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ENANTIOSELECTIVE DEPROTONATION OF CYCLOHEXENE OXIDE TO (*R*)-2-CYCLOHEXEN-1-OL

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Abstract: The reaction of cyclohexene oxide with homochiral lithium amides, prepared from (*S*)-phenylglycine and (*S*)-valine has been studied and (*R*)-2-cyclohexen-1-ol **3** was prepared in a maximum of 72% ee. The optical purity was determined by ^{1}H NMR measurement of the α-methoxy-α-(trifluoromethyl)phenyl acetic acid (MTPA) derivative of the corresponding alcohol.

Enantioselective deprotonation of symmetrical epoxides to optically active allylic alcohols using non-enzymatic methods, where enantiotopic proton selection takes place by homochiral lithium amide bases, is a very challenging area in asymmetric synthesis.[1] Such a conversion of cyclohexene oxide to optically active 2-cyclohexen-1-ol, which is a very useful substrate for synthesis[2], has received much attention.[3-5] (*S*)-2-Cyclohexen-1-ol has been prepared in a maximum of 82% ee using (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine ligand.[5] However, (*R*)-proline is very expensive, and therefore the literature method is not economically viable. Efforts have been made to prepare (*R*)-cyclohexenol using (*S*)-proline

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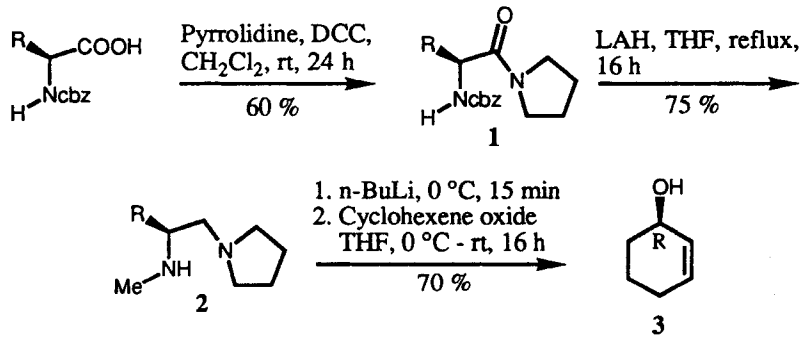
but the enantioselectivity had been moderate.[4c] In this communication, we wish to report the facile conversion of cyclohexene oxide to (*R*)-2-cyclohexen-1-ol **3** using homochiral bases which are prepared from cheap and readily available precursors.

(*S*)-N-cbz-Valine and (*S*)-N-cbz-phenylglycine were converted to diamines **2a** & **2b** respectively (Scheme 1). The deprotonation of cyclohexene oxide was studied with these diamines. Although the chemical yield of (*R*)-cyclohexenol from both the amines is similar (70% yield), the enantioselectivity is different. Amine **2b** gave 72% ee whereas amine **2a** gave only 57% ee. These values are uncorrected to the optical purity of the ligands. Based on optical rotation, the condensed product **1b** showed its optical purity 78.5% ee. In other words, the corrected value of enantiotopic selectivity with ligand **2b** is 91.7% ee.

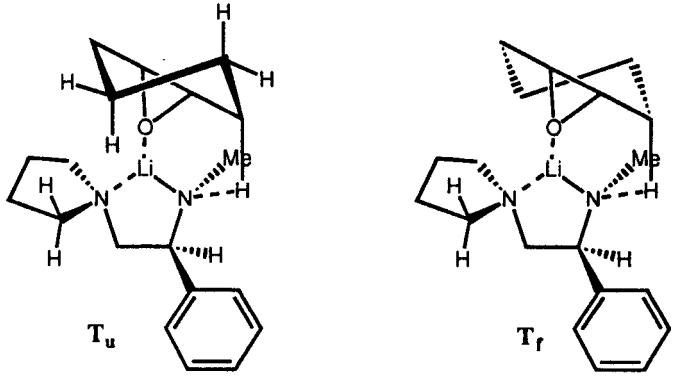


a R = Isopropyl
b R = Phenyl

Scheme I

It is well known that deprotonation of cyclohexene oxide is highly selective for the syn proton that occupies the pseudoaxial orientation. Cyclohexene oxide exists in two equilibrating enantiomeric conformations which must be differentiated by an homochiral base for conversion into optically active allylic alcohol. In the

present case we have rationalized the enantiotopic differentiation with the (*S*)-diamine ligand **2b** by invoking cyclic six-membered transition state models $\mathbf{T_f}$ (favoured) and $\mathbf{T_u}$ (unfavoured) where orientation of Me and Ph groups is anti to each other. Transition state $\mathbf{T_u}$ is unfavoured due to two very strong non-bonding interactions of epoxide's out of plane CH_2s' with phenyl ring and pyrrolidine CH_2. Although $\mathbf{T_f}$ is also associated with one non-bonding interaction (Me with epoxide's CH_2), it is favoured over $\mathbf{T_u}$ because interaction is not severe. The same transtition state can be applied to ligand **2a** as well. The lower enantioselectivity with **2a** indicates that interaction of substituent at chiral carbon atom with epoxide's CH_2 is very crucial. Since phenyl group (A value, 2.9) is bulkier than isopropyl (A value, 2.1), the diamine ligand **2b** gives better enantioselectivity than **2a**.



As the result indicates, it is clear that interaction of phenyl or isopropyl of ligands with epoxide's methylene plays an important role in enantiotopic discrimination of proton.

Experimental Section

General methods: ^1H NMR spectra were recorded on Jeol and Brucker as mentioned, with TMS as internal standard. Chemical shifts are reported in ppm,

and coupling constants are reported in Hz. IR spectra were recorded on Perkin-Elmer 580 and 1320 spectrometers by using samples as neat liquid. Optical rotations were taken on a Jasco DIP-370. Routine monitoring of reactions was performed using silica gel-G obtained from Acme. All the chromatographic separations were done by using silica gel (Acme's, 60-120 mesh). All the reactions were run under an atmosphere of dry nitrogen or argon using flame-dried glassware and freshly distilled and dry solvents from solvent stills. The organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo.

The N-(benzyloxycarbonyl)-(*S*)-phenylglycine & valine were prepared by using the procedure of Corey *et al.*[6]

General procedure for preparation of (1a) & (1b): To a stirred solution of N-(benzyloxycarbonyl)-(*S*)-phenylglycine or valine (4 mmol) in dry CH_2Cl_2 (30 mL), was added dropwise a solution of dicyclohexylcarbodiimide (12 mmol) in 5 mL of CH_2Cl_2 at 0 °C and the mixture was stirred for 20 min. Pyrrolidine (12 mmol) was added and stirring continued at rt for 24 h. The reaction mixture was filtered. The filtrate was washed sequentially with 2% cold HCl, water, and brine. The organic layer was dried and solvent was evaporated in vacuo. Purification by column chromatography over silica gel gave pure cbz-amides **1**.

(*S*)-1-[N-(Benzyloxycarbonyl)valyl]pyrrolidine (1a): Amide **1a** is a viscous liquid; 58 % yield; R_f 0.65 (1:1, EtOAc in pet-ether); $[\alpha]^{25}_D$ +78.25° (*c* 1.6, EtOH); IR (film) 3420, 3280, 3040, 2930, 1700, 1620 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ0.93 (d, J = 7 Hz, 6H), 1.5-2.2 (bm, 5H), 3.1-3.8 (m, 4H), 4.1 (dd, J = 9, 3 Hz, 1H), 4.95 (s, 2H), 6.16 (d, J = 9 Hz, NH, 1H), 7.2 (aromatics, 5H).

(*S*)-1-[N-(Benzyloxycarbonyl)phenylglycyl]pyrrolidine (1b)[7]: Amide **1b** is a viscous liquid; 63 % yield; R_f 0.50 (1:2, EtOAc in pet-ether); $[\alpha]^{25}_D$ +96.5° (*c* 1.9, $CHCl_3$) [lit.[7] maximum $[\alpha]^{25}_D$ -123.0° (*c* 1.06, $CHCl_3$) for R-isomer]; IR

(film) 3410, 3300, 3040, 2980, 1700, 1630 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ1.5–1.95 (m, 4H), 2.8-3.7 (m, 4H), 4.95 (s, 2H), 5.23 (d, J = 9 Hz, 1H), 6.43 (d, J = 9 Hz, NH, 1H), 7.05-7.5 (aromatics, 10H). Anal. calcd for $C_{20}H_{22}N_2O_3$: C, 71.00; H, 6.51; N, 8.28; Found: C, 70.72; H, 6.64; N, 8.32.

General procedure for synthesis of diamines (2a) & (2b): Amides **1a** or **1b** (2 mmol) was dissolved in 30 mL of THF, treated with LAH (4.0 mmol), and stirred under reflux for 16-20 h. Excess of LAH was destroyed by addition of 2-3 drops of EtOAc. Water (100 μl) was added followed by the same amount of 4N NaOH. After 5 min, 300 μl of water was again added and the mixture stirred for 15 min. A white precipitate was filtered off, the filtrate was dried, and solvent evaporated. The diamines were purified by distillation.

(*S*)-N-Methyl-1-isopropyl-2-pyrrolidinoethanamine (2a): Yield 66%; bp 100 °C (bath) at 0.2 mm Hg; $[\alpha]^{25}_D$ +48.97° (*c* 3.0, EtOH); IR (film) 3320, 2960, 2940, 2880, 960 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ0.83 (two doublets, J = 7 Hz, 6H), 1.0-2.7 (bm, 13H), 2.30 (s, 3H). Anal. calcd for $C_{10}H_{22}N_2$: C, 70.59; H, 12.94; Found: C, 70.46; H, 13.02.

(*S*)-N-Methyl-1-phenyl-2-pyrrolidinoethanamine (2b): Yield 70%; bp 100-120 °C (bath) at 0.2 mm Hg; $[\alpha]^{25}_D$ +50.58° (*c* 1.8, EtOH); IR (film) 3380, 3060, 3030, 2960, 2880 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ1.77 (m, 4H), 2.25 (d, J = 3.4 Hz, 1H), 2.30 (s, 3H), 2.38, (s, NH, 1H), 2.45 (m, 2H), 2.62 (m, 2H), 2.84 (t, J = 11.2 Hz, 1H), 3.58 (dd, J = 9.6, 3.4 Hz, 1H), 7.18-7.4 (aromatics, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ23.6, 34.7, 54.14, 63.8, 64.3, 127.0, 127.4, 128.3, 142.8; MS (CI, m/z): 206 (M^++ 2), 205 (M^++ 1), 203, 174 (base peak), 175, 134, 120. Anal. calcd for $C_{13}H_{20}N_2$: C, 76.47; H, 9.80; Found: C, 76.38; H, 9.86.

General procedure for enantioselective deprotonation of cyclohexene oxide: n-BuLi (E-Merck, 1.48 M in hexane, 0.60 mmol) was added to a solution

of (*S*)-diamine **2b** (0.58 mmol) in THF (2.0 mL) at 0 °C. After 15 min stirring, the cyclohexene oxide (0.58 mmol) was added and the mixture stirred for 16 h (0 °C - rt). Most of the THF was removed in vacuo at 0 °C and the reaction mixture was taken up in ether (30 mL). It was washed with water, brine, and dried. Solvent was removed in vacuo at 0 °C and the crude was chromatographed to provide pure (*R*)-2-cyclohexen-1-ol[4] (Yield 70%); $[\alpha]^{25}_{D}$ +110.0° (*c* 1.8, $CHCl_3$) [lit.[3] maximum $[\alpha]^{25}_{D}$ +152.0° (*c* 5, $CHCl_3$)]; ^{1}H NMR (CCl_4, 60 MHz) δ1.33 (s, 1H, -OH), 1.67 (bm, 4H), 1.90 (m, 2H), 4.1 (m, 1H), 5.7 (bs, 2H).

Determination of enantiomeric purity of (*R*)-2-cyclohexen-1-ol 3: The (*R*)-cyclohexenol **3** (5 mg), prepared by using the diamine ligand **2b** was treated with 2 eq of triethylamine and 1.5 eq of (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[8] (MTPA-Cl) in the presence of 1 crystal of DMAP in CH_2Cl_2 in a usual way to provide (*RS*)-Mosher ester. ^{1}H NMR ($CDCl_3$, 400 MHz) δ1.5 (m, 2H), 1.75-2.1 (bm, 4H), 3.5 (bs, 3H), 5.45 (m, 1H), 5.65 (m, 0.86H, *RS*-diastereomer from major *R*-cyclohexenol), 5.75 (m, 0.14 H, *SS*-diastereomer from minor *S*-cyclohexenol), 5.85-6.0 (bm, 1H), 7.25-7.65 (bm, 5H, aromatics). Based on above nmr data, the enantioneric excess of (*R*)-cyclohexenol is 72 %. Based on optical purity of **1b**, the corrected value is 91.7 %ee.

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Refereneces and Notes

1. For recent general reviews in this area, see: (a). Cox, P. J.; Simpkins, N. S., Tetrahedron: Asymmetry, 1991, 2, 1 and references cited therein. (b). Ward, R. S. Chem. Soc. Rev., 1990, 19, 1. (c). Simpkins, N. S. Chem. & Ind., 1988, 387.

2. (a). Sabol, J. S.; Cregge, R. J., Tetrahedron Lett., 1989, 30, 3377. (b). Yamada, S.; Takamura, N.; Mizoguchi, T., Chem. Pharm. Bull., 1975, 23, 2539.

3. Whitesell, J. K.; Felman, S. W., J. Org. Chem., 1980, 45, 755.

4. (a). Asami, M. Bull. Chem. Soc. Japan, 1990, 63, 721. (b). Asami, M. Chem. Lett., 1984, 42, 829. (c). Asami, M.; Kirihara, H. Chem. Lett., 1987, 389.

5. Bhuniya, D.; Singh, V. K., Synth. Comm. (in press).

6. Corey, E. J.; Shibata, S.; Bakshi, R. K., J. Org. Chem., 1989, 53, 2862.

7. Koga, K. in "Organic Synthesis: Modern Trends", ed. by Chizhov, O., Blackwell Scientific Publication, London, 1987, pp. 285.

8. Dale, J. A.; Mosher, H. S., J. Am. Chem. Soc., 1973, 95, 512.

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