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THE MECHANISM OF ASYMMETRIC TRANSFORMATION OF 2-SUBSTITUTED ALKANOIC ACIDS *VIA* CHIRAL OXAZOLINES

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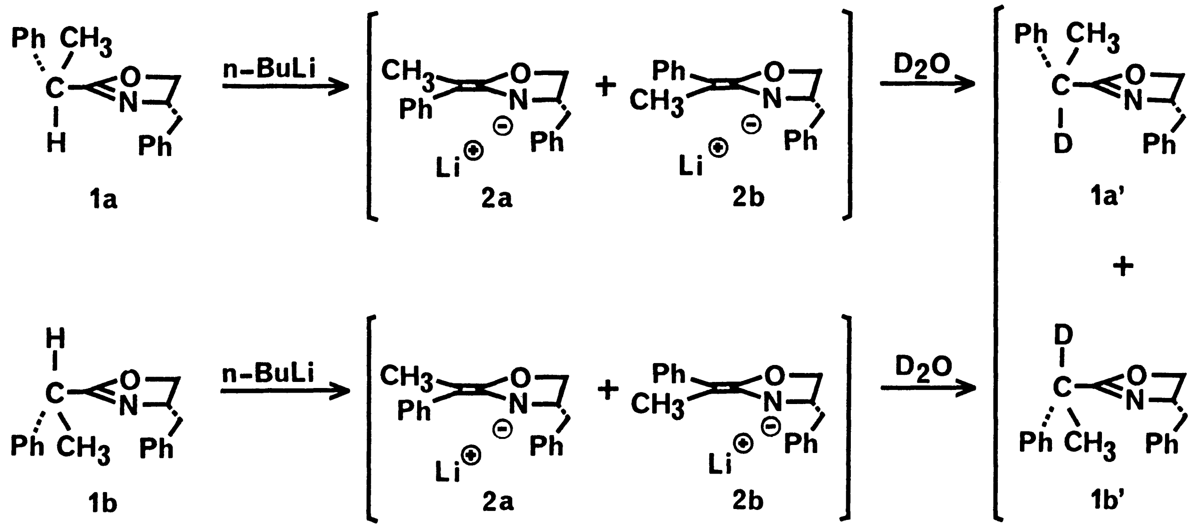
The mechanism of asymmetric transformation of 2-substituted alkanoic acids *via* chiral oxazolines was examined using two epimers of (4*S*)-2-(1-phenylethyl)-4-benzyloxazoline. The transformation in THF was elucidated to be governed by kinetic control, and its process was clarified by measuring the ratio of ^{13}C-labeled lithio oxazolines by ^{13}C NMR.

In previous papers, the asymmetric transformation of 2-phenyl and 2-chloroalkanoic acids was reported.1) The mechanism of the transformation has not yet been known, and the elucidation of it is of particular interest in the study of this unique method. Therefore, the mechanism of the transformation was examined.

The asymmetric transformation already reported was carried out on a mixture of two epimers at C-2 *exo* methine of oxazoline ring.1) In this experiment, to investigate the mechanism of the transformation, two epimers (1a and 1b) of (4*S*)-2-(1-phenylethyl)-4-benzyloxazoline were separated by silica gel chromatography (silica gel 60 pre-packed column (Merck), 40% ether-hexane), and the each epimer was submitted to the transformation separately.2) To assure the quantitative formation of the lithio carbanions (2a and 2b), deuterium oxide was used instead of water to quench the carbanions. Thus, 1a and 1b were converted to the deuterated epimers (1a' and 1b') as shown in Scheme 1.

In a typical experiment, a solution of butyllithium (0.16 ml, 0.2 mmol) in hexane was added dropwise to a solution of 1a(98%) (13.3 mg (0.05 mmol); 1a:1b= 98:2) in dry THF (1 ml) at -78 °C.3) The reaction mixture became yellow indicating the formation of its lithio carbanions. This yellow solution was stirred for 45 min at -78 °C, and then 25% D_2O-THF solution (0.1 ml) was added and allowed to warm to room temperature. The mixture was extracted with ether, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The ratio of 1a' and 1b' in this residue was determined by GLPC(OV-1, 0.3mmϕ × 50 m,170 °C), and deuterium incorporation was detected by MS and ^{1}H NMR. The post metalation period (stirring period of the reaction mixture after the addition of butyllithium) was varied in the range of 5 min, 45 min, and 5 h to examine the effects on the transformation. The mixture of 1a and 1b (1a:1b=49:51)



Scheme 1

and 1b(96%) were also examined as described above and the results are shown in Table 1.

1a(98%) gave a mixture of 1a' and 1b' in a ratio of 8:2, and 1b(96%) gave it in a ratio of 6:4. This difference is not due to insufficient deprotonation from 1a or 1b because deuterium incorporation was above 90% in both cases. In this transformation the configuration at C-2 exo methine of 1a was retained ca. 80%, and on the other hand, inversion of the configuration predominated over retention of it in the case of 1b. Although the ratio of 1a' and 1b' depends on the starting epimers, the ratio is practically independent on the post metalation period.

To examine solvent effects, the transformation was performed in 25% HMPA-THF solution. The results are shown in Table 2. In this case, both 1a(98%) and 1b(96%) gave 1a' and 1b' in a ratio of 4:6 with deuterium incorporation above 90% incontrast with the results obtained in THF.

These indicate that in 25% HMPA-THF solution 2a is in equilibrium with 2b, and the asymmetric transformation performed in THF solution is governed by kinetic control under the experimental conditions.

Table 1. Asymmetric transformation of 1 in THF

post metalation period[a) / min	5		45		300	
1a:1b	1a':1b'	D incorpo. %	1a':1b'	D incorpo. %	1a':1b'	D incorpo. %
98: 2	82:18	96	83:17	97	83:17	95
49:51	71:29	93	71:29	93	68:32	94
4:96	63:37	91	62:38	95	62:38	95

a) Samples were metalated at -78 °C and stirred for the intervals indicated at -78 °C.

Table 2. Asymmetric transformation of **1** in 25% HMPA-THF

1a:**1b**	**1a'**:**1b'**a)	D incorpo.a) %
98: 2	39:61	94
49:51	41:59	91
4:96	41:59	94

a) Post metalation period was 45 min.

Table 3. Asymmetric transformation of ^{13}C-labeled **1** in THF

1a:**1b**	lithio oxazoline ratio	**1a'**:**1b'**
99: 1	94: 6	85:15
74:26	83:17	80:20
49:51	73:27	73:27
26:74	66:34	69:31
3:97	55:45	62:38

This asymmetric transformation consists of the formation of lithio carbanions (**2a** and **2b**) and successive protonation to the carbanions. To clarify the mechanism of the process the ratio of the lithio oxazolines was measured by ^{13}C NMR. A mixture of ^{13}C-enriched **1a** and **1b** at methyl carbon β to oxazoline ring was prepared from (4*S*)-2,4-dibenzyloxazoline and *ca*. 50% enriched [^{13}C]methyl iodide according to the method described by Meyers *et al*.4) The ^{13}C-labeled epimers (**1a** and **1b**) were separated by silica gel column as described before, and five mixtures of the two epimers (**1a**:**1b**=99:1, 72:26, 49:51, 26:74, 3:97) were prepared. The each mixture (26.6 mg, 0.1 mmol) was dissolved in 0.2 ml of dry THF, and 0.17 ml of butyllithium in hexane (1.2 M, 0.2 mmol) was added to the solution at -78 °C. The ^{13}C NMR spectrum of each solution was recorded at -78 °C under quantitative conditions,4,5) and showed a minor peak ($\mathbf{2}_{\mathrm{minor}}$) at 18.1 ppm and a major peak ($\mathbf{2}_{\mathrm{major}}$) at 16.1 ppm.6) After the measurment of the spectrum, 0.2 ml of 25% D$_2$O-THF solution was added to the sample at -78 °C. The ratio of **1a'** and **1b'** of the resulting mixture was determined as described before. The results are shown in Table 3.

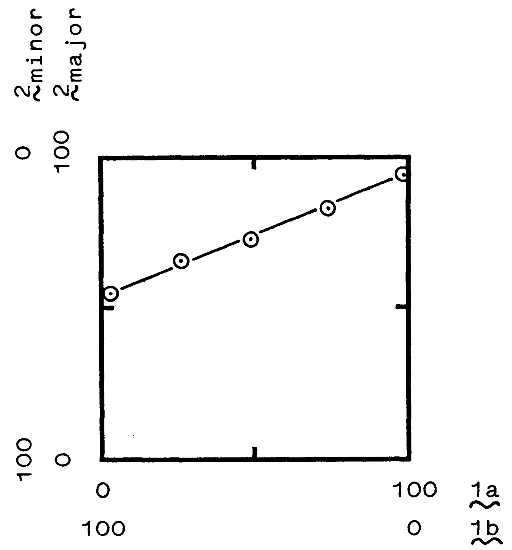


Fig. 1. Relationship between the ratio of **1a** and **1b** and the lithio oxazoline ratio.

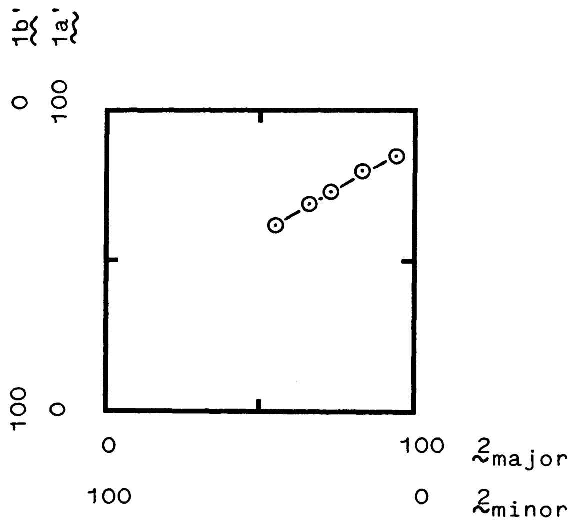
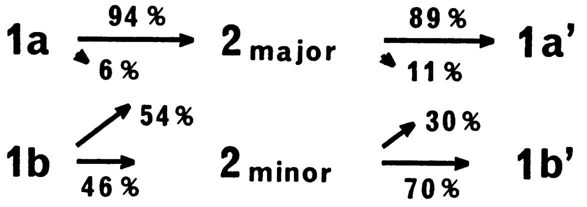


Fig. 2. Relationship between the lithio oxazoline ratio and the ratio of **1a'** and **1b'**.

The relationships between the ratio of 1a:1b and that of lithio oxazoline, and the ratio of lithio oxazoline and that of 1a':1b' are shown in Fig. 1 and 2 respectively. The selectivities of the formation of the lithio oxazolines (2$_{\mathrm{major}}$ and 2$_{\mathrm{minor}}$) from 1a and 1b, and of 1a' and 1b' from the lithio oxazolines are calculated from the slopes of the straight lines in Fig. 1 and 2, and illustrated in Scheme 2. From above results, retention of the stereochemistry of 1a was explained by the selective formation of 2$_{\mathrm{major}}$ from 1a and that of 1a' from 2$_{\mathrm{major}}$. Inversion of the stereochemistry of 1b was accounted for by the preferential formation of 2$_{\mathrm{major}}$ from 1b and by the partial formation of 1a' from 2$_{\mathrm{minor}}$. The further investigation on the reason for the slectivity shown above is in progress.



Scheme 2

References

1) S. Shibata, H. Matsushita, H. Kaneko, M. Noguchi, M. Saburi, and S. Yoshikawa, Chem. Lett., 1981, 217: S. Shibata, H. Matsushita, H. Kaneko, M. Noguchi, M. Saburi, and S. Yoshikawa, Heterocycles, 16, 1901 (1981); S. Shibata, H. Matsushita, H. Kaneko, M. Noguchi, M. Saburi, and S. Yoshikawa, Bull. Chem. Soc. Jpn., 55, 3546 (1982).

2) To determine the absolute configuration at C-2 exo methine of 1a and 1b, the mixture of 1a and 1b (10:90, 133 mg) was hydrolyzed in 3 M H_2SO_4. The configuration of the resulting 2-phenylpropionic acid (yield 88%; $[\alpha]_D^{25}$ -54.8° (c 1.6, $CHCl_3$) o.p. 72%) was the (R) configuration; K. S. Lau, R. W. Fries, J. K. Still, J. Am. Chem. Soc., 96, 4983 (1974); S. P. Bakshi and E. E. Turner, J. Chem. Soc., 1961, 171.

3) Large excess amounts of butyllithium were used to exclude insufficient deprotonation from 1a and 1b.

4) A. I. Meyers, E, S. Snyder, and J. J. H. Ackerman, J. Am. Chem. Soc., 100, 8186 (1978).

5) To assure quantitative conditions, the spin-lattice relaxation time (T_1) determination was performed for the β methyl carbon in 2a and 2b at -78 °C using the standard inversion recovery techniques. The relaxation times of the β methyl carbon for both 2a and 2b were almost identical and equal to 0.25 s. The ^{13}C NMR measurement was carried out using gated decoupling to suppress the Overhauser effect (NOE) (a delay time $(\tau) > 5T_1$).

6) Assingment of the steleochemisty of the lithio oxazolines (2$_{\mathrm{major}}$ and 2$_{\mathrm{minor}}$) is difficult to make from the data at hand.

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