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An Efficient Approach to Chiral *Cis*-3,4-Epoxy Alcohols

Shaojing Hu, Seetharaman Jayaraman,[¥] and Allan C. Oehlschlager*

Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, Canada V5A 1S6

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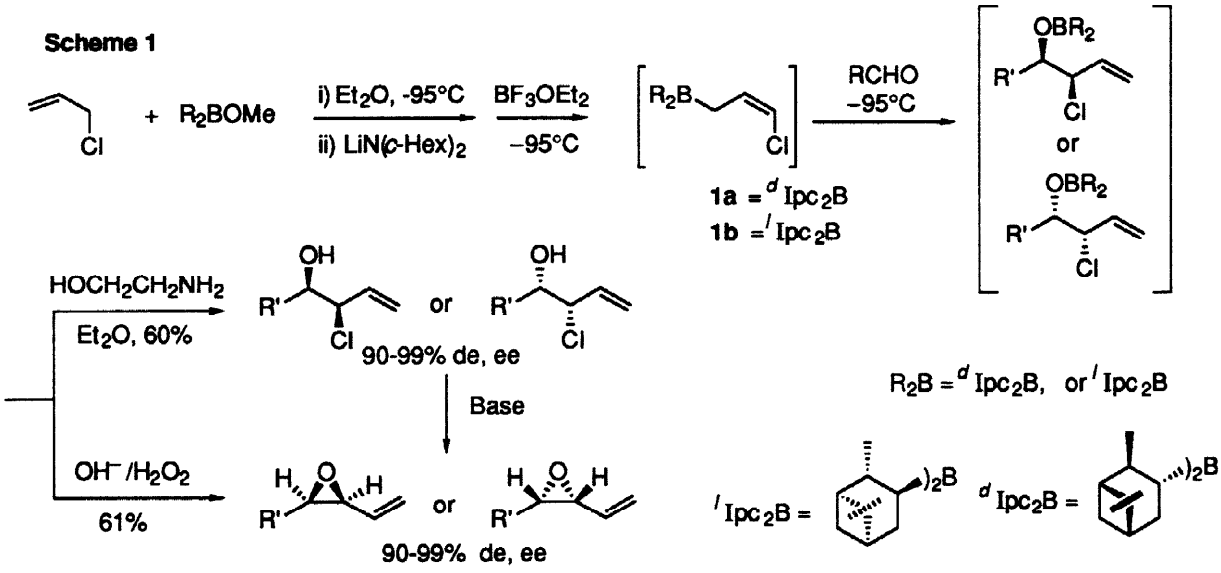
Abstract: A new method for the synthesis of *cis*-3,4-epoxy alcohols has been developed by employing hydroboration of chiral *cis*-vinylepoxides or *syn*-chlorohydrins.

Homoallylic epoxyalcohols are available from vanadium-catalyzed epoxidation of homoallylic alcohols,[1] multi-step conversions of 2,3-epoxy halides derived from the Sharpless asymmetric epoxidation[2] and epoxidation of homoallylic alcohols by Cardillo's route.[3] Sharpless asymmetric epoxidation of homoallylic alcohols is the most practical route to chiral homoallylic epoxyalcohols but this process gives only moderate enantiopurity.[4] We report a novel and efficient approach to chiral *cis*-3,4-epoxy alcohols based on hydroboration of enantioenriched *cis*-vinylepoxides or *syn*-chlorohydrins.

Scheme 1



We have recently shown that (*Z*)-(γ-chloroallyl)diisopinocamphenylboranes **1a**, **1b** (Scheme 1) react with aldehydes to give chiral *syn*-vinylchlorohydrins and *cis*-vinylepoxides in excellent diastereo-and enantioselectivities (≥95% de, 90-99% ee).[5]

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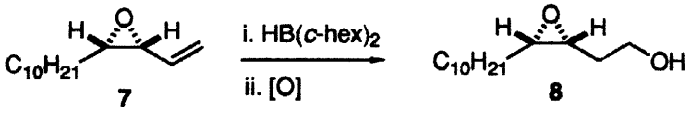
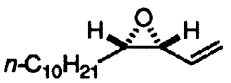
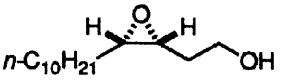
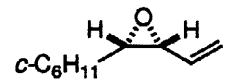
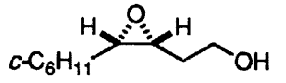
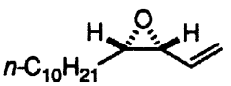
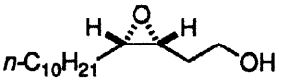
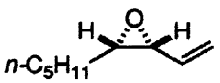
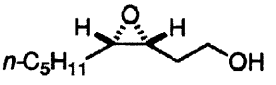
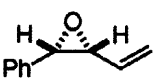
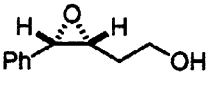
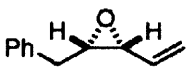
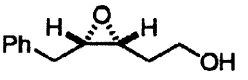
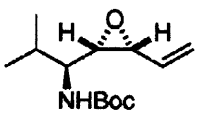
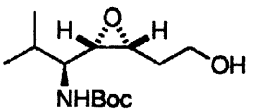


[O]	Yield (%)
H_2O_2/NaOH	0
H_2O_2/NaOAc	10
$NaBO_3/H_2O$	67

Table 1. Hydroboration of *cis*-vinylepoxides [a]

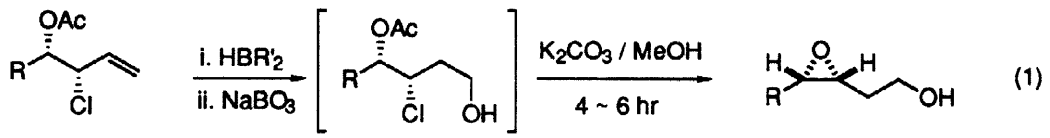
entry	vinylepoxide	borane[b]	3,4-epoxy alcohol[c]	yield(%)[d]
1		9-BBN		0
2		9-BBN		0
3		DCHB		67
4		DCHB		71
5		DCHB		44
6		DCHB		41
7		DCHB		58

[a] Hydroboration was carried out in THF at rt and DCHB was prepared according to reference 7. [b] 1 Equiv of borane used. [c] 3 Equiv of sodium perborate used for oxidation. [d] Isolated yield.

Hydroboration of enantioenriched *cis*-3,4-epoxy-1-tetradecene or *cis*-1-cyclohexyl-1,2-epoxy-3-butene with 9-BBN followed by oxidation with various oxidation reagents did not yield expected *cis*-3,4-epoxy alcohols (Table 1, entry 1-2). Polar products similar to those expected from epoxide opening were detected.[6] When hydroboration was conducted in THF using dicyclohexyborane (DCHB) reaction was completed in 4 hr. Use of solvent such as Et_2O, pentane or toluene resulted in much slower reaction. Choice of oxidizing reagents was crucial for the transformation of organoborane to corresponding 3,4-epoxy alcohols. Sodium perborate was the reagent of choice providing *cis*-3,4-epoxy alcohols in 41-71% yields (Table 1, entry 3-7).[8]

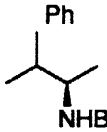
Hydrobration of acetyl protected *syn*-chlorohydrins provides a more efficient route to *cis*-3,4-epoxy alcohols (Table 2). The one pot process involved hydroboration of *syn*-chlorohydrins

in THF, followed by oxidation using 3 equiv of $NaBO_3$ overnight, then the mixture was diluted with methanol (5 ml/mmol of chlorohydrin) and treated with potassium carbonate in another 4-6 hr to give expected alcohols in 65-85% yield (eq 1).[9] Hydroboration with 9-BBN was sluggish compared to DCHB. Increasing the amount of 9-BBN did not increase yield (Table 2, entry 3, 4).



(1)

Table 2. Hydroboration of *syn*-chlorohydrins[a]

entry	chlorohydrin R	borane	chlorohydrin/borane ratio (mol/mol)	time (h)	yield (%)[b]
1	*n*-$C_{10}H_{21}$	9-BBN	1	24	34 (61)[c]
2	*n*-$C_{10}H_{21}$	9-BBN	1	48	37(55)[c]
3	*n*-$C_{10}H_{21}$	9-BBN	1.5	24	40(57)[c,d]
4	*n*-$C_{10}H_{21}$	9-BBN	2	24	20(37)[c,e]
5	*n*-$C_{10}H_{21}$	DCHB	1	4	85
6	*i*-Bu	DCHB	1	4	82
7	Ph	DCHB	1	4	65
8	 NHBoc	DCHB	1	4	77

[a] Hydroboration was carried out in THF at rt and DCHB was freshly prepared according to reference 7. [b] Isolated yield unless noted. [c] Yield in parenthesis was based on recovered starting material. [d] 4.5 Equiv of $NaBO_3$ used. [e] 6 Equiv of $NaBO_3$ used.

Regioselectivity of hydroboration of vinylepoxides or chlorohydrins was sensitive to the purity of dicyclohexyborane. With the purified DCHB excellent regioselectivity was observed.

In summary, hydroboration of *cis*-vinylepoxides and *syn*-chlorohydrins provide access to *cis*-3,4-epoxy alcohols.

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References and Notes

¥ Present address: SynPhar Laboratories, Inc., 4290-91A Street, Edmonton, AB, Canada T6E 5V2.

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[8] Representative experimental procedure:
Hydroboration of *cis*-vinylepoxides: *cis*-(3*R*, 4*S*)-3,4-epoxy-1-tetradecene **7** in THF (420 mg in 1 mL THF) was introduced *via* syringe into 2 mmol of dicyclohexyborane in 2 mL of THF with stirring. Dicyclohexylborane was prepared from freshly distilled cyclohexene and BH_3•SMe_2 and further purified by sublimation.[7] The reaction mixture was stirred at rt for 4 hr. and 910 mg of $NaBO_3$•H_2O and 0.5 mL of H_2O were added. The reaction mixture was stirred overnight then 4 g of K_2CO_3 was added and after 2 hr the mixture was diluted with 15 mL of anhyd. Et_2O. Solid was removed by filtration and washed with Et_2O to give a filtrate which was concentrated under vacuum. Purification by flash chromatography using (hexane: Et_2O,7:3) as the eluant gave 291 mg of *cis*-(3*S*,4*S*)-3,4-epoxy-tetradecan-1-ol, **8**, mp 33-37.5 °C. Twice recrystallization from 1% Et_2O in hexane gave mp 37.7-38.5 °C. $[\alpha]^{23}_D$ – 8.34 (*c* = 2.12, Et_2O); ^{13}C NMR ($CDCl_3$, ppm) 60.81, 56.68, 54.94, 31.88, 30.68, 29.66, 29.56, 29.53, 29.49, 29.28, 27.96, 26.46, 22.63, 14.01. ^1H NMR ($CDCl_3$, ppm) 3.86 (m, 2H), 3.09 (dt, *J* = 8.0, 4.4 Hz, 1H), 2.93 (td, *J* = 5.6, 4.4 Hz, 1H), 1.92-1.26 (m, 21H), 0.87 (t, *J* = 6.8 Hz, 3H). CIMS m/z (isobutane, rel intensity) 229 [M^++1(100)], 211 [(M^+ -18)+ 1(95)]. Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.68; H, 12.44.

[9] Hydroboration of *syn*-chlorohydrins: A solution of 576 mg of *syn*-(3*S*,4*S*)-4-acetoxy-3-chloro-1-tetradecene in 1 mL THF was introduced into 2 mmol of dicyclohexyborane THF solution (2 mL) *via* syringe. Stirring was continued for 4 hr at room temperature. The reaction was quenched after 4 hr at rt by addition of 920 mg of $NaBO_3$•H_2O and 0.5 mL of H_2O. The mixture was stirred overnight then 5 mL of MeOH was added and K_2CO_3 (560 mg) were added sequentially. After 6 hr, the mixture was diluted with 15 mL of anhyd. Et_2O and 15 mL of water. The organic layer was separated and aqueous layer was extracted with Et_2O (2 X 10 mL). The combined extracts was dried over anhyd. Na_2SO_4 and then concentrated in *vacuum*, purified by flash column chromatography (hexane: Et_2O, 7:3) and recrystallized as above to yield 387 mg of *cis*-(3*R*,4*R*)-3,4-epoxy-tetradecan-1-ol, mp 38-38.5 °C. $[\alpha]^{23}_D$ – 8.36 (*c* = 2.14, Et_2O).