# Synthesis of Optically Active 2,5-Dialkylcyclohexane-1,4-diols and Their Application in the Asymmetric Oxidation of Sulfides

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Dedicated to Professor Jintang Wang on the occasion of his 70th birthday

**Abstract:** A simple and efficient approach to obtain optically pure 1,4-diols was established. The asymmetric oxidation of sulfides to sulfoxides with cumyl hydroperoxide in moderate yields and moderate to high enantioselectivities (up to 84%) catalyzed by chiral Ti/1,4-diols complexes has been achieved. A 76% ee value was obtained in the asymmetric synthesis of esomeprazole.

**Key words:** asymmetric oxidation, sulfide, sulfoxide, titanium, resolution

Enantiopure sulfoxides are important intermediates in organic synthesis and used as bioactive ingredients in the pharmaceutical industry. Many efficient approaches have been developed to obtain the enantiomerically pure sulfoxides.[1] Among them, enzymes,[2] chiral oxaziridines, and chiral hydroperoxides[3] afford the valuable methods to achieve this target. Another approach consists of the synthesis of a sulfinylating agent with an electrophilic sulfur of known configuration, followed by the reaction with an organometallic reagent providing highly enantiopure sulfoxides.[4] Amongst all the procedures, asymmetric oxidation of prochiral sulfides with chiral metal complexes is undoubtedly the most attractive way because of its simplicity and atom economy. Since the initial reports by Kagan and Modena in the use of a modified Sharpless reagent[5] in the reaction, many efforts have been devoted to search for an efficient catalytic system. Metal complexes such as Ti,[6] V,[7] Mn,[8] Fe,[9] Nb,[10] Zr,[11] Mo,[12] W,[13] Cu,[14] Al,[15] Pt,[16] and Os[17] have been widely investigated during the past decades. However, few catalytic systems have been applied in the industry.[1e] The development of a practical and efficient catalytic procedure remains a challenge.

Chiral diols are widely employed both as intermediates and as chiral auxiliaries in asymmetric synthesis.[18] Also, optically pure diols are constituents of many natural compounds.[19] Besides the wide utilizations of 1,2-diols, the $C_2$-symmetric chiral 2,5-dialkylcyclohexane-1,4-diol can also be converted into a wide diversity of ligands, which displayed good selectivities in many asymmetric reactions.[20,21] In order to obtain the optically active 2,5-dialkylcyclohexane-1,4-diols, Halterman and co-workers reported their synthetic study involving the use of the expensive $IpcBH_2$ as the chiral hydroboration reagent.[22] Two equivalents of $IpcBH_2$ were required for a single transformation, and this reagent is very inconvenient to be handled. Although the asymmetric catalysis affords a direct way to obtain the optically active compounds, sometimes the optical resolution of the racemic compounds with cheap and natural chiral small molecules still remains an important way due to its simplicity and economy. Herein, we report a simple and efficient approach to obtain the enantiomerically pure 1,4-diols and its successful application in the asymmetric oxidation of sulfides.

The racemic 1,4-diols could be readily prepared by the hydroboration of 1,4-dialkylcyclohexa-1,4-diene with $BH_3{\cdot}SMe_2$ followed by oxidation with basic hydrogen peroxide.[22] After screening various resolution reagents, an efficient resolution approach was finally achieved by treating (±)-**3** with *d*-camphorsulfonyl chloride in $CH_2Cl_2$ at 0 °C (Scheme 1). The two diastereoisomers were readily separated by flash chromatography on silica gel. Treatment of a single diastereomer (such as **4a**) with Na/naphthalene in THF provided the corresponding enantiopure (1*R*,2*R*,4*R*,5*R*)-2,5-dimethylcyclohexane-1,4-diol (**6a**) as white solid in 35% yield after two steps. In the same manner, **6b**, **7a**, and **7b** were also obtained as white solid in similar yields. The absolute configuration of the diols was assigned by comparison of optical rotation with literature values.[21,22]

Since Uemura et al.[6a] reported the utilization of chiral Ti–BINOL complexes in the asymmetric sulfoxidation, several other approaches using chiral titanium–diol complexes have been investigated.[6,23,24] However, many of these can not be considered truly catalytic because stoichiometric amounts of chiral complexes have been used, or the high enantioselectivities mainly attributed to a kinetic resolution process. Very recently, Rosini and co-workers reported the successful application of 1,2-diarylethane-1,2-diols in the asymmetric sulfoxidation with high enantioselectivities and good chemical yields.[6e]

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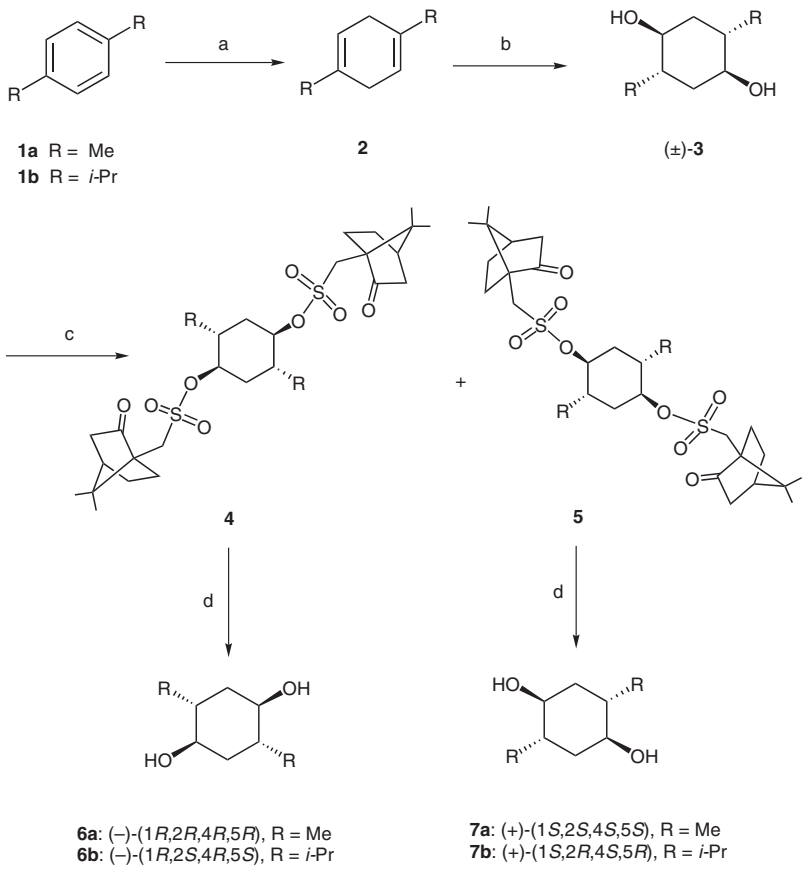


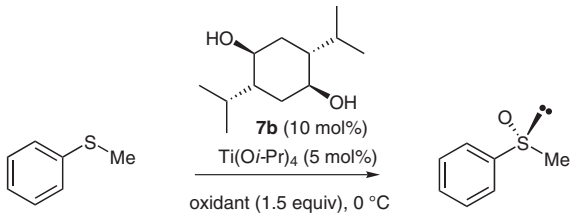

**Scheme 1** *Reagents and conditions*: (a) $Li/NH_3$ (liq)–EtOH, –40 °C; (b) (i) $BH_3{\cdot}SMe_2$, $Et_2O$, –25 °C, (ii) $H_2O_2$, NaOH; (c) *d*-camphorsulfonyl chloride, pyridine, $CH_2Cl_2$, 0 °C; (d) Na/naphthalene, THF, 0 °C, 4 h.

In view of the good asymmetric induction of the chiral 1,4-diols derived ligands in various reactions, we wish to broaden their use in asymmetric catalysis. Using methyl phenyl sulfide as the model substrate and Ti(O*i*-Pr)$_4$ as the precatalyst, we examined the oxidation reaction by using **7b** as the chiral ligand. The influence of parameters such as the nature of hydroperoxide, the reaction temperature, the solvent, and the additive has been investigated. The results are summarized in Table 1. Among the four hydroperoxides investigated, we found cumyl hydroperoxide (CHP) gave the best selectivity in comparison to *tert*-butyl hydroperoxide (TBHP) (entry 2), urea-hydrogen peroxide adduct (UHP) (entry 4), and hydrogen peroxide (entry 1). Of all the five solvents we investigated, $CCl_4$ proved to be the best choice in terms of enantioselectivity. The addition of molecular sieves was revealed to have remarkable improvement on the enantioselectivity. However, addition of a small amount of water did not improve, but decreased both the selectivity and the reactivity (entry 6). A variation of the reaction temperature from 0 to 25 °C caused negative influence on the selectivity (entry 12). No significant change of the selectivity was observed when the reaction was carried out at –20 °C (entry 11). Increasing the catalyst's loading resulted in a slight increase in reactivity and enantioselectivity (entries 13 and 14). Considering the economy of the catalytic system, we chose Ti(O*i*-Pr)$_4$/**7b**/CHP in a ratio of 0.05:0.1:1.5:1 in the presence of MS 4A in carbon tetrachloride at 0 °C as the standard conditions for further investigations.

To study the influence of the steric effects and the configurations of the ligands, we next examined the oxidation reaction using **6a**, **6b**, **7a**, and **7b** under the standard reaction conditions mentioned above. The results are summarized in Table 2. The oxidation of methyl phenyl sulfide with **6a** gave the sulfoxide in comparable yield and with the same ee value, but in the opposite configuration with respect to **7a** (entry 1 vs entry 3). The similar situation was observed in the comparison of **6b** with **7b** (entry 2 vs entry 4). It should be noted that **6a** and **6b** furnished the *S*-enantiomer of the sulfoxide, on the contrary, **7a** and **7b** gave the opposite *R*-enantiomer. All of the four chiral ligands displayed similar reactivities. Compounds **6b** and **7b** are superior to **6a** and **7a** in terms of enantioselectivities, which is probably attributed to the larger hindrance of isopropyl group on the cyclohexane skeleton offering a better discrimination than the methyl group.

Under the standard reaction conditions, the oxidation of a variety of aryl alkyl sulfides catalyzed by Ti(O*i*-Pr)$_4$/**7b** was investigated. The results are summarized in Table 3. Moderate to high yields were obtained in all the cases. The enantioselectivities of sulfoxides varied from 51 to 84%. The highest ee value was observed for the oxidation of 4-chlorophenyl methyl sulfide (entry 6) and 3-methoxyphenyl methyl sulfide gave the corresponding sulfox-

**Table 1** Enantioselective Oxidation of Methyl Phenyl Sulfide with (1*S*,2*R*,4*S*,5*R*)-**7b**[a]



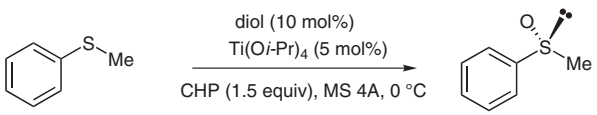

| Entry | Oxidant | Solvent | Additive | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | $H_2O_2$ | $CCl_4$ | MS 4A | 21 | <5 |
| 2 | TBHP | $CCl_4$ | MS 4A | 62 | 57 |
| 3 | CHP | $CCl_4$ | MS 4A | 71 | 77 |
| 4 | UHP | $CCl_4$ | MS 4A | 70 | 65 |
| 5 | CHP | $CCl_4$ | – | 60 | 36 |
| 6 | CHP | $CCl_4$ | $H_2O$ | 48 | 22 |
| 7 | CHP | $CH_2Cl_2$ | MS 4A | 49 | 64 |
| 8 | CHP | $CHCl_3$ | MS 4A | 55 | 58 |
| 9 | CHP | toluene | MS 4A | 56 | 37 |
| 10 | CHP | THF | MS 4A | 72 | 14 |
| 11[d] | CHP | $CCl_4$ | MS 4A | 63 | 76 |
| 12[e] | CHP | $CCl_4$ | MS 4A | 74 | 62 |
| 13[f] | CHP | $CCl_4$ | MS 4A | 75 | 78 |
| 14[g] | CHP | $CCl_4$ | MS 4A | 79 | 83 |

[a] Reaction conditions: Ti(O*i*-Pr)$_4$/**7b**/oxidant/methyl phenyl sulfide = 0.05:0.1:1.5:1. Unless otherwise noted, all reactions were carried out at 0 °C for 36 h.
[b] Isolated yields of sulfoxide.
[c] Determined by HPLC with a Daicel Chiralcel OD-H column. Absolute configuration of the products *R* was assigned by comparison of optical rotation reported in the literature.[24,]
[d] Reaction performed at –20 °C for 48 h.
[e] Reaction performed at 25 °C for 24 h.
[f] Molar ratio: Ti(O*i*-Pr)$_4$/**7b**/CHP/sulfide = 0.1:0.15:1.5:1.
[g] Molar ratio: Ti(O*i*-Pr)$_4$/**7b**/CHP/sulfide = 0.15:0.2:2.0:1.

ide with the lowest ee value (entry 9). The change of the aryl group in the methyl sulfide to probe electronic effects displayed no regular trends in the selectivity. Moreover, moderate yields and enantioselectivities were obtained for the oxidation of aryl benzyl sulfides with a slight higher catalyst loading (entries 10 and 11). In addition, all of the sulfoxides were obtained as *R*-configured.

In most of the reported cases, the enantioselective oxidation of sulfides involved two independent processes, namely, the asymmetric oxidation produced the sulfoxide and its subsequent kinetic resolution was accomplished via further oxidation to sulfone. As good enantioselectivities in the enantioselective oxidation of sulfides with titanium–diol complexes were obtained mostly on account of a kinetic resolution process,[23e] a further study on the rela-

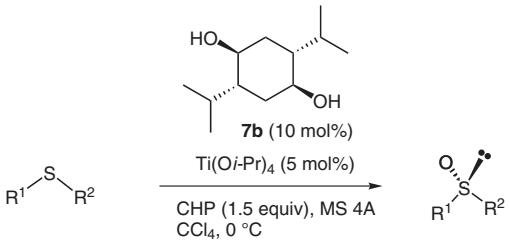
**Table 2** Enantioselective Oxidation of Methyl Phenyl Sulfide with Diols[a]




| Entry | Diols | Yield (%)[b] | ee (%)[c] | Config[d] |
|---|---|---|---|---|
| 1 | **6a** | 74 | 65 | *S* |
| 2 | **6b** | 72 | 76 | *S* |
| 3 | **7a** | 75 | 65 | *R* |
| 4 | **7b** | 73 | 77 | *R* |

[a] Reaction conditions: Ti(O*i*-Pr)$_4$/diol/CHP/methyl phenyl sulfide = 0.05:0.1:1.5:1, in the presence of MS 4A, 0 °C, 36 h.
[b] Isolated yields.
[c] Determined by chiral HPLC with a Daicel Chiralcel OD-H column.
[d] Absolute configuration of the products was assigned by comparison of optical rotation reported in the literature.[24]

**Table 3** Ti(O*i*-Pr)$_4$/(1*S*,2*R*,4*S*,5*R*)-**7b** Catalyzed Asymmetric Oxidation of Sulfides to Sulfoxides[a]




| Entry | $R^1$ | $R^2$ | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | Ph | Me | 71 | 77 |
| 2 | 4-Tol | Me | 53 | 72 |
| 3 | 4-*i*-Pr$C_6H_4$ | Me | 58 | 68 |
| 4 | 2-Br$C_6H_4$ | Me | 72 | 75 |
| 5 | 3-Br$C_6H_4$ | Me | 55 | 54 |
| 6 | 4-Cl$C_6H_4$ | Me | 66 | 84 |
| 7 | 4-$O_2$N$C_6H_4$ | Me | 49 | 81 |
| 8 | 4-MeO$C_6H_4$ | Me | 57 | 66 |
| 9 | 3-MeO$C_6H_4$ | Me | 60 | 51 |
| 10[d] | Ph | Bn | 67 | 72 |
| 11[d] | 4-Tol | Bn | 71 | 65 |

[a] Unless otherwise noted, all reactions were carried out under the following conditions: Ti(O*i*-Pr)$_4$/**7b**/CHP/substrate = 0.05:0.1.1.5:1, in the presence of MS 4A, 0 °C, 36 h.
[b] Isolated yields of sulfoxides.
[c] Determined by HPLC with a Daicel Chiralcel OD-H or OB-H column. Absolute configuration of the products *R* was assigned by comparison of optical rotation reported in the literature.[24,]
[d] Molar ratio Ti(O*i*-Pr)$_4$/**7b**/CHP/substrate = 0.1:0.15.1.5:1.

tionship between enantiomeric excess of sulfoxide and the yield of sulfone under standard reaction conditions was carried out. From the time profile of the oxidation of methyl phenyl sulfide (Figure 1), it can be found that the ee values of sulfoxide did not change significantly during the reaction process, that is, the independence of the enantiomeric excess of the sulfoxide on the amount of sulfone formation. On the basis of this study, we concluded that the ee value of the sulfoxide did not arise from a selectivity enhancement caused by kinetic resolution of the chiral sulfoxide, but by a direct result of the enantioselective oxidation.

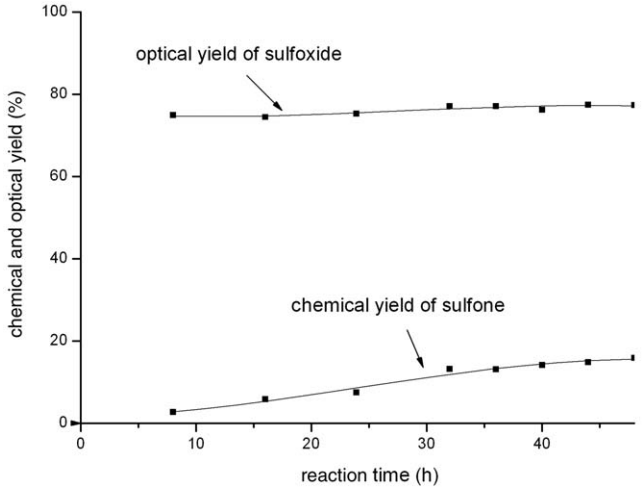
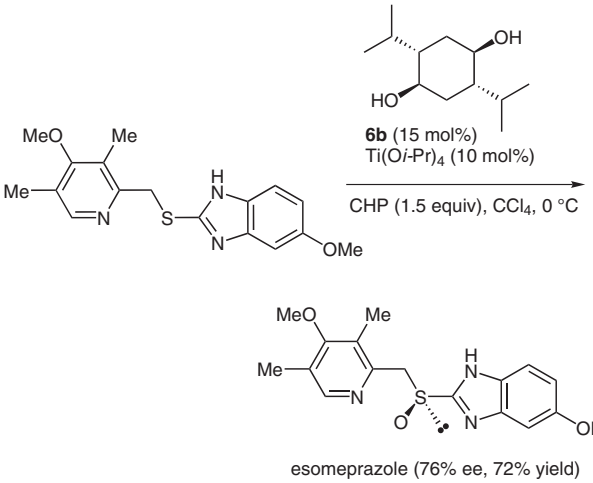



**Figure 1** Time profile of the enantioselectivity (% ee of sulfoxide) and the chemoselectivity (% sulfone)

In pharmaceutical industry, the most remarkable utilization of metal-catalyzed asymmetric oxidation of sulfide is the synthesis of esomeprazole, which is the *S*-enantiomer of omeprazole, a powerful antiulcer agent serving as efficient proton pump inhibitor.[25] A modified Kagan's procedure is the only efficient metal-catalyzed approach to obtain the enantiomeric pure product. We applied our approach in the asymmetric synthesis of (*S*)-esomeprazole. After optimization of the reaction conditions (Ti/**6b**/CHP/sulfide = 0.1:0.15:1.5:1, MS 4A, 0 °C, 36 h), we obtained (*S*)-esomeprazole in a moderate enantiomeric excess (76% ee, yield 72%) (Scheme 2).

In summary, a simple and efficient resolution of racemic 1,4-dialkylcyclohexane-2,5-diols has been realized. The asymmetric oxidation of sulfides with CHP in the presence of MS 4A catalyzed by Ti(O*i*-Pr)$_4$/1,4-diols has been investigated. The main advantage of our approach resided in the use of a catalytic amount of the metal complex and the sulfoxides were obtained in moderate to high enantioselectivities under mild reaction conditions. No kinetic resolution was observed in the oxidation process. Moreover, we employed our catalytic system in the asymmetric synthesis of esomeprazole, which was obtained in 72% yield with 76% ee.




**Scheme 2** Synthesis of esomeprazole

$^1$H NMR data were recorded on a Bruker AMX-300 spectrometer with chemical shifts referenced to $SiMe_4$ as internal standard. Electrospray ionization mass spectra were recorded on Finnigan LCQ Electrospray Mass Spectrometer. Optical rotations were recorded on a PerkinElmer 241 Polarimeter. The ee values were determined by a PerkinElmer 200 HPLC on a chiral Chiralcel OD-H or OB-H column with UV detection at 254 nm. Elemental analyses were carried out on a PerkinElmer 240 C elemental analyzer. All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Toluene and THF were distilled from sodium/benzophenone. $CCl_4$ and $CH_2Cl_2$ were distilled from $CaH_2$. $CHCl_3$ was dried with $K_2CO_3$ and distilled from $P_2O_5$. Petroleum ether (PE) used had bp 60–90 °C. All reactions were carried out under $N_2$. All catalytic reactions were carried out in Schlenk tubes. The enantioselectivities of the chiral 2,5-diisopropylhexane-1,4-diols were determined by HPLC analysis and comparison of optical rotation data with literature values.

**Esterification of Racemic 2,5-Dialkylcyclohexane-1,4-diols (±)-3; General Procedure**

A 50 mL round-bottomed flask was charged with the 1,4-diol (±)-**3** (1.5 mmol) and anhyd pyridine (2 mL) in $CH_2Cl_2$ (20 mL). The mixture was stirred at 0 °C and a solution of *d*-camphorsulfonyl chloride (1.25 g, 5 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise under $N_2$. The mixture was stirred for 4 h at 0 °C and then quenched with aq sat. $NH_4Cl$ (50 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL) and the combined organic phases were dried ($Na_2SO_4$). Flash chromatography of the residue obtained after evaporation of the solvent on silica gel (PE–$CH_2Cl_2$–EtOAc, 3:1:1) gave first the diastereomer **4a** (0.39 g, 45%) and then the other diastereomer **5a** (0.39 g, 45%) from (±)-**3a**. Similarly **4b** (0.42 g, 44%) and then **5b** (0.43 g, 45%) were obtained from (±)-**3b**.

**(1*R*,2*R*,4*R*,5*R*)-1,4-Di-*d*-camphorsulfonato-2,5-dimethylcyclohexane (4a)**

White solid; mp 46–48 °C; $[\alpha]_D^{10}$ +23.6 (*c* 0.7, $CH_2Cl_2$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.86–4.90 (m, 2 H), 3.62–3.58 (m, 2 H), 3.04–2.96 (m, 2 H), 2.51–2.48 (m, 4 H), 2.41–2.09 (m, 8 H), 1.98–1.96 (m, 2 H), 1.94–1.91 (m, 4 H), 1.73–1.68 (m, 2 H), 1.21–0.95 (m, 18 H).

MS (ES): *m*/*z* = 573.8 [M + 1].

Anal. Calcd for $C_{28}H_{44}O_8S_2$: C, 58.71; H, 7.74. Found: C, 58.82; H, 7.89.

**(1*R*,2*S*,4*R*,5*S*)-1,4-Di-*d*-camphorsulfonato-2,5-diisopropylcyclohexane (4b)**
White solid; mp 37–39 °C; $[\alpha]_D^{10}$ +25.6 (*c* 0.8, $CH_2Cl_2$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.90 (m, 2 H), 3.66–3.61 (d, *J* = 15 Hz, 2H), 3.06–3.01(d, *J* = 15 Hz, 2 H), 2.53 (m, 4 H), 2.39–2.03 (m, 8 H), 1.95 (m, 2 H), 1.89–1.85 (m, 4 H), 1.70–1.62 (m, 2 H), 1.45 (m, 2 H), 1.17–0.90 (m, 24 H).

MS (ES): *m*/*z* = 629.8 [M + 1].

Anal. Calcd for $C_{32}H_{52}O_8S_2$: C, 61.15; H, 8.27. Found: C, 61.57; H, 8.57.

**(1*S*,2*S*,4*S*,5*S*)-1,4-Di-*d*-camphorsulfonato-2,5-dimethylpropylcyclohexane (5a)**
White solid; mp 62–64 °C; $[\alpha]_D^{10}$ +42.4 (*c* 0.6, $CH_2Cl_2$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.64–4.58 (m, 2 H), 3.41–3.38 (m, 2 H), 2.95–2.88 (m, 2 H), 2.46–2.43 (m, 4 H), 2.28–2.02 (m, 8 H), 1.92–1.85 (m, 2 H), 1.82–1.76 (m, 4 H), 1.65–1.57 (m, 2 H), 1.22–0.96 (m, 18 H).

MS (ES): *m*/*z* = 573.8 [M + 1].

Anal. Calcd for $C_{28}H_{44}O_8S_2$: C, 58.71; H, 7.74. Found: C, 58.85; H, 7.91.

**(1*S*,2*R*,4*S*,5*R*)-1,4-Di-*d*-camphorsulfonato-2,5-diisopropylcyclohexane (5b)**
White solid; mp 81–83 °C; $[\alpha]_D^{10}$ +33.6 (*c* 0.3, $CH_2Cl_2$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.95 (m, 2 H), 3.61–3.56 (d, *J* = 15 Hz, 2 H), 3.0–2.95 (d, *J* = 15 Hz, 2 H), 2.50–2.45 (m, 4 H), 2.32–2.0 (m, 8 H), 1.92 (m, 2 H), 1.86–1.80 (m, 4 H), 1.71–1.58 (m, 2 H), 1.42 (m, 2 H), 1.21–0.87 (m, 24 H).

MS (ES): *m*/*z* = 629.9 [M + 1].

Anal. Calcd for $C_{32}H_{52}O_8S_2$: C, 61.15; H, 8.27. Found: C, 61.35; H, 8.32.

**Cleavage of the *d*-Camphorsulfonato Group from the Sulfonates 4 and 5; (1*S*,2*R*,4*S*,5*R*)-(+)-2,5-Diisopropylcyclohexane-1,4-diol (7b); Typical Procedure**
A 100 mL three-necked flask was charged with **5b** (1.53 g, 2.44 mmol) and anhyd THF (20 mL). While stirring the mixture at 0 °C, a solution of sodium naphthalide [prepared by treating Na (2 g) with naphthalene (11.4 g) in anhyd THF (200 mL) in a sealed system under $N_2$ for 1 h at r.t.] was added dropwise. The mixture was stirred at 0 °C for 10 h and then warmed to r.t. After several hours, ice water (50 mL) was added. The mixture was extracted with EtOAc (5 × 20 mL) and the combined organic extracts were dried ($Na_2SO_4$). The solvent were removed by rotary evaporation. After purification by column chromatography on silica gel (PE–EtOAc, 2:1), 0.36 g of the desired 1,4-diol **7b** was obtained as a white solid (total yield 35% after two steps); mp 120–122 °C; $[\alpha]_D^{25}$ +36.2 (*c* 0.5, $CH_2Cl_2$); >99% ee (by comparison of optical rotation reported in the literature[22]).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.53 (m, 2 H), 1.91 (m, 2 H), 1.79 (m, 2 H), 1.6 (m, 2 H), 1.48 (m, 2 H), 1.35 (m, 2 H), 0.87 (d, *J* = 7.2 Hz, 6 H), 0.85 (d, *J* = 7.2 Hz, 6 H).

**(1*R*,2*R*,4*R*,5*R*)-(–)-2,5-Dimethylcyclohexane-1,4-diol (6a)**
White solid; mp 121–122 °C; $[\alpha]_D^{25}$ –32.9 (*c* 0.6, $CH_2Cl_2$); >99% ee (by comparison of optical rotation reported in the literature[22]).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.58–3.51 (m, 2 H), 1.92–1.89 (m, 2 H), 1.79–1.68 (m, 4 H), 1.59–1.54 (m, 2 H), 1.02–1.00 (d, *J* = 6.6 Hz, 6 H).

**(1*R*,2*S*,4*R*,5*S*)-(–)-2,5-Diisopropylcyclohexane-1,4-diol (6b)**
White solid; mp 119–120 °C; $[\alpha]_D^{25}$ –36.1 (*c* 0.5, $CH_2Cl_2$); >99% ee (by comparison of optical rotation reported in the literature[22]).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.53 (m, 2 H), 1.91 (m, 2 H), 1.79 (m, 2 H), 1.6 (m, 2 H), 1.48 (m, 2 H), 1.35 (m, 2 H), 0.88 (d, *J* = 7.2 Hz, 6 H), 0.86 (d, *J* = 7.2, 6 H).

**(1*S*,2*S*,4*S*,5*S*)-(+)-2,5-Dimethylcyclohexane-1,4-diol (7a)**
White solid; mp 121–123 °C; $[\alpha]_D^{25}$ +32.9 (*c* 0.5, $CH_2Cl_2$); >99% ee (by comparison of optical rotation reported in the literature[22]).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.57–3.50 (m, 2 H), 1.92–1.88 (m, 2 H), 1.78–1.69 (m, 4 H), 1.59–1.54 (m, 2 H), 1.02–1.00 (d, *J* = 6.6 Hz, 6 H).

**Asymmetric Oxidation of Sulfides to Sulfoxides; Methyl Phenyl Sulfoxide; Typical Procedure (Table 3, Entry 1)**
A solution of Ti(O*i*-Pr)$_4$ (14.8 μL, 0.05 mmol) in $CCl_4$ (2 mL) was added to a Schlenk tube containing MS 4A (50 mg) and **7b** (20 mg, 0.1 mmol). The mixture was stirred for 2 h at r.t. Then the solution was cooled to 0 °C, and methyl phenyl sulfide (1 mmol, 0.13 mL) was added. The above mixture was stirred for another 30 min, then 80% cumyl hydroperoxide (270 μL, 1.5 mmol) was added. After stirring for 36 h at 0 °C, $H_2O$ (10 mL) was added. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (100 mL) and dried ($Na_2SO_4$). The solvent was removed under reduced pressure. The crude products were purified by column chromatography on silica gel (EtOAc–PE, 1.5:1) to give methyl phenyl sulfoxide; yield: 100 mg (71%); oil at r.t. (Lit.[26] mp 29–30 °C).

The rest of the sulfoxides listed in Table 3 were identified by comparison of their analytical and spectral data with the corresponding authentic samples.

**Esomeprazole**
A solution of Ti(O*i*-Pr)$_4$ (30 μL, 0.10 mmol) in $CCl_4$ (3 mL) was added to a Schlenk tube containing MS 4A (50 mg) and **6b** (30 mg, 0.15 mmol). The mixture was stirred for 2 h at r.t. Then the mixture was cooled to 0 °C, and the precursor sulfide (330 mg, 1 mmol) was added. The mixture was stirred for another 30 min, then 80% cumyl hydroperoxide (0.4 mL, 1.5 mmol) was added. After stirring for 36 h at 0 °C, $H_2O$ (20 mL) was added to the mixture. The aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (100 mL) and dried ($Na_2SO_4$). The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc–PE, 1:1) to give esomeprazole (250 mg, 72%) as a clear oil; $[\alpha]_D^{20}$ –118 (*c* 0.1, $CHCl_3$); 76% ee. Chiralcel OD-H, hexane–*i*-PrOH (9:1); flow rate = 0.5 mL/min.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 7.50 (s, 1 H), 6.94 (d, *J* = 8.6 Hz, 1 H), 6.92 (d, *J* = 8.6 Hz, 1 H), 4.71 (s, 2 H), 3.84 (s, 3 H), 3.60 (s, 3 H), 2.19 (s, 3 H), 2.11 (s, 3 H).

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