Aggregative activation in heterocyclic chemistry. Part 4. Metallation of 2-methoxypyridine: unusual behaviour of the new unimetal superbase BuLi–$Me_2N(CH_2)_2OLi$ (BuLi–LiDMAE)

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A series of potential unimetal superbases BuLi–ROLi has been studied in order to increase the basicity/nucleophilicity ratio ([B/N]R) of BuLi. The best [B/N]R ratio is found with BuLi–LiDMAE. This complex base apparently metallates 2-methoxypyridine at the unexpected C-6 position. It is shown that no actual metallated species are formed in the reaction medium, the reaction occurring as the result of a common radical precursor stabilized by an aggregate cluster. Finally, as an application, C-6 substituted 2-methoxypyridines have been obtained in good to excellent yields.

Introduction

The structure of lithium reagents has attracted, and still attracts, considerable attention.[1–4] Numerous very elegant works[4,5] have definitively established that the intricate nature of such derivatives results from equilibria between aggregates and sometimes the corresponding monomer. The structure of the aggregates and the equilibrium positions depend on the lithium reagent, its concentration, the solvating property of the solvent and temperature. All this shows that it is not easy to establish the identity of the actual reactive species during a reaction between a lithium reagent and a substrate. Further, little is generally known about the influence of the substrate undergoing reaction on the reactivity of the starting lithium reagent.[5,7] Finally the very intimate mechanism of such reactions is not yet well elucidated. It thus appears that the study of the chemical behaviour of aggregated lithium reagents might provide some helpful information in the understanding of the properties of lithium derivatives. As part of our studies on aggregative activation[6,7] we undertook the investigations dealing with the generation of unimetal superbases (USB)[7] from BuLi and lithium alkoxides. Indeed our work on sodium amide-containing complex bases showed that sodium alkoxides were very efficient in the generation of a series of $NaNH_2$–RONa reagents with specific properties.[6–8] We thought that analogous activation might take place with lithium reagents although differences between $NaNH_2$–RONa and RLi–R^1OLi had to be expected in the structure and in the optimal amounts of the alkoxides leading to the most efficient bases. From a synthetic point of view a large number of alcohols are commercially available and their lithium salts may be generated *in situ* very easily. In a short communication we reported our first observations about unexpected reactions between a number of super bases BuLi–ROLi (complex bases) and 2-methoxypyridine.[9] It appeared that under our conditions, unusual functionalization of the substrate took place at the C-6 position instead of the C-3 as might have been expected from the directed *ortho* metallation (DOM) principles.[3]

Here we report our investigations aimed at producing the most efficient activating agent ROLi and use of the corresponding new complex bases in the synthesis of 6-substituted 2-methoxypyridines. We also discuss some new observations on the reactivity of aggregates supporting our hypothesis concerning their propensity to promote single electron transfer (SET).[6–7]

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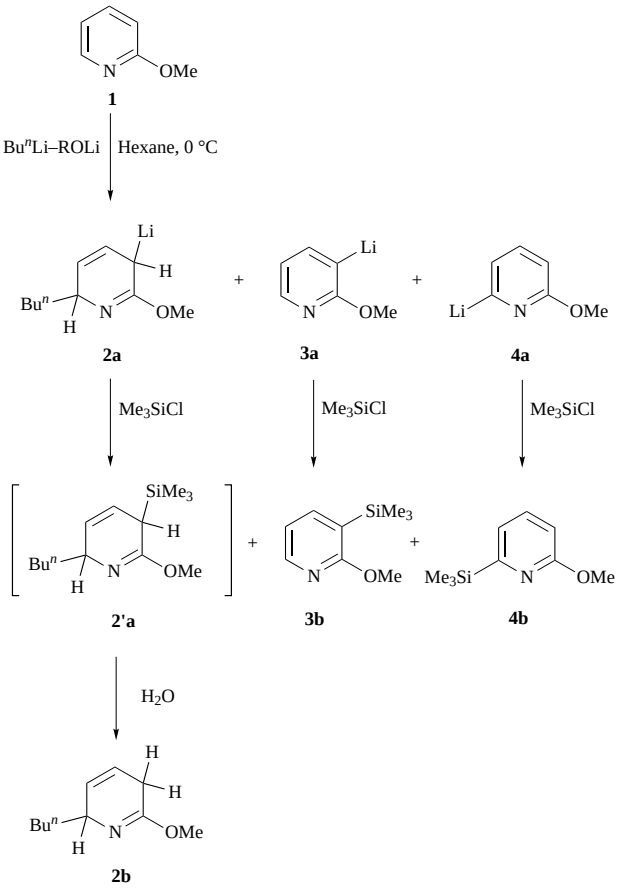


Scheme 1

Results

Influence of ROLi on the properties of BuLi-ROLi USBs

Use of Me_3SiCl as a trapping agent showed that the most general reaction taking place during these metallations was that illustrated in Scheme 1. Addition product **2b** is the only product usually obtained[10] from the reaction of BuLi with **1** while **3b** is currently prepared after metallation of **1** with lithium dialkylamides.[11] To the best of our knowledge **4b** has never been obtained from **1** by direct proton abstraction so we focused our attention on the formation of the corresponding lithium derivative **4a**. First we carried out an exploratory study in order to understand the behaviour of the new complex bases BuLi–

Table 1 Metallation of **1** with BuLi–ROLi[a]

	Complex base		Yields (%)[b]			
Runs	BuLi (equiv)	Activating agent (equiv)	Rec. **1**	**2b**	**3b**	**4b**
1	1	none	0	100	0	0
2	1	Bu^tOLi (1)	0	100	0	0
3	1	$Et(OCH_2CH_2)_2OLi$ (1)	100	0	0	0
4	1	$Me_2N(CH_2)_2OLi$ (1)	30	28	0	42
5	1	TMEDA (1)	53	16	31	0
6	1	$EtOCH_2CH_2OLi$ (1)	66	26	0	7
7	1	$Me_2N(CH_2)_2OLi$ (2)	30	1	17	52
8	1	$Me_2N(CH_2)_2OLi$ (3)	39	3	23	35
9	2	$Me_2N(CH_2)_2OLi$ (2)	27	13	0	60
10	4	$Me_2N(CH_2)_2OLi$ (4)	1	5	0	94
11	4	$Pr^i{}_2N(CH_2)_2OLi$ (4)	0	100	0	0
12	4	$Me_2N(CH_2)_3OLi$ (4)	0	100	0	0
13	4	$Me_2NCH_2CHMeOLi$ (4)	5	83	0	10
14	4	$Me_2NCHMeCHPhOLi$ (4)	3	40	0	56
15	4	$LiOCH_2\overline{CH(CH_2)_3CH_2N}Me$ (4)	3	32	0	64
16	4	$\overline{CH_2(CH_2)_2CH_2N}(CH_2)_2OLi$ (4)	2	10	0	86
17	4	$\overline{CH_2(CH_2)_3CH_2N}(CH_2)_2OLi$ (4)	2	27	0	67

[a] Metallations were performed in a constant volume of hexane (40 ml) at 0 °C for 1 h; condensations were performed with 1.5 equiv. of Me_3SiCl (based on BuLi) in 5 ml of hexane at 0 °C for 1 h. [b] Yields determined by GC capillary analysis.

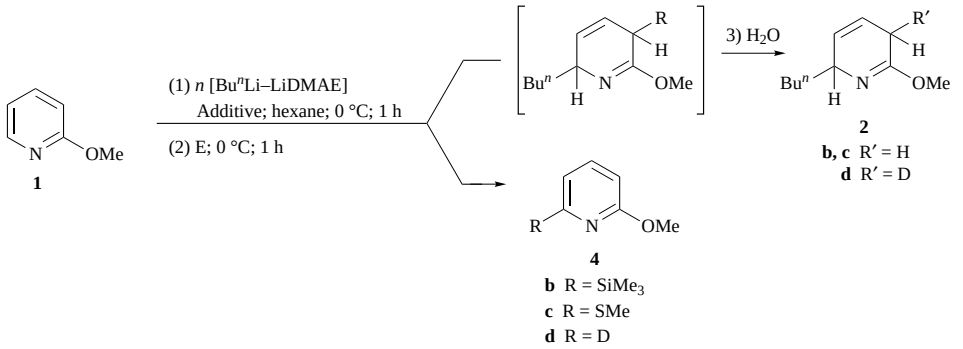
ROLi. The main results are reported in Table 1. Important differences were soon noted between heterogeneous[12] $NaNH_2$–RONa and homogeneous BuLi–ROLi complex bases with respect to the structure of the activating agents. While Bu^tONa and $Et(OCH_2CH_2)_2ONa$ were among the best activating agents of $NaNH_2$,[8] their corresponding lithium salts were found to be completely inefficient. In fact with the former salt, **2b** was obtained as the only product (run 2) and with the latter the starting material was quantitatively recovered (run 3). In contrast, while the sodium salt of dimethylaminoethanol (NaDMAE) only moderately activated $NaNH_2$,[8c] lithium 2-dimethylaminoethanolate (LiDMAE) efficiently increased the [B/N]R ratio of BuLi (runs 4 and 7–10) and, under appropriate conditions, strongly favoured the formation of **4b** (runs 9, 10). Thus, we first hypothesised that the properties of BuLi were influenced by the simultaneous presence of dimethylamino and lithium alkoxide groups in the activating agent. This hypothesis was supported (run 5) by the reaction performed with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in which a *N*,*N*-dimethylamino group replaced the alkoxide one. This classical complexing agent[3b,4d,11b,13] led only to small amounts of **3b** and **2b** but to no **4b**. Interestingly, besides **2b** $EtOCH_2CH_2OLi$ (run 6) led to a small amount of **4b**. This result and the fact that dilithium glycolate (unreported results) was inefficient as an activating agent supported the conclusion that the structure of any activating agent must simultaneously contain an alkoxide group and a lone-paired neutral atom. With regard to the ratio BuLi/activating agent, differences with $NaNH_2$/RONa were also observed. Indeed, with sodium amide-containing complex bases, a ratio of $NaNH_2$/RONa = 2 induced the best activation whatever the reactions performed.[6–8] With BuLi–ROLi, and as far as the selective formation of **4b** was concerned, a ratio of BuLi/ROLi = 1 led to the best results (runs 4, 9, 10). This ratio was adopted in the following investigations particularly because complex bases with a ratio of BuLi/ROLi < 1 led to the competitive formation of **3b** (runs 7, 8), an observation which will deserve further investigation. An excess of lithiating reagent considerably increased the yield of **4b** (runs 9, 10). This result parallels the literature data according to which, for some unknown reason, an excess of lithiating reagents is usually necessary to metallate nitrogen-containing heterocycles.[14] It is interesting to note that under our conditions, the presence of a large excess of BuLi–ROLi led only to very low yields of addition product **2b** (runs 9, 10), the best yields of **4b** being obtained when the ratio of **1**/BuLi/ROLi = 1/4/4 was used (run 10). According to this observation, we retained this ratio in investigations on the effect of the structure of aminoalkoxides (see Table 1; runs 11–17).

Comparison of runs 10 and 11 shows that bulky substituents on the nitrogen of the ethanolamine alkoxide completely suppressed the formation of aggregates appropriate to the C-6 proton abstraction from **1**. This behaviour may be due to a strong steric hindrance which impeded intermolecular interactions together with the classical B strain[15] which flattens nitrogen and decreases its cation complexation ability. Our results completely agree with the well established fact[4,5,7] that stereoelectronic factors play an important part in the formation and properties of aggregates. This was also illustrated by the inefficiency of lithium 3-dimethylaminopropanolate to increase the [B/N]R ratio of BuLi (run 12). From the other data it appeared that with one exception (run 13) lithium salts of aminoethanols with available nitrogen lone pairs constituted good activating agents within the framework of the reaction performed. Interestingly, lithium 2-(pyrrolidinyl)-ethanolate (run 16) was only slightly less efficient than LiDMAE. Without other physicochemical information we cannot further discuss the data reported and particularly the part played by the substituents of alkoxides such as those used in runs 13 or 14. The above reported study encouraged us to subsequently continue our investigations with the most efficient BuLi–LiDMAE base.

Influence of LiBr on the properties of BuLi-LiDMAE

From a synthetic point of view we were concerned with the serious drawbacks that could be brought about by the excess of base necessary to obtain **4a** in excellent yields. On the other hand, it is well known that addition of some additives to lithium reagents changes the structure of their aggregates and thus their properties.[4–5] After short exploratory experiments, we selected LiBr, an additive well known for its ability to interact with lithium reagent aggregates.[5a,16] From an unreported systematic study, a practical general trend emerged as far as the condensation of Me_3SiCl was concerned. (i) In the presence of 3 or 4 equiv. of complex base, addition of LiBr was deleterious. (ii) In contrast, on avoidance of a large excess of base, it was found that in the presence of 1 or 2 equiv. of complex base, addition of LiBr substantially improved the formation of **4b**. However, the best results (see Table 2, runs 1 and 2) were obtained with 2 equiv. of base. Since we have no information about the structure of the aggregates we are unable to discuss these results in detail. Moreover, the empirically determined optimal amount of added LiBr, cannot be of help since this salt

Table 2 Metallation of **1** with BuLi–LiDMAE and trapping with electrophiles: influence of LiBr and electrophiles[a]



Runs	*n*	Additive LiBr (equiv.)	E (equiv)	Yields (%)[b] Rec. **1**	**2b–d**	**4b–d**
1	2	—	Me_3SiCl (2)	27	13	60
2	2	0.25	Me_3SiCl (2)	5	15	75
3	2	—	MeSSMe (2.5)	20	15	63
4	2	0.25	MeSSMe (2.5)	10	15	72
5	2	—	DCl/D_2O (10)	5	61	34[c]
6	2	0.25	DCl/D_2O (10)	6	53	41[c]

[a] Metallations were performed in a constant volume of hexane (40 ml) at 0 °C for 1 h; Me_3SiCl or MeSSMe were added in hexane (5 ml). DCl–D_2O were added without solvent. All electrophiles were allowed to react at 0 °C for 1 h. [b] Yields determined by GC capillary analysis. [c] Deuteriation yields were determined by ^1H NMR spectroscopy.

is sparingly soluble in the reaction medium. Before exploring the synthetic potential of the above results we wanted to check that the yield of **4b** reflected the yield of **4a** in the reaction medium. Indeed it might be thought that aggregates containing **4a** or a precursor of **4a** were formed in low concentration during an equilibrated reaction and that addition of Me_3SiCl displaced the equilibrium towards **4b**. This possibility was investigated in runs 3 to 6 performed with 2 equiv. of base. The results obtained with MeSSMe (runs 3, 4) completely agreed with those obtained with Me_3SiCl. The results obtained with DCl–D_2O (runs 5, 6) were puzzling. Indeed a much larger amount of **2a** was trapped with DCl–D_2O than with Me_3SiCl or MeSSMe. Since the metallations were performed under the same conditions, it must be concluded that **2a** was formed in 50–60 % yields before the trapping with Me_3SiCl or MeSSMe whereas at the end of the condensations, the yields of **2b** and **2c** never exceeded 15% (runs 1–4). A possible explanation could be in the reversible addition of BuLi to **1** associated with a displacement towards **2a** or **4a** during the addition of the electrophile. We discarded this hypothesis for the following reasons. Since the formation of **4a** should be irreversible due to the formation of butane, longer reaction time and/or higher temperature should have led to a considerable increase in the formation of **4a**, which was never observed. Moreover, an increase in the complex base concentration corresponded to a substantial increase in the ratio **4a**:**2a** (see Table 1, runs 9 and 10) when decreased or at least unchanged ratios were expected. Last but not least, no butane evolution was observed during the metallation step. We shall see later that there may be another explanation for this surprising result.

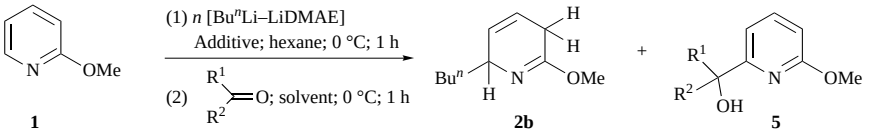
Metallation of 2-methoxypyridine with BuLi–LiDMAE and reaction with carbonyl derivatives

As part of the present study, carbonyl compounds were considered as interesting electrophiles. Indeed with appropriate structures, such substrates may undergo nucleophilic addition and competitive enolization. Given the complex nucleophilic as well as basic properties of our reaction medium, the behaviour of such substrates was expected to be very informative. Moreover, these reactions could provide good access to 6-hydroxymethyl-2-methoxypyridine derivatives. In fact, exploratory experiments showed that the expected pyridine derivatives could be obtained and that the simultaneous addition of THF with the carbonyl substrate could improve the reaction yields. Moreover, from unreported results, a number of useful observations emerge. (i) Only low to fair yields of **5** were obtained when metallations were performed with a stoichiometric amount of base. However these reactions evidenced that LiBr and/or THF improved the yield of **5** to the detriment of **2b**. (ii) While the use of 4 equiv. of base had led to excellent condensation yields with Me_3SiCl (see Table 1) low to fair yields were obtained with carbonyl electrophiles which had to be used in large excess (5 equiv.). Curiously, under these conditions, it was also observed that LiBr had no effect. It even negated the effect of THF which alone strongly favoured the formation of **5**. (iii) Finally, the reactions performed in the presence of 2 equiv. of base appeared to be the most interesting (see Table 3). Under such conditions, as illustrated with acetone, addition of LiBr or THF considerably favoured the formation of **5** (runs 2, 3) and their effects were additive (run 4).

The same behaviour was generally found with other representative carbonyl derivatives (runs 5–12) and under appropriate conditions we were able to obtain the alcohols **5** in good to very good yields. In addition to its influence on the aggregates, it is likely that, thanks to a classical electrophilic assistance,[16] LiBr promotes the condensations of **4a** with the carbonyl derivatives. On the other hand, it appeared that under the same metallation conditions the yield of **2a** deduced from the yields of **2b** varied with the nature of the condensed carbonyl derivative! This observation must be related to that made when we compared the behaviour of Me_3SiCl or MeSSMe with DCl–D_2O (*vide supra*). Since the reversibility of the formation of **2a** is unlikely, the only rational hypothesis is that neither **2a** nor **4a** was actually formed. Both should potentially exist in the form of a common precursor related to the complex base aggregates which would evolve either towards **2a** or **4a** in the presence of the electrophile, depending on the reactivity of the latter. The nature of such a precursor is further discussed hereunder.

At first, it seemed that the observed THF effect disagreed with the hypothesis of an aggregated common precursor. Indeed, the strong solvating power of this solvent relative to hexane, should have led to substantial destruction of the intermediate aggregates with consequent back formation of BuLi

Table 3 Metallation of **1** with BuLi–LiDMAE and condensation with carbonyl derivatives[a]



1 **2b** **5**

5a $R^1 = R^2 = Me$; **5b** $R^1, R^2 = (CH_2)_4$
5c $R^1 = Me$, $R^2 = Et$; **5d** $R^1 = R^2 = c\text{-}C_3H_5$
5e $R^1, R^2 = (CH_2)_7$; **5f** $R^1, R^2 = CH{=}CH(CH_2)_3$
5g $R^1 = R^2 = Ph$; **5h** $R^1 = H$, $R^2 = Bu^t$; **5i** $R^1 = H$, $R^2 = Hex$

Runs	*n*	Carbonyl compound R^1, R^2	equiv	Additive LiBr (equiv.)	Solvent[b] THF (ml)	Yields (%)[c] Rec. **1**	**2b**	**5a–i**
1	2	Me, Me	2.5	—	—	10	80	4
2	2	Me, Me	2.5	0.25	—	10	40	45
3	2	Me, Me	2.5	—	40	8	49	43
4	2	Me, Me	2.5	0.25	40	9	28	54
5	2	$(CH_2)_4$	2.5	0.25	40	7	27	63
6	2	Me, Et	2.5	0.25	40	4	9	80
7	2	$c\text{-}C_3H_5$, $c\text{-}C_3H_5$	2.5	0.25	40	2	9	83
8	2	$(CH_2)_7$	2.5	0.25	40	9	45	45
9	2	$CH{=}CH\text{-}(CH_2)_3$	2.5	0.25	40	5	44	49
10	2	Ph, Ph	2.5	0.25	40	10	44	43
11	2	H, Bu^t	2.5	0.25	40	5	5	88
12	2	H, Hex	2.5	0.25	40	10	32	53

[a] Metallations were performed in a constant volume of hexane (40 ml) at 0 °C for 1 h. [b] Carbonyl compounds were added in hexane (5 ml) or in THF (see Table) and allowed to react at 0 °C for 1 h. [c] Yields determined by GC capillary analysis.

and an increase in the yield of **2b**. In order to clarify this point, we studied the influence of THF on the trapping by DCl/D_2O. Reinforcing our hypothesis, we found that **2d** was formed quantitatively when THF was added 5 min before the trapping. In contrast, addition of a solution of DCl–D_2O in THF gave formation of **4d** (82%). In other words, THF favours the electrophilic condensation of **4a** when this species is formed but it is detrimental to its formation from the precursor. The nature of the products formed resulted from these reverse reactions. However, the evolution of the precursor towards either **2a** or **4a** must be essentially determined by the nature of the electrophile.

Metallation of 2-methoxypyridine and reaction with alkylating agents

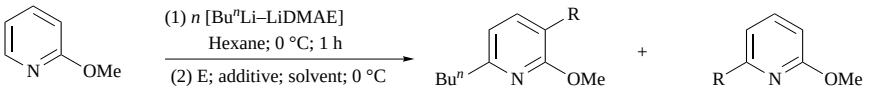
From exploratory experiments performed with these electrophiles, the following data emerged. (i) In hexane without additive, yields were generally low whatever the amounts of complex base used. (ii) No valuable effect of LiBr was observed. (iii) According to our observations during the condensation of carbonyl derivatives, an increase in solvent polarity by addition of THF also increased the reaction yields. However, 4 equiv. of base and 5 equiv. of electrophile were needed to obtain acceptable yields. With only a limited decrease in the yields, this stoichiometry may be reduced to 2 and 2.5 equiv., respectively, by addition of a catalytic amount of cuprous iodide.[17] (iv) The product formed from **2a** aromatised during the work-up to give **6**. Taking these observations into account we performed the reactions reported in Table 4.

From the reported results, it appears that alkyl iodides or sulfates must be preferred to less reactive bromides. Practical and satisfactory yields may be obtained under appropriate conditions with only a limited excess of base and electrophiles (runs 2, 4, 6, 8, 10 and 14). Examination of comparable runs in Tables 4 and 5 which differ only in the nature of the added electrophile confirms that the formation of the putative **2a** and **4a** depends on the nature of the electrophiles and reinforces our hypothesis about the involvement of a common reactive precursor.

Discussion

Comparison of the results obtained during the present work led to the apparently confusing conclusion that the reaction rate of the electrophile added to our reaction medium was the main factor determining the nature of the species formed during the metallation step. Low rates favoured **2a** and high rates did **4a**. It should be noted that the results obtained with the very reactive electrophile DCl–D_2O also agreed with this observation. Indeed in Table 2, the reactive species were trapped (runs 5 and 6) under heterogeneous conditions since the metallations were performed in hexane. Thus, the trapping rate was lower than in the presence of hydrophilic THF, which increased the interaction between the metallated species and the quenching reagent and favoured the formation of **4d**. We confirmed the part played by the reactivity of the electrophiles by trapping with Bu_3SnCl, a very reactive electrophile. Under the metallation conditions which usually led to large amounts of **2b** (see for example Tables 2, 3; runs 5 and 1, respectively) we observed the formation of 2-methoxy-6-(tributylstannyl)pyridine **10** (70%). This result confirms that the reagent obtained by metallation of **1** with BuLi–LiDMAE may quantitatively behave like **4a**. In other words had our study had been performed only with strong electrophiles we should have concluded that metallation at the C-6 position was nearly quantitative. Finally, we verified (see Experimental section) that the products of condensation on the C-6 position were not due to a second metallation of **2a** followed by elimination of BuLi. All these experimental results supported our hypothesis that **2a** and **4a** do not actually exist in our reaction medium but are potentially present in the form of a common reactive precursor. This hypothesis also explains our failure to observe butane evolution during the metallation step throughout the present work. In fact, this took place during the condensation of the electrophiles (see Experimental section). A similar observation was made many years ago during the reaction of the complex bases $NaNH_2$–RONa with Ph_3CH. Although a deep red colour had appeared during the metallation, strong evolution of NH_3 was observed only during the condensation of electrophiles such as $PhCH_2X$.[18] In accordance with our aggregative activation principles we proposed that the

Table 4 Metallation of **1** with BuLi–LiDMAE and condensation with alkylating agents[a]

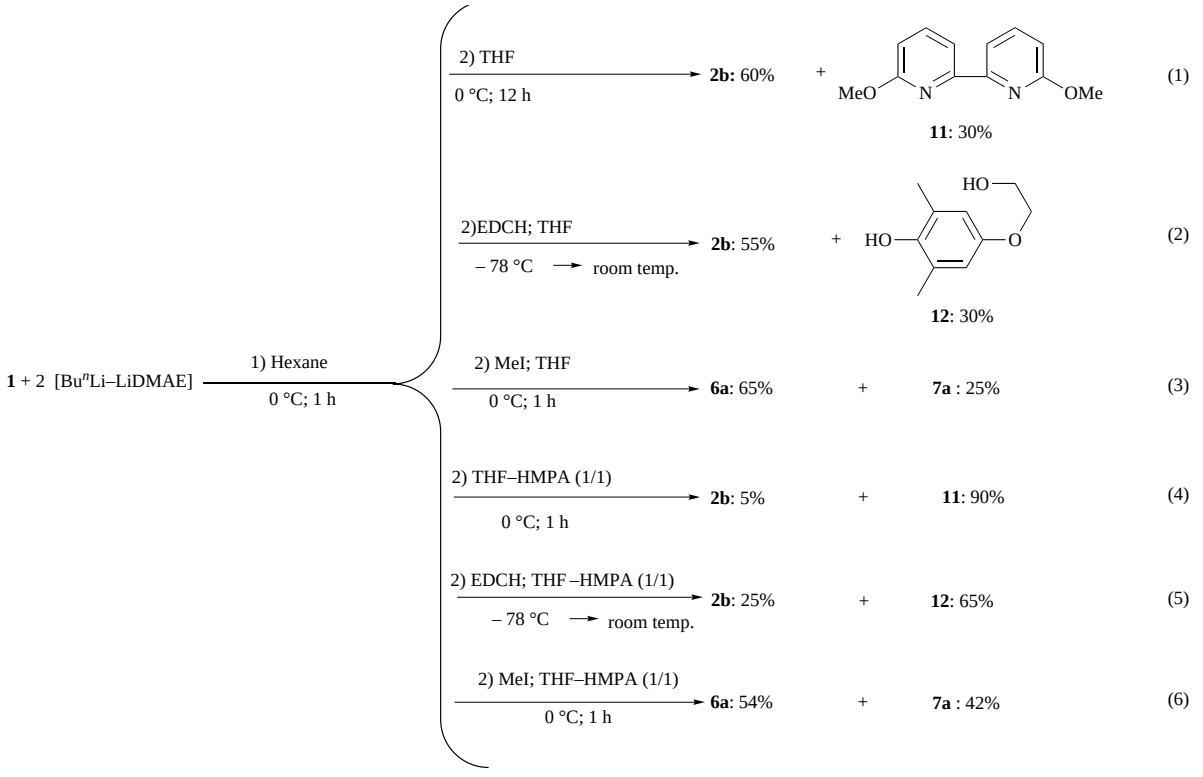


1 **6** **7**

a: R = Me; **b:** R = Et
c: R = Hex; **d:** R = c-$C_6H_{13}(CH_2)_3$

Runs	*n*	E (equiv.)	R	Additive CuI (equiv.)	THF (ml)	Yields (%)[b] Rec. **1**	**6a–d**	**7a–d**
1	4	MeI (5)	Me	—	80	0	25	70
2	2	MeI (2.5)	Me	0.2	40	5	35	59
3	4	Me_2SO_4 (5)	Me	—	80	7	14	70
4	2	Me_2SO_4 (2.5)	Me	0.2	40	18	17	62
5	4	EtI (5)	Et	—	80	0	29	64
6	2	EtI (2.5)	Et	0.2	40	4	42	54
7	4	Et_2SO_4 (5)	Et	—	80	5	16	71
8	2	Et_2SO_4 (2.5)	Et	0.2	40	20	19	60
9	4	Hex-I (5)	Hex	—	80	0	34	60
10	2	Hex-I (2.5)	Hex	0.2	40	6	54	40
11	4	Hex-Br (5)	Hex	—	80	0	64	30
12	2	Hex-Br (2.5)	Hex	0.2	40	5	68	25
13	4	c-$C_6H_{11}(CH_2)_3I$ (5)	c-$C_6H_{11}(CH_2)_3$	—	80	2	44	52
14	2	c-$C_6H_{11}(CH_2)_3I$ (2.5)	c-$C_6H_{11}(CH_2)_3$	0.2	40	8	50	40

[a] Metallations were performed in a constant volume of hexane (40 ml) at 0 °C for 1 h; electrophiles were added in THF and allowed to react at 0 °C for 1 h. [b] Yields determined by GC capillary analysis.



EDCH = 4,4-ethylenedioxy-2,6-dimethylcyclohexane-2,5-dione

Fig. 1

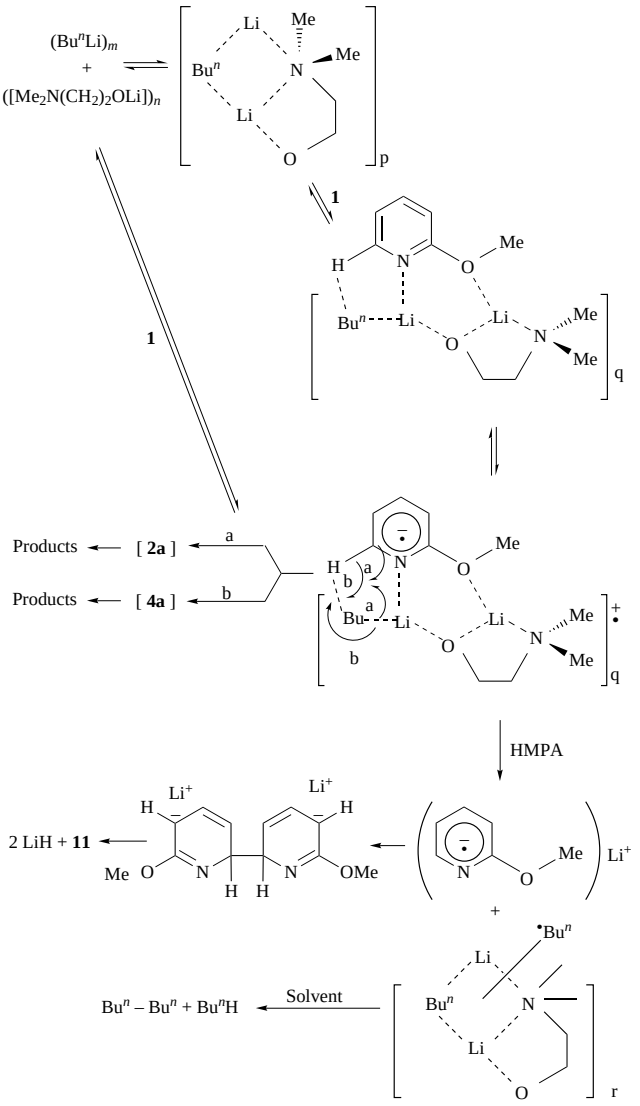
red colour was due to aggregates containing the anion radical $[Ph_3CH]^{\cdot-}$ stabilised by a cluster effect.[19] The presence of such a radical has since been confirmed by EPR.[20] This hypothesis was also supported by the finding that the SET propensity of NaH was considerably increased when this hydride was included in appropriate aggregates NaH–RONa.[8] Such a propensity was exacerbated when low-oxidation state metal species were introduced inside the aggregates to give complex reducing agents (CRA).[6,20] It is worth noting that matrices of aggregates of NaH–RONa stabilise electron-rich low-oxidation state metal species[6] which can normally survive only in the presence of ligands such as phosphines and carbon monoxide *etc*. We attribute this effect, at least partially, to the cluster effect of the aggregates. Taking these published results together with those of the present work, we conclude that the precursor of **2a** and **4a** contains $[2\text{-}MeOC_5H_4N]^{\cdot-}$ in a stabilised state. This being so, it became possible to direct the evolution of the precursor towards the customary free-radical reactions, simply by placing

1 in contact with BuLi–LiDMAE in an appropriate solvent. The reactions reported in Fig. 1 completely agree with our hypothesis.

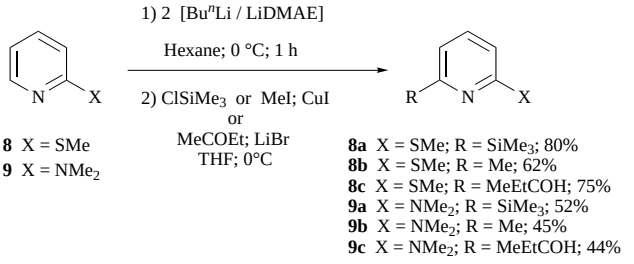
In hexane–THF without an electrophile [Eqn. (1)] we observed the formation in significant yield of a radical-coupling product **11**. Newkome *et al.*[21] showed that under analogous conditions, (*i.e.* the addition of HMPA, a well known radical stabilising solvent[22]), the amount of coupling product was considerably increased. We observed a similar increase [Eqn. (4)] as well as a very large increase in the reaction rate. The radical nature of the reactive intermediate is also supported by the reactions reported in Eqns. (2) and (5) using 4,4-ethylenedioxy-2,6-dimethylcyclohexane-2,5-dione (EDCH) as radical trapping agent.[23] It should be noted that the yield of **12** due to the trapping of the radical intermediate corresponds to the yield of the coupling product **11**, respectively, obtained in Eqns. (1) and (4) under the same solvent conditions. In addition, an EPR study of a sample containing 1 and 2 equiv. of the complex base in hexane showed a large signal ($\Delta H = 11$ G) with a *g*-factor of 2.0023. We were unable to obtain the fine structure but this observation reinforces our hypothesis. Finally, Eqns. (3) and (6) show that, under the corresponding conditions and in the presence of an electrophile, the products resulting from radical reactions were replaced by condensation products. This observation supports the hypothesis of a common precursor with radical-like properties. To sum up, we had to reconcile the following data. (i) Mixing of BuLi and LiDMAE gives a complex base in which the properties of each constituent are much modified and reflect a tight association to give mixed aggregates. (ii) Metallation of 2-methoxypyridine **1** with the complex base does not obey the known DOM effect[3] and takes place at the C-6 position instead of C-3. (iii) Condensation of electrophiles leads to the formation of products coming from the apparent irreversible addition of BuLi to **1** as well as its apparent metallation at the C-6 position. Under given conditions, the ratio of the product formed, unusually, depends on the nature of the trapping electrophile. As a corollary, neither **2a** nor **4a** actually exists in the reaction medium. (iv) A common precursor must potentially contain **2a** and **4a**. (v) The common precursor must possess some radical character stabilised by the aggregate cluster effect. The reactions reported in Scheme 2 tentatively account for the above requirements.

In such a mechanism, the aggregates of the complex bases and, consequently, the alkoxides must have an appropriate structure to fit with the stereoelectronic requirements of the complexation of **1**. This hypothesis explains how a change in the nature of the lithium aminoalkoxides led to an accompanying change in the behaviour of the complex base. Such requirements and their consequences were previously found during our study of *syn* eliminations performed with the CB $NaNH_2$–RONa.[24] At the present time we are unable to provide either a detailed mechanism for the condensation of the electrophile or an explanation for the effect of THF. However, the mechanism proposed opens new areas of investigation and also explains the reactions observed during the metallation of dithioketal with $NaNH_2$–$Et(OCH_2CH_2)_2ONa$.[25]

Finally, we have briefly checked that the reactions presently reported were not limited to 2-alkoxypyridines and that replacement of the oxygen atom by sulfur and nitrogen atoms led to similar results (see Scheme 3).



Scheme 2



Scheme 3

Conclusion

Complex bases BuLi–ROLi have been obtained. According to aggregative activation principles,[7,8] the nucleophilicity/basicity ratio of the BuLi included in these new unimetal superbases[7] may be changed by simply modifying the nature of the activating agent ROLi. A thorough study of BuLi–LiDMAE showed, once again, how the intrinsic properties of bases included in mixed aggregates can be modified. The unusual C-6 metallation of 2-methoxypyridine reflects a surface effect[6] due to an association of the substrates with the aggregates. A similar role of the ions distribution at the aggregates surfaces explained the unique ability of $NaNH_2$–RONa to perform *syn*-eliminations.[7] On the other hand, experimental evidence strongly suggests that the actual metallated species come from a precursor during the electrophile addition. It seems likely that this precursor is of a radical nature and stabilised by a cluster effect, according to aggregative activation.[19] In other words, the role of proton abstraction is once more questioned. It is interesting to note the analogy as illustrated by Eqns. (1) and (2) between the

$$RX + Mg \longrightarrow (RX)^{\cdot-}\ Mg^{\cdot+} \longrightarrow (R\,..\,Mg^{+})\ X^{-} \longrightarrow RMgX \quad (1)$$

$$RH + CB \longrightarrow (RH)^{\cdot-}\ CB^{\cdot+} \longrightarrow R^{-}\ M^{+} \quad (2)$$

mechanism of generation of organometallic reagents from organic halides and a metal and the presently proposed proton abstraction mechanism. Such an analogy also appeared during our study with complex reducing agents.[6] Finally, we have provided a simple preparation of C-6 substituted 2-methoxypyridines. We are actively pursuing further work in this area.

Experimental

General methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz, respectively, with TMS as internal standard and $CDCl_3$ as solvent. *J* Values are given in Hz. GC analysis were performed with an internal standard on a Shimadzu GC-14A apparatus using a HP1 25m column and temperature programming. GC–MS measurements (EI) were performed on a HP5971A spectrometer. HRMS were performed by the Centre de Spectrochimie Organique de l'Université Pierre et Marie Curie (Paris). Elemental analyses were performed by the Service Central d'Analyse du CNRS (Vernaison, France).

Materials

BuLi (1.6 M solution in hexane), 2-methoxypyridine and 2-(*N*,*N*-dimethylamino)pyridine were purchased from Aldrich. 2-Methylthiopyridine was prepared by treating 2-bromopyridine with BuLi at −78 °C followed by quenching with dimethyl disulfide. Hexane and THF were distilled and stored over sodium wire before use. Ether refers to diethyl ether. Alcohols and amino alcohols were commercially available and purified by the usual methods when necessary. LiBr and CuI were dried at 100 °C under reduced pressure for 24 h and used immediately. Chlorotrimethylsilane, dimethyl disulfide, ketones, aldehydes, alkyl halides and acyl chlorides were distilled or recrystallized before use. 4,4-Ethylenedioxy-2,6-dimethylcyclohexane-2,5-dione (EDCH) was prepared from 2,6-dimethylbenzoquinone[23] according to a published procedure.[26]

Typical procedure for metallation of 2-methoxypyridine with 4(BuLi–LiDMAE) and condensation with chlorotrimethylsilane (run 10, Table 1)

A three-necked flask (100 ml) cooled at 0 °C under a nitrogen atmosphere was charged with BuLi (32 mmol, 20 ml). *N*,*N*-Dimethylaminoethanol (16 mmol, 1.42 g) in hexane (10 ml) was then added dropwise to the flask followed after 0.5 h at 0 °C, by 2-methoxypyridine (4 mmol, 440 mg) in hexane (10 ml), also added dropwise. The orange-coloured solution was stirred at 0 °C for 1 h after which chlorotrimethylsilane (16 mmol, 1.76 g) in hexane (5 ml) was introduced. The reaction was allowed to continue for 1 h at 0 °C after which the product yield (GC) was 94%. The solution was finally hydrolysed at 0 °C with 10% aqueous HCl (40 ml). The aqueous layer was extracted twice with ether (20 ml) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was then purified on a Chromatotron (AcOEt–hexane, 5:95, as eluent) to give 2-methoxy-6-trimethylsilylpyridine **4b** (440 mg, 74%).

Typical procedure for metallation of 2-methoxypyridine with 2(BuLi–LiDMAE) in the presence of LiBr and condensation with dimethyl disulfide (run 4, Table 2)

To the above prepared base was added anhydrous LiBr (2 mmol, 175 mg) as a solid. The mixture was stirred at 0 °C for 0.5 h after which 2-methoxypyridine (8 mmol, 870 mg) in hexane (10 ml) was added dropwise to it. The reaction mixture was stirred at 0 °C for 1 h after which a solution of dimethyl disulfide (20 mmol, 1.9 g) in THF (5 ml) was then added dropwise to it. After being allowed to react for 1 h the product yield (GC) was 72%. The solution was finally hydrolysed at 0 °C with 10% aqueous HCl (40 ml). The mixture was then extracted twice with ether (20 ml), and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was then purified on a Chromatotron (AcOEt–hexane, 5:95, as eluent) to give 2-methoxy-6-methylthiopyridine **4c** (830 mg, 67%).

2-Butyl-2,5-dihydro-6-methoxypyridine 2b.[10] δ_H 0.75–1.05 (m, 3H, CH_3), 1.15–1.80 (m, 6H, CH_2), 2.70 (d, 2H, *J* 6.2, $=CCH_2$), 3.70 (s, 3H, CH_3O), 3.90–4.25 (m, 1H, N-CH) and 5.65 (s, 2H, CH=CH).

2-Methoxy-6-trimethylsilylpyridine 4b. δ_H 0.25 (s, 9H, CH_3Si), 3.90 (s, 3H, CH_3O), 6.65 (d, 1H, *J* 8.2, H-3), 7.10 (d, 1H, *J* 8.2, H-5), 7.45 (t, 1H, *J* 8.2 H-4); δ_C −1.25 (CH_3Si), 54.9 (CH_3O), 111.8 (C-5), 124.0 (C-3), 138.5 (C-4), 165.2 (C-2) and 167.2 (C-6); *m*/*z* 181 (M^+); *m*/*z* (EI) 181.0923 (M^+ $C_9H_{15}NOSi$ requires 181.0923).

2-Methoxy-6-methylthiopyridine 4c. δ_H 2.55 (s, 3H, CH_3S), 3.90 (s, 3H, CH_3O), 6.40 (d, 1H, *J* 7.8, H-3), 6.75 (d, 1H, *J* 7.7, H-5) and 7.40 (t, 1H, *J* 7.8, H-4); δ_C 12.9 (CH_3S), 52.95 (CH_3O), 104.9 (C-5), 113.2 (C-3), 138.1 (C-4), 156.8 (C-6) and 163.3 (C-2); *m*/*z* 155 (M^+) (Found: C, 54.05; H, 5.47; N, 9.21; S, 20.37 C_7H_9NOS requires C, 54.19; H, 5.81; N, 9.03, S. 20.65%).

2-Methoxy[6-^{2}H]pyridine 4d. This compound was obtained as a mixture with 2-methoxypyridine; δ_H 3.90 (s, 3H, CH_3O), 6.70 (d, 1H, *J* 8.7, H-3), 7.15 (d, 1H, *J* 7.7, H-5) and 7.40 (t, 1H, *J* 7.8, H-4).

Typical procedure for metallation of 2-methoxypyridine with 2(BuLi–LiDMAE) in the presence of LiBr and condensation with butan-2-one in THF (run 6, Table 3)

To the above prepared base was added solid, anhydrous LiBr (2 mmol, 175 mg). The mixture was stirred at 0 °C for 0.5 h after which 2-methoxypyridine (8 mmol, 870 mg) in hexane (10 ml) was added dropwise to it. The reaction mixture was stirred at 0 °C for 1 h after which a solution of butan-2-one (20 mmol, 1.44 g) in THF (40 ml) was added dropwise to it. After being allowed to react for 1 h the product yield (GC) was 80%. The mixture was finally hydrolysed at 0 °C with 10% aqueous HCl (40 ml). The aqueous layer was extracted with ether (2 × 20 ml) after which it was made alkaline with aqueous NaOH and extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated and the crude product was purified on a Chromatotron [AcOEt–hexane (1:9) as eluent] to give 2-(2-methoxy-6-pyridyl)butan-2-ol **5c** (1.16 g, 70%).

1-(2-Methoxy-6-pyridyl)-1-methylethanol 5a. δ_H 1.50 (s, 6H, CH_3), 3.95 (s, 3H, CH_3O), 4.65 (s, 1H, OH), 6.60 (d, 1H, *J* 7.5, H-3), 6.90 (d, 1H, *J* 7.5, H-5), 7.60 (t, 1H, *J* 7.6, H-4); δ_C 30.4 (CH_3), 53.2 (CH_3O), 71.6 (C-OH), 108.5 (C-5), 110.7 (C-3), 139.6 (C-4), 162.6 (C-6) and 163.9 (C-2); *m*/*z* 167 (M^+) (Found: C, 64.97; H, 8.07; N, 8.62. $C_9H_{13}NO_2$ requires C, 64.67; H, 7.78; N, 8.38%).

1-(2-Methoxy-6-pyridylcyclopentanol 5b. δ_H 1.50–2.00 (m, 8H, CH_2), 3.95 (s, 3H, CH_3O), 4.55 (s, 1H, OH), 6.60 (d, 1H, *J* 7.9, H-3), 6.95 (d, 1H, *J* 7.9, H-5) and 7.60 (t, 1H, *J* 7.8 H-4); δ_C 24 (CH_2), 42.2 (CH_2), 52.9 (CH_3O), 71.2 (C-OH), 107.9 (C-5), 110.8 (C-3), 139.1 (C-4), 161.8 (C-6) and 162.7 (C-2); *m*/*z* 193 (M^+) (Found: C, 68.48; H, 8.07; N, 7.43. $C_{11}H_{15}NO_2$ requires C, 68.39; H, 7.77; N, 7.25%).

2-(2-Methoxy-6-pyridyl)butan-2-ol 5c. δ_H 0.80 (t, 3H, *J* 8, CH_3CH_2), 1.50 (s, 3H, CH_3C), 1.80 (q, 2H, *J* 8, CH_3CH_2), 3.95 (s, 3H, CH_3O), 4.75 (s, 1H, OH), 6.60 (d, 1H, *J* 8.2 H-3), 6.85 (dd, 1H, *J* 8.2, H-5) and 7.60 (dt, 1H, *J* 8.1, H-4); δ_C 8.1 (CH_3CH_2), 28.6 (CH_3C), 36.2 (CH_2C), 53.3 (CH_3O), 74.0 (C-OH), 108.4 (C-5), 111.5 (C-3), 139.5 (C-4), 162.7 (C-6) and 163.0 (C-2); *m*/*z* 181 (M^+) *m*/*z* (CI) 182.1160 [$(M + H)^+$ $C_{10}H_{15}NO_2$ requires 182.1161].

2-Methoxy-6-pyridyl(dicyclopropyl)methanol 5d. δ_H 0.15–0.55 (m, 8H, CH_2C), 1.20 (m, 2H, $CHCH_2$), 3.90 (s, 3H, CH_3O), 4.60

(s, 1H, OH), 6.65 (d, 1H, *J* 7.8, H-3), 7.10 (d, 1H, *J* 7.7, H-5) and 7.60 (t, 1H, *J* 7.8, H-4); δ_C 0.79 (CH), 19.7 (CH_2), 52.7 (CH_3O), 71.2 (C-OH), 107.9 (C-5), 111.8 (C-3), 139.1 (C-4), 161.77 (C-6) and 162.9 (C-2); *m*/*z* 219 (M^+) (Found: C, 70.93; H, 8.05; N, 6.15 $C_{13}H_{17}NO_2$ requires C, 71.23; H, 7.76; N, 6.39%).

1-(2-Methoxy-6-pyridyl)cyclooctanol 5e. δ_H 1.50–2.00 (m, 14H, CH_2), 3.90 (s, 3H, CH_3O), 4.50 (s, 1H, OH), 6.60 (d, 1H, *J* 7.4, H-3), 6.90 (d, 1H, *J* 7.4, H-5) and 7.55 (t, 1H, *J* 7.5, H-4); δ_C 21.9 (CH_2), 24.3 (CH_2), 28.3 (CH_2), 37.3 (CH_2), 53.2 (CH_3O), 75.7 (C-OH), 108.5 (C-5), 111.5 (C-3), 139.3 (C-4), 162.5 (C-6) and 164.1 (C-2); *m*/*z* 235 (M^+) (Found: C, 71.60; H, 9.02; N, 6.15. $C_{14}H_{21}NO_2$ requires C, 71.46; H, 8.99; N, 5.95%).

1-(2-Methoxy-6-pyridyl)cyclohex-2-enol 5f. δ_H 1.10–2.20 (m, 6H, CH_2), 3.90 (s, 3H, CH_3O), 4.85 (s, 1H, OH), 5.60–6.00 (m, 2H, CH=CH), 6.60 (d, 1H, *J* 8.3, H-3), 6.80 (d, 1H, *J* 8.4, H-5) and 7.50 (t, 1H, *J* 8.3, H-4); δ_C 19.1 (CH_2), 24.9 (CH_2), 38.9 (CH_2), 53.3 (CH_3O), 73.2 (C-OH), 108.9 (C-5), 112.6 (C-3), 139.3 (C-4), 162.5 (C-2) and 181.1 (C-6); *m*/*z* 205 (M^+) (Found: C, 70.35; H, 7.29; N, 6.87. $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.82%).

1-(2-Methoxy-6-pyridyl)-1,1-diphenylmethanol 5g. δ_H 3.90 (s, 3H, CH_3O), 5.90 (s, 1H, OH), 6.60 (d, 1H, *J* 6.9, H-3), 6.70 (d, 1H, *J* 6.8, H-5), 7.25 (m, 10H, Ph) and 7.5 (t, 1H, *J* 6.9, H-4); δ_C 53.2 (CH_3O), 76.7 (C-OH), 109.2 (C-5), 115.3 (C-3), 127.9 (CAr), 138.7 (C-4), 145.8.5 (C-6), 164.1 (C-2); *m*/*z* 291 (M^+) (Found: C, 78.48; H, 6.07; N, 4.75. $C_{19}H_{17}NO_2$ requires C, 78.33; H, 5.88; N, 4.81%).

1-(2-Methoxy-6-pyridyl)-2,2-dimethylpropanol 5h. δ_H 0.95 (s, 9H, CH_3C), 3.90 (s, 3H, CH_3O), 4.05 (s, 1H, CHO), 4.30 (s, 1H, OH), 6.65 (d, 1H, *J* 7.3, H-3), 6.80 (d, 1H, *J* 7.3, H-5) and 7.50 (t, 1H, *J* 7.4, H-4); δ_C 25.8 (*C*H_3C), 36.2 (C), 53.1 (CH_3O), 80.0 (CH-OH), 109.1 (C-5), 115.4 (C-3), 138.2 (C-4), 157.5 (C-6) and 162.9 (C-2); *m*/*z* 194 (M^+) (Found: C, 67.93; H, 8.53; N, 7.07. $C_{11}H_{17}NO_2$ requires C, 67.69; H, 8.71; N, 7.18%).

1-(2-Methoxy-6-pyridyl)heptan-1-ol 5i. δ_H 0.95 (m, 3H, CH_3), 1.10–1.50 (m, 8H, 4 CH_2), 1.80 (m, 2H, CH_2), 3.90 (s, 3H, CH_3O), 4.10 (d, 1H, CHO), 4.25 (s, 1H, OH), 6.70 (d, 1H, *J* 7.7, H-3), 6.85 (d, 1H, *J* 7.7, H-5) and 7.50 (t, 1H, *J* 7.7, H-4); δ_C 14.0 (CH_3), 22.5 (CH_2), 22.6–38.2 (CH_2), 53.2 (CH_3O), 79.5 (CHOH), 106.5 (C-5), 113.3 (C-3), 138.5 (C-4), 160.5 (C-6) and 163.1 (C-2); *m*/*z* 223 (M^+) (Found: C, 69.72; H, 9.68; N, 6.12. $C_{13}H_{21}NO_2$ requires C, 69.95; H, 9.41; N, 6.28%).

Typical procedure for metallation of 2-methoxypyridine with 2(BuLi–LiDMAE) and condensation of iodomethane in the presence of CuI and THF (run 2, Table 4)

A three-necked flask (100 ml) cooled at 0 °C under a nitrogen atmosphere was charged with BuLi (32 mmol, 20 ml) to which *N*,*N*-dimethylaminoethanol (16 mmol, 1.42 g), in hexane was then added dropwise. After 0.5 h at 0 °C, the mixture was treated with 2-methoxypyridine (8 mmol, 880 mg) in hexane (10 ml), added dropwise. The mixture was stirred at 0 °C for 1 h after which a solution of iodomethane (20 mmol, 2.84 g) in THF (40 ml) and anhydrous CuI (1.6 mmol, 300 mg) were added simultaneously to it. After 1 h at 0 °C (GC yield was then 59%), the mixture was hydrolysed at 0 °C with water (40 ml). The mixture was extracted with ether (2 × 20 ml) and the extract dried ($MgSO_4$) and evaporated. The crude product was purified on a Chromatotron (hexane as eluent) to give 2-methoxy-6-methylpyridine **7a** (510 mg, 52%).

Compounds **6a**, **6b**, **6c** and **6d** were found to be identical with authentic samples prepared according to a published method.[11b]

2-Butyl-3-methyl-6-methoxypyridine 6a. δ_H 0.95 (m, 3H, CH_3), 1.5 (m, 4H, CH_2), 2.3 (s, 3H, CH_3), 2.8 (t, 2H, *J* 8, CH_2), 4.00 (s, 3H, CH_3O), 6.70 (d, 1H, *J* 7, H-5) and 7.90 (d, 1H, *J* 7, H-4).

2-Butyl-3-ethyl-6-methoxypyridine 6b. δ_H 0.9–1 (m, 6H, CH_3), 1.6 (m, 4H, CH_2), 2.7 (t, 4H, *J* 8, CH_2), 3.95 (s, 3H, CH_3O), 6.65 (d, 1H, *J* 7, H-5) and 7.80 (d, 1H, *J* 7, H-4).

2-Butyl-3-hexyl-6-methoxypyridine 6c. δ_H 1.00 (m, 6H, CH_3), 1.4–1.7 (m, 12H, CH_2), 2.8 (t, 4H, *J* 8, CH_2), 3.95 (s, 3H, CH_3O), 6.70 (d, 1H, *J* 7, H-5) and 7.90 (d, 1H, *J* 7, H-4).

2-Butyl-3-cyclohexylpropyl-6-methoxypyridine 6d. δ_H 0.8–0.9 (m, 3H, CH_3), 1.15–1.20 (m, 8H, 4 CH_2), 1.5–1.75 (m, 11H, CH_2 + CH), 2.7 (t, 4H, *J* 8, CH_2), 3.95 (s, 3H, CH_3O), 6.75 (d, 1H, *J* 7, H-5) and 7.75 (d, 1H, *J* 7, H-4).

6-Methyl-2-methoxypyridine 7a. δ_H 2.4 (s, 3H, CH_3), 3.90 (s, 3H, CH_3O), 6.50 (d, 1H, *J* 7.8, H-3), 6.80 (d, 1H, *J* 7.8, H-5) and 7.5 (t, 1H, *J* 7.7, H-4); δ_C 24.1 (CH_3), 53.2 (CH_3O), 107.1 (C-5), 115.6 (C-3), 138.6 (C-4), 156.2 (C-6) and 163.1 (C-2); *m*/*z* 123 (M^+) (Found: C, 68.13; H, 7.46; N, 11.45. C_7H_9NO requires C, 68.27; H, 7.37; N, 11.37%).

6-Ethyl-2-methoxypyridine 7b. δ_H 1.25 (t, 3H, *J* 8, CH_3), 2.6 (m, 2H, CH_2), 3.95 (s, 3H, CH_3O), 6.50 (d, 1H, *J* 7.6, H-3), 6.70 (d, 1H, *J* 7.5, H-5) and 7.45 (t, 1H, *J* 7.7, H-4); δ_C 13.2 (CH_3), 30.6 (CH_2), 52.8 (CH_3O), 106.8 (C-5), 113.9 (C-3), 138.4 (C-4), 160.2 (C-6) and 163.3 (C-2); *m*/*z* 137 (M^+) (Found: C, 70.13; H, 8.24; N, 10.05. $C_8H_{11}NO$ requires C, 70.04; H, 8.08; N, 10.21%).

6-Hexyl-2-methoxypyridine 7c. δ_H 0.95 (t, 3H, *J* 8, CH_3), 1.35–1.70 (m, 8H, CH_2), 2.85 (t, 2H, *J* 7.8, CH_2C=N), 3.90 (s, 3H, CH_3), 6.50 (d, 1H, *J* 7.7, H-3), 6.80 (d, 1H, *J* 7.7, H-5) and 7.45 (t, 1H, *J* 7.8, H-4); δ_C 13.8 (CH_3), 22.3 (CH_2), 22.3–37.6 (CH_2), 52.8 (CH_3O), 106.7 (C-5), 114.6 (C-3), 138.2 (C-4), 160.1 (C-6) and 163.3 (C-2); *m*/*z* 193 (M^+) (Found: C, 74.65; H, 10.02; N, 7.33. $C_{12}H_{19}NO$ requires C, 74.57; H, 9.91; N, 7.25%).

6-Cyclohexylpropyl-2-methoxypyridine 7d. δ_H 1.15–1.25 (m, 8H, 4 CH_2), 1.50–1.75 (m, 7H, CH + CH_2), 2.60 (t, 2H, *J* 8, CH_2C=N), 3.90 (s, 3H, CH_3), 6.50 (d, 1H, *J* 7.1, H-3), 6.70 (d, 1H, *J* 7.1, H-5) and 7.45 (t, 1H, *J* 7.3, H-4); δ_C 7.3 (CH), 26.1–37.9 (CH_2), 52.8 (CH_3O), 106.7 (C-5), 114.6 (C-3), 138.2 (C-4), 160.1 (C-6) and 163.2 (C-2); *m*/*z* 233 (M^+) (Found: C, 77.35; H, 10.12; N, 6.28. $C_{15}H_{23}NO$ requires C, 77.21; H, 9.93; N, 6.00%).

2-Methylthio-6-trimethylsilylpyridine 8a. δ_H 0.30 (s, 9H, CH_3Si), 2.50 (s, 3H, CH_3S), 7.10 (d, 1H, *J* 7.9, H-3), 7.20 (d, 1H, *J* 8, H-5) and 7.35 (t, 1H, *J* 7.8, H-4); δ_C −1.5 (CH_3Si), 12.5 (CH_3S), 120.4 (C-5), 123.8 (C-3), 133.2 (C-4), 158.4 (C-2) and 167.6 (C-6); *m*/*z* 197 (M^+) (Found: C, 55.08; H, 7.93; N, 7.08. $C_9H_{15}NSSi$ requires C, 54.82; H, 7.61; N, 7.10%).

6-Methyl-2-methylthiopyridine 8b. δ_H 2.45 (s, 3H, CH_3), 2.55 (s, 3H, CH_3S), 6.80 (d, 1H, *J* 7.4, H-3), 6.95 (d, 1H, *J* 7.4, H-5) and 7.40 (t, 1H, *J* 7.3, H-4); δ_C 13.8 (CH_3S), 24.8 (CH_3), 118.2 (C-5), 119.5 (C-3), 136.5 (C-4), 158.7 (C-2) and 159.5 (C-6); *m*/*z* 139 (M^+) (Found: C, 60.65; H, 6.22; N, 10.42. C_7H_9NS requires C, 60.43; H, 6.47; N, 10.07%).

2-Methylthio-6-pyridylbutan-2-ol 9c. δ_H 0.75 (t, 3H, *J* 8, CH_3), 1.50 (s, 3H, CH_3), 1.80 (q, 2H, *J* 8, CH_2), 2.55 (s, 3H, CH_3S), 5.00 (s, 1H, OH), 6.95 (d, 1H, *J* 8.1, H-3), 7.05 (d, 1H, *J* 8.2, H-5) and 7.50 (t, 1H, *J* 8.1, H-4); δ_C 7.9 (CH_3), 13.1 (CH_3S), 28.5 (CH_3), 35.9 (CH_2), 74.1 (C-OH), 114.3 (C-5), 1193 (C-3), 136.6 (C-4), 157.6 (C-2) and 164.7 (C-2), *m*/*z* 197 (M^+) (Found: C, 60.80; H, 7.76; N, 6.92. $C_{10}H_{15}NOS$ requires C, 60.91; H, 7.61; N, 7.11%).

2-Dimethylamino-6-trimethylsilylpyridine 9a. δ_H 0.25 (s, 9H, CH_3Si), 3.10 (s, 6H, CH_3N), 6.45 (d, 1H, *J* 7.8, H-3), 6.75 (d, 1H, *J* 7.8, H-5) and 7.45 (t, 1H, *J* 7.9, H-4); δ_C −1.8 (CH_3Si), 37.7 (CH_3N), 104.9 (C-5), 117.0 (C-3), 135.1 (C-4), 159.1 (C-2) and 165.8 (C-6); *m*/*z* 194 (M^+) (Found: C, 61.56; H, 9.12; N, 14.62. $C_{10}H_{18}N_2Si$ requires C, 61.85; H, 9.28; N, 14.43%).

2-Dimethylamino-6-methylpyridine 9b. δ_H 2.40 (s, 3H, CH_3), 3.15 (s, 6H, CH_3N), 6.30 (d, 1H, *J* 8, H-3), 6.40 (d, 1H, *J* 8, H-5) and 7.30 (t, 1H, *J* 7.9, H-4); δ_C 24.8 (CH_3), 38.2 (CH_3N), 102.8 (C-5), 111.1 (C-3), 137.6 (C-4), 156.9 (C-6) and 158.9 (C-2); *m*/*z* 136 (M^+) (Found: C, 70.23; H, 9.10; N, 20.71. C_7H_9NS requires C, 70.59; H, 8.82; N, 20.59%).

2-Dimethylamino-6-pyridylbutan-2-ol 9c. δ_H 0.75 (t, 3H, *J* 8, CH_3), 1.45 (s, 3H, CH_3), 1.75 (q, 2H, *J* 8, CH_2), 3.10 (s, 6H, CH_3N), 6.45 (d, 1H, *J* 7, H-3), 6.50 (d, 1H, *J* 7, H-5) and 7.50 (t,

1H, *J* 6.9, H-4); δ_C 8.1 (CH_3), 28.5 (CH_3), 35.9 (CH_2), 37.9 (CH_3N), 73.4 (C-OH), 103.2 (C-5), 106.1 (C-3), 138.1 (C-4), 157.2 (C-2) and 162.8 (C-2); *m/z* 194 (M^+) (Found: C, 68.28; H, 9.12; N, 14.27. $C_{11}H_{18}N_2O$ requires C, 68.04; H, 9.28; N, 14.47%).

Preparation of 2-methoxy-6-tributylstannylpyridine 10

A three-necked flask cooled at 0 °C under a nitrogen atmosphere was charged with BuLi (32 mmol, 20 ml) to which *N*,*N*-dimethylaminoethanol (16 mmol, 1.42 g) in hexane (10 ml) was then added dropwise. After 0.5 h at 0 °C the mixture was treated with 2-methoxypyridine (8 mmol, 880 mg) in hexane (10 ml), added dropwise. The solution was stirred at 0 °C for 1 h after which a solution of tributyltin chloride (24 mmol, 7.82 g) in THF (40 ml) was added dropwise to it. After 0.5 h at 0 °C, the yellow solution was hydrolysed at 0 °C with water (40 ml) and then extracted with ether (2 × 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated and the crude product was diluted with hexane (40 ml) and passed down a column of neutral alumina. After evaporation of the eluate, the crude stannylpyridine (GC yield: 94%) was distilled under reduced pressure (140 °C/10 Torr) to yield 2-methoxy-6-tributylstannylpyridine **10** (2.23 g, 70%).

2-Methoxy-6-tributylstannylpyridine 10. δ_H 0.90 (t, 9H, *J* 7, CH_3CH_2), 1.10 (m, 6H, CH_2), 1.35 (m, 6H, CH_2), 1.5 (t, 6H, *J* 8, CH_2Sn), 3.90 (s, 3H, CH_3O), 6.55 (d, 1H, *J* 7.8, H-3), 7.00 (d, 1H, *J* 7.8, H-5) and 7.35 (t, 1H, *J* 7.9, H-4); δ_C 9.6 (CH_2Sn), 13.4 (CH_2CH_3), 27 (CH_2), 28.7 (CH_2), 52.8 (CH_3O), 108.6 (C-5), 125.6 (C-3), 135.5 (C-4), 162.8 (C-2) and 170.3 (C-6) (Found: C, 54.32; H, 3.44; N, 3.23. $C_{18}H_{33}NOSn$ requires C, 54.27; H, 3.27; N, 3.52%).

Homocoupling of 1 by addition of THF–HMPA: synthesis of 6,6′-dimethoxy-2,2′bipyridine 11

2-Methoxypyridine (8 mmol, 870 mg) was allowed to react for 1 h with the 2(BuLi/LiDMAE) base in hexane (50 ml) at 0 °C; a mixture of THF and HMPA (1:1; 100 ml) was then added dropwise to it. The mixture, turning from dark green to dark brown and then becoming colourless, was stirred for 1 h at 0 °C. After work-up, the crude product was treated with ether–hexane mixture (1:1; 100 ml). The precipitated solid was filtered off and recrystallized from hexane to yield **10** (780 mg, 90%) as a pale yellow solid, mp 118 °C (lit.,[27] 119 °C).

Radical-anion trapping using EDCH

2-Methoxypyridine (8 mmol, 870 mg) was allowed to react for 1 h with the base 2 (BuLi–LiDMAE) in hexane (50 ml) at 0 °C, the mixture being cooled to −78 °C. A solution of EDCH[24] (32 mmol, 2.83 g) in THF (50 ml) was added dropwise to the mixture which was then kept for 1 h at −78 °C. After this the mixture was allowed to warm to room temperature. Hydrolysis of the mixture at 0 °C was effected with a THF–H_2O mixture (1:1; 50 ml). Work-up and base extraction (10% aqueous NaOH) gave **12**[29] (400 mg, 30%).

4-(2-Hydroxyethoxy)-2,6-dimethylphenol 12.[29] δ_H 2.25 (s, 6H, CH_3), 3.95, 4.10 (m, 4H, CH_2OAr + CH_2OH) and 6.40 (s, 2H, Ar).

Attempted second metallation of 2a

2-Methoxypyridine (8 mmol, 870 mg) in hexane (5 ml) was added dropwise to a solution of BuLi (8 mmol, 5 ml) at 0 °C; after 0.5 h, **2a** was quantitatively formed (checked by deuteriation). The solution of **2a** was transferred *via* a nitrogen-flushed line into freshly prepared BuLi–LiDMAE base (2 equiv.) at 0 °C in hexane. After 1 h at this temperature, chlorotrimethylsilane (20 mmol, 2.2 g) was added to the mixture which was then kept for 1 h at 0 °C. Work-up gave **2b** (95%) with no trace of **4b**.

Procedure for measurement of butane evolution

The reaction was performed in a Schlenck apparatus connected to a vacuum pump (250 Torr) *via* a trap immersed in liquid nitrogen. After each reaction step, the trap was disconnected from the Schlenck apparatus, stopped at one extremity whilst the other was connected to a volume measurement device. The trap was then allowed to heat to room temperature whilst the volume of butane was measured. The volumes measured for a typical run [see Table 2; run 1): BuLi (32 mmol), DMAE 16 mmol), 2-methoxypyridine (8 mmol), $ClSiMe_3$ (20 mmol)] are reported in the following table.

Base preparation	2-methoxypyridine **1** (1 h; 0 °C)	TMSCl (1 h; 0 °C)	H_2O
V/ml[a]	*V*/ml[a]	*V*/ml[a]	*V*/ml[a]
300 (384)	0 (0)	85 (115)	160 (243)

[a] Corrected by deducing dilation volume (50 ml). Butane was characterised by GC–MS: *m/z* 58 (M^+). The number in parentheses are the theoretical volumes taking into account the GC analysis of the reaction medium after hydrolysis (Recovered **1**, 25%; **2b**, 13%; **4b**, 60%)

Acknowledgements

We thank Professor G. Queguiner for helpful recommendations and Professor A. Merlin for EPR measurements. We are also grateful to Dr Ph. Amard for correction of our English and to the editor for useful corrections.

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Paper 7/01914I
Received 18*th March* 1997
Accepted 29*th May* 1997