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Stereoselective cyanosilylation of α-sulfinylketimines or its covalently stabilized enamine tautomers. Synthesis of enantiomerically pure α-sulfinylmethyl-α-amino nitriles

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Abstract—α-Sulfinylketimines and β-sulfinylenamines undergo reaction with delivery cyanide reagents such as TMSCN or TBDMSCN in the presence of either stoichiometric excesses of $ZnCl_2$ or $ZnBr_2$, or catalytic amount of $Yb(TfO)_3$. The use of $ZnCl_2$ in alcohol solvents provides the best diastereoselectivity. It is mediated by a chelated transition state, the *p*-tolyl group driving the anti attack of the reagent. By using $Yb(TfO)_3$ poor diastereoselectivities but good yields are obtained. It seems that an iminium derivative originated by metal coordination with either the nitrogen or oxygen atom in the substrate is responsible for the observed results. Interestingly, β-sulfinylenamines provide analogous α-amino nitriles in the same reaction conditions. It allowed the cyanosilylation of the covalently stabilized enamines arising from unstable β-sulfinyl aldehydes.

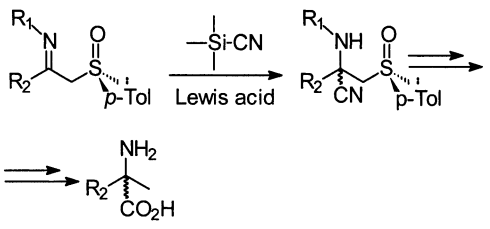
1. Introduction

Chiral α-sulfinylketimines have shown to be useful enolizable synthons. The regio- and diastereoselectivity of the addition reactions of its aza-enolates derivatives to β-substituted ene-esters are controlled by the chiral sulfinyl moiety. The synthetic utility of these processes has been developed by us to achieve 4,6-disubstituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones with high yields and entire diastereoselectivity.[1,2] The easy reductive fission of the C–S bond with Raney Nickel, and further in situ hydrogenation of the C=C bond, originates enantiomerically pure 4,6-disubstituted δ-lactams which display a high synthetic utility.[3,4] In a different way, the α-sulfinylketimines can be turned into chiral α-sulfinylmethyl-α-amino nitriles with different cyanation reagents as TMSCN or TBDMSCN in the presence of Lewis acids as catalysts in a like-Strecker reaction. The subsequent oxidative hydrolysis and reductive fission of the C–S bond affords α-amino acid derivatives (Scheme 1).

In fact, the asymmetric Strecker synthesis that was described for the first time by Harada[5] for the preparation of L-alanine starting from acetaldehyde, (*S*)-α-methylbenzylamine (*S*-α-MBA) and NaCN, is a convenient method for the synthesis of proteinogenous and non-proteinogeneous α-amino acids.[6] Since then, numerous modifications of Harada's experimental protocol have been described[7] which can be classified into the following three categories:

(i) The use of other suitable cyanide sources as TMSCN[8] or diethyl phosphorocyanidate.[9]
(ii) The employment of the most widely applied chiral auxiliary, α-MBA, as well as further arylalkylamines like α-*tert*butylbenzylamine, and α-ethylbenzylamine,[10] α-phenylglycinol,[11] *N*-benzylphenylglycinol,[12] and aryl sulfinimines.[13]
(iii) The introduction of chiral catalytic systems to achieve high selectivities from metal salts and chiral ligands.[14]

In this work, we have explored the application of the methodology described by Garcia-Ruano et al.[15] for the



Scheme 1.

Keywords: cyanosilylation; α-sulfinylketimines; β-sulfinylenamines; diastereoselective synthesis; chiral sulfoxides; Lewis acid; Strecker reaction; α-amino acids derivatives; β-sulfinyl-α-amino nitriles.

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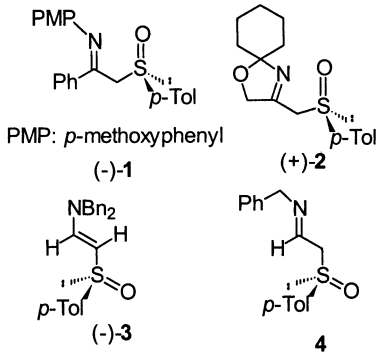
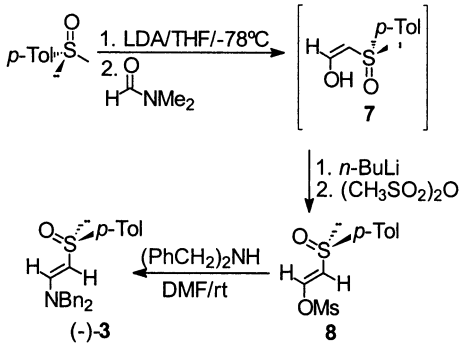


Chart 1.



Scheme 3.

diastereoselective synthesis of α-cyanhydrins derived from chiral β-ketosulfoxides to chiral α-sulfinylketimines **1** and **2** (Chart 1), in order to achieve chiral α-amino acids derivatives with a quaternary asymmetric carbon (Scheme 1). Furthermore, the behavior of the chiral β-sulfinylenamine **3** derived from unstable aldimine **4** has been investigated in the same reaction conditions. It will allow us to spread out the experimental protocol to other unstable aldimines which can be easily derivatized to β-sulfinylenamines to accomplish its tautomeric stabilization.

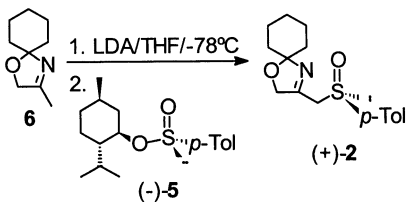
2. Results and discussion

The compound **1** was obtained from 1-phenylethyliden (4-methoxyphenyl) azane and (−)-(S_S)-menthyl *p*-toluenesulfinate **5** (ee>98%) following the procedure described by Garcia-Ruano et al.[16] The compound **2** was prepared from 2-oxazoline **6** following a similar procedure (Scheme 2).[17] In both cases, the reaction occurs with an entire inversion of the chiral sulfur configuration.[18]

The compound **3** was accomplished from mesylate **8** and dibenzylamine, whereas the derivative **8** was accessible from (+)-(R_S)-methyl *p*-tolylsulfoxide such as it is outlined in Scheme 3.[19] The intermediate compounds **7** and **8** were transformed without previous isolating, and the compound **3** was obtained in a 58.5% overall yield.

The *E*-configuration of the double bond of the compound (−)-**3** was confidently assigned from the observed vicinal coupling constant for vinyl hydrogens (^3J=13.2 Hz).

Preliminary hydrocyanation essays with diethylaluminium cyanide in the presence of $ZnCl_2$ using the reaction conditions previously described by Davis[13c] and by Garcia-Ruano[15a] (normal and inverse addition of the reagents, respectively) on the compounds **1**–**3** were carried out. In all the cases the results were unsuccessful since the sulfenylated derivative originated by reduction was the sole isolated product.



Scheme 2.

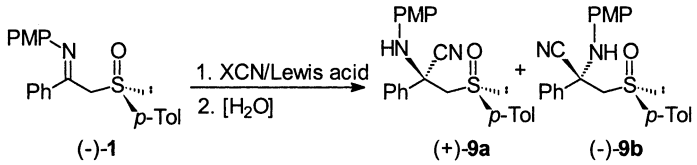
Taking into account that the cyanide addition to imines is a reversible process,[20] the α-amino nitriles could be configurationally unstable in solution. Hence, some previous experiments to ensure a kinetic control were performed. Thus, the cyanosilylation reagents (TMSCN and TBDMSCN) in the presence of catalytic amounts of $Yb(TfO)_3$ or stoichiometric ones of $ZnCl_2$ were used. The most reliable results were achieved in CH_2Cl_2 as solvent by using $Yb(TfO_3)$, whereas different solvents (THF or ROH) and relative excesses of cyanosilylation reagent and catalyst had to be used for each substrate when $ZnCl_2$ was used. By mixing the reagents at 0°C for 30 min, and leaving the reaction mixture to stand at room temperature for 6–12 h, the stereoselectivity appeared to be unchanged into the limits that the conversion was modified.

Additional experiments on the work up of the reactions were also needed to make in order to prove the stability of the adducts. Thus, hydrolysis of reaction mixture at 0°C with saturated NH_4Cl solution showed to be the best method when $ZnCl_2$ was used. On the other hand, addition of a saturated Na_2CO_3 solution to the reaction mixture obtained in the presence of $Yb(TfO)_3$ at 0°C was the selected method. The purification of reaction mixtures was carried out by flash chromatography on silica gel. The α-sulfinylmethyl-α-amino nitriles become stables during their handling and standing at −5°C for two months. However, the derivatization to α-sulfonylmethyl-α-amino carboxamides is strongly recommended to prevent their decomposition such as it has been made in one of the cases (vide infra).

2.1. Cyanosilylation reactions of compound (−)-1

The observed results in the cyanation reactions of (−)-**1** with TMSCN and TBDMSCN in the presence of $ZnCl_2$ or $Yb(TfO)_3$ (10 mol%) have been collected in Table 1. The mixtures of α-amino nitriles **9a** and **9b** were isolated by flash chromatography on silica gel (hexanes/ethyl acetate: 2:1) of the remaining α-sulfinylketimine (−)-**1** and (*R*)-[(4-methylphenyl)sulfinyl]-1-phenylethanone which was originated by hydrolysis of (−)-**1**. The separation of α-amino nitriles **9a** and **9b** was carried out by flash chromatography on silica gel (hexanes/ethyl acetate: 4:1–2:1) from enriched mixtures of these isomers. Diastereomeric ratio was determined by ^{1}H NMR analysis (200 MHz) of the reaction

Table 1. Cyanosilylation reactions of compound (−)-**1**



(-)-**1** (+)-**9a** (-)-**9b**

Entry	XCN	Lewis acid (L.A.)	**1**/XCN/L.A.	Solvent	Yield (%)[a]	**9a/9b**[b]
1	TMSCN	$ZnCl_2$	1:1:1	*i*-PrOH	60	86:14
2	TBDMSCN	$ZnCl_2$	1:1:2	*i*-PrOH	25	83:17
3	TMSCN	$Yb(TfO)_3$	1:1:0.1	CH_2Cl_2	80	63:37
4	TBDMSCN	$Yb(TfO)_3$	1:1:0.1	CH_2Cl_2	51	64:36

All reactions were carried out by mixing the reagents at 0°C for 30 min, next 12 h at rt.
[a] Overall isolated yields.
[b] Determined from ^1H NMR spectra of the mixtures.

mixtures by integration of the AB systems (CH_2–S^*O) observed for **9a** and **9b**.

The best chemical yields were reached with TMSCN whatever that may be the Lewis acid ($ZnCl_2$ or $Yb(TfO)_3$; Table 1; entries 1 versus 2 and 3 versus 4). On the other hand, the diastereomeric ratio **9a/9b** dropped significantly when $Yb(TfO)_3$ was used instead $ZnCl_2$ (Table 1; entries 1 versus 3 and 2 versus 4). The diastereoselectivity observed with $ZnCl_2$ must be confidently related with the highest stereodifferentiating effect of the sulfinyl group which could be originated by a restricted rotation of CH_2–S^*O bond. Because of the ability of this Lewis acid to provide chelated complex with the nitrogen and oxygen atoms of the sulfinyl group,[21] a complex like **10** (Fig. 1) in a half-chair conformation could be taken into account, the pseudo-equatorial arrangement of the bulkiest *p*-tolyl group driving the facial selectivity via a *si* approach (*anti* attack) to afford **9a** as major diastereomer.

On the contrary, the low observed diastereoselectivity in the presence of $Yb(TfO)_3$ can be explained on the basis of opened transition states. Thus, an iminium derivative arising from **1** via ligand substitution in the catalyst could be the actual kinetic substrate (Fig. 2). The selection of two conformations (A and B) in a fast interconversion equilibrium would lead to two competitive reaction paths by an *anti* attack of the cyanation reagent with regard to the *p*-tolyl group.

The assumption of this different behaviour for $Yb(TfO)_3$ and $ZnCl_2$ must be related with the easily of the former to give reactions of ligand substitution. Further, its catalytic role is related to the ability to give transmetalated species as it has been reported.[22,23]

The dual stereochemical behaviour of (−)-**1** allows tentatively to assign the (R_S,*S*) and (R_S,*R*) absolute configurations to **9a** and **9b**, respectively. All attempts to achieve the chemical correlation with L-phenylalanine were unsuccessful by the difficulty concerning to the deprotection of the N–PMP substituted group with ceric ammonium nitrate.[24] However, this assignment will be confirmed later taking into account the spectroscopic behaviour of **9a** and **9b** and that of the other α-amino nitriles (vide infra).

2.2. Cyanosilylation reactions of the compound (+)-2

The observed results in the cyanation reactions of (+)-**2** with TMSCN and TBDMSCN in the presence of $ZnCl_2$ or $Yb(TfO)_3$ (10 mol%) have been collected in Table 2.

Firstly, an extensive decomposition of the compound (+)-**2** occurred when excesses (5:1) of TMSCN or TBDMSCN and $ZnCl_2$ (2:1) were used. It is probably due to the lability

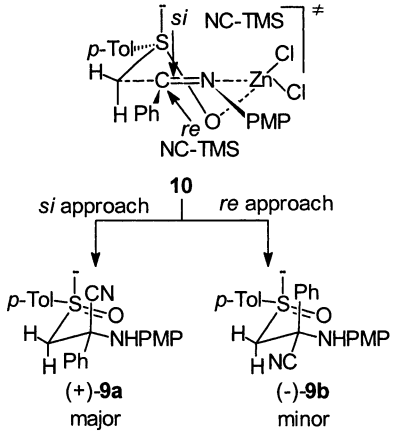


Figure 1. Proposed stereochemical model for the cyanosilylation reactions of (−)-**1** with $ZnCl_2$.

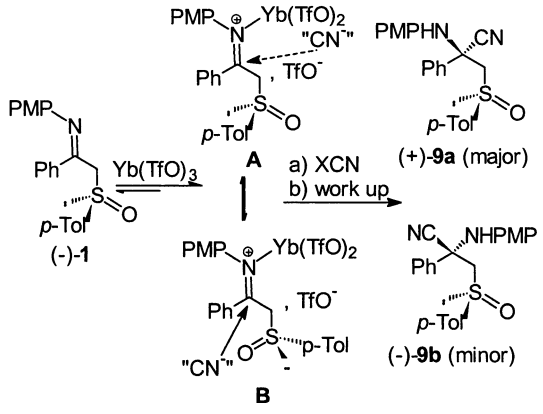
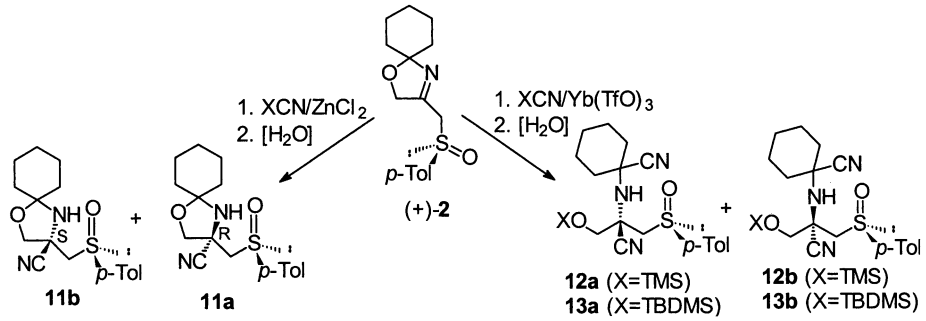


Figure 2. Proposed stereochemical pathways for the cyanosilylation reactions of (−)-**1** in the presence of $Yb(TfO)_3$ as catalyst.

Table 2. Cyanosilylation reactions of the compound (+)-**2**



Entry	XCN	Lewis acid (L.A.)	**2**/XCN/L.A.	Solvent	Yield (%)[a]	**11a/11b**[b]	**12a/12b**[b]	**13a/13b**[b]
1	TMSCN	$ZnCl_2$	1:2.2:1	*i*-PrOH	28	72:28	–	–
2	TMSCN	$Yb(TfO)_3$	1:3:0.1	CH_2Cl_2	–	–	–	–
3	TMSCN	$Yb(TfO)_3$	1:5:0.1	CH_2Cl_2	98	–	56:44	–
4	TBDMSCN	$Yb(TfO)_3$	1:5:0.1	CH_2Cl_2	84	–	–	55:45

All reactions were carried out by mixing the reagents at 0°C for 30 min, next 12 h at rt.
[a] Overall isolated yields.
[b] Determined from ^{1}H NMR spectra of the mixtures.

of cyclic ketal against $ZnCl_2$.[22] Only in the reported reaction conditions in Table 2 (entry 1), the reaction mixture was clean although the yield was poor.

On the other hand, the reactions of (+)-**2** and TMSCN in the presence of $Yb(TfO)_3$ were unsuccessful when excesses of reagent lower than 5:1 were used. However, good yields in the dicyano derivatives **12a/12b** or **13a/13b** were achieved by using a large excess (5 equiv.) of the cyanation reagent (Table 2, entries 3 and 4) although the observed diastereoselectivity was very low.

In all the cases, each pair of diastereomeric α-amino nitriles was separated from unreacted starting compound (+)-**2** by a flash chromatography on silica gel (hexanes/ethyl acetate: 1:4) although their separation was unsuccessful in all tested conditions. The structure of compounds **11**–**13** was confidently assigned by elemental analysis and IR, ^{1}H and ^{13}C NMR spectra. Diastereomeric ratios were determined by integration of the key signals of ^{1}H NMR spectra of reaction mixtures.

Focussing our attention on the observed chemical shifts for the methylenic hydrogens of the carbon bearing the sulfinyl group (AB system), the pairs **11a/11b**, **12a/12b**, **13a/13b** can be assembled in two groups: **11a**, **12b**, **13b** and **11b**, **12a**, **13a**. Thus, the isomers of the first group display a larger difference between δ_A and δ_B ($\Delta\delta>0.25$ ppm) than the isomers of the second group ($\Delta\delta<0.15$ ppm). In addition, the sense of the diastereoselectivity for the formation of the pair **11a/11b** (Table 2, entry 1) must be the same than for the pair **9a/9b** (Table 1; entry 1). Thus, the (R_S,*R*) and (R_S,*S*) absolute configurations can be tentatively assigned to compounds **11a**, **12b**, **13b** and **11b**, **12a**, **13a**, respectively (notice that the priority of the groups attached to the new stereogenic center is changed in the compounds **11**–**13** with regard to **9**).[25] In fact, the compounds **9a** and **9b** display the same difference for the chemical shifts of methylenic hydrogens (**9a**: $\Delta\delta=0.357$ ppm; **9b**: $\Delta\delta=0.350$ ppm) although in a lesser extent than the compounds **11**–**13**. This decrease can be probably related with the superposition of other differentiation effects such as the ring currents due to the presence of the aryl groups in the epimers **9a** and **9b**. Other spectroscopic data were irrelevant in order to establish the configurational assignment although it will be definitively established by ^{1}H NMR analysis of the stereo analogous α-amino nitriles **14a** and **14b** arising from cyanosilylation of the compound **3** since the absolute configuration of **14a** and **14b** was unequivocally established by chemical correlation (vide infra).

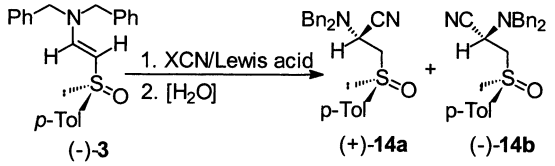
The stereochemical pathway of the reactions reported in Table 2 is entirely similar to that observed for compound **1**, although a generalized decrease of the stereoselectivity was observed for the reactions of compound **2** and a light inversion of diastereoselectivity occurred when $Yb(TfO)_3$ was used as catalyst (Table 2; entries 3 and 4). On the other hand, the cyclic ketal is opened by attack of the cyanide. It allows to suggest that the acid catalysis implies to the ketal oxygen atom[26] to give the epimeric *N*-cyclohexylidene intermediates which are transformed in the dicyano α-amino nitriles **12** or **13** by attack of a second molecule of the reagent. A similar behavior has been described in other nucleophilic reactions of the compound **2**.[17]

2.3. Cyanosilylation reactions of compound (−)-3

The observed results in the cyanosilylation reactions of the compound (−)-**3** with TMSCN and TBDMSCN in the presence of $ZnBr_2$, $ZnCl_2$ and $Yb(TfO)_3$ (10 mol%) have been collected in Table 3.

Firstly, the influence of the catalyst nature was tested in non-protic solvents (THF or CH_2Cl_2) by using TMSCN as reagent (entries 1, 2 and 7) and the best yield was achieved with $ZnBr_2$ or $ZnCl_2$ (stoichiometric excess 2:1; entries 1 and 2). A scarcely increase of the diastereoselectivity was observed by using a protic solvent (*i*-PrOH, entry 3 versus 2) while the highest selectivity was accomplished by

Table 3. Cyanosilylation reactions of the compound (−)-**3**



Entry	XCN	L.A.	**3**/XCN/L.A.	Solvent	Yield (%)[a]	**14a/14b**[b]
1	TMSCN	$ZnBr_2$	1:1:2	THF	95	59:41
2	TMSCN	$ZnCl_2$	1:1:2	THF	95	60:40
3	TMSCN	$ZnCl_2$	1:1:2	*i*-PrOH	76	65:35
4	TBDMSCN	$ZnCl_2$	1:1:2	MeOH	95	63:37
5	TBDMSCN	$ZnCl_2$	1:1:2	*i*-PrOH	88	72:28
6	TBDMSCN	$ZnCl_2$	1:1:2	*t*-BuOH	75	67:33
7	TMSCN	$Yb(TfO)_3$	1:1:0.1	CH_2Cl_2	55	55:45
8	TBDMSCN	$Yb(TfO)_3$	1:1:0.1	CH_2Cl_2	24	51:49
9	TBDMSCN	$Yb(TfO)_3$	1:5:0.1	CH_2Cl_2	85	52:48

All reactions were carried out by mixing the reagents at 0°C for 30 min, next 12 h at rt.
[a] Overall isolated yields.
[b] Determined from ^{1}H NMR spectra of the mixtures.

combining the stereodifferentiating effect of solvent, Lewis acid and reagent (TBDMS, entry 5). Attempts to increase the stereodifferentiating effect of protic solvent (MeOH or *t*-BuOH; entries 4 and 6) were unsuccessful.

Newly, $Yb(TfO)_3$ gave the lowest stereoselectivities and a high drop in the yields (entries 7 and 8) although the last effect could be compensated by increasing the XCN excess (entry 9).

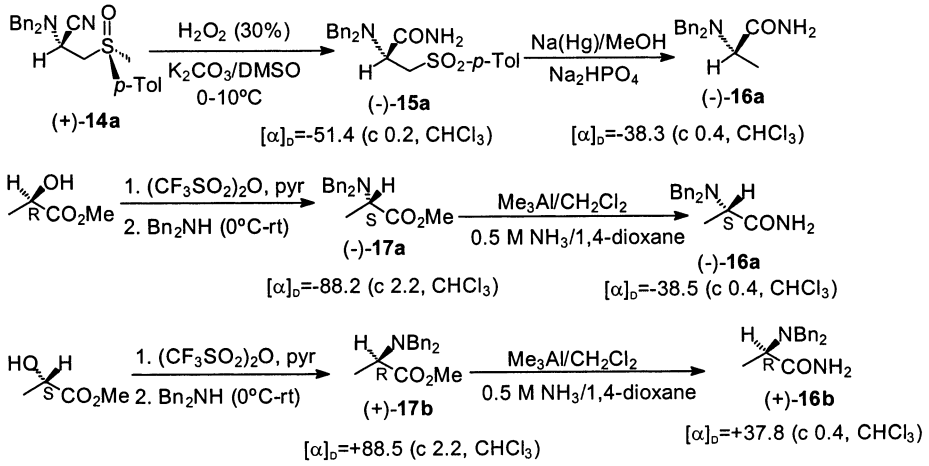
The reaction mixtures were analyzed by ^{1}H NMR (200 MHz) and the diastereoselectivity determined by integration of the signals at 4.324 (dd, 1H, ^3J=5.2, 10.4 Hz, H–C*) and 3.623 (AB, 2H, ^2J=13.7 Hz, CH_2Ph) of the compound **14a** and at 3.423 (AB, 2H, ^2J=13.3 Hz, CH_2Ph) and 3.288 (dd, 1H, ^2J=13.2 Hz, ^3J=7.8 Hz, CH_2–S*) of the compound **14b**. Both epimers **14a** and **14b** were separated by flash chromatography on silica gel (dichloromethane/ether: 10:1) and the overall yields (Table 3) are in isolated products. Structural characterization was established from elemental analysis and their IR, ^{1}H and ^{13}C NMR spectroscopic data.

The major isomer (+)-**14a** was derivatized to the α-sulfonylcarboxamide (−)-**15a** by reaction with H_2O_2 (30% vol) and K_2CO_3 in DMSO (0–10°C).[27]

The subsequent reductive fission of the C–S bond of (+)-**15a** with Na(Hg) (Na_2HPO_4, MeOH) at rt led to 2-[(*N*,*N*)-dibenzylamino]propanamide (−)-**16a** ($[\alpha]_D$= −38.3 ($CDCl_3$, *c* 0.4)) (Scheme 4).[28]

Determination of the optical purity of **16a** was done by a ^{1}H NMR lanthanide induced shifts (LIS) study using (+)-Eu(hfc)$_3$ in $CDCl_3$. Only a single enantiomer could be detected and thus the sample is >97% ee.

Furthermore, the compounds **16a** and its enantiomer **16b** were independently obtained from enantiomerically pure methyl lactates (available from Aldrich Co.) using transformations of proved stereochemistry (Scheme 4).[29,30] Both compounds **16a** and **16b** displayed a similar optical purity to that of the problem sample (**16a**, ee>97%) such as it was established from a ^{1}H NMR LIS study using (+)-Eu(hfc)$_3$ in $CDCl_3$ and the observed rotatory power.



Scheme 4.

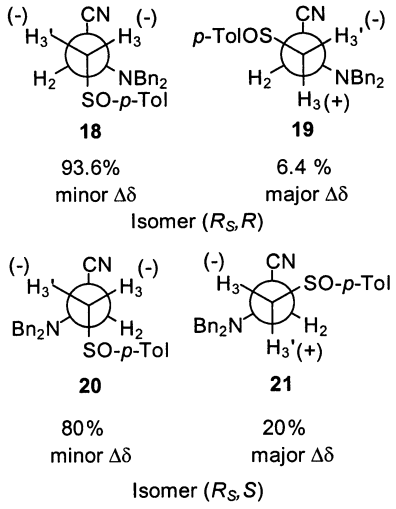


Figure 3. Conformational analysis of (R_S,*R*) and (R_S,*S*) epimers of compound **18** and anisotropic effects of the cyano group on the chemical shifts of hydrogens H_3 and $H_{3'}$. The (−) and (+) marks denote a deshielding or shielding, respectively, of the hydrogens H_3 and $H_{3'}$. $\Delta\delta$ is the absolute difference between the observed chemical shifts of these hydrogens.

So, we assigned the (*S*) and (*R*) configurations to compounds (−)-**16a** and (+)-**16b** obtained by us from enantiomerically pure (*R*) and (*S*) methyl lactates. The comparison of the rotatory power of synthetic samples with that of the carboxamide (−)-**16a** obtained from (+)-**14a** allows to assign the (*R*) absolute configuration to (+)-**14a**. The opposed (*S*) absolute configuration can be assigned to the epimer (−)-**14b**.

On the other hand, the ^{1}H NMR spectra of the epimers **14a** and **14b** show some significant differences. Thus, the minor isomer **14b** displays a larger difference for the chemical shifts of the methylenic hydrogens of the carbon C3 ($\Delta\delta$= 0.215 ppm) than the major isomer **14a** ($\Delta\delta$=0.076 ppm). Furthermore, the observed vicinal coupling constants for hydrogens H_2, H_3 and $H_{3'}$ are very different for both epimers. Thus, the isomer **14b** shows two identical vicinal coupling constants (^3J=7.8 Hz) for hydrogens H_3 and $H_{3'}$ whereas the isomer **14a** displays two different couplings (^3J=5.2 and 10.4 Hz) for these hydrogens. These observations can be justified regarding the deduced results from the conformational analysis of the (R_S,*R*) and (R_S,*S*) epimers of compound **14**. The search of conformational space was made with the *Conformer* utility of the molecular modeling software package Chem3D[31] and the energy of the selected conformations was minimized by a PM3 semiempirical calculation.[32] In accordance with the results of this conformational analysis, four conformations were selected for each epimer with a significant predominance of the conformations **18** and **20** for (R_S,*R*) and (R_S,*S*) isomers, respectively (Fig. 3). The other three conformations can be clustered as **19** and **21** for each epimer taking into account the relative arrangement of *N*,*N*-dibenzylamino and sulfinyl groups.

Table 4. Observed qualitative differences for chemical shifts ($\Delta\delta$) of methylenic hydrogens of the carbon bearing the sulfinyl group and configurational assignment for epimers **a** and **b** of α-amino nitriles **9**, **11**–**14**

Isomers	Observed $\Delta\delta$	Absolute configuration
9a, **11a**, **12b**, **13b**, **14b**	Major	**9a**(*S*), **11a**(*R*), **12b**(*R*), **13b**(*R*), **14b**(*S*)
9b, **11b**, **12a**, **13a**, **14a**	Minor	**9b**(*R*), **11b**(*S*), **12a**(*S*), **13a**(*S*), **14a**(*R*)

Thus, the (R_S,*R*) epimer is conformationally more homogeneous than the (R_S,*S*) isomer. In the most stable conformation for both epimers, the *N*,*N*-dibenzylamino and sulfinyl groups adopt a relative synclinal arrangement whereas in the other three conformations the relative orientation of these groups is antiperiplanar. The selection of the major conformations **18** and **20** can be due to a stabilizing interaction between the lone pair of nitrogen and the unoccupied d orbitals of the hypervalent sulfur.[33] As the relative arrangements of hydrogens H_2/H_3 and H_2/$H_{3'}$ are changed in the conformations of one and other isomer, the vicinal coupling constants between the hydrogens H_2 and H_3/$H_{3'}$ must be more averaged for (R_S,*S*) isomer than for (R_S,*R*) epimer. In accordance with the observed vicinal coupling constants for compounds **14a** (^3J=5.4 and 10.5 Hz) and **14b** (^3J=7.8 Hz), the (R_S,*R*) and (R_S,*S*) absolute configurations can be assigned to isomers **14a** and **14b**, respectively, in accordance with the results of the chemical correlation.

On the other hand, the observed differences for chemical shifts of hydrogens H_3 and $H_{3'}$ ($\Delta\delta$) can be justified taking into account the relative arrangement of the cyano group and the referred hydrogens because the magnetic anisotropy of the nitrile group can be the origin of those differences. In accordance with the field magnetic anisotropy of the cyano group,[34] the hydrogens H_3 and $H_{3'}$ must be deshielded in the major conformations **18** and **20** whereas in the clustered conformations **19** and **21** one of these hydrogens is shielded because there is an antiperiplanar arrangement between H_3 or $H_{3'}$ and the cyano group. Then, the highest difference will be observed for the epimer which displays the major relative weight of the clustered conformations, that is the (R_S,*S*) isomer. In accordance with the observed chemical shifts for hydrogens H_3 and $H_{3'}$ in the epimers **14a** (δ_{H3}= 2.856 ppm, $\delta_{H3'}$=2.932 ppm, $\Delta\delta$=0.076 ppm) and **14b** (δ_{H3}=3.073 ppm, $\delta_{H3'}$=3.288 ppm, $\Delta\delta$=0.215 ppm), the (R_S,*R*) and (R_S,*S*) absolute configurations can be assigned to the isomers **14a** and **14b**, respectively. These relationships are in accordance with the configurational assignment established by chemical correlation (vide supra).

By extension, this configurational assignment established from observed chemical shifts for hydrogens H_3 and $H_{3'}$ can be applied to the α-amino nitriles **9**, **11**–**13**. The results of this approach have been collected in Table 4.

In accordance with the absolute configurational assignment established for the α-amino nitriles **14a** and **14b**, an inverse diastereoselectivity is observed for the cyanosilylation of the β-sulfinylenamine (−)-**3** with regard to that expected from the α-sulfinylimine **4** (Chart 1) if the same stereochemical model proposed to explain the cyanosilylation reaction of α-sulfinylketimines is assumed (vide supra). It has a practical consequence since derivatizating the ketimines to their covalently stabilized enamines, the

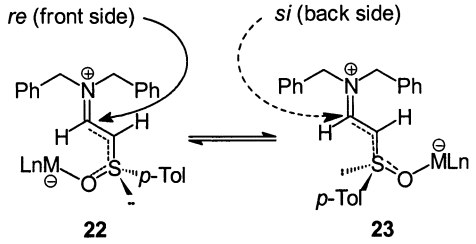


Figure 4. Competitive transition states for the cyanosilylation reaction of (−)-**3** in the presence of ZnX_2 or $Yb(TfO)_3$.

minor epimer which is obtained by cyanosilylation of the former could be achieved in good yield.

In order to explain these results, a different stereochemical model to that outlined in Fig. 1 must be proposed. Thus, the actual kinetic substrate could be an iminium derivative formed by coordination of sulfinyl group with the metal of catalyst.[35] Then, if a fast equilibrium conformational is assumed (Fig. 4; **22→23**) to describe the nature of this substrate in solution, the application of the Curtin–Hammett principle[36] to the two reaction pathways printed out in Fig. 4 (**22**: *re* attack versus **23**: *si* attack) affords a light stereoselectivity in accordance with the observed results ($k_{re} \geq k_{si}$).

3. Conclusions

Diastereoselective synthesis of α-*p*-tolylsulfinylamino nitriles bearing a quaternary chiral carbon have been accomplished by cyanosilylation reactions from enantiomerically pure α-*p*-tolylsulfinylketimines. The $TMSCN/ZnCl_2$ system, in *i*-PrOH as solvent, seems to be the best one since provides fairly yields compatibles with a high stereoselectivity, although the structural nature of the substrate could become critical. In order to achieve the two diastereomeric amino nitriles, $Yb(TfO)_3$ gives the highest yields. Alternatively, β-sulfinylenamines can also be transformed in the synthetical goals with delivery CN silyl reagents such as TMSCN and $ZnCl_2$ as mediator. Mechanistic pathways of these reactions have been proposed to explain both the nature of the products as well as the diastereoselectivity.

4. Experimental

4.1. Methods and materials

Melting points were determined in a Gallemkamp apparatus in open capillary tubes and are uncorrected. Optical rotations were measured at room temperature (20–23°C) using a Perkin–Elmer 241 MC polarimeter (concentration in g/100 mL). Infrared spectra were recorded on a Perkin–Elmer 781 IR Spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, in a Bruker AC-200 spectrometer using $CDCl_3$ and the chemical shifts (δ) refer to TMS (^1H) or deuterated chloroform (^{13}C) signals. Coupling constants (J) are reported in hertz. Multiplicities in proton spectra are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and bs (broad singlet). Elemental analyses were performed with a Perkin–Elmer 2400 C, H, N analyzer.

All reactions in non-aqueous media were carried out in flame-dried glassware under argon atmosphere. Reagents and solvents were handled by using standard syringe techniques. Tetrahydrofuran (THF) was distilled from sodium and benzophenone, dimethylformamide (DMF) from calcium hydride and dichloromethane (DCM) from P_2O_5. In all other cases commercially available reagent-grade solvents were employed without purification. Analytical TLC was routinely used to monitor reactions. Plates precoated with Merck silica gel 60 F_{254} of 0.25 mm thickness were used, with UV light, either anisaldehyde: sulfuric acid: ethanol (2:1:100) or 7% ethanolic phosphomolibdic acid-heat as developing agents. Merck silica gel 60 (230–400 ASTM mesh) was employed for column chromatography. Deactivated silica gel was performed by eluting with 2% aqueous solution of $NaHCO_3$/MeOH (5:95, v/v) until the pH of eluents was basic, and then passing through it dry acetone. Chemicals for reactions were used as purchased from Aldrich Chemical Co. (4-Methoxyphenyl) 1-phenylethyliden azane,[37] 4-methyl-2,2-pentamethylene-2,5-dihydrooxazol **6**[17] and (*R*)-(*E*)-2-(*p*-tolylsulfinyl)vinyl methanesulfonate **8**[19] were accomplished following the reported procedures, their spectroscopic and analytical data being in accordance with those described in the literature. (−)-Menthyl *p*-toluenesulfinate **5** was prepared using Posner's organic synthesis procedure.[38]

4.2. Synthesis of α-sulfinyl ketimines 1 and 2. Typical procedure

n-Butyl lithium (6 mmol) in hexane was added dropwised at −40°C to a stirred solution of diisopropylamine (6 mmol) in THF (20 mL). The mixture was kept at −10°C for 30 min, cooled to −40°C, and the imine (3 mmol) in THF (10 mL) was added dropwise during ca. 45 min. The mixture was kept at −10°C for 45–60 min, cooled to −78°C, and (−)-(*S*)-menthyl *p*-toluenesulfinate **5** (3 mmol) in THF (10 mL) was added dropwise. After being stirred for 2 h at −78°C, the reaction mixture was quenched with a few drops of methanol; the mixture was brought to rt and the solvents evaporated off under reduced pressure at rt. The residue was dissolved in DCM, the organic phase was washed with brine, separated off, and dried on $MgSO_4$. The solvent was removed under reduced pressure at rt and the residue was purified by flash chromatography.

4.2.1. (*R*)-[1-Phenyl-2-(*p*-tolylsulfinyl)] (4-methoxyphenyl)-ethyliden azane 1. (Detectable small amounts of other tautomeric forms (<13%) were observed). From (4-methoxyphenyl) 1-phenylethyliden azane: R_f 0.6 (Hex/EtOAc 3:1). 87% yield. Yellow solid: mp 77°C (hexane). $[\alpha]_D$= −161.8 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 1630, 1090 cm^{-1}. ^1H NMR δ 2.39 (s, 3H, CH_3), 3.81 (s, 3H, CH_3O), 4.40, 4.10 (AB, 2H, J=12.6 Hz, CH_2S^*), 6.55 (dd, 2H, J=8.8, 1.5 Hz, H–PMP), 6.84 (dd, 2H, J=7.2, 1.5 Hz, H–PMP), 7.23 (m, 4H, H–Tol), 7.48 (m, 3H, Ph), 7.95 (dd, 2H, J=7.9, 1.7 Hz, Ph). Calculated Analysis for $C_{22}H_{21}NO_2S$ % C 72.69, H 5.83, N 3.85. Found: C 72.61, H 5.72, N 3.85.

4.2.2. (*R*)-2,2-Pentamethylene-4-(*p*-tolylsulfinyl)methyl-2,5-dihydrooxazol 2. From **6**: R_f 0.2 (Hex/EtOAc 2:1). 86% yield. Yellow oil. $[\alpha]_D$=+170 (*c* 0.34, EtOH). IR ($CHCl_3$) 1720, 1090 cm^{-1}. ^1H NMR δ 1.30–1.70 (m,

10H), 2.417 (s, 3H, CH_3), 3.837 (s, 2H, CH_2–S^*), 4.456, 4.521 (AB, 2H, ^2J=14.9 Hz, CH_2O), 7.343 (d, 2H, J=8.1 Hz, H_{ortho}), 7.523 (d, 2H, J=8.1 Hz, H_{ortho}). ^{13}C NMR δ 21.41, 23.21, 25.03, 36.35, 36.43, 57.02, 75.38, 97.40, 110.75, 124.24, 130.01, 139.05, 142.14, 161.62. Calculated Analysis for $C_{16}H_{21}NO_2S$ %: C 65.93, H 7.28, N 4.81. Found: C 65.68, H 7.12, N 4.75.

4.3. Synthesis of (*R*)-(*E*)-*N*,*N*-dibenzyl-[2-(*p*-tolylsulfinyl)-vinyl]amine 3

To 600 mg (2.3 mmol) of **8** in anhydrous DMF (10 mL) were added 2.2 mL (11.5 mmol) of dibenzylamine and the mixture was stirred at rt for 12 h. Next, water (5 mL) was added and the aqueous phase was extracted with EtOAc (4×5 mL). The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then purified by flash chromatography on deactivated silica gel EtOAc/hexane: 3:1). Obtained 770 mg of **3** (92%) as white solid. Mp: 77°C. $[\alpha]_D$=−168.8 (*c* 1, $CHCl_3$). ^1H NMR δ 2.38 (s, 3H, Me–Ar), 4.29, 4.28 (AB system, 4H, ^2J=15.0 Hz, 2× CH_2Ph), 5.30 (d, 1H, ^3J=13.2 Hz, =CHS(O)), 7.51–7.17 (m, 15H, Ar, =CHS(O)). ^{13}C NMR δ 21.29, 55.8, 101.70, 124.66, 127.63, 127.95, 128.91, 129.46, 135.77, 139.78, 143.79, 150.13. Calculated Analysis for $C_{23}H_{23}NOS$ %: C 76.41, H 6.42, N 3.87. Found: C 76.45, H 6.34, N 3.90.

4.4. General procedure for cyanosilylation reactions

To a solution of the imine (0.5 mmol) in 6 mL of solvent at 0°C, either $ZnCl_2$ (1 M in Et_2O; 1–2 mmol) or $Yb(TfO)_3$ (10 mol%) was added dropwise, and the solution was stirred for 15 min at this temperature. Next, TMSCN or TBDMSCN in the stoichiometric excess pointed out in each case (see Tables 1–3) was added in drops at 0°C and the reaction mixture was stirred for 30 min at this temperature, and further for 12 h at rt. Two different works up were carried out:

The reaction mixtures arising from $R_3SiCN/ZnCl_2$ were quenched with saturated aqueous solution of NH_4Cl (5 mL), while those ones from $R_3SiCN/Yb(TfO)_3$ were treated with saturated aqueous solution of Na_2CO_3, after the solvent (DCM) being evaporated in vacuum at rt. In all the cases the aqueous phase was extracted with Et_2O (3×5 mL) and the combined organic extracts were washed with brine, separated off, and dried over Na_2SO_4. The solvent was removed under reduced pressure at rt and the reaction mixture was purified by flash chromatography

4.4.1. Compound 9a. (Hex/EtOAc: 4:1). Colorless oil. $[\alpha]_D$=+252.6 (*c* 0.66, $CHCl_3$). IR ($CHCl_3$): 3290, 2940, 2253 cm^{-1}. ^1H NMR δ 2.407 (s, 3H, Me–Ar), 2.933, 3.290 (AB, 2H, ^2J=13.6 Hz, CH_2–S^*), 3.696 (s, 3H, OMe), 6.422 (bs, 1H, NH), 6.50–6.56 (m, 2H, H_{ortho} PMP), 6.66–6.77 (m, 2H, H_{ortho} PMP), 7.30–7.45 (m, 5H, Ph), 7.55–7.70 (m, 4H, H_{ortho} Tol). ^{13}C NMR δ 21.4, 55.5, 62.2, 68.2, 114.4, 117.9, 118.5, 123.9, 125.3, 129.3, 129.5, 130.4, 137.0, 138.6, 139.3, 142.8, 153.8. Calculated Analysis for $C_{23}H_{22}N_2O_2S$ %: C 70.73, H 5.69, N 7.17. Found: C 70.65, H 5.73, N 7.07.

4.4.2. Compound 9b. (Hex/EtOAc: 2:1). Colorless oil. $[\alpha]_D$=−14.5 (*c* 0.42, $CHCl_3$). IR ($CHCl_3$): 3290, 2940, 2240 cm^{-1}. ^1H NMR δ 2.416 (s, 3H, Me–Ar), 3.249, 3.599 (AB, 2H, ^2J=13.7 Hz, CH_2–S^*), 3.699 (s, 3H, OMe), 5.896 (s, 1H, NH), 6.52–6.57 (m, 2H, H_{ortho} PMP), 6.69–6.73 (m, 2H, H_{ortho} PMP), 7.35–7.48 (m, 7H, Ph), 7.69–7.70 (m, 2H, H_{ortho} Tol). ^{13}C NMR δ 21.4, 55.5, 60.5, 68.5, 114.5, 117.3, 118.5, 124.1, 126.2, 129.4, 130.3, 136.5, 138.9, 142.7, 153.5. Calculated Analysis for $C_{23}H_{22}N_2O_2S$ %: C 70.73, H 5.69, N 7.17. Found: 70.70, H 5.60, N 7.25.

4.4.3. Compound 11a/11b. (Hex/EtOAc: 1:4). Colorless oil. IR ($CHCl_3$): 3290, 2960, 2252 cm^{-1}. ^1H NMR (**11a**) δ 1.4–1.9 (m, 10H, cyclohexyl), 2.427 (s, 3H, Me–Ar), 3.026 (bs, 1H, NH), 3.228, 3.481 (AB, 2H, ^2J=14.0 Hz, CH_2–S^*), 3.993, 4.075 (AB, 2H, ^2J=11.8 Hz, CH_2O), 7.30–7.50 (m, 2H, Tol), 7.55–7.65 (m, 2H, Tol). ^1H NMR (**11b**) δ 1.4–1.9 (m, 10H, cyclohexyl), 2.389 (s, 3H, Me–Tol), 2.637 (bs, 1H, NH), 3.346, 3.490 (AB, 2H, ^2J=13.8 Hz, CH_2–S^*), 4.088, 4322 (AB, 2H, ^2J=12.1 Hz, CH_2O), 7.30–7.50 (m, 2H, Tol), 7.55–7.65 (m, 2H, Tol). Calculated Analysis for $C_{17}H_{22}N_2O_2S$ %: C 64.11, H 6.98, N 8.80. Found: C 64.17, H 6.91, N 8.88.

4.4.4. Compound 12a/12b. (Hex/EtOAc: 1:4). Colorless solid. IR ($CHCl_3$): 3292, 2864, 2245 cm^{-1}. ^1H NMR (**12a**) δ 0.178 (s, 9H, $SiMe_3$), 1.5–2.0 (m, 8H, cyclohexyl), 2.2–2.4 (m, 2H, cyclohexyl), 2.435 (s, 3H, Me–Tol), 3.110 (bs, 1H, NH), 3.295 (s, 2H, CH_2–S^*), 4.100, 4.216 (AB, 2H, ^2J=10.3 Hz, CH_2O), 7.30–7.39 (m, 2H, Tol), 7.53–7.62 (m, 2H, Tol). ^{13}C NMR (**12a**) δ −0.524, 21.41, 22.30, 22.38, 24.58, 37.16, 37.96, 54.47, 56.80, 61.13, 66.29, 118.17*, 121.68*, 123.89, 130.32, 139.92, 142.24*. ^1H NMR (**12b**) δ 0.228 (s, 9H, $SiMe_3$), 1.5–2.0 (m, 8H, cyclohexyl), 2.2–2.4 (m, 2H, cyclohexyl), 2.435 (s, 3H, Me–Ar), 2.971, 3.381 (AB, 2H, ^2J=13.9 Hz, CH_2–S^*), 3.214 (bs, 1H, NH), 3.681, 4.280 (AB, 2H, ^2J=10.3 Hz, CH_2O), 7.30–7.39 (m, 2H, Tol), 7.53–7.62 (m, 2H, Tol). ^{13}C NMR (**12b**) δ −0.574, 21.41, 22.50, 22.65, 24.58, 37.39, 38.12, 54.66, 57.67, 63.50, 66.70, 119.47*, 121.99*, 124.04, 130.24, 139.92, 142.35* (*interchangeable signals). Calculated Analysis for $C_{21}H_{31}N_3O_2SSi$ %: C 60.38, H 7.50, N 10.06. Found: C 60.45, H 7.42, N 9.82.

4.4.5. Compound 13a/13b. (Hex/EtOAc: 1:4). Colorless solid. IR ($CHCl_3$): 3292, 2858, 2250 cm^{-1}. ^1H NMR (**13a**) δ 0.186 (s, 3H, Me–Si), 0.200 (s, 3H, Me–Si), 0.950 (s, 9H, *t*-Bu), 1.4–1.9 (m, 10H, cyclohexyl), 2.434 (s, 3H, Me–Ar), 3.171 (bs, 1H, NH), 3.279, 3.340 (AB, 2H, ^2J= 13.6 Hz, CH_2–S^*), 4.149, 4.255 (AB, 2H, ^2J=10.3 Hz, CH_2O), 7.30–7.39 (m, 2H, Ar), 7.53–7.62 (m, 2H, Ar). ^{13}C NMR (**13a**) δ −5.48*, −5.39*, 18.15, 22.29, 22.54, 24.59, 37.17, 38.00, 54.43, 57.07, 61.90, 66.71, 118.77, 122.02, 123.89, 130.35, 139.86, 142.42 (*interchangeable signals). ^1H NMR (**13b**) δ 0.137 (s, 3H, Me–Si), 0.147 (s, 3H, Me–Si), 0.920 (s, 9H, *t*-Bu), 1.4–1.9 (m, 10H, cyclohexyl), 2.434 (s, 3H, Me–Ar), 3.130 (bs, 1H, NH), 2.968, 3.414 (AB, 2H, ^2J=13.9 Hz, CH_2–S^*), 3.715, 4.336 (AB, 2H, ^2J=10.3 Hz, CH_2O), 7.30–7.39 (m, 2H, Ar), 7.53–7.62 (m, 2H, Ar). ^{13}C NMR (**13b**) δ −5.47*, −5.42*, 21.42, 22.39, 22.69, 25.72, 37.57, 38.09, 54.70, 57.61, 63.50, 67.19, 119.46, 121.63, 124.00, 130.25, 139.91, 142.19 (*interchangeable signals).

Calculated Analysis for $C_{24}H_{37}N_3O_2SSi$ %: C 62.69, H 8.13, N 9.14. Found: C 62.84, H 8.21, N 9.24.

4.4.6. Compound 14a. (DCM/Et_2O: 10:1). White solid. Mp 124°C, $[\alpha]_D$=+25.0 (*c* 3.9, $CHCl_3$). IR (KBr): 3290, 2857, 2250 cm^{-1}. ^1H NMR δ 2.383 (s, 3H, Me), 2.856 (dd, 1H, ^2J=13.4 Hz, ^3J=5.2 Hz, CH_2–S*), 2.932 (dd, 1H, ^2J=13.4 Hz, ^3J=10.4 Hz, CH_2–S*), 3.623, 3.971 (AB, 2×2H, ^2J=13.7 Hz, CH_2Ph), 4.324 (dd, 1H, ^3J=5.2 Hz, 10.4, H–C*), 7.15–7.55 (m, 14H, Ar). Calculated Analysis for $C_{24}H_{24}N_2OS$ %: C 74.18, H 6.24, N 7.21. Found: C 73.86, H 5.97, N 7.09.

4.4.7. Compound 14b. (DCM/Et_2O: 10:1). Colorless oil. IR (CCl_4): 3294, 2863, 2260 cm^{-1}. ^1H NMR δ 2.394 (s, 3H, Me), 3.073 (dd, 1H, ^2J=13.2 Hz, ^3J=7.8 Hz, CH_2–S*), 3.288 (dd, 1H, ^2J=13.2 Hz, ^3J=7.8 Hz, CH_2–S*), 3.423, 3.965 (AB, 2×2H, ^2J=13.3 Hz, CH_2Ph), 3.959 (t, 1H, ^3J=7.8 Hz, H–C*), 7.15–7.55 (m, 14H, Ar). Calculated Analysis for $C_{24}H_{24}N_2OS$ %: C 74.18, H 6.24, N 7.21. Found: C 73.97, H 6.12, N 7.27.

4.5. Hydrolysis of sulfinylamino nitriles to sulfonylamino amides[38]

To a solution of sulfinylamino nitrile (0.181 mmol) in DMSO (3 mL) cooled in an ice–water bath were added K_2CO_3·1.5H_2O (4 mg) and dropwise 30% H_2O_2 (30 μL) keeping the temperature at 10°C. After stirring for 15 min, water (0.6 mL) was added. A white solid forms, which was filtered, washed with water and dried in vacuum (0.1 torr) at room temperature.

4.5.1. (*R*)-2-(*N*,*N*-Dibenzylamino)-3-(*p*-tolylsulfonyl)-propanamide 15a. Compound **15a** was obtained from **14a** in 91% yield after crystallization (ethyl acetate/hexane). MP 140°C (white solid). $[\alpha]_D$=−51.4 (*c* 0.2, $CHCl_3$). IR (KBr): 3462, 3352, 1691, 1147 cm^{-1}. ^1H NMR δ 2,331 (s, 3H, Me–Tol), 3.026 (dd, 1H, ^3J=5.6 Hz, 12.2, H–C*), 3.432 (t, 1H, ^2J=^3J=12.2 Hz, CH_2SO_2), 3.478 (dd, 1H, ^2J=12.2 Hz, ^3J=5.6 Hz, CH_2SO_2), 3.567, 3.704 (AB, 2×2H, ^2J=13.6 Hz, 2×CH_2Ph), 5.776 (bs, 1H, NH_2), 6.492 (bs, 1H, NH_2), 7.08–7.32 (m, 12H, H–Ar), 7.470 (d, 2H, *J*=8.8 Hz, H_{ortho}). Calculated Analysis for $C_{24}H_{26}N_2O_3S$ %: C 68.21, H 6.21, N 6.63. Found %: C 68.20, H 6.14, N 6.68.

4.6. Desulfuration of sulfonylamino amides

To a solution of sulfonylamino amide (0.28 mmol) in MeOH (5 mL) at −20°C were added Na_2HPO_4 (0.11 mmol) and 5% Na–Na·Hg (668 mg, 1.45 mmol) keeping the temperature at 20°C. After stirring for 12 h saturated aqueous solution of NH_4Cl (6 mL) was added and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography.

4.6.1. (*S*)-2-(*N*,*N*-Dibenzylamino)propanamide 16a. Compound **16a** was accomplished from **15a** in 91.5% yield. Flash chromatography (hexane/EtOAc: 1:2, R_f 0.42). Isolated as white solid. MP 103°C. $[\alpha]_D$=−38.3 (*c* 0.4, $CHCl_3$). ^1H NMR δ 1.296 (d, 3H, ^3J=7.1 Hz, Me), 3.407 (q, 1H, ^3J=7.1 Hz, H–C*), 3.416, 3.795 (AB, 2×2H, ^2J=13.2 Hz, 2×CH_2Ph), 5.920 (bs, 1H, NH_2), 7.135 (bs, 1H, NH_2), 7.2–7.4 (m, 10H, Ph). ^{13}C NMR δ 7.06, 54.41, 57.34, 127.36, 128.22, 128.55, 138.80, 176.82. Calculated Analysis for $C_{17}H_{20}N_2O$ %: C 76.07, H 7.53, N 10.44. Found %: C 76.10, H 7.44, N 10.32.

4.7. Chemical sequence to establish the configurational correlation of 16a[29,30]

To a stirred solution of (*R*)-(+)- or (*S*)-(−)-methyl lactate (1.040 g, 10.0 mmol) in DCM (20 mL) at 0°C, was added triflic anhydride (1.90 mL, 11.0 mmol) followed by 2,6-lutidine (1.28 mL, 11.0 mmol). After stirring for 15 min, dibenzylamine (6.00 mL, 31.0 mmol) in DCM (10 mL) was added dropwise to the solution. The resulting mixture was stirred for 2 h at rt and then concentrated by evaporation in vacuum. The residue was dissolved in hexane (150 mL), passed through a short pad of silica gel, and concentrated again to provide dibenzylamino ester **17a** or **17b** as a pale yellow oil. This material was carried out on the next step without further purification.

A 2.5 M solution of $AlMe_3$ (0.8 mL, 2.0 mmol) in hexane was slowly added at rt to a solution of 2.0 mmol of ammonia in 5 mL of DCM. The mixture was stirred at rt for 15 min and **17a** or **17b** (566 mg, 2.0 mmol) was added. The mixture was warmed up 25–40°C until TLC analysis indicated that the reaction had gone to completion. The reaction was carefully quenched with diluted HCl (2%) and extracted with DCM (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuum to afford the carboxamide.

4.7.1. Methyl (*S*)-2-(*N*,*N*-dibenzylamino)propanoate 17a. Obtained 2.80 g from (*R*)-(+)-lactate (100%). $[\alpha]_D$=−88.2 (*c* 2.2, $CHCl_3$). ^1H NMR δ 1.32 (d, 3H, ^3J=6.5 Hz Me), 3.51 (q, 1H, ^3J=6.5 Hz, H–C*), 3.59, 3.84 (AB, 2×2H, ^2J= 13.9 Hz, 2×CH_2Ph), 3.73 (s, 3H, OMe), 7.40–7.35 (m, 10H, Ph). Calculated Analysis for $C_{18}H_{21}NO_2$ %: C 76.28, H 7.48, N 4.94. Found: C 76.35, H 7.40, N 4.86.

4.7.2. Methyl (*S*)-2-(*N*,*N*-dibenzylamino)propanoate 17b. Obtained 2.80 g from methyl (*S*)-(−)-lactate (100%). $[\alpha]_D$=+88.5 (*c* 2.2, $CHCl_3$).

4.7.3. (*R*)-2-(*N*,*N*-Dibenzylamino)propanamide 16a. Obtained 439 mg. from **17a** (82%). White solid. MP 103°C. $[\alpha]_D$=−38.5 (*c* 0.4, $CHCl_3$).

4.7.4. (*S*)-2-(*N*,*N*-Dibenzylamino)propanamide 16b. Obtained 466 mg. from **17b** (87%). White solid. MP 103°C. $[\alpha]_D$=+37.8 (*c* 0.4, $CHCl_3$).

4.8. Optical yields determination

A lanthanide induced shifts (LIS) study was carried out on a sample of 12 mg of **16a** (arising from **15a**) using (+)-Eu(hfc)$_3$ (0.5 equiv.) in $CDCl_3$. In addition, samples of **16a** and **16b** prepared from methyl esters **17a** and **17b**, respectively, were also analyzed in these conditions. A racemic sample was first used to monitor the lanthanide

induced shifts, which was prepared from methyl (+/−)-lactate following the procedure above reported from the enantiomeric ones. The signals corresponding to the *ortho* hydrogens of the two benzyl groups were clearly shifted between +0.4 and +0.8 ppm. From this analysis, the optical purity of all tested samples was established as ≥97% ee.

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