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Combinations of Alkyllithiums and Lithium Aminoalkoxides for Generation of Functional Pyridine Organometallics and Derivatives

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Keywords: Metalation / Lithium / Lithiation / N heterocycles / Pyridines / Electrophilic substitution / Regioselectivity / Ligands

This account covers the current status of pyridine metallation with alkyllithium/lithium aminoalkoxide reagents and follows a previous review focusing on pioneering works on the *n*BuLi/LiDMAE reagent. An updated overview of the scope of metallation with this superbase is presented, together with the development of new reagents and synthetic applications based on selective lithiation methodology.

Introduction

Thanks to their unique electronic and coordinating properties, pyridine-based compounds are among the most important heterocycles involved in a wide spectrum of applications such as pharmaceutical, coordination and supramolecular chemistry, catalysis and energy transfer processes (luminescence, photovoltaics). These multiple applications call for the availability of even more sophisticated compounds with easily tuneable properties for screening purposes. The use of pyridine organometallics offers an attractive and promising route to these compounds. In this context, regioselective lithiation has attracted much attention during the past decades because it offers fast access to numerous functional compounds. Besides halogen–lithium exchange with bromo- or iodopyridines, which has proven to be an efficient process,[1–3] deprotonative lithiation from the pyridine parent compounds also represents a straightforward route to functional derivatives. Unfortunately, the π-deficiency of pyridines has long limited the scope of this latter reaction, due to nucleophilic attack on the azomethine bond by alkyllithiums. To overcome this side-reaction and to promote lithiation, alternatives such as the use of sterically hindered LDA[4–9] or LTMP[10–14] have been proposed. Unfortunately, equilibrated reactions were observed, implying trapping of lithiopyridines in situ.[15] As a consequence, efforts have been devoted to turning nucleophilic

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Yves Fort was born in the Ardennes, France. He received his Ph.D. in 1983 under the supervision of Prof. Jean-Pierre Pete at Reims University. He successively held a postdoctoral and a CNRS researcher position in Nancy (France), where he obtained his Doctorat d'Etat es Sciences Physiques in 1987 under the supervision of Prof. Paul Caubère. In 1988, he carried out postdoctoral studies on acrylic monomers at the Atochem company in Carling (France). In 1998 he was appointed to a position as Professor at Nancy University and from 2009 he has been Director of the Structure and Reactivity of Complex Molecular Systems (UMR CNRS 7565). His current research interests lie in polar (Li, Na) and transition metal (Ni, Co, Pd, ...) organometallic chemistry directed towards organic synthesis, with emphasis on heterocyclic functionalisation, cascade reactions and new nanomaterials for catalysis or electronics.

alkyllithium compounds into metallating agents by increasing their basicity/nucleophilicity ratio, with a particular focus on the most common and easy to handle *n*BuLi. One way to increase this ratio would be to enhance the basicity through association with lithium-chelating diamines such as TMEDA or chiral diamines (see **A** in Figure 1).[16,17] or to employ the superbase known as LICKOR (*n*BuLi/*t*BuOK) developed by Schlosser et al.[18,19] and Lochman et al.,[20–22] which contains potassium alkoxide as a highly electron-rich complexing agent (**B** in Figure 1). This family of bimetallic reagents has proven to be powerful in the aliphatic, aromatic and heteroaromatic series.[23,24] More recently, a new class of superbases based on association between alkyllithiums and lithium aminoalkoxides has emerged, designed with the goals of enhancing the basicity by complexation and of inhibiting nucleophilicity through the formation of sterically hindered aggregates (**C**, Figure 1).[25,26]

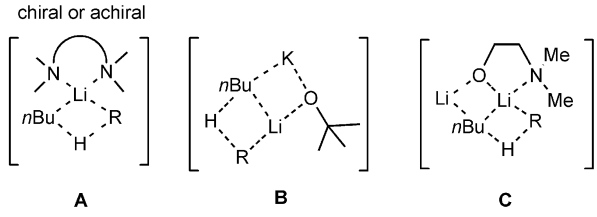
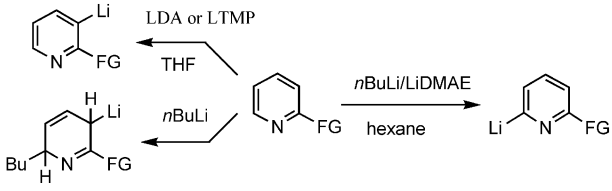


Figure 1. Various concepts for *n*BuLi activation in deprotonation reactions.

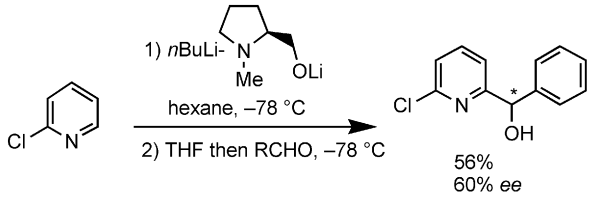
The most popular reagent, named *n*BuLi/LiDMAE [LiDMAE = $Me_2N(CH_2)_2OLi$], effected unprecedented clean α-metallations of pyridine derivatives instead of the usual nucleophilic additions encountered with *n*BuLi or the *ortho*-directed lithiations promoted by dialkylamides (Scheme 1).[27]



Scheme 1. Selectivities of lithiation of 2-substituted pyridine.

The incorporation of the chiral lithium aminoalkoxide LiPM [LiPM = Li(*N*-methylpyrrolidine)methoxide] allowed the enantioselective addition of pyridyllithium to aldehydes (Scheme 2).[28] This process was unprecedented because the same reagent performed chemo-, regio- and enantioselective functionalization, leading to chiral pyridylcarbinols in a one-pot fashion.

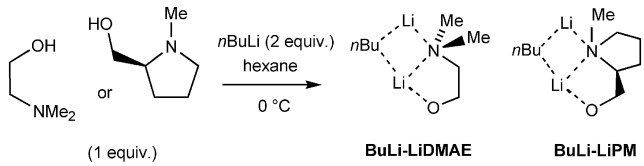
Following a previous review focused on pioneering works on *n*BuLi/LiDMAE,[27] the current account summarizes the progress made on structural knowledge of the reagent, metallation of pyridine derivatives with it and the development of new congeners, as well as the synthetic usefulness of this methodology.



Scheme 2. Regio- and enantiocontrol through the use of *n*BuLi/LiPM.

Preparative and Structural Aspects

The RLi/ROLi reagents are easily prepared by mixing an alkyllithium (2 equiv.) with the amino alcohol (1 equiv.) at 0 °C in an apolar noncoordinating solvent. Obviously, the structures depicted in Scheme 3 are oversimplified if the strong propensities of alkyllithiums to form mixed aggregates are taken into account.



Scheme 3. Preparation of *n*BuLi/ROLi reagents.

Such aggregation states have recently been established for *n*BuLi/LiPM aggregates on the basis of DFT calculations at the B3LYP/6–31G(d) level. It was found that a hexameric form (3:3) was the major species in hexane, whereas in THF a tetramer (2:2) was mainly present (Figure 2).[29]

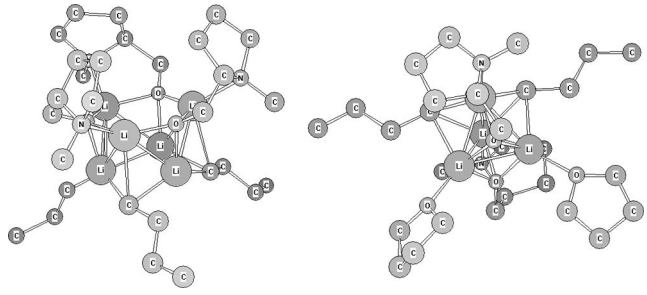


Figure 2. Computed aggregation states of *n*BuLi/LiPM. Hexamer $(n\text{BuLi/LiPM})_3$ in hexane (left) and tetramer $(n\text{BuLi/LiPM})_2(\text{THF})_2$ in THF (right). Hydrogen atoms have been omitted for clarity.

As shown in 2D NMR experiments (^{6}Li–^{1}H correlations),[30] the structures of the aggregates were strongly dependent upon the natures of the aminoalkoxides, especially with regard to steric effects. In the case of *n*BuLi/LiDMAE, cross-peaks were observed between the lithium signals and protons of both *n*BuLi and LiDMAE, indicating a highly aggregated state (Figure 3, top). In contrast, when LiDMAE was replaced by $i\text{Pr}_2N(CH_2)_2OLi$, with a

more hindered nitrogen atom, the aminoalkoxide chain protons were found to correlate only with one lithium peak and *n*BuLi, with the remaining signals indicating a strong influence of nitrogen coordination on the formation of aggregates (Figure 3, bottom). This aggregation step was found to be critical for the reaction outcome. Indeed, the *n*BuLi/*i*$Pr_2N(CH_2)_2OLi$ combination was found to give exclusively nucleophilic addition on treatment with 2-methoxypyridine, whereas *n*BuLi/LiDMAE induced C-6-metallation in up to 90% yield.[25,26]

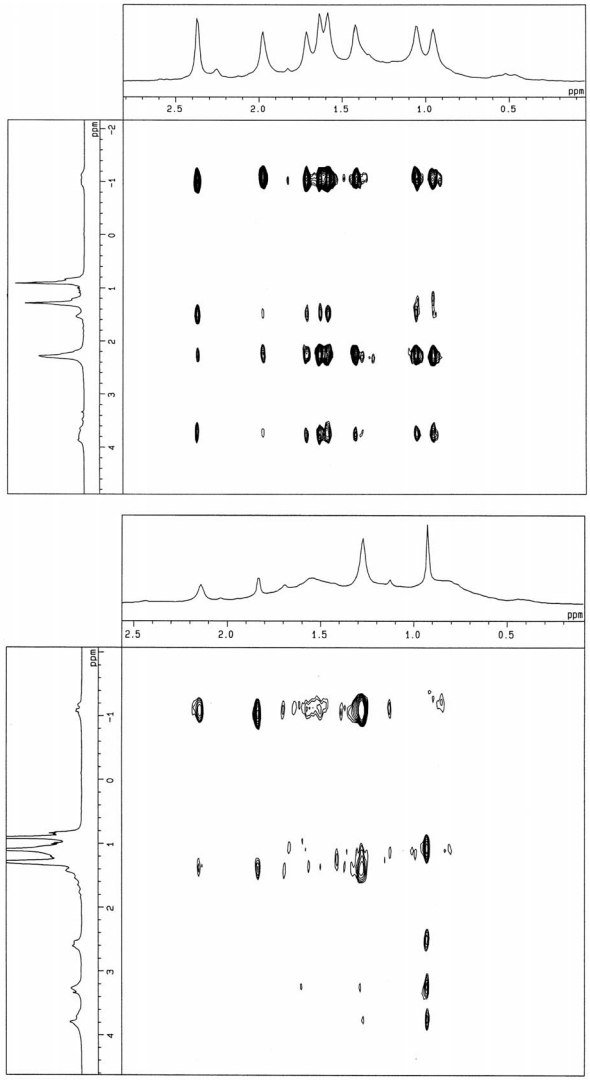


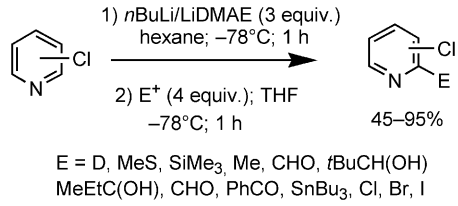
Figure 3. ^6Li–^1H 2D NMR (600 MHz) at –80 °C for *n*BuLi/LiDMAE (top) and *n*BuLi/*i*$Pr_2N(CH_2)_2OLi$ (bottom).

A feature common to all metallations with these reagents was the strong solvent dependence of the chemoselectivity. While the regioselective C-6-lithiation was maintained in noncoordinating solvents such as hexane, toluene or cumene, switching to THF, Et_2O [a notable amount of metallation (40%) could be obtained in this solvent, however] or dioxane promoted nucleophilic addition instead of metallation.[25,27]

Lithiation of Halopyridines and Functionalization

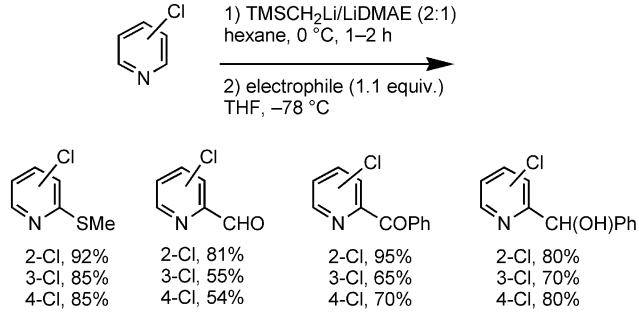
Lithiation of Chloropyridines

Chloropyridines are compounds of particular interest because the preservation of the C–Cl bond offers a potential source of further functionalization through S_NAr or organometallic couplings. The chlorine atom in 2-chloropyridine was known to direct metallation at C-3 with LDA as basic reagent,[31–33] whereas *n*BuLi or *n*BuLi/TMEDA essentially afforded addition products.[34] Metallation with *n*BuLi/LiDMAE at –78 °C resulted in regioselective lithiation at C-6, with tolerance of the C–Cl bond and no nucleophilic addition onto the azomethine bond of pyridine.[35] The reaction was successfully extended to 3- and 4-chloropyridines,[36] which on treatment with LDA usually give the kinetic C-4- and C-3-lithiated products, respectively.[37] The chemo- and regioselectivities were maintained, leading to a range of functional chloropyridines (Scheme 4).



Scheme 4. Lithiation of chloropyridines with *n*BuLi/LiDMAE.

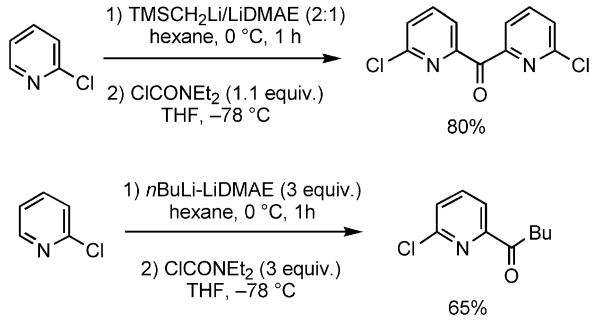
Remarkable progress in this reaction was recently made with use of a new combination of Me_3SiCH_2Li ($TMSCH_2Li$) and LiDMAE in a 2:1 ratio.[38] This reagent was prepared as described in Scheme 5 with 3 equiv. of $TMSCH_2Li$ and 1 equiv. of DMAE. The metallation of chloropyridines could be performed under noncryogenic conditions (0 °C) with a smaller amount of base and consequently a smaller amount of electrophilic reagent, due to a lower nucleophilicity than the *n*BuLi/LiDMAE reagent (Scheme 5).



Scheme 5. Lithiation of chloropyridines with $TMSCH_2Li$/LiDMAE.

A nice illustration of the lower nucleophilicity of $TMSCH_2Li$/LiDMAE was found on treatment of lithiopyridine with diethylcarbamoyl chloride (Scheme 6). With

*n*BuLi/LiDMAE the reaction afforded a butyl ketone rather than the dipyridyl ketone formed with $TMSCH_2Li$/LiDMAE.



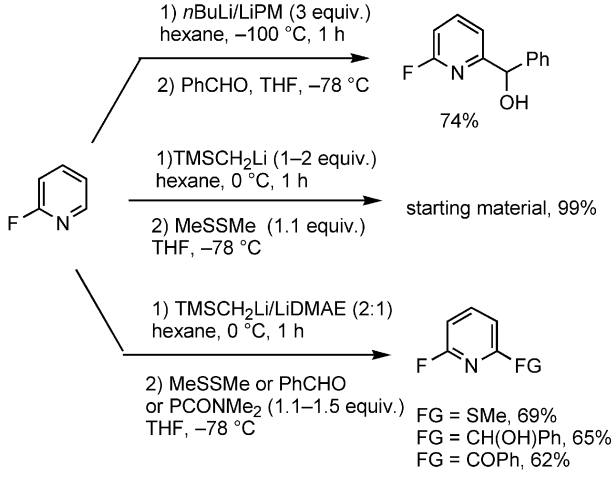
Scheme 6. Comparison of the nucleophilicities of *n*BuLi and $TMSCH_2Li$.

This clearly indicated that *n*BuLi attacked the intermediate amide function and $TMSCH_2Li$ did not. In this case the latter reagent was found to be less nucleophilic than the pyridyllithium.

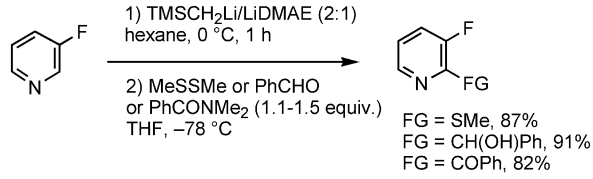
Lithiation of Fluoropyridines

Fluoropyridines are also important substrates because fluorine is far more electronegative than chlorine, inducing dramatic changes in the reactivity of the pyridine ring. The consequences are strong increases in the electrophilicity[34] and proton acidities, especially for those *ortho* to fluorine, so major changes in chemo- and regioselectivity can be expected. These electronic properties have also made the introduction of fluorine into heterocyclic structures of great interest for pharmaceutical purposes, due to the isosteric characters of fluorine and hydrogen.

The lithiation of fluoropyridines needs very low temperatures in order to avoid degradation and rapid isomerizations of lithio intermediates. 2-Fluoropyridine has been lithiated successfully at C-6 by treatment with *n*BuLi/LiPM and *n*BuLi/LiDMAE. The temperature had to be maintained at –100 °C to avoid substrate degradation.[28] The lithiation of 3-fluoropyridine has also been studied. The C-2 lithiation of this substrate was less easily directed because the proton at C-4 was also highly activated by the fluorine group. This necessitated thorough control of temperature and use of the appropriate lithiating agent.[5,39,40] With $TMSCH_2Li$/LiDMAE (2:1), however, noncryogenic lithiation could be performed successfully with fluoropyridines (Scheme 7). The reagent was found to be fully tolerant of the C–F bond even at 0 °C. Interestingly, the metallation occurred only when LiDMAE was present in the reagent.[38] The reaction was extended to 3-fluoropyridine, which was lithiated exclusively at C-2. In this case $TMSCH_2Li$ and LiDMAE had to be used in a 1:1 ratio to control the regioselectivity (Scheme 8).



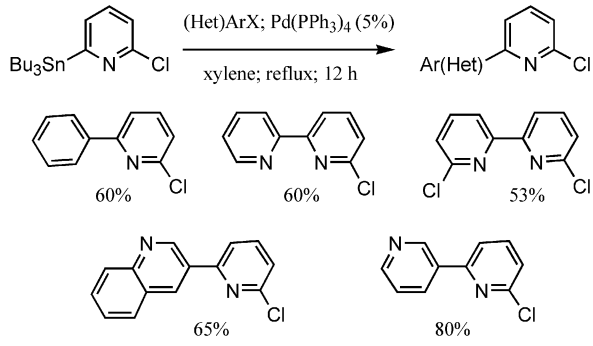
Scheme 7. Lithiation of 2-fluoropyridine.



Scheme 8. Lithiation of 3-fluoropyridine.

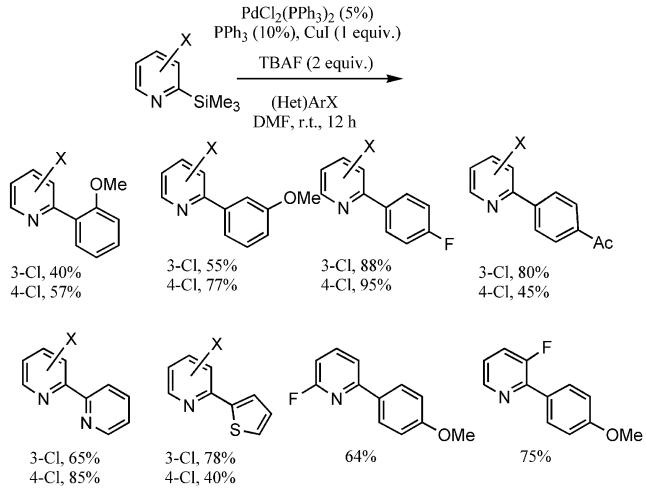
Cross-Couplings of Functionalised Chloropyridines

The selective C-2-lithiations of chloro- and fluoropyridines allowed the preparation of synthetically useful compounds for preparation of reactive bi(het)aryl compounds. The tin derivative shown in Scheme 9 was successfully engaged in Stille cross-couplings.[35]



Scheme 9. Synthesis of chlorinated polyheterocycles.

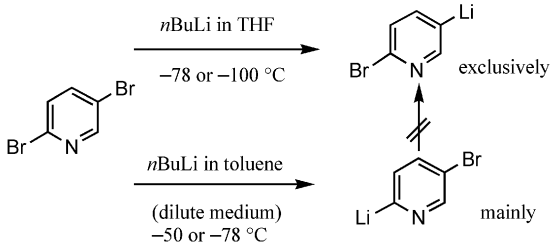
A recent development has been the first use of (halogenopyridyl)silanes, easily prepared by our lithiation/silylation sequences, as activated precursors in Hiyama cross-couplings (Scheme 10).[41] During this study it was found that (chloro- and fluoropyridyl)trimethylsilanes efficiently afforded a range of bi(het)aryl compounds under milder conditions than with other coupling methods. Polarization of the C–Si bond by the electron-withdrawing halogen substituents probably allowed the couplings to occur, because 2-(trimethylsilyl)pyridine failed to react under the same conditions.[41]



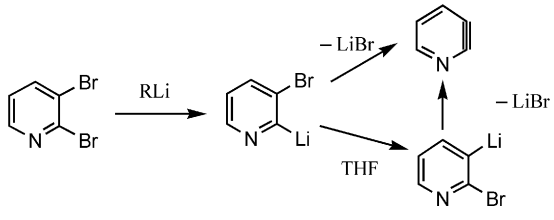
Scheme 10. Hiyama cross-coupling of pyridyltrimethylsilanes.

Bromine–Lithium Exchange in Dibromopyridines

Dibromopyridines are versatile heterocyclic compounds. Their unique reactivity has been nicely exploited in syntheses both of ligands[42,43] and of bioactive molecules.[44] Depending on the positions of the bromines on the pyridine ring, selective functionalizations can be achieved. In this context, halogen–lithium exchange has received much attention, especially with 2,3- and 2,5-dibromopyridines, and efficient methodologies to control the exchange regioselectivity have been developed (Scheme 11). With *n*BuLi, control over regioselectivity necessitates low temperatures (–78 or –100 °C) and diluted media to avoid isomerizations.[45,46] In addition to the potential isomerization of lithiated species, the formation of pyridyne through elimination of lithium bromide can also occur with 2,3-dibromopyridine if the reaction is performed under noncryogenic conditions (Scheme 12).



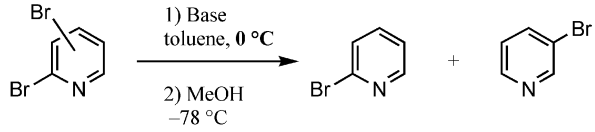
Scheme 11. Isomerization in lithiation of 2,5-dibromopyridine.



Scheme 12. Isomerization and pyridyne formation in 2,3-dibromopyridine.

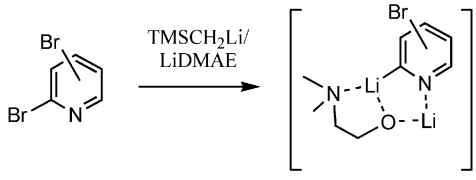
A search for new reagents capable of promoting selective bromine–lithium exchange in these substrates under easily applicable conditions was therefore necessary. The solution was found in the use of $TMSCH_2Li$/LiDMAE (2:1) in toluene. With this reagent the exchange was accomplished cleanly at 0 °C in a short time (0.5 h) with both the substrates and without any degradation (Table 1).[47] Furthermore, LiDMAE acted as a stabilizing agent for the 2-lithiointermediates, thus avoiding isomerizations into the more stable species. Interestingly, no formation of pyridine, as assessed by furan trapping experiments, was detected in reactions with 2,3-dibromopyridine.[2]

Table 1. Base effects in bromine–lithium exchange in dibromopyridines.



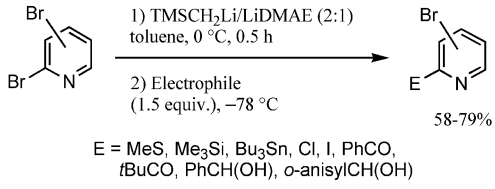
Substrate	Base	2-Br-pyridine	3-Br-pyridine
2,5-Br_2-pyridine	*n*BuLi/LiDMAE	degradation	
	$TMSCH_2Li$	29%	38%
	$TMSCH_2Li$/LiDMAE (2:1)	4%	95%
2,3-Br_2-pyridine	*n*BuLi/LiDMAE	degradation	
	$TMSCH_2Li$	20%	80%
	$TMSCH_2Li$/LiDMAE (2:1)	–	>98%

These unprecedented reactivities were explained in terms of coordination of 2-lithiopyridine by lithium aminoalkoxide combined with a fast deprotonation at 0 °C by $TMSCH_2Li$ (Scheme 13).



Scheme 13. Proposed stabilisation of 2-lithio-bromopyridines by LiDMAE.

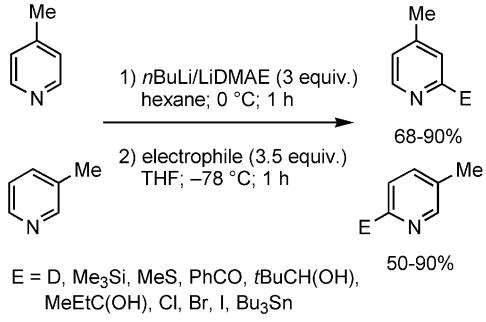
The clean lithiation process allowed the preparation of a range of bromopyridine derivatives in good yields. Note also that the amount of electrophile used is very low, thanks to the weak nucleophilicity of $TMSCH_2Li$ (Scheme 14).



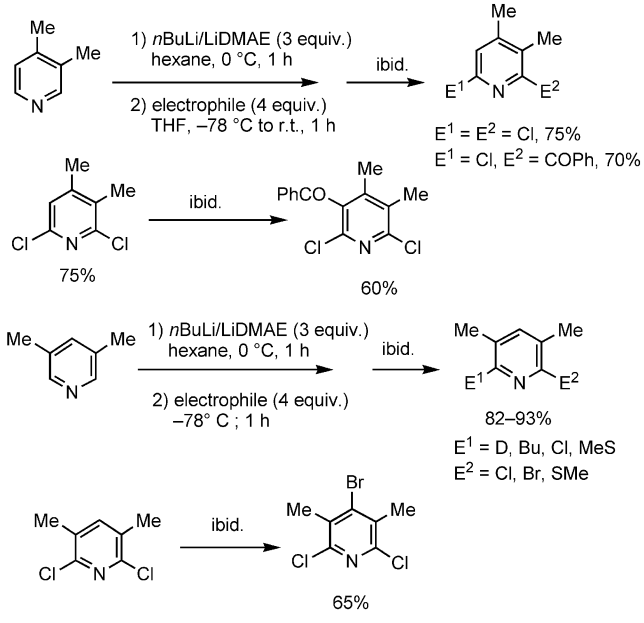
Scheme 14. Selective synthesis of functional bromopyridines.

Lithiation of Picolines and Lutidines

In our quest for selective functionalization of compounds with retention of reactive substituents we have investigated the selective ring lithiation of picolines and lutidines. The retention of the acidic side chains might provide new routes to useful heterocyclic building blocks, because these methyl groups might subsequently be transformable into aldehydes or carboxylic acids or could be subjected to olefination to prepare conjugated molecules or might be selectively metallated.[48] Because of the higher acidity of the methyl group,[49] these compounds were metallated only at their methyl groups when LDA or LTMP were used.[50] With *n*BuLi/LiDMAE, however, the metallation of 3- or 4-picoline was exclusively directed towards the pyridine ring, leaving the methyl group unaffected (Scheme 15).[51] The lithiation occurred at C-2, although 3-picoline additionally underwent an unprecedented *para*-lithiation, due to the steric effect of the methyl group.[52]



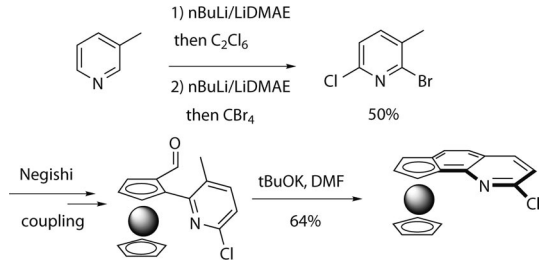
Scheme 15. Lithiation of picolines with *n*BuLi/LiDMAE.



Scheme 16. Synthesis of polyfunctional pyridines by sequential lithiations.

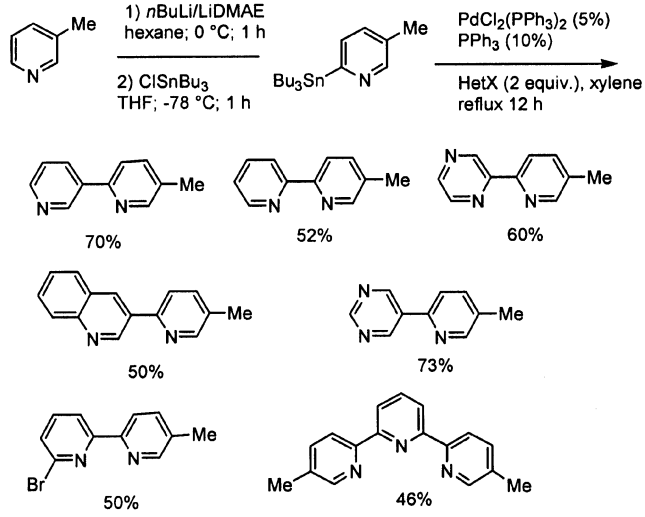
By the same methodology it was possible to perform monolithiations and sequential lithiations of lutidines to afford new reactive heterocyclic building blocks (Scheme 16).[51,53]

The iterative lithiation of 3-picoline was recently exploited in our group for the synthesis of ferrocenoisoquinolines (Scheme 17).[54]



Scheme 17. Synthesis of ferrocenoisoquinolines by sequential lithiation of 3-picoline.

Picoline-based polyheterocycles have been prepared by cross-coupling of the above tin derivatives. A one-pot lithiation–stannylation–coupling sequence was developed on this occasion (Scheme 18).[55]

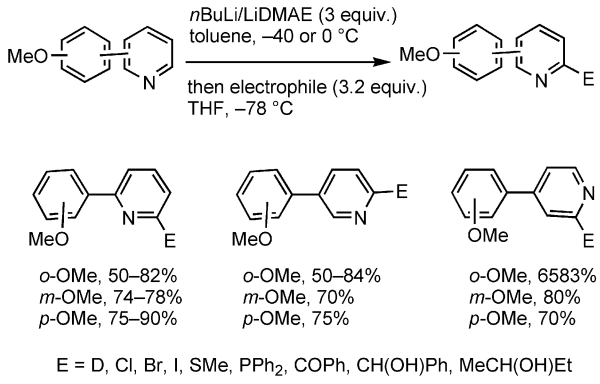


Scheme 18. Lithiation/stannylation/coupling sequence.

Lithiation of Anisylpyridines

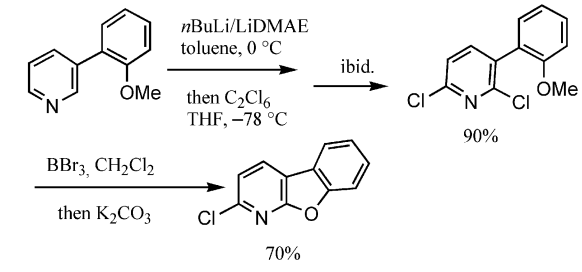
Pyridylphenols are key structures for biologically active molecules (e.g., adrenergic receptor ligands),[56] metal ligands for asymmetric synthesis[57] or building blocks for supramolecular architectures.[58] They are generally prepared from halogenated heterocycles by Pd-catalysed Suzuki[58] or Ni-catalysed Corriu–Kumada–Tamao[59,60] cross-couplings followed by a demethylation step. We have developed an efficient methodology for the functionalisation of anisylpyridines by treatment with the *n*BuLi/LiDMAE superbase, which effected the first selective directed pyridine

lithiation of these compounds α to nitrogen, leading to an array of new functional compounds (Scheme 19).[61] No *ortho*-directing effects of the methoxy groups resulting in metallation of the anisole rings were observed.



Scheme 19. Lithiation of anisylpyridines.

The usefulness of the methodology for the synthesis of functional pyridylphenols was illustrated with chlorinated compounds, which are useful precursors for further introduction of diversity. After demethylation the phenols were engaged in cyclisations under basic conditions to afford chlorinated benzofuropyridines (Scheme 20).[61]



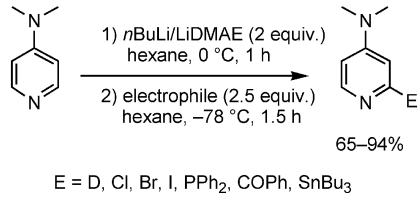
Scheme 20. Synthesis of benzofuropyridines.

Lithiation of Aminopyridines and Related Compounds

C-2-Lithiation of DMAP and 4-PPY

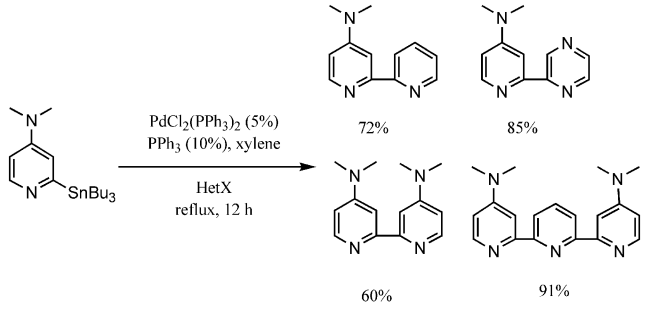
(Dialkylamino)pyridines display unique electronic properties due to the delocalization of their external nitrogens' lone pairs through the π-deficient pyridine rings, greatly increasing the electron density at their pyridine nitrogens. The consequence is a significantly enhanced nucleophilicity of the pyridine nitrogen, which has been extensively exploited. The most popular congener is certainly 4-(dimethylamino)-pyridine (4-DMAP), which has been found to be highly efficient as an organocatalyst for acylation reactions.[62–64] Current developments in the field of (dialkylamino)pyridines, especially in asymmetric organocatalysis,[65,66] call for the elaboration of even more sophisticated analogues. As a consequence, the incorporation of functional groups on the pyridine ring has been the focus of much attention.

We achieved an unprecedented direct lithiation with the *n*BuLi/LiDMAE reagent (Scheme 21)[67] This new process avoids the need for the conventional activation–regeneration sequence, as well as the formation of disubstituted derivatives encountered in the Lewis-acid-assisted lithiation procedures described in the literature.[68]



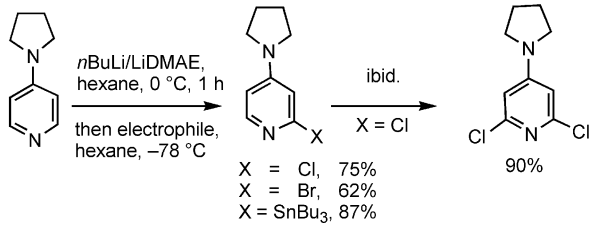
Scheme 21. C-2 lithiation of 4-DMAP with *n*BuLi/LiDMAE.

The availability of tin and halogenated derivatives allowed the preparation of new ligands (Scheme 22).[67]



Scheme 22. Synthesis of DMAP-based polyheterocycles.

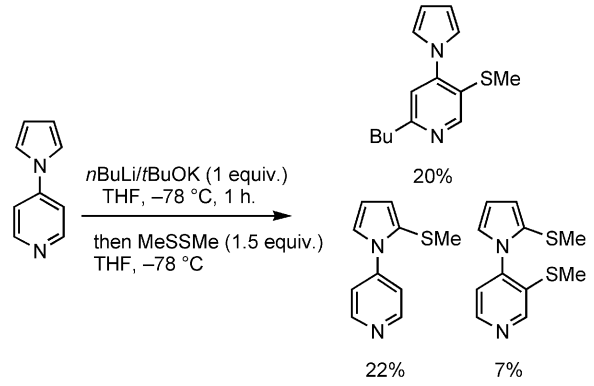
This methodology was also applied successfully to 4-pyrrolidinopyridine (4-PPY) (Scheme 23).[69]



Scheme 23. Lithation of 4-PPY.

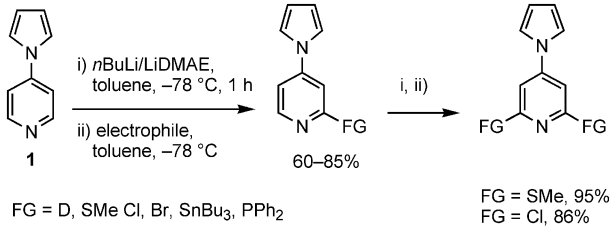
Lithiation of Pyrrolopyridines

4-(1*H*-1-Pyrrolyl)pyridine has interesting applications as an electron-releasing ligand.[70] In our hands, treatment with *n*BuLi, *t*BuLi or *n*BuLi/TMEDA only resulted in nucleophilic addition on the pyridine ring, whereas after treatment with LDA or LTMP the compound was fully recovered. On the other hand, treatment with LICKOR led to metallation α to the pyrrole nitrogen and at C-3 of the pyridine ring, in agreement with the selectivity observed with phenylpyrrole (Scheme 24).[71] The nucleophilic addition product was also present in notable amounts in the mixture.



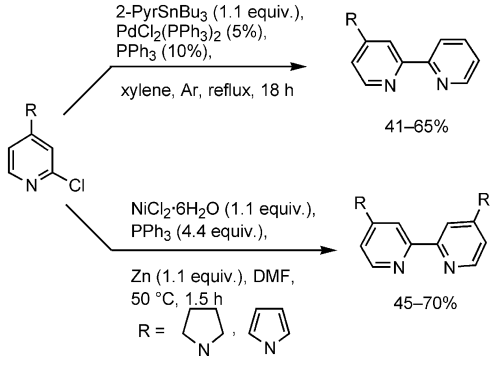
Scheme 24. Reaction of 4-pyrrolopyridine in the presence of LICKOR.

In contrast, use of *n*BuLi/LiDMAE at low temperature (–78 °C) effected a clean lithiation of the pyridine ring, allowing the introduction of substituents potentially reactive for further functionalization reactions and ligand synthesis.[72] The preparation of some 2,6-disubstituted derivatives through an iterative lithiation was achieved with substrates bearing base-tolerant substituents (Scheme 25).

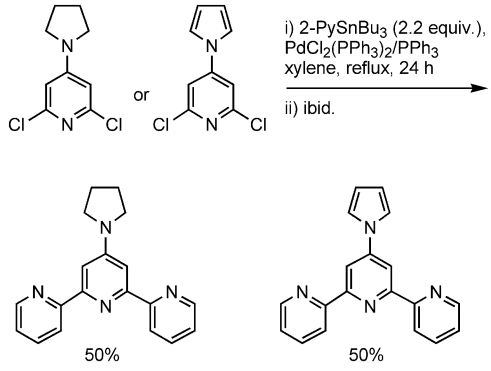


Scheme 25. C-2 lithiation of 4-pyrrolopyridine with *n*BuLi/LiDMAE.

The obtained 4-PPY and 4-pyrrolopyridine derivatives were next involved in cross-couplings leading to new bipyridine and terpyridine ligands (Scheme 26 and Scheme 27),[69,72] the ruthenium complexes of which displayed interesting electronic properties further exploited in dye solar cells.[73]



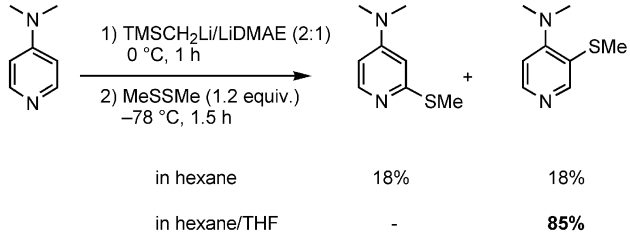
Scheme 26. Synthesis of pyrrole- and pyrrolidine-based bipyridines.



Scheme 27. Synthesis of pyrrole- and pyrrolidine-based terpyridines.

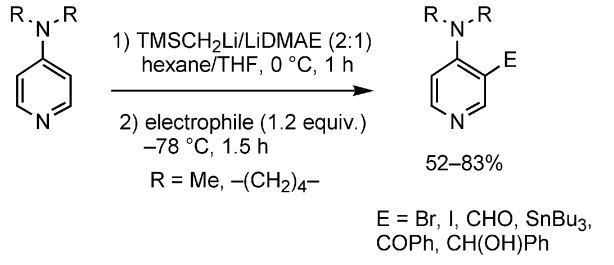
C-3 Lithiation of DMAP and 4-PPY

C-3 lithiation was challenging. Despite the higher acidity of the H-3 proton it had never been directly lithiated, due to the low propensity of the dialkylamino group to promote *ortho*-lithiation. We showed for the first time, however, that the $TMSCH_2Li$/LiDMAE reagent promoted this reaction (Scheme 28).[74] In this case the metallation had to be performed in a hexane/THF mixture to prevent aggregation between the superbase and the pyridine nitrogen.



Scheme 28. Effect of THF on lithiation of 4-DMAP.

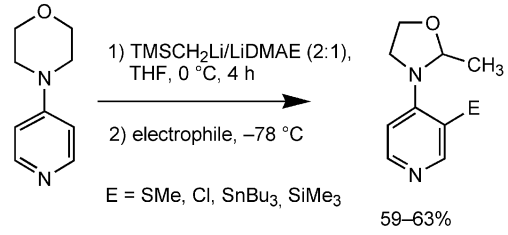
A range of functionalities have been introduced cleanly at C-3 of DMAP and 4-PPY by use of this new methodology (Scheme 29).[74]



Scheme 29. Functionalization of DMAP and 4-PPY at C-3.

Interestingly, when the same reaction conditions were applied to 4-morpholinopyridine a ring contraction occurred concomitantly with the C-3 lithiation, giving a straightforward route to functional *N*-pyridyloxazolidines (Scheme 30).[75] Note that the use of *n*BuLi/LiDMAE with such a substrate led to exclusive C-6 lithiation of the pyr-

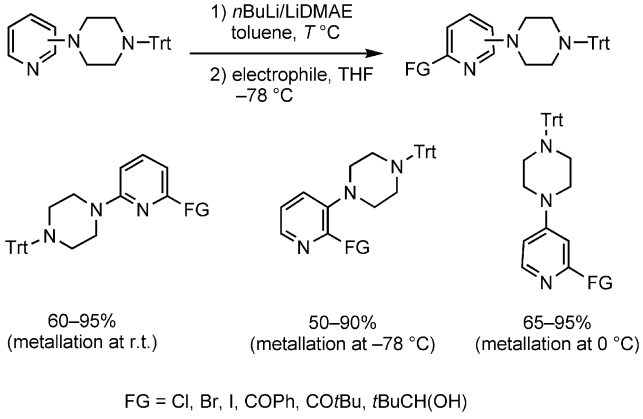
idine ring with preservation of the integrity of the morpholine ring.[76] A mechanism involving a ring-opening and a classical *exo-trig* cyclization was postulated.



Scheme 30. Synthesis of *N*-pyridyloxazolidines functionalised at C-3.

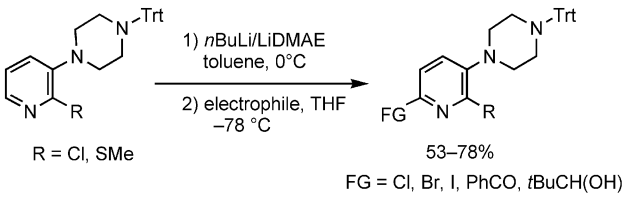
Lithiation of Pyridylpiperazines

Pyridylpiperazines and their analogues are key units in a wide range of relevant pharmacophores with a broad spectrum of activity.[77] Variation in the nature of and the substitution on the (het)aryl ring on piperazine dramatically influences the intrinsic activity. The number of available substituted pyridylpiperazines remains limited, due to a lack of efficient methodologies for introduction of diversity on the pyridine ring. We showed that lithiation could be successfully achieved by use of *n*BuLi/LiDMAE. The reagent effected metallation of the pyridine even in the presence of the strongly coordinating piperazine units (Scheme 31).[78] The process was found to be sensitive to the metallation temperature.



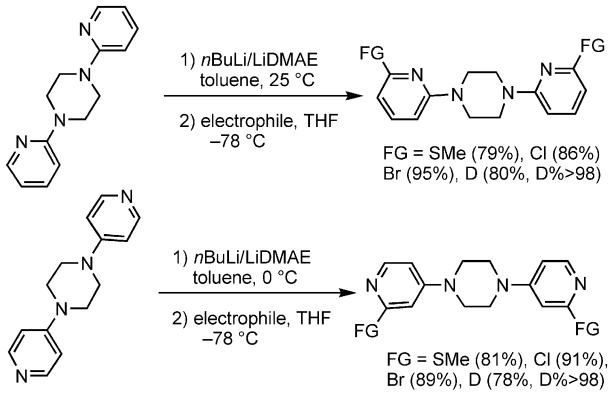
Scheme 31. Lithiation of pyridylpiperazines at C-2 and temperature effects.

Sequential lithiation proceeded as well, giving access to disubstituted derivatives (Scheme 32).



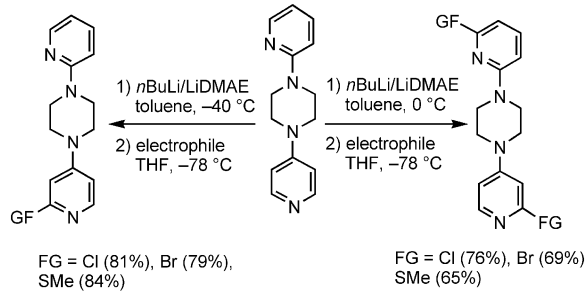
Scheme 32. Synthesis of polyfunctional pyridylpiperazines.

Another interesting and unprecedented reaction was the lithiation of dipyridylpiperazines.[79] The difunctionalization of symmetrical compounds occurred cleanly (Scheme 33).



Scheme 33. One-pot dilithiation of dipyridylpiperazines.

The temperature effects observed for pyridylpiperazines in Scheme 32 were exploited to control the mono- or dilithiation of asymmetrical derivatives (Scheme 34).

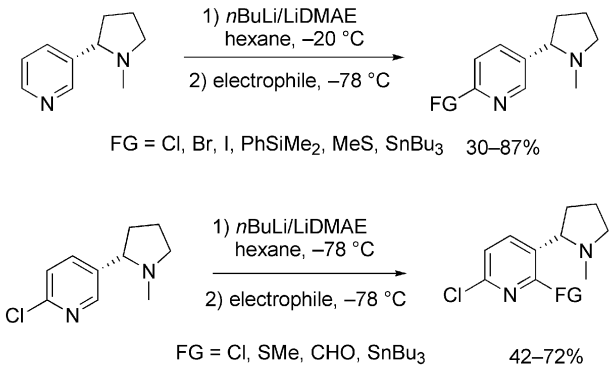


Scheme 34. Temperature-controlled mono-/dilithiation of dipyridylpiperazines.

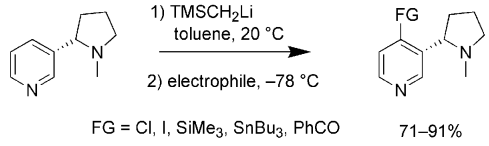
Selective Lithiation of (*S*)-Nicotine

(*S*)-Nicotine is a naturally abundant chiral alkaloid, efficient for the treatment of neurodegenerative diseases, but with many side effects. This drawback has motivated the synthesis of (*S*)-nicotine analogues with expected lower toxicity through lithiation of the pyridine ring. Recently Comins and co-workers have successfully used the *n*BuLi/LiDMAE reagent for this purpose. Regioselective functionalization at C-2 was achieved[80] and subsequent lithiation of the chlorinated substrate led to a range of 2,6-disubstituted derivatives in good yields (Scheme 35).[81] This methodology was also a key step in a synthesis of (*S*)-brevicolline.[82]

The $TMSCH_2Li$ or $TMSCH_2Li$/LiDMAE reagents afforded a new selectivity by lithiating exclusively the C-4 position of (*S*)-nicotine (Scheme 36).[83]



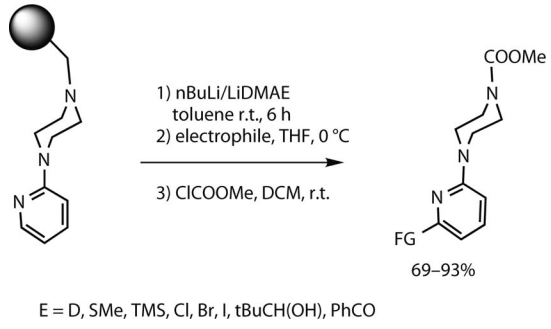
Scheme 35. Lithiation of (*S*)-nicotine with *n*BuLi/LiDMAE.



Scheme 36. C-4-Lithiation of (*S*)-nicotine with $TMSCH_2Li$.

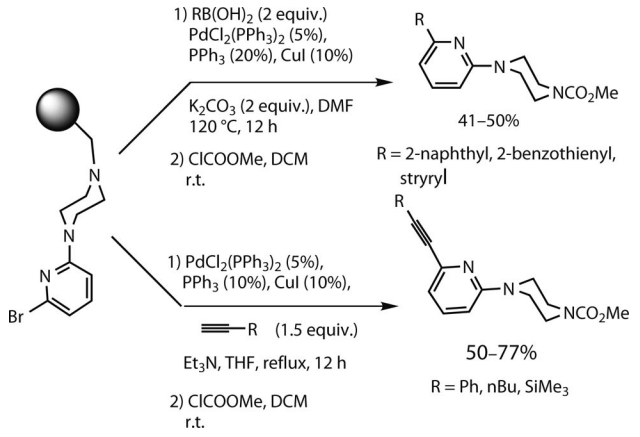
Solid-Phase Lithiation of Pyridylpiperazine

Taking the biological interest of functional pyridylpiperazines into account we examined methodologies for the preparation of libraries of such compounds. We showed that *n*BuLi/LiDMAE could effect proper lithiation of polymer-bound pyridylpiperazine with full tolerance of the polystyrene support.[84] The preparation of useful 6-substituted 2-pyridylpiperazines was achieved after subsequent electrophilic quenching and cleavage with methyl chloroformate (Scheme 37).



Scheme 37. Lithiation of polymer-bound pyridylpiperazines.

The brominated derivatives prepared above were directly subjected to Suzuki and Sonogashira cross-couplings on solid phase, yielding new functional pyridylpiperazines with good overall yields after cleavage (Scheme 38).[85]



Scheme 38. Solid-phase cross-couplings of pyridylpiperazines.

Conclusions

This update of our first review on *n*BuLi/LiDMAE illustrates well the synthetic potential of this superbase as well as improvements achieved by modification of the alkyllithium part of the reagent. Both noncryogenic and more economical deprotonations and bromine–lithium exchanges on pyridine derivatives for the preparation of synthetically useful pyridine organometallics are now available. Additionally, new selectivities have been discovered, greatly enriching the scope of metallations with the RLi/LiDMAE combinations. The synthetic usefulness of the methodology has been clearly demonstrated by the efficient preparation of new potentially biologically active compounds and polypyridine ligands.

Acknowledgments

The authors are indebted to all co-workers who contributed to the success of this story and thank C. J. Woltermann and FMC Lithium for supporting the $TMSCH_2Li$ investigations. H. Karthabil and M. Ruiz-Lopez are also acknowledged for computational chemistry calculations.

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