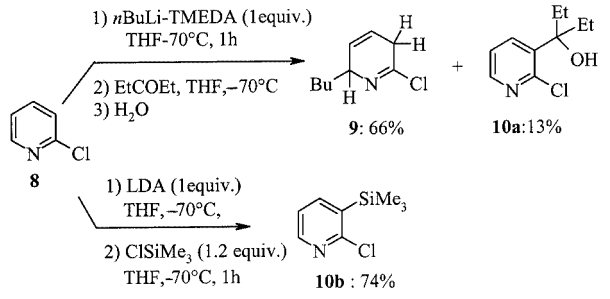
In the same way, the metallation of 2-chloropyridine (**8**) was of particular interest. The chlorine atom was known to

Table 5. C-6 functionalization of 2-hetero-substituted pyridines; E = D, SMe, RC(OH)R′, Alkyl, $SnBu_3$



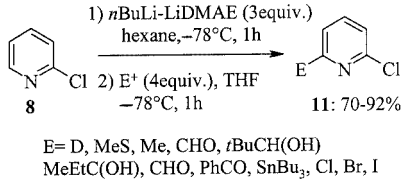
1	R = OMe	40–84%
5	R = SMe	60–80%
6	R = NMe_2	44–52%

direct metallation at C-3 with LDA as basic reagent,[7d,23] while *n*BuLi or *n*BuLi/TMEDA essentially afforded addition products (Scheme 4).[24]



Scheme 4. Treatment of **8** with conventional lithiating agents

The metallation performed with *n*BuLi/LiDMAE resulted in regioselective lithiation at C-6, with tolerance of the C−Cl bond and no nucleophilic addition onto the azomethine bond of pyridine.[25] Once more, association between *n*BuLi and LiDMAE contributed to strong inhibition of the nucleophilicity of *n*BuLi. In addition, the classical chlorine atom-induced *ortho*-directed metallation at C-3 was impeded (Scheme 5). This was a particularly useful lithiation process, since the preservation of the C−Cl bond offered a potential source of further functionalization of compounds **11** through S_NAr or organometallic couplings.

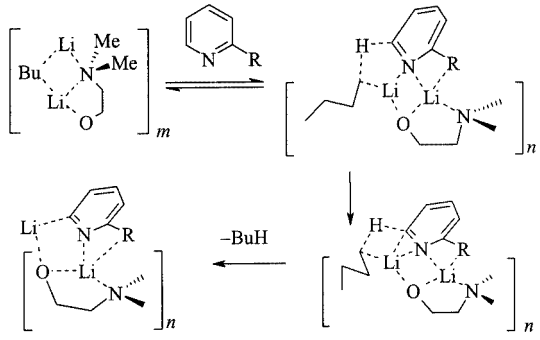


Scheme 5. *n*BuLi/LiDMAE-mediated C-6 lithiation of 2-chloropyridine

Mechanistic Considerations

The experiments described above, performed with **1**, **5**, **6**, or **8**, caused us to propose a lithiation mechanism involving formation of aggregates between the *n*BuLi/LiDMAE reagent and the substrate, through lithium complexation by the pyridine nitrogen atom and the heteroatom at C-2. The presence of two lithium cations in the basic reagent was critical to promote double complexation of the pyridine nucleus. Aggregates were assumed firstly to deliver *n*BuLi near the 6-H proton and secondly to ensure stabilization of the formed 6-lithiated intermediate. Evidently, formation of such aggregates could not be involved in treatment with lithium dialkylamides in THF (Scheme 6).

Nevertheless, the complete inhibition of the DOM effect,[18] especially with **1** and **8**, was found intriguing, since the Mulliken charges on 3-H and 6-H are very close in both substrates (Figure 1).



Scheme 6. Proposed mechanism for C-6 lithiation

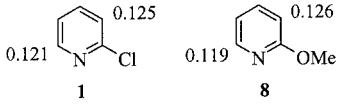
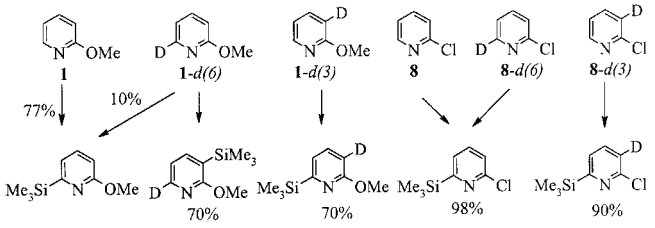


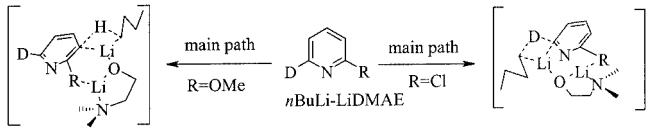
Figure 1. PM3-calculated Mulliken charges

It was therefore assumed that selectivity was governed rather by complexation than by proton acidities and we wondered whether *n*BuLi/LiDMAE-induced C-6 lithiation was direct or the result of a previous 3-lithio intermediate equilibration. Lithiation of derivatives with the prospective hydrogens (3-H or 6-H) replaced by deuterium revealed, especially with **8**, a strong preference of *n*BuLi/LiDMAE for the C-6 position even in the presence of an isotopic effect (Scheme 7).[26]



Scheme 7. Lithiation of deuterated compounds with *n*BuLi/LiDMAE

However, a difference was noted during lithiation of derivatives **1**-*d*(*6*) and **8**-*d*(*6*). With **1**-*d*(*6*), deuterium at C-6 was not completely abstracted and lithiation occurred mainly at C-3. Since the O-Li interaction is assumed to be stronger than the Cl−Li one, the methoxy group probably competes more than chlorine with the pyridine nitrogen in lithium complexation. The consequence is delivery of the butyl base farther from the 6-position with **1**-*d*(*6*) than with **8**-*d*(*6*), allowing C-6 and mainly C-3 lithiation in the former case. On the other hand, prevalent complexation by pyridine nitrogen with **8**-*d*(*6*) puts the butyl base closer to the 6-position and produces subsequent exclusive C-6 lithiation (Scheme 8). This revealed the influence of lithium com-



Scheme 8. Effect of heteroatom-complexing ability on lithiation of deuterated derivatives

plexation ability of the heteroatom at C-2 on the metallation regioselectivity.

Lithiation of Pyridines Bearing Heteroatoms at C-3 or C-4

The experiments described above showed the ability of a heteroatom at C-2 to compete with the pyridine nitrogen for lithium complexation. We therefore examined such competition with substrates bearing *ortho*-directing heteroatoms at C-3 or C-4 on the pyridine ring (Figure 2).

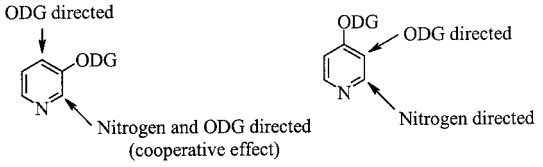
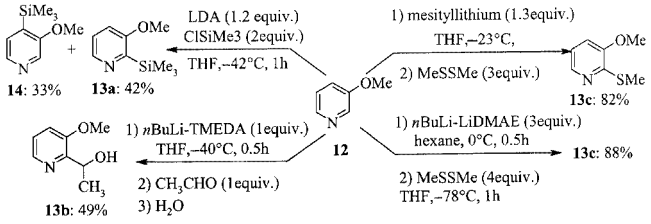


Figure 2. Competition between the ODG (*ortho*-directing group) and pyridine nitrogen

As shown in Figure 2, an ODG is ambivalent with C-3 substituted pyridines, as it can compete with pyridine nitrogen for complexation (deprotonation at C-4) or provide a cooperative effect (deprotonation at C-2). With the C-4 substituted isomer, only competition between ODG and nitrogen should be observed.

Lithiation of 3- and 4-Methoxypyridines

The literature reports several examples of lithiation of 3-methoxypyridine (**12**). Different efficiencies and selectivities have been obtained, depending on the lithiating agent and the conditions used (Schem 9).

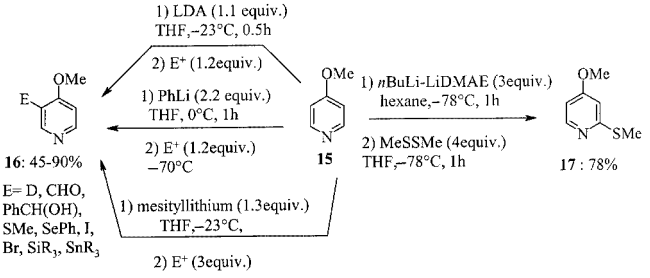


Scheme 9. Treatment of 3-methoxypyridine (**12**) with conventional lithiating agents and with *n*BuLi/LiDMAE.

As a general trend, with LDA,[9d] *n*BuLi/TMEDA,[27] or mesityllithium[9d] in THF, **12** was lithiated mainly at C-2 to afford compounds **13a**–**c**, probably as a consequence of a cooperative effect between the pyridine nitrogen and the methoxy group for lithium complexation (Schem 9). With *n*BuLi/LiDMAE in hexane, the above selectivity was also observed after 30 min of metallation at 0 °C (Schem 9).[28]

Lithiation of 4-methoxypyridine (**15**) was more informative about the competition between the methoxy group and the pyridine nitrogen. Indeed, exclusive C-3 lithiation was observed with LDA,[29] PhLi,[30] or mesityllithium[9d] in THF, providing various 3,4-disubstituted derivatives **16**.

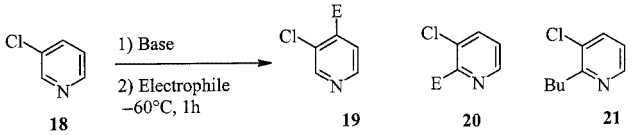
With *n*BuLi/LiDMAE in hexane, in contrast, a complete reversal of selectivity was observed, and lithiation was exclusively directed at C-2 when metallation was performed at –78 °C, to afford **17**.[28] Hexane probably favored aggregate formation near the pyridine nitrogen here. It is also remarkable that with **12** and **15** the *n*BuLi/LiDMAE never produced any trace of *n*BuLi nucleophilic addition product (Scheme 10).



Scheme 10. Lithiation of 4-methoxypyridine (**15**) with conventional lithiating agents and with *n*BuLi-LiDMAE

Lithiation of 3- and 4-Chloropyridines

The extent of the pyridine nitrogen-directed versus chelating substituent-directed lithiation was further examined by treatment of *n*BuLi/LiDMAE with 3- and 4-chloropyridines (**18** and **22**). These compounds had previously been lithiated with LDA and with activated *n*BuLi. With 3-chloropyridine (**18**), LDA in THF exclusively gave **19**,[31] while *n*BuLi/TMEDA or *n*BuLi/crown ether in diethyl ether gave a mixture of regioisomers **19** and **20** contaminated by addition product **21**.[23] With *n*BuLi/LiDMAE, C-2 metallation was obtained exclusively. Such selective lithiation was used to prepare a range of useful 2,3-disubstituted pyridine derivatives **20** (Scheme 11).[32]



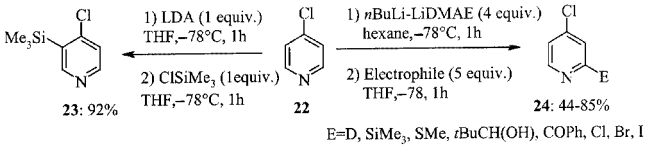
	19	20	21
LDA (1equiv.) THF,–60°C, 1h E=TMS	96%	-	-
*n*BuLi-TMEDA (1equiv.) diethylether,–60°C, 1h E=TMS	9%	60%	20%
*n*BuLi-(18-crown-6) (1equiv.) diethylether,–60°C, 1h E=TMS	75%	20%	5%
*n*BuLi-LiDMAE (3 equiv.) hexane;–60°C; 1h	-	47-85%	-

E=D, SMe, *t*BuCH(OH), COPh, Cl, Br, I

Scheme 11. Lithiation of **18** with conventional lithiating agents and with *n*BuLi/LiDMAE

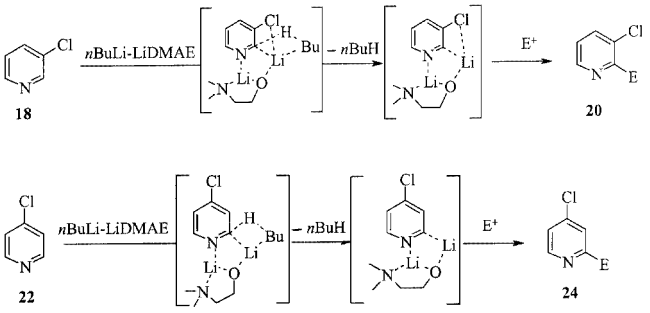
While 4-chloropyridine (**22**) was known to give C-3 substituted isomer **23** with LDA[30,33] or *n*BuLi/TMEDA in THF,[7d] an opposite selectivity was observed with *n*BuLi/LiDMAE in hexane, lithiation occurring exclusively at C-2, as already observed with 4-methoxypyridine (**15**), and providing compounds **24**.[28] This once more indicated strong

lithium complexation at the nitrogen atom in the presence of aminoalkoxide (Scheme 12).



Scheme 12. Lithiation of **22** with conventional lithiating agents and with *n*BuLi/LiDMAE

The origin of this selectivity for 3- and 4-chloropyridine could be explained by formation of lithium aggregates neighboring the nitrogen atom, thus directing the metallation at C-2 and stabilizing the subsequently formed lithiated species. The exclusive formation of the C-2-substituted product with 3-chloropyridine could be explained by cooperative complexation of lithium by chlorine atom, pyridine nitrogen, and aminoalkoxide (Scheme 13).

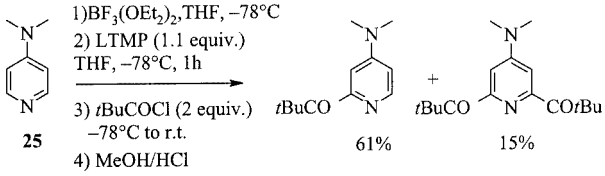


Scheme 13. Proposed mechanism for the C-2 lithiation of **18** and **22**

Lithiation of 4-(Dimethylamino)pyridine

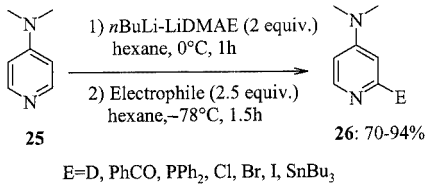
In view of the unprecedented selectivity obtained with 4-chloropyridine (**22**) and with 4-methoxypyridine (**15**), the lithiation of pyridines bearing other potentially directing substituents at C-4 was investigated.

In this context, the metallation of 4-DMAP (**25**) was particularly interesting. This substrate has been used extensively as a powerful acylation catalyst.[34] Its analogues have recently been used as ligands for transition metals,[35] catalysts for ester methanolysis,[36] or enantioselective acyl transfer.[37] Until our work, only one lithiation method was known to functionalize the pyridine ring of 4-DMAP through reaction between a BF_3/DMAP complex and LTMP.[37a,38] Unfortunately, because of the strong increase in proton acidity induced by BF_3-complexation, the lithiation also gave the disubstituted side product (Scheme 14).



Scheme 14. Lithiation of **25** by the Kessar reagent

Interestingly, *n*BuLi/LiDMAE performed the first direct α-monolithiation of 4-DMAP, avoiding the tedious activation/lithiation/decomplexation sequence described above (Scheme 15).[39]



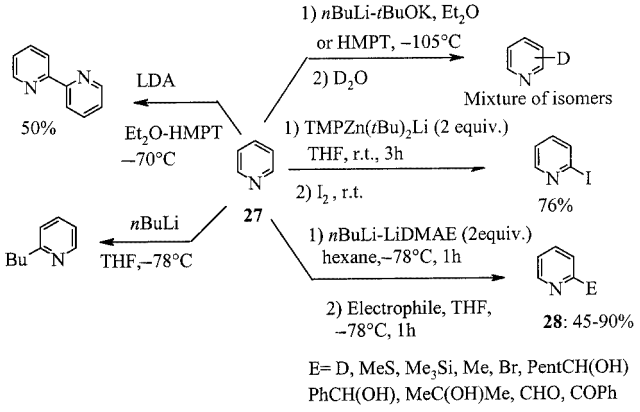
Scheme 15. Selective C-2 lithiation of 4-DMAP (**25**)

This unprecedented direct and selective lithiation could be explained by the formation of aggregates as depicted for 4-chloropyridine in Scheme 14 (**22**). In this case, lithium complexation by the pyridine nitrogen was probably strongly enhanced by the electron-releasing dimethylamino group at the 4-position.

In summary, lithiation with *n*BuLi/LiDMAE in hexane occurred at C-2 in the cases of Cl, OMe, and NMe_2. This confirmed our previous observations during lithiation of unsubstituted heterocycles.

Lithiation of Pyridine and Quinoline

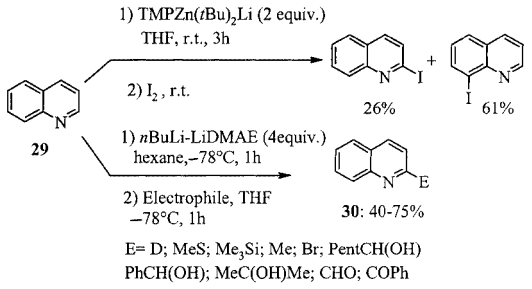
The metallation of pyridine (**27**) is known to be a hard task, since it is highly sensitive to nucleophilic attack by alkyllithiums.[8] Use of LDA gave bipyridine,[40] while *n*BuLi/*t*BuOK (LICKOR) furnished a mixture of regioisomers.[41] Kondo et al. only recently succeeded in stabilizing the organometallic species at C-2[42] by using the TMPZn/$(t\text{Bu})_2$Li reagent. With *n*BuLi/LiDMAE, we had previously observed a highly chemo- and regioselective lithiation at C-2 (Scheme 16).[43]



Scheme 16. Treatment of pyridine with lithiating agents and *n*BuLi/LiDMAE

The reaction was also successfully applied to the more electrophilic quinoline (**29**). Although nucleophilic addition could not be totally suppressed in this case (typically 10−20%), C-2-substituted derivatives **30** were nevertheless

obtained in good yields.[43] Note that with **29**, the Kondo reagent mainly gave substitution at C-8[42] (Scheme 17).

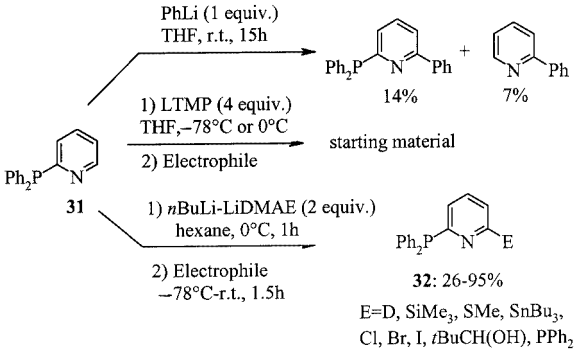


Scheme 17. Lithiation of quinoline with the Kondo reagent and with *n*BuLi/LiDMAE

Lithiation of Pyridines Bearing Base-Sensitive Substituents

Lithiation of 2-(Diphenylphosphanyl)pyridine

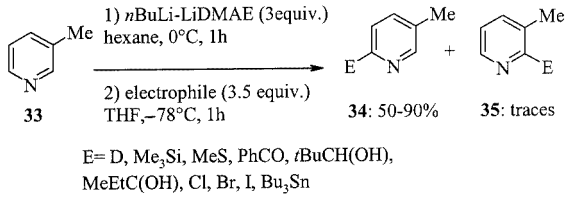
In their work on reactions between 2-diphenylphosphanylpyridine (**31**) and aryllithiums, Oae and co-workers[44] reported that both the diphenylphosphanyl group and the pyridine ring were sensitive to nucleophilic addition, and the same result was obtained in our hands with *n*BuLi.[45] We also showed that LTMP did not give any metallation product, indicating the inefficiency of the PPh_2 group in directing lithiation. The behavior of *n*BuLi/LiDMAE was found to be far more interesting, since the PPh_2 group was fully tolerated and lithiation occurred regioselectively at C-6,[45] yielding a wide range of new functional P−N and P−N−P ligands **32** (Scheme 18).[1d]



Scheme 18. Reaction of **31** with lithiating agents and BuLi/LiDMAE

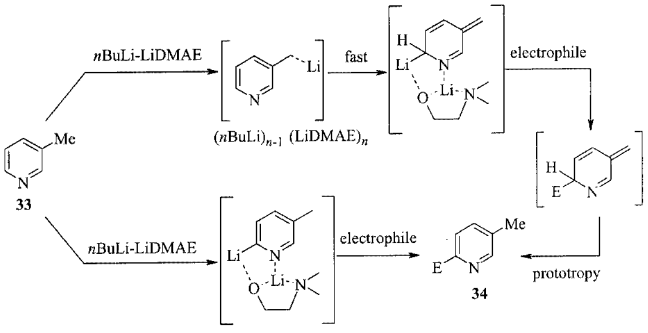
Lithiation of 3-Picoline

The strong affinity of *n*BuLi/LiDMAE for protons at C-2 on pyridines was also illustrated in the lithiation of 3-picoline (**33**). Because of the higher acidity of the methyl group, these compounds have been metallated only at the methyl group when using LDA.[46] With *n*BuLi/LiDMAE, the metallation was exclusively directed towards the pyridine ring, leaving the methyl group unaffected. In addition, 3-picoline mainly underwent *para*-lithiation, giving an unprecedented direct route to compounds **34** (Scheme 19).



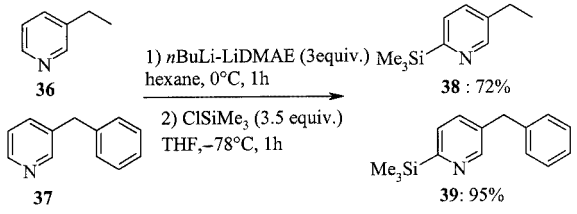
Scheme 19. Lithiation of 3-picoline with *n*BuLi/LiDMAE

Taking into account the formation of product **35** in only trace amounts and the higher acidity of methyl protons, direct lithiation of the pyridine ring could not be the single mechanistic pathway. We have therefore proposed another mechanism, depicted in Scheme 20, involving lithium migration from a previously formed pyridylmethyllithium towards the C-2 position on the pyridine ring favored by lithium aggregates.



Scheme 20. Proposed mechanism for C-6 lithiation of 3-picoline (**33**)

Such a ring-selective metallation has also successfully been applied to other monosubstituted pyridines bearing acidic side chains, such as 3-ethylpyridine (**36**) and 3-benzylpyridine (**37**), which gave the corresponding C-6 substituted derivatives **38** and **39**, respectively, in good yields. The selectivity in the latter case was remarkable, in view of the acidity of the benzylic protons (Scheme 21).[48]

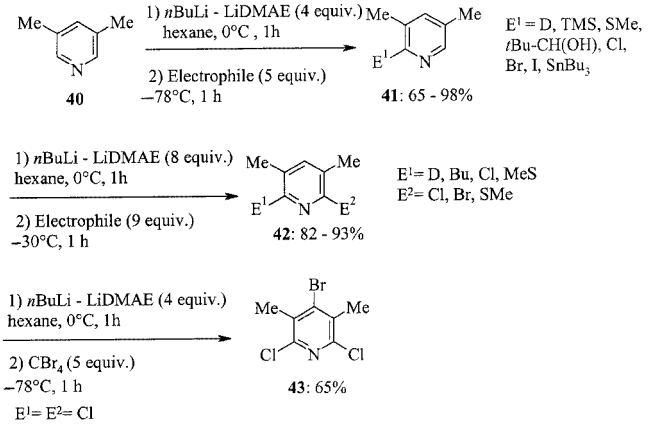


Scheme 21. Lithiation of 3-ethyl- and 3-benzylpyridine at C-6

Disubstituted substrates were also lithiated. 3,5-Lutidine (**40**) underwent an efficient sequential lithiation to provide a wide range of new reactive heterocyclic building blocks **41**−**43** (Scheme 22).[49]

Regio-/Enantioselective Functionalization

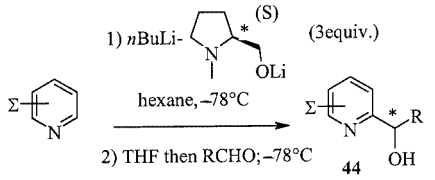
We have also demonstrated that enantioselective functionalization can be achieved by incorporation of a chiral aminoalkoxide into the reagent. Indeed, the chiral pyridyl



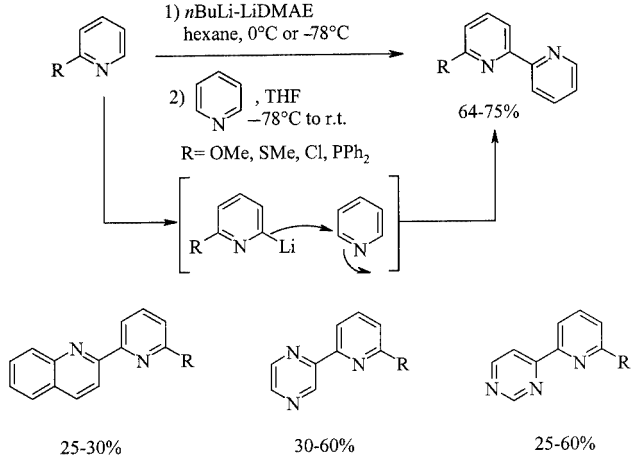
Scheme 22. Sequential lithiation of 3,5-lutidine (**40**)

alcohols **44**, useful ligand substructures for asymmetric synthesis,[1b–1c,37] have been directly accessed through lithiation of pyridines with an *n*BuLi/lithium (*S*)-*N*-methyl-2-pyrrolidine methoxide reagent and addition to prochiral carbonyl moieties (Table 6).[50]

Table 6. *n*BuLi/lithium (*S*)-*N*-methyl-2-pyrrolidine methoxide-mediated synthesis of chiral pyridylcarbinols



Σ	R	*ee* %	Yield %
2–Cl	Ph	53	60
2-Cl	p-MeO-Ph	45	61
2-Cl	p-Cl-Ph	23	56
2-F[51]	Ph	30	74
3-Me	Ph	39	47



Scheme 23. Preparation of 2,2′-bis(heterocycles)

This was the first straightforward route to compounds **44**, which are generally prepared by enantioselective reduction of pyridyl ketones.[1b][37a]

Preparation of 2,2′-Bis(heterocycles)

The *n*BuLi/LiDMAE-induced selective C-6 lithiation also proved to be a simple and direct route to 2,2′-bis(heterocycles)[22a,25,45] through nucleophilic addition of lithiated pyridines to electrophilic heterocycles (Chichibabin reaction[8b,52]), (Scheme 23).

Conclusion

We hope that this review contributes to making *n*BuLi/lithium aminoalkoxide aggregates attractive reagents. Beside their good compatibility with sensitive substituents, these reagents display unprecedented chemo- and regioselectivity in the pyridine series. The encouraging enantioselectivities obtained with chiral aminoalkoxides should give access, after some improvement, to new optically active derivatives. We really think that this new family of reagents now has to be considered as a new tool for selective functionalization of pyridine nucleus. Work to extend the scope of this new methodology is now in progress.

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