

Sulfoximine–Titanium Reagents in Enantioselective Trimethylsilylcyanations of Aldehydes*

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Chiral titanium reagents derived from optically active sulfoximines and $\text{Ti}(\text{O-}i\text{-Pr})_4$ promote the asymmetric addition of trimethylsilyl cyanide to aldehydes affording cyanohydrins in high yields with good enantioselectivities (up to 91% ee). The ligand structure and the reaction conditions have been optimized. With substoichiometric amounts of the sulfoximine–titanium reagent the product is obtained in decreased yield with lower enantiomeric excess. The molecular structures of (*R*)-*S*-(2-hydroxyphenyl)-*S*-methyl sulfoximine [(*R*)-**4a**] and (*R*)-*S*-(2-hydroxyphenyl)-*S*-(1,1-dimethylethyl) sulfoximine [(*R*)-**4d**] have been determined by X-ray diffraction analysis.

Cyanohydrins are valuable intermediates for the synthesis of various chiral compounds, such as α -hydroxy carbonyl derivatives and β -amino alcohols.^{1–5} A number of enantioselective methods for the preparation of optically active cyanohydrins have been developed affording the desired products in high enantiomeric excess.^{6,7} Both bio- and chemo-catalysts are applicable for catalyzing asymmetric cyanide additions to aldehydes. Among the metal-containing reagents used in this transformation,^{8–20} chirally modified titanium species^{11–20} have been found to be most successful. Promoters and catalysts prepared from $\text{Ti}(\text{O-}i\text{-Pr})_4$ and chiral ligands, such as tartrate derivatives^{12–15} or Schiff's bases derived from chiral β -amino alcohols and salicylaldehyde^{16–19} lead to cyanohydrins in high enantiomeric excess. With the latter system, *ligand accelerated catalysis*²¹ has been observed. Usually, trimethylsilyl cyanide is used as the cyanide source. Its asymmetric addition to the aldehyde followed by desilylation of the intermediate cyanosilyl ether gives the corresponding cyanohydrin in good yield, Scheme 1.

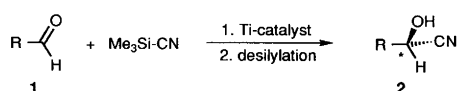
Metal-containing reagents can also be used for enantioselective hydrocyanations of aldehydes with *hydrogen cyanide*.^{22–24} However, for these transformations,

enzymes⁶ or cyclodipeptides^{25–31} are commonly the catalysts of choice.

Herein we describe novel asymmetric trimethylsilylcyanations of aldehydes using titanium reagents prepared *in situ* from $\text{Ti}(\text{O-}i\text{-Pr})_4$ and chiral sulfoximines.³²

Results and discussion

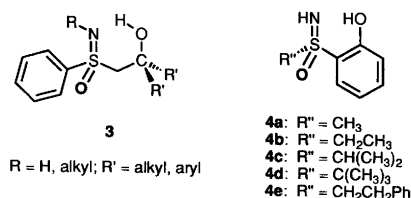
Synthesis of the ligands. We have previously demonstrated that optically active β -hydroxy sulfoximines **3** can be successfully used in catalyzed enantioselective borane reductions of carbonyl compounds (ketones^{33,34} and imine derivatives³⁵) and asymmetric diethylzinc additions to aldehydes³⁶ and chalcones.³⁷ Attempts to utilize ligands of this type in titanium-catalyzed transformations remained unsuccessful, presumably due to weak ligand-to-metal interactions. We therefore turned our attention to the synthesis of sulfoximines of type **4** hoping for improved binding properties through the more acidic phenolic hydroxy group.



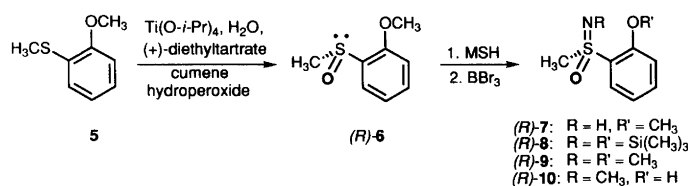
Scheme 1.

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Optically active (*R*)-**4a** was obtained as a colorless solid by enantioselective sulfur oxidation of 2-methoxyphenyl methyl sulfide (**5**) using Kagan's method,^{38–42} followed by sequential stereospecific



Scheme 2.

imation of the resulting sulfoxide (*R*)-6 with *o*-mesitylenesulfonylhydroxylamine (MSH) (Scheme 2).^{43,44} Demethylation of (*R*)-7 with BBr₃ completed a sequence whereby both enantiomers of **4a** could be prepared. The molecular structure of (*R*)-4a was confirmed by X-ray crystal structure determination.

Sulfoximine (*R*)-4b was prepared by *N,O*-bis-silylation of (*R*)-4a with an excess of hexamethyldisilazane to give (*R*)-8 followed by deprotonation with butyllithium in hexane and reaction with iodomethane. Acidic work-up and purification by column chromatography afforded pure (*R*)-4b in 55% yield. Use of the same reaction sequence, bis-silylation, deprotonation and reaction with the appropriate alkyl halide, gave sulfoximines (*R*)-4c–e, respectively. X-Ray crystallography confirmed the molecular structure of (*R*)-4d. *N*-Methylated sulfoximine (*R*)-10 was synthesized by Eschweiler–Clark methylation of (*R*)-7 to give (*R*)-9 (71%) followed by *O*-demethylation with BBr₃ (55%).

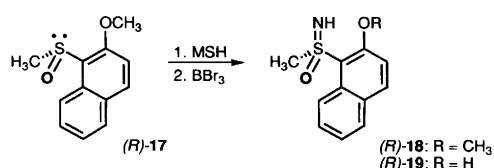
Attempts to prepare substituted derivatives **13–16** (Scheme 3) were unsuccessful owing to the low reactivity of sulfoxides **11** and **12** towards MSH.

Naphthyl derivative (*R*)-19 was obtained from the corresponding known sulfoxide (*R*)-17⁴⁵ via imination (MSH; 57%) followed by demethylation (BBr₃; 84%) of the resulting sulfoximine (*R*)-18 (84%) (Scheme 4).

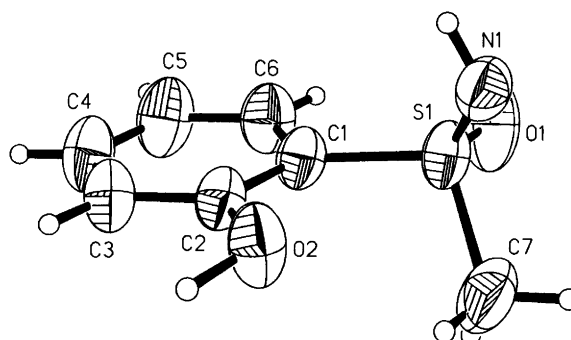
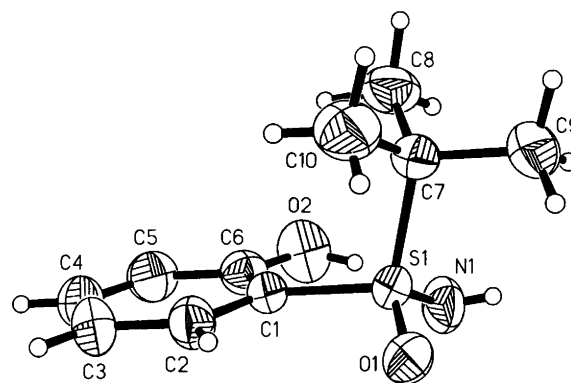
X-Ray crystal structure determinations of (R)-4a and (R)-4d. Recrystallization from chloroform solutions afforded colorless crystals of solvent-containing (*R*)-4a and solvent-free (*R*)-4d. Their solid-state molecular structures were determined by X-ray crystallography.⁴⁶ ORTEP plots are given in Figs. 1 and 2.



Scheme 3.



Scheme 4.

Fig. 1. Solid state molecular structure of (*R*)-4a.Fig. 2. Solid state molecular structure of (*R*)-4d.

In the solid state, sulfoximines (*R*)-4a and (*R*)-4d have very similar conformations. The dihedral angles C(7)–S(1)–C(1)–C(6) of $-123.6(3)^\circ$ in (*R*)-4a and $92.1(2)^\circ$ in (*R*)-4d indicate that the alkyl substituents at sulfur are almost perpendicular to the plane of the aromatic ring. In both compounds the sulfoximine oxygens are *anti* to the phenolic hydroxyl group [O(1)–S(1)–C(1)–C(2): in (*R*)-4a = $173.7(3)$, in (*R*)-4d = $24.4(2)$]. Intramolecular hydrogen bonding between the phenolic hydrogen and the sulfoximine nitrogen was detected only in (*R*)-4d. With the exception of the S(1)–C(1) bond [(*R*)-4a: $177.1(4)$, (*R*)-4d: $176.6(2)$], the bonds between the substituents and sulfur in (*R*)-4d are slightly longer than those in (*R*)-4a [S(1)–O(1): (*R*)-4a = $144.3(3)$, (*R*)-4d = $145.3(2)$; S(1)–N(1): (*R*)-4a = $151.2(3)$, (*R*)-4d = $152.3(2)$; S(1)–C(7): (*R*)-4a = $176.3(4)$, (*R*)-4d = $183.3(2)$]. Other intramolecular atom distances and torsion angles differ insignificantly.

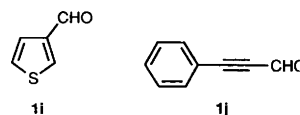
Enantioselective trimethylsilylcyanation of aldehydes. Treatment of (*R*)-4a with Ti(*O-i-Pr*)₄ in dichloromethane

gave a yellow solution containing a catalytically active species for the asymmetric addition of trimethylsilyl cyanide to aldehydes.³² Thus, in the presence of stoichiometric amounts of $\text{Ti}(\text{O-}i\text{-Pr})_4$ and 1.1 equiv. of sulfoximine (*R*)-**4a**, trimethylsilylcyanation of benzaldehyde (**1a**) at -50°C led to high aldehyde conversion (96% as determined by NMR spectroscopy) and formation of the corresponding silylated cyanohydrin. Subsequent acidic cleavage of the trimethylsilyl group (5% aqueous HF) afforded (*S*)-mandelonitrile [(*S*)-**2a**] in 72% yield with 91% ee (Table 1). After the reaction, (*R*)-**4a** was easily recovered (70–90%). Attempts to increase the asymmetric induction by lowering the reaction temperature to -65°C or varying the concentration (0.2–1 M) did not significantly influence the ee. The optical yield did not change with reaction time. The use of (*R*)-**19** as a ligand gave (*S*)-**2a** with 81% ee.

Utilizing the conditions which had been optimized for the Me_3SiCN addition to benzaldehyde, trimethylsilylcyanation of several aldehydes was investigated. A variety of substrates including substituted aromatic, aliphatic, and α,β -unsaturated aldehydes were silylcyanated with good enantiocontrol (Table 1). The enantiomeric excesses of the cyanohydrins were determined by ^{19}F NMR, GC or HPLC analysis of the corresponding α -methoxy- α -(trifluoromethyl)phenylacetic esters (MTPA esters).^{47,48} Attempts to analyze the extent of asymmetric induction via *O*-acetylmandelic esters were unsuccessful owing to partial racemization during the DCC coupling with *O*-acetylmandelic acid. Comparison of the optical rotation values with those reported in the literature revealed that cyanohydrins with the *S*-configuration were obtained when sulfoximine (*R*)-**4a** was used as the ligand.

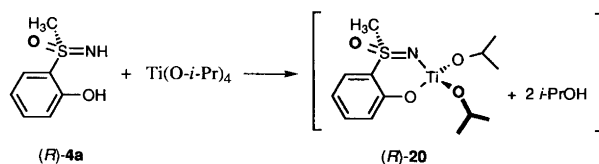
Compared with the TMSCN addition to benzaldehyde, reactions of sterically more hindered aromatic carbonyl compounds gave products with a lower enantiomeric excess. Thus, cyanohydrin **2c**, which was obtained from *ortho*-substituted 2-methoxybenzaldehyde (**1c**), was obtained in only 74% ee (compared with 91% ee for **2a**). The same trend was observed in the aliphatic series. Whereas hexanal (**1e**) and α -monobranched cyclohexanecarbaldehyde (**1f**) were silylcyanated equally well

giving cyanohydrins **2e** and **2f**, respectively, with 89% ee, further substitution at the α position lowered the enantiomeric excess. Thus, product **2g** derived from 2,2-dimethylpropanal (**1g**) had only an 81% ee and cyanohydrin **2h** from (*E*)-cinnamaldehyde (**1h**) was obtained with 79% ee. Trimethylsilylcyanation of the thiophene derivative **1i** gave the addition product **2i** in low yield (37%) with only 37% ee. Owing to rapid decomposition during the standard MTPA-ester synthesis of cyanohydrin **2j** obtained from phenylpropynal (**1j**), the ee remained undetermined.



We next investigated the effectiveness of the sulfoximine–titanium system for mediating the addition of hydrogen cyanide to aldehydes. Assuming that the reaction between sulfoximine (*R*)-**4a** and $\text{Ti}(\text{O-}i\text{-Pr})_4$ generates a new titanium-containing species of type **20**, two equivalents of isopropyl alcohol have to be liberated. If this alcohol is involved in the reaction pathway, it can either interact with **20** forming a dynamic associate, or it can react with Me_3SiCN to generate HCN. The latter should therefore also be considered as a cyanide source and good enantiocontrol in hydrocyanation with HCN is desirable.⁴⁹

The reaction of hydrogen cyanide with benzaldehyde (**1a**) mediated by the sulfoximine–titanium system derived from (*R*)-**4a** (Scheme 5) and $\text{Ti}(\text{O-}i\text{-Pr})_4$ occurred smoothly at -50°C , and after 16 h cyanohydrin **2a** was isolated in 89% yield as an 82:18 *S/R* enantiomer mixture. Thus, even if HCN is the cyanide source in the



Scheme 5.

Table 1. Enantiomeric excesses resulting from TMSCN additions to aldehydes mediated by (*R*)-**4a** and $\text{Ti}(\text{O-}i\text{-Pr})_4$.

| Entry | Aldehyde | Cyanohydrin | % Yield ^a | %Ee ^b |
|-------|---|-------------------------|----------------------|------------------|
| 1 | Benzaldehyde (1a) | (<i>S</i>)- 2a | 72 (96) | 91 |
| 2 | 4-Methoxybenzaldehyde (1b) | (<i>S</i>)- 2b | 60 | 87 |
| 3 | 2-Methoxybenzaldehyde (1c) | (<i>S</i>)- 2c | 72 (92) | 74 |
| 4 | 1-Naphthaldehyde (1d) | (<i>S</i>)- 2d | 92 (97) | 76 |
| 5 | Hexanal (1e) | (<i>S</i>)- 2e | 64 | 89 |
| 6 | Cyclohexanecarbaldehyde (1f) | (<i>S</i>)- 2f | 70 (97) | 89 |
| 7 | 2,2-Dimethylpropanal (1g) | (<i>S</i>)- 2g | 70 | 81 |
| 8 | (<i>E</i>)-Cinnamaldehyde (1h) | (<i>S</i>)- 2h | 63 | 79 |
| 9 | Thiophene-3-carbaldehyde (1i) | (<i>S</i>)- 2i | 37 | 37 |

^a Isolated as cyanohydrins by column chromatography; conversion in parentheses (as determined by ^1H NMR spectroscopy).

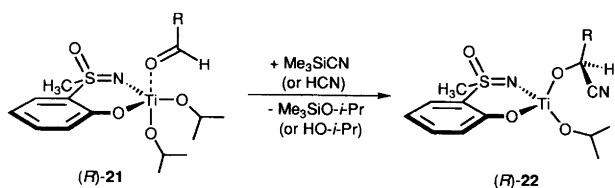
^b Ee determined by GC or HPLC analysis of the corresponding MTPA esters (see the Experimental section).

TMSCN–aldehyde reaction good enantiocontrol in the cyanohydrin formation can still be achieved.

Having determined the overall potential of the stoichiometric sulfoximine–titanium system for chirality transfer we next focussed on *catalytic* variants for the cyanohydrin formation. Use of an *in-situ* catalyst prepared by mixing of 20 mol% of Ti(O-*i*-Pr)₄ and 22 mol% of (*R*)-**4a** in dichloromethane afforded (*S*)-mandelonitrile (**2a**) after 20 h at -45°C in only 28% yield with 44% ee. Stirring for a longer period of time gave a higher product yield, but the enantiomeric excess was significantly lower (60 h at -45°C : 79% yield, 23% ee). This decrease in enantioselectivity was interpreted as an indication of the formation of several active species during the reaction, each of which mediated the Me₃SiCN addition at different rates and with different enantiomeric excesses.²¹ Raising the temperature from -45 to -10°C lowered the extent of asymmetric induction (7% ee). At 25°C only racemic **2a** was obtained. Changing the solvent from CH₂Cl₂ to propionitrile, toluene or CCl₄ did not improve the chemical yield or the enantioselectivity in the cyanohydrin formation (at -45°C after 18 h: 13, 36 and 27% ee, respectively).

The difference in product yields between the stoichiometric and the catalytic version of the reaction was attributed to inefficient regeneration of the catalytically active species. In the presumed reaction pathway, (*R*)-**20** serves as chiral Lewis acid and anti-coordination of the aldehyde^{50–52} at the less hindered β face of (*R*)-**20** is followed by *Re* cyanation of (*R*)-**21** and loss of alkoxide to give (*R*)-**22** (Scheme 6). Slow product liberation from the latter species then blocks the catalyst and prevents turnover.

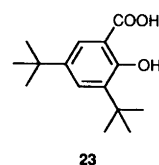
In Oguni's tartrate–titanium system for asymmetric cyanohydrin formation^{14,15} turnover and extent of asymmetric induction are significantly influenced by the mode of catalyst preparation (freeze–drying) and the presence of the subsequently added alcohol. We therefore investigated the dependence of the chemical yield and the ee of the product on the concentration of isopropyl alcohol in the sulfoximine–titanium system. Removal of the isopropyl alcohol produced by the alkoxide exchange reaction giving (*R*)-**20** by azeotropic distillation with toluene gave a species which resulted in low catalytic activity and enantioselectivity (16% yield, 21% ee). Azeotropic removal of the alcohol followed by addition of 40 mol% of isopropyl alcohol did not restore the enantioselectivity of the original system (25% yield, 28% ee). Catalysts obtained by mixing of 22 mol% of (*R*)-**4a** and 20 mol%



Scheme 6.

of Ti(O-*i*-Pr)₄ tolerated the additional presence of 60 mol% of isopropyl alcohol (29% yield, 46% ee). Addition of 200 mol% of isopropyl alcohol, however, inhibited cyanohydrin formation and only traces of **2b** were detected by TLC. The use of 20 mol% of water as an additive gave cyanohydrin **2a** in 27% yield with 24% ee. Attempts to increase the catalyst turnover by liberating the cyanohydrin from (*R*)-**22** through silylation with trimethylsilyl trifluoroacetate (40 mol%) were unsuccessful (17% yield, 8% ee). In the presence of LiClO₄ (100 mol%, -27°C , 16 h, CH₂Cl₂) a yield of 24% and 5% ee of (*S*)-**2a** was obtained. The addition of 1,2-ethanediol reversed the absolute configuration of the product. However, the ee of (*R*)-**2a** was low (9%) with a yield of 61%.

Recently, Carreira *et al.* reported that 3,5-di-*tert*-butylsalicylic acid (**23**) had positive effects on the yields, enantioselectivity and catalytic efficiency of titanium-catalyzed Mukaiyama-type aldol additions.^{53,54} In the sulfoximine–titanium catalyst system described here, carboxyanions, such as those derived from **23** or salicylic acid inhibited the catalysis or gave a product with a lower enantiomeric excess (20% yield, 34% ee).



In an attempt to improve the enantioselectivity, the ligand structure was varied. Increasing the size of the alkyl substituent at the sulfoximine sulfur had only a small effect on the extent of asymmetric induction in the standard trimethylsilylcyanation of **1a** (Table 2). The best ligand in this series was found to be **4e** having a 2-phenylethyl substituent at sulfur. In this catalytic version of the TMSCN addition **4e** afforded **2a** with 47% ee. In all cases *S*-configured products were obtained. The low chemical yields after 18 h at -45°C reflect the

Table 2. Enantiomeric excesses resulting from TMSCN additions to benzaldehyde catalyzed by various sulfoximines and Ti(O-*i*-Pr)₄.^a

| Entry | Sulfoximine | % Yield ^b | % Ee ^c |
|-------|-------------------------|----------------------|-------------------|
| 1 | (<i>R</i>)- 4a | 29 | 43 |
| 2 | (<i>R</i>)- 4b | 25 | 40 |
| 3 | (<i>R</i>)- 4b | 72 ^d | <5 |
| 4 | (<i>R</i>)- 4c | 27 | 43 |
| 5 | (<i>R</i>)- 4c | 60 ^d | 18 |
| 6 | (<i>R</i>)- 4d | 26 | 40 |
| 7 | (<i>R</i>)- 4e | 32 | 47 |
| 8 | (<i>R</i>)- 10 | 60 | 0 |

^a Use of 20 mol% of Ti(O-*i*-Pr)₄ and 22 mol% of sulfoximine in CH₂Cl₂ at -45°C for 20 h. ^b Isolated as cyanohydrins by column chromatography. ^c Ee determined by GC of the corresponding MTPA esters (see the Experimental part). ^d Reaction time 60 h.

limited catalyst turnover. Longer reaction times led to improved yields but lower asymmetric induction (entries 3 and 5). *N*-Methylated sulfoximine (*R*)-**10** gave a more active catalyst, however, addition product **2a** was found to be racemic.

Other metallic reagents (20 mol%) have also been tested in the catalyzed asymmetric trimethylsilylcyanation of benzaldehyde (**1a**) using (*R*)-**4a** (22 mol%) as chiral ligand (CH₂Cl₂, -45 °C, 18 h). Cyanohydrin **2a** was obtained in low enantiomeric excess when Ti(*O*-*t*-Bu)₄ (22% ee), Ti(OEt)₄ (4% ee), Ti(*O*-*i*-Pr)₂Cl₂ (37% ee) or Ti(*O*-*i*-Pr)₃Cl (11% ee) was used. Ti(OEt)₂Cl₂ and AlMe₃ (in toluene) afforded a racemic product. In all cases the chemical yield was low (<35%).

Experimental

General methods. All reactions were carried out in flame-dried glassware under argon using anhydrous solvents. Evaporation of solvents was performed under reduced pressure using a Büchi rotary evaporator. All solvents were purified prior to use. Products were isolated by column or flash chromatography on SiO₂ (Si 60, Merck, 40–63 μm) and detected by UV or revealed by coloration with aqueous basic potassium permanganate solution. ¹H and ¹³C NMR: ARX 200, AC 300 (all Bruker); chemical shifts in values relative to tetramethylsilane (δ=0) for protons and CDCl₃ (δ=77) for carbon atoms. MS: CH 7 A, Varian. Optical rotations: Perkin-Elmer 241 (*l*=1 dm). Elemental analyses: CHN-Rapid, Haraeus. GC: Siemens Sichromat 3 (integration: Shimadzu C-R3A); column: Durabond DB-5, 0.3 mm × 30 m. HPLC: Merck (pump: L-6200A, detector: L-4250, UV-VIS); columns: Nucleosil 120–3 (CS-Chromatographie Service) and Chiralcel OD (Daicel), 25 cm × 0.46 cm i.d. Ethyl-*O*-(mesitylsulfonyl)acetohydroxamate,^{43,44} trimethylsilyl cyanide,⁵⁵ and menthyl 2-methoxynaphthylsulfinate⁴⁵ were synthesized according to published procedures. Ti(*O*-*i*-Pr)₄ was purchased from Merck, distilled and stored under argon. All aldehydes were distilled and stored under argon. Cumene hydroperoxide, (*R,R*)-(+)-diethyl tartrate and boron tribromide were purchased from Aldrich and used without further purification. (*R*)-(-)-MTPA chloride was obtained from JPS Chimie.

General procedures for the titanium-mediated TMSCN addition to various aldehydes. To a stirred solution of (*R*)-**4a** (235 mg, 1.375 mmol) in dichloromethane (3 ml) was added Ti(*O*-*i*-Pr)₄ (0.365 ml, 1.250 mmol). The resulting yellow solution was stirred at ambient temperature for 1 h, after which the mixture was cooled to -50 °C. The aldehyde (1.250 mmol) was added dropwise followed by trimethylsilyl cyanide (0.315 ml, 250 mg, 2.520 mmol). Stirring was continued at this temperature for 20–24 h. The reaction mixture was then quenched with an aqueous solution of HF (5%, 2 ml) and stirred vigorously for 30 min at ambient temperature. After

neutralization with NaHCO₃ the mixture was extracted by dichloromethane (5 × 5 ml). The combined organic extracts were dried over MgSO₄, filtered, and then concentrated under reduced pressure. The residue was column chromatographed (silica gel; eluent: hexane-*tert*-butyl methyl ether), affording (*S*)-cyanohydrins. The enantiomeric excesses of the products were determined by ¹⁹F NMR spectroscopy, GC, or HPLC analysis of the corresponding MTPA esters. Sulfoximine (*R*)-**4a** was recovered in 70–90% yield by elution of the chromatography column with *tert*-butyl methyl ether.

(*S*)-2-Hydroxy-2-phenylacetonitrile [(*S*)-**2a**]. Yield: 126 mg (0.91 mmol, 72%). [α]_D²⁴ -39.1° (*c* 1.6, CHCl₃); ¹H NMR (CDCl₃): δ 2.87 (br s, 1 H), 5.52 (s, 1 H), 7.37–7.60 (m, 5 H). The ee (91%) was determined by GC analysis of the corresponding MTPA ester: *t*_r of *S,S*-diastereomer 26.7 min; *t*_r of *R,S*-diastereomer 27.4 min [120 °C, 0.4 °C min⁻¹].

(*S*)-2-Hydroxy-2-(4-methoxyphenyl)acetonitrile [(*S*)-**2b**]. Yield: 123 mg (0.75 mmol, 60%). [α]_D²⁴ -39.7° (*c* 1.6, CHCl₃); ¹H NMR (CDCl₃): δ 3.40 (br s, 1 H), 3.82 (s, 3 H), 5.45 (s, 1 H), 6.93 (d, 2 H, *J* 8.65 Hz), 7.43 (d, 2 H, *J* 8.65 Hz). The ee (87%) was determined by HPLC analysis of the corresponding MTPA ester: *t*_r of *S,S*-diastereomer 16.3 min; *t*_r of *R,S*-diastereomer 19.0 min [eluent: hexane-ethyl acetate 20:1; flow: 0.5 ml min⁻¹].

(*S*)-2-Hydroxy-2-(2-methoxyphenyl)acetonitrile [(*S*)-**2c**]. Yield: 139 mg (0.91 mmol, 72%). [α]_D²⁴ -3.6° (*c* 1.4, CHCl₃); ¹H NMR (CDCl₃): δ 3.75 (d, 1 H, *J* 8.44 Hz), 3.92 (s, 3 H), 5.57 (d, 1 H, *J* 7.85 Hz), 6.95–7.03 (m, 2 H), 7.37–7.42 (m, 2 H). The ee (74%) was determined by HPLC analysis of the corresponding MTPA ester: *t*_r of *S,S*-diastereomer 16.0 min; *t*_r of *R,S*-diastereomer 19.3 min [eluent: hexane-ethyl acetate 20:1; flow: 0.5 ml min⁻¹].

(*S*)-2-Hydroxy-2-(1-naphthyl)acetonitrile [(*S*)-**2d**]. Yield: 211 mg (1.15 mmol, 92%). [α]_D²⁴ -62.6° (*c* 1.4, CHCl₃); ¹H NMR (CDCl₃): δ 3.31 (s, 1 H), 6.09 (s, 1 H), 7.43–7.61 (m, 3 H), 7.76 (d, 1 H, *J* 7.10 Hz), 7.90 (d, 2 H, *J* 7.86 Hz), 8.08 (d, 1 H, *J* 8.07 Hz). The ee (76%) was determined by HPLC analysis of the corresponding MTPA ester: *t*_r of *S,S*-diastereomer 10.2 min; *t*_r of *R,S*-diastereomer 11.6 min [eluent: hexane-ethyl acetate 20:1; flow: 0.5 ml min⁻¹].

(*S*)-2-Hydroxyheptanenitrile [(*S*)-**2e**]. Yield: 102 mg (0.80 mmol, 64%). [α]_D²⁴ -11.5° (*c* 1.1, CHCl₃); ¹H NMR (CDCl₃): δ 0.91 (t, 3 H, *J* 6.91), 1.25–1.42 (m, 4 H), 1.45–1.55 (m, 2 H), 1.80–1.88 (m, 2 H), 3.43 (b, s, 1 H), 4.46 (t, 1 H, *J* 6.72). The ee (89%) was determined by GC analysis of the corresponding MTPA ester: *t*_r of *S,S*-diastereomer 22.4 min; *t*_r of *R,S*-diastereomer 23.3 min [120 °C, 0.4 °C min⁻¹].

(*S*)-2-Cyclohexyl-2-hydroxyacetonitrile [(*S*)-2f]. Yield: 121 mg (0.87 mmol, 70%). $[\alpha]_D^{24} -6.2^\circ$ (*c* 1.9, CHCl₃); ¹H NMR (CDCl₃): δ 1.02–1.38 (m, 6 H), 1.60–1.87 (m, 5 H), 3.60 (br s, 1 H), 4.22 (d, 1 H, *J* 6.28 Hz). The ee (89%) was determined by GC analysis of the corresponding MTPA ester: *t*_r of *S,S*-diastereomer 27.0 min; *t*_r of *R,S*-diastereomer 28.0 min [120 °C, 0.4 °C min⁻¹].

(*S*)-3,3-Dimethyl-2-hydroxybutanenitrile [(*S*)-2g]. Yield: 100 mg (0.88 mmol, 70%). $[\alpha]_D^{24} -20.9^\circ$ (*c* 1.1, CHCl₃); ¹H NMR (CDCl₃): δ 1.07 (s, 9 H), 3.30 (s, 1 H), 4.13 (s, 1 H). The ee (81%) was determined by GC analysis of the corresponding MTPA ester: *t*_r of *S,S*-diastereomer 17.1 min; *t*_r of *R,S*-diastereomer 18.0 min [120 °C, 0.4 °C min⁻¹].

(*S*)-(E)-2-Hydroxy-4-phenyl-3-butenenitrile [(*S*)-2h]. Yield: 126 mg (0.79 mmol, 63%). $[\alpha]_D^{24} -24.4^\circ$ (*c* 1.3, CHCl₃); ¹H NMR (CDCl₃): δ 3.56 (s, 1 H), 5.13 (d, 1 H, *J* 5.92 Hz), 6.22 (dd, 1 H, *J* 5.92 Hz, *J* 15.87 Hz), 6.87 (d, 1 H, *J* 15.87 Hz), 7.28–7.39 (m, 5 H). The ee (79%) was determined by HPLC analysis of the corresponding MTPA ester: *t*_r of *S,S*-diastereomer 9.6 min; *t*_r of *R,S*-diastereomer 11.0 min [eluent: hexane–ethyl acetate 20:1, flow: 0.5 ml min⁻¹].

(*S*)-2-Hydroxy-2-(3-thienyl)acetonitrile [(*S*)-2i]. Yield: 65 mg (0.47 mmol, 37%). $[\alpha]_D^{24} -30.7^\circ$ (*c* 1.1, CHCl₃); ¹H NMR (CDCl₃): δ 3.30 (s, 1 H), 5.55 (s, 1 H), 7.18 (dd, 1 H, *J* 1.24 Hz, *J* 5.03 Hz), 7.38–7.41 (m, 1 H), 7.49–7.51 (m, 1 H). The ee (37%) was determined by HPLC analysis of the corresponding MTPA ester: *t*_r of major diastereomer 11.7 min; *t*_r of minor diastereomer 13.9 min [eluent: hexane–ethyl acetate 20:1, flow: 0.5 ml min⁻¹]. Absolute configuration unconfirmed.

Titanium-mediated HCN additon to benzaldehyde (1a). This followed the general procedure for the Ti-mediated TMSCN addition using: 235 mg (1.375 mmol) of sulfoximine (*R*)-4a, 3 ml of CH₂Cl₂, 0.365 ml (1.250 mmol) of Ti(O-*i*-Pr)₄, 0.125 ml (1.250 mmol) of benzaldehyde and 0.400 ml (355 mg, 13.2 mmol) of hydrogen cyanide. After 18 h the reaction mixture was quenched with an aqueous solution of HF (5%, 2 ml) and the product was isolated as described in the protocol of the stoichiometric TMSCN addition reaction (using silica gel; eluent: petroleum ether–*tert*-butyl methyl ether 5:1). Yield: 149 mg (89%) of (*S*)-mandelonitrile [(*S*)-2a] with 64% ee.

General procedure for the titanium-catalyzed TMSCN additon to benzaldehyde (1a) using various sulfoximines. To a stirred solution of the sulfoximine (0.55 mmol) in CH₂Cl₂ (2.5 ml) was added Ti(O-*i*-Pr)₄ (0.180 ml, 0.50 mmol). The resulting yellow solution was stirred at ambient temperature for 1 h after which, the mixture was cooled to –45 °C. Benzaldehyde (0.250 ml, 2.46 mmol) was added dropwise followed by trimethylsilyl cyanide (0.750 ml, 595 mg, 6.0 mmol). Stirring was

continued at this temperature for 18 h. The reaction mixture was then quenched with an aqueous solution of HF (5%, 2 ml) and the product was isolated as described in the protocol for the stoichiometric TMSCN addition reaction (silica gel; eluent: petroleum ether–*tert*-butyl methyl ether 5:1). The yields and optical purities are given in Table 2.

Syntheses of the sulfoximines

2-Methoxyphenyl methyl sulfide (5). To TMEDA (50 ml) was added a hexane solution of butyllithium (1.45 mol l⁻¹, 180 ml, 0.26 mol) at 0 °C. After stirring of the mixture for 20 min at ambient temperature methyl phenyl ether (24.0 ml, 24.17 g, 0.223 mol) was added dropwise. Stirring of the resulting suspension was continued for 30 min at 45 °C. THF (80 ml) was then added, and the solution was cooled to –78 °C. Dropwise addition of dimethyl disulfide (24.0 ml, 22.6 g, 0.240 mol) was followed by warming to room temperature and stirring overnight. The mixture was then quenched with water (200 ml), and extracted five times with diethyl ether (50 ml each). The combined organic extracts were dried over MgSO₄, and then the solvent was evaporated off under reduced pressure. The residue was distilled, affording 22.5 g (0.146 mol, 62%) of 5. B.p. 58–62 °C/0.1 hPa, 121–122 °C/25 hPa; ¹H NMR (CDCl₃): δ 2.13 (s, 3 H), 3.89 (s, 3 H), 6.81–6.85 (m, 1 H), 6.91–6.99 (m, 1 H) 7.10–7.18 (m, 2 H); ¹³C NMR (CDCl₃): d 14.7, 55.7, 110.0, 121.1, 125.9, 126.1, 126.7, 156.2.

(*R*)-2-Methoxyphenyl methyl sulfoxide [(*R*)-6]. To a solution of (*R,R*)-(+)-diethyl tartrate (17.1 ml, 20.6 g, 100 mmol) in dichloromethane (420 ml) was added Ti(O-*i*-Pr)₄ (14.6 ml, 14.2 g, 50 mmol) at ambient temperature. After 10 min water (0.9 ml, 50 mmol) was added dropwise to the pale yellow solution. Stirring was continued vigorously for 25 min. After the addition of 2-methoxyphenyl methyl sulfide (15.4 g, 100 mmol), the solution was cooled to –30 °C and stirred for 40 min at this temperature. Then cumene hydroperoxide (14.8 ml, 15.24 g, 100 mmol) was added dropwise and the reaction mixture was kept at –23 °C overnight. Hydrolysis with water (17.0 ml) was followed by vigorous stirring for 90 min at ambient temperature. A sintered-glass funnel was partially filled with Celite (Celite height: approx. 2 cm) and impregnated with dichloromethane. The suspension resulting from the hydrolysis was filtered through Celite under suction. The Celite was washed several times with technical grade dichloromethane. In order to accelerate filtration, the surface of the Celite was disturbed from time to time with a spatula. The filtrate (1000 ml) was added to a mixture of 2 M sodium hydroxide (240 ml) and a solution of saturated aqueous sodium chloride (120 ml) and the combined solutions were vigorously stirred for 1 h. The organic phase was separated, dried over MgSO₄, filtered and concentrated under reduced pressure. Column chromatography (silica gel;

eluent: petroleum ether–*tert*-butyl methyl ether 4:1), and elution of the sulfoxide with *tert*-butyl methyl ether afforded 17.2 g of (*R*)-**6**. Two recrystallizations from hexane (150 ml and 120 ml) gave 10.3 g (60.5 mmol, 61%) of enantiopure (*R*)-**6** (HPLC analysis). $[\alpha]_D^{24} + 340.0^\circ$ (*c* 1.5, acetone); $^1\text{H NMR}$ (CDCl_3): δ 2.73 (s, 3 H), 3.85 (s, 3 H), 6.88 (d, 1 H, *J* 8.20 Hz), 7.18 (t, 1 H, *J* 7.51 Hz), 7.42 (td, 1 H, *J* 1.75 Hz, *J* 7.50 Hz), 7.78 (dd, 1 H, *J* 1.75 Hz, *J* 7.50 Hz); $^{13}\text{C NMR}$ (CDCl_3): δ 41.1, 55.6, 110.5, 121.6, 124.5, 131.9, 133.0, 154.7.

(*R*)-*S*-2-Methoxyphenyl *S*-methyl sulfoximine [(*R*)-**7**]. Ethyl *o*-(mesitylsulfonyl)acetohydroxamate (17.1 g, 60 mmol) was dissolved in dioxane (15 ml) and the solution was cooled to 0 °C. Perchloric acid (70%, 7.5 ml) was added dropwise at a rate to maintain the temperature at approximately 5 °C. The resulting suspension was stirred at 0 °C for 10 min. Then ice–water (50 ml) was added and the crude *o*-mesitylenesulfonylhydroxylamine (MSH) was filtered off, washed three times with ice–water (20 ml each), and dissolved in dichloromethane (40 ml). The solution was separated from water, dried over magnesium sulfate, filtered and added to solid (*R*)-**6** (5.0 g, 29.4 mmol). After 2 h the reaction mixture was treated with 10% sodium hydroxide (20 ml), and extracted five times with dichloromethane (20 ml each). The combined extracts were washed with saturated aqueous sodium chloride (20 ml), dried over magnesium sulfate, filtered and concentrated under reduced pressure. Column chromatography (silica gel; eluent: *tert*-butyl methyl ether for the sulfoxide, then *tert*-butyl methyl ether–methanol 2:1 for the sulfoximine) afforded 3.2 g (17.3 mmol) of sulfoximine (*R*)-**7** (59%) and 1.1 g (6.5 mmol) of (*R*)-**6** (22%). $[\alpha]_D^{24} - 32.0^\circ$ (*c* 1.6, CHCl_3); Anal. calcd. for $\text{C}_8\text{H}_{11}\text{NO}_2\text{S}$: C 51.87, H 5.99, N 7.56. Found: C 51.81, H 5.84, N 7.40; MS [*m/z* (% rel. int.)]: 185 (11, [M^+]), 184 (37), 156 (20), 94 (27), 92 (66), 91 (35), 80 (64), 77 (100), 63 (22), 51 (20); $^1\text{H NMR}$ (CDCl_3): δ 2.77 (br s, 1 H), 3.22 (s, 3 H), 3.94 (s, 3 H), 6.98–7.07 (m, 2 H), 7.48–7.89 (m, 1 H), 7.90 (dd, 1 H, *J* 1.47 Hz, *J* 7.75 Hz); $^{13}\text{C NMR}$ (CDCl_3): δ 43.9, 56.1, 112.2, 120.5, 129.2, 131.2, 134.6, 156.6.

(*R*)-*S*-2-Hydroxyphenyl *S*-methyl sulfoximine [(*R*)-**4a**]. To a stirred solution of (*R*)-**6** (1.85 g, 10 mmol) in dichloromethane (20 ml) was added dropwise a 1 M solution of boron tribromide (20 ml, 20 mmol) in dichloromethane at –78 °C. The reaction mixture was warmed to room temperature overnight. The resulting suspension was carefully quenched with water, neutralized with NaHCO_3 and the mixture was extracted five times with dichloromethane (20 ml each). The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. Column chromatography (silica gel; eluent: petroleum ether–*tert*-butyl methyl ether 1:1) gave 1.61 g (94%) of (*R*)-**4a**. $[\alpha]_D^{24} - 10.4^\circ$ (*c* 1.4, CHCl_3); Anal. calcd. for $\text{C}_7\text{H}_9\text{NO}_2\text{S}$: C 49.10, H 5.30, N 8.18. Found: C 49.25, H 5.60, N 7.81;

MS [*m/z* (% rel. int.)]: 171 (100, [M^+]), 110 (14), 109 (25), 108 (22), 107 (20), 80 (30), 65 (33), 64 (18), 63 (25), 52 (13); $^1\text{H NMR}$ (CDCl_3): δ 3.16 (s, 3 H), 6.93–7.00 (m, 2 H), 7.43–7.51 (m, 1 H), 7.69–7.74 (m, 1 H); $^{13}\text{C NMR}$ (CDCl_3): δ 48.3, 119.1, 119.9, 122.1, 128.4, 136.0, 156.5.

The molecular structure of (*R*)-**4a** was confirmed by X-ray crystallography.

(*R*)-*S*-Ethyl *S*-2-hydroxyphenyl sulfoximine [(*R*)-**4b**]. A suspension of (*R*)-**4a** (342 mg, 2 mmol) in hexamethyldisilazane (3 ml) was stirred at 80–85 °C for 40 min. During this period the sulfoximine dissolved completely. The solution was concentrated under reduced pressure and the residue was dissolved in THF (10 ml). A hexane solution of butyllithium (1.5 mol l^{-1} , 2 ml, 3 mmol) was added dropwise at 0 °C. The yellow solution was stirred for 5 min, and then allowed to reach room temperature. Iodomethane (0.2 ml, 455 mg, 3.2 mmol) was added and the resulting mixture was stirred overnight. Hydrolysis with a saturated solution of ammonium chloride (5 ml) was followed by extraction of the reaction mixture with dichloromethane ($5 \times 5 \text{ ml}$). The combined organic extracts were dried over MgSO_4 , filtered, and then concentrated under reduced pressure. Column chromatography (silica gel; eluent: petroleum ether–*tert*-butyl methyl ether 1.5:1) gave 205 mg (1.11 mmol) (55%) of (*R*)-**4b**. $[\alpha]_D^{24} - 1.4^\circ$ (*c* 1.8, CHCl_3); Anal. calcd. for $\text{C}_8\text{H}_{11}\text{NO}_2\text{S}$: C 51.87, H 5.99, N 7.56. Found: C 52.20, H 6.06, N 7.39; MS [*m/z* (% rel. int.)]: 185 (46, [M^+]), 140 (100), 109 (25), 96 (25), 92 (40), 80 (22), 65 (63), 64 (23), 63 (32), 39 (47); $^1\text{H NMR}$ (CDCl_3): δ 1.26 (t, 3 H, *J* 7.40 Hz), 3.13–3.30 (m, 2 H), 6.93–6.99 (m, 2 H), 7.44–7.47 (m, 1 H), 7.64–7.68 (m, 1 H); $^{13}\text{C NMR}$ (CDCl_3): δ 7.7, 54.3, 118.8, 119.1, 119.6, 128.9, 135.9, 157.2.

(*R*)-*S*-2-Hydroxyphenyl *S*-1-methylethyl sulfoximine [(*R*)-**4c**]. A suspension of (*R*)-**4a** (500 mg, 2.92 mmol) in hexamethyldisilazane (4 ml) was stirred at 80–85 °C for 40 min. During this period the sulfoximine dissolved completely. The solution was concentrated under reduced pressure and the residue was dissolved in THF (15 ml). A hexane solution of butyllithium (1.0 mol l^{-1} , 9 ml, 9.0 mmol) was added dropwise at 0 °C. The yellow solution was stirred for 5 min, and then allowed to reach room temperature. Iodomethane (0.55 ml, 1.25 g, 8.8 mmol) was added and the mixture was then stirred at ambient temperature for 30 min. It was then cooled to 0 °C after which a hexane solution of butyllithium solution (1.0 mol l^{-1} , 1.5 ml, 1.5 mmol) was added, the mixture was warmed to room temperature and treated with additional iodomethane (0.55 ml, 1.25 g, 8.8 mmol). The solution was stirred overnight and then quenched with methanol (2 ml). Stirring was continued for 30 min, and then a saturated solution of NH_4Cl (5 ml) was added. The mixture was extracted five times with 5 ml of dichloromethane each. The combined organic extracts

were dried over MgSO_4 , filtered, and then concentrated under reduced pressure. Column chromatography (silica gel; eluent: petroleum ether–*tert*-butyl methyl ether 1.5:1) afforded 70 mg (0.38 mmol, 13%) of (*R*)-**4b** and 345 mg (1.73 mmol, 59%) of (*R*)-**4c**. $[\alpha]_D^{24} + 13.9^\circ$ (*c* 0.32, CHCl_3); Anal. calcd. for $\text{C}_9\text{H}_{13}\text{NO}_2\text{S}$: C 54.24, H 6.57, N 7.03. Found: C 54.23, H 6.89, N 6.88; MS [*m/z* (% rel. int.)]: 199 (14, [M^+]), 140 (100), 109 (23), 96 (29), 92 (35), 65 (51), 63 (26), 43 (60), 41 (21), 39 (36); $^1\text{H NMR}$ (CDCl_3): δ 1.33 (d, 3 H, *J* 6.82 Hz), 1.28 (d, 3 H, *J* 6.82 Hz), 3.29 (septet, 1 H, *J* 6.82 Hz), 6.98 (m, 2 H), 7.46–7.52 (m, 1 H), 7.64–7.67 (m, 1 H); $^{13}\text{C NMR}$ (CDCl_3): δ 15.0, 16.1, 59.2, 117.3, 118.6, 119.5, 129.3, 135.9, 157.7.

(*R*)-*S*-2-Hydroxyphenyl *S*-1,1-dimethylethyl sulfoximine [(*R*)-**4d**]. A suspension of (*R*)-**4d** (345 mg, 1.73 mmol) in hexamethyldisilazane (3 ml) was stirred at 80–85 °C for 40 min. During this period the sulfoximine dissolved completely. The solution was concentrated under reduced pressure. Then the residue was dissolved in THF (10 ml). A hexane solution of butyllithium (1.90 mol l^{-1} , 2.7 ml, 5.2 mmol) was added dropwise at 0 °C. The yellow solution was stirred for 5 min, and then the solution was allowed to reach room temperature. To the solution was added iodomethane (0.32 ml, 728 mg, 5.2 mmol), and then the mixture was stirred overnight. The reaction mixture was quenched with methanol (2 ml) and stirred for 30 min. Then a saturated solution of NH_4Cl (5 ml) was added and the mixture was extracted five times with 5 ml of dichloromethane each. The combined organic extracts were dried over MgSO_4 , filtered, and then concentrated under reduced pressure. Column chromatography (silica gel; eluent: petroleum ether–*tert*-butyl methyl ether 1.5:1) gave 198 mg (0.93 mmol, 54%) of (*R*)-**4d**. $[\alpha]_D^{24} + 17.8^\circ$ (*c* 1.9, CHCl_3); Anal. calcd. for $\text{C}_{10}\text{H}_{15}\text{NO}_2\text{S}$: C 56.31, H 7.08, N 6.56. Found: C 55.96, H 7.39, N 6.37; MS [*m/z* (% rel. int.)]: 213 (5, [M^+]), 157 (40), 141 (16), 140 (100), 139 (11), 109 (12), 92 (13), 65 (15), 57 (41), 41 (25); $^1\text{H NMR}$ (CDCl_3): δ 1.30 (s, 9 H), 6.85–6.94 (m, 2 H), 7.39–7.48 (m, 1 H), 7.60 (dd, 1 H, *J* 1.75 Hz, *J* 8.0 Hz); $^{13}\text{C NMR}$ (CDCl_3): δ 23.2, 63.8, 115.5, 118.6, 118.7, 130.7, 135.9, 158.1.

The molecular structure of (*R*)-**4d** was confirmed by X-ray crystallography.

(*R*)-*S*-2-Hydroxyphenyl *S*-2-phenylethyl sulfoximine [(*R*)-**4e**]. The reaction was carried out as described for the synthesis of (*R*)-**4b** using 514 mg (3 mmol) of (*R*)-**4a**, 4 ml of hexamethyldisilazane, 2.1 ml of a solution of butyllithium in hexane (1.6 mol l^{-1} , 3.3 mmol) and 0.40 ml of benzyl bromide (570 mg, 3.3 mmol). Column chromatography (silica gel; eluent: petroleum ether–*tert*-butyl methyl ether 1.5:1) gave 408 mg (1.56 mmol, 52%) of (*R*)-**4e**. $[\alpha]_D^{24} + 26.4^\circ$ (*c* 1.9, CHCl_3); Anal. calcd. for $\text{C}_{14}\text{H}_{15}\text{NO}_2\text{S}$: C 64.34, H 5.79, N 5.36. Found: C 64.10, H 6.00, N 5.52; MS [*m/z* (% rel. int.)]: 261 (3, [M^+]), 157 (40), 140 (53), 105 (100), 104 (35), 103 (13), 79

(16), 77 (21); $^1\text{H NMR}$ (CDCl_3): δ 3.00–3.05 (m, 2 H), 3.44–3.50 (m, 2 H), 6.96–7.02 (m, 1 H), 7.10–7.13 (m, 1 H), 7.19–7.29 (m, 1 H), 7.46–7.52 (m, 1 H), 7.69–7.73 (m, 1 H); $^{13}\text{C NMR}$ (CDCl_3): δ 29.2, 61.0, 119.1, 119.3, 119.9, 127.0, 128.3, 128.5, 128.9, 136.1, 137.1, 157.2.

(*R*)-*N,S*-Dimethyl *S*-2-methoxyphenyl sulfoximine [(*R*)-**9**]. A mixture of (*R*)-**4a** (1.0 g, 5.4 mmol), formic acid (41.3 ml) and formaldehyde (37%, 9.5 ml) was refluxed for 3 days. The excess of formic acid and formaldehyde was then removed under reduced pressure. The residue was dissolved in 1 M sulfuric acid (5 ml) and the resulting solution was extracted three times with *tert*-butyl methyl ether. An aqueous solution of NaOH (2 M) was added dropwise until the mixture became slightly basic. The mixture was extracted five times with dichloromethane (5 ml each) and the combined organic extracts were dried over MgSO_4 , filtered, and then concentrated under reduced pressure. The residue was distilled and 760 mg (3.8 mmol, 71%) of (*R*)-**9** were obtained. Anal. calcd. for $\text{C}_9\text{H}_{13}\text{NO}_2\text{S}$: C 54.24, H 6.57, N 7.03. Found: C 53.73, H 6.90, N 6.65; MS [*m/z* (% rel. int.)]: 199 (34, [M^+]), 198 (41), 169 (56), 153 (43), 136 (45), 125 (56), 121 (73), 94 (85), 92 (49), 77 (100); $^1\text{H NMR}$ (CDCl_3): δ 2.60 (s, 3 H), 3.26 (s, 3 H), 3.99 (s, 3 H), 7.11–7.16 (m, 2 H), 7.57–7.61 (m, 1 H), 7.94–7.99 (m, 1 H); $^{13}\text{C NMR}$ (CDCl_3): δ 29.5, 42.7, 55.9, 111.9, 120.4, 125.3, 131.8, 134.5, 156.6.

(*R*)-*N,S*-Dimethyl *S*-2-hydroxyphenyl sulfoximine [(*R*)-**10**]. The reaction was carried out as described for the synthesis of (*R*)-**4a** using 400 mg (2 mmol) of (*R*)-**9**, 2 ml of dichloromethane and 2 ml (2 mmol) of a 1 M solution of boron tribromide in dichloromethane. Column chromatography (silica gel; eluent: petroleum ether–*tert*-butyl methyl ether 1:1) gave 205 mg (1.1 mmol, 55%) of (*R*)-**10**. $[\alpha]_D^{24} - 45.0^\circ$ (*c* 1.8, CHCl_3); Anal. calcd. for $\text{C}_8\text{H}_{11}\text{NO}_2\text{S}$: C 51.87, H 5.98, N 7.56. Found: C 51.67, H 6.08, N 7.41; MS [*m/z* (% rel. int.)]: 185 (100, [M^+]), 156 (20), 141 (80), 122 (28), 108 (17), 107 (17), 94 (16), 65 (26); $^1\text{H NMR}$ (CDCl_3): δ 2.90 (s, 3 H), 3.12 (s, 3 H), 6.95–7.00 (m, 2 H), 7.45–7.51 (m, 1 H), 7.68–7.71 (m, 1 H); $^{13}\text{C NMR}$ (CDCl_3): δ 28.5, 42.7, 119.0, 119.6, 119.9, 128.4, 135.8, 157.1.

(*R*)-*S*-2-Methoxynaphthyl *S*-methyl sulfoxide [(*R*)-**17**].⁴⁵ To a solution of methylmagnesium iodide in 20 ml diethyl ether [prepared from 0.65 ml (1.48 g, 10.4 mmol) of iodomethane and 0.27 g (11.1 mmol) of magnesium] was added solid menthyl 2-methoxynaphthyl sulfinate (3.60 g, 9.7 mmol). The mixture was stirred overnight, and then quenched with a saturated aqueous solution of NH_4Cl (5 ml). The reaction mixture was extracted five times with 5 ml of dichloromethane each. The combined organic extracts were dried over MgSO_4 , filtered, and then concentrated under reduced pressure. Column chromatography (silica gel; eluent: petroleum ether–*tert*-butyl

methyl ether) gave 1.12 g (5.1 mmol, 53%) of (*R*)-**17**. Anal. calcd. for $C_{12}H_{12}O_2S$: C 65.43, H 5.49. Found: C 65.23, H 5.28; MS [m/z (% rel. int.)]: 220 (34, [M^+]), 206 (15), 205 (100), 203 (11), 188 (16), 159 (12), 147 (24); 1H NMR ($CDCl_3$): δ 3.08 (s, 3 H), 4.01 (s, 3 H), 7.25 (d, 1 H, J 9.21 Hz), 7.38–7.44 (m, 1 H), 7.52–7.58 (m, 1 H), 7.81 (m, 1 H), 7.94 (d, 1 H, J 9.08 Hz), 9.04 (m, 1 H); ^{13}C NMR ($CDCl_3$): δ 39.1, 56.8, 112.8, 122.4, 124.4, 127.8, 128.7, 129.5, 131.9, 133.9, 155.8.

(*R*)-*S*-2-Methoxynaphthyl *S*-methyl sulfoximine [(*R*)-**18**]. The reaction was carried out as described for the synthesis of (*R*)-**7** using 3.0 g (10.5 mmol) of ethyl *O*-(mesitylsulfonyl)acetohydroxamate, 2 ml of dioxane, 1.2 ml of perchloric acid (70%) and 1.0 g (4.54 mmol) of (*R*)-**17**. After the addition of MSH (2 h) the reaction mixture was treated with 10% sodium hydroxide (5 ml) and extracted five times with dichloromethane (5 ml each). The solvent was then evaporated off, and the residue was treated with a 1 M solution of HCl (5 ml). The mixture was extracted three times with dichloromethane (5 ml each). To the aqueous solution was added a 1 M solution of NaOH (6 ml), and then the mixture was extracted five times with dichloromethane (5 ml each). The combined extracts were washed with saturated aqueous sodium chloride (5 ml), dried over magnesium sulfate, filtered and concentrated under reduced pressure, affording 609 mg (2.59 mmol, 57%) of (*R*)-**18**. Anal. calcd. for $C_{12}H_{13}NO_2S$: C 61.25, H 5.57, N 5.95. Found: C 60.91, H 5.63, N 5.73; MS [m/z (% rel. int.)]: 235 (100, [M^+]),

234 (35), 172 (27), 144 (46), 142 (32), 128 (22), 127 (55), 115 (40), 114 (33); 1H NMR ($CDCl_3$): δ 3.30 (br s, 1 H), 3.45 (s, 3 H), 4.09 (s, 3 H), 7.32 (d, 1 H, J 9.14 Hz), 7.41–7.46 (m, 1 H), 7.57–7.62 (m, 1 H), 7.80 (d, 1 H, J 8.12 Hz), 8.01 (d, 1 H, J 8.96 Hz), 9.29 (d, 1 H, J 8.96 Hz); ^{13}C NMR ($CDCl_3$): δ 48.0, 57.1, 113.4, 124.0, 124.5, 128.4, 128.7, 129.5, 130.7, 135.4, 155.9.

(*R*)-*S*-2-hydroxynaphthyl *S*-methyl sulfoximine [(*R*)-**19**]. The reaction was carried out as described for the synthesis of (*R*)-**4a** using 385 mg (1.64 mmol) of (*R*)-**18**, 4 ml of dichloromethane and 3.3 ml (3.3 mmol) of a 1 M solution of boron tribromide in dichloromethane. Column chromatography (silica gel; eluent: petroleum ether–*tert*-butyl methyl ether) gave 305 mg (1.38 mmol, 84%) of (*R*)-**19**. [α] $_D^{24}$ –55.7° (c 1.9, $CHCl_3$); Anal. calcd. for $C_{11}H_{11}NO_2S$: C 59.71, H 5.01, N 6.33. Found: C 59.60, H 5.20, N 6.21; MS [m/z (% rel. int.)]: 222 (14), 221 (100, [M^+]), 158 (18), 146 (17), 144 (22), 130 (25), 115 (36), 114 (33), 63 (15), 58 (26); 1H NMR ($CDCl_3$): δ 3.41 (s, 3 H), 7.13 (d, 1 H, J 9.19 Hz), 7.38–7.43 (m, 1 H), 7.58–7.64 (m, 1 H), 7.79 (d, 1 H, J 8.09 Hz), 7.91 (d, 1 H, J 8.82 Hz), 8.72 (d, 1 H, J 8.82 Hz); ^{13}C NMR ($CDCl_3$): δ 48.2, 121.0, 122.4, 123.9, 128.6, 128.8, 129.5, 130.4, 136.8, 159.0.

X-Ray crystal structure determinations. Unit cell parameters were determined by centering 45 (for **4a**) and 25 (for **4d**) strong, independent reflections. Data collections were performed on four-circle diffractometers P4

Table 3. Crystal data and details of refinements for the X-ray diffraction studies of (*R*)-**4a** and (*R*)-**4d**.

| Data | (<i>R</i>)- 4a | (<i>R</i>)- 4d |
|--|-------------------------|-------------------------|
| Crystal dimensions/mm | 0.40 × 0.30 × 0.20 | |
| Crystal system | Hexagonal | Monoclinic |
| Space group | $P 6_1$ | $P 2_1$ |
| Z | 6 | 2 |
| a /pm | 1382.0(2) | 682.0(1) |
| b /pm | 1382.0(2) | 649.4(1) |
| c /pm | 862.5(2) | 1247.1(2) |
| α /° | 90 | 90 |
| β /° | 90 | 97.49(3) |
| γ /° | 120 | 90 |
| V /nm ³ | 1.4266(4) | 547.6(2) |
| ρ_{calcd} /Mg m ⁻³ | 1.280 | 1.294 |
| θ_{max} | 36.27 | 59.95 |
| Radiation (λ /pm) | MoK α (71.073) | CuK α (154.178) |
| Scan mode | ω | ω - θ |
| Temperature of measurement/K | 293(2) | 293(2) |
| No. of measured reflections | 3426 | 3542 |
| No. of independent reflections | 1337 | 1621 |
| No. of observed reflections [$I > 2\sigma(I)$] | 1180 | 1605 |
| No. of reflections included in refinement | 1333 | 1611 |
| μ /mm ⁻¹ | 0.300 | 2.432 |
| No. of parameters | 115 | 139 |
| R [(on F , for refl. $I > 2\sigma(I)$)] | 0.0386 | 0.0372 |
| $wR2$ (on F^2 , all data) | 0.1053 | 0.0728 |
| Goodness-of-fit (all omitted data) | 1.059 | 0.995 |
| No. of omitted 'bad' reflection | 4 | 10 |
| $\Delta\rho$ /e nm ⁻³ | 239/–0.204 | 227/–202 |

Table 4. Final positional and isotropic equivalent displacement parameters ($m^2 \times 10^{-20} = \text{\AA}^2$) for (R)-**4a** (e.s.d.s given in parentheses).

| Atom | x | y | z | U(eq) |
|--------|------------|------------|------------|------------|
| S(1) | 0.70908(8) | 0.57872(8) | 0.96996(9) | 0.0505(3) |
| O(1) | 0.8196(3) | 0.6287(3) | 1.0362(4) | 0.0893(11) |
| N(1) | 0.6311(2) | 0.6199(3) | 1.0204(3) | 0.0530(8) |
| O(2) | 0.5323(2) | 0.4738(2) | 0.7275(3) | 0.0641(7) |
| C(1) | 0.7268(3) | 0.5830(3) | 0.7663(4) | 0.0467(9) |
| C(2) | 0.6365(3) | 0.5320(3) | 0.6652(4) | 0.0480(9) |
| C(3) | 0.6561(3) | 0.5411(4) | 0.5077(5) | 0.0586(10) |
| C(4) | 0.7620(4) | 0.6006(4) | 0.4527(5) | 0.0674(12) |
| C(5) | 0.8524(4) | 0.6524(4) | 0.5488(5) | 0.0749(13) |
| C(6) | 0.8367(3) | 0.6443(4) | 0.7076(5) | 0.0622(11) |
| C(7) | 0.6367(5) | 0.4362(4) | 1.0214(6) | 0.0769(13) |
| C(100) | 1.0805(16) | 0.9403(16) | 0.3418(28) | 0.109(5) |
| C(200) | 1.0664(22) | 1.0980(22) | 0.2307(32) | 0.146(8) |
| C(300) | 1.024(22) | 0.9543(22) | 0.4449(34) | 0.142(8) |

Table 5. Final positional and isotropic equivalent displacement parameters ($m^2 \times 10^{-20} = \text{\AA}^2$) for (R)-**4d** (e.s.d.s given in parentheses).

| Atom | x | y | z | U(eq) |
|-------|------------|------------|-------------|-----------|
| S(1) | 1.00390(6) | 0.55074(8) | 0.66093(3) | 0.0383(2) |
| O(1) | 1.0053(3) | 0.7664(2) | 0.63013(12) | 0.0540(4) |
| N(1) | 1.1170(3) | 0.3918(4) | 0.6034(4) | 0.0572(6) |
| O(2) | 1.2232(3) | 0.1745(3) | 0.7801(2) | 0.0688(5) |
| C(1) | 1.1143(3) | 0.5271(4) | 0.79653(13) | 0.0382(5) |
| C(2) | 1.1107(4) | 0.7005(3) | 0.8615(2) | 0.0471(5) |
| C(3) | 1.1908(4) | 0.6934(4) | 0.9691(2) | 0.0595(7) |
| C(4) | 1.2756(4) | 0.5126(4) | 1.0097(2) | 0.0589(7) |
| C(5) | 1.2830(4) | 0.3435(4) | 0.9466(2) | 0.0564(6) |
| C(6) | 1.2054(3) | 0.3462(4) | 0.8376(2) | 0.0454(5) |
| C(7) | 0.7429(3) | 0.4815(3) | 0.6587(2) | 0.0435(5) |
| C(8) | 0.7294(4) | 0.2632(4) | 0.6999(2) | 0.0623(7) |
| C(9) | 0.6528(4) | 0.4953(4) | 0.5396(2) | 0.0584(7) |
| C(10) | 0.6446(4) | 0.6327(5) | 0.7269(2) | 0.0692(7) |

(Siemens for **4a**) and CAD4 (Enraf-Nonius for **4d**). The usual corrections were applied. The structures were solved by direct methods using the program SHELXS-86 (Sheldrick, 1990). Anisotropic least-squares refinements were carried out on all non-H atoms using the program SHELXL-93 (Sheldrick, 1993). Hydrogen atoms are in calculated positions. Scattering factors were taken from the *International Tables for Crystallography*, Vol. IV, Table 2.2B. Crystal data and other numerical details of the structure determinations are listed in Table 3. Final positional and isotropic equivalent displacement parameters ($m^2 \times 10^{-20} = \text{\AA}^2$) with e.s.d.s are summarized in Tables 4 and 5.

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