Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 1963–1968

# Remote stereocontrol mediated by the sulfinyl group: hydrocyanation of 2-*p*-tolylsulfinyl benzaldehyde

José Luis García Ruano,* Ana M. Martín-Castro,* Francisco Tato and Diego J. Cárdenas

*Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain*

Received 7 March 2005; accepted 27 April 2005

**Abstract**—Enantiomerically pure cyanohydrins derived from 2-*p*-tolylsulfinyl benzaldehyde can be obtained by reaction with different hydrocyanating reagents in the presence of $Yb(OTf)_3$ or $Y(OTf)_3$.

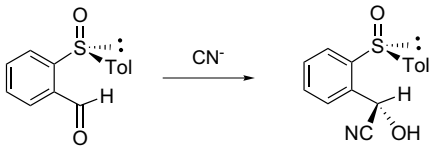

## 1. Introduction

As has been extensively documented, enantiomerically pure cyanohydrins are attractive building blocks as synthetic intermediates in the preparation of α-hydroxy acids,[1] which are frequently involved in the synthesis of peptides, α-hydroxy ketones,[2] α-halonitriles,[3] and a number of natural products.[4] As a consequence, much effort has been focused on their asymmetric synthesis.[5] However, the successful results achieved in reactions with aldehydes[5] contrast with the much lower number of efficient methods to obtain cyanohydrins derived from ketones.[6] This suggests that the search for methods allowing the stereocontrolled quaternization of the hydroxylic carbon at the cyanohydrins derived from aldehydes could be a new strategy to obtain cyanohydrins derived from ketones and therefore would significantly widen the access to these compounds.

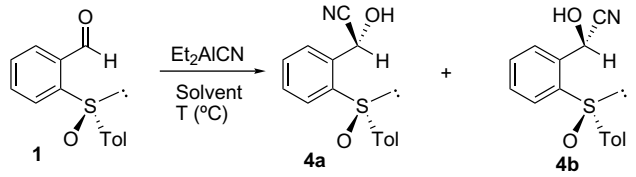
Over the last few decades, the sulfinyl group has been extensively used as a chiral auxiliary due to its high versatility, as well as its easy incorporation into organic substrates and its ready removal from the target molecules. Several years ago, our research group reported the efficiency of the sulfinyl group to control the stereoselectivity of different nucleophilic additions to β-ketosulfoxides.[7] In particular, excellent results were obtained in their hydrocyanation reactions with $Et_2AlCN$, giving rise to diastereomerically pure sulfinylcyanohydrins.[8] More recently we initiated a program focused on the evaluation of the sulfinyl group's ability as a remote chiral auxiliary. In this field, from the excellent results obtained in reactions of 2-*p*-tolylsulfinyl substituted benzyl carbanions with different electrophiles,[9] it can be inferred that the sulfinyl group is also efficient at controlling the stereoselectivity at nucleophilic centers separated by three bonds from the stereogenic sulfur (1,4-asymmetric induction). Other research groups have proven that this efficiency can also be maintained for electrophilic centers located at similar positions. Thus, Solladie et al. reported the stereoselective reduction of γ-ketosulfoxides[10] and Toru and co-workers published noteworthy results concerning the reactions of 2-formyl-1-sulfinylnaphthalenes with Grignard reagents.[11] However, when the latter reactions were studied on 2-sulfinylbenzaldehydes, the stereocontrol was not efficient unless 2,4,6-triisopropylphenyl sulfoxides were used as the chiral auxiliaries,[12] which decreased the synthetic interest of these reactions due to the drawbacks derived from the non-trivial preparation of the starting materials. Despite the poor results obtained by Toru from 2-*p*-tolylsulfinyl benzaldehyde, we decided to explore its behavior of such a chiral auxiliary in the hydrocyanation reactions of this substrate, because these nucleophilic additions on β-ketosulfoxides[13] had exhibited better stereoselectivity control than the corresponding alkylation reactions. Regardless of the obtained results, our goal was quaternization of the benzyl carbon at the resulting cyanohydrins by taking advantage of the ability shown by the *ortho*-sulfinyl group in controlling the stereoselectivity at such a carbon.[9] Thus, we report herein the results of the reaction of (*S*)-2-*p*-tolylsulfinylbenzaldehyde **1** with different hydrocyanating reagents and propose a reasonable stereochemical model supported by theoretical calculations (Scheme 1).

* Corresponding authors. E-mail: joseluis.garcia.ruano@uam.es

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.04.031




Scheme 1.




Scheme 3.

## 2. Results and discussion

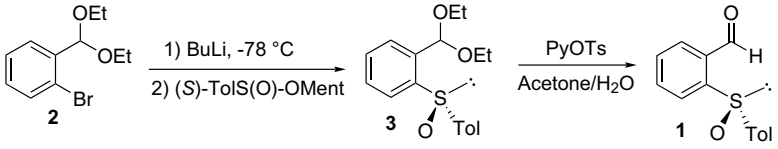
Enantiomerically pure (*S*)-2-*p*-tolylsulfinylbenzaldehyde **1** was prepared in high overall yield over a two-step sequence starting from commercially available 2-bromobenzaldehyde diethyl acetal. Sulfinylation and subsequent hydrolysis of the acetal function of **3** afforded our target molecule **1** (Scheme 2).[14]

Initially we studied the reactions of compound **1** with $Et_2AlCN$ under different conditions (solvent, temperature, addition mode—direct or inverse, amount of reagent, see Scheme 3).

Significant results concerning yields and diastereomeric ratios are indicated in Table 1. In the absence of Lewis acids, reactions in THF both at −20 °C and −78 °C provided diastereomeric mixtures of cyanohydrins **4a** and **b** with low de's. The composition of these mixtures remained unaltered with the reaction times, which exerted only little influence on the conversion degree (entries 1–4). Similar results were obtained in $CH_2Cl_2$ (entries 5 and 6). When toluene was used as the solvent some changes in the composition of the reaction mixtures were observed (entries 7–10), which suggests that an equilibrium between **4a** and **b** occurs under these conditions. However, none of these changes was synthetically significant.

Next we considered the influence of different Lewis acids on the course of the reaction. The hydrocyanation did not work in the presence of some of them [$Sc(OTf)_3$, $Sn(OTf)_2$]. However, the results were highly satisfactory in the presence of $Yb(OTf)_3$ (entries 11–13) and $Y(OTf)_3$ (entry 14), yielding **4a** as the major or exclusive (at −78 °C) diastereoisomer.

Configurational assignment for **4a** was unequivocally established by chemical correlation with the commercially available (*R*)-mandelamide **5** (Kowa Fine Chemicals). Such a correlation was performed by hydrolysis of the cyano group at **4a** followed by desulfinylation of the crude mixture without further purification (Scheme 4). It is noteworthy that the hydrolysis took place under very mild conditions ($HBF_4$/NaI at rt), contrasting with the usually strong conditions required to transform nitriles into amides,[15] and evolved with simultaneous reduction of the sulfinyl into a sulfenyl group. It suggests that the reaction proceeds with anchimeric assistance of the sulfinyl group, as demonstrated in other sulfinyl nitriles.[16]

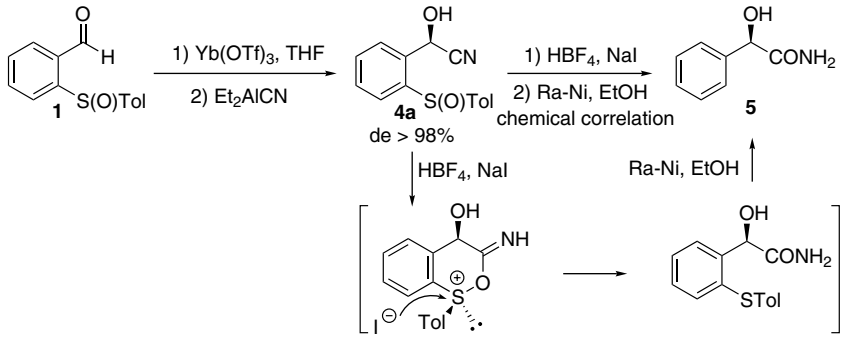



Scheme 2.

**Table 1.** Reaction of **1** with $Et_2AlCN$ under different conditions (Scheme 3)

| Entry | Solvent | *T* (°C) | Time | Lewis acid | Conversion (%) | Ratio **4a**:**4b**[a] (Yield, %) |
|---|---|---|---|---|---|---|
| 1 | THF | −20 | 1 min | — | 100 | 70:30 |
| 2 | THF | −20 | 2 h | — | 100 | 70:30 |
| 3 | THF | −78 | 5 min | — | 83 | 56:44 |
| 4 | THF | −78 | 2 h | — | 100 | 56:44 |
| 5 | $CH_2Cl_2$ | −20 | 5 min | — | 75 | 50:50 |
| 6 | $CH_2Cl_2$ | −20 | 2 h | — | 100 | 50:50 |
| 7 | Toluene | −20 | 5 min | — | 60 | 35:65 |
| 8 | Toluene | −20 | 15 min | — | 60 | 26:74 |
| 9 | Toluene | −20 | 30 min | — | 50 | 62:38 |
| 10 | Toluene | −20 | 2 h | — | 20 | 65:35 |
| 11 | THF | −20 | 5 min | $Yb(OTf)_3$ | 75 | 75:25 |
| 12 | THF | −20 | 30 min | $Yb(OTf)_3$ | 100 | 75:25 |
| 13 | THF | −78 | 2 h | $Yb(OTf)_3$ | 100 | >98(92):<2 |
| 14 | THF | −78 | 2 h | $Y(OTf)_3$ | 100 | 96(82):4 |

[a] Determined by integration of well-separated signals in the $^1H$ NMR spectra of the crude mixture.




**Scheme 4.**

The almost complete stereoselectivity observed for reactions conducted under $Yb(OTf)_3$ or $Y(OTf)_3$ catalysis suggests that the metal must be able to form a stable seven-membered chelated species with both the sulfinyl and carbonyl oxygens, which have only one face accessible to attack by the hydrocyanating reagent. In the absence of the catalyst, $Et_2AlCN$ apparently is unable to form similar seven-membered chelates, despite it being efficient in forming six-membered ones with β-ketosulfoxides.[8] As a consequence, the association of the aluminum only to the sulfinyl oxygen followed by a barely stereoselective intramolecular transfer of the cyanide to the carbonyl group would account for the low observed stereoselectivity in the absence of $Yb(OTf)_3$ or $Y(OTf)_3$.

In order to support this stereochemical proposal we performed DFT calculations on yttrium complexes **A** derived from $Y(OTf)_3$. Since the reactions performed well in $CH_2Cl_2$, which is a non-coordinating solvent, the model complexes included the bidentate organic ligand along with three bidentate triflates, to give coordination number eight. Several starting geometries differing in the conformation of the seven member chelate were fully optimized using the B3LYP hybrid functional. The optimized complexes show a distorted square anti-prism arrangement around Y. The carbonyl and the sulfoxide ligands can occupy two coordination sites corresponding either to the same or different faces of the anti-prism. The most stable complexes show the chelate within the same face. For this type of geometry, several arrangements of the triflate ions were considered. The resulting complexes lie within a range of 0.7 kcal $mol^{-1}$, and show a very similar conformation for the seven member ring. The carbonyl group is coplanar with the aromatic ring, and exhibits a very different steric hindrance for both faces (see Figs. 1–3). The nucleophilic attack on the less hindered face is fully consistent with the observed stereoselectivity. When the sulfoxide and the carbonyl join different faces of the anti-prism, less stable complexes (ca. 5 kcal $mol^{-1}$) are obtained, although they support the same stereochemical outcome.

According to this model, the stereoselectivity is only dependent on the catalyst and therefore the role of the hydrocyanating reagent must be irrelevant. In this sense, we performed the hydrocyanation with different trialkylsilyl cyanides in the presence of $Yb(OTf)_3$ in order to obtain protected and, therefore, more stable, silylated cyanohydrins. The reactions with TMSCN and

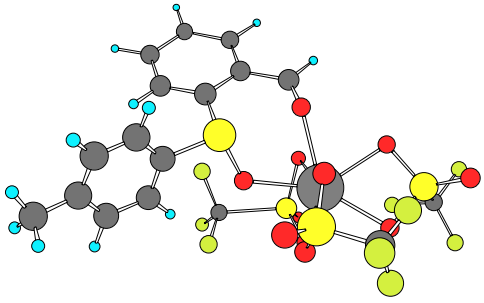


**Figure 1.**

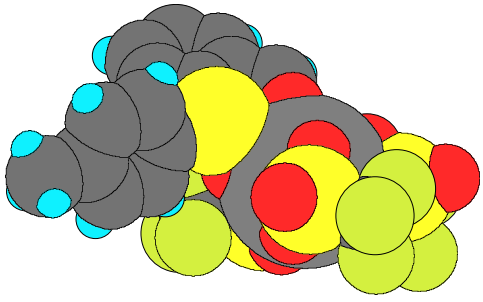


**Figure 2.**

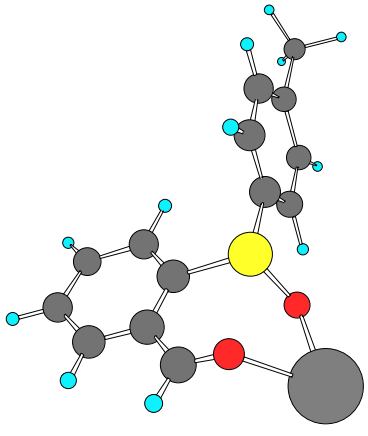
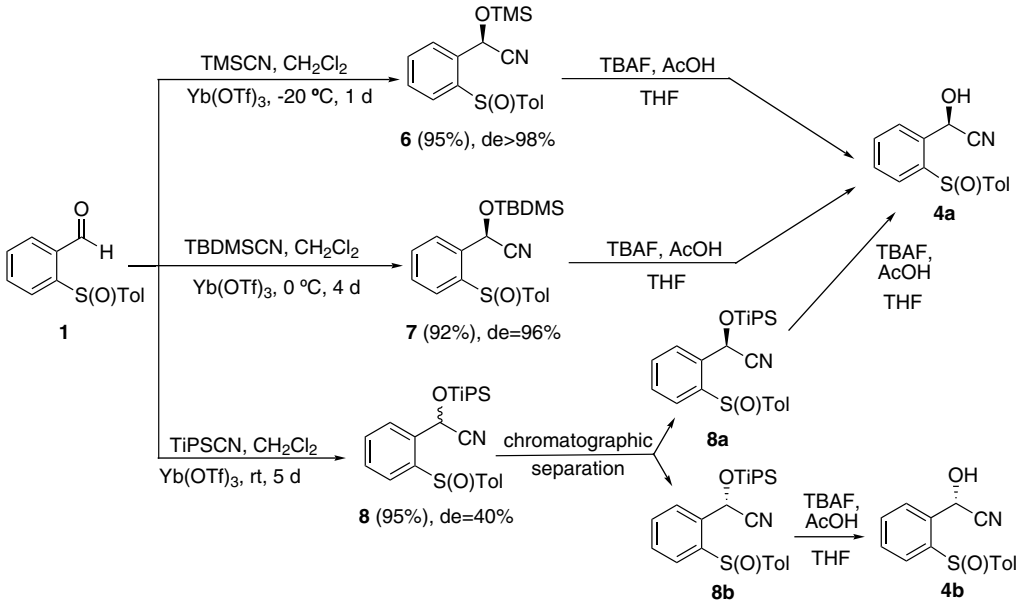


**Figure 3.**




**Scheme 5.**

TBDMSCN proceeded at low temperatures affording the *O*-silylated cyanohydrins **6** and **7**, respectively, in high yields with excellent levels of diastereoselectivity (Scheme 5). These results are particularly interesting in the case of exploiting of the so obtained enantiomerically pure cyanohydrins as chiral synthons for further synthetic transformations, which frequently use *O*-protected derivatives as starting materials. Conversely, reactions with TIPSCN[17] did not evolve completely stereoselectively due to the higher temperature required to reach completion (Scheme 5).

Diastereomerically pure *O*-silylated cyanohydrins **6** and **7** can be readily correlated with **4b** (thus confirming their configurational assignment) by treatment with TBAF/AcOH (Scheme 4). This correlation reinforces our hypothesis, which postulates the scarce role of the hydrocyanating reagent on the stereochemical course of these reactions catalyzed by $Yb(OTf)_3$.

## 3. Conclusions

From the above results we can conclude that the hydrocyanation of (*S*)-2-*p*-tolylsulfinylbenzaldehyde with $Et_2AlCN$ and $R_3SiCN$ is highly stereoselective in the presence of some Lewis acids such as $Yb(OTf)_3$ or $Y(OTf)_3$ as a consequence of the cyanide attack on a chelate involving aldehyde and sulfoxide coordination with the metal, as proven by the calculation at a DFT level.

## 4. Experimental

### 4.1. Computational methods

The calculations were performed with the GAUSSIAN 98 series of programs.[18] The geometries of all complexes were optimized at the DFT level using the B3LYP hybrid functional.[19] The standard 3-21G basis set was used for C, H, O, F, and S, while the LANL2DZ relativistic pseudopotential was used for Y. Harmonic frequencies were calculated at the same level of theory to characterize the stationary points and to determine the zero-point energies (ZPE).[20]

### 4.2. General methods

NMR spectra were obtained in a Bruker spectrometer (300 and 75 MHz for $^1H$ and $^{13}C$, respectively) in $CDCl_3$ solutions. Melting points were measured using a Gallemkamp apparatus in open capillary tubes. Mass spectra (MS) were determined at $FAB^+$. Specific rotations were measured in a Perkin–Elmer 241 MC polarimeter. All reactions were carried out in anhydrous solvents and under an argon atmosphere. THF and $Et_2O$ were distilled from sodium-benzophenone under argon. $CH_2Cl_2$ was distilled from $P_2O_5$. Flash column chromatography was performed using silica gel Merk-60 (230–400 mesh). Enantiomeric excesses were determined by HPLC using a column CHIRALPAK AD as a chiral stationary phase. Aldehyde **1**,[3] acetal **3**[3] and TIPSCN[17] were prepared following previously reported procedures.

### 4.3. General procedure for hydrocyanation

**4.3.1. With $Et_2AlCN$.** A solution of 244.3 mg (1 mmol) of (*S*)-2-(*p*-tolylsulfinyl)benzaldehyde **1** in 5 mL of THF was added dropwise into a solution of 2.5 mL (2.5 mmol) of $Et_2AlCN$ 1 M in toluene diluted in 10 mL of THF at −78 °C. The mixture was stirred at −78 °C for 2 h. The reaction mixture was transferred by cannula (by applying a positive argon pressure to the reaction flask) into a mixture of 2.5 mL of methanol and 2.5 mL of concentrated HCl, cooled at −78 °C. The resulting mixture was vigorously stirred at −78 °C for 1 h, poured into a mixture of 1.5 mL of concentrated HCl and 1.5 mL of ice-water, and extracted with

$CH_2Cl_2$ (3 × 5 mL). The extracts were washed with water (10 mL), dried over $Na_2SO_4$, and the solvent evaporated at a reduced pressure.

**4.3.2. With $Et_2AlCN/X(OTf)_3$ (X = Yb, Y).** A solution of 244.3 mg (1 mmol) of (*S*)-2-(*p*-tolylsulfinyl)benzaldehyde **1** and 1 mmol of $Yb(OTf)_3$ or $Y(OTf)_3$ in 5 mL of THF was stirred for 30 min at room temperature and then added dropwise into a solution of 2.5 mL (2.5 mmol) of $Et_2AlCN$ 1 M in toluene diluted in 10 mL of THF at −78 °C. The resulting mixture was vigorously stirred at −78 °C for 1 h and then worked up as in method A.

### 4.4. (2*R*,(S)*S*)-2-Hydroxy-2-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile 4a

The product was purified by crystallization from hexane–ethyl ether. Yield: 92%; mp: 134–136 °C; white solid; $[\alpha]_D^{20} = -58.4$ (*c* 1, $CHCl_3$); IR (KBr): 3176, 2401, 1060, 1009 $cm^{-1}$; $^1H$ NMR: $\delta$ 7.83 (dd, *J* 1.6 and 7.7 Hz, 1H), 7.76 (dd, *J* 1.6 and 7.7 Hz, 1H), 7.62 (td, *J* 1.6 and 7.7 Hz, 1H), 7.55 (td, *J* 1.59 and 7.7 Hz, 1H), 7.39 and 7.29 (AA′BB′ system, 4H), 5.83 (s, 1H), 4.78 (br s, OH), 2.39 (s, 3H); $^{13}C$ NMR: $\delta$ 142.1, 142.0, 138.9, 136.4, 133.1, 130.5, 130.4, 130.1, 129.6, 124.7, 117.5, 60.9, 21.4; MS (FAB+) *m/z* 272 $[M+1]^+$; HRMS $[M+1]^+$: calcd for $C_{15}H_{13}NO_2S$: 271.0667. Found: 272.07452.

### 4.5. (2*R*)-Mandelamide 5

A solution of 271.4 mg (1 mmol) of cyanohydrin (2*R*,(S)*S*)-**4a** in 10 mL of anhydrous $CH_2Cl_2$ at 0 °C, 0.6 mL (9 mmol) of fluoroboric acid was added. The mixture was stirred for 4 h at rt. Then 1.5 g (10 mmol) of NaI was added and the resulting mixture stirred at rt. After 15 h, the mixture was treated with 5 mL of water, and extracted with $CH_2Cl_2$ (3 × 5 mL). The extracts were washed with aqueous $NaHSO_3$, dried over $Na_2SO_4$, and concentrated at a reduced pressure. The residue was dissolved in THF and added onto a suspension of Ra–Ni in THF at rt. After 24 h, the reaction mixture was filtered over Celite and the solvent evaporated. The product was purified by flash column chromatography (AcOEt–hexane 2:1). Yield: 55%. $[\alpha]_D^{20} = -7.8$ (*c* 0.32, acetone) (from a 70:30 enantiomeric mixture of **4a**) {lit.[21] $[\alpha]_D = +73.0$ (*c* 1.20, acetone)}.

### 4.6. General procedures for silylcyanation

A solution of 244.3 mg (1 mmol) of aldehyde **1** and 62.5 mg (1 mmol) $Yb(OTf)_3$ in 5 mL of $CH_2Cl_2$ was stirred for 30 min at rt and then the corresponding silylcyanide (5 mmol) was added. The temperature and reaction time are indicated in each case. In reactions with TMSCN, the crude mixture was evaporated at a reduced pressure without additional work up. For the rest of $R_3SiCN$ reagents, the resulting mixture was quenched with a saturated aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$ (3 × 5 mL). The extracts were dried over $Na_2SO_4$ and the solvent evaporated at a reduced pressure. The residue was purified as indicated in each case.

### 4.7. (2*R*,(S)*S*)-2-[2-(*p*-Tolylsulfinyl)phenyl]-2-(trimethylsilyloxy)acetonitrile 6

The reaction was stirred at −20 °C for 24 h and the protected cyanohydrin purified by flash column chromatography (AcOEt–hexane 1:3). Yield: 95%; white solid; mp: 142–143.2 °C; $[\alpha]_D^{20} = -67.8$ (*c* 1, $CHCl_3$); IR (KBr): 2401, 1215, 756 $cm^{-1}$; $^1H$ NMR: $\delta$ 7.88–7.85 (m, 1H), 7.82–7.79 (m, 1H), 7.62–7.58 (m, 2H), 7.48 and 7.30 (AA′BB′ system, 4H), 6.21 (s, 1H), 2.40 (s, 3H), 0.23 (s, 9H); $^{13}C$ NMR: $\delta$ 142.9, 141.6, 141.2, 135.2, 131.9, 130.5, 130.0, 128.4, 127.2, 125.4, 118.0, 59.5, 21.1, −0.3.

### 4.8. (2*R*,(S)*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile 7

The reaction was stirred at 0 °C for 4 days and the protected cyanohydrin was isolated by flash column chromatography (AcOEt–hexane 1:6). Yield: 92%; colorless oil; $[\alpha]_D^{20} = -111.2$ (*c* 1, $CHCl_3$); IR (film): 2401, 1216, 755 $cm^{-1}$; $^1H$ NMR: $\delta$ 7.91–7.87 (m, 1H), 7.81–7.78 (m, 1H), 7.66–7.58 (m, 2H), 7.49 and 7.32 (AA′BB′ system, 4H), 7.32 (d, *J* 7.8 Hz, 2H), 6.17 (s, 1H), 2.42 (s, 3H), 0.92 (s, 9H), 0.23 (s, 3H), 0.07 (s, 3H); $^{13}C$ NMR: $\delta$ 141.9, 141.8, 140.8, 135.7, 131.9, 130.1, 128.4, 127.0, 125.5, 118.1, 59.0, 23.4, 21.2, 17.9, −3.1, −3.2. Anal. Calcd for $C_{21}H_{27}NO_2SSi$: C, 65.41; H, 7.06; N, 3.63; S, 8.32. Found: C, 64.91; H, 7.14; N, 3.59; S, 8.02.

### 4.9. (2*R*,(S)*S*)- and (2*S*,(S)*S*)-2-[2-(*p*-Tolylsulfinyl)phenyl]-2-(triisopropylsilyloxy)acetonitrile 8a and 8b

The reaction was stirred at rt for 5 d and both diastereoisomers isolated by flash column chromatography (AcOEt–hexane 1:8). Diastereoisomer (2*R*,(S)*S*)-**8a**: yield: 65%; white solid; mp: 72–74 °C; $[\alpha]_D^{20} = -89.4$ (*c* 1.0, $CHCl_3$); IR (KBr): 2401, 1215, 756 $cm^{-1}$; $^1H$ NMR: $\delta$ 7.99–7.94 (m, 1H), 7.85–7.82 (m, 1H), 7.63–7.60 (m, 2H), 7.50 and 7.32 (AA′BB′ system, 4H), 6.15 (s, 1H), 2.42 (s, 3H), 1.21–1.11 (m, 3H), 1.08 (d, *J* 6.1 Hz, 9H), 0.99 (d, *J* 6.1 Hz, 9H); $^{13}C$ NMR: $\delta$ 142.3, 141.2, 140.6, 136.0, 131.0, 130.3, 129.9, 128.1, 126.9, 125.9, 118.1, 58.8, 21.4, 17.7, 17.6, 11.8. Anal. Calcd for $C_{25}H_{35}NO_2SSi$: C, 67.40; H, 7.78; N, 3.28; S, 7.50. Found: C, 67.10; H, 7.60; N, 3.26; S, 7.38. Diastereoisomer (2*S*,(*S*)*S*)-**8b**: yield: 20%; white solid; mp: 78–79 °C; $[\alpha]_D^{20} = -46.1$ (*c* 1.0, $CHCl_3$); IR (KBr): 2401, 1216, 756 $cm^{-1}$; $^1H$ NMR: $\delta$ 7.97–7.92 (m, 1H), 7.91–7.87 (m, 1H), 7.68–7.66 (m, 2H), 7.52 and 7.32 (AA′BB′ system, 4H), 6.13 (s, 1H), 2.41 (s, 3H), 1.25–1.15 (m, 3H), 1.13 (d, *J* 5.8 Hz, 9H), 1.05 (d, *J* 6.2 Hz, 9H); $^{13}C$ NMR: $\delta$ 142.2, 141.9, 140.6, 135.7, 132.1, 130.5, 130.3, 127.6, 125.6, 125.5, 118.3, 59.2, 21.4, 17.7, 17.6, 11.8. Anal. Calcd for $C_{25}H_{35}NO_2SSi$: C, 67.40; H, 7.78; N, 3.28; S, 7.50. Found: C, 67.18; H, 7.76; N, 3.24; S, 7.41.

### 4.10. General procedures for the deprotection of silylcyanohydrins

To a solution of silylcyanohydrin (1 mmol) and AcOH (5 mmol) in 5 mL of THF, TBAF (5 mmol) was added

portionwise and the reaction stirred at rt for 16 h. The mixture was diluted with 5 mL of water and extracted with $Et_2O$ ($3 \times 5$ mL). The organic layer was washed with brine (5 mL), dried over $Na_2SO_4$, and the solvent evaporated under a reduced pressure.

## Acknowledgements

We thank CAICYT (Grant BQU2003-04012) and MEC (CTQ2004-02040/BQU) for financial support. One of us (F.T.) thanks Comunidad Autonoma de Madrid for a predoctoral fellowship. Centro de Computación Científica (UAM) is gratefully acknowledged for computation time.

## References

1. Schwindt, M. A.; Belmont, D. T.; Carlson, M.; Franklin, L. C.; Hendrickson, V. S.; Karrick, G. L.; Poe, R. W.; Sobieray, D. M.; Van de Vusse, J. *J. Org. Chem.* **1996**, *61*, 9564.
2. Pirrung, M. C.; Shuey, S. W. *J. Org. Chem.* **1994**, *59*, 3890; Ohta, S.; Yamashita, M.; Arita, K.; Kajiura, T.; Kawasaki, I.; Noda, K.; Izumi, M. *Chem. Pharm. Bull.* **1995**, *43*, 1294.
3. Stelzer, U.; Effenberger, F. *Tetrahedron: Asymmetry* **1993**, *4*, 161.
4. Sadyandy, R.; Fernandes, R. A.; Kumar, P. *ARKIVOC* **2005**, *3*, 36; Kamal, A.; Shaik, A. A.; Sandbhor, M.; Malik, M. S. *Tetrahedron: Asymmetry* **2004**, *15*, 3939; Xiaobao, Y.; Shengjun, L.; Chengwen, H.; Hongbin, Z. *Tetrahedron* **2003**, *59*, 8551; Yus, M.; Ramon, D. J.; Prieto, O. *Eur. J. Org. Chem.* **2003**, *15*, 2745; Ginesta, X.; Pasto, M.; Pericas, M. A.; Riera, A. *Org. Lett.* **2003**, *5*, 3001; Cho, B. T.; Kang, S. K.; Shin, S. H. *Tetrahedron: Asymmetry* **2002**, *13*, 1209; Saotome, C.; Ono, M.; Akita, H. *Tetrahedron: Asymmetry* **2000**, *11*, 4137; Effenberger, F.; Roos, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1085; Sugai, T.; Kakeya, H.; Ohta, H. *J. Org. Chem.* **1990**, *55*, 4643.
5. Brunel, J.-M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752; He, K.; Zhou, Z.; Wang, L.; Li, K.; Zhao, G.; Zhou, Q.; Tang, C. *Tetrahedron* **2004**, *60*, 10505; Chang, C.-W.; Yang, C.-T.; Hwang, C.-D.; Uang, B.-J. *Chem. Commun.* **2002**, 54; You, J.-S.; Gau, H.-M.; Choi, M. C. K. *Chem. Commun.* **2000**, 1963; Hwang, C.-D.; Hwang, D.-R.; Uang, B.-J. *J. Org. Chem.* **1998**, *63*, 6762.
6. He, B.; Chen, F.-X.; Li, Y.; Feng, X.; Zhang, G. *Eur. J. Org. Chem.* **2004**, *22*, 4657; Avi, M.; Fechter, M. H.; Gruber, K.; Belaj, F.; Poechlauer, P.; Griengl, H. *Tetrahedron* **2004**, *60*, 10411.
7. Carreño, C.; García Ruano, J. L.; Martín, A. M.; Pedregal, C.; Rodríguez, J. H.; Rubio, A.; Sanchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120; Bueno, A. B.; Carreño, M. C.; Fischer, J.; García Ruano, J. L.; Peña, B.; Peñas, L.; Rubio, A. *Tetrahedron Lett.* **1991**, *32*, 3191.
8. García Ruano, J. L.; Martín Castro, A. M.; Rodríguez, J. H. *Tetrahedron Lett.* **1991**, *32*, 3195; García Ruano, J. L.; Martín Castro, A. M.; Rodríguez, J. H. *J. Org. Chem.* **1992**, *57*, 7235; Escribano, A.; García Ruano, J. L.; Martín Castro, A. M.; Rodríguez, J. H. *Tetrahedron* **1994**, *50*, 7567; Cifuentes García, M. M.; García Ruano, J. L.; Martín Castro, A. M.; Rodríguez Ramos, J. H.; Fernández, I. *Tetrahedron: Asymmetry* **1998**, *9*, 859.
9. García Ruano, J. L.; Carreño, M. C.; Toledo, M. A.; Aguirre, J. M.; Aranda, M. T.; Fischer, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2736; García Ruano, J. L.; Alemán, J.; Soriano, J. F. *Org. Lett.* **2003**, *5*, 677; García Ruano, J. L.; Alemán, J. *Org. Lett.* **2003**, *5*, 4513; García Ruano, J. L.; Aranda, M. T.; Aguirre, J. M. *Tetrahedron.* **2004**, *60*, 5383.
10. Solladie, G.; Colobert, F.; Somny, F. *Tetrahedron Lett.* **1999**, *40*, 1227.
11. Nakamura, S.; Yasuda, H.; Watanabe, Y.; Toru, T. *Tetrahedron Lett.* **2000**, *41*, 4157; Nakamura, S.; Yasuda, H.; Watanabe, Y.; Toru, T. *J. Org. Chem.* **2000**, *65*, 8640.
12. Nakamura, S.; Oda, M.; Yasuda, H.; Toru, T. *Tetrahedon* **2001**, *57*, 8469.
13. García Ruano, J. L.; Martín Castro, A. M.; Rodríguez Ramos, J. H. *Rec. Res. Develop. Org. Chem.* **2000**, *4*, 261.
14. Lai, C.-Y.; Mak, W.-L.; Chan, E. Y. Y.; Sau, Y.-K.; Zhang, Q.-F.; Lo, S. M. F.; Williams, I. D.; Leung, W.-H. *Inorg. Chem.* **2003**, *42*, 5863–5870.
15. Sarel, S.; Newman, M. S. *J. Am. Chem. Soc.* **1956**, *78*, 5416; Tsai, L.; Miwa, T.; Newman, M. S. *J. Am. Chem. Soc.* **1957**, *79*, 2530; Becke, F.; Fleig, H.; Pässler, P. *Liebigs Ann. Chem.* **1971**, *749*, 198; Houser, C. R.; Hoffenberg, D. S. *J. Org. Chem.* **1955**, *20*, 1448; Hauser, C. P.; Eby, C. J. *J. Am. Chem. Soc.* **1957**, *79*, 725.
16. García Ruano, J. L.; Martín Castro, A. M.; Rodríguez Ramos, J. H. *Tetrahedron Lett.* **1996**, *37*, 4569.
17. Cunico, R. F.; Kuan, C. P. *J. Org. Chem.* **1990**, *55*, 4634.
18. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O. J.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, R.; Gomperts, R. L.; Martin, D. J.; Fox, T.; Keith, M. A.; Al-Laham, C. Y.; Peng, I.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.9, Gaussian, Inc.: Pittsburgh, PA, 1998.
19. Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098; Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
20. Atomic coordinates and calculated energies for the main stationary points are available from the corresponding author.
21. Wu, S. Y. *Agricult. Biol. Chem.* **1989**, *53*, 165.