

ASYMMETRIC TRANSFORMATION OF 2-PHENYLALKANOIC
ACIDS VIA OXAZOLINE DERIVATIVES

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Asymmetric transformation of 2-phenylalkanoic acids via
oxazoline derivatives was investigated. (S)-Phenylalaninol was
used as a chiral auxiliary in the transformation, and the acids
were obtained in the optical yields of 29-53%.

In a previous paper, the second order asymmetric transformation of alanine
via imidazoline derivatives was reported, and (S)-alanine was converted into
(R)-alanine in the optical yield of 94%.¹⁾ Although (R)-alanine was obtained
in the high optical purity, crystallization of imidazoline derivatives was
indispensable for the transformation.

In this paper, we wish to report the asymmetric transformation of
2-phenylalkanoic acids via oxazoline derivatives, in which crystallization of
the derivatives is not essential. Oxazoline derivatives, which had been
originally used by Meyers et al. for the asymmetric synthesis of carbonyl
compounds,²⁾ were applied for the study of this asymmetric transformation.
Oxazolines (II_{a-e}) were prepared by the reaction of (4S)-(-)-2,4-dibenzyl-2-
oxazoline (I) and alkyl iodides. The asymmetric transformation was performed
by protonation of the lithio anions of II_{a-e} by water.

II_{a-e} were prepared as follows. The mixture of (S)-phenylalaninol (7.6 g)
and ethyl 2-phenylethylimidate (8.3 g) was heated (120-130°C) for 12 h with
stirring. Distillation of the product gave I (8.93 g, 71.2%, bp 144-146°C/19
Pa).³⁾ II_{a-e} were synthesized by the alkylation of I with alkyl iodides
according to the method described by Meyers et al.²⁾ The alkylation was carried
out in THF at -78°C using butyllithium as a base. The results are summarized in
Table 1.

Asymmetric induction of this alkylation step was examined by hydrolysis of
II_{a-e} to the corresponding acids. For example, II_b (279 mg) was suspended in
10 ml of 6 N-H₂SO₄, and the suspension was refluxed for 4.5 h. The product was
distilled (bulb to bulb) to give 151 mg of 2-phenylbutyric acid. This acid was
identified by its IR, MS, and NMR spectra. The results are shown in Table 2.

Table 3. Hydrolysis of II after the asymmetric transformation

	Yield (%)	$[\alpha]_D^{25}$ (°)	Lit. $[\alpha]_D$ (°)	O.P. ^{a)} (%)	Conf.
III _a	83	+22 (c 1.7, CHCl ₃)	+76.3 (c 1.6, CHCl ₃) ^{b)}	29	(S)
III _b	74	+39 (c 2.6, C ₆ H ₆)	+96.6 (c 1.5, C ₆ H ₆) ^{c)}	41	(S)
III _c	77	+33 (c 2.1, CHCl ₃)	+62.5 (c 2, CHCl ₃) ^{d)}	52	(S)
III _d	74	+40 (c 1.8, C ₆ H ₆)	-74.9 (c 1.7, C ₆ H ₆) ^{e)}	53	(S)
III _e	83	+38 (c 0.9, C ₆ H ₆)	-71.4 (c 0.8, C ₆ H ₆) ^{e)}	53	(S)

a) Optical purities are 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 G. Willdeck, Ark. Kemi, 9, 333 (1956).

using II_b. Under Ar, 55.8 mg of II_b in 0.2 ml of dry THF was cooled to -78°C, and 0.17 ml of butyllithium (1.4 M solution) in hexane was added dropwise. Each anion 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, and evaporated to give II_b. The ratios of two

diastereomers of II_b were determined

by peak area measurements of methyl peaks of the diastereomers in the NMR spectra. The results are summarized in Table 4. Table 4 shows that this asymmetric transformation is not affected by temperature.

One possible mechanism of this asymmetric transformation is a base catalyzed thermodynamically controlled one as illustrated in Scheme 2. To examine the mechanism of the transformation, two experiments were carried out.

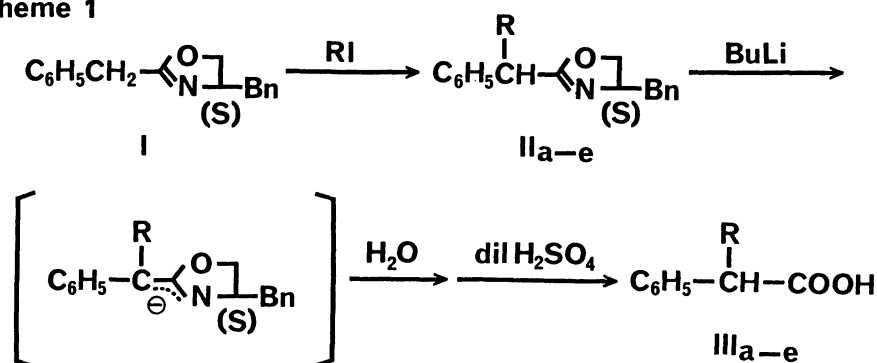
(1) II_e (241 mg) was dissolved in a mixture of 2 N-LiOH (2 ml) and THF (2 ml), and, after 12 h vigorous stirring at room temperature, II_e was hydrolyzed as described above to give 125 mg of III_e (81% yield from II_e, $[\alpha]_D^{25}$ -2.6° (c 0.85, C₆H₆) 3.6% o.p. (R) conf.). (2) The lithio anion of II_e was generated from 321 mg of II_e as described above, and the protonation to the anion was carried out by a mixture of 6 N-HCl (1 ml) and THF (1 ml). The hydrolysis of the product (6 N-HCl, reflux 4.5 h) gave 149 mg of III_e (72% yield from II_e, $[\alpha]_D^{25}$ +29° (c 0.84, C₆H₆) 40% o.p. (S) conf.).

These results indicate that configurations and optical yields of the produced acids were not governed by thermodynamic control. Although the precise

Table 4. The effect of temperature on the asymmetric transformation

Temp (°C)	Ratio of the two diastereomers
0	72 : 28
-20	71 : 29
-40	72 : 28
-60	70 : 30
-78	71 : 29

Scheme 1



Bn = C₆H₅CH₂-, R = a: CH₃-, b: C₂H₅-, c: (CH₃)₂CH-, d: n-C₄H₉-, e: n-C₅H₁₁-

Table 1. Alkylation of I

	Yield ^{a)} (%)	[α] _D ^{25b)} (°)
II _a	59	-39 (c 1.0, EtOH)
II _b	67	-26 (c 1.0, EtOH)
II _c	66	-33 (c 1.0, EtOH)
II _d	64	-25 (c 1.0, EtOH)
II _e	71	-20 (c 1.0, EtOH)

a) Yields are based on I and have not been optimized.

b) [α] = 100α / l(dm)c(g/100 ml).

Table 2. Hydrolysis of II

	Yield (%)	[α] _D ²⁵ (°)	O.P. ^{a)} (%)	Conf.
III _a	79	+1 (c 1.6, CHCl ₃)	2	(S)
III _b	92	+17 (c 1.6, C ₆ H ₆)	18	(S)
III _c	80	-6 (c 1.9, CHCl ₃)	10	(R)
III _d	84	+8 (c 1.8, C ₆ H ₆)	10	(S)
III _e	81	+11 (c 0.8, C ₆ H ₆)	16	(S)

a) Optical purities are based upon the highest literature values available (see Table 3).

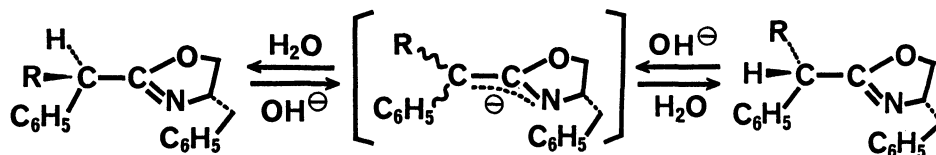
The asymmetric transformation was carried out as follows. Under Ar, 279 mg of II_b in 1 ml of dry THF was cooled to -78°C, and 0.86 ml of butyllithium (1.4 M solution) in hexane was added. The mixture was stirred for 45 min at -78°C, and then 50% aq. THF (2 ml) was added at this temperature. The mixture was allowed to warm to room temperature, and the oxazoline was extracted with ether. This oxazoline was hydrolyzed (6 N-H₂SO₄, reflux 4.5 h), and the product was distilled (bulb to bulb) to give 122 mg of III_b. The results of the asymmetric transformation are summarized in Table 3.

The chiral acids were prepared in the optical yields of 29-53% as shown in Table 3. Table 2 and 3 indicate that the asymmetric induction was attributable to the asymmetric transformation, and not to the alkylation step. In the transformation, as the bulk of the alkyl substituents increased, the optical yields increased. It is noteworthy that no difficulty in the hydrolysis process was observed even if a bulky substituent was present, though the difficulty was encountered in the asymmetric synthesis of the chiral acids reported by Meyers *et al.*²⁾

The effect of temperature on the asymmetric transformation was examined

mechanism of the asymmetric transformation is still unclear, the ratio of the enantiomers of the acids is probably governed by the stereospecific anion formation and succeeding stereospecific protonation to the anion. Further investigations on the mechanism and applications for other 2-substituted alkanolic acids are in progress.

Scheme 2



References and Note

- 1) S. Shibata, H. Matsushita, M. Noguchi, M. Saburi, and S. Yoshikawa, Chem. Lett., 1978, 1305; S. Shibata, H. Matsushita, K. Kato, M. Noguchi, M. Saburi, and S. Yoshikawa, Bull. Chem. Soc. Jpn., 52, 2938 (1979).
- 2) A. I. Meyers, Acc. Chem. Res., 11, 375 (1978); A. I. Meyers, D. L. Temple, R. L. Nolen, and E. D. Mihelich, J. Org. Chem., 39, 2778 (1974); A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, J. Am. Chem. Soc., 98, 567 (1976).
- 3) Oxazoline (I): $[\alpha]_D^{25} -43.7^\circ$ (c 1.08, EtOH); IR (KBr film) 1665, 1603, and 1496 cm^{-1} ; 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 ppm (10H, m); MS m/e 251.1321 (M^+ , $\text{C}_{17}\text{H}_{17}\text{ON}$; calcd 251.1310).

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