Regioselective directed lithiation of *N*-Boc 3-hydroxypyrrolidine. Synthesis of 2-substituted 4-hydroxypyrrolidines

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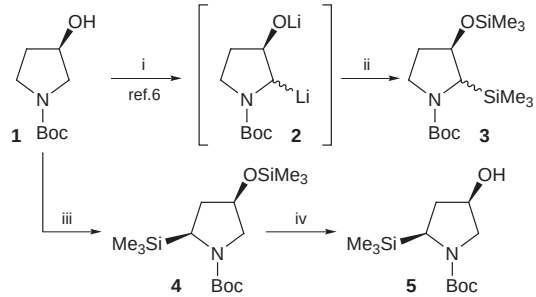
***N*-Boc 3-hydroxypyrrolidine 1 undergoes directed *C*-lithiation at C5 and not, as previously reported, at C2; the resulting dilithiated intermediate 6 has been trapped by a range of electrophiles to give 2-substituted 4-hydroxypyrrolidines 7.**

Directed metallation provides a versatile method for achieving substitution adjacent (α) to an amino moiety and this is a process which has found widespread application within heterocyclic chemistry.[1] The presence of additional and appropriately positioned heteroatom residues can, by providing additional activation, also enable regiochemical control to be exercised in the metallation (usually lithiation) step.[2–4] For example, *N*-Boc pyrrolidines[3] and piperidines[4] carrying a methoxy residue at C3 have been shown to undergo lithiation at C2 which is then followed by loss of MeOLi to give the corresponding cyclic enamine. Choosing a C3 substituent that is a poorer leaving group should, by suppressing β-elimination, allow this residue to be retained in the resulting product and this concept has been successfully applied to *O*-based heterocycles.[5]

More recently, this approach has also been utilised for *N*-heterocycles and Pandey and Chakrabarti[6] have reported that *N*-Boc 3-hydroxypyrrolidine **1** undergoes lithiation (at −78 °C using Bu^{s}Li, THF–TMEDA) followed by silylation to give exclusively the *C,O*-disilylated adduct **3** (in 86% yield), an intermediate that was then later employed in an alkaloid synthesis (Scheme 1).‡ These authors suggest that the sense of regiocontrol 'was expected due to the directing effects of the hydroxy group for the initial metallation reaction' and the implication of this claim is that the *C,O*-dilithiated species **2** is involved.

As part of a broader programme, we have had cause to examine the lithiation of **1** and two key issues are apparent. Firstly, in our hands, *C*-lithiation of **1** does not occur at −78 °C and, secondly, at higher temperatures when *C*-lithiation does take place, the only products observed are those resulting from lithiation distal to the C3 hydroxy, rather than proximal as claimed by Pandey. We have achieved lithiation of *N*-Boc 3-hydroxypyrrolidine **1** using Bu^{s}Li (2.2 equiv.) in THF–TMEDA at −78 °C and then allowing the solution to warm to −46 °C. After 2 h, the mixture is then recooled (to −78 °C) and Me_3SiCl (2.2 equiv.) was added giving, after work up, the *cis*-2,4-disubstituted adduct **4** as the only observed disilylated product (Scheme 1).



Scheme 1 *Reagents and conditions*: i, (ref. 6) Bu^{s}Li, THF–TMEDA, −78 °C; ii, Me_3SiCl (2.2 equiv.); iii, (this work) Bu^{s}Li (2.2 equiv.), THF–TMEDA, −78 °C to −46 °C, 2 h, cool to −78 °C, then Me_3SiCl (75%); iv, Bu_4NCl, KF, MeCN (100%)

Adduct **4** was then desilylated (at oxygen) to give **5** which proved to be a more suitable intermediate for assignment of both regio- and stereo-chemistry. This was carried out by ^{1}H NMR (COSY and NOE difference) analysis and, in addition, the relative stereochemistry of **5** has been established by X-ray crystallographic analysis (Fig. 1).§

The results of our study point towards the intermediacy of the *C,O*-dilithiated species **6** (and not **2**) as the only detectable intermediate (based on trapping) produced by lithiation of *N*-Boc-3-hydroxypyrrolidine **1**, however, the relative configuration of **6** has not been investigated.

The broader synthetic scope of this regiospecific lithiation chemistry has been further developed and intermediate **6** has been trapped with a range of electrophiles, including primary alkyl halides and enolizable aldehydes, to give the corresponding *N*-Boc 2-substituted 4-hydroxypyrrolidines **7** (Scheme 2, Table 1).¶ Yields for adducts **7**‖ have not been optimised because in most cases only modest *cis*/*trans* selectivity was observed. This likely reflects a combination of a highly reactive intermediate, *i.e.* **6**, with a lack of a significant conformational bias associated with the five membered ring, but we have established that *cis*/*trans* is kinetically controlled: attempts to lithiate *cis*-**7e** (using the standard reaction conditions), and thereby provide evidence for an equilibration pathway, failed.

In summary, *C*-lithiation of *N*-Boc 3-hydroxypyrrolidine (**1**) takes place distal to the hydroxy (lithioalkoxy) function but nevertheless offers a versatile and synthetically useful entry into 2-substituted 4-hydroxypyrrolidines. Our observations con-

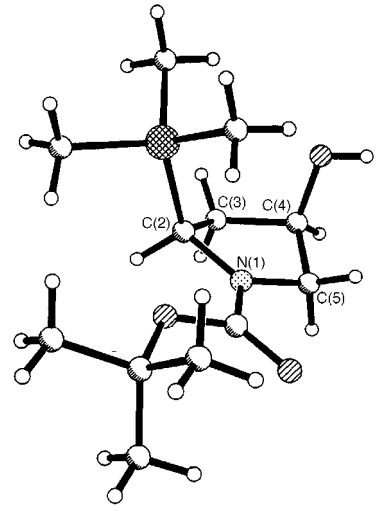
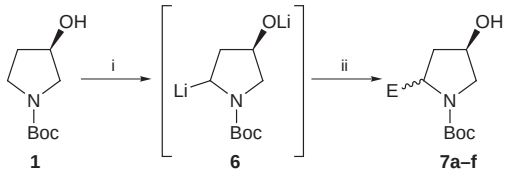
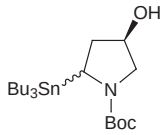
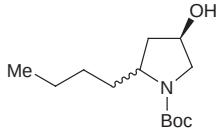
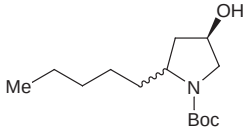
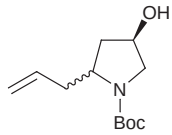
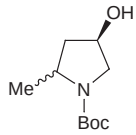
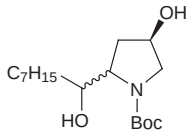


Fig. 1 Molecular structure of **5**



Scheme 2 *Reagents and conditions*: Bu^{s}Li (2.2 equiv.), THF–TMEDA, −78 °C to −46 °C, 2 h; ii, cool to −78 °C, then E^+ (2.2 equiv.) (see Table 1)

Table 1 Trapping of **6** with different electrophiles

Electrophile	2-Substituted 4-hydroxypyrrolidine (**7**) % yield and *trans*/*cis* ratio
Bu_3SnCl	 **7a** 50% 1 : 1
Br–Me	 **7b** 37% 1 : 1
Br–Me	 **7c** 39% 1 : 1
Br	 **7d** 59% 1 : 1
Me_2SO_4	 **7e** 65% 5 : 1 (see text)
Octanal	 **7f** 39% 1 : 1 (see text)

cerning *C*-lithiation clearly conflict with those described earlier[6] by Pandey and Chakrabarti. This is a concern but until this group publishes either detailed experimental protocols or compound data, it is not possible to identify those factors that might account for this apparent contradiction.

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Notes and References

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‡ Metallation of **1** is described[6] as having taken place at −78 °C. No spectroscopic data was reported for the *C*,*O*-disilylated adduct **3** which was also indicated as an unspecified mixture of diastereomers.

§ When we carried out lithiation and quenching of **1** at −78 °C (and the solution was not allowed to warm above this temperature) then only the *O*-silyl ether of **1** was observed. This monosilylated product was also observed as a minor component (in 15% yield) in the generation of **4**. The exclusive formation of *cis*-**4** has not yet been investigated but intramolecular delivery involving participation by oxygen cannot be ruled out. Data for **4**: $[\alpha]_D^{24}$ + 43.3 (*c* 1, CH_2Cl_2); δ_H(400 MHz, C_6D_6) 4.03 (1 H, m, H4), 3.69 (1 H, m, H5), 3.30–3.23 (2 H, m, H2 and H5), 1.91 (1 H, m H3), 1.78 (1 H, m, H3), 1.56 (9 H, s); δ_C(100 MHz, $CDCl_3$) (doubling due to rotamer populations) 154.9/154.5, 79.6/78.6, 71.0/70.2, 54.5/54.3, 46.3/46.0, 37.3/36.8, 28.5, −0.2, −1.8. Data for **5**: mp 107–110 °C (pentane–EtOAc); $[\alpha]_D^{24}$ + 57.4 (*c* 1, CH_2Cl_2); δ_H(300 MHz, $CDCl_3$) 4.39 (1 H, pentet, *J* 5.9, H 4α), 3.78 (1 H, d d, *J* 11.7, 5.9, H5α), 3.30 (1 H, dd, *J* 9.2, 7.2, H2α), 3.05 (1H, dd, *J* 11.7, 5.9, H5β), 2.26 (1 H, dddd, *J* 12.8, 9.2, 5.9, 0.7, H3α), 1.78 (1 H, m, H3β), 1.69 (1 H, br s, OH), 1.46 (9 H, s, Bu^t) and 0.10 (9 H, s, Me_3Si). Stereochemical assignments are based on NOE difference studies. The crystal structure of **5** was determined from data collected on a Siemens SMART diffractometer (λ = 0.71073 Å) at 173(2) K. The structure was solved by direct and Fourier methods and refined by least squares against all F^2 data corrected for absorption. *Crystal data*: $C_{12}H_{25}NO_3Si$, *M* = 259.4, orthorhombic, space group $P2_12_12_1$, *a* = 6.159(1), *b* = 24.957(4), *c* = 9.709(2) Å, *U* = 1492.5(5) Å^3, *Z* = 4, D_c = 1.15 g cm^{-3}, μ = 0.156 mm^{-1}, 3382 unique data, θ < 27.4°, R_1 = 0.043. CCDC 182/194.

¶ All lithiation reactions shown in Table 1 were carried out as described in the following example: to a solution of *N*-Boc (3*R*)-hydroxypyrrolidine **1** (189 mg, 1 mmol) in THF (5 cm^3) at −78 °C was added TMEDA (0.34 cm^3, 2.21 mmol) followed by Bu^{s}Li (1.7 cm^3, 1.3 M in cyclohexane, 2.21 mmol). The resulting bright yellow reaction mixture was warmed to −46 °C, stirred for 2 h, then recooled to −78 °C, and dimethyl sulfate (0.21 cm^3, 2.21 mmol, dried over 4 Å MS) was added dropwise. The reaction mixture was then allowed to warm slowly to room temperature (over 5 h) and, after this time, water (5 cm^3) and CH_2Cl_2 (7 cm^3) were added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 cm^3), the organic extracts were combined, and dried (K_2CO_3). Concentration *in vacuo* and purification of the residue by flash chromatography (light petroleum–EtOAc) gave *N*-Boc 2-methyl-4-hydroxypyrrolidine **7e** (131 mg, 65%) as a 5 : 1 mixture of diastereomers. Recrystallisation gave the major (*cis*) diastereomer as colourless crystals. Data for *cis*-**7e**: mp 88–89 °C (light petroleum–EtOAc); $[\alpha]_D^{24}$ + 21.1 (*c* 1, CH_2Cl_2). The *cis* stereochemistry of this major adduct has also been conformed by X-ray crystallographic analysis, details of which will be described elsewhere.)

‖ Enantiomerically pure (*R*)-**1** was used in these initial studies. Carbamate resonance complicated interpretation of the NMR data associated with adducts **7** but where this was an issue it was overcome by *N*-deprotection (using TFA, CH_2Cl_2, room temp.) to give the corresponding free amine. The formation of stereoisomers at C2, rather than a mixture of C2/C5 regioisomers, was confirmed by Swern oxidation of the *cis*/*trans* mixture to give a single 2-substituted pyrrolidin-4-one; this process was carried out for adducts **7b**–**e**. Octanal gave **7f** as an inseparable 1 : 1 mixture of two of the four possible products, but the stereochemistry of these products has not been assigned. In addition, all new compounds have been characterised by spectroscopic methods and either elemental analysis or HRMS.

1 P. Beak, A. Basu, D. J. Gallagher, Y. S. Park and S. Thayumanavan, *Acc. Chem. Res.*, 1996, **29**, 552; M. Gray, M. Tinkl and V. Snieckus, in *Comprehensive Organometallic Chemistry*, ed. E. W. Abel and F. G. A. Stone, Elsevier, New York, vol. 11, ch. 1; P. Beak, W. J. Zajdel and D. B. Reitz, *Chem. Rev.*, 1984, **84**, 471.

2 D. L. Comins and M. A. Weglarz, *J. Org. Chem.*, 1988, **53**, 4437; for a recent example involving a desymmetrisation process, see M. Lautens, E. Fillion and M. Sampat, *J. Org. Chem.*, 1997, **62**, 7080. Steric factors also play a role in determining regiochemical control in spite of the presence of a (sulfur-based) directing group, see D. J. Hart, J. Li, W.-L. Wu and A. P. Kozikowski, *J. Org. Chem.*, 1997, **62**, 5023.

3 M. Giles, M. S. Hadley and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 1990, 831.

4 P. Beak and W. K. Lee, *J. Org. Chem.*, 1993, **58**, 1109.

5 V. Wittmann and H. Kessler, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1091; P. Lesimple and J.-M. Beau, *Bioorg. Med. Chem.*, 1994, **2**, 1319; O. Frey, M. Hoffmann, V. Wittmann, H. Kessler, P. Uhlmann and A. Vasella, *Helv. Chim. Acta*, 1994, **77**, 2060; D. Mazeas, T. Skrydstrup and J.-M. Beau, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1383; M. Hoffmann and H. Kessler, *Tetrahedron Lett.*, 1994, **35**, 6067; D. Urban, T. Skrydstrup, C. Riche, A. Chiaroni and J.-M. Beau, *Chem. Commun.*, 1996, 1883. For a review of carbohydrate-based C1 nucleophiles, see J.-M. Beau and T. Gallagher, *Top. Curr. Chem.*, 1997, **87**, 1.

6 G. Pandey and D. Chakrabarti, *Tetrahedron Lett.*, 1996, **37**, 2285.

7 D. A. Fletcher, R. F. McMeeking and D. J. Parkin, *J. Chem. Inf. Comput. Sci.*, 1996, **36**, 746.

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