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Unsaturated 1,2-amino alcohols and ethers from aziridines and organolithiums

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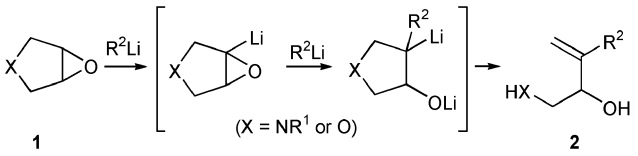
Organolithium-induced ring-opening of aziridines of 2,5-dihydrofuran (5 and 8) and 1,4-dimethoxybut-2-ene (16, 17 and 23) gives 3-substituted 2-aminobut-3-en-1-ols 9–15 and amino ethers 18–20 and 24–26.

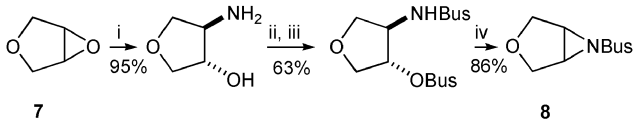
The 1,2-amino alcohol motif is a common structural component in bioactive natural products and many pharmaceutical agents; it is also present in useful synthetic intermediates, auxiliaries, and ligands in catalysis.[1] Consequently, considerable importance is attached to new methods to access this moiety. We recently reported the reactions of organolithiums with 2,5-dihydro-pyrrole (and -furan) epoxides **1** (X = NR^1 or O) to give 3-substituted 1-aminobut-3-en-2-ols (and but-3-ene-1,2-diols) **2** (Scheme 1).[2]

Compared with epoxides, the reactions of aziridines with organolithiums have been far less explored.[3] However, tosyl-protected aziridines have recently been shown to undergo α-lithiation and subsequent rearrangement to give C–H insertion products.[4] The insertion of Bu^sLi into an α-lithiated aziridine (resulting in alkene generation, but with concomitant loss of the amino functionality) has also been observed.[5] In the present paper we communicate the reactions of dihydrofuran aziridines (*e.g.* **5**, Scheme 2) with organolithiums, as a promising new strategy to unsaturated 1,2-amino alcohols **6**; the latter are regioisomeric to the amino alcohols **2** (X = NR^1) obtainable *via* Scheme 1, and offer the additional potential of providing, after oxidation,[6] access to unsaturated α-amino acids.



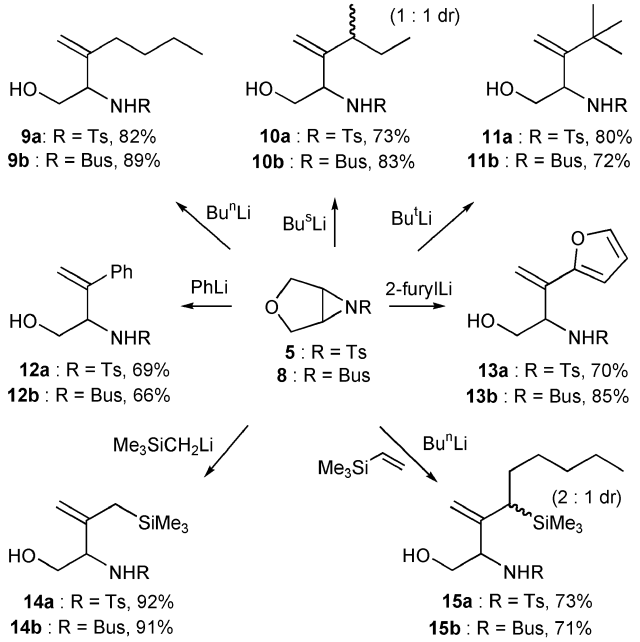
Scheme 1

As both tosyl and *tert*-butylsulfonyl (Bus) nitrogen protection proved useful in our earlier studies,[2] the corresponding protected aziridines were examined in the current chemistry. The tosyl-protected aziridine **5** could not be directly prepared by Sharpless aziridination[7] of 2,5-dihydrofuran, but was readily accessed in two steps from *cis*-but-2-ene-1,4-diol (**3**) by aziridination,[7] followed by ring-closure of the resulting aziridine diol **4**[8] under Mitsunobu conditions using diisopropyl azodicarboxylate (DIAD, Scheme 2).[9] Since direct aziridination of diol **3** could not be achieved using BusNClNa,[10] the Bus-protected aziridine **8** was synthesised in four steps from commercially available dihydrofuran epoxide (**7**), according to Scheme 3.

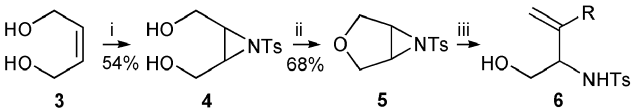


Scheme 3 *Reagents and conditions*: i, NH_4OH (35% in H_2O, 13 equiv.), Pr^iOH, 80 °C, 12 h; ii, Bu^tSOCl (2.2 equiv.), Et_3N (2.5 equiv.), MeCN–DMF (5 : 1), 0 °C, 5 h; iii, MCPBA (2.2 equiv.), CH_2Cl_2, 0 °C to 25 °C, 1 h; iv, K_2CO_3 (12 equiv.), MeCN, 25 °C, 24 h.

With aziridinyltetrahydrofurans **5** and **8** in hand, a study was undertaken of their propensity to undergo organolithium-induced alkylative double ring-opening. Initially, addition of tosyl-protected aziridine **5** to Bu^nLi (3 equiv) was examined at −78 °C in three different solvents (Et_2O, THF and toluene), and pleasingly the desired amino alcohol **9a** (Scheme 4) was observed in all three cases (in 66%, 82%,† and 38% yields, respectively).[11] The scope of the reaction was then investigated using different types of organolithiums in THF. Secondary, tertiary, aryl and heteroaryl organolithiums all generated the corresponding unsaturated amino alcohols **10a–13a** in good yields. Versatile allylsilane functionality[12] was also readily introduced using Me_3SiCH_2Li, or a combination of an organolithium with a vinylsilane.[13] Aziridine **8**, bearing the acid-labile Bus protecting group,[14] also proved to be a viable substrate with the same range of organolithiums, and in general the yields were similar to those found with tosyl-protected aziridine **5**.



Scheme 4



Scheme 2 *Reagents and conditions*: i, TsNClNa (1.1 equiv.), $PhMe_3NBr_3$ (0.1 equiv.), MeCN, 25 °C, 3 d; ii, DIAD (1.5 equiv.), PPh_3 (1.5 equiv.), THF, −78 °C, 1 h, then 25 °C, 7 d; iii, RLi (see text).

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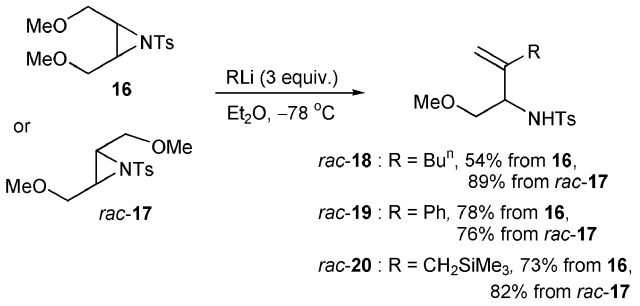
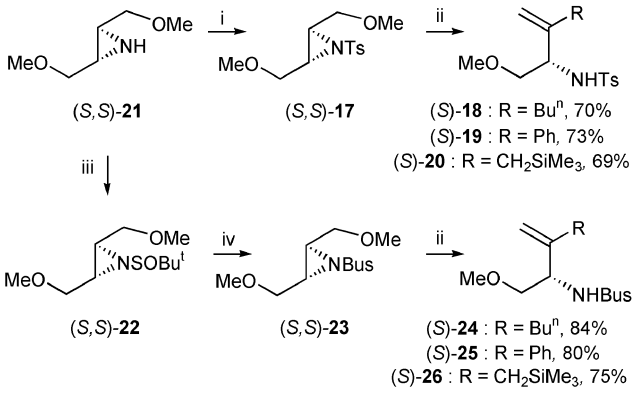
In contrast to dihydrofuran epoxide **1** (X = O), epoxides of acyclic allylic ethers have been reported not to undergo organolithium-induced alkylative ring-opening.[2a,c] This may be due to comparatively reduced acidity at the oxiranyl carbon.[15] It is therefore also of significance that aziridines of such ethers were found to successfully undergo this chemistry in Et_2O (Scheme 5). Both *cis*-aziridine **16** [prepared by methylation of aziridine diol **4** using Ag_2O (3.5 equiv.), MeI (6 equiv.), Et_2O, 25 °C, 2 d, 90%] and *trans*-aziridine *rac*-**17** (prepared in 42% yield by Sharpless aziridination of *trans*-1,4-dimethoxybut-2-ene[16]) gave a range of unsaturated amino ethers *rac*-**18**–**20**.



Scheme 5

Enantioselective desymmetrisation studies of aziridines **5**, **8** and **16** in the presence of a chiral diamine ligand such as (−)-sparteine[2d,e,g,17] has so far only produced low levels of asymmetric induction.[18] However, tartaric acid-derived enantiopure *trans*-aziridines (*S*,*S*)-**17** and (*S*,*S*)-**23** [both prepared by protection of aziridine (*S*,*S*)-**21**][19] underwent ring-opening analogous to *rac*-**17** (Scheme 6). Chiral HPLC analysis of (*S*)-**18** established that no loss of enantiopurity occurred during the alkylative ring-opening process. This latter strategy has the potential for accessing a diverse range of enantiopure unsaturated amino ethers.



Scheme 6 *Reagents and conditions*: i, TsCl (1.5 equiv.), Et_3N (1.5 equiv.), MeCN, 25 °C, 18 h (83%); ii, RLi (3 equiv.), Et_2O, −78 °C, 1 h, then −78 °C to 0 °C, 3 h; iii, Bu^tSOCl (1.1 equiv.), Et_3N (1.5 equiv.), THF, 0 °C, 12 h (61%); iv, MCPBA (1.1 equiv.), CH_2Cl_2, 0 °C, 1 h (89%).

In conclusion, we have demonstrated a new entry to acyclic unsaturated 1,2-amino alcohols and ethers, based on the organolithium-induced ring-opening of aziridines[20] of 2,5-dihydrofuran and 1,4-dimethoxybut-2-enes. The work provides the first examples of retention of the valuable amino functionality arising from insertion of organolithiums into α-lithiated aziridines.

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Notes and references

† A solution of aziridine **5** (96 mg, 0.40 mmol) in THF (4 cm^3) was added dropwise to a stirred solution of Bu^nLi (1.6 mol dm^{-3} in pentane; 0.75 cm^3, 1.2 mmol) at −78 °C. After 1 h at −78 °C, the reaction mixture was allowed to warm to 0 °C over 3 h, then aq. HCl (1 mol dm^3; 5 cm^3) was added. The reaction mixture was extracted with Et_2O (3 × 10 cm^3), the combined organic layers dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography [SiO_2, gradient elution 30% to 100% Et_2O in light petroleum (bp 30–40 °C)] gave amino alcohol **9a** as a colourless oil (98 mg, 82%); R_f 0.15 (petrol–Et_2O, 1 : 1); ν_{max}/cm^{-1} 3502 brs, 3277 brs, 2953 m, 2929 m, 1647 w, 1598 w, 1326 m, 1159 s, 1093 m, 956 w, 901 w and 814 m; δ_H (400 MHz; $CDCl_3$) 7.74 (2 H, d, *J* 8.0, Ar), 7.36 (2 H, d, *J* 8.0, Ar), 5.59–5.30 (1 H, br, m, NH), 4.92 (1 H, s, H of $=CH_2$), 4.83 (1 H, s, H of $=CH_2$), 3.81–3.75 (1 H, m, CHN), 3.62–3.53 (2 H, m, CH_2OH), 2.42 (3 H br, s, CMe and OH), 1.89–1.73 (2 H, m, CH_2), 1.29–1.05 (4 H, m, 2 × CH_2) and 0.84 (3 H, t, *J* 7.0, Me); δ_C (100 MHz, $CDCl_3$) 145.6 (C=), 143.5 (CSO_2), 137.2 (*C*Me), 129.6 (CH), 127.3 (CH), 112.4 (=CH_2), 64.1 (CH_2OH), 59.3 (CHN), 33.1 (CH_2), 29.6 (CH_2), 22.3 (CH_2), 21.5 (C*Me*) and 13.8 (CH_2*Me*); *m*/*z* (CI+) 315 (M + NH_4^+, 45%), 189 (100), 144 (52) and 112 (30); Found M + NH_4, 315.1747. $C_{15}H_{27}N_2O_3S$ requires *M* 315.1742.

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