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Boron trifluoride etherate-assisted ring opening of ethylene oxide by a chiral organolithium: enantioselective synthesis of (*R*)-*N*-Boc-2-(2-hydroxyethyl)pyrrolidine

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Abstract—A practical synthesis of (*R*)-*N*-Boc-2-(2-hydroxyethyl)pyrrolidine in high enantiomeric purity is described. The synthesis involves $BF_3{\cdot}Et_2O$-assisted ring opening of ethylene oxide by a homochiral carbanion (*R*)-**3**, which is derived from sparteine-mediated asymmetric deprotonative lithiation of 1-Boc-pyrrolidine.
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1. Introduction

(−)-Sparteine-mediated asymmetric deprotonative lithiation has emerged as a powerful synthetic tool to generate 'chiral carbanions', thanks to the pioneering work by Hoppe and Hense[1] and Beak et al.[2] Capturing the chiral information from these organolithium species through alkylations, or by addition to carbonyl compounds, has resulted in numerous applications in asymmetric synthesis.[3–9] A recent paper introduced a readily accessible (+)-sparteine surrogate,[10] allowing preparation of these chiral organolithiums in both enantiomeric forms; considerably expanding the scope of this methodology. One remaining limitation of this chemistry is that the dipole-stabilized chiral organolithiums are configurationally stable only at very low temperature (−78 to −40 °C) and in select solvents (diethyl ether, THF, and hydrocarbon solvents).[11,12] Under these conditions, alkylations using less reactive electrophiles, such as epoxides, alkyl bromides, or alkyl chlorides, do not proceed efficiently. Electrophiles that are suitable for this chemistry are thus limited to strong electrophiles such as TMSCl, Bu_3SnCl, alkyl iodides, aldehydes, and ketones.[13] Herein, we report the first example of an intermolecular alkylation of a chiral organolithium with an epoxide activated by $BF_3{\cdot}Et_2O$, resulting in an efficient, enantioselective synthesis of (*R*)-Boc-2-hydroxyethylpyrrolidine. Although Lewis acid-assisted ring opening of epoxides by achiral organolithiums is well precedented,[14,15] to the best of our knowledge, investigations into the configurational stability of chiral organolithiums under such alkylation conditions have not been reported.

2. Results and discussion

In connection with one of our drug discovery projects, we needed multi-gram quantities of (*R*)-Boc-2-hydroxyethylpyrrolidine, (*R*)-**1**, in good enantiomeric purity (Fig. 1). Compound **1** is a versatile precursor used in the construction of natural products such as anthramycin,[16] lydicamycin,[17] halosaline,[18] and cuscohygrine,[19] as well as many bioactive molecules such as Clemastine (antihistamine),[20] and SB-269970 ($5HT_7$ receptor antagonist).[21]

The most commonly used methods to synthesize compound (*R*)-**1** involved multi-step sequences from expensive, chiral starting materials such as D-prolinol or D-proline,[21–24] which are not suitable for large-scale synthesis. Shown in Scheme 1 is a typical example.

Use of asymmetric deprotonative lithiations mediated by commercially available (−)-sparteine and (+)-sparteine surrogate have allowed access to chiral carbanions in either enantiomeric form.[10,11] Reference methodologies generally rely on reaction of the chiral carbanions with

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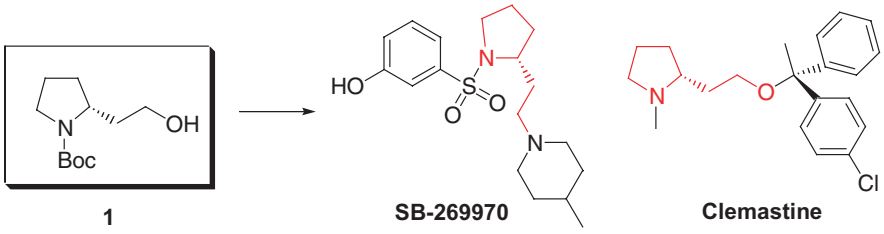
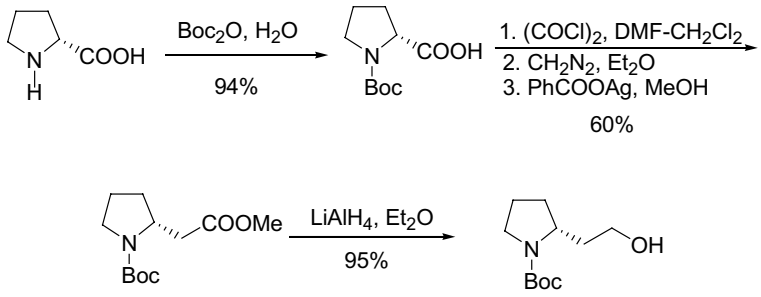


Figure 1.

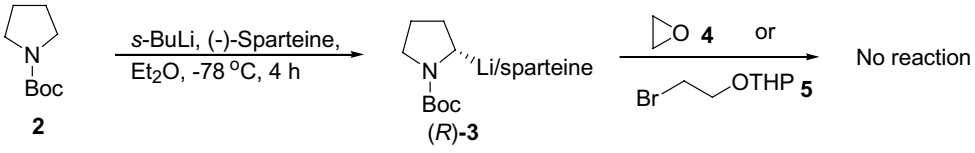


Scheme 1.

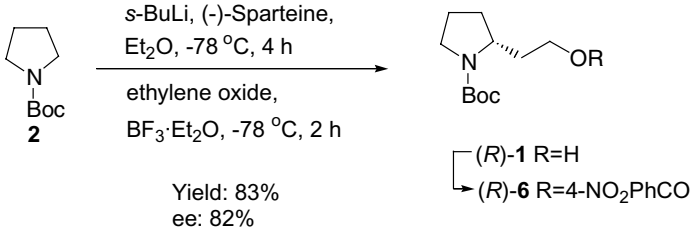
strong electrophiles. Alternatively, epoxide electrophiles may be used in intramolecular processes in the absence of epoxide activation by a Lewis acid. In contrast, we envisioned that an intermolecular alkylation of (*R*)-**3** with a strained cyclic ether in the presence of a Lewis acid would provide (*R*)-**1**. We investigated this approach first using conventional methodology, by applying standard *s*-BuLi/(−)-sparteine conditions as described by Beak (Scheme 2).[13] To that end, (*R*)-**3** was prepared and the ethereal solution was treated with less reactive electrophiles such as ethylene oxide **4** and protected 2-bromoethanol **5**. No reaction was observed in either case, and unreacted starting materials were recovered. Modifying the reactivity of the chiral organolithium/sparteine complex by transmetallation to copper[25,26] or magnesium,[27] also failed to yield any desired alkylation.

Lewis acids are known to activate epoxides for nucleophilic attack by coordinating to the oxygen atom.[28] $BF_3{\cdot}Et_2O$ has proven to be the most efficient Lewis acid suitable for activation of epoxides towards alkyl/aryllithiums at low temperature (−78 °C).[14,15] In theory, strongly basic sparteine could compete with an epoxide for the Lewis acid and thus potentially compromise the configurational integrity of the chiral organolithium (*R*)-**3**. However, we reasoned that a fast epoxide ring opening must be the decisive event and an equilibrium containing some epoxide–Lewis acid complex should drive the reaction forward before epimerization of (*R*)-**3** might occur. Results from our experiments indicate that this indeed is the case.

The chiral organolithium/sparteine complex (*R*)-**3** was generated in diethyl ether using the standard conditions, and the complex was treated with ethylene oxide, followed by 1 equiv of $BF_3{\cdot}Et_2O$ (Scheme 3). The reaction proceeded smoothly to afford the desired (*R*)-Boc-2-hydroxyethylpyrrolidine (*R*)-**3** in very good yield (83%)



Scheme 2.



Scheme 3.

and enantioselectivity (ee = 82%). The enantiomeric excess (ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative (*R*)-**6**, which was prepared from (*R*)-**1** upon treatment with *p*-nitrobenzoyl chloride. We observed that the order of reagent addition in the reaction as described above is the most preferred in obtaining good results. For example, addition of the epoxide, pre-complexed with $BF_3{\cdot}Et_2O$, to the organolithium gave lower yields and ee's. Reverse addition of the chiral organolithium to the pre-complexed epoxide also gave very low yields, presumably due to premature breakdown of the organolithium/sparteine complex.

In conclusion, an efficient, one-step method was developed to synthesize compound (*R*)-**1**, a versatile precursor of many bioactive molecules. High yield and ee were obtained from inexpensive starting materials. Nucleophilic ring opening of an epoxide by a chiral organolithium, promoted by $BF_3{\cdot}Et_2O$, in high efficiency and enantioselectivity, expands the scope of this methodology and should find many useful applications.

3. Experimental

Proton and carbon NMR spectra were recorded at Bruker 500 NMR spectrometer (^{1}H, 500 MHz; ^{13}C, 125 MHz). Infrared spectroscopy was performed on a Nicolet Avatar 360 FT-IR. Flash column chromatography was performed using Merck silica gel 60. 1-Boc-pyrrolidine[29] and racemic (±)-1-Boc-2-(2-hydroxy-ethyl)-pyrrolidine[30] were prepared according to literature procedures. *s*-BuLi, (−)-sparteine, ethylene oxide, $BF_3{\cdot}Et_2O$ and 4-nitrobenzoyl chloride were purchased from Aldrich and used without further purification. All glassware was flame dried prior to use.

3.1. (+)-(2*R*)-1-Boc-2-(2-hydroxy-ethyl)-pyrrolidine (*R*)-1

(−)-Sparteine (24.7 g, 105 mmol, 1.2 equiv) in 250 mL of Et_2O was cooled to −78 °C under N_2 and then 1-Boc-pyrrolidine (15 g, 88 mmol, 1.0 equiv) was added by syringe. After stirring at −78 °C for 10 min, *s*-BuLi (81 mL, 1.3 mol/L, 1.2 equiv) was added dropwise and the resulting mixture was stirred at −78 °C for 4 h. A solution of ethylene oxide (5.8 g, 130 mmol, 1.5 equiv) in 20 mL of Et_2O, which was pre-cooled to −78 °C, was transferred to the previous flask via cannula under N_2 and then $BF_3{\cdot}Et_2O$ (18.7 mL, 130 mmol, 1.5 equiv) was added dropwise over 30 min. The reaction was monitored by GC analysis. After stirring at −78 °C for 2 h, the reaction mixture was slowly warmed to rt and water (5 mL) was added. The organic layer was washed with 5% aq H_3PO_4 (100 mL) and brine (50 mL), then dried over Na_2SO_4. Evaporation of the solvent afforded a colorless oil (18.3 g, 85 mmol, 97%). Purification by distillation (bp 110 °C/ ~ 0.5 Torr) gave the desired (*R*)-**1** (15.5 g, 72 mmol, 83%). The optical rotation was compared with the literature value to assign the absolute configuration: Observed $[\alpha]_D$ = +21 (*c* 1.0, EtOH). Literature value for the *S*-enantiomer $[\alpha]_D$ = −57 (*c* 1.0, benzene).[31] ^{1}H NMR ($CDCl_3$) δ 4.40 (br s, 1H), 4.25–4.0 (m, 1H), 3.80–3.45 (m, 2H), 3.40–3.20 (m, 2H), 2.20–1.50 (m, 6H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 154.39, 77.72, 57.01, 51.43, 44.37, 36.30, 29.09, 26.36, 21.46. IR (neat) 2970.0 (w), 1668.4 (s), 1397.2 (s), 1365.4 (s), 1166.3 (s). EI-MS (70 eV): *m*/*z* (%): 215 (2, M^+); 170 (17, $M^+-CH_2CH_2OH$), 158 (8, $M^+-C_4H_9$), 142 (15, $M^+-C_4H_9O$), 114 (100, $M^+-C_4H_9OCO$). HRMS (ES) Calcd for $C_{11}H_{22}NO_3$ [M^++H], 216.1600; Found, 216.1610. GC (HP-5MS 30 m × 0.25 mm × 0.25 m column; oven temp 55 °C; ramp 10 °C/min; final temp 270 °C; mass selective detector) R_T = 12.1 min.

3.2. (+)-(2*R*)-1-Boc-2-[2-(4-Nitro-benzoyloxy)-ethyl]-pyrrolidine (*R*)-6

A solution of compound (***R***)-**1** (crude product before distillation, 100 mg, 0.46 mmol, 1 equiv), Et_3N (71 mg, 0.70 mmol, 1.5 equiv) and 4-nitrobenzoyl chloride (0.13 g, 0.70 mmol, 1.5 equiv) in 10 mL of CH_2Cl_2 was stirred at rt for 16 h. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. Column chromatography of the crude product with EtOAc/hexanes as eluent afforded the title compound as a white solid (100 mg, 0.27 mmol, 59%). The racemic sample was prepared in the same way. ^{1}H NMR ($CDCl_3$) δ 8.30–8.2 (m, 3, 2H), 8.21–8.16 (m, 2H), 4.50–4.30 (m, 2H), 4.10–3.85 (m, 1H), 3.50–3.20 (m, 2H), 2.40–1.60 (m, 6H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 144.21, 152.52, 133.59, 128.98, 128.62, 121.46, 77.58, 61.82, 52.59, (44.45, 44.02), (31.87, 31.26), (29.06, 28.24), 26.45, (21.78, 20.96). IR (neat): 2966.6 (w), 1724.9 (s), 1688.4 (s), 1528.7 (s), 1392.9 (s), 1275.3 (s). HRMS (ES) Calcd for $C_{18}H_{25}N_2O_6$ [M^++H], 365.1713; Found, 365.1716. Chiral HPLC analysis was performed on a Hewlett Packard 1100 (Chiralpak AD column, 4.6 × 50 mm, mobile phase EtOH/hexanes = 85/15, Flow rate 1 mL/min). Retention times were 4.94 min (*R*-enantiomer) and 5.87 min (*S*-enantiomer), respectively. The ee of the product, determined by area integration was found to be 82%.

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