Catalytic Asymmetric Cyclization of Some Bromohydrins with Chiral Cobalt Complex

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Synopsis. Asymmetric cyclization of a variety of bromohydrins with base was examined in the presence of an optically active cobalt(salen) type complex. Optically active oxiranes of modest optical purities were obtanied. *erythro*-3-Bromo-2-butanol and *threo*-3-bromo-2-butanol were cyclized similarly, and only *trans*-2,3-dimethyloxirane and *cis*-2,3-dimethyloxirane were obtained, respectively, indicating that the cyclization of bromohydrin proceeds by complete S_N2 type reaction.

An optically active cobalt (salen) type complex, (1*R*,2*R*)-*N*,*N*′-disalicylidene-1,2-cyclohexanediaminatocobalt(II), Co*, whose structure is well-defined as square-planar tetradentate Schiff base complex,[1] has been used as a catalyst for several kinds of asymmetric reaction, such as the kinetic resolution of oxiranes,[1] one-step synthesis of optically active oxiranes from racemic chlorohydrins,[2] asymmetric fixation of carbon dioxide,[3] and others.[4] In the course of our studies on the asymmetric synthesis of optically active oxiranes, we report here our attempts to evaluate the effect of alkyl substituents of bromohydrins on the asymmetric induction, and also to explore the mechanistic feature of the reaction.

Experimental

Measurements. The NMR spectra were taken on a JEOL JNM-PS-100 spectrometer. Optical rotations were determined by means of a Perkin-Elmer model 241 polarimeter. The GLC analyses were carried out with a Hitachi model K-53 or Yanagimoto model G80 Gas Chromatograph equipped with a column containing PEG. IR spectra were measured using a Hitachi model EPI-G3 spectrometer.

Materials. 2-Bromo-1-propanol was prepared from 2-bromopropanoic acid by treating with $SOCl_2$ and then with $LiAlH_4$; bp 58—59 °C/20 mmHg (1 mmHg=133.322 Pa), yield 50%. 1-Bromo-2-propanol was prepared by the $LiAlH_4$ reduction of bromoacetone; bp 50 °C/16 mmHg, yield 15%. 2-Bromo-1-butanol was prepared by the $LiAlH_4$ reduction of 2-bromobutanoyl bromide; bp 65—66 °C/15 mmHg, yield 50%. 1-Bromo-3,3-dimethyl-2-butanol was prepared according to the procedure of Jackman et al.[5] *erythro*-3-Bromo-2-butanol and *threo*-3-bromo-2-butanol were prepared by the method of Bigley et al.[6]

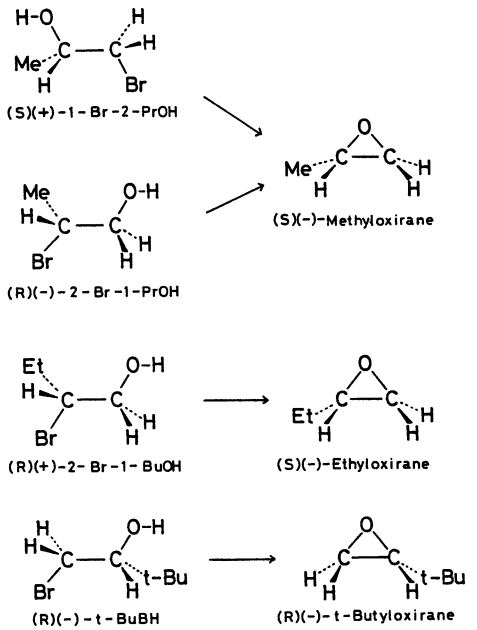
Asymmetric Reaction of Bromohydrins. Catalytic amount of Co* and K_2CO_3 (base) were added into a flask, and dried at 130—150 °C for 3 h in vacuo. To the flask were added the solvent and the substrate under a dry nitrogen atmosphere with stirring. After an appropriate reaction time, the mixture was analyzed by gas chromatography. The oxirane formed and the unreacted bromohydrin were seperated by fractional distillation and the optical activity was measured. The structure of the oxirane was confirmed by GC, IR, and NMR.

The optical purities (e.e.) of oxiranes were evaluated from the following values; $[\alpha]_D$=+12.53° (neat) for optically pure (*R*)(+)-methyloxirane;[7,9] $[\alpha]_D^{16}$=+12.4° for (*R*)-ethyloxirane;[8] $[\alpha]_D^{25}$=−20.4° (neat) and $[\alpha]_D^{25}$=−18.1° (*c* 1.83 benzene) for (*R*)-*t*-butyloxirane;[9] $[\alpha]_D^{25}$=+59.0° for (2*R*,3*R*)-2,3-dimethyloxirane.[11] The expected optical purities (e.e.$_{calcd}$)[2a] of methyloxirane were evaluated from the optical purities of the unreacted substrate by assuming the reaction to proceed by kinetic resolution mechanism : e.e.$_{calcd}$(%)($[\alpha]_D/[\alpha_o]_D$)×{(100−conv.)/conv.}×100; $[\alpha_o]_D$=−14.4° (neat) for (*R*)-(−)-2-bromo-1-propanol.[10]

Results and Discussion

Asymmetric Cyclization of Propylene Bromohydrins. The asymmetric cyclization of 2-bromo-1-propanol and 1-bromo-2-propanol were carried out with K_2CO_3 in the presence of Co*. The results are summarized in Table 1.

Optically active methyloxirane was formed selectively from 2-bromo-1-propanol and 1-bromo-2-propanol. The configuration of methyloxirane, both from the two substrates, was S, which was also the case with the corresponding chlorohydrins.[2a] The optical activity of methyloxirane formed and unreacted substrate show that (*R*)-(−)-2-bromo-1-propanol reacted preferentially to form (*S*)-(−)-methyloxirane by the inversion of asymmetric carbon. In the reaction of 1-bromo-2-propanol, the unreacted substrate could not be recovered and thus the optical rotation was not



Scheme 1.

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Table 1. Synthesis of Optically Active Methyloxirane (MO) by the Cyclization of Propylene Bromohydrin (2-Br-1-PrOH or 1-Br-2-PrOH)

Substrate	Co* mmol	K_2CO_3[a] PBH	Solv[b]	Temp °C	Time day	conv[c] %	MO[d] PBH %	MO [α]D[e] °	MO e.e.[f] %	PBH [α]D[g] °	PBH e.e.calcd[h] %
2-Br-1-PrOH	0.5	1/2	Diox	25	5	14	72	—	—	+ 1.70	72
	0.5	2/3	Diox	25	5	37	89	−3.40	27.1	+ 2.93	34
	0.5	3/2	Diox	25	5	59	78	−1.83	14.6	+ 5.10	19
	0.5	2/1	Diox	25	5	84	70	−1.30	10.4	+10.58	14
	0	1/2	Diox	25	5	10	91	0	0	0	0
	0.5	1/2	Diox	40	2	63	34	−2.65	21.1	—	—
	0.5	1/2	Diox	5—10	7	39	70	−3.17	25.2	+ 2.93	34
	0.5	1/2	PrOH	25	5	58	73	−0.09	0.7	+ 0.13	0.7
	0	1/2	PrOH	25	5	47	76	0	0	0	0
	0.5	1/2	DCE	25	5	67	57	−0.10	0.7	+ 0.16	0.5
	0	1/2	DCE	25	5	45	71	0	0	0	0
1-Br-2-PrOH	0.5	1/2	Diox	25	5	51	47	−1.20	9.6	—	—
	0	1/2	Diox	25	5	29	53	0	0	0	0

a) Molar ratio of K_2CO_3 to PBH; 1/2=60/120 (mmol/mmol), 2/3=80/120 (mmol/mmol), 3/2=120/80 (mmol/mmol), 2/1=80/40 (mmol/mmol). b) 40 cm^3, Diox: dioxane, PrOH: 1-propanol, DCE: 1,2-dichloroethane. c) Conversion of PBH. d) MO formed/ PBH converted (mol/mol)×100. e) Specific rotation of MO formed. f) Optical purity of MO. g) Specific rotation of unreacted PBH recovered. h) Optical purity of MO evaluated from the optical purity of unreacted PBH.

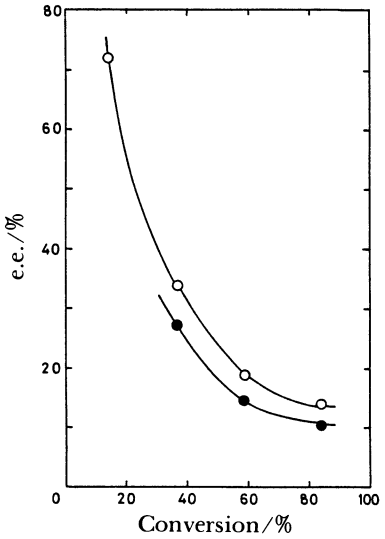


Fig. 1. The relation between e.e. (observed and calculated) of methyloxirane and conversion of 2-bromo-1-propanol. —○— e.e. of methyloxirane calculated from recovered 2-bromo-1-propanol, —●— e.e. of methyloxirane.

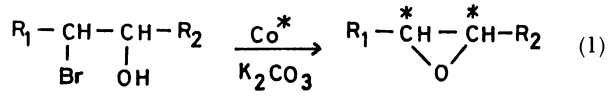
measured. However, the formation of (*S*)-(−)-methyloxirane (Table 1) indicates that (*S*)-(+)-1-bromo-2-propanol is preferentially cyclized because the asymmetric center is not involved in this cyclization reaction.

As the conversion increased, the optical purity of methyloxirane decreased, as shown in Fig. 1, showing that this asymmetric cyclization proceeds by the kinetic resolution. The highest optical yield of isolated methyloxirane was 27.1%, achieved in the reaction of 2-bromo-1-propanol with K_2CO_3 in dioxane at 37% of conversion. Much higher enantioselectivity is expected at the initial stage of this reaction. As the solvent for this asymmetric reaction, dioxane was found to be the best among the solvents examined; 1-propanol and 1,2-dichloroethane were found poor as the solvent, probably because the reaction proceeds significantly even without the asymmetric catalyst in these solvents.

Optical purity of methyloxirane did not vary significantly as reaction temperature was changed (at 40 °C, 21% e.e.; 25 °C, 24%; 5—10 °C, 21—25%); the high enantioselectivity was not observed even at lower temperature.

The observed e.e. values of methyloxirane are lower than the e.e.calcd values. The following explanation might be possible for the above differences between e.e. and e.e.calcd; (1) the racemization of the prefered enantiomer of the substrate may occur in the cyclization by the catalysis of cobalt complex, (2) a side reaction with high enantioselectivity may take place in parallel with the above kinetic resolution. As by-products for the reaction, a small amount of propylene carbonate and polyether were confirmed by GC, IR, and NMR.

Asymmetric Cyclization of Some Bromohydrins. The interaction of chiral catalyst and the substrate is crucial for asymmetric induction in the catalytic asymmetric reaction. To evaluate the effect of substituent, a variety of bromohydrins were synthesized and the asymmetric cyclization were carried out with K_2CO_3 (Eq. 1).



(1)

The results are summarized in Table 2. Corresponding oxiranes were formed selectively in every cases. From 2-bromo-1-butanol, (*S*)-(−)-ethyloxirane was formed in 8.9% e.e., which was much lower than that for methyloxirane. The configuration of oxirane formed was S, which was the same as that of methyl-

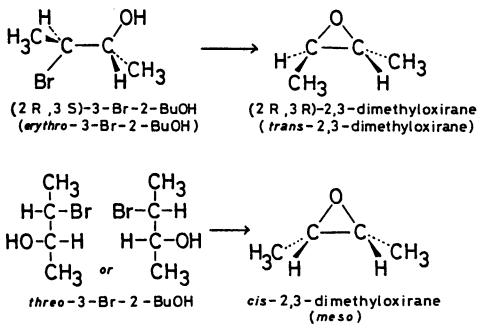
Table 2. Synthesis of Optically Active Oxiranes by the Asymmetric Cyclization of Bromohydrins[a)]

Substrate[b)]	Co* / mmol	K_2CO_3[c)] / Sub	Solv[d)]	Conv[e)] / %	Oxir[f)] / Sub %	Oxirane $[\alpha]_D$[g)] / °	Oxirane Config	Oxirane e.e.[h)] / %	Sub $[\alpha]_D$[i)] / °
BBH	0.5	50/137	Diox	33	76	−0.46	S	3.7	—
2-Br-1-BuOH	0.1	50/132	Diox	28	93	−1.11	S	8.9	−1.78
2-Br-1-BuOH	0	50/132	Diox	Trace	—	0	—	0	0
t-BuBH	0.5	50/100	CH_2Cl_2	33	97	−0.72[j)]	R	4.0	+1.42
t-BuBH	0	50/100	CH_2Cl_2	20	94	0	—	0	0
erythro-3-Br-2-BuOH	0.1	40/ 80	Diox	18	94	+5.97	R,R	10	−0.47
threo-3-Br-2-BuOH	0.1	40/ 80	Diox	37	86	0	—	0	+0.26

a) Solvent 40 cm^3, 25 °C, 5 days. b) BBH: commercial butylene bromohydrin (1-bromo-2-butanol/2-bromo-1-butanol=4/1), 2-Br-1-BuOH: 2-bromo-1-butanol, *t*-BuBH: 1-bromo-3,3-dimethyl-2-butanol, *erythro*-3-Br-2-BuOH: *erythro*-3-bromo-2-butanol, *threo*-3-Br-2-BuOH: *threo*-3-bromo-2-butanol. c) Molar ratio of K_2CO_3 to substrate (mmol/mmol). d) Diox: dioxane. e) Conversion of substrate. f) Oxirane formed/substrate converted (mmol/mmol). g) Specific rotation of oxirane formed. h) Optical purity of oxirane formed. i) Specific rotation of unreacted substrate recovered. j) Measured in benzene (*c* 13.0).

oxirane. The absolute configuration of 2-bromo-1-butanol is not known but based on the similarity of the reaction with 2-bromo-1-propanol, the absolute configuration of (+)-2-bromo-1-butanol is considered to be R. From 1-bromo-3,3-dimethyl-2-butanol(*t*-BuBH), (*R*)-(−)-*t*-butyloxirane was obtained. The optical purity of *t*-butyloxirane (4.0% e.e.) is also much lower than that of methyloxirane. The configuration of (−)-*t*-BuBH, which is preferentially cyclized in this reaction, is considered to be R, since the asymmetric carbon of the substrate does not participate in the cyclization as described for 1-bromo-2-propanol. Judging from the above two cases, the bulky groups do not necessarily induce high asymmetric induction. It is also interesting to note that methyl- and ethyloxirane were obtained in *S* configuration while *t*-butyloxirane in R configuration.

3-Bromo-2-butanol has two isomers, *erythro*-3-bromo-2-butanol and *threo*-3-bromo-2-butanol, which would be helpful in examining the mechanistic feature of this asymmetric cyclization. When the reaction proceeds by the complete S_N2 type cyclization, only *trans*-2,3-dimethyloxirane will be formed from *erythro*-3-bromo-2-butanol, and only *cis*-2,3-dimethyloxirane will be formed from *threo*-3-bromo-2-butanol. As was expected, the NMR and GC analyses of the products showed that only trans-oxirane was formed from erythro-isomer and only cis-oxirane from threo-isomer. The above results indicate that the reaction proceeds exclusively via the S_N2 mechanism in the presence of cobalt(salen) type complex. This results



Scheme 2.

lead to the conclusion that racemization of the selected substrate, mentioned before, is not likely to occur.

The optical activities of the substrate and product show that (2*R*,3*S*)-3-bromo-2-butanol[12] reacted preferentially to form (2*R*,3*R*)-dimethyloxirane by the inversion of the carbon at 3-position having bromide function. The results with 1-bromo-2-propanol and 2-bromo-1-propanol suggest that the S configuration is favored at the carbon bearing OH group, while R configuration at the carbon bearing Br atom. The result for (2*R*,3*S*)-3-bromo-2-butanol was, however, contrary to the prediction. It indicates that the enantioselection at the asymmetric moiety of the chiral cobalt complex is vulnerable to various factors. The idea of "Template"[13] may explain the results.

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