

# Titanium-Catalyzed Tandem Sulfoxidation-Kinetic Resolution Process: A Convenient Method for Higher Enantioselectivities and Yields of Chiral Sulfoxide

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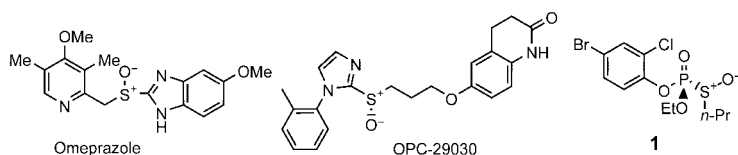
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Dedicated to Joe P. Richmond on the occasion of his 60<sup>th</sup> birthday.

**Abstract:** A one-pot, titanium-catalyzed tandem sulfoxidation-kinetic resolution process, which combines asymmetric oxidation (at lower temperature) and kinetic resolution (at room temperature), has been developed. Excellent ees (up to >99.9%) and higher chemical yields of sulfoxides were obtained and the results compared favorable with those from either oxidation or kinetic resolution.

**Keywords:** asymmetric oxidation; homogeneous catalysis; kinetic resolution; sulfoxides; tandem process; titanium

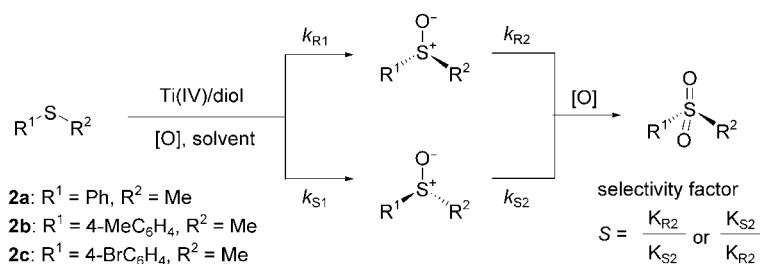
Many chiral sulfoxides exhibit interesting biological activities and show promise as therapeutic agents.<sup>[1–4]</sup> For example, omeprazole and some of its derivatives are used as proton-pump inhibitors to treat acid-related diseases,<sup>[2]</sup> OPC-29030 is used as a platelet adhesion inhibitor,<sup>[3]</sup> and compound **1** derived *in vivo* from the corresponding phosphorothiolate is believed to be responsible for the inhibitory action of acetylcholine esterase.<sup>[4]</sup>



In addition, optically active sulfoxides are valuable chiral auxiliaries and intermediates in contemporary organic synthesis.<sup>[5,6]</sup> Consequently, the development of methodologies to synthesize enantiopure sulfoxides has become an important pursuit in chemical research.

Recently, it has been shown that nucleophilic displacement of diastereomeric sulfonates, *via* dynamic kinetic resolution using DAGOH technology,<sup>[7]</sup> or stereochemically differentiating oxathiazolidine-2-oxide<sup>[8]</sup> with organometallic reagents provides highly enantiopure sulfoxides. Chiral oxaziridine derivatives with a camphor skeleton have also been used as chiral oxidants to afford sulfoxides in up to 96% ee.<sup>[9]</sup> However, stoichiometric chiral auxiliaries and reagents are required in these reactions. Based on transition metal-promoted sulfoxidation, Kagan et al. reported a modified Sharpless procedure in which the sulfides were oxidized by *tert*-butyl hydroperoxides. Again, it was necessary to use stoichiometric diethyl tartrate (DET) and titanium to attain very high ee values.<sup>[10]</sup>

A great variety of transition metals and enzymes has been tested for catalytic asymmetric sulfoxidation, but the enantioselectivities usually ranged from low to moderate.<sup>[11]</sup> Of particular relevance here is the Ti(IV)/diol-catalyzed process. Uemura and co-workers reported moderate ees with good yields at low temperature (at 0 °C or lower) by using a titanium complex prepared *in situ* from titanium tetraisopropoxide, chiral binaphthol and various amounts of water.<sup>[12,13]</sup> High enantiomeric excesses (up to 96%) were achieved at 25 °C with CCl<sub>4</sub> as solvent, but the chemical yields were very low (28% for PhSCH<sub>3</sub> and 44% for *p*-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SCH<sub>3</sub>). Similarly, Ti(IV)/H<sub>2</sub>O/(*R,R*)-diphenylethane-1,2-diol complexes<sup>[14,15]</sup> afforded 70–80% ees and 60–73% yields for aryl alkyl sulfides whilst the titanium(IV) complexes of (*R,R*)-DET<sup>[16]</sup> and (*R,R*)-di-*tert*-butylethane-1,2-diol<sup>[17]</sup> gave only modest yield and/or enantioselectivity. In these reactions, an accompanying kinetic resolution of the sulfoxide enantiomers leading to the formation of the sulfone had inevitably been the bane for obtaining good yields (Figure 1). However, the kinetic resolution of racemic sulfoxides alone with the Ti(IV)/BINOL/H<sub>2</sub>O



**Figure 1.** A schematic diagram showing the successive pathways of the Ti(IV)/diol-catalyzed oxidation of sulfides.

**Table 1.** Ti(IV)/BINOL-catalyzed oxidation of thioanisole: reaction time study.<sup>[a]</sup>

Entry	Time [h]	Sulfoxide		Sulfide Yield [%]	Sulfone Yield [%]
		Yield [%] <sup>[b]</sup>	ee [%] <sup>[c, d]</sup>		
1	3	38	47	57	–
2	6	77	53	20	3
3	9	85	63	–	15
4	10	83	67	–	17
5	12	80	71	–	20
6	15	76	75	–	24

<sup>[a]</sup> Reaction conditions: PhCH<sub>3</sub>, sulfide/(*S*)-BINOL/Ti(*O*-*i*-Pr)<sub>4</sub>/H<sub>2</sub>O/TBHP (decane solution of TBHP was used) = 1.0:0.2:0.1:0.2:2.0, 0 °C, N<sub>2</sub>.

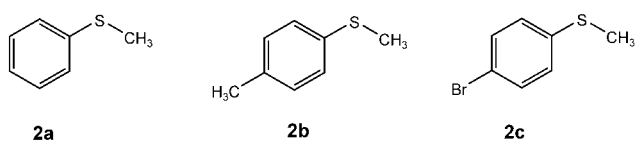
<sup>[b]</sup> Yields of isolated products.

<sup>[c]</sup> Determined by HPLC analysis on a Daicel Chiralcel OB column.

<sup>[d]</sup> All in the *S* configuration.

system has been shown to be an effective method for the preparation of enantiomerically pure sulfoxides,<sup>[12]</sup> albeit with low isolated yields.

In our continued study of the Ti(IV)/BINOL-catalyzed reactions,<sup>[18]</sup> we envisaged that, by harnessing the different rates of the *in situ* conversion of the individual enantiomeric sulfoxides to the sulfone under the reaction conditions, acceptable yields and a high enantioselectivity of the former might be achieved. In this paper we report the excellent results obtained by using a one-pot method involving sequentially different reaction conditions.



Thioanisole (**2a**; PhSCH<sub>3</sub>) was first chosen as a model substrate for the study of the relationship between the conversion of sulfide and the enantioselectivity of the sulfoxide thus formed (Table 1). After a number of initial experiments, we found that the system worked best when the ratio of sulfide/(*S*)-BINOL/Ti(*O*-*i*-Pr)<sub>4</sub>/H<sub>2</sub>O/*t*-BuOOH (TBHP) was 1.0:0.2:0.1:0.2:2.0 in toluene, and this combination was maintained throughout this study. Our system is slightly different from the opti-

mized conditions of Uemura et al.; we use a decane solution of TBHP as the oxidation agent in order to control the amount of water exactly and we found that the 1:1 ratio of BINOL to water gives better results in our experiment. When the reaction was carried out at 0 °C for 3 h, a 38% yield of sulfoxides with 47% ee was obtained and 57% substrate was recovered (entry 1). The formation of sulfone took place even before full conversion of the starting sulfide. Thus, after 6 h both the ee value and the chemical yield of the sulfoxide were higher and 3% sulfone and 20% sulfide were recovered (entry 2). The sulfide was converted completely in approximately 9 h with moderate enantiomeric excess and good yield of the sulfoxide (entry 3). Even higher ee values could be obtained if the reaction time was further increased but at the expense of yield (entries 4 to 6).

We next investigated the effect of temperature on the kinetic resolution of racemic phenyl methyl sulfoxide. Table 2 lists the results of this kinetic study with the (*S*)-BINOL/Ti(*O*-*i*-Pr)<sub>4</sub>/H<sub>2</sub>O/*t*-BuOOH system (Table 2). The reaction was very slow at –20 to –10 °C and gave low enantioselectivities (entries 1 and 2). At 0 °C, the reaction was still quite slow. When the reaction temperature was further increased, both the ee value and the reaction rate were enhanced, but the yield of the sulfoxide dropped correspondingly (entries 4 and 5). At 25 °C and after 8 h of reaction, the selectivity factor *S*, a measure of the effectiveness of a kinetic resolution process under a particular set of conditions,<sup>[19]</sup>

reached 7.49, one of the highest achieved for this reaction.

Having found the optimal time for a trade-off between sulfoxide yield and enantioselectivity (Table 1, entry 4) and the temperature at which the kinetic resolution of the sulfoxide was most efficient (Table 2, entry 6), we then combined the procedures in a one-pot reaction. The reaction mixture was first stirred at 0 °C for 10 h in toluene, followed by stirring at 25 °C for a designated period to allow for a faster kinetic resolution. As indicated in Table 3, the ee of the product from **2a** was improved from 67% to 75% and the chemical yield decreased marginally from 83% to 80% (entries 1 vs. 2) after 0.25 h of

resolution. After 2 h at 25 °C, the enantioselectivity increased to > 99.9% ee with 62% yield (Table 3, entry 5). Although the yield declined with increasing time for kinetic resolution, to the best of our knowledge, the yield was still twice as high as the best yield recorded for a metal-catalyzed sulfoxidation with this level of enantioselectivity for this substrate. The product from substrate **2b** was also separated in > 99.9% enantiopurity with 65% yield (2.7 times better than the best reported) after 3 h of resolution (entry 7), and the product from **2c** in 96% ee with 58% yield after 4 h (entry 10).

Another BINOL derivative, (*S*)-6,6'-dibromo-BINOL, was also tested for the asymmetric oxidation of thioanisole (**2a**), by adopting the above reaction conditions. Generally lower enantioselectivities were obtained. However, the rate of the asymmetric oxidation was much faster in this case. For instance, only 3 h at 0 °C were sufficient to accomplish a satisfying conversion of the sulfide to the sulfoxide, in spite of a much inferior ee detected (Table 3, entry 11), indicating the requirement of a different set of optimized conditions. As the reaction time was prolonged at the same reaction temperature, the ee only improved moderately whilst a reduction of chemical yield was observed (entries 11–13). Obviously, the kinetic resolution was not very efficient at 0 °C. The best ee (*ca.* > 99.9, entry 14) was obtained when the reaction was carried out at 0 °C for 3 h and then at 25 °C for 1.5 h.

In conclusion, a practical and convenient method for achieving high enantioselectivities while improving the chemical yields in the oxidation of sulfides to sulfoxides has been demonstrated using a Ti(IV)/BINOL system

**Table 2.** Determination of the optional temperature for the kinetic resolution of racemic phenyl methyl sulfoxides using (*S*)-BINOL/Ti(O-*i*-Pr)<sub>4</sub>/H<sub>2</sub>O/*t*-BuOOH in toluene.<sup>[a]</sup>

Entry	Temp. [°C]	Time [h]	Yield [%] <sup>[b]</sup>	Ee [%] <sup>[c]</sup>	<i>S</i> <sup>[d]</sup>
1	−20	72	56	21	2.10
2	−10	72	40	52	3.32
3	0	8	67	31	5.91
4	10	8	46	66	6.88
5	25	8	29	95	7.49

<sup>[a]</sup> Reaction conditions: PhCH<sub>3</sub>, (±)-sulfoxides/(*S*)-BINOL/Ti(O-*i*-Pr)<sub>4</sub>/H<sub>2</sub>O/TBHP (decane solution) = 1.0:0.2:0.1:0.2:2.0, N<sub>2</sub>.

<sup>[b]</sup> Isolated yield of the unreacted sulfoxide.

<sup>[c]</sup> Determined by HPLC analysis on a Daicel Chiralcel OB column and all products are in *S* configuration.

<sup>[d]</sup> The selectivity factor was calculated according to an equation reported by Kagan et al.<sup>[19]</sup>

**Table 3.** A sequential Ti(IV)-catalyzed sulfoxidation and kinetic resolution of sulfides and the resulting sulfoxides with (*S*)-BINOL and its derivatives.<sup>[a, b]</sup>

Entry	Ligand	At 0 °C [h]	At 25 °C [h]	Sulfide	Sulfoxide <sup>[c, d]</sup>	
					Yield [%]	ee [%]
1	<i>(S)</i> -BINOL	10	0	<b>2a</b>	83	67
2		10	0.25		80	75
3		10	1.0		76	89
4		10	1.5		70	96
5		10	2.0		<b>62</b>	> <b>99.9</b>
6		10	2.0	<b>2b</b>	76	96
7		10	3.0		<b>65</b>	> <b>99.9</b>
8		10	1.5		<b>2c</b>	68
9		10	2.0	61		92
10		10	4.0	<b>58</b>		<b>96</b>
11	<i>(S)</i> -6,6'-Br <sub>2</sub> -BINOL	3	0	<b>2a</b>		90
12		6	0		75	31
13		10	0		62	43
14		3	1.5		<b>35</b>	> <b>99.9</b>

<sup>[a]</sup> Reaction conditions: PhCH<sub>3</sub>, sulfide/diol/Ti(O-*i*-Pr)<sub>4</sub>/H<sub>2</sub>O/TBHP (decane solution of TBHP was used.) = 1.0:0.2:0.1:0.2:2.0, N<sub>2</sub>.

<sup>[b]</sup> The enantioselective oxidation was performed at 0 °C and the kinetic resolution was carried out at 25 °C.

<sup>[c]</sup> Yield of isolated product.

<sup>[d]</sup> ee determined by HPLC analysis on a Daicel Chiralcel OB column.

by performing the asymmetric oxidation of sulfide and subsequent kinetic resolution in tandem in the same reaction vessel. This method is effective only when two important reaction condition profiles have been predetermined: (i) the time and temperature at which a compromise between sulfoxide yield and ee appears to be reasonable, and (ii) the temperature at which the kinetic resolution *via* the unavoidable oxidation of the resulting enantiomeric sulfoxides is most efficient.

## Experimental Section

### Typical Procedure for the One-Pot Tandem Catalytic Oxidation of Sulfides and their Kinetic Resolution

To a solution of (*S*)-BINOL (57.0 mg, 0.20 mmol) in toluene (6 mL) was added dropwise  $\text{Ti}(\text{O}-i\text{-Pr})_4$  (29.5  $\mu\text{L}$ , 0.10 mmol). After the mixture was stirred for 20 minutes at room temperature,  $\text{H}_2\text{O}$  (3.6  $\mu\text{L}$ , 0.20 mmol) was added. To the resulting homogeneous solution was added phenyl methyl sulfide (117  $\mu\text{L}$ , 1.0 mmol), and the mixture was stirred at room temperature for 30 min. The solution was then cooled to 0 °C, followed by the addition of TBHP (70% in decane, 0.30 mL, 2 mmol). The mixture was stirred at 0 °C for 10 h and then at 25 °C for another 90 min before being diluted with  $\text{CH}_2\text{Cl}_2$  and dried over  $\text{Na}_2\text{SO}_4$  for a few min. After filtration and evaporation of the solvent, the residue was immediately purified by preparative TLC ( $\text{Et}_2\text{O}$  as eluent) or column chromatography ( $\text{EtOAc}$ ). Phenyl methyl sulfoxide was isolated in 70% yield. The ee value of the sulfoxide was determined by HPLC on a Daicel Chiralcel OB column ( $\lambda = 254 \text{ nm}$ ; *n*-hexane:*i*-PrOH = 80:20; 1.0 mL/min.).

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## References and Notes

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