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Asymmetric Transformation of 2-Phenyl- and 2-Chloroalkanoic Acids *via* Chiral Oxazolines

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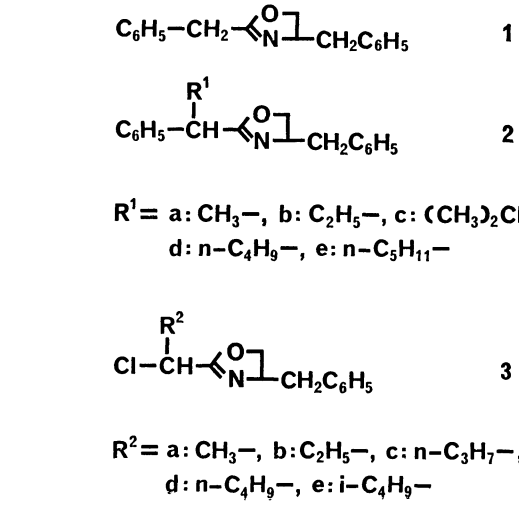
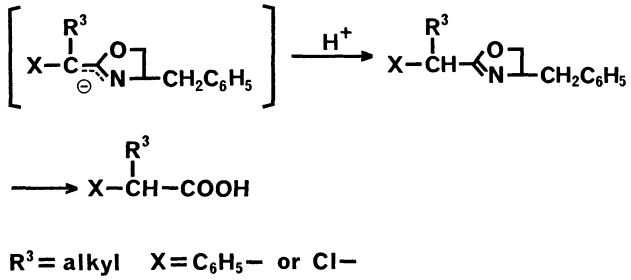
Asymmetric transformation of racemic 2-phenyl- and 2-chloroalkanoic acids *via* oxazolines into the corresponding optically active acids was investigated using (*S*)-phenylalaninol as a chiral auxiliary. The asymmetric transformation was performed by metalation of the oxazolines with butyllithium followed by protonation of the resulting lithiooxazolines. 2-Phenyl- and 2-chloroalkanoic acids were obtained in the optical yields of 29—53% and 45—73%, respectively, by the acidic hydrolysis of the chiral oxazolines thus formed. The mechanism of the asymmetric transformation was discussed.

Asymmetric transformation of racemic compounds into a single optically active form remains a major challenge in organic synthesis.[1] The great majority of work on the transformation has dealt with atropisomers.[2] Recently, optical activation of racemic aldehydes or ketones *via* enamines and of racemic amino acids *via* cobalt complexes has been reported.[3]

Although preparation of optically active alkanoic acids is important,[4] the asymmetric transformation of racemic alkanoic acids into optically active form has not been reported except for amino acids.[3] Therefore, in this study the asymmetric transformation of racemic 2-substituted alkanoic acids was intended, and 2-phenyl- and 2-chloroalkanoic acids were used as examples.[5] Chiral oxazolines, which had been originally used by Meyers *et al.* for the asymmetric synthesis of carbonyl compounds, were applied for the study of this asymmetric transformation.[6]

Oxazolines **2a**—**e** were prepared by alkylation of (4*S*)-(−)-2,4-dibenzyl-2-oxazoline (**1**), and **3a**—**e** were prepared from corresponding imidates and (*S*)-phenylalaninol. After metalation of **2** and **3** with butyllithium, the resulting lithio carbanions were quenched by addition of water (Scheme 1). Subsequent hydrolysis of **2** and **3** gave optically active 2-phenyl- and 2-chloroalkanoic acids respectively. The extent of asymmetric induction in the metallation and protonation process was monitored by examining the optical rotations of the obtained acids or diastereomer ratios of the oxazolines with NMR or GLPC analysis.





Scheme 1.

Experimental

IR spectra were measured with a JASCO A-3 spectrometer, high resolution mass spectra were recorded with a Hitachi M-80 mass spectrometer, optical rotations were measured with a JASCO Digital Automatic Polarimeter Model DIP-181, and ^{1}H NMR spectra were obtained with a JNM-PS-100 spectrometer (100 MHz). Chemical shifts are expressed in δ downfield from TMS as an internal standard. GLPC analysis was carried out on a Shimadzu Gas Chromatograph GC-7A equipped with a hydrogen flame ionization detector.

(4S)-(−)-2,4-Dibenzyl-2-oxazoline (1). A mixture of (*S*)-phenylalaninol[7] (7.6 g, 0.05 mol) and ethyl 2-phenylacetimidate[8] (8.3 g, 0.05 mol) was heated (120—130 °C) for 12 h with stirring. Distillation of the product gave 8.93 g (71%) of **1**: bp 144—146 °C (19 Pa); $[\alpha]_D^{25}$ −43.7° (*c* 1.08, EtOH); IR (neat) 1665 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ=2.68 (1H, dd), 3.08 (1H, dd), 3.58 (2H, s), 3.92 (1H, dd), 4.14 (1H, dd), 4.36 (1H, m), and 7.3 (10H, m); Found: *m/e* 251.1321. Calcd for $C_{17}H_{17}ON$: M, 251.1310.

Preparation of (4S)-2-(2-Phenylalkyl)-4-benzyloxazolines ***2a***—***c***. **2a**—**e** were prepared from **1** and alkyl iodides according to the method described by Meyers *et al.*[9]

2a: Yield 59% based on **1**; bp 164—168 °C (400 Pa); $[\alpha]_D^{25}$ −39.3° (*c* 1.04, EtOH); IR (neat) 1660 cm^{-1} (C=N); Found: *m/e* 265.1453. Calcd for $C_{18}H_{19}NO$: M, 265.1467.

2b: Yield 67% based on **1**; bp 143—145 °C (12 Pa); $[\alpha]_D^{25}$ −26.4° (*c* 1.02, EtOH); IR (neat) 1660 cm^{-1} (C=N); Found: *m/e* 279.1606. Calcd for $C_{19}H_{21}NO$ 279.1623.

2c: Yield 66% based on **1**; bp 144—148 °C (13 Pa);

$[\alpha]_D^{25}$ −32.7° (*c* 1.0, EtOH); IR (neat) 1660 cm^{-1} (C=N); Found: *m/e* 293.1801. Calcd for $C_{20}H_{23}NO$: M, 293.1780.

2d: Yield 64% based on **1**; bp 141—144 °C (9 Pa); $[\alpha]_D^{25}$ −24.8° (*c* 1.05, EtOH); IR (neat) 1660 cm^{-1} (C=N); Found: *m/e* 307.1927. Calcd for $C_{21}H_{25}NO$: M, 307.1936.

2e: Yield 71% based on **1**; bp 158—162 °C (11 Pa); $[\alpha]_D^{25}$ −19.8° (*c* 1.03, EtOH); IR (neat) 1662 cm^{-1} (C=N); Found: *m/e* 321.2116. Calcd for $C_{22}H_{27}NO$: M, 321.2093.

Preparation of (4S)-2-(2-Chloroalkyl)-4-benzyloxazolines ***3a—e***.

3a: Ethyl 2-chloropropionimidate hydrochloride was prepared from 2-chloropropionitrile according to the method described by McElvain and Nelson:[10] mp 90.5—91 °C; IR (Nujol) 1670 cm^{-1} (C=N). Ethyl 2-chloropropionimidate hydrochloride (8.6 g, 0.05 mol) and (*S*)-phenylalaninol (8.3 g, 0.055 mmol) was dissolved in 100 ml of dry dichloromethane and stirred for 10 h at room temperature. The reaction mixture was condensed under reduced pressure, and the residue was purified by chromatography on silica gel, and distilled to give 8.35 g (75% yield from ethyl 2-chloropropionimidate hydrochloride) of **3a**: bp 124—126 °C (200 Pa); $[\alpha]_D^{25}$ −70.7° (*c* 1.04, MeOH); IR (neat) 1662 cm^{-1} (C=N); Found: 223.0771. Calcd for $C_{12}H_{14}NOCl$: M, 223.0765.

3b: 2-Chlorobutyronitrile (10.4 g, 0.1 mol) and ethyl alcohol (5.06 g, 0.11 mol) was dissolved in 10 ml of dry ether, and dry hydrogen chloride gas was saturated. After 1 h at room temperature, the reaction mixture was condensed under reduced pressure, the residue was suspended in 150 ml of dry ether and 25 ml of triethylamine was added. Resulting white precipitate was filtered off and filtrate was concentrated. Distillation of the residue gave ethyl 2-chlorobutyrimidate (10.5 g, 70%); bp 86—88.5 °C (8665 Pa); IR (neat) 1660 cm^{-1} (C=N). Ethyl 2-chlorobutyrimidate (3.0 g, 0.02 mol) and (*S*)-phenylalaninol (3.62 g, 0.024 mol) were dissolved in 40 ml of dry dichloromethane, and to this mixture boron trifluoride etherate (0.284 g, 0.002 mol) and triethylamine (0.202 g, 0.002 mol) were added. The reaction mixture was stirred for 2 d at room temperature, and resulting white precipitate was filtered off, and filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel, and then distilled to give 2.85 g (60%) of **3b**: bp 133—137 °C (200 Pa); $[\alpha]_D^{25}$ −60.2° (*c* 1.01, MeOH); IR (neat) 1662 cm^{-1} (C=N); Found: *m/e* 237.0906. Calcd for $C_{13}H_{16}NOCl$: M, 237.0921.

3c: This material was prepared from ethyl 2-chlorovalerimidate according to the method described for **3b** in 65% yield: bp 136—140 °C (267 Pa); $[\alpha]_D^{25}$ −60.1° (*c* 1.02, MeOH); IR (neat) 1663 cm^{-1}; Found: *m/e* 251.1073. Calcd for $C_{14}H_{18}NOCl$: M, 251.1077.

3d: This material was prepared from ethyl 2-chlorohexanimidate hydrochloride according to the method described for **3a** in 80% yield: bp 143.5—145.5 °C (267 Pa); $[\alpha]_D^{25}$ −57.6° (*c* 1.02, MeOH); IR (neat) 1663 cm^{-1} (C=N); Found: *m/e* 265.1227. Calcd for $C_{15}H_{20}ONCl$: M, 265.1234.

3e: This material was prepared from ethyl 2-chloro-4-methylvalerimidate hydrochloride as described for **3a** in 82% yield; bp 143.5—146 °C (267 Pa); $[\alpha]_D^{25}$ −57.9° (*c* 1.02, MeOH); IR (neat) 1660 cm^{-1} (C=N); Found: *m/e* 265.1215; Calcd for $C_{15}H_{20}ONCl$: M, 265.1234.

Hydrolysis of ***2*** *before the Asymmetric Transformation.* **2b** (279 mg, 1 mmol) was suspended in 10 ml of 3 M (1 M=1 mol dm^{-3}) sulfuric acid and the suspension was refluxed for 4.5 h. The acidic solution was extracted with ether, and the ethereal solution was extracted with 5% aqueous potassium carbonate. The alkaline solution was acidified (pH 1) with hydrochloric acid, and extracted with ether. The ethereal solution was dried and concentrated, and the residue was distilled (bulb to bulb: 145—155 °C (bath temperature) (200 Pa)) to give 151 mg (92%) of (*S*)-(+)-2-phenylbutyric acid. The 2-phenylalkanoic acids (Table 1) were obtained as described above and the structures of the compounds were identified by their IR, Mass, and ^1H NMR spectra.

Hydrolysis of ***2*** *after the Asymmetric Transformation.* Under an argon atmosphere, **2b** (279 mg, 1 mmol) in 1 ml of dry tetrahydrofuran was cooled to −78 °C, and 0.86 ml of butyllithium (1.4 M solution) in hexane was added dropwise. The mixture was stirred for 45 min at −78 °C, and then 50% aqueous tetrahydrofuran was added at this temperature. The mixture was allowed to warm to room temperature, and the oxazoline was extracted with ether. This oxazoline was hydrolyzed as described above, and 122 mg (74%) of (*S*)-(−)-2-phenylbutyric acid was obtained. The 2-phenylalkanoic acids (Table 2) were obtained as described above.

Hydrolysis of ***3*** *before the Asymmetric Transformation.* **3b** (713 mg, 3 mmol) was suspended in 30 ml of 1 M hydrochloric acid and the suspension was kept at 80 °C for 1.5 h under stirring. The acidic solution was treated as described for **2b**, and 300 mg (82%) of (*R*)-(+)-2-chlorobutyric acid was isolated. The 2-chloroalkanoic acids (Table 3) were obtained as described above and the structures of the compounds were identified by their IR, MS, and ^1H NMR spectra.

Hydrolysis of ***3*** *after the Asymmetric Transformation.* **3b** (713 mg, 3 mmol) was dissolved in 3 ml of dry tetrahydrofuran and the solution was cooled to −78 °C under an argon atmosphere. To the solution, 2.77 ml of butyllithium (1.3 M solution) in hexane was added dropwise, and the mixture was stirred at −78 °C. After 45 min, 3 ml of 25% aqueous tetrahydrofuran was added to the mixture and the oxazoline

Table 1. Hydrolysis of **2a—e** before the asymmetric transformation

	Yield %	$[\alpha]_D^{25}$ 10^4 degree ml g^{-1} dm^{-1}	Lit $[\alpha]_D^{25}$ 10^4 degree ml g^{-1} dm^{-1}	Optical[a] purity %	Absolute configuration
2a	79	+1.5 (*c* 1.6, $CHCl_3$)	+76.3 (*c* 1.6, $CHCl_3$)[b]	2	*S*
2b	92	+17.1 (*c* 1.6, C_6H_6)	+96.6 (*c* 1.5, C_6H_6)[c]	18	*S*
2c	80	−5.9 (*c* 1.9, $CHCl_3$)	+62.5 (*c* 2, $CHCl_3$)[d]	10	*R*
2d	84	+7.7 (*c* 1.8, C_6H_6)	−74.9 (*c* 1.7, C_6H_6)[e]	10	*S*
2e	81	+11.2 (*c* 0.8, C_6H_6)	−71.4 (*c* 0.8, C_6H_6)[e]	16	*S*

a) Optical purities were based upon the highest literature values available. b) S. P. Bakshi and E. E. Turner, *J. Chem. Soc.*, **1961**, 171. c) Ph. Gold-Aubert, *Helv. Chim. Acta*, **41**, 1512 (1958). d) C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohashi, and H. S. Mosher, *J. Org. Chem.*, **32**, 2797 (1967). e) K. Pettersson and Willdeck, *Ark. Kemi*, **9**, 333 (1956).

Table 2. Hydrolysis of **2a—e** after the asymmetric transformation

	Yield / %	$[\alpha]_D^{25}$ / 10^4 degree ml g^{-1} dm^{-1}	Optical[a] purity / %	Absolute configuration
2a	83	+21.8 (*c* 1.7, $CHCl_3$)	29	*S*
2b	74	+39.2 (*c* 2.6, C_6H_6)	41	*S*
2c	77	+32.7 (*c* 2.1, $CHCl_3$)	52	*S*
2d	74	+40.0 (*c* 1.8, C_6H_6)	53	*S*
2e	83	+37.7 (*c* 0.9, C_6H_6)	53	*S*

a) Optical purities were based upon the highest literature values available (See Table 1.)

Table 3. Hydrolysis of **3a—e** before the asymmetric transformation

	Hydrolysis *t* / h	Yield / %	$[\alpha]_D^{25}$ (CH_3OH) / 10^4 degree ml g^{-1} dm^{-1}	Lit $[\alpha]_D$ (CH_3OH) / 10^4 degree ml g^{-1} dm^{-1}	Optical[a] purity / %	Absolute configuration
3a	1.5	94	+0.13 (*c* 5.2)	+17.3 (*c* 0.5)[b]	1	*R*
3b	1.5	82	+0.33 (*c* 5.1)	+12.7 (*c* 0.4)[b]	3	*R*
3c	1.5	86	+0.43 (*c* 5.1)	−13.3[c]	3[e]	*R*
3d	1.5	61	0 (*c* 5.0)	−11.7[c]	0	*RS*
	4.5	88	0 (*c* 5.0)		0	*RS*
3e	1.5	45	+5.73 (*c* 5.2)	−24.4 (*c* 5)[d]	24[e]	*R*
	6	91	+0.51 (*c* 5.1)		2[e]	*R*

a) Optical purities were based upon the highest literature values available. b) H. Hashimoto and H. Simon, *Angew. Chem.*, **87**, 111 (1975). c) W. Gaffield and W. G. Galetto, *Tetrahedron*, **27**, 915 (1971). d) T. Polonski, *Tetrahedron*, **31**, 347 (1975). e) The diastereomeric composition of **3c—e** suggested that the optical purities of the obtained acids were lower than the calculated values (See Table 4).

Table 4. Hydrolysis of **3a—e** after the asymmetric transformation

	Hydrolysis *t* / h	Yield / %	$[\alpha]_D^{25}$ (CH_3OH) / 10^4 degree ml g^{-1} dm^{-1}	Optical[a] purity / %	Absolute configuration	Diastereomeric composition
3a	1.5	73	+7.77 (*c* 5.1)	45	*R*	71 : 29[e]
3b	1.5	72	+6.56 (*c* 5.2)	52	*R*	75 : 25[e]
3c	1.5	71	+9.85 (*c* 5.2)	74[b]	*R*	77 : 23[d]
3d	1.5	52	+8.88 (*c* 5.0)	76[b]	*R*	76 : 24[d]
	4.5	74	+8.48 (*c* 5.1)	73[b]	*R*	
3e	1.5	62	+16.2 (*c* 5.1)	66[b]	*R*	76 : 24[d]
	6	79	+15.0 (*c* 5.1)	62[b]	*R*	

a) Optical purities were based upon the highest literature values available (see Table 3). b) The diastereomeric compositions of **3c—e** suggested that the optical purities of the obtained acids were lower than the calculated values. c) The diastereomeric composition was determined by ^1H NMR analysis. d) The diastereomeric composition was determined by GLPC analysis.

was extracted with ether. This oxazoline was hydrolyzed as described above, and 266 mg (72%) of (*R*)-(+)-2-chlorobutyric acid was isolated. The 2-chloroalkanoic acids (Table 4) were obtained as described above.

Measurement of Diastereomeric Composition of ***3*** *after the Asymmetric Transformation.* **3a** (112 mg, 0.5 mmol) was dissolved in 0.5 ml of dry tetrahydrofuran and the solution was cooled to −78 °C under an argon atmosphere. To the solution 0.5 ml of butyllithium (1.2 M solution) in hexane was added dropwise and the mixture was stirred at −78 °C. After 45 min, 0.5 ml of 25% aqueous tetrahydrofuran was added to the mixture and the oxazoline was extracted with ether. The ethereal solution was dried over Na_2SO_4 and concentrated under reduced pressure. **3b—e** were treated as described above, and the ratios of the diastereomers of **3a** and **3b** were calculated from their ^1H NMR spectra, and those of **3c—e** were estimated by peak area measurement of the GLPC (column: OV-101 0.27 mm×50 m, temperature 100—240 °C).

Mutarotation of ***3d****.* **3d** (2.66 g, 10 mmol) was treated with 12 mmol of butyllithium in the same manner as described for the asymmetric transformation of **3b**, and then the prepared carbanion was quenched by addition of water. The product was purified with chromatography on silica gel (dichloromethane) to give 2.39 g (90%) of epimerized **3d**: $[\alpha]_D^{25}$ −46.4° (*c* 1.03, MeOH). This epimerized **3d** (1.33 g, 5 mmol) was dissolved in 50 ml of 2 M KOH–MeOH solution, and the solution was kept at 25 °C. An aliquot of the solution was used for the measurement of the mutarotation at 589 nm at 25 °C. Just after the preparation of the alkaline solution, 20 ml of the solution was removed and diluted with 200 ml of water. This solution was saturated

with NaCl, and **3d** was extracted with ether. **3d** was hydrolyzed as described for **3b** to give 156 mg (52%) of (*R*)-(+)-2-chlorohexanoic acid. After 24 h, 20 ml of the alkaline solution was treated as described above to give 161 mg (53%) of (*S*)-(−)-2-chlorohexanoic acid.

The Effect of Temperature in the Asymmetric Transformation of 2b. Under an argon atmosphere, 55.8 mg (0.2 mmol) of **2b** in 0.2 ml of dry tetrahydrofuran was cooled to −78 °C, and 0.17 ml of butyllithium (1.4 M solution) in hexane was added dropwise. Each carbanion solution, thus prepared, was stirred for 45 min at temperatures of 0, −20, −40, −60, and −78 °C. Then, water was added to the solutions at the temperatures, and the solutions were extracted with ether. The ether extracts were washed with brine, dried, and evaporated to give **2b**. The ratios of two diastereomers of **2b** were determined by peak area measurements of methyl peaks of the diastereomers in the ^{1}H NMR spectra.

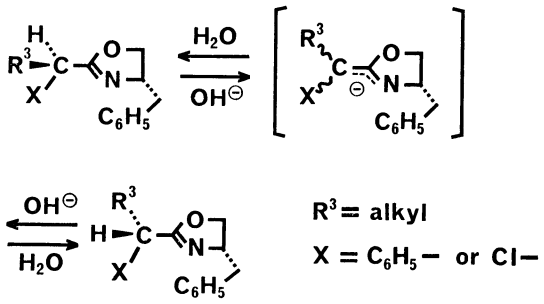
Results and Discussion

Asymmetric Transformation of 2. Hydrolysis of **2a**—**e** after the asymmetric transformation gave the corresponding acids in the optical yields of 29—53% as shown in Table 2. Because **2a**—**e** were prepared by alkylation of the chiral oxazoline (**1**), asymmetric induction by this alkylation step was possible. Hydrolysis of **2a**—**e** before the asymmetric transformation gave the corresponding optically active acids in the optical yields of 2—18% (Table 1). The results shown in Tables 1 and 2 indicate that the asymmetric induction is attributable to the asymmetric transformation, and not to the alkylation step.

Asymmetric Transformation of 3. In preliminary expeiments, racemization of optically active 2-chloroalkanoic acids under the hydrolysis conditions of **2** (3 M sulfuric acid, reflux 4.5 h) was observed. Therefore, weaker acid (1 M hydrochloric acid) and lower heating temperature (80 °C) were employed for the hydrolysis of **3**. **3a**—**c** were hydrolyzed for 1.5 h, and in the case of **3d** and **3e**, hydrolysis were prolonged to 4.5 and 6 h respectively because of low hydrolysis yields. Hydrolysis of **3** (**3a**—**c** 1.5 h, **3d** 4.5 h, **3e** 6 h) before the asymmetric transformation gave the corresponding acids in the optical yields of less than 5%.

Hydrolysis of **3** after the asymmetric transformation gave the corresponding acids in the optical yields of 45—73% (Table 4). The results shown in Tables 3 and 4 indicate that the asymmetric induction is definitely due to the transformation. The optical purities of the acids were calculated based upon the highest literature values available, but there was some doubt that the optical purities of the compared data were insufficient from the preparation methods described in the literatures. Therefore, the diastereomeric composition of **3a**—**e** after the asymmetric transformation was measured by ^{1}H NMR or GLPC. The results are listed also in Table 4. Although the calculated optical purities of **3a** and **3b** correspond to the diastereomeric compositions, the calculated optical purities of **3c**—**e** disagree with the compositions of **3c**—**e**. From the diastereomeric compositions of **3c**—**e**, the enantiomeric purities of **3c**—**e** are expected to be about 50%. Asymmetric synthesis of 2-chloroalkanoic acids *via* chiral oxazolines was reported by Meyers *et al.*, and in their synthesis, the 2-chloroalkanoic acids corresponding to **3a**, **3b**, and **3d** were prepared in the optical yields of 3—28%.[11] It is noteworthy that in the present transformation, using simple chiral auxiliary (*S*)-phenylalaninol, 2-chloroalkanoic acids can be obtained in fairly good optical purities compared with the Meyers' asymmetric synthesis.

Mutarotation. One possible mechanism of this asymmetric transformation is a base catalyzed epimerization governed by thermodynamic control as illustrated in Scheme 2. To examine whether this asymmetric transformation was governed by the thermodynamic control or not, the mutarotation of **3d** was measured. **3d** was treated with butyllithium followed by addition of water to give epimerized **3d**. This epimerized **3d** was dissolved in an alkaline solution (2 M KOH–MeOH), and optical rotation of **3d** was recorded. If the asymmetric induction had been governed by the thermodynamic control, optical rotation of this epimerized **3d** was not expected to change. However, as shown in Fig. 1 mutarotation of the epi-



Scheme 2.

Table 5. Hydrolysis of **3d** before and after the equilibrium

Mutarotation t / h	$[\alpha]_D^{25}$ (CH_3OH) / 10^4 degree ml g^{-1} dm^{-1}	Optical[a] purity / %	Absolute configuration
0	+7.63 (*c* 5.14)	65.2	*R*
24	−0.87 (*c* 5.07)	7.4	*S*

a) Optical purities were based upon the highest literature values available (See Table 3).

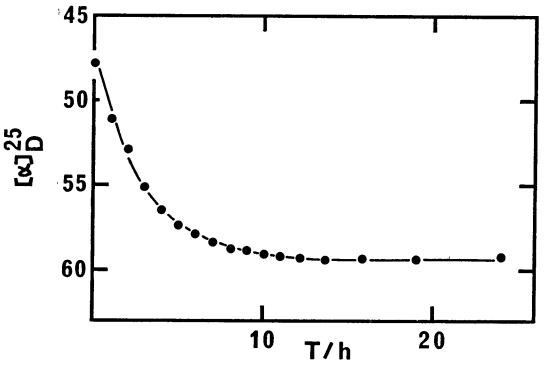


Fig. 1. Mutarotation of **3d** (0.1 M) in 2 M KOH–MeOH at 25 °C.

merized **3d** was observed. The optical rotation did not change after 12 h indicating that the epimerization attained equilibrium under the conditions. Two aliquots of **3d**, which were taken from the alkaline solution at 0 and 24 h, were hydrolyzed to give 2-chlorohexanoic acid. Specific rotations of the acid at 0 and 24 h are shown in Table 5. Under the epimerization conditions, the contribution of asymmetric induction governed by thermodynamic control is revealed to be small in the asymmetric transformation.

Isotopic Labeling Study. When butyllithium solution was added to the solutions of **2** or **3**, the reaction mixture became yellow suggesting the formation of lithio carbanion (**4**). The formation of the carbanion was confirmed by quenching the carbanion using deuterium oxide. After the treatment described above, exo methine proton of the oxazoline ring of **2** and **3** was shown from ^{1}H NMR spectra to be substituted by deuterium. The extent of deuterium incorporation to **2** and **3** was calculated from their mass spectra to be 90—98% and 80—90%, respectively. These results indicate that this asymmetric transformation proceeds through the formation of lithio carbanion (**4**), and subsequent protonation of the carbanion.

Effects of Temperature. The effects of temperature on the asymmetric transformation was examined using **2b**. Lithio carbanion of **2b** was prepared in tetrahydrofuran at −78 °C using butyllithium. Each anion solution, thus prepared, was stirred for 45 min at temperatures of 0, −20, −40, −60, and −78 °C, and then quenched with water. The ratios of two diastereomers of **2b** were determined by ^{1}H NMR spectra. The results are summarized in Table 6. The ratios are not affected by temperature.

Table 6. The effects of temperature on the asymmetric transformation

Temperature °C	Diastereomeric composition
0	72 : 28
−20	71 : 29
−40	72 : 28
−60	70 : 30
−78	71 : 29

Possible Mechanisms of Asymmetric Transformation. On the basis of the results presented above, this asymmetric transformation is assumed to proceed through stereoselective formation of lithio carbanion and protonation to the carbanion. Observation that there are virtually no effects of temperature on the extent of asymmetric induction suggested that both the ratios of the isomeric anions **4a** and **4b**, and stereoselectivity of protonation to the anions are not changed between −78 and 0 °C. According to the chiralities of the obtained 2-substituted alkanoic acids, two mechanisms (A) and (B) are probable to accommodate this asymmetric transformation and they are illustrated in Scheme 3.[12] In mechanism (A) isomeric lithiooxazoline **4a** predominates over **4b** and protonation occurs from the bottom side of the oxazoline ring. As shown in mechanism (B), a reversal of the predominant isomeric anions and a reversal of the direction of protonation gave the same result indicated in the mechanism (A). Although mechanism (A) is supported by lithium–arene π coordination effect,[13] no evidence to exclude mechanism (B) is available at present. To establish the mechanism for this asymmetric transformation further investigation is now in progress.

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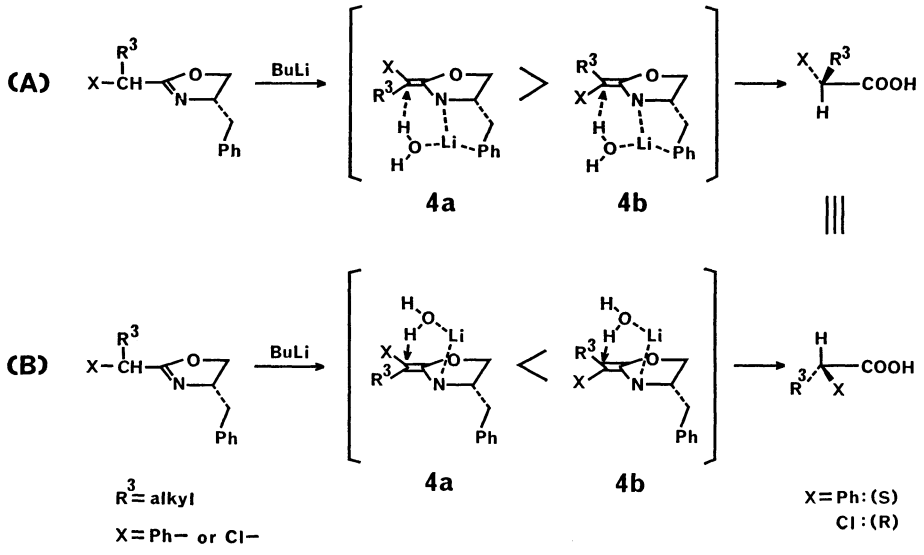

Scheme 3.

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