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Remote stereocontrol by sulfinyl groups: hydrocyanation of δ-ketosulfoxides

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Abstract—Reactions of (2-*p*-tolylsulfinyl)benzyl alkyl (and aryl) ketones (δ-ketosulfoxides) with Et_2AlCN in the presence of $Yb(OTf)_3$ take place in a completely stereoselective manner, demonstrating the efficiency of the sulfinyl group in the control of the stereoselectivity of 1,5-asymmetric hydrocyanation processes as well as the ability of $Yb(OTf)_3$ to form chelated species with ketosulfoxides. The behavior of their methyl derivatives at the benzylic position is dependent on the configuration at the chiral carbon. The resulting sulfinyl cyanohydrins were readily transformed into α-hydroxyamides by hydrolysis of the CN group and hydrogenolysis of the C–S bond.

1. Introduction

Remote stereocontrol (1,*n*-asymmetric induction with $n>3$) is one of the most intriguing challenges to be solved in asymmetric synthesis.[1] The functional groups used to achieve it are usually able to form chelated species involving the prochiral centers and appropriate Lewis acids.[2] The sulfinyl oxygen has shown its ability to control 1,4-asymmetric induction processes on both electrophilic[3] and nucleophilic[4] centers. However, to our knowledge, prior to our recent paper[5] dealing with the reduction of δ-ketosulfoxides **1** (1,5-asymmetric induction) with DIBAL/$Yb(OTf)_3$ and L-Selectride, no efficient stereocontrolled reaction with the sulfinyl chiral inductor located farther away from the reaction centers had been reported.

Asymmetric hydrocyanation of carbonyl compounds is a very interesting transformation due to the high value of the resulting cyanohydrins as synthetic intermediates.[6] Consequently, many methods have been reported for their preparation. Excellent results have been obtained starting from aldehydes,[7] but the applicability of those methods is much more restricted in the case of ketones,[8,9,10] probably due to the higher tendency of the cyanohydrins to undergo retrohydrocyanation, as a consequence of their lower stability, and also due to a higher steric hindrance around the carbonyl group precluding the cyanide addition.

The sulfinyl group has proved to be a highly efficient controlling element in the asymmetric hydrocyanation of α-sulfinyl ketones, with yields and de's higher than 98%.[11] Starting from α-sulfinyl aldehydes, the obtained results were less satisfactory presumably due to the instability of the resulting cyanohydrins.[12] In order to investigate whether the ability of the sulfinyl group to efficiently control the stereoselectivity of the reduction of δ-ketosulfoxides[5] can be extended to processes involving C–C bond formation, we have studied the hydrocyanation reactions of those same δ-ketosulfoxides. In this paper, we report the results obtained in reactions of 2-(*p*-tolylsulfinyl)benzyl alkyl (and aryl) ketones (**1a–d**), their methyl derivatives at the benzylic position (**6a** and **6b**), and the aldehyde **1e** with Et_2AlCN (all of them 1,5-asymmetric induction processes), under various conditions as well as the transformation of the resulting cyanohydrins into hydroxyamides.

2. Results and discussion

The synthesis of compounds **1a–e** was performed following previously reported procedures.[4g] The reaction of the δ-ketosulfoxides **1a–c** and **1e** with Et_2AlCN (2.5 equiv) in THF for 2–3 h at −78 °C yielded mixtures of two cyanohydrins **2** and **3**, which could not be separated by chromatography (Table 1). The reactivity of **1d** was lower,[13] requiring 3 h at 0 °C to reach completion (entry 7).

Keywords: Stereoselective cyanohydrins synthesis; α-Hydroxyamides; Remote stereocontrol; Sulfinyl group mediated carbonyl hydrocyanation.
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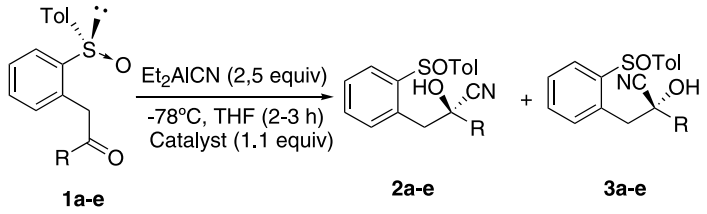
Table 1. Reaction of **1a–e** under different hydrocyanation conditions



1a-e **2a-e** **3a-e**

a = Me; b = *i*-Pr; c = *n*-Pr; d = Ph; e = H.

Entry	Substrate	Catalyst	2:3 Ratio[a]	Yield (%)
1	**1a**	—	48:52	98
2	**1a**	$Yb(OTf)_3$	>98:<2	98
3	**1b**	—	>98:<2	91
4	**1b**	$Yb(OTf)_3$	>98:<2	98
5	**1c**	—	68:32	98
6	**1c**	$Yb(OTf)_3$	>98:<2	98
7	**1d**	—	58:42[b]	97
8	**1d**	$Yb(OTf)_3$	85:15	98
9	**1e**	—	63:37	95[c]
10	**1e**	$Yb(OTf)_3$	>98:<2	90[c]

[a] Determined by ^{1}H NMR.
[b] 0 °C.
[c] Crude yield determined by ^{1}H NMR.

The yields were excellent but the stereoselectivity was very low except for **1b**, which afforded exclusively diastereoisomer **2b** (entry 3).

Next, we studied the influence of $Yb(OTf)_3$ on the reaction course (Table 1). Compounds **1a–c** and **1e** reacted in a completely stereoselective manner yielding exclusively diastereoisomers **2a–c** and **2e**[14] (entries 2, 4, 6, and 10). It is remarkable that the same cyanohydrin **2b**[15] was also obtained in the absence of catalyst. However, **1d** (R=Ph) did not react with a complete stereoselectivity, and a 85:15 mixture of **2d**:**3d** (70% de, entry 8) was obtained. Yields of **2a–c** were >95% after crystallization, but **2e** could not be purified and decomposed by chromatography. Some trials with TMSCN gave worse results.

Spectroscopic differences between compounds **2** and **3** allowed their differentiation, though the magnitude of these differences was not sufficient to assign their relative configuration. However, their structure and configuration were unequivocally established by X-ray diffraction studies for compounds **2a** and **2b**.[15] The configurational assignment of **2c–e** was deduced from their ^{1}H NMR parameters and by assuming that the stereochemical course of the hydrocyanation is similar for the whole series of ketosulfoxides.

It is noteworthy that the $Yb(OTf)_3$-promoted hydrocyanation and the DIBAL/$Yb(OTf)_3$ reduction[5] of **1a–d** produce similar stereochemical results, which suggests a similar mechanistic pathway for both reactions. The approach of the reagent (DIBAL or Et_2AlCN) to the less hindered face of the chelated species **A**, formed by association of the catalyst to the sulfinyl and carbonyl oxygens, would account for the stereochemical results (Fig. 1). The lower stereoselectivity observed in the hydrocyanation of phenyl derivative **1d** (which also happened in the DIBAL reduction) can be explained as a consequence of the lower basicity of its carbonyl oxygen, therefore yielding less stable chelates. In the absence of $Yb(OTf)_3$, the stereochemical outcome of the reaction of **1a–d** with Et_2AlCN was also similar to the DIBAL reaction, both yielding mixtures of diastereoisomers, so that a common hypothesis can be proposed for both reactions.[5]

Next, we studied the hydrolysis of the cyanohydrins, which are prone to dehydrocyanation processes, into the much more stable carboxamide derivatives. The study of these

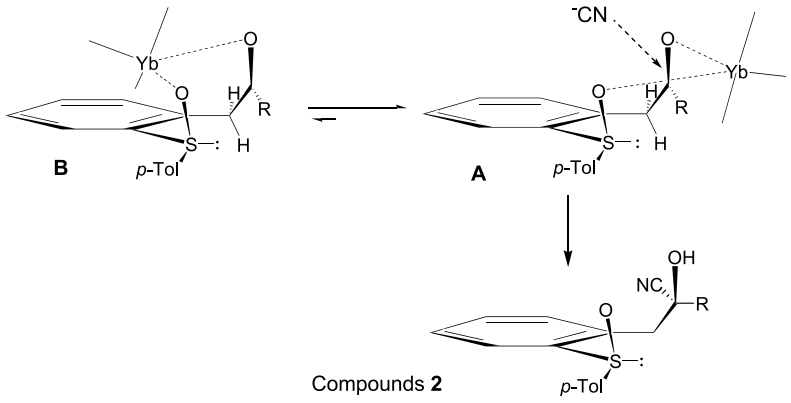
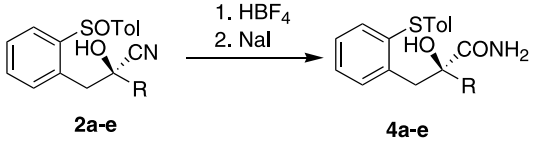


Figure 1. Stereochemical model accounting for the observed results.

transformations also aimed to examine whether the ability of the sulfinyl group to act as an anchimeric assistant in the hydrolysis of the CN group at β-sulfinyl nitriles[12,16] as conserved for δ-sulfinyl nitriles such as **2a–d**. The hydrolysis of the sulfinyl cyanohydrins was performed under very mild conditions (HBF_4 followed by addition of NaI). The sulfinyl carboxamides **4a–d** were obtained as the major products, but sulfinyl ketones and sulfinyl cyanohydrins were also formed as byproducts in most of the cases. A detailed study of the reaction allowed us to find the experimental conditions affording compounds **4** in higher yields (Table 2). At −78 °C, **4a** was exclusively obtained from **2a** in 95% yield. Under similar conditions the 85:15 mixture of **2d**+**3d** yielded **4d** (70% ee) in 71% isolated yield. Compounds **4b** and **4c** were obtained in 73 and 50% yields, respectively, after refluxing **2b** and **2c**, respectively, in CH_2Cl_2 with HBF_4 and addition of NaI at room temperature.

Table 2. Hydrolysis of δ-sulfinyl nitriles

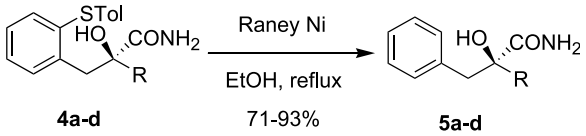


2a-e **4a-e**

Entry	Substrate	*T* (°C)	Product	Yield (%)
1	**2a**	−78	**4a**	95
2	**2b**	40	**4b**	73
3	**2c**	40	**4c**	50
4	**2d**+**3d**	−78	**4d** (70% ee)	71

These conditions are milder than those usually required for obtaining amides from nitriles,[8a,17] which suggests a remote anchimeric assistance of the sulfinyl group in accordance with a mechanism similar to that proposed for the hydrolysis of β-sulfinyl nitriles[12,16] (Fig. 2).

Compounds **4a–d** were transformed into amides **5a–d**, which exhibit interesting anticonvulsant properties,[18] by desulfinylation with Raney nickel in refluxing ethanol (Scheme 1).



4a-d **5a-d**

Scheme 1.

Finally, we studied the reactions of the α-methyl derivatives **6a** and **6′a** with Et_2AlCN. Our aim was to evaluate the relative influence of both of the substrate's stereogenic centers the sulfur atom group and the α-carbon on the stereoselectivity. The synthesis of the above compounds, as well as their configurational assignment had been previously reported.[4g] The best reaction conditions found for the hydrocyanation of **1a–e** (adding the sulfoxide to a THF solution of Et_2AlCN at −78 °C) were applied to **6a** and **6′a**, yielding the mixtures of cyanohydrins **7a–8a** and **7′a–8′a**, respectively (Table 3).

After 2 h, the hydrocyanation of **6a** (entry 1) produced a 1:1 mixture of **7a** and **8a**. At shorter reaction times, the conversion was not complete and the stereoselectivity remained very low. When the hydrocyanation was performed under $Yb(OTf)_3$ catalysis, it was completely stereoselective, yielding only **7a** in 90% yield (entry 2). The transformation of **6′a**, epimer of **6a** at C-α, produced a different result. After 1 h, the reaction of **6′a** with Et_2AlCN gave a mixture of epimers, **8′a** being the major one (entry 3), however, the stereoselectivity increased with the time (entry 4) and became complete after 2 h, yielding only **8′a** (de>98%) in 88% yield (entry 5). Under $Yb(OTf)_3$ catalysis, **6′a** afforded a 70:30 mixture of **7′a** and **8′a**.

The configurational assignment of compounds **7a**, **7′a**, **8a**, and **8′a** was based on the assumption that the configurations at the sulfur atom and the benzylic carbon must be identical to those of their respective precursors, which had been previously assigned. Thus, it was only necessary to determine the configuration at the hydroxylic carbon. The absolute configuration of **8′a** was unequivocally established as *R* by X-ray analysis.[15] Additionally, the oxidation of pure cyanohydrins **7a** and **8′a** with MCPBA yielded two enantiomeric sulfones **9** and *ent*-**9**, respectively (Scheme 2) thus allowing us to assign the configuration of **7a** as *S* at its hydroxylic carbon. The absolute configuration of the other two compounds, **7′a** and **8a**, was assigned as indicated in Table 2 based on the fact that they are epimers at the hydroxylic carbon of compounds **8′a** and **7a**, respectively.

The stereochemical outcome of the hydrocyanation of **6a** and **6′a** under $Yb(TfO)_3$ catalysis is identical to that observed in the analogous reduction reactions.[5] Hence, only **6a** reacted in a completely stereoselective manner. Therefore, the herein described results can be explained by using the same models and assuming that the chelated species formed from **6′a** is disfavored due to steric congestion (Fig. 3).[19] The stereoselectivity observed for **6′a** in the absence of $Yb(TfO)_3$ and its changes with the reaction time must be a consequence of the equilibration between the two possible cyanohydrins (**7′a** and **8′a**) and the higher stability of **8′a**.

Finally, the hydrolysis of the cyano groups at methylated sulfinyl cyanohydrins **7′a** and **8′a** with HBF_4/NaI has been attempted in order to obtain the corresponding sulfinylamides. However, all attempts were unsuccessful, which

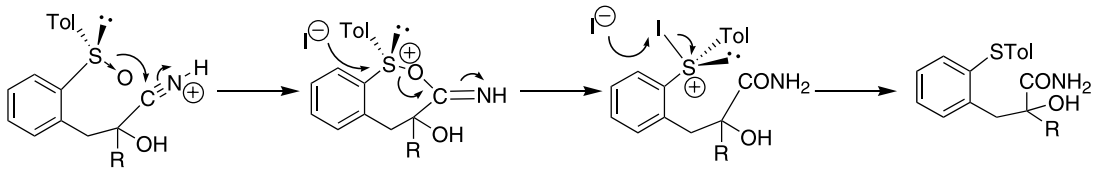
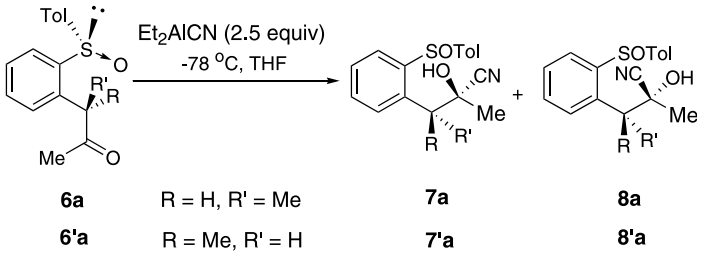


Figure 2. Anchimeric assistance of the SO group in the hydrolysis of the CN into $CONH_2$.

Table 3. Hydrocyanation of **6a** and **6′a**

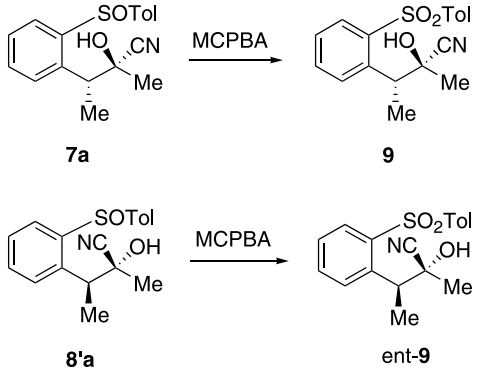


6a R = H, R' = Me **7a** **8a**

6'a R = Me, R' = H **7'a** **8'a**

Entry	Substrate	Reaction time (h)	**7**:**8** or (**7′**:**8′**)[a]	Isolated yield (%)
1	**6a**	2	50:50	86
2	**6a**[b]	2	>98:<2	90
3	**6′a**	1	(20:80)	[c]
4	**6′a**	1.5	(11:89)	[c]
5	**6′a**	2	(<2:>98)	88
6	**6′a**[b]	2	(70:30)	92

[a] Ratio determined by ^{1}H NMR.
[b] In the presence of $Yb(OTf)_3$ (1.1 equiv).
[c] Not determined.



Scheme 2.

indicates that anchimeric assistance in the hydrolysis is not available for these substrates. Assuming that the reaction proceeds as indicated in Figure 2, the failure could be a consequence of the low stability of the seven membered ring intermediates (like **A** in Fig. 1), due to the steric interactions of the benzylic methyl group with the neighboring quaternary carbon. In summary, we have described the stereoselective hydrocyanation of the δ-sulfinyl ketones **1a–d** as well as that of the two epimers **6a** and **6′a** and the aldehyde **1e**. The results indicate that the sulfinyl group is an efficient controlling group for of the stereoselectivity of these C–C bond forming processes, despite the remote position occupied by the chiral inducer (1,5-asymmetric induction).

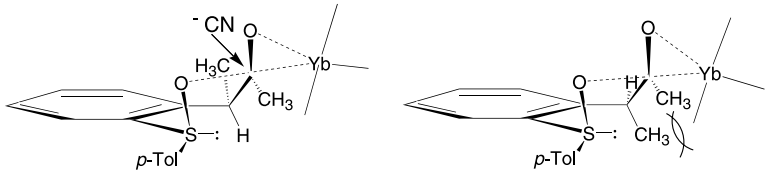
3. Experimental

3.1. General methods

NMR spectra were obtained in $CDCl_3$ solutions at 300 and 75 MHz for ^{1}H and ^{13}C NMR, respectively (*J* values are given in hertz). Melting points were measured in open capillary tubes and are uncorrected. De's were evaluated by integration of well-separated signals of the ^{1}H NMR spectra. All hydrocyanations were carried out under argon atmosphere in anhydrous solvents. THF was distilled from sodium–benzophenone under argon. Flash-column chromatography was perfomed using silica gel (230–400 mesh).

3.2. General procedures for hydrocyanation

Method A. Et_2AlCN. A solution of (0.36 mmol) of ketosulfoxide **1** in 2.7 mL of THF was dropwise added into a solution of diethyl aluminum cyanide (0.90 mmol) in 4.0 mL of THF at −78 °C (**1e** needs 0 °C to reach complete conversion), and the mixture was stirred for 2 h (3 h in the case of **1e**). The reaction mixture was transferred via cannula (by application of a positive argon pressure to the reaction flask) into a solution of 1.5 mL of methanol and 1.5 mL of concentrated HCl at −78 °C. The resulting mixture was vigorously stirred for 1 h at −78 °C, poured into a solution of 1.2 mL of concentrated HCl and 1.2 mL of ice-water, and extracted with CH_2Cl_2. The extracts were



Compound **6a** Compound **6'a**

Figure 3. Stereochemical model accounting for **6a** and **6′a** behavior.

washed with water (1.5 mL), dried and the solvent was evaporated.

Method B. $Et_2AlCN/Yb(OTf)_3$. A solution of ketosulfoxide **1** (0.36 mmol) and $Yb(OTf)_3$ (0.40 mmol) in 2.7 mL of THF was stirred for 30 min at room temperature and then dropwise added into a solution of of diethyl aluminum cyanide (0.90 mmol) in 4.0 mL of THF at −78 °C (**1e** needs 0 °C to reach complete conversion), and the mixture was stirred for 2 h (3 h in the case of **1e**). The work-up was effected as in method A.

3.2.1. [2*S*,(S)*S*]-2-Hydroxy-2-methyl-3-[2-(*p*-tolylsulfinyl)-phenyl]propanenitrile (2a). Compound **2a** was obtained by method B and crystallized from ethyl acetate–hexane. Yield: 98%; white solid; mp: 130–132 °C; $[\alpha]_D^{20}$ −19.9 (*c* 0.6, $CHCl_3$); IR (KBr): 3310, 3056, 1021 cm^{-1}; ^1H NMR: δ 7.62–7.26 (m, 8H), 6.46 (s, OH), 3.68 and 2.84 (AB system, $J=14.1$ Hz, 2H), 2.39 (s, 3H), 1.56 (s, 3H); ^{13}C NMR: δ 143.2, 141.5, 139.0, 134.7, 134.3, 132.2, 130.1, 129.3, 128.1, 124.9, 122.8, 66.8, 41.8, 26.6, 21.3; MS (FAB) *m/z* 300 $(M+1)^+$; HRMS $(M+1)^+$: calcd for $C_{17}H_{18}NO_2S$: 300.1058; found: 300.1044.

3.2.2. [2*R*,(S)*S*]-2-Hydroxy-2-methyl-3-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (3a). Compound **3a** was obtained by method A and crystallized from ethyl acetate–hexane. It could not be isolated diastereomerically pure and was characterized from a mixture of **2a**+**3a**. White solid; ^1H NMR: (representative parameters) δ 6.14 (s, OH) 3.35 and 2.91 (AB system, $J=14.1$ Hz, 2H), 2.38 (s, 3H), 1.70 (s, 3H); ^{13}C NMR: (representative parameters) δ 142.4, 141.3, 139.5, 135.5, 132.8, 129.6, 124.7, 121.5, 68.8, 42.4, 30.1.

3.2.3. [2*R*,(S)*S*]-2-Hydroxy-3-methyl-2-[2-(*p*-tolylsulfinyl)benzyl]butanenitrile (2b). Compound **2b** was obtained by method B and crystallized from ethyl acetate–hexane. Yield: 98%; white solid; mp: 130–131 °C; $[\alpha]_D^{20}$ +32.2 (*c* 1.0, $CHCl_3$); IR (KBr): 3279, 2973, 1010 cm^{-1}; ^1H NMR: δ 7.53–7.24 (m, 8H), 6.14 (s, OH), 3.39 and 3.33 (AB system, $J=14.5$ Hz, 2H), 2.39 (s, 3H). 2.01 (sp, $J=$ 6.4 Hz, 1H), 1.20 (d, $J=6.3$ Hz, 3H), 1.16 (d, $J=6.3$ Hz, 3H); ^{13}C NMR: δ 143.4, 142.0, 138.3, 135.2, 133.6, 131.9, 130.1, 128.3, 128.0, 125.7, 120.6, 75.6, 38.1, 36.0, 21.3, 17.8, 17.2; MS (FAB) *m/z* 328 $(M+1)^+$; HRMS $(M+1)^+$: calcd for $C_{19}H_{22}NO_2S$: 328.1371; found: 328.1356.

3.2.4. [2*S*,(S)*S*]-2-Hydroxy-2-[2-(*p*-tolylsulfinyl)benzyl]-pentanenitrile (2c). Compound **2c** was obtained by method B and crystallized from ethyl acetate–hexane. Yield: 98%; white solid; mp: 136–138 °C; $[\alpha]_D^{20}$ +12.9 (*c* 0.8, $CHCl_3$); IR (KBr): 3421, 3251, 2959, 1010 cm^{-1}; ^1H NMR: δ 7.56–7.25 (m, 8H), 6.35 (s, OH), 3.56 and 3.04 (AB system, $J=14.1$ Hz, 2H), 2.39 (s, 3H). 1.76–1.66 (m, 4H), 0.98 (m, 3H); ^{13}C NMR: δ 143.3, 141.7, 138.8, 134.7, 134.3, 132.1, 130.1, 129.0, 128.1, 125.1, 121.9, 70.8, 41.4, 40.8, 21.3, 17.7, 13.8; MS (FAB) *m/z* 328 $(M+1)^+$; HRMS $(M+1)^+$: calcd for $C_{19}H_{22}NO_2S$: 328.1371; found: 328.1368. Anal. Calcd for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28; S, 9.79. Found: C, 69.10; H, 6.46; N, 4.29; S, 9.71.

3.2.5. [2*R*,(S)*S*]-2-Hydroxy-2-[2-(*p*-tolylsulfinyl)benzyl]-pentanenitrile (3c). Compound **3c** was obtained by method A and crystallized from ethyl acetate–hexane. It could not be isolated diastereomerically pure and was characterized from a mixture of **2c**+**3c**. White solid; ^1H NMR: (representative parameters) δ 5.99 (s, OH), 3.34 and 2.79 (AB system, $J=14.1$ Hz, 2H), 2.38 (s, 3H); ^{13}C NMR: (representative parameters) δ 142.2, 141.3, 139.6, 135.7, 134.5, 128.9, 124.5, 120.9, 72.5, 41.02, 21.2, 17.4.

3.2.6. [2*R*,(S)*S*]-and-(2*S*,(S)*S*)-2-Hydroxy-2-phenyl-3-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (2d+3d). Compound **2d**+**3d** were obtained by method B and crystallized from ethyl acetate–hexane. Their characterization was accomplished as a 85:15 mixture of diastereoisomers **2d**+**3d**. Yield: 98% (diastereoisomeric mixture); white solid; IR (KBr): 3184, 2890, 1082, 1009 cm^{-1}; ^1H NMR: δ 7.68–7.18 (m, 16H), 6.34 (s, OH), 6.32 (s, OH), 3.93 and 3.11 (AB system, $J=13.7$ Hz, 2H, (**2d**)), 3.54 and 3.09 (AB system, $J=14.5$ Hz, 2H, (**3d**)), 2.39 (s, 3H, (**2d**)), 2.32 (s, 3H, (**3d**)); ^{13}C NMR: δ 142.8, 141.5, 141.3, 139.0, 138.9, 134.7, 133.5, 132.7, 131.7, 130.1, 130.0, 129.5, 129.2, 128.6, 128.2, 127.9, 125.6, 124.8, 124.6, 122.1, 120.5, 74.4, 72.3, 44.8, 44.5, 21.2; MS (FAB) *m/z* 362 $(M+1)^+$; HRMS $(M+1)^+$: calcd for $C_{22}H_{20}NO_2S$: 362.1215; found: 362.1224.

3.2.7. [2*S*,(S)*S*]-2-Hydroxy-3-[2-(*p*-tolylsulfinyl)phenyl]-propanenitrile (2e). Compound **2e** was obtained by method B and could not be purified. Crude yield: 90%; yellow oil; $[\alpha]_D^{20}$ −52.7 (*c* 3.9, $CHCl_3$); IR ($CHCl_3$): 3251, 2870, 1719, 1010 cm^{-1}; ^1H NMR: δ 7.67–7.64 (m, 1H), 7.43–7.13 (m, 7H), 4.38 (dd, $J=8.8$, 5.4 Hz, 1H), 3.29 (dd, $J=13.5$, 8.8 Hz, 1H), 2.99 (dd, $J=14.9$, 6.1 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR: δ 142.8, 141.5, 139.8, 134.8, 132.1, 130.0 (2C), 128.3, 127.5, 125.0, 119.7, 61.2, 36.8, 21.1; MS (FAB) *m/z* 286 $(M+1)^+$; HRMS $(M+1)^+$: calcd for $C_{16}H_{16}NO_2S$: 286.0902; found 286.0892.

3.2.8. [2*R*,(S)*S*]-2-Hydroxy-3-[2-(*p*-tolylsulfinyl)phenyl]-propanenitrile (3e). Compound **3e** was obtained by method A. It was characterized from a mixture **2e**+**3e** because it could not be isolated diastereomerically pure. Yellow oil; ^1H NMR: (representative parameters) δ 4.51 (t, $J=6.4$ Hz, 1H), 3.22 (dd, $J=14.3$, 6.2 Hz, 1H), 3.11 (dd, $J=14.5$, 6.9 Hz, 1H); ^{13}C NMR: (representative parameters) δ 143.1, 141.8, 134.1, 119.5, 61.1, 30.1, 22.4.

3.2.9. [2*S*,3*R*,(S)*S*]-2-Hydroxy-2-methyl-3-[2-(*p*-tolylsulfinyl)phenyl]butanenitrile (7a). Hydrocyanation of ketosulfoxide **6a** following method B afforded **7a** as a white solid. It was crystallized from ethyl acetate–hexane; mp 174–176 °C; $[\alpha]_D^{20}$ −38.3 (*c* 2.6, $CHCl_3$); ^1H NMR δ 7.72–7.69 (m, 1H), 7.57–7.29 (m, 7H), 4.30 (m, OH, 1H), 3.67 (q, $J=6.7$ Hz, 1H), 2.39 (s, 3H), 1.67 (s, 3H), 1.35 (d, $J=6.7$ Hz, 3H); ^{13}C NMR δ 143.8, 142.6, 139.3, 139.2, 131.7, 130.3, 128.6, 128.3, 126.3, 125.3, 120.9, 72.3, 43.4, 27.9, 21.5, 17.1; MS (FAB) *m/z* 314.1 $[M+1]^+$, 287.1 (M^+-CN); HRMS $[M+1]^+$: calcd for $C_{18}H_{20}NO_2S$: 314.1215; found: 314.1200.

Hydrocyanation of ketosulfoxide **6a** following method A afforded a 50:50 mixture of **7a** and **8a**. ^1H NMR: (representative parameters of **8a**) δ 4.70 (m, OH, 1H),

3.62 (q, J=6.7 Hz, 1H), 1.42 (s, 3H), 1.35 (d, J=6.7 Hz, 3H).

3.2.10. [2*S*,3*S*,(S)*S*]-2-Hydroxy-2-methyl-3-[2-(*p*-tolylsulfinyl)phenyl]butanenitrile (7′a). Hydrocyanation of compound **6′a** following method B afforded a mixture 70:30 of diastereoisomers **7′a** and **8′a**, as a white solid. Compound **7′a** was crystallized from AcOEt–hexane and characterized from a mixture 91:9 of diasteroisomers, mp 175–177 °C; $[\alpha]_D^{20}$ −15.5 (*c* 2.2, $CHCl_3$); ^{1}H NMR δ 7.78 (dd, J=7.6, 1.2 Hz, 1H), 7.58 (dd, J=7.6, 1.2 Hz, 1H), 7.48–7.41 (m, 2H), 7.29–7.23 (m, 4H), 6.33 (br s, OH, 1H), 3.95 (q, J=7.1 Hz, 1H), 2.37 (s, 3H), 1.38 (s, 3H), 1.02 (d, J=7.1 Hz, 3H). ^{13}C NMR δ 142.6, 141.0, 140.3, 140.1, 132.6, 131.1, 129.9, 127.8, 124.4, 122.9, 70.9, 41.1, 21.2, 20.9, 15.9; MS (FAB) *m*/*z* 314.1 $[M+1]^+$, 287.1 (M^+-CN); HRMS $[M+1]^+$: calcd for $C_{18}H_{20}NO_2S$: 314.1215; found: 314.1204.

3.2.11. [2*R*,3*S*,(S)*S*]-2-Hydroxy-2-methyl-3-[2-(*p*-tolylsulfinyl)phenyl]butanenitrile (8′a). Hydrocyanation of ketosulfoxide **6′a** following method A afforded **8′a** as a white solid. It was crystallized from ethyl acetate–hexane; mp 157–159 °C; $[\alpha]_D^{20}$ −66.7 (*c* 1.8, $CHCl_3$); ^{1}H NMR δ 7.82–7.75 (m, 2H), 7.64 (t, J=5.9 Hz, 1H), 7.46 (t, J=7.6 Hz, 1H), 7.29–7.24 (m, 4H), 5.39 (m, OH, 1H), 3.60 (q, J=7.3 Hz, 1H), 2.38 (s, 3H), 1.65 (s, 3H), 1.06 (dd, J=7.3 Hz, 1H). ^{13}C NMR δ 142.3, 141.7, 140.9, 140.6, 133.4, 130.1, 130.0, 129.9, 127.7, 124.4, 120.3, 72.9, 42.5, 28.8, 21.2, 16.4; MS (FAB) *m*/*z* 314.1 $[M+1]^+$; HRMS $[M+1]^+$: calcd for $C_{18}H_{20}NO_2S$: 314.1215, found: 314.1216.

3.3. Hydrolysis of cyanohydrins into sulfinyl hydroxy amides. General procedure with HBF_4

To a solution of cyanohydrin (0.24 mmol) in 1.7 mL of anhydrous CH_2Cl_2 were added 0.32 mL of fluoboric acid at the indicated temperature. The mixture was stirred for 6 h and then 96 mg (0.64 mmol) of NaI were added at room temperature. It was stirred for 15 h and the resulting mixture was treated with 1.6 mL of water and extracted with CH_2Cl_2. The extracts were washed with aqueous $NaHSO_3$, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (ethyl acetate–hexane 1:1).

3.3.1. (2*S*)-2-Hydroxy-2-methyl-3-[2-(*p*-tolylthio)-phenyl]propanamide (4a). Reaction temperature: −78 °C. Yield: 95%; white solid; mp: 120–122 °C; $[\alpha]_D^{20}$ −58.9 (*c* 0.4, $CHCl_3$); IR (KBr): 3417, 2919, 1629, 803 cm^{-1}; ^{1}H NMR: δ 7.35–7.10 (m, 8H), 6.64 (s, NH), 5.35 (s, NH), 3.38 (s, OH), 3.34 and 3.28 (AB system, J=14.1 Hz, 2H), 2.33 (s, 3H), 1.50 (s, 3H); ^{13}C NMR: δ 177.8, 137.4, 137.2, 135.4, 132.5, 132.0, 131.1, 130.7, 130.1, 127.9, 127.7, 77.4, 42.4, 27.1, 21.0; MS (FAB) *m*/*z* 302 $(M+1)^+$; HRMS $(M+1)^+$: calcd for $C_{17}H_{20}NO_2S$: 302.1215; found: 302.1220.

3.3.2. (2*R*)-2-Hydroxy-3-methyl-2-[2-(*p*-tolylthio)-benzyl]butanamide (4b). Reaction temperature: 40 °C. Yield: 73%; white solid; mp: 125–127 °C; $[\alpha]_D^{20}$ −46.3 (*c* 0.3, $CHCl_3$); IR (film): 3447, 2884, 1539, 773 cm^{-1}; ^{1}H NMR: δ 7.37–7.09 (m, 8H), 6.54 (s, NH), 5.26 (s, NH), 3.39 (s, OH), 3.37 and 3.13 (AB system, J=14.1 Hz, 2H), 2.33 (s, 3H), 2.18 (sp, J=6.8 Hz, 1H), 1.04 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H); ^{13}C NMR: δ 176.7, 137.8, 137.4, 134.8, 132.5, 132.0, 130.4, 130.2, 128.0, 127.7, 82.7, 39.3, 35.6, 21.0, 17.5, 15.8; MS (FAB) *m*/*z* 330 $(M+1)^+$; HRMS $(M+1)^+$: calcd for $C_{19}H_{24}NO_2S$: 330.1528; found: 330.1509.

3.3.3. (2*S*)-2-Hydroxy-2-[2-(*p*-tolylthio)benzyl]pentanamide (4c). Reaction temperature: 40 °C. Yield: 50%; yellow oil; $[\alpha]_D^{20}$ −46.4 (*c* 0.8, $CHCl_3$); IR (film): 3396, 2873, 1564, 809 cm^{-1}; ^{1}H NMR: δ 7.35–7.10 (m, 8H), 6.58 (s, NH), 5.39 (s, NH), 3.30 (s, OH), 3.28 (s, 2H), 2.33 (s, 3H), 2.01–1.91 (m, 1H), 1.74–1.25 (m, 3H), 0.92 (t, J=7.2 Hz, 3H); ^{13}C NMR: δ 177.0, 137.2, 135.3, 132.5, 132.0, 130.6, 130.2, 129.9, 127.9, 127.8, 126.1, 80.1, 42.5, 41.9, 21.0, 16.7, 14.2; MS (FAB) *m*/*z* 252 $(M+Na)^+$; HRMS $(M+Na)^+$: calcd for $C_{19}H_{23}NO_2NaS$: 352.1347; found: 352.1341.

3.3.4. 2-Hydroxy-2-phenyl 3-[2-(*p*-tolylthio)phenyl]-propanamide (4d). Reaction temperature: −78 °C. Compound **4d** was characterized from an enantiomeric 85:15 mixture. Yield: 71%; white solid; $[\alpha]_D^{20}$ −4.3 (*c* 1.0, $CHCl_3$); IR (film): 3472, 2923, 1680, 1492 cm^{-1}; ^{1}H NMR: δ 7.72–7.69 (m, 2H), 7.39–7.10 (m, 11H), 6.70 (s, NH), 5.48 (s, NH), 3.98 (s, OH), 3.90 and 3.54 (AB system, J=14.1 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR: δ 175.7, 142.4, 137.4, 136.8, 135.6, 132.3, 132.0, 130.8, 130.7, 130.2, 128.2, 128.0, 127.7, 125.3, 80.3, 42.3, 21.0; MS (FAB) *m*/*z* 319 $(M-CONH_2)^+$; HRMS M^+: calcd for $C_{22}H_{21}NO_2S$: 363.1293; found: 363.1279. Anal. Calcd for $C_{22}H_{21}NO_2S$: C, 72.70; H, 5.82; N, 3.85; S, 8.82. Found: C, 72.70; H, 5.81; N, 3.98; S, 8.76.

3.4. C–S bond cleavage. General procedure

An excess of activated Raney nickel was added onto a solution of thioether **4** in a minimal amount of absolute EtOH. The reaction was refluxed for 12 h, filtered through a Celite pad and the solvent was evaporated.

3.4.1. (*S*)-2-Hydroxy-2-methyl-3-phenylpropanamide (5a). The residue was purified by flash chromatography (ethyl acetate–hexane 1:1). Yield: 80%; colorless oil; $[\alpha]_D^{20}$ −51.2 (*c* 1.1, $CHCl_3$); IR (film): 3347, 2924, 1667 cm^{-1}; ^{1}H NMR: δ 7.39–7.26 (m, 5H), 6.57 (s, NH), 5.56 (s, NH), 3.33 and 2.88 (AB system, J=13.4 Hz, 2H), 2.39 (s, OH), 1.51 (s, 3H); ^{13}C NMR: δ 178.2, 135.6, 130.3, 128.6, 127.2, 75.9, 45.4, 26.3; MS (EI) *m*/*z* 179 M^+; HRMS M^+: calcd for $C_{10}H_{13}NO_2$: 179.0946; found: 179.0941.

3.4.2. (*R*)-2-Benzyl-2-hydroxy-3-methylbutanamide (5b). The residue was purified by washing with hexane. Yield: 71%; white solid; mp: 116–118 °C; $[\alpha]_D^{20}$ −15.4 (*c* 0.9, $CHCl_3$); IR (film): 3493, 2965, 1679 cm^{-1}; ^{1}H NMR: δ 7.33–7.22 (m, 5H), 6.31 (s, NH), 5.34 (s, NH), 3.32 and 2.82 (AB system, J=13.2 Hz, 2H), 2.3 (sp, J=6.6 Hz, 1H), 1.07 (d, J=6.6 Hz, 3H), 1.01 (d, J=6.6 Hz, 3H); ^{13}C NMR: δ 177.0, 135.7, 130.2, 128.6, 127.1, 81.0, 42.4, 35.5, 17.6, 16.3; MS (EI) *m*/*z* 207 M^+; HRMS M^+: calcd for $C_{12}H_{17}NO_2$: 207.1259; found: 207.1250.

3.4.3. (*S*)-2-Benzyl-2-hydroxypentanamide (5c). The residue was purified by washing with hexane. Yield: 93%;

white solid; mp: 116–118 °C; $[\alpha]_D^{20}$ −15.8 (*c* 1.4, $CHCl_3$); IR (film): 3472, 3306, 2935, 1659 cm^{-1}; ^1H NMR: δ 7.27–7.15 (m, 5H), 6.40 (s, NH), 5.47 (s, NH), 3.21 and 2.75 (AB system, $J=13.3$ Hz, 2H), 2.16 (s, OH),1.87 (ddd, $J=13.7$, 11.9, 4.4 Hz, 1H), 1.52–1.58 (m, 3H), 0.85 (t, $J=7.3$ Hz, 3H); ^{13}C NMR: δ 177.0, 135.7, 130.2, 128.6, 127.1, 81.0, 42.4, 35.5, 17.6, 16.3; MS (EI) *m/z* 207 M^+; HRMS M^+: calcd for $C_{12}H_{17}NO_2$: 207.1259; found: 207.1251.

3.4.4. 2-Hydroxy-2,3-diphenylpropanamide (5d). The residue was purified by flash chromatography (ethyl acetate/hexane 1:1) and washed with hexane to afford **5d**, that was characterized from an enantiomeric 85:15 mixture. Yield: 92%; white solid; $[\alpha]_D^{20}$ +21.8 (*c* 0.5, $CHCl_3$); IR (film): 3497, 3381, 2923, 1668 cm^{-1}; ^1H NMR: δ 7.71–7.68 (m, 2H), 7.41–7.19 (m, 8H), 6.54 (s, NH), 5.35 (s, NH), 3.85 and 3.15 (AB system, $J=13.5$ Hz, 2H), 2.75 (s, OH); ^{13}C NMR: δ 175.8, 141.8, 134.9, 130.5, 128.7, 128.3, 127.8, 127.5, 125.2, 78.9, 45.5; MS (EI) *m/z* 207 $(M+1)^+$; HRMS $(M+1)^+$: calcd for $C_{15}H_{16}NO_2$: 242.1181; found: 242.1178.

3.5. Oxidation of the sulfinyl group. General procedure

A solution of the corresponding hydroxysulfoxides **7a** and **8′a** in $CDCl_3$ was added to a NMR tube containing an excess of previously dried ($MgSO_4$) MCPBA solution in the same solvent. The NMR signals were obtained from the crude mixtures.

3.5.1. (2*S*,3*R*)-2-Hydroxy-2-methyl-3-[2-(*p*-tolylsulfonyl)phenyl]butanenitrile (9) and (2*R*,3*S*)-2-hydroxy-2-methyl-3-[2-(*p*-tolylsulfonyl)phenyl]butanenitrile (*ent*-9). ^1H NMR δ 8.03–7.75 (m), 3.89 (q, $J=6.9$ Hz, 1H), 2.37 (s, 3H), 1.56 (s, 3H), 1.16 (d, $J=6.9$ Hz, 3H).

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