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A CATALYTIC ENANTIOSELECTIVE SYNTHESIS OF CHIRAL MONOSUBSTITUTED OXIRANES

E. J. Corey and Christopher J. Helal

Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

Summary: *A new catalytic enantioselective synthesis of monosubstituted oxiranes has been developed from achiral trichloromethyl ketones by (a) enantioselective carbonyl reduction, (b) selective bis-dechlorination and (c) base-induced ring closure of the resulting chlorohydrins.*

The reduction of trichloromethyl ketones **1** by catecholborane catalyzed by oxazaborolidine **2** has been shown to produce trichloromethyl carbinols **3** of exceptionally high enantiomeric purity[1] and predictable absolute configuration.[2] Advantage has been taken of the ready availability of these trichloromethyl carbinols for the synthesis of enantiomerically pure α-amino[1a] and α-hydroxy acids[1b] (Scheme I). This paper describes the application of chiral trichloromethyl carbinols to the general synthesis of terminal epoxides of high enantiomeric purity. Other methods which have been used for the enantioselective production of such synthetically versatile terminal epoxides include the asymmetric epoxidation[3] and dihydroxylation of olefins,[4] the use of chiral auxiliaries,[10a] resolution,[5] and via natural sources such as optically active 1,2-diols,[6] and α-amino acids.[7]

The process for the transformation of trichloromethylcarbinols **3** into chiral terminal epoxides is outlined in Scheme II. Selective dechlorination of **3** was effected by Bu_3SnH generated using a catalytic amount of Bu_3SnCl (0.25 equiv), with $NaCNBH_3$ (purified by precipitation from THF solution with CH_2Cl_2) as reductant and AIBN as initiator in EtOH at reflux to give **4**.[8] Chiral HPLC analysis of the resultant chlorohydrins **4** or 500 MHz ^1H NMR analysis of the corresponding (*R*)-MTPA esters revealed no racemization under the dechlorination reaction conditions. In general, the chlorohydrins were not isolated.[9] Upon completion of the dechlorination, EtOH was removed *in vacuo*, Et_2O and NaOH (2M, 8 equiv) were added, and the mixture was stirred vigorously. Isolation of the oxiranes, requiring only filtration through a small silica plug and removal of solvent, provided chiral epoxides in good overall yields as shown in Table 1.[9,10]

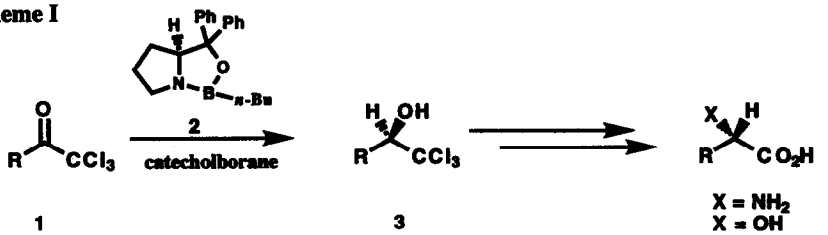
The simplicity and practicality of this catalytic enantioselective route to 1-substituted oxiranes is apparent from the sample experimental procedure which follows. The new process provides the first efficient route to a number of chiral epoxides which previously have not been made by chemical procedures, for example, 3,3-dimethyl-1,2-epoxybutane (entry *d* in Table 1), prepared earlier only by yeast fermentation of 1-hydroxy-3,3-dimethyl-2-butanone[9] and ring closure in two steps. This work demonstrates still another facet of the utility of

chiral trichloromethylcarbinols in synthesis. Their ready availability by a catalytic enantioselective reduction with efficient recovery of the chiral catalyst precursor should be emphasized.[11]

(*R*)-4-Phenyl-1,1,1-trichloro-2-butanol. Addition of 4-phenyl-1,1,1-trichloro-2-butanone (1.59 g, 7.4 mmol) to a solution of preformed oxazaborolidine catalyst **2** (3.7 mL, 0.2 M in toluene, 0.74 mmol, 0.1 equiv), cooling to -78 °C and dropwise addition of freshly distilled catecholborane (5.5 mL, 11 mmol, 2M in toluene) over 10 min with vigorous stirring resulted in a white precipitate which dissolved after 4 h giving a colorless solution. After 12 h at -78 °C the homogenous reaction was quenched with methanolic HCl (1.8 mL, 0.5 M) and allowed to warm to 23 °C. Partial concentration *in vacuo* afforded a fine white precipitate ((*S*)-α,α-diphenylprolinol•HCl) which was recovered by filtration. The filtrate was diluted with 40 mL of ether, washed with pH 13 buffer until colorless (6 x 20 mL), then brine (3 x 10 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford 1.54 g (96%) of (*R*)-4-phenyl-1,1,1-trichloro-2-butanol as a colorless solid after filtration through a short plug of silica gel (sg) (10 : 1 hexane–ethyl acetate); mp 53-5 °C; $[\alpha]_D^{23}$ +49.4° (c = 2.39, $CHCl_3$); 95% ee by HPLC analysis; ^1H NMR (270 MHz, $CDCl_3$) δ 7.4-7.2 (m, 5H), 4.0 (ddd, 1H, J = 9.3, 5.4, 1.6 Hz), 3.0 (m, 1H), 2.8 (d, 1H, J = 5.4 Hz, -OH), 2.75 (m, 1H), 2.4 (m, 1H), 2.0 (m, 1H); FTIR (neat) 3400, 1455 cm^{-1}; CIMA 289 $[M+Cl]^-$; HRMS: calcd. for $[C_{10}H_{11}Cl_3O+Cl]^-$: 288.9535; found: 288.9517.

(*R*)-(3,4-epoxybutyl)benzene. (*R*)-4-phenyl-1,1,1-trichloro-2-butanol (298 mg, 1.18 mmol), $NaCNBH_3$ (185 mg, 2.9 mmol, 2.5 equiv), azobisisobutyronitrile (AIBN) (10 mg, 0.06 mmol, 0.05 equiv) and EtOH (1.3 mL, degassed), under N_2 were treated with Bu_3SnCl (95.6 mg, 0.29 mmol, 0.25 equiv) and heated to reflux . After 2 h additional AIBN (20 mg, 0.12 mmol, 0.1 equiv) was added and the reaction mixture was heated for an additional 1.5 h. The reaction was then allowed to cool room temperature and concentrated *in vacuo*. Et_2O (1 mL) and NaOH (2M, 4.7 mL, 9.4 mmol, 7 equiv) were added and the mixture was vigorously stirred at room temperature. After 5.5 h NaCl (2 g) and pentane (10 mL) were added to the reaction vessel. The aqueous and organic layers were separated, the aqueous layer was extracted with 2 : 1 pentane–ether (3 x 8 mL), the organic extracts were dried over Na_2SO_4, and concentrated *in vacuo* without external heating. Filtration through a short plug of silica gel (16 : 1 pentane–EtOAc) afforded (*R*)-(3,4-epoxybutyl)-benzene as a colorless oil (117 mg, 67%). $[\alpha]_D^{23}$ + 16.4° (c = 1.4, acetone), lit.$[\alpha]_D^{23}$ + 18° (c = 0.3, acetone); ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (m, 2H),. 2.47 (dd, J = 2.7, 5.0 Hz, 1 H), 2.7-2.85 (m, 3H), 2.96 (m, 1H), 7.15-7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.23, 34.37, 47.31, 51.85, 126.11, 128.46, 128.54, 141.36; FTIR ($CDCl_3$) 758, 829, 903, 1455, 1496, 2292, 2990, 3027 cm^{-1}; [M+]: HRMS: calcd. for $[C_{10}H_{12}O]$: 148.0888; found: 148.0894.

Scheme I



Scheme II

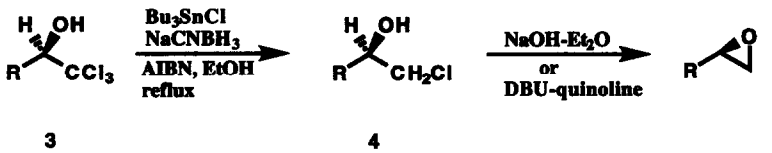
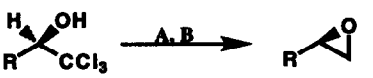
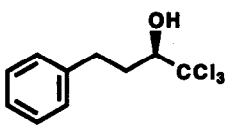
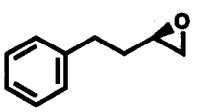
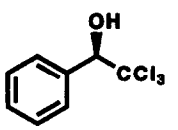
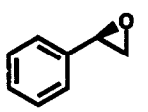
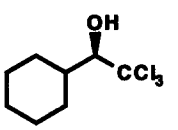
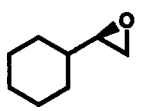
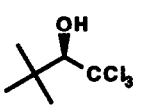


Table 1. Terminal Epoxides from Dechlorination/Ring Closure Process



Entry	Carbinol	Epoxide	Yield(%)	ee%
a			67	96[a]
b			68	98[b]
c			75	90[c]
d			59	96[d]

A. $NaCNBH_3$, Bu_3SnCl, AIBN, EtOH, reflux. B. NaOH, Et_2O (a-c) or DBU, quinoline (d).

a Determined for the trichloromethyl carbinol and chlorohydrin by chiral HPLC analysis.

b Determined for the trichloromethyl carbinol and epoxide by chiral HPLC analysis.

c Determined for the trichloromethyl carbinol by 500 MHz ^1H NMR analysis of the (*R*)-MTPA ester.

d Determined for the chlorohydrin by 500 MHz ^1H NMR analysis of the (*R*)-MTPA ester and for the epoxide by comparison of optical rotation.[9]

References and Notes

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9. The chlorohydrin resulting from the dechlorination of (*R*)-1,1,1-trichloromethyl-3,3-dimethyl-2-butanol was isolated and purified by silica gel chromatography (20 : 1 to 10 : 1 pentane–Et_2O). $[\alpha]_D^{23}$ -36.1° (c = 0.37, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 9H), 2.29 (d, J = 2.64 Hz, 1H), 3.46 (m, 2H), 3.77 (ddd, J = 1.2, 3.85, 7.68); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.85, 34.69, 48.43, 79.21. ^1H NMR (500 MHz, $CDCl_3$, Mosher esters) δ = 0.983 (minor), 0.907 (major). Conversion to the epoxide was achieved in the following manner: (*R*)-1-chloro-3,3-dimethyl-2-butanol (1.02 g, 1 mL, 7.5 mmol) and DBU (1.25 g, 1.23 mL, 8.2 mmol) were stirred under N_2 at 18 °C for 2 h. Quinoline (2 mL) was then added and the reaction temperature was increased to 60 °C. One hour later additional quinoline (3 mL) was added and the temperature was increased to 70 °C. After 1 h the reaction vessel was cooled to room temperature, and a Hickman distillation receiver with dry ice condensor was placed on the flask. The epoxide was distilled directly into the Hickman distillation receiver (100 mm, 120 °C). (*R*)-*t*-Butyloxirane was isolated (564 mg, 75%) as a colorless liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 9H), 2.59 (dd, J = 2.9, 4.1 Hz, 1H), 2.63 (t, J = 4.4 Hz, 1H), 2.72 (dd, J = 3.0, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.50, 30.50, 44.02, 60.06. $[\alpha]_D^{23}$ -17.4° (c = 0.52, benzene), lit. $[\alpha]_D^{23}$ -18.1° (c = 1.83, benzene). (a) Sato, A.; Hirano, T.; Tsuruta, T. *Makromol. Chem.* **1975**, 176, 1187. (b) Sepulchre, M.; Supulchre, A. M. *Bull. Soc. Chim. Fr.* **1973**, *3*, 1164. (c) Guette, J. P.; Spassky, N. *Bull. Soc. Chim. Fr.* **1972**, *11*, 4217.
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