

Reactions of enantiopure β -ketimino sulfoxides with Et_2AlCN . Scope and limitations in asymmetric synthesis of α -aminonitriles

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Dedicated to Professor Eusebio Juaristi on occasion of his 55th birthday

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Abstract

Results obtained in the reactions of Et_2AlCN with exocyclic, endocyclic, and acyclic α -*p*-tolylsulfinyl ketimines are reported. Good conversions and satisfactory stereochemical results are obtained exclusively from cyclic ketimines. Imine-enamine equilibrium accounts for the incomplete conversions and low reactivities observed for acyclic amines. Configurational assignments and mechanistic proposals are based on the conformational analysis of substrates and products.

Keywords: Asymmetric hydrocyanation, β -ketimino sulfoxides, chiral α -amino nitriles

Introduction

The asymmetric Strecker reaction has been widely studied because of the importance of the resulting α -amino nitriles.¹ However, practically all these methods, some of them exhibiting a very high efficiency, have been applied to aldehydes with the aim of obtaining α -amino acids. When the reaction is applied to ketones the results are not so good, which accounts for the small number of results that have been reported,² despite the great interest of the α -alkylsubstituted amino acids.³

Over the past decades our research group reported excellent results for the hydrocyanation of enantiomerically pure α -sulfinyl ketones affording the corresponding cyanohydrins. Excellent stereoselectivities (de's > 98%) and very good yields were obtained in reactions of acyclic ketones with Et_2AlCN .⁴ Similar results were observed in reactions from cyclic compounds,⁵ but the yields were lower starting from α -sulfinyl aldehydes,⁶ presumably due to the instability of these substrates. These results made us to devise a parallel study focused on the hydrocyanation

of enantiomerically pure sulfinyl imines, as an alternative two-step method to the Strecker reaction, allowing the preparation of α -alkyl (or aryl) α -amino nitriles, not readily attainable through most of the aboved-mentioned methods. Additionally interesting is the fact that the resulting amino nitriles would preserve the chiral auxiliary, which would offer several possibilities of further transformation due to the chemical versatility of the sulfinyl group. The recent publication of a paper dealing with hydrocyanation of sulfinyl imines,⁷ prompted us to report our results in this field. The current paper describes the hydrocyanation reactions of acyclic (**1** and **2**), exocyclic (**3** and **4**), and endocyclic (**5** and **6**) α -sulfinyl ketimines (**Figure 1**) with diethylaluminum cyanide (Et_2AlCN) under different conditions.

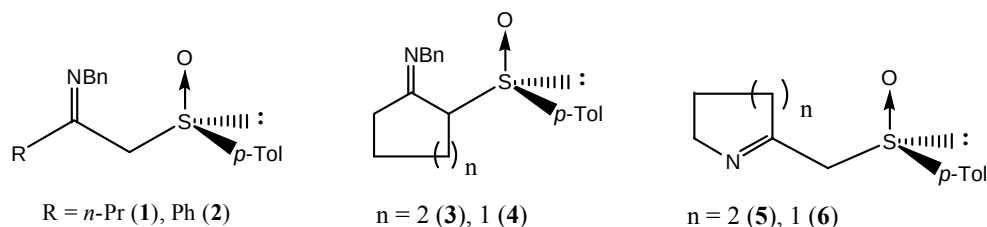
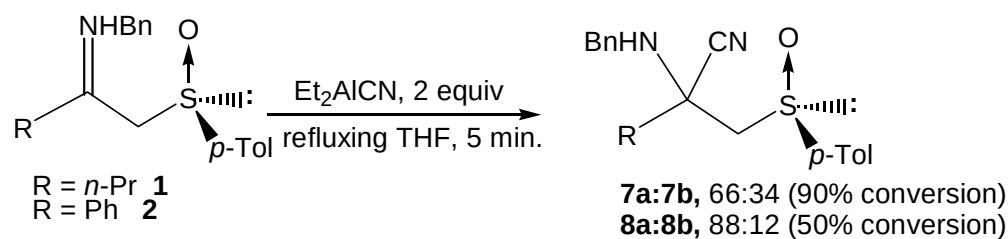


Figure 1

Results and Discussion

The syntheses of all the optically pure sulfinyl imines used as the starting materials were performed following previously reported procedures. Initially we studied the behavior of acyclic α -sulfinyl imines **1** and **2**⁸ with Et_2AlCN , under the best reported conditions for the hydrocyanation of α -sulfinyl ketones (2 equiv., $-20\text{ }^\circ\text{C}$, 2 h⁴). The starting sulfinyl imines were recovered practically unaltered in all cases. An increase in the reaction time (up to 24 h) and in the amount of Et_2AlCN (up to 6 equiv) afforded a 90% of transformation into the corresponding amino nitriles derived from **1**. However a moderate stereoselectivity was observed in all cases (ca. 30% de's) and any change in the reagent addition mode did not improve these results (Scheme 1). An increase in the temperature led to a substantial decrease in the reaction time and in the required amount of Et_2AlCN . Thus, compound **1** was transformed into **7** (as a mixture of diastereoisomers) in just 5 minutes with 2 equiv of the reagent in refluxing THF, but neither the conversion degree (90%) nor the diastereoselectivity (32% de) could be improved. Starting from **2**, a lower conversion (50%) but a better stereoselectivity (76% de) was achieved (Scheme 1) under the best conditions found (2 equiv of Et_2AlCN in refluxing THF). Bearing in mind that the hydrocyanation of sulfinyl ketones had been reported as a practically instantaneous process, and the equilibration of the resulting cyanamines could be responsible for the low stereoselectivity, we checked the composition of the reaction mixtures at shorter reaction times, thus favouring a kinetic control. However, the analysis of the crude reaction mixtures after 5, 30, 60 and 120 minutes, evidenced that the stereoselectivity remained unaltered at different reaction times.

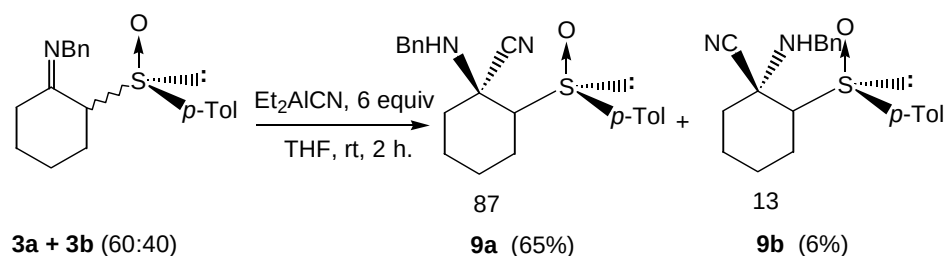
Moreover, no improvement in the reactivity and/or stereoselectivity was detected when the reactions were performed in the presence of TMSOTf.⁹



Scheme 1

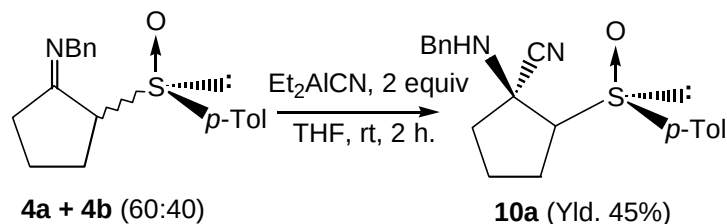
In addition to the lower reactivity of the sulfinyl imines as compared with their corresponding carbonyl derivatives, the tautomeric equilibrium imine-enamine (the latter being the major or even the exclusive tautomer in most of the imino derivatives) can be invoked to explain the behaviour of the α -sulfinyl imines with Et_2AlCN . In the case of the DIBAL-H reductions of these compounds, where we found similar problems, they were circumvented in the presence of Lewis acids such as ZnX_2 , presumably due to their ability to stabilize the iminic structure by formation of chelated species.¹⁰ However, the reactions of **1** and **2** with Et_2AlCN in the presence of such metallic salts improved neither the degree of transformation nor the stereoselectivity of the hydrocyanation. Similar unsuccessful results were observed by conversion of the imines into iminium salts by treatment with an organic acid, despite these conditions had also improved the reactivity of β -enamino sulfoxides in other reduction process.¹¹ All attempts to isolate and purify the components of the reaction mixtures by chromatography failed, due to the decomposition of the reaction products into the original starting α -sulfinyl ketones by retrohydrocyanation and subsequent hydrolysis. In order to get more stable compounds to be isolated and characterised, several attempts were made to transform the cyano group into a carboxamide function. The previously reported conditions (HBF_4/NaI) to achieve this transformation for other cyanosulfoxides¹² were unfruitful with these substrates, just leading to the reduction of the sulfinyl group into a sulfenyl one. As all attempts to isolate and purify the obtained sulfinyl amino nitriles by chromatography failed, they were characterised from the ^1H NMR spectra of the crude mixtures.

Much better results were obtained in the hydrocyanation of cyclic sulfinyl imines **3** and **4**. The slow addition of the reagent (6 equiv.) in THF onto a solution of **3**¹³ (as a 80:20 mixture of **3a** and **3b**, epimers at C-2) in the same solvent (the opposite addition mode to that leading to the best results from acyclic compounds), afforded a 87:13 mixture of **9a** and **9b** (two of the four possible diastereomers) after 2 h. at room temperature with a conversion of 90% (Scheme 2). In refluxing THF decomposition of the starting material was detected. **9a** and **9b** could be separated and purified by chromatography in 65% and 6% yields, respectively (Scheme 2). The different diastereoisomeric ratios of the starting and resulting products indicate that epimerization at C- α is taking place in some extent.



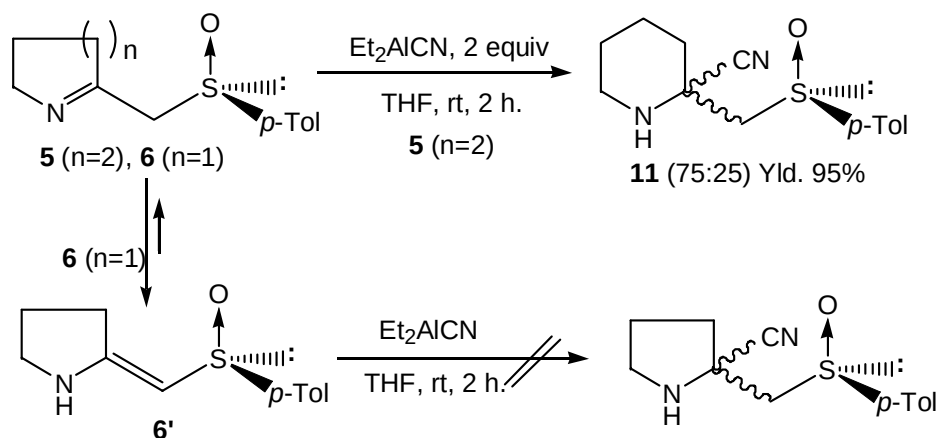
Scheme 2

N-benzyl 2-*p*-tolylsulfinyl cyclopentaneimine **4** was synthesized following a previously reported procedure.¹⁴ Reaction of **4** with only 2 equiv of reagent was complete after 2 h at room temperature and it proceeded with a complete diastereoselectivity (>98% de) only yielding **10a**. However, this amino nitrile was obtained only in 45% isolated yield, probably due to its decomposition via retrohydrocyanation during its chromatographic purification (Scheme 3). As the purification of **9a**, **9b**, and **10a** could be made by flash column chromatography, their configurational assignment was also possible (vide infra).



Scheme 3

Hydrocyanation of endocyclic sulfinyl imine **5**¹⁰ was carried out under the previously used conditions for the reaction of substrates **1-4** (dropwise addition of the reagent onto **5** at room temperature) to afford a 75:25 mixture of amino nitriles **11a** and **11b** (65% combined yield), with complete transformation of the starting sulfinyl imine. The use of Lewis acids as catalysts improved these results, the best ones being those obtained in the presence of CeCl_3 (95% combined isolated yield). However, no substantial change in the stereoselectivity was detected (Scheme 4). When the reaction temperature raised, no hydrocyanation product was obtained and the substrate decomposed. The mixture **11a** and **11b** could be neither separated nor purified by flash column chromatography, although the obtained 75:25 diastereomeric mixture could be purified by crystallization from hexane- CH_2Cl_2 .



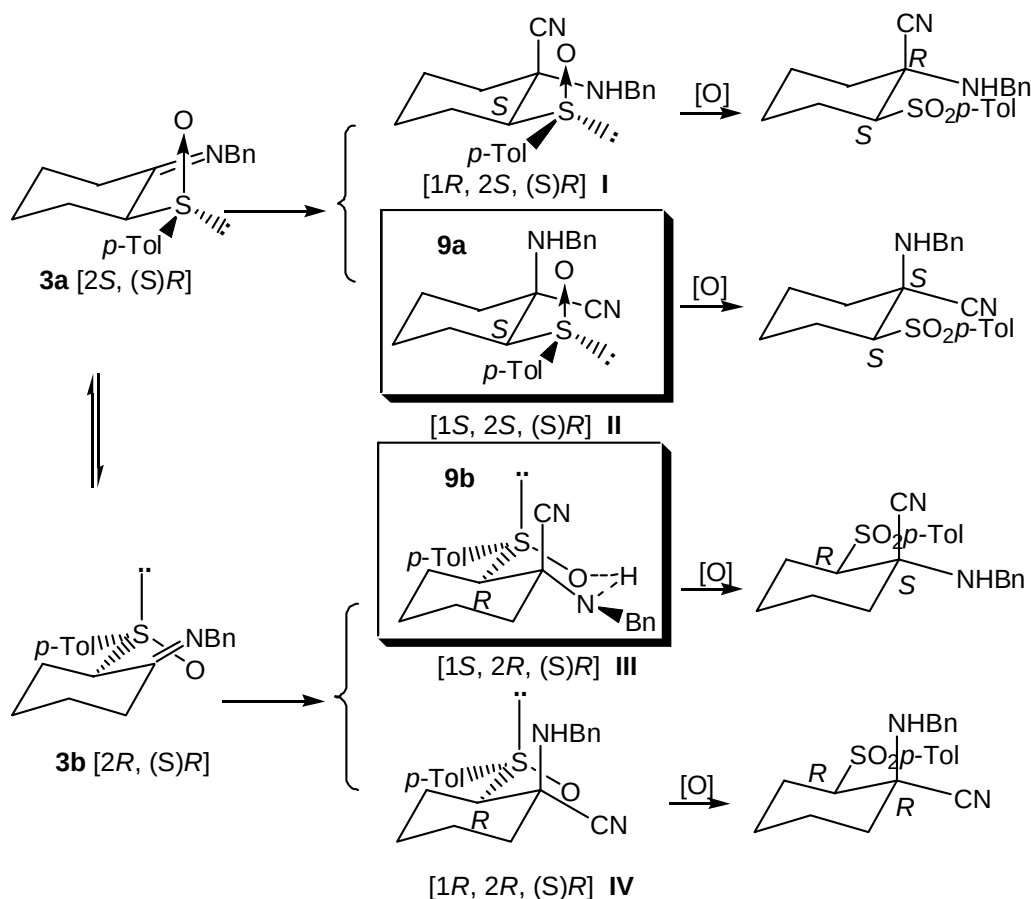
Scheme 4

Endocyclic imine **6**¹⁵ did not react under any of the previously assayed conditions for substrates **1-5**. This is not unexpected on the basis on the high stability of the exocyclic double bonds at five-membered rings, which will stabilize the enaminic tautomer of **6'** thus accounting for its lack of reactivity (Scheme 4).

Configurational Assignment of **9a** and **9b** and Mechanistical Proposal

The configurational assignment of sulfinyl imines was only possible for the cyclohexane derivatives **9a** and **9b**, the only couple of diastereoisomers whose separation and characterization had been possible. On this basis we postulated a reasonable mechanistic proposal accounting for the stereochemical results, which in its term allow us to assign the configuration of the rest of the compounds described in this paper.

In Scheme 5 are depicted the structure of the two starting compounds **3a** and **3b**, bearing *R* configuration at sulfur (it remains unaltered during the hydrocyanation process). They are epimers at C- α that equilibrate via enamine. The structures of the four possible amino nitriles resulting from their hydrocyanation, **I-IV**, are depicted in Scheme 5 in their presumably most stable conformations. As they must exhibit only one group in axial arrangement, the sulfinyl group will always adopt the equatorial orientation. Regarding the conformations around the C–S bond, we have depicted those with the *p*-tolyl group adopting an antiperiplanar arrangement with respect to the quaternary nitrogenated carbon thus minimizing the steric interactions. Out of these four possible isomers, only two of them, **9a** and **9b**, were obtained in the reaction of **3** with Et_2AlCN , which reveals that the reaction is highly stereoselective.



Scheme 5

In tables 2 and 3 are indicated the ^1H and ^{13}C NMR chemical shifts of the cyclohexyl amine moiety at the two isolated amino nitriles **9a** and **9b**. Their most significant differences deal with the chemical shifts of C-3 and H-3a. The former one is markedly shielded and the latter is deshielded in **9a**, which cannot be attributed to the presence of either the amino or the cyano group in an axial arrangement at C-1, since the effect of these substituents in this arrangement at C-3 (and C-5) is not very different from each other.¹⁶ Hence, the sulfinyl group must be responsible for such differences. It is well documented the strong deshielding effect of the sulfinyl oxygen towards the 1,3-parallel hydrogen atoms.¹⁷ Otherwise it has also been reported that the non-bonding electron pair at sulfur strongly shields any carbon atom in a relative antiperiplanar arrangement.¹⁷ Both structural factors must be present at **9a**, and are responsible for the values of $\Delta\delta \text{ C-3} = 5.5 \text{ ppm}$ and $\Delta\delta \text{ H-3a} = 0.86 \text{ ppm}$ as compared with those of **9b** (see Tables 1 and 2). Bearing in mind all these data, diastereoisomers **I** and **II** are the only ones able to adopt the proper spatial arrangement able to account for the spectroscopic parameters of **9a** (Scheme 5), but that of **I** would be destabilized by strong dipolar repulsion between the S-O and CN bonds.¹⁸⁻²⁰ It suggests that the configuration [1S, 2S, (S)R] (diastereomer **II**) must be assigned to the major amino nitrile **9a**.

Table 1. ^{13}C NMR chemical shifts of sulfinyl amino nitriles **9**

	C-1	C-2	C-3	C-4	C-5	C-6
9a	59.6	67.6	16.3	23.9	19.4	34.4
9b	61.8	67.7	21.8	24.4	23.1	36.9

Table 2. ^1H NMR chemical shifts of sulfinyl amino nitriles **9**

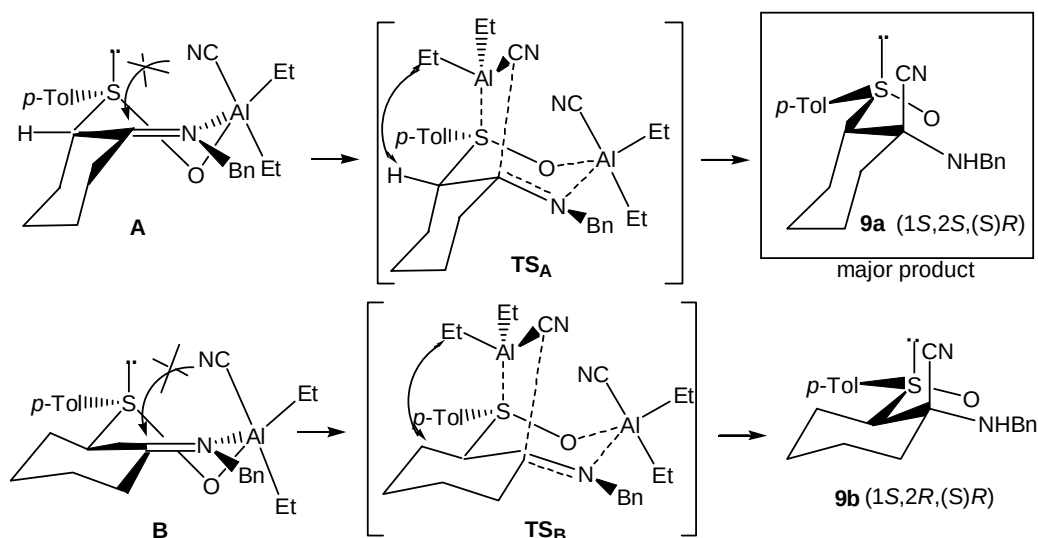
	H-2	H-3a	H-3e	H-4a	H-4e	H-5a	H-5e	H-6a	H-6e	NH
9a	2.70	2.20	1.40	1.28	1.90	1.52	1.84	1.71	2.48	2.40
9b	2.92	1.52	1.28	1.15	1.78	1.53	1.80	1.48	2.52	4.70

The independent oxidation of **9a** and **9b** afforded two sulfones showing different ^1H NMR spectra, which proves that they are not enantiomers.²¹ It suggests that configuration [1*S*, 2*R*, (S)*R*], corresponding to diastereoisomer **III**, must be assigned to **9b** (see Scheme 5). The high value of the chemical shift observed for the aminic proton (4.70 ppm, Table 2), suggesting that it is intramolecularly associated by hydrogen bond, reinforces this configurational assignment because compound **IV** cannot exhibit such an association.

Hydrocyanation mechanism

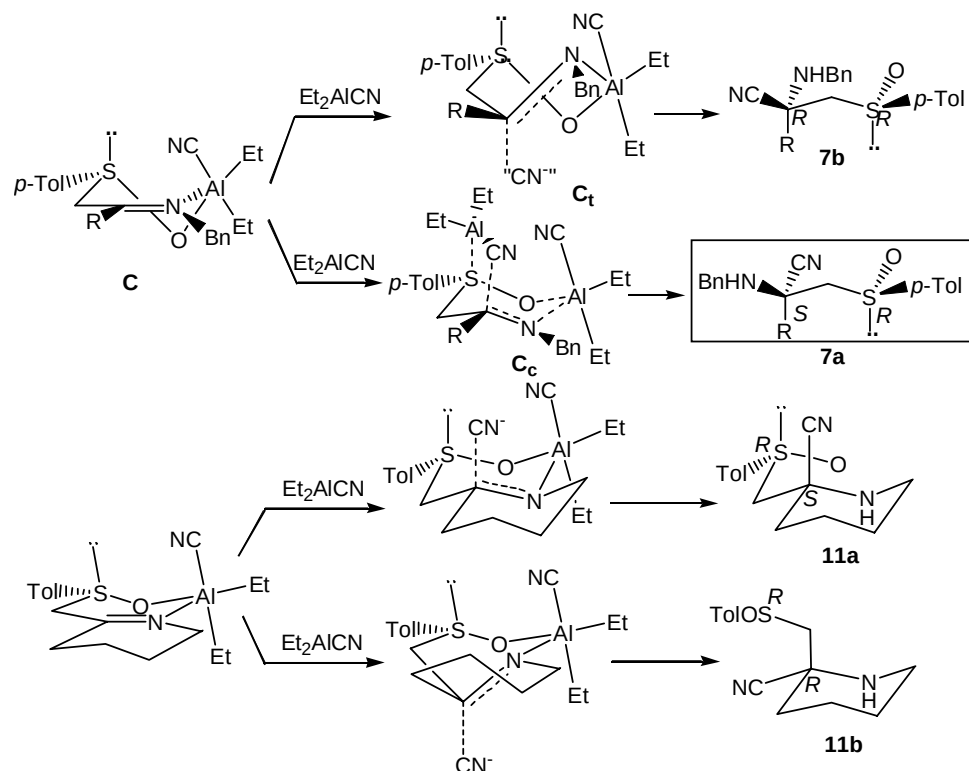
There are some differences in the behavior of our sulfinyl imines with respect to that reported for the corresponding sulfinyl ketones.^{4,5} Firstly, the expected lower reactivity of the imines is enhanced by the imine-enamine equilibrium, which is significantly shifted to the latter in acyclic compounds. Otherwise, imines require at least two equivalents of Et_2AlCN (only one equivalent was enough for the reaction of ketones to reach completion) and their evolution is less stereoselective, which suggests that the hydrocyanation of $\text{C}=\text{O}$ and $\text{C}=\text{N}$ bonds must follow different mechanistic pathways. The association of the aluminum to the sulfinyl and carbonyl oxygens of **3a** and **3b** would result in the formation of the pentacoordinated species **A** and **B** (Scheme 6). The intramolecular transfer of the cyanide group from these species (which had been postulated in the case of β -ketosulfoxides) would explain the exclusive formation of **9a** and **9b**, but it does not account for the 2 equivalents of reagent that are required. Therefore we assume that **A** and **B** are not reactive enough to suffer the intramolecular cyanide transfer, but require the attack of a second molecule of Et_2AlCN . The approach of the reagent must take place to the face allowing its association with the lone electron pair at sulfur (Scheme 6). The higher stability of TS_A with respect to that TS_B (the $(\text{Et}/\text{H})_{1,3-\text{p}}$ interaction is smaller than the $(\text{Et}/\text{CH}_2)_{1,3-\text{p}}$ one, see Scheme 6) and the equilibration of the two epimeric imines, **A** and **B**, under the acidic conditions of the medium, would explain that **9a** is formed as the major adduct. The complete stereoselectivity observed in reactions of **4**, which yields only **10a**, could be explained on the basis that the higher planarity of the cyclopentane ring provokes a *quasi*-eclipsing interaction between the *p*-tolyl group with H in TS_A or CH_2 in TS_B thus increasing their

energetic difference. It suggests that (1*S*,2*S*,(*S*)*R*) must be the configuration of the only obtained diastereoisomer **10a**.



Scheme 6

On the basis of similar considerations, acyclic imines would form the chelated species **C** (Scheme 7) with the reagent. The attack of the second molecule could take place from the upper or lower face of the chelate, thus yielding chair-like (TS_c) or twist-like (TS_t) transition states. By assuming that the intrinsic higher stability of TS_c with respect to TS_t is not completely compensated by the steric repulsion exerted by the CN group at the chelate to the approach of the reagent to the upper face, configuration (*S*,*R*) must be assigned to the major diastereoisomer **7a** and **8a** (Scheme 7). A similar reasoning would allow to assign configuration (*S*,*R*) to **11a**, the major diastereoisomer obtained from **5** (Scheme 7).



Scheme 7

As a conclusion, we have reported that the hydrocyanation of β -imino sulfoxides with Et_2AlCN yields aminonitriles with stereoselectivities ranging from moderate to good, the best results having been obtained for exocyclic imines. The reactivity is lower than that of their corresponding carbonylic precursors and decreases as a consequence of the imine-enamine equilibrium.

Experimental Section

General Procedures. All moisture sensitive reactions were performed in flame-dried glasswares equipped with rubber septa under positive pressure of argon. Silica gel 60 (230-400 mesh ASTM) and DC-Alufolien 60 F₂₅₄ were used for flash column chromatography and analytical TLC, respectively. Melting points were determined in a Gallenkamp apparatus in open capillary tubes and are uncorrected. Microanalyses were performed with a *Perkin Elmer* 2400 CHN and *Perkin Elmer* 2400 C-10II CHNS/O analysers. NMR spectra were determined in a CDCl_3 solutions, unless otherwise is indicated, at 300 and 75 MHz for ^1H and ^{13}C NMR respectively; chemical shifts (δ) are reported in ppm and J values are given in hertz. The IR spectra frequencies are given in cm^{-1} . Compounds **1**,⁸ **2**,⁸ **3**,¹³ **5**,¹⁰ and **6**¹⁵ were synthesized and purified according to previously described procedures.

***N*-Benzyl-2-[(*R*)-*p*-tolylsulfinyl]cyclopentaneimine (4).**¹⁴ To a solution of 3.3 mmol of diisopropylamine in anhydrous THF (10 mL), cooled at -78°C under argon, was added a solution of 2.3 M BuLi (3.1 mmol) in hexanes. The mixture was stirred at -78°C for 30 min and then a solution of *N*-benzylcyclopentaneimine (3.0 mmol) in THF (20 mL) was slowly added. It was stirred for 15 min and a freshly prepared 0.3 M solution of MgBr₂ in THF was added. After 20 min at -78°C menthyl (*S*)-*p*-toluenesulfinate (1 mmol) in THF (10 mL) was added. The resulting mixture was stirred at rt for 1 h and the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane (3×10 mL), the organic extracts were dried (Na₂SO₄) and the solvent was removed at reduced pressure. The crude mixture was purified by flash column chromatography using hexane:acetone:triethylamine (4:3:1) as the eluent to afford a mixture of *N*-benzyl-2-[(*S*)-*p*-tolylsulfinyl]-1-cyclopenteneimine and *N*-benzyl-2-[(*R*)-*p*-tolylsulfinyl]cyclopentaneimine (**4a** + **4b**, 60:40). Yield: 90%. $[\alpha]_{\text{D}}^{25} +106.0$ (*c* 1.0, CH₂Cl₂). IR (CHCl₃): 3480, 2920, 1610, 1500, 1010, 810 cm⁻¹. ¹H NMR (**enamine**): 5.44 (t, 1H, *J* 6.2 Hz), 4.40 (d, 2H, *J* 7.0 Hz); ¹H NMR (**4a** + **4b**): 4.63 (s, 2H, *J* 6.2 Hz), 4.61 (s, 2H, *J* 6.2 Hz), 3.53 (t, 1H, *J* 7.0 Hz), 3.29 (t, 1H, *J* 7.0 Hz).

Reactions of enantiopure β -ketimino sulfoxides with Et₂AlCN. General procedure

To a solution of α -sulfinyl imine (1 mmol, 1 equiv.) in 3 mL of anhydrous THF, under argon, was added a 1 M solution of Et₂AlCN in toluene, previously diluted to 0.1 M in anhydrous THF. The reaction mixture was stirred under the conditions (temperature and reaction time) indicated in each case. The reaction was quenched with water (3 mL) and the organic layer was extracted with dichloromethane (2×5 mL). The organic extracts were dried (MgSO₄) and the solvent was removed at reduced pressure.

(*R*)- and (*S*)-2-(Benzylamino)-2-[(*R*)-*p*-tolylsulfinyl]methylpentanenitrile (7). A mixture **7a** + **7b** (66:34) was obtained from the reaction of imine **1** with 2.0 equiv. of Et₂AlCN in refluxing THF for 5 min. The transformation was not complete, and a 10% of the unaltered substrate was recovered. The crude reaction decomposed upon column chromatography. IR (CHCl₃): 3420, 3040, 2239, 1580, 1500, 1460, 1030, 810 cm⁻¹. ¹H NMR (**major diastereoisomer**): 3.16 and 2.94 (AB system, 2H, *J* 14.0 Hz). ¹H NMR (**minor diastereoisomer**): 3.39 and 3.03 (AB system, 2H, *J* 13.7 Hz).

(*R*)- and (*S*)-2-(Benzylamino)-2-phenyl-3-[(*R*)-*p*-tolylsulfinyl]propanenitrile (8). A mixture **8a** + **8b** (88:12) was obtained from the reaction of imine **2** with 2.0 equiv. of Et₂AlCN in refluxing THF for 5 min. The transformation was of 50%, and the unaltered substrate was recovered. The crude reaction decomposed upon column chromatography. IR (CHCl₃): 3418, 3040, 2240 1580, 1507, 1460, 1030, 810 cm⁻¹. ¹H NMR (**major diastereoisomer**): 3.31 and 2.87 (AB system, 2H, *J* 14.5 Hz). ¹H NMR (**minor diastereoisomer**): 3.46 and 3.27 (AB system, 2H, *J* 13.3 Hz).

[1*S*,2*S*,(*S*)*R*]- and [1*S*,2*R*,(*S*)*R*]-1-(Benzylamino)-2-[*p*-tolylsulfinyl]cyclohexanecarbonitrile (9a** and **9b**).** A mixture **9a** + **9b** (87:13) was obtained from the reaction of imine **3** with 6.0 equiv. of Et₂AlCN in THF at rt for 2 hours. Both diastereoisomers were separated and purified

by flash column chromatography, using hexane:acetone 7:1 as the eluent. **Diastereoisomer [1S,2S,(S)R]-9a**: Yield: 65%. mp: 131-132 °C. $[\alpha]_D + 99$ (*c* 1.0, CHCl₃). IR (CHCl₃): 3300, 3000, 2240, 1500, 1220, 1100, 1050, 820 cm⁻¹. ¹H NMR: 7.45 and 7.32 (AA'BB' system, 4H), 7.46-7.27 (m, 5H), 4.05-3.85 (m, 2H), 2.67 (dd, 1H, *J* 10.5 and 3.8 Hz), 2.41 (s, 3H), 2.46-1.20 (m, 8H). ¹³C NMR: 141.5, 138.7, 138.4, 129.1 (2C), 128.5 (2C), 128.3 (2C), 127.3, 124.3 (2C), 120.7, 67.6, 59.6, 48.2, 34.4, 23.9, 22.9, 21.8, 21.5. Anal. calcd. for C₂₁H₂₄N₂OS: C, 71.56; H, 6.87; N, 7.95. Found: C, 71.44; H, 6.83; N, 7.89. **Diastereoisomer [1S,2R,(S)R]-9b**: Yield: 6%. $[\alpha]_D + 126$ (*c* 1.0, CHCl₃). IR (CHCl₃): 3300, 3000, 2239, 1510, 1210, 1100, 1030, 820 cm⁻¹. ¹H NMR: 7.64-7.25 (m, 9H), 4.66 (m, 1H), 4.08-3.83 (m, 2H), 2.91 (dd, 1H, *J* 13.2 and 4.2 Hz), 2.41 (s, 3H) 2.52-1.08 (m, 8H). ¹³C NMR: 143.2, 139.3, 138.4, 129.8 (2C), 128.5 (2C), 128.3 (2C), 127.3, 124.6 (2C), 119.9, 67.6, 61.6, 48.2, 36.9, 24.4, 23.1, 21.8, 21.5.

[1S,2S,(S)R]-1-(Benzylamino)-2-[p-tolylsulfinyl]cyclopentanecarbonitrile (10a). It was obtained diastereomerically pure from the reaction of imine **4** with 2.0 equiv. of Et₂AlCN in THF at rt for 2 hours. It was purified by flash column chromatography, using hexane:acetone 7:1 as the eluent. Yield: 45%. mp: 131-132 °C. $[\alpha]_D + 230$ (*c* 0.5, CHCl₃). IR (CHCl₃): 3300, 2980, 1600, 1450, 1310, 1150, 1080, 1030, 810 cm⁻¹. ¹H NMR: 7.63-7.26 (m, 9H), 4.19-3.73 (m, 1H), 3.60-3.50 (m, 1H), 3.80 (m, 1H), 3.18 (t, 1H, *J* 7.3 Hz), 2.42 (s, 3H) 2.49-1.35 (m, 6H). ¹³C NMR: 142.9, 139.7, 138.9, 130.1 (2C), 128.5 (2C), 128.3 (2C), 127.3, 125.0 (2C), 119.1, 71.0, 66.8, 50.5, 39.7, 23.6, 21.5, 20.8. Anal. calcd. for C₂₀H₂₂N₂OS: C, 70.97; H, 6.55; N, 8.27. Found: C, 70.54; H, 6.36; N, 8.04.

(2S,(S)R)- and (2R,(S)R)-2-{[p-Tolylsulfinyl]methyl}-2-piperidinecarbonitrile (11a and 11b). It was obtained by hydrocyanation in the presence of CeCl₃. 1.5 mmol of the Lewis acid was stirred in the presence of 1 mmol of imine **5** at rt in THF for 30 min. The mixture was slowly added onto a solution of 2 mmol of Et₂AlCN in THF. The reaction mixture was stirred at rt for 2 h to afford a 75:25 diastereoisomeric mixture. Both diastereoisomers could not be separated because they decomposed upon column chromatography. The mixture crystallized from hexane:dichloromethane. Yield: 95%. $[\alpha]_D + 203$ (*c* 1.0, CHCl₃, 75:25 mixture **11a:11b**). IR (CHCl₃): 3300, 2940, 1140, 1080, 1040 cm⁻¹. MS: 235 (9) (M⁺-26), 186 (100), 139 (39), 123 (19), 91 (50), 69 (19). ¹H NMR (**11a** + **11b**): 7.60 and 7.35 (AA'BB' system, 4H (**11a**)), 7.52 and 7.35 (AA'BB' system, 4H (**11b**)), 3.20 and 2.77 (AB system, 2H, *J* 12.5 Hz (**11a**)), 3.13 and 2.95 (AB system, 2H, *J* 12.5 Hz (**11b**)), 3.12-3.05 (m, 4H), 1.82-1.68 (m, 12H). ¹³C NMR (**11a**): 142.1, 137.6, 128.8 (2C), 123.8 (2C), 119.3, 68.2, 56.7, 42.7, 36.1, 29.5, 24.1, 21.5. Anal. calcd. for C₁₄H₂₀N₂OS: C, 63.60; H, 7.62; N, 10.60. Found: C, 63.16; H, 7.56; N, 10.58.

Acknowledgements

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20. This interaction has been described as considerably unstabilizing for other compounds (see refs. 18 and 19) to such an extent as to make the conformational participation of the rotamer exhibiting such an interaction practically inexistent.
21. The reaction was carried out in an NMR tube in order to be monitored by ^1H NMR. A solution of 0.04 mmol (1.3 equiv) of *m*-CPBA in 0.3 mL of CDCl_3 was added into a solution of 0.03 mmol (1.0 equiv) of amino nitrile in 0.3 mL of CDCl_3 until the signals of the starting material were not observed by ^1H NMR. No 2-(*p*-tolylsulfonyl)aminonitrile was isolated to avoid partial decomposition of the product under the basic conditions required for the workup. Hence, ^1H NMR are those deduced from the spectra of the reaction mixtures. (1*S*,2*S*)-1-(Benzylamino)-2-[*p*-tolylsulfinyl]cyclohexanecarbonitrile was prepared by oxidation of [1*S*,2*S*,(*S*)*R*]-**9a**: δ 7.76-7.26 (m, 9H), 5.49 (s, 1H), 4.28 and 3.85 (AB system, 2H, *J* 13.2 Hz), 4.00 (s, 1H), 2.42 (s, 3H), 2.71-1.52 (m, 8H). (1*S*,2*R*)-1-(Benzylamino)-2-[*p*-tolylsulfinyl]cyclohexanecarbonitrile was prepared by oxidation of [1*S*,2*R*,(*S*)*R*]-**9b**: δ 7.82-7.28 (m, 9H), 5.74 (s, 1H), 4.14 and 3.89 (AB system, 2H, *J* 13.4 Hz), 3.60 (dd, 1H, *J* 3.0 and 13.0 Hz), 2.45 (s, 3H), 2.42-1.20 (m, 8H).