Solid State Kinetic Resolution of β-Ionone Epoxide and Dialkyl Sulphoxides in the Presence of Optically Active Host Compounds. The First Enantioselective Host–Guest Inclusion Complexation in the Solid State

Fumio Toda,* Koji Mori, Yoshitaka Matsuura and Hiroshi Akai

Department of Industrial Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790, Japan

Kinetic resolution of β-ionone epoxide and some dialkyl sulphoxides is achieved in the solid state in the presence of an optically active host compound, and is confirmed to proceed *via* a combination process of enantioselective inclusion complexation and selective oxidation in the solid state; enantioselective complexation in the solid state is also observed for oximes.

In the expectation of enantioselective epoxidation of β-ionone **2** to the optically active 4-(1,2-epoxy-2,6,6-trimethylcyclohexyl)but-3-en-2-one **4** with *m*-chloroperbenzoic acid (MCPBA) in a 1 : 1 inclusion complex **3**[1] with the optically active host, (−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[5.4]decane **1**,[2] the complex **3** was treated with MCPBA in the solid state. Although only the racemic **4** (**4a**) was produced when an equimolar amount of MCPBA was used (reaction 1), (+)-**4** (**4b**) was obtained together with (−)-**5** (**5c**) in the yields shown in Table 1 when two or three molar amounts of MCPBA are used (reactions 2 and 3).[3] However, only the racemic **5** (**5a**) was produced when four molar amounts of MCPBA are used (reaction 4). The data in Table 1 show that the epoxidation of β-ionone **2** in the complex **3** occurs non-enantioselectively (reaction 1); however, the Baeyer–Villiger oxidation of the β-ionone oxide **4** to ester **5** occurs enantioselectively (reactions 2 and 3). Nevertheless, the enantioselectivity of the Baeyer–Villiger reaction disappear when the reaction is complete (reaction 4).[4]

These results can be interpreted by an enantioselective inclusion complexation in the solid state between the initially formed **4a** and **1**, namely, **1** includes **4b** selectively in the solid state to form the 1 : 1 complex of **1** and **4b**, and the remaining non-complexed **4c** is oxidized further to **5c** with MCPBA. As the oxidation of the **4c** proceeds further, the optical purity of **4b** increases (reaction 3). However, only the racemic product **5a** is formed when the Baeyer–Villiger reaction is completed (reaction 4). It is reasonable since the initially formed epoxidation product is a racemic one, **4a** (reaction 1), and its complete oxidation should give the racemic Baeyer–Villiger reaction product **5a** (reaction 4).

Although host–guest complexation in the solid state has been established to proceed efficiently in a short time,[3] no enantioselective complexation in the solid state has yet been

Table 1 Oxidation of **2** in **3** with MCPBA in the solid state[a]

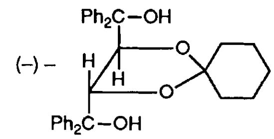
		Product			
	Molar equivalent of	4		5	
Reaction	MCPBA to **2**	Yield (%)[b]	E.e. (%)[c]	Yield (%)[b]	E.e. (%)[c]
1	1	73	0[d]	0	—
2	2	43	66[e]	33	72[f]
3	3	29	88[e]	55	36[f]
4	4	0	—	88	0[g]

[a] Reactions were carried out by keeping the mixture at room temperature for 2 days. [b] All yields were determined by ^{1}H NMR spectroscopy. [c] All optical purities were determined by measuring the ^{1}H NMR spectra in $CDCl_3$ in the presence of chiral shift reagent, $Eu(hfc)_3$.† [d] Product is **4a**. [e] Product is **4b**. [f] Product is **5c**. [g] Product is **5a**.

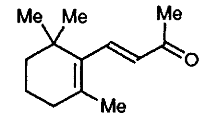
Table 2 Solid state kinetic resolution of **6** by selective oxidation with MCPBA in the presence of **8**[a]

	Product		
Sulphoxide	Yield (%)[b]	$[\alpha]_D/°$ (c 0.15, EtOH)	e.e. (%)[c]
rac-**6a**	(+)-**6a** 38	+44.2	37
rac-**6b**	(+)-**6b** 51	+51.6	42.7
rac-**6c**	(+)-**6c** 40	+25.6	25
rac-**6d**	(+)-**6d** 7	+69	100

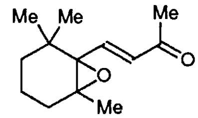
[a] Reactions were carried out by keeping the mixture for 2 days at room temperature. [b] Isolated yield. [c] All optical purities were determined by measuring the ^{1}H NMR spectra in $CDCl_3$ in the presence of chiral shift reagent, (−)-2,2′-dihydroxy-1,1′-binaphthyl[9].



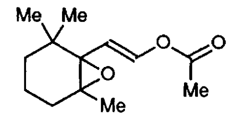
1



2

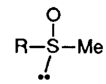


4

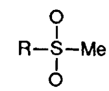


5

a: racemic
b: (+) -form
c: (−) -form

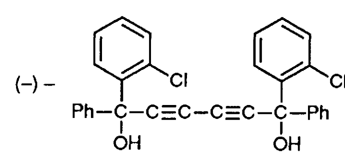


6



7

a: R = n-Pent
b: R = n-Hex
c: R = n-Hep
d: R = n-Oct



8

known. The enantioselective complexation in the solid state was proven by the following experiment. A mixture of finely powdered **1** (1.2 g, 4.8 mmol) and **4a** (1.2 g, 2.4 mmol) was kept at room temperature for 1 day and then washed with hexane to give a complex of **1** and **4b** (1.3 g) as crystals and hexane solution. From the complex, **4b** of 88% enantiomeric excess (e.e.)[5]† (0.29 g, 24%) was obtained by distillation *in vacuo*. From the hexane solution, **4c** of 36% e.e. (0.6 g, 50%) was obtained.

From the data shown in Table 1, it is also clear that the Baeyer–Villiger oxidation of **4** to **5** proceeds more slowly in the complex **3** than does the oxidation of **4** alone. Namely, although **4b** which is included in the complex **3** is not oxidized, **4c** which is not included is oxidized into **5c** (reactions 2 and 3 in Table 1).‡ It has also been established that the Baeyer–Villiger oxidation proceeds much faster in the solid state than in solution.[6]

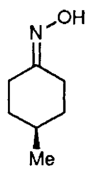
Interestingly, the enantioselective oxidation of β-ionone **2** in the complex **3** into the optically active β-ionone oxide **4b** in the solid state occurred efficiently in the presence of a small amount of water. For example, keeping a mixture of finely powdered **3** (1.7 g), MCPBA (1.24 g), and water (5 ml) at room temperature for 3 days gave **4b** of 54% e.e. (0.41 g, 81%). This is really due to an enantioselective oxidation of β-ionone **2** in the complex **3**. This dramatic change is probably not due to a solubility effect, since the solubility of MCPBA in water is very low,[7] and since the enantioselective epoxidation did not occur in the presence of hexane instead of water, although the solubility of MCPBA in hexane is about ten times more than that in water.[7]

Similar solid state kinetic resolution of dialkyl sulphoxides **6a–d** was achieved by their selective oxidation to dialkyl sulphones **7a–d** with MCPBA in the presence of (−)-1,6-di(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol **8**.[8] For example, a mixture of sulphoxide **6a** (1 g) and **8** (1.8 g) was kept at room temperature for 1 day, and then mixed with MCPBA (0.64 g) and kept for a further 1 day. From the reaction mixture, (+)-**6a** of 37% e.e. (0.38 g, 38%) was obtained. In a similar way, **6b–d** were also kinetically resolved (Table 2).[9] On mixing **6** and **8**, (+)-**6** is enantioselectively included and the non-complexed (−)-**6** is oxidized to **7** by further mixing with MCPBA. In this case, magnesium monoperoxyphthalate (MMPP) can be used instead of MCPBA. For example, treatment of **6c** and **6d** with the host **8** and then with MMPP and a small amount of water in the solid state gave (+)-**7c** of 55.8% e.e. and (+)-**7d** of 100% e.e. in 65 and 50% yields, respectively.

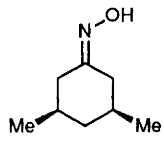
Much more efficient enantioselective inclusion in the solid state was observed for oximes **9**, **10**. A mixture of the host **8** and *rac*-oxime **9** was irradiated with ultrasound (28 kHz) for 8 h, and the reaction mixture was washed with light petroleum to leave an insoluble 1 : 1 complex of **8** and (+)-**9** in 94.9% yield, which upon treatment with H_2SO_4 in the solid state according to the reported method[10] gave the Beckmann

† All the optical purities were determined by measuring the ^{1}H NMR spectra in the presence of the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), $Eu(hfc)_3$ (99+ %) in $CDCl_3$.

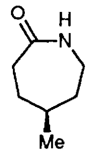
‡ Optically active **5** has not been reported so far.



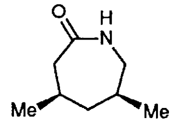
9



10



11



12

rearranged product (+)-**11** of 79.4% e.e. in 68% yield. Therefore, the optical purity of the (+)-**9** in the complex with the host **8** should be higher than 79.4% e.e. By a similar method, inclusion complex of the host **8** and (+)-**10** of more than 68.9% e.e. was obtained in 96% yield, which upon treatment with H_2SO_4 gave (−)-**12** of 68.9% e.e. in 64.2% yield.

We thank the Ministry of Education, Science and Culture, Japan, for a Grant-in-Aid for Scientific Research on Priority Areas, No. 01628004.

Received, 12th July 1990; Com. 0/03148H

References

1 F. Toda, K. Tanaka and T. Fujiwara, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 662.

2 F. Toda, A. Satō, K. Tanaka and T. C. W. Mak, *Chem. Lett.*, 1989, 873; D. Seebach, A. K. Back, R. Imwinkelried, A. Roggo and A. Wonnacott, *Helv. Chim. Acta*, 1987, **70**, 954.

3 F. Toda, K. Tanaka and A. Sekikawa, *J. Chem. Soc., Chem. Commun.*, 1987, 279.

4 It is well established that the epoxidation of **2** occurs much faster than does the Baeyer–Villiger reaction. J. A. Findlay and W. D. Mackay, *Can. J. Chem.*, 1971, **49**, 2369; S. Isoe, S. B. Hyeon, H. Ichikawa, S. Katsumura and T. Sakan, *Tetrahedron Lett.*, 1968, 5561.

5 Optically pure **4b** and **4c** have been prepared first by a dehydration of optically active 1,2-*cis*-dihydroxy derivative of **2**, and the absolute configuration of **4b** and **4c** has been determined to be (5*S*, 6*R*) and (5*R*, 6*S*), respectively. M. Acemoglu, W. Eschenmoser and H. C. Eugster, *Helv. Chim. Acta*, 1981, **64**, 2691.

6 F. Toda, M. Yagi and K. Kiyoshige, *J. Chem. Soc., Chem. Commun.*, 1988, 958.

7 *Reagents for Organic Synthesis*, eds. L. F. Fieser and M. Fieser, Wiley, New York, 1967, vol. 1, p. 135.

8 F. Toda, K. Tanaka, T. Omata, K. Nakamura and T. Ōshima, *J. Am. Chem. Soc.*, 1983, **105**, 5151.

9 All the optical purities of **6** were determined by measuring the ^1H NMR spectra in the presence of the chiral shift reagent, (−)-2,2′-dihydroxy-1,1′-binaphthyl according to the reported procedure. F. Toda, K. Mori, J. Okada, M. Node, A. Itoh, K. Oomine and K. Fuji, *Chem. Lett.*, 1988, 131.

10 F. Toda and H. Akai, *J. Org. Chem.*, 1990, **55**, 4973. Since the optically active oximes [(+)-**9** and (+)-**10**] easily racemize in non-complexed form, their optical purity was determined for the Beckmann rearranged products, (+)-**11** and (−)-**12**, respectively.