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Activation of Benzylic Amines Towards Regioselective Metallation by Borane Complex Formation

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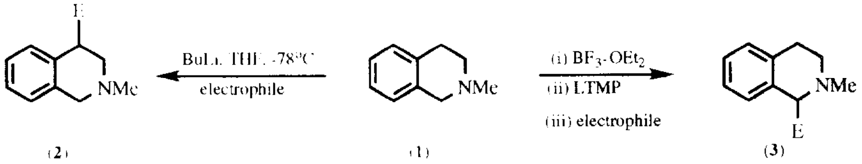
Abstract: Formation of borane complexes of *N*, *N*-dimethylbenzylamine **4** and *N* methyltetrahydroisoquinoline **1** facilitates regioselective metallation of these systems using BuLi, giving benzylic anions which react with a range of electrophiles.

The formation of carbanions α to nitrogen by metallation of amines and their derivatives is a rich area of chemistry which has sustained the interest of organic chemists over many years.[1] Since the direct metallation of amines is not usually a synthetically useful option,[2] the strategy usually followed is to activate the amine by the formation of a derivative, for example an amide, carbamate, *N*-nitroso, or formamidine.[3] Most of these methods are applied to derivatives of secondary amines of the form RR'NX, where X is the activating group. However, a recent innovation has been the activation of tertiary amines towards deprotonation by Lewis acid complexation with BF_3, e.g. Scheme 1.[4]

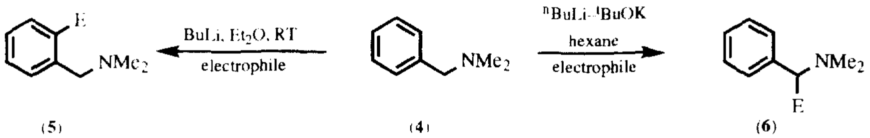


Scheme 1

Metallation of *N*-methyltetrahydroisoquinoline **1** with BuLi, followed by electrophilic quench normally gives C-4 substitution products **2**, whereas the use of BF_3 in combination with either LTMP or ^{s}BuLi as the base gives C-1 substitution products **3** in moderate yield (*ca.* 40–50%).

Our own interest in this area of carbanion chemistry centres on the use of more stable amine–borane complexes of tertiary amines, which might fulfil the dual role of activating adjacent CH groups towards deprotonation whilst also providing a convenient protecting group for the amine function.[5] Herein we show that amine borane complexes of the form RR'R''N–BH_3 show great potential in this regard, facilitating regioselective substitution of benzylic amines with "abnormal" regiochemistry, as shown in Scheme 1.

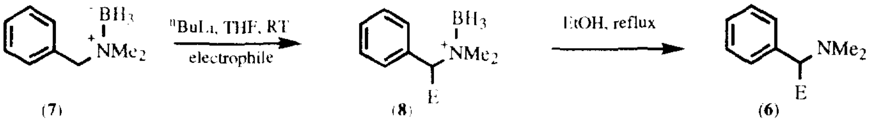
We initially focused on *N,N*-dimethylbenzylamine **4** as a substrate for metallation studies. Metallation of this substrate with ^{n}BuLi is reported to proceed slowly in Et_2O at room temperature to give exclusively *ortho* substituted products **5**, whereas access to α-substituted products **6** is possible by use of butylsodium or ^{n}BuLi–^{t}BuOK mixtures, Scheme 2.[6]



Scheme 2

We reasoned that borane adduct formation would enhance the CH acidity at the benzylic position in **4** whilst removing the donor ability of the amine lone pair which presumably facilitates *ortho*-lithiation in the free amine. It was therefore anticipated that borane complexation of **4** would promote rapid metallation of the system, and would provide the unusual benzyl anion regiochemistry. Preliminary experiments showed that both borane and chloroborane react with **4** to give stable, analytically pure, adducts, whilst other boranes, such as $BCl(C_6H_{11})_2$ and BCl_2Ph clearly formed adducts (TLC), but these were not stable to work-up and purification. In subsequent metallation trials the readily available borane adduct **7** proved most amenable to substitution chemistry.[7] Treatment of borane adduct **7** with 2 equiv. of ^{n}BuLi in THF at room temperature, followed by cooling to -78°C and addition of an appropriate electrophile gave good yields of the desired benzylic substituted products, Table 1.[8]

Table 1: Substitution of Borane Complex 7 via Metallation



electrophile	D_2O	Me_3SiCl	MeI	EtI	allylBr	BnBr	PhCHO	^{t}BuCHO	PhCOPh	$ClCO_2Me$	CO_2
(**7**)→(**8**) (%)	98[a]	70	54	59	64	35	44[b]	-	-	53	-
(**8**)→(**6**) (%)	-	90	86	87	92	96	95	-	-	-	-
(**7**)→(**6**) (%)[c]	-	71	61	64	-	44	56	62[b]	51	62	59

a - The recovered material showed 76–92% deuterium incorporation by ^{1}H NMR.

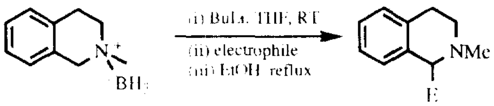
b - Only the major diastereomer was isolated.

c - Indicates yield of **6** obtained, avoiding isolation of intermediate **8**, by directly heating the crude reaction mixture from the metallation to reflux in EtOH. In the cases of reactions using ^{t}BuCHO, PhCOPh and CO_2 isolation of the intermediate **8** proved difficult.

Examination of the ^{1}H NMR spectrum of the deuterated product indicated that metallation had indeed proceeded in a highly regioselective fashion at the benzylic (α-position), rather than the *ortho*, position. This was confirmed by close examination of the TLC and NMR spectra of the silylated product **6** (E = $SiMe_3$), which showed no trace of the *ortho*-silylated product, synthesized independently by direct metallation of amine **4**. As can be seen from Table 1, the metallated borane complex reacts with a good range of electrophiles to give α-substituted products, it being possible in most cases to isolate complexes **8** in which the borane group is retained.[9]

We have also tested the borane activation method on the borane complex **9**, derived from tetrahydroisoquinoline **1**, one of the amines examined by Kessar and co-workers using BF_3 as the activating Lewis acid, Table 2.[10]

Table 2: Substitution of Complex 9 via Metallation



(**9**) (**3**)

electrophile	D_2O	MeI	Me_3SiCl	PhCHO
(**9**) → (**3**) (%)	100[a]	79	64	60[b]

a - The recovered material showed *ca.* 100% deuterium incorporation by ^{1}H NMR.

b - Two diastereoisomers were obtained in a ratio of 8:1

As we had hoped, the metallation of **9** shows the same modified regiochemistry previously described for the Lewis acid methodology employing BF_3. In fact the chemical yields of **3** for the reactions shown in Table 2 involving MeI, Me_3SiCl and PhCHO are significantly higher than those quoted for the BF_3 method (or comparable, taking into account the yield in the separate complex-forming step), which is surprising, considering that Kessar *et. al.* comment that use of BH_3 as activator and ^{n}BuLi as the base give "inferior results".

In conclusion, we have shown that amine-borane complexes, derived from benzylic amines are capable of efficient substitution via metallation, the complexes displaying complementary metallation regiochemistry to the free amines. Studies are presently directed at examining the scope of this approach with non-benzylic amines and to using the method for asymmetric synthesis by employing chiral boranes.

Acknowledgements

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References and Footnotes

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7. *Preparation and data for borane -amine 7*

   A solution of BH_3·THF (5 ml of a 1M solution in THF, 5 mmol) was added dropwise to a stirred solution of *N,N*-dimethylbenzylamine (0.675 g, 5 mmol) in THF (20 ml) at 0 °C. The solution was stirred for 30 min at which time TLC (20 % Et_2O in petroleum ether) showed complete consumption of starting material. The solvent was removed under reduced pressure, and the resulting white solid purified by flash chromatography on silica gel (20 % Et_2O in petroleum ether as eluant) to give **7** as a white solid (0.71g, 95%). Analytically pure material was obtained by recrystallisation from Et_2O–petroleum ether, followed by drying under high vacuum for 24 h, to give **7** (0.605 g, 81%), m.p. 103 °C; (Found: C, 72.37; H, 11.08; N, 9.26. $C_9H_{16}BN$ requires C, 72.53; H, 10.82; N, 9.40%); ν_{max} $(CHCl_3)/cm^{-1}$ 2951, 2366, 2320, 2273, 1468, 1164 and 860; δ_H (250 MHz, $CDCl_3$) 0.80–2.50 (3H, v. br., BH_3), 2.51 (6H, s), 3.99 (2H, s), and 7.30–7.42 (5H, m); δ_C (68 MHz, $CDCl_3$) 49.4 (2 x CH_3), 67.2 (CH_2), 128.2 (CH), 128.8 (CH), 130.9 (C) and 132.0 (CH).
8. *Typical procedure for substitution of 7 via metallation*

   A solution of ^nBuLi (1.25 ml of a 1.6M solution in hexanes, 2.0 mmol) was added dropwise to a solution of complex **7** (154 mg, 1.0 mmol) in THF (10 ml) at -78 °C under an atmosphere of N_2. The solution was then warmed to RT for 1 h, before recooling to -78 °C and addition of Me_3SiCl (0.63 ml, 5.0 mmol) as a single portion. After 2 min the cooling bath was removed and the reaction mixture allowed to warm to room temperature for 30 min before addition of saturated aqueous $NaHCO_3$ solution (10 ml). The phases were separated and the aqueous layer extracted further with Et_2O (2 x 10 ml). The combined organic extracts were then washed with saturated brine (*ca.* 20 ml), dried over $MgSO_4$ and concentrated under reduced pressure to yield a colourless oil. The crude material was then purified by flash chromatography on silica gel (5% Et_2O in petroleum ether as eluant) to give complex **8** (E = $SiMe_3$) as an oil that slowly solidified after drying under high vacuum (161 mg, 70%).

   The reason for the requirement for excess base (1.7–2.0 equiv. of ^nBuLi) is not yet known.
9. However, in other cases, most notably in reactions involving aldehydes and ketones, isolation of **8** was difficult, and it proved much more efficient to convert the crude product from the metallation into the free amine **6** (indicated by yields in bottom line of Table 1). In other cases, such as the reaction with $PhCH_2Br$, the yields are modest due to difficulties in separation of the product from minor amounts of unreacted starting material.
10. The procedures for the preparation and metallation of complex **9**, m.p. 92–94 °C, are similar to those given above for complex **7**.

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