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Kinetic Resolution of Sulfoxides Catalyzed by Chiral Titanium–Binaphthol Complex

Naoki Komatsu, Masaya Hashizume, Toshio Sugita, and Sakae Uemura*

Division of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-01, Japan

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The highly stereoselective synthesis of chiral sulfoxides are of great interest because they are useful chiral synthons.[1] Chiral sulfoxides of high enantiomeric excess have been prepared mainly by (1) the optical resolution of diastereomeric sulfinates[2] or their analogues[3] followed by the reaction with organometallic reagent (Andersen-type synthesis) and (2) the direct asymmetric oxidation of prochiral sulfides to sulfoxides by means of modified Sharpless oxidant (Kagan oxidant),[4] Davis oxidants,[5] and our oxidation system using a titanium–binaphthol catalyst.[6] Although several examples[7] have been reported, kinetic resolutions have not been effective for obtaining sulfoxides of high ee. During the continuation of our studies on the asymmetric oxidation of sulfides to sulfoxides,[6] we found that kinetic resolution of racemic sulfoxides could be catalyzed by a chiral titanium–binaphthol complex to give the optically pure sulfoxides in moderate chemical yields under very mild conditions. The procedure reported herein seems to present the most facile and convenient method to obtain optically pure sulfoxides (Scheme I).

Scheme I

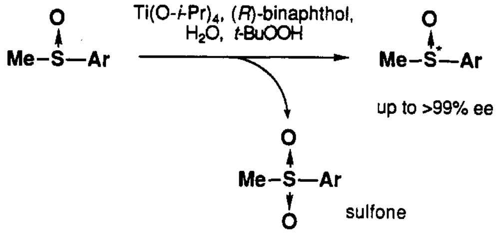

Table I. Catalytic Kinetic Resolution of Racemic Aryl Methyl Sulfoxides[a]

run	Ar	solvent	reactn condns temp (°C)/ time (h)	yield[b] (%)	ee[c] (confign) (%)
1	*p*-tolyl	CCl_4	25/8	24	>99 (*R*)
2[d]	*p*-tolyl	CCl_4	0/47	33	92 (*R*)
3[d]	*p*-tolyl	CCl_4	−20/72	53	21 (*R*)
4	*p*-tolyl	CH_2Cl_2	25/8	23	85 (*R*)
5	*p*-tolyl	toluene	25/8	31	97 (*R*)
6	*p*-tolyl	ether	25/9	32	3 (*R*)
7	*p*-tolyl	THF	25/9	26	2 (*R*)
8	*p*-BrC_6H_4	CCl_4	25/10	26	>99 (*R*)
9	Ph	CCl_4	25/6	26	>99 (*R*)
10	*p*-$NO_2C_6H_4$	CCl_4	25/8	9	13

[a] Sulfoxide/(*R*)-(+)-binaphthol/Ti(O-*i*-Pr)$_4$/H_2O/70% aqueous TBHP = 1.0/0.10/0.050/1.0/1.0 under aerial conditions unless otherwise noted. [b] Isolated yield of a chiral sulfoxide based on the racemic sulfoxide. [c] Determined by HPLC on a Daicel Chiralcel OB column. [d] Sulfoxide/(*R*)-(+)-binaphthol/Ti(O-*i*-Pr)$_4$/H_2O/70% aqueous TBHP = 1.0/0.20/0.10/2.0/1.0.

Kinetic Resolution of Sulfoxides. The following catalytic system and reaction conditions were employed unless otherwise noted: (*R*)-(+)-binaphthol/Ti(O-*i*-Pr)$_4$/H_2O = 0.10/0.050/1.0 mol equiv relative to the racemic sulfoxide; 1.0 mol equiv of commercial 70% aqueous *tert*-butyl hydroperoxide (TBHP) as an oxidant; 25 °C under aerial conditions. After being stirred for 6–10 h at 25 °C, the chiral sulfoxide was easily isolated by submitting the reaction mixture directly to short column chromatography on silica gel with diethyl ether as eluent. The ee value of the sulfoxide was determined by HPLC on a Daicel Chiralcel OB column, and its configuration was determined by optical rotation.

Typical results together with their reaction conditions are summarized in Table I. Optically pure sulfoxides were obtained in moderate yields under optimum conditions (runs 1, 8, and 9) except for *p*-nitrophenyl methyl sulfoxide (run 10). As far as the reaction temperature is concerned (runs 1–3), the best result was obtained at 25 °C (>99% ee, run 1). Since the stereoselectivities in kinetic resolution[8] are generally highly dependent on the conversion of the reactant, the lower ee's in runs 2 and 3 are probably due to lower reaction rates. The nature of the solvent also had a remarkable effect upon the stereochemical outcomes (runs 1 and 4–7 of Table I). The use of dichloromethane and nonpolar solvents such as carbon tetrachloride and toluene afforded high ee's (runs 1, 4, and 5), while the resolution failed in ethereal solvents such as diethyl ether and tetrahydrofuran (THF). These observed solvent effects of dichloromethane and ether solvents were in sharp contrast to those in asymmetric oxidations of sulfides to sulfoxides[6] in spite of employing the same catalytic system; nonpolar solvents were favorable in both cases.

The time course of the ee value and the concentration of a sulfoxide is shown in Figure 1 in the case of run 1 of Table I. Figure 2 illustrates the change of the concentration of (*R*)- or (*S*)-sulfoxide calculated from the ee values

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(1) For recent reviews on the synthesis and application of chiral sulfoxides, see: (a) Andersen, K. K. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons, Ltd.: Chichester, England, 1988; Chapter 3, pp 55–94. (b) Solladie, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press.: Oxford, England, 1991; Chapter 1.5, Vol. 6, pp 133–170. (c) Posner, G. H. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons, Ltd.: Chichester, England, 1988; Chapter 16, pp 823–849. (d) Kagan, H. B.; Rebiere, F. *Synlett* **1990**, 643. (e) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72.

(2) (a) Andersen, K. K. *Tetrahedron Lett.* **1962**, *93*. (b) Andersen, K. K.; Gaffield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637. (c) Ferández, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789.

(3) (a) Rebiere, F.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 3659. (b) Rebiere, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991. (c) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977.

(4) (a) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Org. Synth.* **1989**, *68*, 49. (b) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135. (c) Kagan, H. B.; Duñach, E.; Nemecck, C.; Pitchen, P.; Samuel, O.; Zhao, S. H. *Pure Appl. Chem.* **1985**, *57*, 1911. (d) Duñach, E.; Kagan, H. B. *Nouv. J. Chim.* **1985**, *9*, 1. (e) Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188. (f) Pitchen, P.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 1049.

(5) (a) Davis, F. A.; Reddy, R. T.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428. (b) Davis, F. A.; Reddy, R. T.; Weismiller, M. C. *J. Am. Chem. Soc.* **1989**, *111*, 5964.

(6) (a) Komatsu, N.; Nishibayashi, Y.; Sugita, T.; Uemura, S. *Tetrahedron Lett.* **1992**, *33*, 5391. (b) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529.

(7) (a) Toda, F.; Mori, K.; Matsuura, Y.; Akai, H. *J. Chem. Soc., Chem. Commun.* **1990**, 1591. (b) Davis, F. A.; Billmers, J. M. *J. Org. Chem.* **1983**, *48*, 2672. (c) Sharpless, K. B.; Behres, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure. Appl. Chem.* **1983**, *55*, 589. (d) Annunziata, R.; Borgogno, G.; Montanari, F.; Quici, S. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 113.

(8) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

0022-3263/93/1958-7624$04.00/0

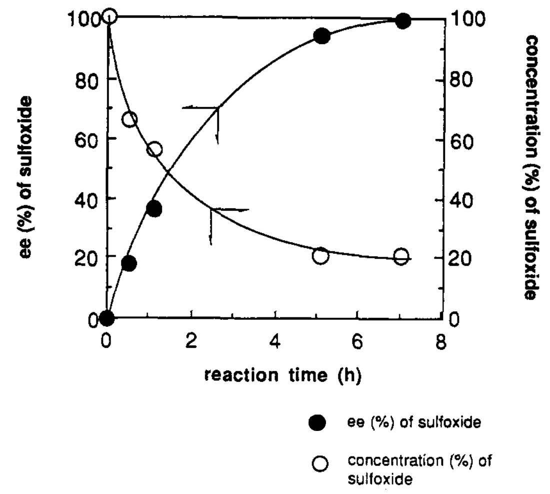

Figure 1. Time course of the ee (%) and the concentration (%) of methyl *p*-tolyl sulfoxide in run 1 of Table I.

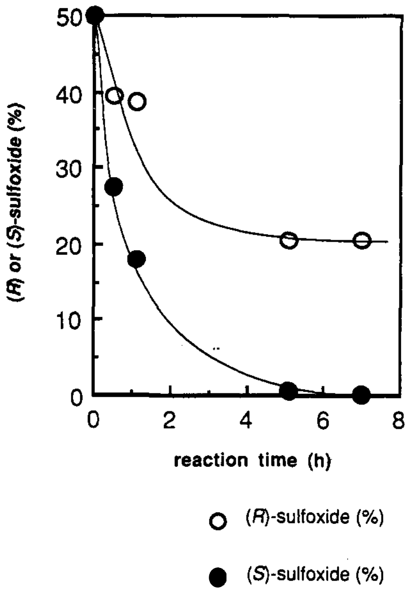

Figure 2. Time course of the concentration (%) of (*R*)- or (*S*)-methyl *p*-tolyl sulfoxide in run 1 of Table I.

and the concentrations of the sulfoxide. From these figures, it is clear that the chiral titanium–binaphthol complex recognizes (*R*)- and (*S*)-sulfoxides and catalyzes predominantly the oxidation of (*S*)-sulfoxide. The pseudo-first-order rate constants of (*R*)- and (*S*)-sulfoxides to the sulfone, k_R and k_S, were determined from the initial slope in the logarithm of the concentration of the corresponding sulfoxides *vs* reaction time. In this case the ratio of the two rate constants, k_S/k_R, was 2.6.

The Effect of Water. We have shown that the presence of water was necessary in the preparation step of the titanium–binaphthol catalyst to obtain high ee of sulfoxides in the catalytic asymmetric oxidation of sulfides to sulfoxides.[6] We have used similar procedures for this kinetic resolution of sulfoxides. Further investigation on the effect of added water, however, revealed that water was not necessarily needed at the preparation step of the catalyst (1 h duration before addition of the sulfoxide and TBHP; see Experimental Section) in this oxidation using an aqueous TBHP, an almost 100% ee of the sulfoxide being obtained without the added water. We also confirmed separately that completely anhydrous conditions by the use of TBHP toluene solution instead of aqueous TBHP afforded the sulfoxide with a very poor ee (<13%). These facts indicate that water was required at the oxidation step and not at the preparation step of the catalyst.

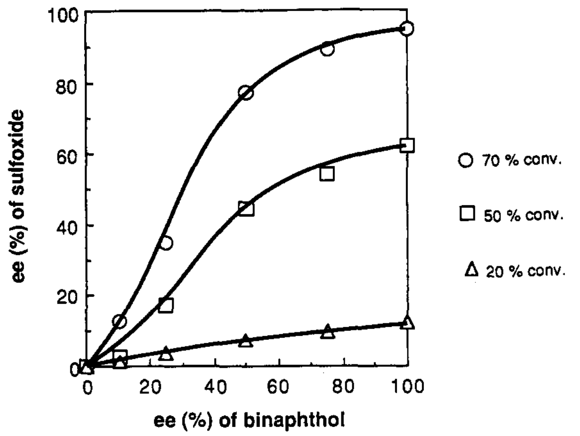

Figure 3. Plots of the ee (%) of methyl *p*-tolyl sulfoxide *vs* the ee (%) of binaphthol at various conversion.

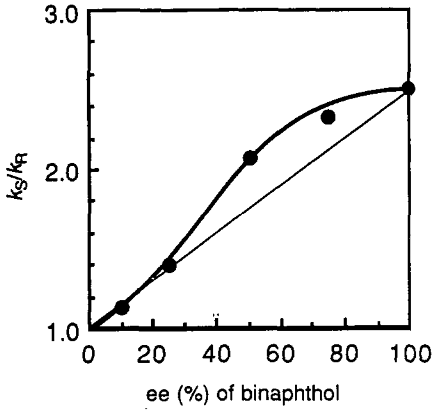

Figure 4. Amplified property of chiral recognition of the binaphthol–titanium catalytic system in the kinetic resolution of methyl *p*-tolyl sulfoxide.

On the other hand, the addition of much water at the preparation step of the catalyst slowed the resolution rate; thus, in the cases of addition of 2.0 and 4.0 mol equiv of water to the starting sulfoxide, 94% and 81% ee's were obtained, respectively, for 8 h's oxidation with an aqueous TBHP. However, when the reaction mixture was stirred for a further 2 h (total reaction time, 10 h), >99% ee was obtained without any decrease in the chemical yield. This fact shows that the addition of more than 2.0 mol equiv of water at the preparation step of the catalyst only slows the resolution rate, but it does not give any effect on the chiral recognition property of the catalyst.

Positive Nonlinear Effect of Chiral Recognition Properties. Figure 3 illustrates the correlation between the ee of sulfoxide and the ee of binaphthol at various conversions. Although the effect is very small at the beginning of this resolution (for example, 20% conversion), the apparent positive nonlinear effect was shown in chiral recognition of this catalytic system at 50 and 70% conversion. The correlation between the ee of binaphthol and the k_S/k_R ratio is shown in Figure 4 which also confirmed an amplified property in this oxidation.

Experimental Section

General Procedures. HPLC analyses were performed on a HLC-803A instrument (Tosoh) with UV-8011 detector (Tosoh) using 25% 2-propanol/hexane as an eluent at 40 °C. GLC analyses were performed on a Shimadzu GC-14A (3-mm × 2-m glass column packed with 10% Silicone SE-30 on Chromosorb W or 5% Silicone OV-17 on Chromosorb W) with flame-ionization detector and N_2 as carrier gas. Optical rotations were measured on a JASCO DIP-360 polarimeter.

Materials. Carbon tetrachloride and toluene were distilled from $CaCl_2$ and stored over molecular sieves 4A under nitrogen. Diethyl ether and tetrahydrofuran (THF) were distilled from $LiAlH_4$ and stored similarly. Commercially available 70% aqueous TBHP and $Ti(O\text{-}i\text{-}Pr)_4$ were used without any purification. (*R*)-(+)-1,1′-Binaphthol was purchased from Wako Pure Chemical Ind. Ltd. and used without further purification. The racemic sulfoxides were prepared according to the reported method.[9]

Typical Experimental Procedure for the Kinetic Resolution of Sulfoxides. To a CCl_4 (2 mL) solution of binaphthol (0.050 mmol) were introduced $Ti(O\text{-}i\text{-}Pr)_4$ (0.025 mmol) and H_2O (0.50 mmol) using a syringe under ambient atmosphere at room temperature. After the resulting brown solution was stirred magnetically at the same temperature for 1 h, the sulfoxide (0.50 mmol) was introduced using a syringe at 25 °C. After 0.5 h, 70% aqueous TBHP (0.50 mmol) was introduced using a syringe, and the mixture was stirred for 6–10 h. The reaction mixture was directly submitted to column chromatography with Wakogel C-200 silica gel (eluent: diethyl ether) to afford the solid chiral sulfoxide (sulfone was eluted first). When the obtained sulfoxide showed a pale yellow color, it was purified further by flash column chromatography. The ee and the configuration of the recovered sulfoxides were determined by HPLC using Daicel Chiralcel OB column and by the optical rotation, respectively.

For the experiment of eight times scale using 4.0 mmol (618.8 mg) of racemic methyl *p*-tolyl sulfoxide at 25 °C for 8 h, the corresponding optically pure sulfoxide (>99%) was isolated in 21.1% yield (0.842 mmol, 129.9 mg).

Monitoring of the Resolution on GLC and HPLC. An aliquot of the reaction mixture taken out by a microsyringe was submitted to TLC (Kieselgel 60 F_{254}), and the band of the sulfoxide was extracted with CH_2Cl_2. The solution was analyzed by HPLC to determine the ee of the sulfoxide. Another aliquot of the reaction mixture was analyzed by GLC to determine the concentrations of the sulfoxide and the sulfone.

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[9] Balicki, R.; Kaczmarek, L.; Nantka-Namirski, P. *Liebigs Ann. Chem.* 1992, 883.

Additions and Corrections

Vol. 55, 1990

Yoshinori Yamamoto* and Naoki Asao. Copper Azide as a New Reagent for Syn-S_N2 Displacement of γ-Sulfonyloxy α,β-Unsaturated Esters.

Page 5304, column 1, line 11. Phosphonate should read phosphate. We thank Professor Bruce H. Lipshutz for bringing this error to our attention.

Vol. 57, 1992

Michele Decouzon, Otto Exner, Jean-François Gal,* and Pierre-Charles Maria. The Gas-Phase Basicity of Hydroxamic Acid Derivatives.

Page 1622, column 1, Table I, entry 7. The experimental ΔG for $CH_3CONHCH_3$ (entry 7) relative to cyclopropylamine should read ≈ -2.2 kcal mol^{-1} (instead of -0.22 kcal mol^{-1}). The GB value for entry 7 remains unchanged.

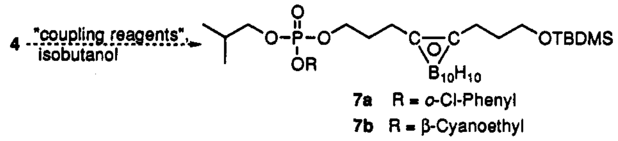
Vol. 58, 1993

George R. Newkome,* Xiaofeng Lin, Chen Yaxiong, and Gregory H. Escamilla. Two-Directional Cascade Polymer Synthesis: Effects of Core Variation.

Page 3125, ref 22. The versions of QUANTA and CHARMm used were inadvertently omitted from the paper. The calculated values reported were obtained using QUANTA version 3.2 and CHARMm version 21.4.

Robert R. Kane, Christine S. Lee, Karin Drechsel, and M. Frederick Hawthorne*. Solution-Phase Synthesis of Boron-Rich Phosphates.

Page 3228. Corrected Scheme IV.



Yumin Liu and Jeffrey Schwartz*. The Species Prepared from Sodium Borohydride and *N,N*-Dimethylformamide Reduces or Dimethylaminates Organic Halides.

Page 5006. Corrected Scheme II.