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First one-pot chemo-, regio- and enantioselective functionalisation of pyridine compounds mediated by BuLi-(*S*)-(−)-*N*-methyl-2-pyrrolidine methoxide

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Abstract—BuLi-(*S*)-(−)-*N*-methyl-2-pyrrolidine methoxide (noted BuLi–LiPM*) is the first superbase promoting an unprecedented regioselective C-6 lithiation of pyridine compounds while controlling the asymmetric addition on aldehydes.

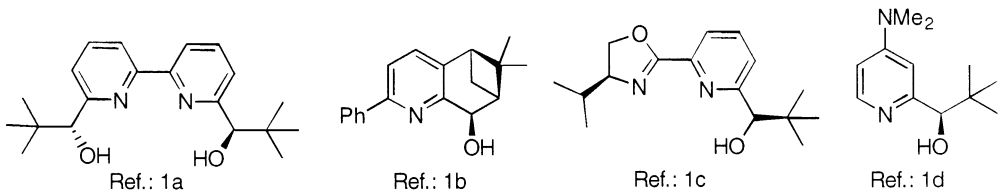
1. Introduction

Pyridylalcohols are excellent candidates as chiral substructures of several ligands for asymmetric synthesis and kinetic resolution (Scheme 1).[1] Obviously, the ease of determining such species in enantiomerically pure form shows their synthetic usefulness. Two methodologies have emerged during the past decade. The most efficient synthesis of non-racemic pyridylalcohols reported to date is a multistep reaction involving subsequent asymmetric reduction of the corresponding pyridylketones by chiral borane.[1a] Several diastereoselective approaches have also been described based on trapping organolithium intermediates with optically active ketones.[2]

Recently, our laboratory has reported the usefulness of BuLi–$Me_2N(CH_2)_2OLi$ (noted BuLi–LiDMAE) for the metallation of pyridine compounds in apolar solvents. The aminoalkoxide increases the BuLi basicity/nucleophilicity ratio,[3] this superbase then prevents the classical nucleophilic addition of BuLi onto the heteroaromatic ring. Furthermore, an unprecedented regioselective lithiation at C-α of the pyridinic ring is obtained avoiding the classical halogen–metal exchange on the corresponding brominated derivatives (Scheme 2).

In connection with these studies, we aimed to develop a new and useful superbase formed by association of BuLi with chiral vicinal aminoalkoxides.[4] The obtained BuLi–R*OLi reagent should allow direct and regioselective metallation of the pyridinic ring while controlling unprecedented asymmetric addition of the formed pyridyl lithium to aldehydes.

In our recent work,[5] we have shown that the BuLi–LiDMAE superbase promoted the clean C-6 functionalisation of 2-chloropyridine. This reaction was chosen as a model since the C–Cl bond could also offer further sources of functionalisation. Thus, we first studied the reaction with several aminoalkoxides using the best



Scheme 1.

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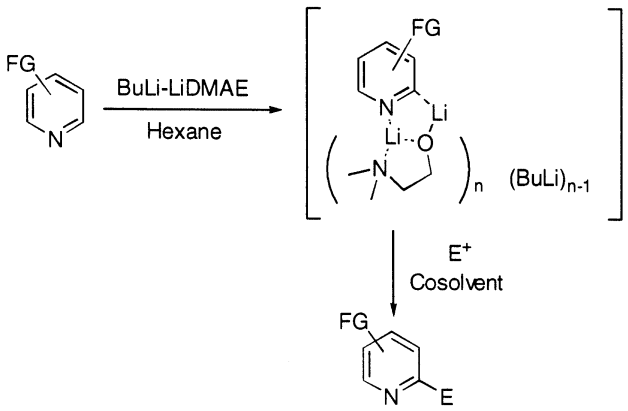


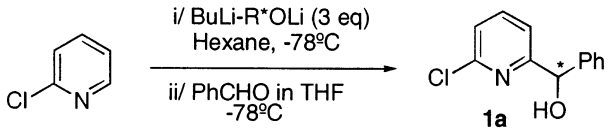
Scheme 2.

conditions previously determined with benzaldehyde as the electrophile (Scheme 3, Table 1).[5]

2. Results and discussion

As previously reported,[3a] the reaction course was critically dependent on the aminoalkoxide structure. Except (*S*)-(−)-methyl-2-pyrrolidine methanol, which led to 35% e.e. (Table 1, entry 6), no other chiral auxiliary induced any enantioselection. Some of them (Table 1, entries 1, 3, 4) even led to complete 2-chloropyridine degradation by nucleophilic addition. It may be concluded that these aminoalkoxides did not contribute to increase the BuLi basicity/nucleophilicity ratio and did not allow the formation of a superbase. In this context, comparison of entries 1 and 2 indicated the dramatic effect of substitution at the neighbourhood of the nitrogen atom since 2-methyl-2-dimethylamino ethoxide led to complete substrate degradation, while the 1-methyl-2-dimethylamino ethoxide produced **1a** in good yield. This difference indicated the probable strong implication of the nitrogen atom in the lithium aggregates. Finally, structural modification of the prolinol structure in order to increase steric hindrance and thus facial differentiation led to disappointing results. Indeed, even a slight change in the nitrogen substituent by replacing methyl with ethyl resulted in complete substrate degradation (Table 1, entry 7). The same observation was made varying substituents on the side chain (Table 1, entries 8–10).

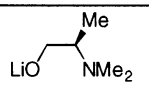
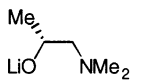
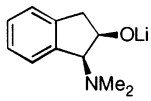
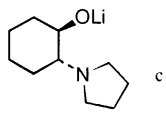
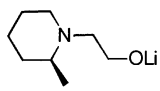
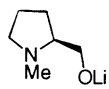
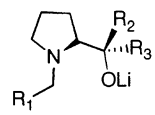
Thus, we decided to investigate in more detail the reaction conditions with the BuLi–Li (*S*)-(−)-*N*-methyl-2-pyrrolidine methoxide (noted BuLi–LiPM*) reagent (Table 2). At first, we thought that the order of introduction of the cosolvent could have an influence on enantioselection. Indeed, the structure of lithium aggregates is known to be changed by incorporation of chelating solvents.[6] THF was then introduced before benzaldehyde and a remarkable increase of e.e. (from 35 to 58%) was obtained (Table 1, entry 6/Table 2, entry 1). A decrease of THF resulted in a dramatic drop in e.e. (Table 2, entry 2). The asymmetric induction and yield were not significantly modified by lowering the temperature (Table 2, entry 3). The effect of cosolvent on e.e. was also crucial and a screening of various solvents at −78°C revealed THF as the best one (Table 2, entries 1, 4–7). Finally, the BuLi/LiPM*/2-chloropyridine ratio was varied (Table 2, entries 8–11). Even with a large excess of chiral alkoxide, the asymmetric process was not improved (Table 2, entry 11).[7]



Scheme 3.

To illustrate the versatility and synthetic value of the reaction for the preparation of chiral polyfunctional pyridines, we used the conditions determined in Table 2

Table 1. Functionalisation of 2-chloropyridine mediated by BuLi–R*OLi

Entry	R*OLi	ee[a]	Yield[b] of **1a**
1		–	[f] –
2		0	63
3		–	[f] –
4	 [c]	–	[f] –
5		0	42
6		35	62
			
7	R_1: Me; R_2, R_3: H	–	[f] –
8	R_1: H; R_2, R_3: Ph	–	[f] –
9	R_1, R_2: H; R_3: Ph[d]	–	[f] –
10	R_1, R_2: H; R_3: Me[e]	–	[f] –

[a]Determined by ^{31}P NMR spectroscopy, see experimental section. [b]Yields of isolated product, after column chromatography. [c]Racemic form. [d]Diastereomeric ratio : 95/5. [e]Diastereomeric ratio : 68/32. [f]Decomposition of 2-chloropyridine.

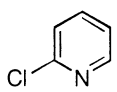
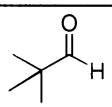
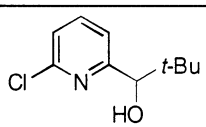
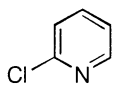
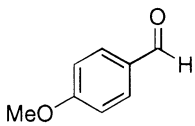
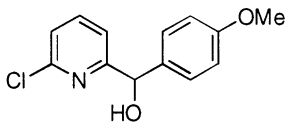
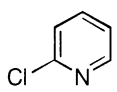
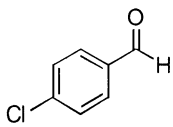
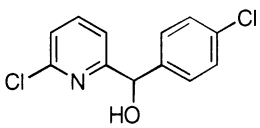
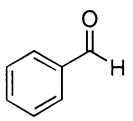
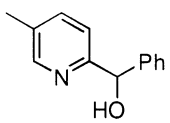
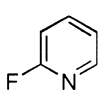
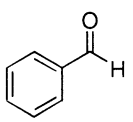
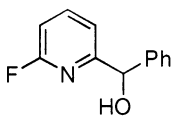
Table 2. Functionalisation of 2-chloropyridine mediated by BuLi–LiPM*

Entry	BuLi/LiPM*/substrate	T (°C)	Cosolvent[a]	E.e.[b]	**1a** (%)[c]
1	3/3/1	−78	THF (1/1)	58	59
2	3/3/1	−78	THF (10/1)	28	59
3	3/3/1	−110	THF (1/1)	58	63
4	3/3/1	−78	Et_2O (1/1)	0	55
5	3/3/1	−78	DMM (1/1)	41	63
6	3/3/1	−78	DME (1/1)	13	65
7	3/3/1	−78	–[d]	0	63
8	1/1/1	−78	THF (1/1)	39	23
9	2/2/1	−78	THF (1/1)	46	51
10	4/4/1	−78	THF (1/1)	53	59
11	3/6/1	−78	THF (1/1)	28	57

[a] Hexane/cosolvent ratio given in parentheses.
[b] Determined by ^{31}P NMR spectroscopy, see Section 3.
[c] Yields of isolated product, after column chromatography.
[d] Without cosolvent.

(entry 1) to examine the condensation of several pyridine compounds with various representative aldehydes (Table 3). As shown, products **1b–f** were generally obtained in good yields and moderated e.e.s. 3-Picoline (Table 3, entry 4) had to be metalated at 0°C to ensure efficient functionalisation. The instability of the 6-lithio-2-fluoropyridine implied to perform both metallation and condensation of 2-fluoropyridine at −100°C (Table 3, entry 5). Note that the BuLi–LiPM* superbase promoted the clean C-6 functionalisation of 3-picoline (Table 3, entry 4), according to our previous observations with BuLi–LiDMAE.[3f] As recently reported by Collum,[8] the key step of stereocontrol can be connected to the incorporation of aldehyde in a precomplex including chiral alkoxide and a lithiated compound. The formation of this precomplex seems to be unfavourable when the aldehyde is substituted by an electron-withdrawing group, the incorporation being prevented by increasing the reactivity of aldehyde (Table 3, entry 3).

Table 3. Functionalisation of pyridine compounds mediated by aBuLi–LiPM*

Entry	Pyridine	Aldehyde	Product		ee[a]	Yield[b]
1				**1b**	35	62
2				**1c**	45	61
3				**1d**	23	56
4[c]				**1e**	39	47
5[d]				**1f**	30	74

Reactions were performed with BuLi/LiPM*/Pyridine ratio : 3/3/1, at –78°C in hexane and THF as cosolvent. [a]Determined by ^{31}P NMR spectroscopy, see experimental section. [b]Yields of isolated product, after column chromatography. [c]Metallation was performed at 0°C and condensation at –78°C. [d]Metallation and condensation were performed at -100°C.

In summary, we have shown that BuLi–LiPM* is the first ambivalent superbase allowing regioselective metallation of pyridine rings and asymmetric addition of lithiated pyridine reagents to aldehydes. This valuable one-pot method was found to be a simple route to chiral functional pyridine derivatives. Work is now in progress to elucidate the mechanism of the lithiation and the structure of aggregate(s) in order to optimise and extend this new regio- and enantioselective process.

3. Experimental

The reactions were carried out under a nitrogen atmosphere. All solvents were distilled and stored over sodium. Column chromatography was carried out at normal pressure, using silica gel 60 (0.063–0.200 nm, Merck). Optical rotation ($[\alpha]_D^{20}$) measurements were obtained using a Perkin–Elmer 141 polarimeter. The e.e.s were determined by ^{31}P NMR spectroscopy after derivatisation with (*R*,*R*)-*N*,*N*′-diisopropylcyclohexane-1,2-diazaphospholidine.[9] Mass spectra were recorded on a Hewlett Packard 5871, and are reported as fragmentation in *m*/*z* with relative intensities (%) in parentheses. NMR spectra were recorded on a Bruker 400 (^1H at 400.1 MHz, ^{13}C at 100.6 MHz, ^{31}P at 162.0 MHz).

3.1. General procedure for the preparation of 1a–f

n-BuLi (6 mL of a 1.6 M solution in hexanes; 9.6 mmol) was added dropwise to a solution of (*S*)-(−)-*N*-methyl-2-pyrrolidine methanol (552 mg, 4.8 mmol) in hexane (3 mL) cooled at 0°C. After 30 min at 0°C, the reaction medium was cooled at −78°C and a solution of pyridine compound (1.6 mmol) in hexane (1 mL) was added. After 1 h at this temperature, THF (10 mL) was added dropwise to the orange solution, and stirred for 10 min. The dark-red solution was treated with a solution of the appropriate aldehyde (8 mmol) in THF (2 mL). The reaction mixture was maintained at −78°C for 30 min. Hydrolysis was then performed at this temperature with water (5 mL) followed by extractions at room temperature with diethyl ether (2×20 mL). After drying over $MgSO_4$ and evaporation of solvents, the crude product was purified by chromatography on silica gel using hexane–AcOEt as eluent.

Data for **1a**: ^1H NMR ($CDCl_3$, 300 K): $\delta=7.57$ (t, $J=7.8$ Hz, 1H), 7.39–7.25 (m, 5H), 7.21 (d, $J=7.8$ Hz, 1H), 7.10 (d, $J=7.8$ Hz, 1H), 5.74 (s, 1H), 4.47 (bs, 1H). ^{13}C NMR ($CDCl_3$, 300 K): $\delta=163.1$, 150.6, 142.7, 139.9, 129.0, 128.4, 127.3, 123.3, 120.0, 75.5. MS (EI) *m*/*z* (rel. int.): 220 (28), 219 (100), 142 (35), 114 (33), 113 (50), 79 (37), 78 (37), 77 (54). $[\alpha]_D^{20}=+91.6$ (*c* 1.98, $CHCl_3$). E.e. 58%.

Data for **1b**: ^1H NMR ($CDCl_3$, 300 K): $\delta=7.61$ (t, $J=7.8$ Hz, 1H), 7.22 (d, $J=7.8$ Hz, 1H), 7.16 (d, $J=7.8$ Hz, 1H), 4.34 (s, 1H), 3.74 (bs, 1H), 0.92 (s, 9H). ^{13}C NMR ($CDCl_3$, 300 K): $\delta=162.2$, 150.0, 138.7, 123.0, 121.4, 80.8, 36.4, 26.3. MS (EI) *m*/*z* (rel. int.): 184 (2, $M^{+\bullet}$ −15), 166 (7), 143 (91), 142 (100), 114 (4), 113 (15), 112 (4), 78 (7), 57 (14), 52 (5), 51 (7). $[\alpha]_D^{20}=+7.1$ (*c* 1.11, $CHCl_3$). E.e. 35%.

Data for **1c**: ^1H NMR ($CDCl_3$, 300 K): $\delta=7.58$ (t, $J=7.6$ Hz, 1H), 7.29 (d, $J=8.8$ Hz, 2H), 7.21 (d, $J=7.6$ Hz, 1H), 7.13 (d, $J=7.6$ Hz, 1H), 6.88 (d, $J=8.8$ Hz, 2H), 5.71 (d, $J=4.2$ Hz, 1H), 4.50 (d, $J=4.5$ Hz, 1H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 300 K): $\delta=163.3$, 159.7, 150.5, 139.8, 134.9, 128.7, 123.2, 119.9, 114.4, 75.1, 55.7. MS (EI) *m*/*z* (rel. int.): 250 (40), 249 (100, $M^{+\bullet}$), 137 (100), 113 (34), 112 (31), 94 (18), 78 (18), 77 (25), 66 (10). $[\alpha]_D^{20}=+80.2$ (*c* 1.50, $CHCl_3$). E.e. 45%.

Data for **1d**: ^1H NMR ($CDCl_3$, 300 K): $\delta=7.60$ (t, $J=7.8$ Hz, 1H), 7.34–7.28 (m, 4H), 7.22 (d, $J=7.8$ Hz, 1H), 7.13 (d, $J=7.8$ Hz, 1H), 5.73 (s, 1H), 4.70 (bs, 1H). ^{13}C NMR ($CDCl_3$, 300 K): $\delta=162.5$, 150.7, 141.1, 140.1, 134.2, 129.2, 128.7, 123.6, 119.9, 74.8. MS (EI) *m*/*z* (rel. int.): 255 (57), 254 (64, $M^{+\bullet}$), 253 (100), 142 (26), 141 (32), 140 (20), 114 (31), 113 (73) 78 (27), 77 (40). $[\alpha]_D^{20}=+37.9$ (*c* 0.98, $CHCl_3$). E.e. 23%.

Data for **1e**: ^1H NMR ($CDCl_3$, 300 K): $\delta=8.31$ (s, 1H),7.39–7.23 (m, 6H), 7.04 (d, $J=8.0$ Hz), 5.71 (s, 1H), 2.26 (s, 3H). ^{13}C NMR ($CDCl_3$, 300 K): $\delta=158.8$, 148.5, 143.9, 138.0, 132.3, 128.9, 128.1, 127.4, 121.2, 75.3, 18.5. MS (EI) *m*/*z* (rel. int.): 199 (92, $M^{+\bullet}$), 198 (100), 180 (19), 122 (32), 93 (40), 92 (30), 77 (23), 65 (14). $[\alpha]_D^{20}=+56.4$ (*c* 1.41, $CHCl_3$). E.e. 39%.

Data for **1f**: ^1H NMR ($CDCl_3$, 300 K): $\delta=7.73$ (q, $J=7.6$ Hz, 1H), 7.42–7.28 (m, 5H), 7.15 (dd, $J=7.6$, 2.4 Hz, 1H), 6.82 (dd, $J=7.6$, 2.4 Hz, 1H), 5.75 (s, 1H), 4.32 (bs, 1H). ^{13}C NMR ($CDCl_3$, 300 K): $\delta=163.2$ (d, $J_{C-F}=242.0$ Hz), 161.4 (d, $J_{C-F}=10.8$ Hz), 142.7, 142.3 (d, $J_{C-F}=7.6$ Hz), 129.0, 128.4, 127.3, 118.6 (d, $J_{C-F}=35.9$ Hz), 75.4. MS (EI) *m*/*z* (rel. int.): 203 (100, $M^{+\bullet}$), 202 (80), 184 (21), 174 (14), 126 (14), 107 (15), 97 (76), 77 (51), 51 (32). $[\alpha]_D^{20}=+37.1$ (*c* 1.01, $CHCl_3$). E.e. 30%.

References

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