(-)-Sparteine mediated α-deprotonation of quinuclidine *N*-oxide

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Dedicated to Dr. Sukh Dev, on his 80th birthday

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Abstract

Addition of RLi to a mixture of quinuclidine *N*-oxide (**1**) and (-)-sparteine in toluene at -78°, followed by quenching with benzaldehyde gives threo (**3,** 34% ee) and erythro (**4**, 40% ee) adducts with moderate enantioselectivity. Reaction of RLi with **1** followed by treatment with (-)-sparteine prior to electrophile addition affords racemic products while no deprotonation is observed when **1** is treated with a preformed complex of RLi and (-)-sparteine. These results indicate that only a sequential association of **1** with RLi and (-)-sparteine leads to the complex undergoing enantioselective deprotonation.

Keywords: Quinuclidine *N*-oxide, (-)-sparteine, enantioinduction

Introduction

The quinuclidine ring is a part of the structure of cinchona and some indole alkaloids which exhibit well known physiological activities.[1] Some functionalised synthetic quinuclidines have also been identified as specific muscarinic agonists with potential in Alzheimer's dementia therapy.[2] Moreover, quinuclidine compounds have proved to be effective catalytic chiral control elements in a wide range of reactions.[3] However, not many synthetic routes are available to access quinuclidine derivatives, specially in an enantioselective manner. Recently, Lygo *et al.* have have used Sharpless epoxidation to induce asymmetry and stereodivergent cyclisation of the resulting diols to form quinuclidine alcohols **2** (Fig. 1).[3,4] Herein we describe our results concerning enantioselective synthesis of **2** using (-)-sparteine (sp) as an added chiral ligand in the Barton elaboration of quinuclidine *N*-oxide (**1**).[5] (-)-Sparteine mediated enantioinduction at carbanionic centres is a well established strategy of asymmetric synthesis and pioneering work of Beak and Hoppe has delineated mechanistic pathways of enantioselective lithiation and substitution.[6a-f] These studies are based on amine derivatives such as amides and carbamates and invoke lithium association with a coordinating site of the substrate in the enantio-differentiating

species. However, amine N-oxides which also have a strongly lithium coordinating oxygen site have remained unexplored. In this context the present approach is of synthetic as well as mechanistic interest.

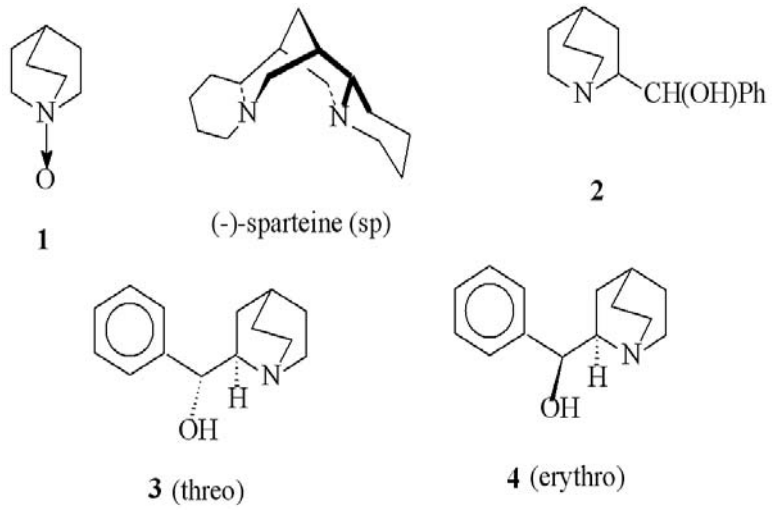


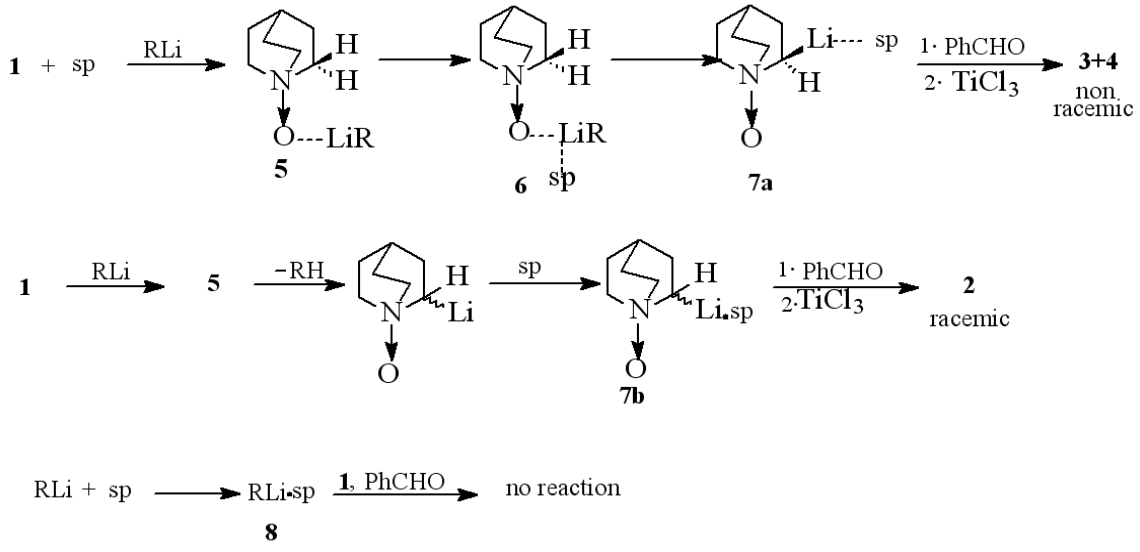
Figure 1

Results and Discussion

Lithiation of quinuclidine *N*-oxide was carried out by adding *s*-BuLi to a stirred suspension of **1** and (-)-sparteine in THF at –78°. After 3 hr benzaldehyde was introduced and the product was deoxygenated with $TiCl_3$ to give, after chromatographic separation on silica gel, pure racemic amino alcohols **2**, threo in 23% yield and erythro in 32% yield (Fig. 1). In diethyl ether this reaction proceeded with modest enantioselectivity to furnish alcohols **3** [34% enantioexcess (ee)] and **4** (36% ee). The enantioexcess and absolute configuration of these alcohols was determined by comparison of specific rotation values with those reported in the literature.[4] It is interesting to note that while the absolute configuration of our predominant erythro enantiomer (**4**) is the same as that of the Lygo compound, it is opposite in case of the threo isomer.[4] Efforts to improve enantioselectivity by change of base (*n*-BuLi, t-BuLi) or solvent (toluene: hexane 1:1; toluene: hexane 9:1; toluene: ether 9:1) gave products with similar or lower ee values. Only in pure toluene were ee values in the 40-50% range obtained. The erythro isomer could be rapidly enriched by crystallisation from toluene e.g. a single crystallisation from this solvent raised the ee value from 40 to 64%.

In mechanistic terms, formation of enantioenriched products by the above-described procedure can be explained by an enantioselective deprotonation or by enantioinduction at the post deprotonation stage. The latter possibility was discounted by adding (-)-sparteine to the reaction mixture after deprotonation of **1** with RLi, as the alcohols obtained by this method were

racemic (Scheme 1). Deprotonation did not occur when a preformed complex of RLi and (-)-sparteine was cannulated into a stirred suspension of *N*-oxide **1** in toluene, as no product formation was observed on reaction with benzaldehyde. In view of the unexpected nature of this observation in toluene, the experiment was repeated several times with no change in the results. These findings do not fit into any standard mechanistic pathway postulated for chiral ligand mediated lithiation-electrophile reaction sequences.[6] A plausible rationalisation is depicted in scheme 1. The key element of this proposal is that when RLi is added to a mixture of **1** and (-)-sparteine, it sequentially complexes with **1** and sp to give the tricomplex **6** which undergoes enantioselective deprotonation (**1-5-6-7a**)[7]. On the other hand, RLi already complexed to sparteine (**8**, in monomeric or aggregated form) does not associate further with **1** to give **6,** nor does it abstracts a proton from **1**. The latter inference may seem surprising but in a related work also we have observed that RLi readily deprotonates a BF_3 complex of N-methyltetrahydroisoquinoline, yet deprotonation by a preformed RLi-sparteine complex does not occur under otherwise identical conditions.[8]



Scheme 1

Experimental Section

All the reactions were carried out under a nitrogen atmosphere in flame-dried apparatus using standard syringe-septum techniques. Reaction solvents were distilled over sodium/benzophenone. Quinuclidine *N*-oxide (**1**) was freshly distilled over CaH_2 prior to use.[9] *s*-BuLi as a solution in pentane was prepared according to the reported method and was titrated against *sec*-butyl alcohol using 1,10-phenanthroline as an indicator.[10,11] 2-(Phenylhydroxymethyl)quinuclidine (**2**) was characterized by comparison of its ^{1}H NMR data

and m.p. with literature values.[4,12] Enantiomeric excess was determined by comparison of observed specific optical rotation values with the reported values.[4] For erythro isomer ee was also determined by CSP-HPLC (using phenomenex chirex CSP-3022 column using hexane/methanol/ dichloroethane/trifluoroacetic acid as the eluent) and by ^{1}H NMR spectral analysis.[13]

To a suspension of *N*-oxide **1** in diethyl ether (0.18 M), (-)-sparteine (1.1 equiv.) was added at room temperature. The reaction mixture was cooled to –78°C and *sec*-BuLi (1.1 equiv., 2.2N) was added slowly. The resulting solution was stirred at -78 C for 3 hr before the addition of benzaldehyde (1.1 equiv.). Stirring was continued for 1 hr at -78°C and for an additional hour after warming of the reaction mixture to room temperature. The reaction was quenched by adding saturated aqueous NH_4Cl. A solid material consisting of the starting and product N-oxide settled down immediately. It was washed with ether to remove (-)-sparteine and neutral materials. The solid material was reduced in situ by a freshly prepared concentrated solution of $TiCl_3$ in 2N HCl. The mixture was made strongly basic by the addition of 15% NaOH solution, and it was vigorously stirred until the solid had turned light grey. The mixture was filtered and the residue washed with ether. The filtrate was dried and the solvent evaporated in vacuo to give the mixture of diastereomeric amino alcohols **3** and **4** after filtration through a pad of silica gel using hexane, ethyl acetate, Et_3N (50:50:1) as the solvent system, or the mixture of **3** and **4** was separated through flash chromatography on silica gel.

Data for **3:** yield (18%); m.p. 73-75° (Lit.[5,12] m.p. 75-76.5°); $[\alpha]_D$ = +16.7°(c 1.12, EtOH), lit[4] $[\alpha]_D$ = - 49° (c 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.09–1.13 (m, 1H), 1.23–1.35 (m, 1H), 1.43–1.52 m, 4H), [C-3H, C-5H, C-7H,]; 1.75-1.76 (br s, 1H, C-4H,); 2.70-2.79 (m, 2H), 2.91-2.96 (m, 2H), 3.00-3.10 (m, 1H) [C-2H, C-6H, C-8H]; 3.8 (br s, 1H, OH, D_2O exchangeable); 4.36 (d, J = 10Hz, 1H, C-9H); 7.25-7.41 (m, 5H, ArH).

Data for **4:** yield (21%); m.p. 139-141° (Lit.[5,12] m.p. 142°); $[\alpha]_D$ = + 36.4 (c 1.12, EtOH), lit[4] $[\alpha]_D$ = + 100° (c 1.15, $CHCl_3$); retention time in CSP-HPLC (major peak : 5.73 min.; minor peak : 6.24min.); ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.41–1.70 (m, 6H) [C-3H, C-5H, C-7H,]; 1.80-1.88 (br s, 1H, C-4H,); 2.2 (br s, 1H, OH, D_2O exchangeable); 2.55-2.65 (m, 1H), 2.70-2.80 (m, 2H), 3.10-3.22 (m, 1H) [C-6H, C-8H,]; 2.90-3.0 (m, 1H, C-2H); 4.75 (d, J = 6Hz, 1H, C-9H); 7.21-7.39 (m, 5H, ArH).

Acknowledgements

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References

1. Yakhontov, L. N. in *Advances in Heterocyclic Chemistry*, Katritzky, A.R., A.J. Boulton, Eds.;Academic Press, Inc.:New York, 1970, Vol. 11, p 473.
2. (a) Baker, R.; Street, L. J.; Reeve, A.J.; Saunders, J. *J. Chem. Soc. Chem. Commun*. **1991**, 760. (b) Ashwood, M.S.; Gibson,A.W.; Houghton, P.G.; Humphrey, G.R.; Roberts, D.C.; Wright, S.H.B. *J. Chem. Soc., Perkin Trans. 1* **1995**, 641.
3. (a) Sharpless, K.B.; Amberg.W.; Benani,Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K-S.; Kwong,H.-L.; Morikawa, K.; Wang, Z –M.; Xu, D.; Zhang, X. –L. *J.Org. Chem.* **1992**, *57*, 2768. (b) Smaardijk, A.A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135. (c) O'Donnell, M.J. in *Catalytic Asymmetric Synthesis;* Ojima, I. Ed.; VCH: Weinheim, 1993. pp 389. (d) Simon, K.E.; Ibbotson, A.; Johnston, P.; Plum, H.; Wells, P.B. *J. Cat.* **1994**, *150*, 321.
4. Lygo, B.; Croby, J.; Lowden, T.R.; Wainwright, P.G. *Tetrahedron Lett.* **1997**, *38*, 2343.
5. Barton, D.H.R.; Beugelmans, R.; Young, R.N. *Nouv. J. Chim.* **1976**, *2*, 363.
6. (a) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905. (b) Beak, P.; Basu, A.; Gallaghar, D.J.; Park, Y.S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. (c) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (d) P. Beak, D. R. Anderson, M. D. Curtis, J. M. Laumer, D. J. Pippel, G. A. Wisenbergurger, Acc. *Chem. Res.* **2000**, *33*, 715. (e) Schlosser, M.; Limat, D.J. *J. Am. Chem. Soc.* **1995**, *117*, 12342. (f) Behrens, K.; Frohlich, R.; Meyer, O.; Hoppe, D. *Eur. J. Org. Chem.* **1998**, 2397.
7. Deprotonation of N-oxides through complexation with RLi has been postulated; Beugelmans, R.; Benadjila-Iguertsira, L.; Chastanet, J.; Negron, G.; Roussi, G. *Can. J. Chem.* **1985**, *63*, 725. One of the referees has suggested that it is more probable that the N-oxide (**1**) and (-)-sparteine first associate, and then interact with RLi in the deprotonation.
8. Mahendru, M.; Ph.D. Thesis, Panjab University, Chandigarh, India, 2001.
9. For preparation of quinuclidine *N*-Oxide (**1**) and $TiCl_3$ reduction procedure, see Sharpless, K.B.; Kolb, H.C.; Anderson, P.G. *J. Am. Chem. Soc.* **1994**, *116*, 1278.
10. (a) Turner, E.E.; Bryce-Smith, D. *J. Chem. Soc.* 1953, 861. (b) Gilman, H.; Morton Jr., J.W. *Org. React.* (N.Y.) **1954**, *8*, 258. (c) Tyler, L.J.; Sommer, L.H.; Whitmore, F.C. *J. Am. Chem. Soc.* **1948**, *70*, 2876.
11. Watson, S.C.; Eastham, J.F. *J. Organomet. Chem.* 1967, *9*, 165.
12. Braschler, V.; Grob, C.A.; Kaiser, A. *Helv. Chim. Acta.* 1963, *46*, 2646.
13. H-9 proton exhibits two sets of doublets with peak areas proportional **to** the relative ratio of the enantiomers. (a) Williams, T.; Pitcher, R.G.; Bommer, P.; Gutzwiller, J.; Uskokovic, M. *J. Am. Chem. Soc.* **1969**, *91*, 1871. (b) Weisman, G.R. In *Asymmetric synthesis*; Morrison, J.D., Ed.; Academic Press, Inc, New York, 1983, Vol**.** 1, Chapter 8.