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Asymmetric rearrangement of *N*-Boc 7-azanorbornene oxide: use of aryllithiums for enantioselective deprotonation

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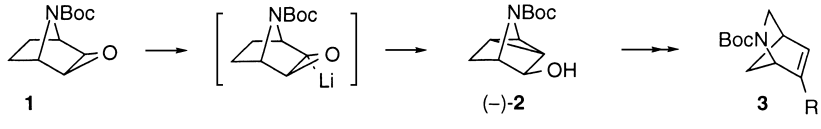
Abstract

The enantioselective α-deprotonation-rearrangement of *N*-Boc 7-azanorbornene oxide **1** using aryllithiums in the presence of (−)-sparteine **4** or bisoxazolines **5a–c** to give azanortricyclanol **2** in up to 87% *ee* is described.

We recently reported the preparation and α-deprotonation-rearrangement of *N*-Boc 7-azanorbornene oxide **1** using LDA (1.6 equiv., Et_2O, 0°C, 5 min) to give azanortricyclanol **2** (52%, Eq. 1).[1] Alcohol **2** was used in a radical rearrangement approach to 6-substituted 2-azabicyclo[2.2.1]hept-5-enes **3**, in particular, to analogues of the highly potent non-opioid analgesic nicotinic acetylcholine receptor agonist epibatidine.[1] Here we communicate our preliminary results concerning the enantioselective deprotonation of the achiral epoxide **1** which allow for an asymmetric entry to alcohol **2** and hence systems such as **3**.



1 (−)-**2** **3** (1)

Enantioselective deprotonation of epoxide **1** was first examined with lithium (*S,S*)-bis(1-phenyl)ethylamide [(3 equiv.), Et_2O, 0°C], which gave alcohol (−)-**2** in low yield (20%) and *ee* (9%).[2] This compares with our earlier studies on the related rearrangement of *exo*-norbornene oxide **1** (NBoc = CH_2) using the same base which gives nortricyclanol (−)-**2** (NBoc = CH_2) in 73% yield and 49% *ee*.[3] The low *ee* found for azanortricyclanol (−)-**2** could arise from (enantiomeric) rotamers, due to the NBoc group, compromising the symmetrical character of the epoxide **1** and the orientation of the Boc group then influencing the deprotonation step. However, a significant increase in *ee* (65%), but not yield (12%),[4] of azanortricyclanol (−)-**2**[5] was observed using Bu^sLi (3 equiv.) in combination

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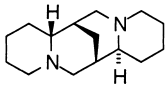
with (−)-sparteine **4** (3 equiv., −78°C, Et_2O, 5 h then warming to ambient temperature over 12 h, Table 1, entry 1). We had previously found that similar conditions with *exo*-norbornene oxide gave (−)-nortricyclanol in 43% yield and 49% *ee*.[3] Changing the organolithium from Bu^sLi to PhLi with (−)-sparteine **4** significantly increased the yield of alcohol (−)-**2** to 50%, whilst not compromising the *ee* (59%, entry 2). This result led us to investigate further the use of aryllithiums for enantioselective deprotonation of epoxide **1** (Table 1, entries 3–6). The aryllithiums were prepared by lithium–bromine exchange from ArBr (3 equiv.) using Bu^tLi (6 equiv.) in the presence of (−)-sparteine **4** (3 equiv.) at −78°C in Et_2O.[6] PhLi prepared by this method led to a slightly lower *ee* (49%, entry 3) compared with that observed (59%, entry 2) using commercially available PhLi (Aldrich). The use of more sterically hindered aryllithiums, 2-tolyllithium and 2-methyl-4-anisyllithium,[6] improved the *ee* of alcohol **2** to 77% (entries 4 and 5). However, increasing the steric hindrance further, using mesityllithium, resulted in a lower yield and much reduced *ee* (15%) of alcohol **2** (entry 6). Xu and co-workers observed slightly improved *ee*s in the conjugate addition of aryllithiums (formed by lithium–bromine exchange) to α,β-unsaturated esters in the presence of (−)-sparteine **4** by doubling the quantity of **4** used, and this was rationalised on the basis of formation of a complex between lithium halide and **4**.[6,7] However, using 2-methyl-4-anisyllithium (3 equiv.) with (−)-sparteine **4** (6 equiv.) did not lead to an improvement in the *ee* of alcohol (−)-**2** (57% yield, 69% *ee*).

Table 1
Yields and *ee*s of alcohol (−)-**2** from epoxide **1** using RLi in the presence of (−)-sparteine **4**



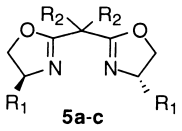
4

Entry	RLi	Yield	*Ee*
1	Bu^sLi (Aldrich)	12%	65%
2	PhLi (Aldrich)	50%	59%
3	PhLi	61%	49%
4	2-TolylLi	61%	77%
5	2-Methyl-4-anisylLi	60%	77%
6	MesitylLi	43%	15%

We previously introduced C_2-symmetric bisoxazolines **5a**–**c** as ligands for alkyllithiums in enantioselective deprotonation (of cyclooctene oxide).[3] Although the *ee*s obtained in that study (up to 66% using Bu^sLi/bisoxazoline **5c**) were not as good as those found with (−)-sparteine **4**, we were interested in examining bisoxazolines with epoxide **1** as, unlike the sparteines, bisoxazolines provide straightforward access to either enantiomer of a chiral product from an achiral substrate and bisoxazoline substituents can be easily modified to enhance *ee*.[8] Promising *ee*s of alcohol (+)-**2** were observed when the commercially available bisoxazoline **5a** was used with either Bu^sLi or PhLi (Table 2, entries 1 and 2), however the yields were modest due to poor conversion of epoxide **1**.

The good *ee* of alcohol (+)-**2** obtained with PhLi (76%) led us to investigate the use of other aryllithiums with bisoxazoline **5a**–**c** (Table 2, entries 3–8). It was found that both the *ee* and, in particular, the yield of (and conversion to) alcohol (+)-**2** are quite sensitive to the aryllithium–bisoxazoline combination used. Both the valine- and *tert*-leucine-derived ligands **5a** and **5b** gave improved yields of alcohol (+)-**2** on moving from PhLi to *o*-substituted aryllithiums (compare entry 2 with 3 and 4, and entry 5 with 6), with the valine ligand **5a** delivering the better yields; only with the valine ligand **5a** was a rise in *ee* also observed. Use of valine-derived bisoxazoline **5c**, which possesses a sterically more demanding diisobutyl-substituted bisoxazoline bridge compared with diethyl-substituted **5a**, allowed the reaction with PhLi (but not with 2-methyl-4-anisyllithium, compare entry 8 with 4) to proceed to completion and gave the best *ee* of alcohol **2** obtained in the present study (87%, entry 7).

Table 2
Yields and *ee*s of alcohol (+)-**2** from epoxide **1** using RLi in the presence of bisoxazolines **5a**–**c**



5a-c

Entry	Ligand	Base	Yield[a]	*Ee*
1	**5a** (R_1 = Pr^i, R_2 = Et)	Bu^sLi (Aldrich)	37% (51%)	63%
2	**5a** (R_1 = Pr^i, R_2 = Et)	PhLi (Aldrich)	36% (66%)	76%
3	**5a** (R_1 = Pr^i, R_2 = Et)	2-TolylLi	53% (64%)	82%
4	**5a** (R_1 = Pr^i, R_2 = Et)	2-Methyl-4-anisylLi	63%	83%
5	**5b** (R_1 = Bu^t, R_2 = Et)	PhLi (Aldrich)	15% (26%)	74%
6	**5b** (R_1 = Bu^t, R_2 = Et)	2-Methyl-4-anisylLi	40% (60%)	72%
7	**5c** (R_1 = Pr^i, R_2 = Bu^i)	PhLi (Aldrich)	51%	87%
8	**5c** (R_1 = Pr^i, R_2 = Bu^i)	2-Methyl-4-anisylLi	21% (75%)	65%

[a] yield in parentheses based on recovered epoxide **1**.

In summary, in the asymmetric α-deprotonation-rearrangement of *N*-Boc 7-azanorbornene oxide **1** to azanortricyclanol **2** with aryl- lithiums, *ee*s of up to 77% and 87% were obtained using (−)-sparteine **4** and bisoxazoline **5c**, respectively.[10] Although the combination of aryllithiums with external chiral ligands has been used in addition reactions to obtain selectivity between enantiotopic faces (e.g. of alkenes and imines)[6,9] and between enantiotopic groups (e.g. epoxide termini,[11] and for the generation of planar chirality[12]), to our knowledge our results are the first examples of such combinations for enantioselective deprotonation.

Acknowledgements

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4. The major product (74%) of the reaction of epoxide **1** with Bu^sLi/**4** is *N*-Boc *cis*-2-amino-6-(but-2-yl)cyclohex-5-en-1-ol {$[\alpha]_D^{24}$ +52.8 (*c* 1 in $CHCl_3$)}; a study of this process will be reported in due course. Such cyclohexenol products were not observed using substituted aryllithiums/**4** (or in the reactions reported in Table 2).
5. The absolute stereochemistry of the major enantiomer of the alcohol **2** obtained with either lithium (*S*,*S*)-bis(1-phenyl)ethylamide or RLi/**4** is the same, is as shown in Eq. 1, and was established by comparison of the opposite directions of the optical rotations of *N*-Boc 2-azabicyclo[2.2.1]hept-5-ene **3** (R = H, Eq. 1) prepared by radical deoxygenation/rearrangement (Ref. 1) of alcohol (−)-**2**, and prepared by $LiAlH_4$ reduction followed by Boc protection (Arakawa, Y.; Yasuda, M.; Ohnishi, M.; Yoshifuji, S. *Chem. Pharm. Bull*. **1997**, *45*, 255–259) of commercially available (Aldrich, 99% *ee*) (1*R*)-(−)-2-azabicyclo[2.2.1]hept-5-en-3-one. The sense of asymmetric induction observed with epoxide **1** using lithium (*S*,*S*)-bis(1-phenyl)ethylamide or RLi/**4** parallels that observed with *exo*-norbornene oxide and in our medium-ring study (Ref. 3).
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