

Lewis Acid Complexed Heteroatom Carbanions; A New Concept for α -Metallation of Tertiary Amines[†]

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BF₃ complexes of typical benzylic, allylic and saturated *N*-methyl tertiary amines were α -lithiated, with lithium tetramethylpiperidide (LTMP) or *sec*-butyllithium, and were treated with electrophiles.

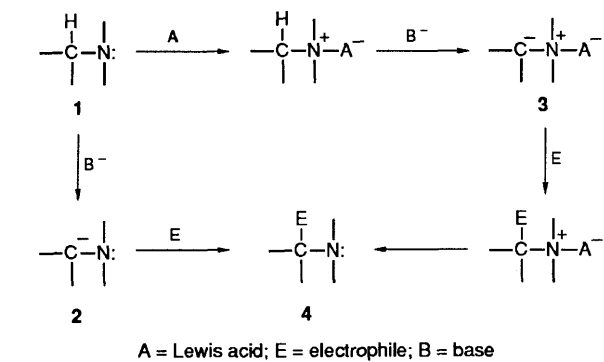
This Communication describes the concept of facilitating α -deprotonation of heteroatom compounds by complexation with a Lewis acid, and shows its utility for regioselective formation of C–C bonds in some tertiary amines (Scheme 1).[‡] Tertiary amines offer a real test of this idea since nitrogen, unlike phosphorus and sulphur, does not provide sufficient

stabilisation to an adjoining negative charge^{1–3} and for generation of α -carbanions indirect procedures, *e.g.* displacement from stannanes⁴ or sulphides,⁵ have been resorted to. In fact no methodology for direct elaboration of this class of compounds (**1** → **2** → **4**) seems available⁶ in spite of obvious applicability in total synthesis and in conversion of one amine to another of more useful properties.⁷

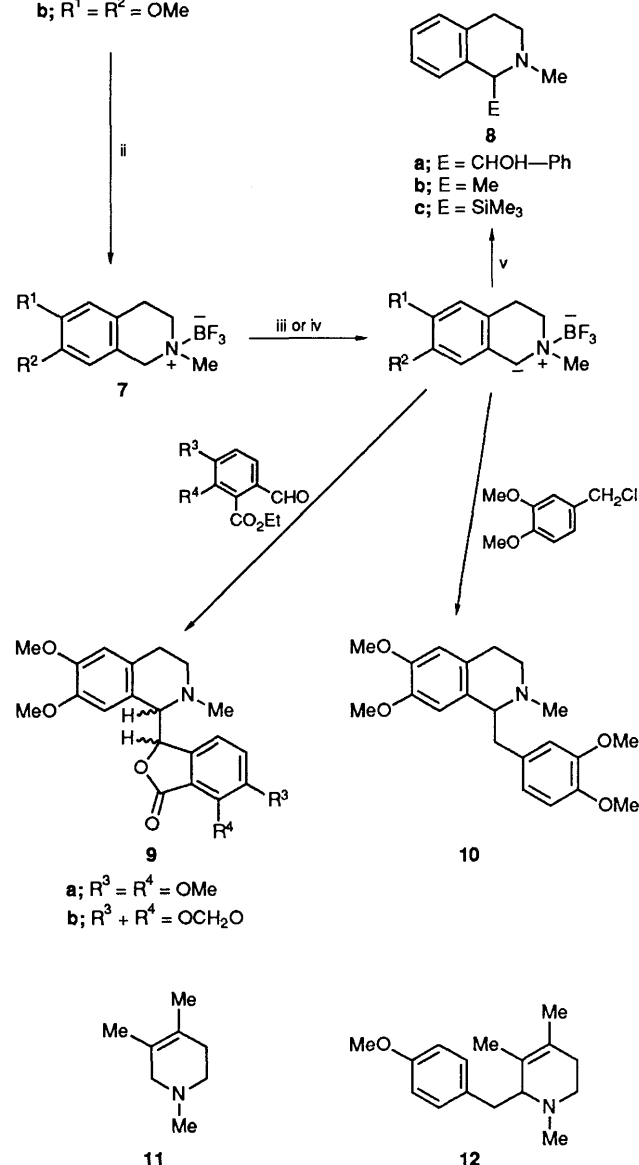
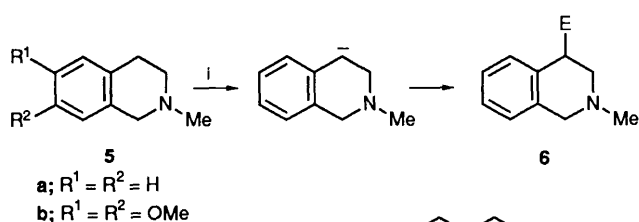
The above approach envisages use of a strong base in the presence of a complexed strong Lewis acid, and depends upon averting reaction between the two, possibly through a steric and/or hard soft acid and base (HSAB) mismatch.⁸ As a test case we selected *N*-methyltetrahydroisoquinoline **5a** which is deprotonated with *n*-butyllithium at C(4) (**5** → **6**, Scheme 2) in preference to C(1), as is its chromium carbonyl complex.^{9,10} In contrast, treatment of BF₃ complex **7a** with lithium tetramethylpiperidide (LTMP) in tetrahydrofuran (THF) at –78°C,

[†] Part of this work was presented at the 17th IUPAC International Symposium, New Delhi, February 1990; *Pure and Appl. Chem.*, 1990, **62**, 1397 (seminar lectures).

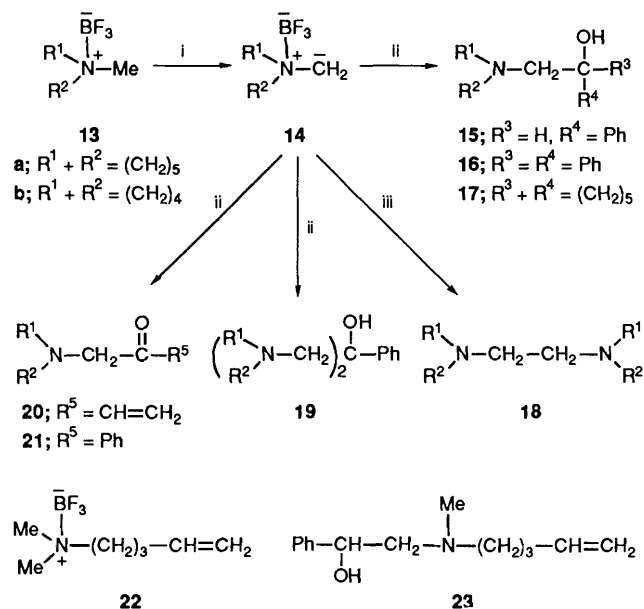
[‡] The dipole generated in the complex should stabilise the carbanion **3**. This strategy does not seem to have been explored systematically in spite of the wide interest in α -metallation of heteroatom compounds and the established role of Lewis acid complexes in promoting nucleophilic α -cleavage. See refs. 2, 3 and 8.



Scheme 1



Scheme 2 Reagents and conditions: i, BuLi, THF, -78 °C; ii, BF₃·Et₂O (1.05 equiv.); iii, LTMP (1.1 equiv.), THF, -78 °C, 1 h; iv, Bu^tLi (1.1 equiv.), THF, -78 °C, 1 h; v, electrophile (1.1 equiv.), -78 °C, 30 min, then HCl (5%)



Scheme 3 Reagents and conditions: i, Bu^tLi, THF, -78 °C, 1 h; ii, electrophile (1.1 equiv.), -78 to 0 °C, then HCl (5%); iii, I₂ (1.0 equiv.), then Na₂S₂O₅ (aq.)

followed by reaction with benzaldehyde, methyl iodide or trimethylsilyl chloride afforded the C(1) substitution products **8a** (50%),¹¹ **8b** (42%) and **8c** (47%) respectively. In the case of the methoxy substituted substrate **7b** use of *sec*-butyllithium was necessary to get, after reaction with appropriate electrophiles, (±)-alkaloids **9a** (cordrastine, 39% *erythro*- and 8% *threo*-isomer), **9b** (24% corlumine and 20% adlumine) and **10** (41% laudanosine).¹² A similar reaction of amine **11** with *p*-methoxybenzyl chloride gave (±)-**12** (42%), a precursor of the drug metazocine.¹³

To find out if aminocarbanions devoid of benzylic or allylic stabilisation can also be formed, *N*-methylpiperidine complex **13a** was exposed to *sec*-butyllithium.¹⁴ Subsequent reaction with benzaldehyde gave **15a**¹⁵ in 79% yield. The alcohols **16a**¹⁶ (70%), **17a**¹⁷ (68%), **15b**¹⁷ (68%) and **16b**¹⁶ (65%) were obtained similarly. The intermediate **14a** also reacted, for example, with iodine furnishing 1,4-diamine **18a**¹⁸ (65%) while methyl iodide led to *N*-ethylpiperidine (51%).¹⁹ Reaction of **14a** with ethyl benzoate (0.5 mol) gave the diamino-carbinol **19a** (72%) whereas methyl acrylate and benzonitrile

§ All compounds were characterised by ¹H NMR spectroscopy and mass spectrometry. M.p.s of known compounds, or their derivatives, corresponded with literature values. The identity of phthaloid alkaloids was further confirmed by direct comparison with samples obtained by known routes. Selected data for **8a**: m.p. 103–104 °C (EtOAc); ¹H NMR (CDCl₃) δ 6.8–7.3 (m, 7H, ArH); 6.53 (d, 1H, ArH); 5.06 (d, 1H, ArCHOH, *J* 4.0 Hz); 3.83 (d, 1H, CH-N, *J* 4.0 Hz); 3.78 (s, 1H, OH, D₂O exchangeable); 2.45–3.15 (m, 4H, Ar-CH₂-CH₂-N); 2.6 (s, 3H, NCH₃); *m/z* (relative intensity), 146 [(M⁺, -107), 100], 106 [(M⁺ -147), 10]. For **16**: m.p. 58–59 °C (EtOH); hydrochloride m.p. 228–230 °C; ¹H NMR (CDCl₃): δ 7.2–7.8 (m, 10H, ArH); 4.9 (s, 1H, OH, D₂O exchangeable); 3.3 (s, 2H, N-CH₂); 2.3 [m, 4H, -N-(CH₂)₂]; 1.4 [m, 6H, -(CH₂)₃]; *m/z* (relative intensity), 263 [(M⁺ - 18), 2], 98 [(M⁺ - 183), 100].

¶ Reported yields are for pure compounds isolated through chromatography and/or crystallisation. Based on recovered starting materials yields from **7a** and **7b** are 20–25% higher. TLC of crude basic fractions does not reveal formation of any major by-products. Use of *n*- and *tert*-butyllithium as the base or BCl₃, BH₃ and Me₃Al as the Lewis acid gave inferior results. Lithium–fluorine bridging may be involved in the case of BF₃ complex.

|| The reasons for better yields from **13**, in comparison to **7**, are not clear. Lower regioselectivity in metallation of the latter could be a factor.

afforded the ketones **20a** (69%) and **21a**²⁰ (50%), respectively. Metallation was successful even in the presence of a competing allylic site, as shown by the synthesis of alcohol **23** (65%) from the complex **22**.

Lewis acid promoted metallation can have many synthetic applications in tertiary amines and, possibly, in other heteroatom compounds.²¹

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