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Syntheses with Organoboranes. VI. Kinetic Resolution of Vinylic Epoxides by the Reduction with Chiral Dialkylboranes

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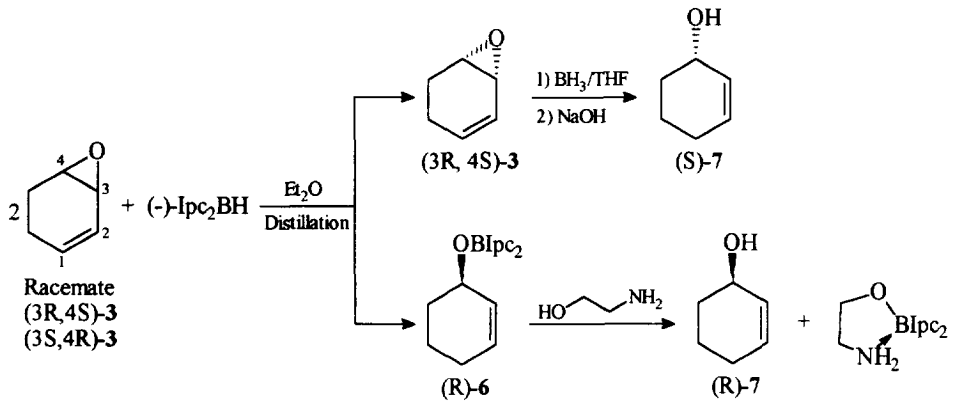
Abstract: The synthesis of enantiomerically enriched 2-vinyloxirane and monoepoxides of 1,3-cycloalkadienes by kinetic resolution of racemates with Ipc_2BH, 2-$^{d}Icr_2BH$ and 4-$^{d}Icr_2BH$ of high enantiomeric purity is described.

Chiral vinylic epoxides are of growing importance as building blocks for the synthesis of natural products.[1] Racemates are readily available by monoepoxidation of 1,3-dienes [2] or dehydrohalogenation of unsaturated halohydrins.[3] However, access to pure enantiomers or enantiomerically enriched compounds is limited and only a few optically active vinylic epoxides have been prepared by multistep syntheses.[4] Recently, Jacobsen [5] reported an enantioselective monoepoxidation of cyclic 1,3-dienes catalyzed by a chiral manganese complex leading to products in 33–73 % yield and 52–71 % ee. Several years ago we described a stereoselective reduction of vinylic epoxides with borane and 9-borabicyclo[3.3.1]nonane to allylic alcohols.[6] Ready access to dialkylboranes of high optical purity prompted us to apply this reaction for kinetic resolution of racemic vinylic epoxides.

2-Vinyloxirane **1** and monoepoxides of 1,3-cycloalkadienes **2–5** with 5–8 membered rings were used as representative epoxides. Diisopinocampheylborane ((–)- and (+)-Ipc_2BH),[7] di-2-isocaranylborane (2-$^{d}Icr_2BH$)[8] and di-4-isocaranylborane (4-$^{d}Icr_2BH$) [8] of >99 % ee were prepared by hydroboration of (+)- or (–)-α-pinene, (+)-2-carene and (+)-3-carene of high optical purity with borane-dimethyl sulfide, respectively. The reductions were carried out in 2 : 1 (epoxide/dialkylborane) molar ratio in diethyl ether. The dialkylboranes are only slightly soluble and progress of the reaction can be easily controlled by observing the amount of precipitate. The reaction is completed when a clear solution is obtained. Enantiomerically enriched unreacted epoxides, **1** (20 % ee) and **2–5** (40–54 % ee) were readily isolated by distillation directly from the reaction mixture in 40–49 % yields (Table 1).[9]

The reduction products, enantiomerically enriched allylic alcohols, were liberated from their dialkylborinates either by treatment with ethanolamine or by oxidation of the esters with standard alkaline hydrogen peroxide (Scheme 1 and Table 1).



Scheme 1

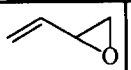
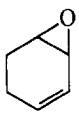
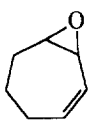
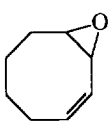
As demonstrated earlier,[6] the reduction of vinylic epoxides with borane and dialkylboranes proceeds with the double bond shift and the epoxide ring opening. The allylic alcohol produced retains configuration of the epoxide at C_4. Consequently, the enantiomerically enriched unreacted epoxide has an opposite configuration at C_4, e.g., (3R,4S)-**3** and (R)-7 (Scheme 1). For the determination of enantiomeric excess, the enantiomerically enriched epoxides were reduced with borane to the corresponding allylic alcohols (Scheme. 1) and their MTPA esters were analyzed by GC using a capillary column.

2-Vinyloxirane of the same configuration was obtained in 11 % ee and 20 % ee from the reduction with (–)-Ipc_2BH and 2-$^dIcr_2BH$. The monoepoxides of 1,3-cycloalkadienes were obtained in higher enantiomeric excess (40–54 % ee). For these epoxides (–)-Ipc_2BH and 2-$^dIcr_2BH$ produced consistently enantiomers of opposite configuration. 4-$^dIcr_2BH$ and (–)-Ipc_2BH gave enantiomerically enriched epoxides **3**–**5** with similar % ee. Enantiomeric excess of the unreacted epoxides was increasing when the reductions were carried at lower temperatures. However, lowering the temperature slowed down the reduction considerably (Table 1).

The reactivity of the dialkylboranes toward vinylic epoxides decreases in the following order Ipc_2BH > 2-$^dIcr_2BH$ > 4-$^dIcr_2BH$. At –25°C, the most reactive Ipc_2BH reacts with **1**–**5** in 8–24 h whereas for 2- and 4-$^dIcr_2BH$ the reaction time becomes impractically long. For all the epoxides examined, 2-$^dIcr_2BH$ gave higher % ee than Ipc_2BH or 4-$^dIcr_2BH$. Consequently, it is the preferred reagent.

In conclusion, kinetic resolution of vinylic epoxides by the reduction with diisocaranylboranes or Ipc_2BH is a simple and direct method for the preparation of enantiomerically enriched epoxides. It also allows for convenient configurational assignment of enantiomerically enriched epoxide if the configuration of the corresponding allylic alcohol is known. Both enantiomers can be prepared using readily available enantiomeric Ipc_2BH. Although 2-$^dIcr_2BH$ and 4-$^dIcr_2BH$ are available only as single enantiomers, they often give products of opposite configuration. The enantiomeric excess achieved by this method using 2-$^dIcr_2BH$ is slightly lower as compared to the enantioselective epoxidation of 1,3-cycloalkadienes[5], and the yields are similar.

Table 1. Kinetic Resolution of Vinylic Epoxides **1–5** with Chiral Dialkylboranes [a]

Racemic epoxide	Reagent [b]	Temp. °C	Time h	Enantiomerically enriched epoxide				Alcohol [f]	
				Yield [c] %	$[\alpha]_D^{20}$ (neat) deg	ee [d] %	Conf. [e]	$[\alpha]_D^{20}$ (neat) deg	Conf. [g] (% ee)
 **1**	(–)-Ipc_2BH	–25	8	40	–0.92	11 [h]	R [i]	—	—
	2-^{d}Icr_2BH	–25/–10	120/24	33	–1.67	20 [h]	R [i]	—	—
 **2**	(–)Ipc_2BH	0	4	37	–40.0	29	3R,4S	+39.2	R (27)
	(–)Ipc_2BH	–25	16	44	–44.4	32	3R,4S	+47.6	R (33)
	2-^{d}Icr_2BH	0	3.5	29	+49.6	36	3S,4R	–48.9	S (33)
	2-^{d}Icr_2BH	–25	84	33	+55.6	40	3S,4R	–57.8	S (40)
	4-^{d}Icr_2BH	0	5	30	–1.2	1	3R, 4S	+1.0	R (1)
 **3**	(–)-Ipc_2BH	0	4.5	41	+35.1	24	3R,4S	+24.6	R (22)
	(–)-Ipc_2BH	–25	12	43	+45.6	30	3R,4S	+32.5	R (29)
	(+)-Ipc_2BH	0	5	40	–37.6	25	3S,4R	–26.2	S (23)
	2-^{d}Icr_2BH	0	6	42	–77.2	52	3S,4R	–56.0	S (50)
	2-^{d}Icr_2BH	–10	58	49	–80.0	54	3S,4R	–60.6	S (54)
	4-^{d}Icr_2BH	0	16	40	+36.4	24	3R,4S	+24.8	R (22)
	4-^{d}Icr_2BH	–25	188	37	+51.4	35	3R,4S	+38.1	R (34)
 **4**	(–)-Ipc_2BH	0	5.5	38	+6.6	13	3S,4R	–3.9	S (11)
	(–)-Ipc_2BH	–25	15	39	+10.6	21	3S,4R	–7.6	S (22)
	2-^{d}Icr_2BH	0	36	49	–15.0	30	3R,4S	—	R (31)
	2-^{d}Icr_2BH	–10	227	45	–23.4	46	3R,4S	—	R (48)
	4-^{d}Icr_2BH	0	115	48	+4.0	8	3S,4R	—	S (10)
 **5**	(–)-Ipc_2BH	0	6	46	–2.6	7	3S,4R	+3.5	S (7)
	(–)-Ipc_2BH	–25	24	49	–4.6	12	3S,4R	+6.8	S (13)
	2-^{d}Icr_2BH	0	43	36	+15.0	39	3R,4S	—	R (38)
	2-^{d}Icr_2BH	–10	139	42	+16.2	42	3R,4S	—	R (44)
	4-^{d}Icr_2BH	0	190	49	+4.3	11	3R,4S	—	R (12)

[a] All reactions were carried out as described in footnote 9. [b] (–)- and (+)-Ipc_2BH, 2-^{d}Icr_2BH and 4-^{d}Icr_2BH of >99 % ee were prepared from (+)- and (–)-α-pinene, (+)-2-carene and (+)-3-carene, respectively. [c] Isolated yields. [d, e] For **2–5** ee's were determined by GC analysis of MTPA esters of allylic alcohols obtained by the reduction of enantiomerically enriched epoxides with borane in tetrahydrofuran. Configurations of the alcohols were assigned by comparing signs of rotation with the literature data: (S)-(–)-2-cyclopentenol [10], (S)-(–)-2-cyclohexenol [11], (S)-(–)-2-cycloheptenol [11], (S)-(+)-2-cyclooctenol [12]. [f] Product alcohol obtained by the reduction of racemic epoxide. [g] Configuration and % ee was determined by comparing signs of rotation with the literature data [10-12] and by GC analysis of MTPA esters. [h, i] Configuration and % ee was assigned / determined by comparing specific rotation with the highest reported rotation for (S)-(+)-**1**, $[\alpha]_D^{25}$ +8.306 °,100 % ee [4c].

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9. Representative procedure: 2-^{d}Icr$_2$BH (5.70 g, 20 mmol) was added with stirring to a solution of 3,4-epoxy-1-cyclohexene (3.84 g, 40 mmol) in diethyl ether (40 mmol) at 0°C under nitrogen. The mixture was stirred at 0°C until a clear solution was formed (6 h). The unreacted epoxide was isolated by distillation, 1.60 g, 42 % yield, bp. 48-50° C/29 mm Hg, $[\alpha]_D^{20} - 77.2°$ (neat), 52 % ee. Lit.[11] $[\alpha]_D^{24} - 56.6°$ (c 0.53, $CHCl_3$)
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