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Stereoselective Quaternization of α-Amino Phenylacetonitriles Mediated by a Remote Sulfinyl Group†

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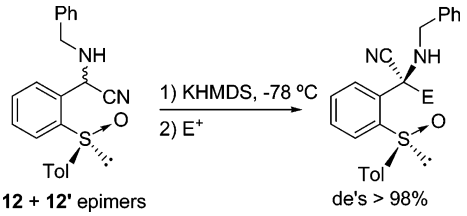
Received March 23, 2007



Enantiomerically pure α-substituted α-amino phenylacetonitriles have been readily prepared from 2-*p*-tolylsulfinylbenzaldimines following a two-step sequence: a moderately stereoselective hydrocyanation of the imines and a completely stereoselective quaternization of the resulting diastereoisomeric mixture of α-amino phenylacetonitriles with different alkylating or acylating reagents in the presence of KHMDS. Theoretical calculations support a stereoselectivity control exerted by the remote sulfinyl group, as long as it is responsible for the conformational preferences of the benzyllithium intermediates, which suffer the attack of the electrophiles to the less hindered diastereotopic face.

Introduction

Hydrocyanation of imines has been extensively studied due to the large interest in the resulting α-amino nitriles not only because of their versatility as building blocks in the preparation of countless organic compounds but also due to their inherent reactivity.[1] Consequently, there have been reported many hydrocyanating systems for the preparation of aldimine-derived amino nitriles.[2] Moreover, several general methods for the synthesis of α-amino nitriles making use of a one-pot, three-component condensation of aldehydes, amines, and cyanide in the presence of different catalytic systems have also been described.[3] By contrast, the number of reports concerning hydrocyanation of ketimines is considerably smaller,[2h] probably due to the easy reversibility of the hydrocyanation process (most of the reported diastereoselective[4] and enantioselective[5] hydrocyanations having been restricted to cyclic or methyl ketimines).

† This article is dedicated to Professor Dr. Vicente Gotor on the occasion of his 60th birthday.

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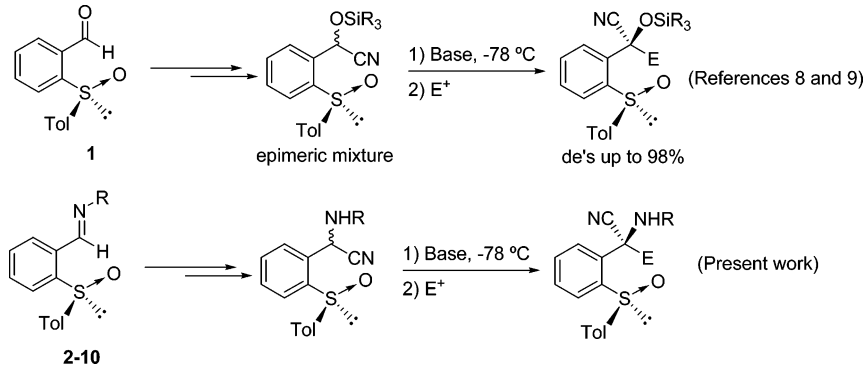
10.1021/jo0705519 CCC: $37.00
Published on Web 07/13/2007

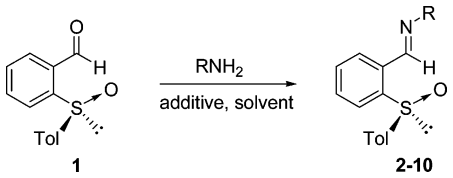
SCHEME 1



Additionally, it is well-known that reactions of metalated α-amino nitriles with the appropriate electrophiles (alkyl or acyl halides, epoxides, aldehydes, and Michael acceptors) afford ketimine-derived amino nitriles.[6] The racemic version of this methodology has been applied as an intermediate step in the synthesis of a number of naturally occurring or pharmacologically active compounds.[7] Nevertheless, a low and not easily predictable stereocontrol has been found in the few asymmetric reactions of lithiated α-amino nitriles, containing enantiopure amine auxiliaries, with Michael acceptors[6b−d] and aldehydes.[6e] Therefore, the search for efficient general methods for synthesizing optically pure α,α-disubstituted α-amino nitriles is currently an important challenge in asymmetric synthesis.

Recently we have reported a highly stereoselective method for the hydrocyanation of 2-*p*-tolylsulfinyl benzaldehyde (**1**).[8] The hydrocyanation of the corresponding ketones was not so successful, and their optically pure cyanohydrins were prepared by a highly diastereoconvergent quaternization of the anions resulting from *O*-protected cyanohydrins derived from aldehyde **1**, with a series of electrophiles (Scheme 1).[9] Significant differences in the stereochemical evolution of C═O and C═N bonds under hydrocyanation conditions had been previously evidenced for *β*-keto-[10] and *β*-iminosulfoxides[4b] (only the first ones could be hydrocyanated in a completely stereoselective way), but there were no precedents describing differences of behavior between oxygenated and nitrogenated carbanions under quaternization conditions. Therefore, the results reported in refs 8 and 9 prompted us to investigate the behavior of imines **2** derived from **1** under different hydrocyanating conditions, as well as the reaction of the resulting mixtures of α-amino-(2-*p*-tolylsulfinyl)phenyl acetonitriles under quaternization conditions, with the aim of developing a ready access to hydrocyanated phenyl ketimine derivatives. These results are reported in this paper.

TABLE 1. Synthesis of (*S*)-2-*p*-Tolylsulfinyl Benzaldimines 2−10



entry	R	additive	solvent	*T* (°C)	*t* (h)	imine	yield (%)
1	C_6H_5	Na_2SO_4	CH_2Cl_2	rt	16	**2**	91
2	4-MeO-C_6H_4	Na_2SO_4	CH_2Cl_2	rt	16	**3**	86
3	4-NO_2-C_6H_4	Na_2SO_4	toluene	108	96	**4**	75
4	$C_6H_5CH_2$	Na_2SO_4	CH_2Cl_2	rt	16	**5**	87
5	4-CF_3-$C_6H_4CH_2$	Na_2SO_4	CH_2Cl_2	rt	16	**6**	87
6	4-MeO-$C_6H_4CH_2$	Na_2SO_4	CH_2Cl_2	rt	16	**7**	93
7	*i*-Bu	Na_2SO_4	CH_2Cl_2	rt	16	**8**	90
8	$MeSO_2$	Et_3N, $TiCl_4$	CH_2Cl_2	40	5	**9**	65
9	*p*-$TolSO_2$	Et_3N, $TiCl_4$	DCE	83	4	**10**	82

Results

The syntheses of the optically pure sulfinyl imines used as the starting materials for hydrocyanation reactions were performed following conventional procedures from (*S*)-2-*p*-tolylsulfinyl benzaldehyde (**1**)[8] (Table 1). Reactions of **1** with arylamines (entries 1−3), benzylamines (entries 4−6), and isobutylamine (entry 7), were accomplished in high yields in the presence of an excess of Na_2SO_4. Treatment of **1** with methyl and *p*-tolyl sulfonamides (R = $MeSO_2$, *p*-$TolSO_2$ in Table 1) in the presence of Et_3N and $TiCl_4$ also afforded the corresponding *N*-*p*-tolylsulfinylbenzylidene sulfonamides[11] (entries 8 and 9) in good yields.

Hydrocyanation of freshly prepared sulfinylbenzaldimines **2**−**10** was assayed with Et_2AlCN under different experimental conditions (solvent, temperature, reaction time, amount of reagent, and addition mode). Diastereoselectivities were lower at temperatures below 0 °C. Similarly, less polar solvents (CH_2Cl_2, toluene) decreased the reactivity (longer reaction times

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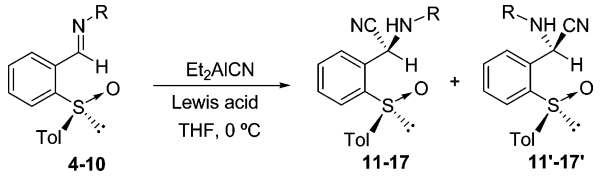
TABLE 2. Hydrocyanation of Sulfinylimines 4−10



entry	imine	R	*t* (h)	Lewis acid	amino nitriles	**11−17:11′−17′** ratio (yield [%])[b]
1	**4**	4-NO_2-C_6H_4	2	−	**11** + **11′**	39:61 (75)
2	**4**	4-NO_2-C_6H_4	2	$Yb(OTf)_3$	**11** + **11′**	28:72
3	**5**	$C_6H_5CH_2$	2	−	**12** + **12′**	48:52 (90)
4	**5**	$C_6H_5CH_2$	2	$Yb(OTf)_3$	**12** + **12′**	29:71
5	**6**	4-CF_3-$C_6H_4CH_2$	16	−	**13** + **13′**	41:59 (86)
6	**6**[a]	4-CF_3-$C_6H_4CH_2$	16	−	**13** + **13′**	36:64
7	**7**	4-MeO-$C_6H_4CH_2$	16	−	**14** + **14′**	40:60 (88)
8	**8**	*i*-Bu	16	−	**15** + **15′**	49:51 (74)
9	**9**	$MeSO_2$	2	−	**16** + **16′**	58:42 (86)
10	**9**	$MeSO_2$	2	$Yb(OTf)_3$	**16** + **16′**	61:39
11	**10**	*p*-$TolSO_2$	2	−	**17** + **17′**	90:10 (90)
12	**10**	*p*-$TolSO_2$	2	$Yb(OTf)_3$	**17** + **17′**	89:11
13	**10**[a]	*p*-$TolSO_2$	2	$Yb(OTf)_3$	**17** + **17′**	85:15
14	**10**[a]	*p*-$TolSO_2$	1	−	**17** + **17′**	91:9

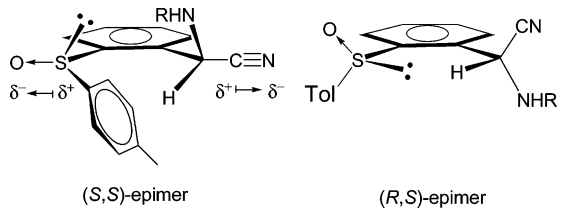
[a] Inverse addition. [b] Combined yield of both diastereoisomers

being needed) and did not improve the diastereoselectivity. In some cases, TMSCN was also used as the cyanide source. The best results were obtained in THF using an excess (4 equiv) of Et_2AlCN (TMSCN gave poorer results). Under these optimized conditions the reactions with different imines are summarized in Table 2.

N-Phenylimine **1** and *N*-*p*-methoxyphenylimine **2** did not react with an excess of Et_2AlCN under any of the studied conditions. Imines **4**−**9** provided diastereoisomeric mixtures with low stereoselectivities (Table 2). When the reactions evolved under $Yb(OTf)_3$ catalysis, slight changes in the epimeric ratio were observed in some cases, but they were not so large as to provide highly stereoselective transformations. We have also investigated the role of the temperature in the reactions catalyzed by $Yb(OTf)_3$. The best results were detected at 0 °C, which suggests that lower temperatures must hinder the association of the catalyst to the basic centers of the substrates. Finally, in some cases, the addition mode of the reagent also had a small influence on the stereoselectivity. Only imine **10** evolved with high levels of stereoselectivity (de's ranged between 70 and 80%), which were scarcely modified by the above-mentioned factors (entries 11−14).

The combined yields obtained in these reactions are usually higher than 74%, but the isolation of each diastereoisomer was rather difficult due to the easy retrohydrocyanation observed during chromatographic purifications. From the stereochemical point of view, the main conclusion deduced from the results collected at Table 2 is that the control exerted by the sulfinyl group on the stereoselectivity of the hydrocyanation reactions of imines **4**−**9** was only moderate, much lower than that observed in similar processes catalyzed by $Yb(OTf)_3$ from the corresponding aldehyde.[8] By contrast, **10** reacted with high stereoselectivity (70−80% de) regardless the experimental conditions. These results suggest that the composition of the mixtures obtained from reactions of **4**−**9** is the consequence of a thermodynamic equilibration of the resulting amino nitriles with the starting imines. Only those mixtures obtained from **10** correspond to kinetic control processes, probably due to the higher stability of the amide anion derived from **17** and **17′**, which makes difficult the retrohydrocyanation.

TABLE 3. δ Values for the Benzylic Protons of Amino Nitriles 11−17 and 11′−17′



R	amino nitrile	^1H δ (CH−CN)	amino nitrile	^1H δ (CH−CN)	$\Delta\delta$
4-NO_2-C_6H_4	**11**	6.56	**11′**	6.80	0.34
$C_6H_5CH_2$	**12**	4.85	**12′**	5.45	0.60
4-CF_3-$C_6H_4CH_2$	**13**	4.95	**13′**	5.46	0.51
4-MeO-$C_6H_4CH_2$	**14**	4.81	**14′**	5.41	0.60
i-Bu	**15**	4.84	**15′**	5.42	0.58
$MeSO_2$	**16**	5.89	**16′**	6.07	0.18
p-$TolSO_2$	**17**	5.72	**17′**	6.07	0.35

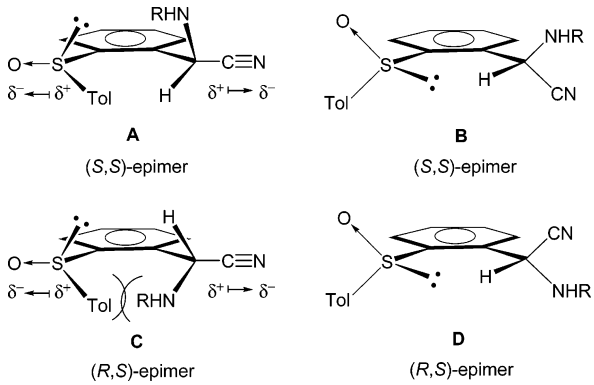
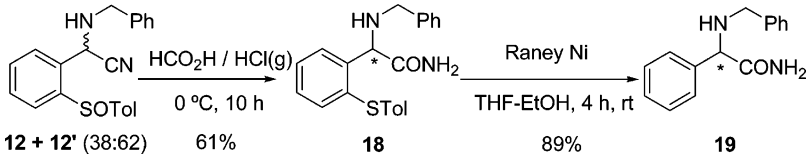


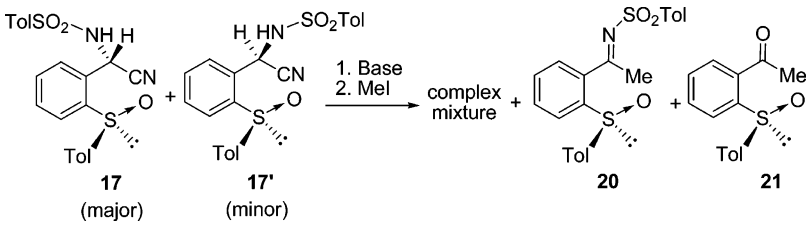
FIGURE 1. Presumably most stable conformations for [2*S*,(S)*S*] and [2*R*,(S)*S*] epimers (**11**−**17** and **11′**−**17′**).

Configurational assignment of epimers **11**−**17** and **11′**−**17′** was initially based on their ^1H NMR spectra. The main difference between both epimers is the chemical shift of their benzylic protons, which is clearly lower for isomers **11**−**17** ($\Delta\delta \approx 0.5-0.6$ ppm for *N*-alkylderivatives and ~0.18−0.35 ppm for *N*-aryl and *N*-sulfonylderivatives, Table 3). In Figure 1 are depicted presumably the most stable conformations for both epimers, taking into account the fact that the strong dipolar repulsion between the C≡N and S→O bonds will arrange them as far as possible unless it involves strong steric interactions. Thus, a significant population can be expected for rotamers **A** and **B**, respectively stabilized by dipolar and steric factors, at the (*S*,*S*)-epimers (Figure 1), the first one presumably being favored. By contrast, the sterically favored **D** rotamers must be clearly predominant for the (*R*,*S*)-epimers as a result of the strong steric restrictions of the electrostatically stabilized **C** conformations. The spatial arrangement of the benzylic proton at **A** rotamers suggests that it will be shielded by the aromatic ring at the (*S*,*S*) epimers (see Table 3 graphic), whereas it is not the case for such a proton in the most populated **D** conformation for the (*R*,*S*) isomers. Therefore, the chemical shifts of the benzylic protons at (*S*,*S*) epimers should be lower than those of the (*R*,*S*) isomers. This criteria allowed us to assign the (*S*,*S*) configuration to epimers **11**−**17**. This assignment was unequivocally confirmed by X-ray diffraction analysis of

SCHEME 2



SCHEME 3



compounds **13′** and **17**, which exhibit the absolute configurations [2*R*,(S)*S*] and [2*S*,(S)*S*],[12] respectively.

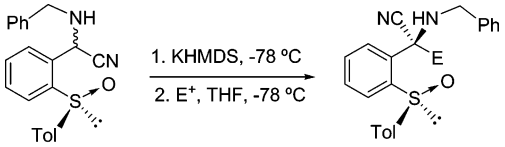
In order to corroborate this configurational assignment, a **12** + **12′** mixture (38:62) was hydrolyzed (HCl(g)/HCO_2H, 0 °C, 10 h) into the corresponding sulfenyl α-amino amide (**18**),[13] which was subsequently desulfenylated (Raney Ni, THF/EtOH). The resulting α-amino amide **19** exhibits an $[\alpha]^{20}_D$ value of −16.6 (*c* 0.5, $CHCl_3$), of the sign opposite to that reported for enantiomerically pure (*S*)-(2-benzylamino)-2-phenylacetamide (**19**) {$[\alpha]^{20}_D$ +71 (*c* 1.0, $CHCl_3$)}.[14] This result confirms that the starting **12** + **12′** mixture was enriched in the epimer with *R* configuration at carbon, which means that the major epimer **12′** has [2*R*,(S)*S*] configuration (Scheme 2).

All attempts to achieve the hydrocyanation of ketimines were unsuccessful, since they were recovered unaltered after several hours under hydrocyanating conditions. This prompted us to explore the use of the mixtures of amino nitriles obtained from *o*-sulfinylbenzaldimines as starting materials for quaternization processes. Initially, we used mixtures **17** + **17′** as the starting material. Treatment of these mixtures with 1−4 equiv of base (LHMDS, KHMDS, LDA, *n*-BuLi) followed by addition of 1−8 equiv of MeI, allowing the reaction to evolve at different temperatures (from −78 °C up to rt), invariably led to complex mixtures where only *N*-[2-(*p*-tolylsulfinyl)phenylethylidene]-*p*-toluenesulfonamide (**20**) and methyl 2-[*p*-(tolylsulfinyl)phenyl]-ketone (**21**) could be detected in ∼10% yield determined by ^{1}H NMR (Scheme 3). The low proportion of these compounds, which would result from quaternization of **17** + **17′** followed by elimination of HCN and hydrolysis of the resulting ketimine, suggests that they must be formed in secondary processes.

Next we explored the behavior of *N*-benzylamino nitriles **12** + **12′** as the starting materials for quaternization processes, because the CH acidity of α-amino nitriles derived from aromatic aldehydes is known to be larger than their NH acidity,[15] and therefore, it should be expected that benzylic carbanion would be exclusively formed by using 1 equiv of base, thus precluding the undesired base-induced elimination of HCN (retro-Strecker reaction) from the substrate and/or from the quaternization product. Thus, when diastereomeric **12** + **12′** mixtures were treated with KHMDS (Table 4) and the resulting anion reacted with MeI, compound **22** was obtained as a single diastereoisomer in an 81% isolated yield (entry 1, Table 4). Similar results were obtained in the presence of 18-crown-6 ether (entry 2, Table 4), which suggests that the role of the cation is not crucial for the stereochemical course of the reaction. We also studied the reactions of mixtures **12** + **12′** with other alkylating reagents such as ethyl triflate, benzyl bromide, and allyl bromide, which yielded compounds **23**, **24**, and **25**, respectively, as single diastereoisomers (entries 6−8). Analogously, reaction of **12** + **12′** with $ClCO_2Me$ afforded **26** as the exclusive acylation product (entry 9). All these reactions are extraordinarily clean and proceed in high yields with a complete control of the stereoselectivity, giving compounds **23** (R = Et, entry 6), **24** (R = Bn, entry 7), **25** (R = allyl, entry 8), and **26** (R = CO_2Me, entry 9) respectively, as single diastereoisomers (determined by NMR analysis of the crude reactions). The use of other bases such as LHMDS and NHMDS did not produce any change in the yields or stereoselectivities of these reactions.

The results indicated in Table 4 suggested a scarce influence of the nature of the electrophile on the stereoselectivity control, which therefore seems to be exclusively related to the structure

TABLE 4. Reactions of Amino Nitriles 12 + 12′ with Different Electrophiles



entry	electrophile	*t* (h)	product	dr[a] (yield,[b] %)
1	MeI	1	**22**	>98:<2 (81)
2	MeI (18-crown-6)	2	**22**	>98:<2
3	EtOTf	2	**23**	>98:<2 (79)
4	$PhCH_2Br$	2	**24**	>98:<2 (77)
5	$CH_2{=}CH{-}CH_2Br$	2	**25**	>98:<2 (82)
6	$ClCO_2Me$	0.5	**26**	>98:<2 (84)
7	MeOH	0.5	**12** + **12′**	3:97 (78)
8	HCl(g)	0.5	**12** + **12′**	20:80
9	HBF_4	0.5	**12** + **12′**	20:80

[a] Determined by ^{1}H NMR from the crude reaction. [b] Isolated yields.

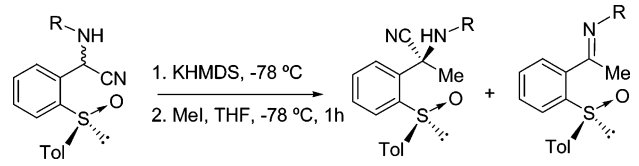
(12) Crystallographic data (excluding structure factors) for **13′**, **17**, and **23** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers 638581, 638582, and 638583, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: +44(0)-1223-366033 or e-mail: deposit@ccdc.cam.uk].

(13) The reduction of the sulfinyl into the sulfenyl group takes place under conditions used for the hydrolysis of the CN group.

(14) Hassan, N. A.; Bayer, E.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, *22*, 3747.

(15) Kison, C.; Meyer, N.; Opatz, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5662.

SCHEME 4



R = $C_6H_5CH_2$ (**12** + **12'**)	81% (**22**)	15% (**27**)
R = 4-CF_3-$C_6H_4CH_2$ (**13** + **13'**)	57% (**28**)	10% (**29**)
R = 4-MeO-$C_6H_4CH_2$ (**14** + **14'**)	56% (**30**)	27% (**31**)
R = *i*-Bu (**15** + **15'**)	- (**32**)	56% (**33**)

of the metalated carbanion. It prompted us to investigate whether protonation of the carbanion derived from the mixture **12** + **12′** would be able to provide one diastereoisomer with high de, which had not been achieved by direct hydrocyanation from **5**. The reaction of a diastereoisomeric 60:40 mixture of **12** and **12′** with KHMDS and further quenching with MeOH provided a 3:97 mixture of **12** + **12′** epimers (entry 7, Table 4), which indicated that protonation also was highly stereoselective. The epimer obtained as predominant is [2*R*,(S)*S*]-**12′**, as it could be unequivocally determined by X-ray analysis (vide infra). Surprisingly, it exhibits the configuration (*R*) at α-carbon, which is the opposite one to that observed for the quaternization products **22**−**26**. These results indicate different stereochemical pathways for protonation and quaternization reactions that are not easy to explain. The use of other sources of protonation, such as HCl(g) and HBF_4 (entries 8−9, Table 3) provided 20:80 mixtures of **12** + **12′**, indicating a lower stereoselectivity but maintaining the preference for the epimer **12′**.

The absolute configuration of the only diastereoisomer, **23**, obtained from the reaction of **12** + **12′** with EtOTf, was unequivocally determined as [2*S*,(S)*S*] by X-ray diffraction studies.[12] We have assigned the same stereochemistry to isomers **22** and **24**−**26**, **28**, and **30**, obtained as the exclusive products from reactions of (*S*)-sulfoxides (Table 4 and Scheme 3).

In order to check the possible influence of intramolecular π-stacking interactions between the aryl rings at the *N*-benzyl moiety and the benzylic carbanion on the observed diastereoselectivity, we studied the behavior of other amino nitriles (**13**−**14**) bearing substituents of different electronic character at the benzyl ring. We also studied the *N*-isobutyl derivative **15**, with no benzyl group at the structure. The results are indicated in Scheme 4. Amino nitriles **13** and **14** evolved with complete stereoselectivity into **28** and **30**, respectively, under the same methylation conditions optimized for **12**. Only one quaternization product (**32**) was also detected by ^{1}H NMR and MS starting from amino nitrile **15**, but it could not be isolated because its chromatographic purification only afforded imine **33**, resulting from the retrohydrocyanation process from **32**. As we can see from Scheme 4, imines **27**, **29**, and **31** were also obtained in all these reactions as a consequence of the instability of the quaternary amino nitriles under the conditions used for their chromatographic purification, which decreased the isolated yields of the amino nitriles. These results suggest that the influence of the substituent at the benzylic position is not relevant in the stereoselectivity control, which must be exclusively dependent on the sulfinyl configuration.

The high levels of diastereoselectivity observed in these reactions can be explained by assuming a stereoconvergent course involving the formation of a common intermediate for both epimeric starting nitriles **12** and **12′**. These intermediates must be benzylic carbanions with the negative charge delocalized at both the ring and the nitrogen of the CN group. Conformational preferences of the anion can be governed by electrostatic and/or steric grounds. The strong dipolar repulsion between the S−O and CN bonds should favor conformations **A** (Figure 2), exhibiting both dipoles arranged in the opposite direction. By contrast, steric effects would determine the predominance of **B** rotamers, due to the larger size of the NHBn group with respect to the CN one. In turn, the formation of a hydrogen bond between the NH and the sulfinyl oxygen would explain a significant population of **C** rotamer (Figure 2).

In order to clarify this point we have performed some theoretical calculations. The structures of possible conformations (Figures 3, 4 and 5) have been studied at DFT (B3LYP)[16] level by using the Gaussian03 program.[17] The standard 6-31G(d) basis set was used for all the atoms except iodine, for which the LANL2DZ basis set supplemented with a d function of exponent 0.289 was used.[18] Harmonic frequencies were calculated at the same level of theory to characterize the stationary points and to determine the zero-point energies (ZPE). In the model structures **I**, **II**, and **III**[19] (analogous to **A**, **B**, and **C**) the methyl group in the *p*-tolyl ring has been eliminated, and the benzyl group at nitrogen has been changed by a methyl one (Figure 3). For **I** and **II** we have also calculated the influence of the orientation of the substituents at nitrogen on the energy, maintaining the lone electron pair oriented toward the sulfur. Other structures with the N−H bond directed toward the sulfur atom (**I″**) or to the oxygen atom (**III**) were also studied.

According to these calculations, rotamers **I** and **I′** are the most stable ones, which allow us to conclude that dipolar repulsion is the main factor controlling the conformational preferences of the carbanion. On the other hand, according to the distances between N1 and S[20] and based on the NBO[21] analysis, there is a stabilizing interaction between N1 and the sulfinyl group ($n^2 \rightarrow \pi^{*0}$) which also contributes to stabilize these conformations. It is in agreement with the higher stability of **I** with respect to that of **I″** where such an interaction is much smaller. Thus, intermediate **I″** is quite less stable despite the presence of a small hydrogen bond, S···H−N. In the case of intermediate **III,**

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(17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision B.03; Gaussian, Inc.: Wallingford, CT, 2004.

(18) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213. (d) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

(19) Other structures varying the conformation around S−Ph or C−NHMe bonds turned out to be less stable.

(20) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441 (van der Waals radii values in Å: H = 1.20; N = 1.55; S = 1.80; O = 1.52).

(21) Natural bond orbital method of Weinhold: Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

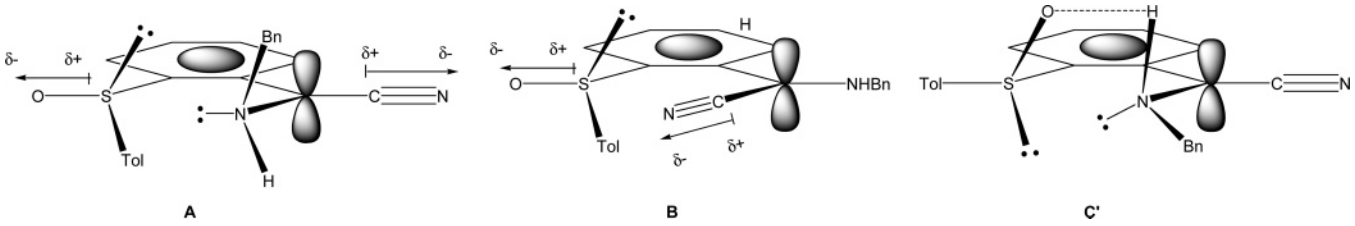

FIGURE 2. Plausible conformations for benzylic carbanion.

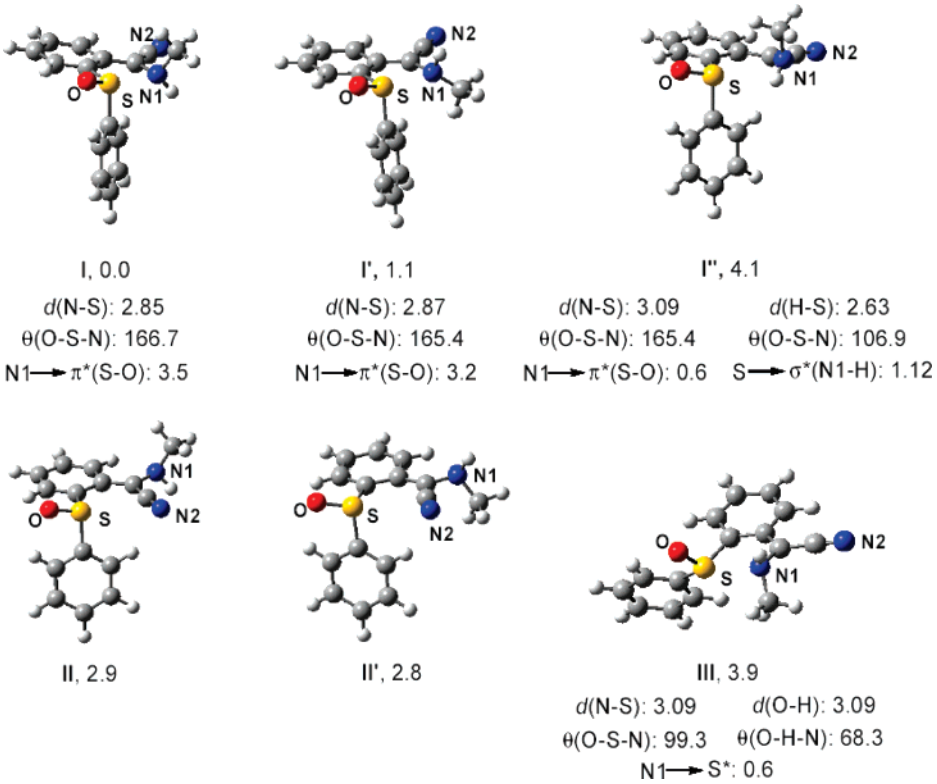

FIGURE 3. Structures and relative energies (kcal·mol^{-1}) of the presumably most stable conformations of benzylic carbanion. ZPE correction included. Selected bond distances (Å) and orbital interactions (kcal·mol^{-1}) evaluated by means of a second-order perturbational analysis of the Fock matrix on the NBO basis are also indicated.

due to the orientation of the groups, an effective hydrogen bond SO···H−N cannot be formed to compensate dipolar repulsion, and only a small interaction N−S ($n^2 \rightarrow d^0$) is possible. As a result, **III** is quite less stable than **I**. Finally, the orientation of the substituents at nitrogen are not significant for **B** conformations (**II** and **II′** have a similar energy content), but it is significant for the **A** ones (**I** is 1.1 kcal·mol^{-1} more stable than **I′**) as a consequence of the steric repulsions between Ph and Me groups.

Another interesting point concerns the distribution of the negative charge on the different atoms at the anion, because it must be related to the preferred places for the association of the metal. For species **I** and **I′**, the negative charge of the carbanion is delocalized, and the nitrogen supports a larger negative charge (−0.48 au) than the benzylic carbon (−0.17 to −0.18 au). It suggests the preference of the metal to be associated to the nitrogen. Additionally, the sulfinyl oxygen has also a high density of negative charge as a consequence of the nature of the S−O bond (−0.99 au). We have calculated the energy associated to species $\mathbf{IV_C}$, $\mathbf{IV_O}$, and $\mathbf{IV_N}$ (Figure 4) with the metal respectively associated to such atoms at rotamer **I**, the most stable one of the previous calculations. We have also evaluated the stability of species $\mathbf{V_C}$ with the metal joined to the carbon but stabilized by the sulfinyl oxygen, because it has been found as the most stable species for other less delocalized benzylic carbanions.[22] Taking into account that the stereoselectivity is not dependent on the cation present during the reaction, in the model structures Li^+ has been used due to its simpler coordination mode. Dimethylamine, that comes from the simplified base, and dimethylether, as the simplified model solvent, were used as the rest of the ligands. According to the higher electron density on sulfinyl oxygen, these calculations reveal that $\mathbf{IV_O}$ is the most stable species; quite close is $\mathbf{V_C}$, followed by $\mathbf{IV_N}$, that has also been proposed by other authors from NMR studies for similar benzylic carbanions lacking the sulfinyl group.[1,23] Finally $\mathbf{IV_C}$ is the least stable due to its higher steric interactions.

Looking at these structures,[24] $\mathbf{IV_O}$ and $\mathbf{V_C}$ would afford the same diastereoselectivity since their lower faces show less steric

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(23) Enders, D.; Kirchhoff, J.; Gerdes, P.; Mannes, D.; Raabe, G.; Runsink, J.; Boche, G.; Marsch, M.; Ahlbrecht, H.; Sommer H. *Eur. J. Org. Chem.* **1998**, 63.

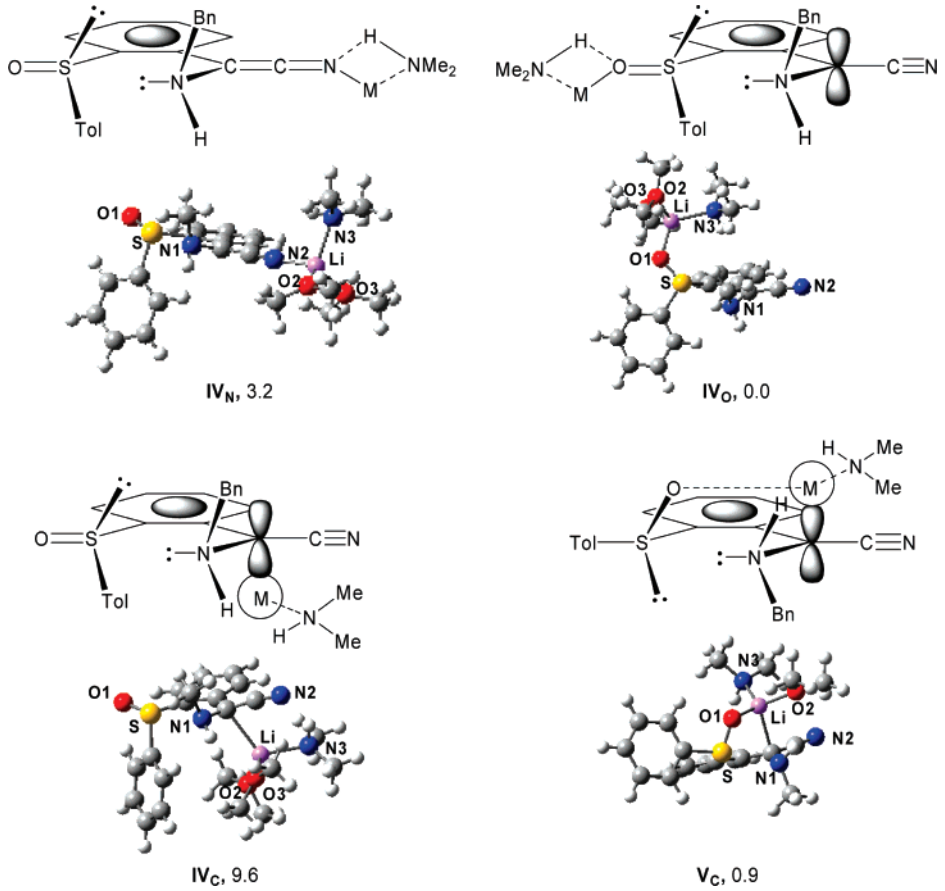

FIGURE 4. Structures and relative energies (kcal·mol^{-1}) of species with the metal associated to different atoms of benzylic carbanion. The energy corresponding to $\mathbf{V_C}$ has been evaluated as $\mathbf{V_C}$ + dimethylether − $\mathbf{IV_O}$. ZPE correction included.

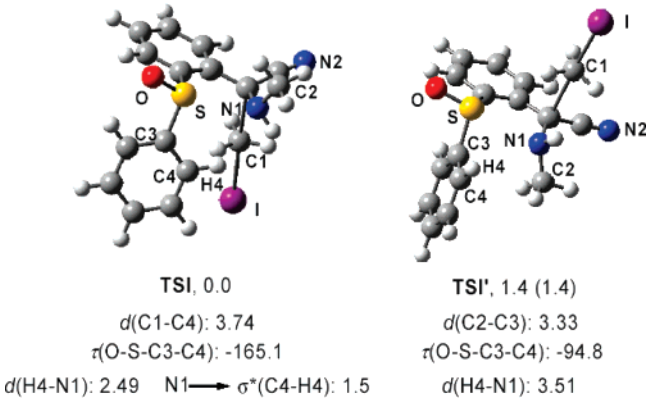

FIGURE 5. Structures and relative energies (kcal·mol^{-1}) of plausible transition states involved in the reaction of benzylic carbanions with MeI. ZPE correction is included. Free energy correction calculated at −78 °C is indicated in brackets. Selected bond distances (Å), dihedral angles (deg) and orbital interactions (kcal·mol^{-1}) evaluated by means of a second-order perturbational analysis of the Fock matrix on the NBO basis are also indicated.

hindrance for the approximation of an electrophile. However, the fact that the stereoselectivity is not dependent on the presence of a crown ether during the reaction suggests that the coordination to the metal would take place far from the reaction center, which is in agreement with the evolution of the reaction through species such as $\mathbf{IV_O}$. Thus, in order to understand the origin of the stereoselectivity, an additional simplification can be made. The stereoselectivity could be determined by the difference in the energy content between transition states with structures quite similar to those indicated in Figure 5 as **TSI** and **TSI′**. These structures result from the approximation of the electrophile (MeI has been used as a model) to the less hindered face of the most stable **A** conformation of the benzylic carbanion (we have considered the attack to rotamers **I** and **I′** because they are not too different in energy, see Figure 3). As it can be seen in Figure 5, **TSI**, yielding compounds with [2*S*,(S)*S*] configuration, is more stable than **TSI′**, yielding compounds with [2*R*,(S)*S*] configuration, for 1.4 kcal·mol^{-1}. This difference in energy content at −78 °C predicts a dr of 97:3, which is in excellent agreement with the experimental results. Steric interactions between the groups located at the lower face must be higher in **TSI′** than in **TSI** according to the distances between the carbon atoms of CH_3NH or CH_3I and the nearest carbon atom of the Ph group. This fact forces the Ph group to adopt a different conformation in **TSI′** with respect to that in **TSI** (compare dihedral angles) with the loss of a weak stabilizing hydrogen bond between H4 and N1.[19] It can be expected that the presence of the benzyl group instead of the methyl one at the nitrogen used in the calculations will predict that energetic differences between **TSI** and **TSI′** will be even larger than 1.4 kcal·mol^{-1}. From a steric point of view, these results suggest that the

(24) It is interesting to note that the distances between N1 and S in all these structures are smaller than the sum of their van der Waals radii[19] (it is also the case for intermediates I, II, and III, Figure 3), which could be a consequence of the stabilizing electronic interactions that have been found between the coplanar sulfur and nitrogen functions [$\mathbf{IV_N}$: *d*(N−S): 2.86, N1→p*(S−O): 3.20; $\mathbf{IV_O}$: *d*(N−S): 2.91, N1→2p*(S−O): 2.82; $\mathbf{V_C}$: *d*(N−S): 2.71, N1→s*(S−C_{Tol}): 5.93].

orientation of the benzyl group at nitrogen, which is dependent on that of the *p*-tolyl group at sulfur, is mainly responsible for stereoselectivity control.

As a conclusion, we have demonstrated that reactions of compounds **2** with hydrocyanating reagents yielding mixtures of α-amino phenylacetonitrile derivatives are moderately stereoselective, whereas the reaction of the hydrocyanated mixtures with alkylating or acylating reagents in the presence of KHMDS takes place in a completely stereoselective way, only yielding compounds with configuration *S* at benzylic carbon, thus allowing the synthesis of enantiomerically pure α-substituted α-amino phenylacetonitriles. DFT calculations support that the efficient stereoselectivity control exerted by the sulfinyl group is mainly related to its electrostatic interactions with the cyano group governing the conformational preferences of the benzylic anion intermediate.

Experimental Section

General Procedure for the Synthesis of 2-(*S*)-Sulfinylbenzaldimines 2, 3, 5−8. To a solution of aldehyde **1** (244.3 mg, 1 mmol) in anhydrous CH_2Cl_2 (5 mL), in the presence of an excess amount of Na_2SO_4,was added the corresponding amine (1 mmol), and the reaction was stirred for 16 h at rt. The reaction mixture was filtered through a Celite pad, and the solvent was evaporated. The products were purified by crystallization.

(±)-*N*-((*E*)-{2-[(4-Methylphenyl)sulfinyl]phenyl}methylene)-aniline (2). Aniline was used as the starting amine, and the product was purified by crystallization from CH_2Cl_2/hexane. Yield: 91%; white solid; mp 92−94 °C; IR (KBr): 1628, 1026, 767 cm^{-1}; ^1H NMR: δ 8.56 (s, 1H), 8.39 (dd, J = 1.4 and 7.8 Hz, 1H), 7.82 (dd, J = 1.6 and 7.5 Hz, 1H), 7.69 (td, J = 1.6 and 7.5 Hz, 1H), 7.57 (dd, J = 1.6 and 7.2 Hz, 1H), 7.50 and 7.12 (AA′BB′ system, 4H), 7.40−7.30 (m, 2H), 7.27−7.18 (m, 1H), 7.08−7.02 (m, 2H), 2.28 (s, 3H); ^{13}C NMR: δ 156.5, 150.4, 146.0, 143.4, 140.9, 133.7, 131.5, 131.1, 130.5, 129.5 (2C), 129.1, 126.5, 126.3 (2C), 125.3, 120.7, 21.2; MS (FAB^+) *m*/*z* 320 $(M + H)^+$; HRMS (FAB^+) calcd for $C_{20}H_{18}NOS$ $(M + H)^+$: 320.1103; found: 320.1094.

(±)-(*E*)-4-Methoxy-*N*-[2-(*p*-tolylsulfinyl)benzylidene]aniline (3). *p*-Anisidine was used as the starting amine, and the product was purified by crystallization from CH_2Cl_2/hexane. Yield: 86%; white solid; mp 80−82 °C; IR (KBr): 1626, 1247, 1029, 754 cm^{-1}; ^1H NMR: δ 8.62 (s, 1H), 8.43 (dd, J = 1.2 and 7.5 Hz, 1H), 7.83 (dd, J = 1.5 and 7.5 Hz, 1H), 7.70 (td, J = 1.5 and 7.5 Hz, 1H), 7.58−7.48 (m, 1H), 7.50 and 7.21 (AA′BB′ system, 4H), 7.16 and 6.94 (AA′BB′ system, 4H), 3.83 (s, 3H), 2.32 (s, 3H); ^{13}C NMR: δ 158.7, 154.1, 145.5, 143.4, 143.1, 140.7, 134.0, 131.0, 130.7, 130.4, 129.4 (2C), 126.1 (2C), 125.2, 122.1 (2C), 114.3 (2C), 55.3, 21.2; MS (ESI^+) *m*/*z* 350 $(M + H)^+$; HRMS (ESI^+) calcd for $C_{21}H_{20}NO_2S$ $(M + H)^+$: 350.1209; found: 350.1199.

***N*-((*E*,*S*)-{2-[(4-Methylphenyl)sulfinyl]phenyl}methylene)-1-phenylmethanamine (5).** Benzylamine was used as the starting amine, and the product was purified by crystallization from CH_2Cl_2/hexane. Yield: 87%; white solid; $[\alpha]^{20}_D$ −257.3 (*c* 1.0, $CHCl_3$); mp 84−86 °C; IR (KBr): 1626, 1061, 753 cm^{-1}; ^1H NMR: δ 8.52 (s, 1H), 8.37 (dd, J = 1.1 and 7.5 Hz, 1H), 7.75−7.65 (m, 2H), 7.55 (td, J = 1.1 and 7.5 Hz, 1H), 7.39 and 7.09 (AA′BB′ system, 4H), 7.34−7.20 (m, 5H), 4.84 and 4.73 (AB system, J = 14.1 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR: δ 158.7, 145.4, 143.4, 140.7, 138.4, 133.7, 131.1, 130.6, 130.4, 129.6 (2C), 128.5 (2C), 127.9 (2C), 127.0, 126.3 (2C), 125.2, 64.5, 21.2; MS (EI^+) *m*/*z* 334 $(M + H)^+$; HRMS (EI^+) calcd for $C_{21}H_{20}NOS$ $(M + H)^+$: 334.1260; found: 334.1271.

***N*-((*E*,*S*)-{2-[(4-Methylphenyl)sulfinyl]phenyl}methylene)-1-[4-(trifluoromethyl)phenyl] methanamine (6).** *p*-Trifluoromethylbenzylamine was used as the starting amine, and the product was used without further purification. Yield: 87%; white solid; $[\alpha]^{20}_D$ −228.4 (*c* 1.0, $CHCl_3$); mp 116−118 °C (CH_2Cl_2/hexane); IR (KBr): 1326, 1216, 756 cm^{-1}; ^1H NMR: δ 8.55 (s, 1H), 8.45 (d, J = 7.7 Hz, 1H), 7.79−7.67 (m, 2H), 7.64−7.58 (m, 1H), 7.59 and 7.37 (AA′BB′ system, 4H), 7.41 and 7.09 (AA′BB′ system, 4H), 4.86 and 4.78 (AB system, J = 14.5 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR: δ 159.5, 144.9, 143.2, 142.5, 142.4, 140.6, 133.2, 131.0, 130.9, 130.4, 129.3 (2C), 128.8 (q, ^2J = 32.3 Hz, $C-CF_3$), 127.8 (2C), 126.1 (2C), 125.1, 125.0 [q, ^3J = 3.9 Hz, $(CH)_2C-CF_3$], 124.0 (q, ^1J = 272.2 Hz, CF_3), 63.7, 20.9; MS (EI^+) *m*/*z* 401 (M^+); HRMS (EI^+) calcd for $C_{22}H_{18}F_3NOS$ (M^+): 401.1061; found: 401.1045.

***N*-((*E*,*S*)-{2-[(4-Methylphenyl)sulfinyl]phenyl}methylene)-1-(4-methoxyphenyl)methanamine (7).** *p*-Methoxybenzylamine was used as the starting amine, and the product was used without further purification. Yield: 93%; white solid; $[\alpha]^{20}_D$ −259.2 (*c* 1.0, $CHCl_3$); mp 120−122 °C (CH_2Cl_2/hexane); IR (KBr): 1512, 1248, 1058, 755 cm^{-1}; ^1H NMR: δ 8.41 (s, 1H), 8.37 (d, J = 6.9 Hz, 1H), 7.73−7.64 (m, 2H), 7.54 (t, J = 6.9 Hz, 1H), 7.41 and 7.09 (AA′BB′ system, 4H), 7.17 and 6.88 (AA′BB′ system, 4H), 4.77 and 4.66 (AB system, J = 14.1 Hz, 2H), 3.82 (s, 3H), 2.31 (s, 3H); ^{13}C NMR: δ 158.6, 158.2, 145.2, 143.4, 140.7, 133.6, 130.9, 130.5, 130.4, 130.3, 129.4 (2C), 129.1 (2C), 126.2 (2C), 125.0, 113.8 (2C), 63.8, 55.2, 21.2; MS (FAB^+) *m*/*z* 364 $(M + H)^+$; HRMS (FAB^+) calcd for $C_{22}H_{22}NO_2S$ $(M + H)^+$: 364.1371; found: 364.1381.

2-Methyl-*N*-((*E*,*S*)-{2-[(4-methylphenyl)sulfinyl]phenyl}methylene)propan-1-amine (8). Isobutylamine was used as the starting amine, and the product was used without further purification. Yield: 90%; pale yellow oil; $[\alpha]^{20}_D$ −208.4 (*c* 1.0, $CHCl_3$); IR (film): 1650, 1028, 764 cm^{-1}; ^1H NMR: δ 8.35 (m, 1H), 8.31 (dd, J = 1.2 and 7.5 Hz, 1H), 7.68−7.59 (m, 2H), 7.52 (dd, J = 1.2 and 7.5 Hz, 1H), 7.46 and 7.14 (AA′BB′ system, 4H), 3.46 (ddd, J = 1.4, 6.6, and 11.3 Hz, 1H), 3.27 (ddd, J = 0.9, 6.6, and 11.3 Hz, 1H), 1.93 (sept, J = 6.6 Hz, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR: δ 157.5, 145.1, 143.7, 140.6, 133.9, 130.7, 130.4, 130.3, 129.5 (2C), 126.1 (2C), 125.1, 69.4, 29.5, 21.2, 20.6, 20.5; MS (ESI^+) *m*/*z* 300 $(M + H)^+$; HRMS (ESI^+) calcd for $C_{18}H_{22}NOS$ $(M + H)^+$: 300.1416; found: 300.1427.

***N*-((*E*,*S*)-{2-[(4-Methylphenyl)sulfinyl]phenyl}methylene)-4-nitroaniline (4).** A solution of aldehyde **1** (244.3 mg, 1 mmol) and nitroaniline (145 mg, 1.05 mmol) in toluene (25 mL), in the presence of an excess amount of Na_2SO_4, was heated at reflux in a Dean−Stark apparatus for 96 h. The reaction was cooled at rt, filtered through a Celite pad, and the solvent was evaporated. The product was purified by crystallization from CH_2Cl_2/hexane. Yield: 75%; yellow solid; mp 68−70 °C; $[\alpha]^{20}_D$ −375.6 (*c* 1.0, $CHCl_3$); IR (KBr): 1701, 1587, 1310, 1028, 726 cm^{-1}; ^1H NMR: δ 8.58 (s, 1H), 8.41 (dd, J = 1.1 and 7.9 Hz, 1H), 8.27 and 7.07 (AA′BB′ system, 4H), 7.90 (dd, J = 1.1 and 7.9 Hz, 1H), 7.80 (td, J = 1.1 and 7.9 Hz, 1H), 7.64 (td, J = 1.1 and 7.9 Hz, 1H), 7.43 and 7.17 (AA′BB′ system, 4H), 2.33 (s, 3H); ^{13}C NMR: δ 159.2, 156.1, 146.4, 145.8, 142.9, 141.4, 132.9, 132.6, 131.9, 130.9, 129.8 (2C), 126.4 (2C), 125.9, 125.1 (2C), 121.1 (2C), 21.3; MS (FAB^+) *m*/*z* 365 $(M + H)^+$; HRMS (FAB^+) calcd for $C_{20}H_{17}N_2O_3S$ $(M + H)^+$: 365.0954; found: 365.0958.

General Procedure for the Synthesis of (*S*)-2-Sulfinylbenzaldimines 9−10. To a solution of aldehyde **1** (244.3 mg, 1 mmol) and sulfonamide (1 mmol) in CH_2Cl_2 or DCE (6 mL) at rt under argon was added Et_3N (202 mg, 0.279 mL, 2 mmol) and $TiCl_4$ (95 mg, 0.055 mL, 0.5 mmol). The resulting mixture was heated at reflux for 5 h. The reaction was hydrolyzed with 1 M HCl (2 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 mL) and dried (Na_2SO_4), and the solvent was evaporated.

***N*-((*E*,*S*){2-[(4-Methylphenyl)sulfinyl]phenyl}methylene)-methanesulfonamide (9).** Methanesulfonamide (95.1 mg, 1 mmol) was used as the starting amine, and CH_2Cl_2 (6 mL) was used as the solvent. The product was purified by crystallization from CH_2Cl_2/hexane. Yield: 65%; white solid; mp 74−76 °C; $[\alpha]^{20}_D$

−106.6 (*c* 0.5, $CHCl_3$); IR (KBr): 1612, 1322, 1149, 805, 753 cm^{-1}; ^1H NMR: δ 9.25 (s, 1H), 8.40 (dd, J = 1.4 and 7.8 Hz, 1H), 7.97 (dd, J = 1.4 and 7.8 Hz, 1H), 7.88 (td, J = 1.4 and 7.8 Hz, 1H), 7.64 (td, J = 1.4 and 7.8 Hz, 1H), 7.50 and 7.20 (AA′BB′ system, 4H), 3.04 (s, 3H), 2.31 (s, 3H); ^{13}C NMR: δ 168.1, 149.2, 142.0, 141.9, 135.3, 133.5, 131.0 (2C), 130.1, 129.3, 126.2 (2C), 125.7, 40.4, 21.3; MS (ESI^+) *m*/*z* 322 $(M + H)^+$; HRMS (ESI^+) calcd for $C_{15}H_{16}NO_3S_2$ $(M + H)^+$: 322.0566; found: 322.0553.

4-Methyl-*N*-((*E*,*S*)-{2-[(4-methylphenyl)sulfinyl]phenyl}-methylene)benzenesulfonamide (10). *p*-Toluenesulfonamide (171.2 mg, 1 mmol) was used as the starting amine, and DCE (6 mL) was used as the solvent. The product was purified by flash column chromatography (EtOAc/hexane, 1:1). Yield: 82%; white solid; mp 171−173 °C; $[\alpha]^{20}_D$ −248.0 (*c* 1.0, $CHCl_3$); IR (KBr): 1610, 1330, 1207, 815, 786 cm^{-1}; ^1H NMR: δ 9.23 (s, 1H), 8.37 (dd, J = 1.2 and 7.9 Hz, 1H), 7.92 (dd, J = 1.2 and 7.9 Hz, 1H), 7.84 (td, J = 1.2 and 7.9 Hz, 1H), 7.81 and 7.34 (AA′BB′ system, 4H), 7.59 (td, J = 1.2 and 7.9 Hz, 1H), 7.43 and 7.12 (AA′BB′ system, 4H), 2.45 (s, 3H), 2.30 (s, 3H); ^{13}C NMR: δ 166.4, 149.2, 145.0, 141.9, 141.7, 135.0, 134.6, 133.6, 130.9, 129.9 (2C), 129.8 (2C), 129.5, 128.2 (2C), 126.2 (2C), 125.3, 21.7, 21.3; MS (FAB^+) *m*/*z* 398 $(M + H)^+$; HRMS (FAB^+) calcd for $C_{21}H_{20}NO_3S_2$ $(M + H)^+$: 398.0884; found: 398.0887.

General Procedures for the Synthesis of α-Amino Nitriles 11−17/11′-17′. Method A. To a solution of imine (0.1 mmol) in THF (1 mL) under argon was added 1 M toluene solution of Et_2AlCN. The resulting mixture was stirred at rt for 2−16 h. The reaction was slowly hydrolyzed with saturated aqueous potassium sodium tartrate·$4H_2O$ (1 mL) and stirred for 30 min. The organic layer was separated, washed with saturated aqueous NaCl (1 mL), and dried (Na_2SO_4), and the solvent was evaporated.

Method B. A solution of imine (0.1 mmol) in THF (1 mL) under argon was added dropwise to a 1 M toluene solution of Et_2AlCN (0.4 mmol) in THF (4 mL). The resulting mixture was stirred at 0 °C for 2−16 h. The reaction was slowly hydrolyzed with saturated aqueous potassium sodium tartrate·$4H_2O$ (1 mL) and stirred for 30 min. The organic layer was separated, washed with saturated aqueous NaCl (1 mL) and dried (Na_2SO_4), and the solvent was evaporated.

Method C. A solution of imine (0.1 mmol) and $Yb(OTf)_3$ (0.1 mmol) in THF (1 mL) under argon was added dropwise to a 1 M toluene solution of Et_2AlCN (0.4 mmol) in THF (4 mL). The resulting mixture was stirred at 0 °C for 2−16 h. The reaction was slowly hydrolyzed with saturated aqueous potassium sodium tartrate·$4H_2O$ (1 mL) and stirred for 30 min. The organic layer was separated, washed with saturated aqueous NaCl (1 mL) and dried (Na_2SO_4), and the solvent was evaporated.

[2*S*,(S)*S*]- and [2*R*,(S)*S*]-{2-[(4-Methylphenyl)sulfinyl]phenyl}-[(4-nitrophenyl)amino]acetonitrile (11 + 11′). It was prepared as a diastereoisomeric 39:61 mixture from imine **4** following **method A** using 2 equiv of Et_2AlCN (reaction time: 8 h). It was crystallized from $CHCl_3$/hexane. Yield: 75%; yellow solid; ^1H NMR (**11** + **11′** mixture, d_6-DMSO): δ 8.25 (d, J = 8.1 Hz, 1H), 8.18 and 6.94 (AA′BB′ system, 4H), 8.17 and 6.93 (AA′BB′ system, 4H), 8.02−7.95 (m, 3H), 7.89−7.82 (m, 3H), 7.81−7.73 (m, 3H), 7.54 and 7.34 (AA′BB′ system, 4H), 7.39 and 7.24 (AA′BB′ system, 4H), 6.80 (d, J = 9.0 Hz, 1H), 6.56 (d, J = 7.9 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (**11** + **11′** mixture, d_6-DMSO): δ 152.0, 151.6, 145.8, 145.2, 142.5, 142.3, 142.2, 141.9, 139.7, 139.6, 133.3, 133.1, 132.6, 132.5, 132.1 (2C), 130.9 (2C), 130.7 (2C), 129.5, 129.3, 128.1, 127.4, 126.9 (2C), 126.8 (2C), 126.0 (2C), 125.8 (2C), 118.7, 118.5, 113.6 (2C), 46.3, 46.2, 21.8, 21.7; MS (FAB^+) *m*/*z* 392 $(M + H)^+$; HRMS (FAB^+) calcd for $C_{21}H_{18}N_3O_3S$ $(M + H)^+$: 392.1068; found: 392.1062.

[2*S*,(S)*S*]- and [2*R*,(S)*S*]-(Benzylamino){2-[(4-methylphenyl)-sulfinyl]phenyl}acetonitrile (12 + 12′). It was prepared as a diastereoisomeric 48:52 mixture from imine **5** following **method A** using 2 equiv of Et_2AlCN (reaction time: 8 h). It was used in further reactions without any purification. Crystallization from $CHCl_3$/hexane gave [2*R*,(S)*S*]-**12′** as a pure diastereoisomer. Yield: 44%; white solid; mp 116−118 °C; $[\alpha]^{20}_D$ −90.7 (*c* 1.0, $CHCl_3$); IR (KBr): 2230, 1216, 1031, 755 cm^{-1}; ^1H NMR: δ 7.83−7.79 (m, 1H), 7.77−7.71 (m, 1H), 7.58−7.49 (m, 4H), 7.31−7.16 (m, 7H), 5.45 (s, 1H), 4.02 and 3.93 (AB system, J = 11.8 Hz, 2H), 2.36 (s, 3H), 1.84 (bs, 1H); ^{13}C NMR: δ 144.9, 141.6, 141.3, 137.2, 133.6, 131.8, 130.7, 129.9 (2C), 128.7 (2C), 128.6 (2C), 128.1, 127.8, 127.6, 125.3 (2C), 117.7, 51.9, 50.7, 21.3; MS (FAB^+) *m*/*z* 361 $(M + H)^+$; HRMS (FAB^+) calcd for $C_{22}H_{21}N_2OS$ $(M + H)^+$: 361.1374; found: 361.1366. Diastereoisomer [2*S*,(S)*S*]-**12** was characterized from a **12** + **12′** mixture; ^1H NMR: δ 8.13−8.07 (m, 1H), 7.76−7.13 (m, 12H), 4.85 (s, 1H), 4.05−3.78 (m, 2H), 2.35 (s, 3H), 2.06 (bs, 2H); ^{13}C NMR: δ 144.7, 141.3, 141.0, 137.0, 133.3, 131.5, 130.5, 129.6 (2C), 128.5 (2C), 128.3 (2C), 127.7, 127.4, 125.1 (2C), 117.4, 51.0, 50.5, 21.2.

[2*S*,(S)*S*]- and [2*R*,(S)*S*]-{2-[(4-Methylphenyl)sulfinyl]phenyl}-{[4-(trifluoromethyl)benzyl]amino}acetonitrile (13 + 13′). It was prepared as a diastereoisomeric 41:59 mixture from imine **6** following **method A** using 4 equiv of Et_2AlCN (reaction time: 2 h). It was used in further transformations without any purification. Crystallization from $CHCl_3$/hexane gave [2*R*,(S)*S*]-**13′** as a pure diastereoisomer. Yield: 38%; yellow solid; mp 142−144 °C; $[\alpha]^{20}_D$ −53.1 (*c* 1.0, $CHCl_3$); IR (KBr): 2229, 1325, 1133, 1063, 774 cm^{-1}; ^1H NMR: δ 7.83−7.79 (m, 1H), 7.78−7.72 (m, 1H), 7.58−7.44 (m, 2H), 7.52 and 7.20 (AA′BB′ system, 4H), 7.47 and 7.31 (AA′BB′ system, 4H), 5.46 (s, 1H), 4.07 and 3.97 (AB system, J = 12.4 Hz, 2H), 2.37 (s, 3H), 1.94 (bs, 1H); ^{13}C NMR: δ 144.4, 141.6, 141.3, 133.5, 132.0, 130.8, 130.0 (q, ^2J = 32.3 Hz, *C*-CF_3), 129.9 (2C), 128.8 (2C), 128.4, 127.9, 125.5 [q, ^3J = 3.7 Hz, (*C*H)$_2$C−CF_3], 125.4 (2C), 124.0 (q, ^1J = 271.9 Hz, CF_3), 117.5, 51.2, 50.7, 21.3; MS (ESI^+) *m*/*z* 429 $(M + H)^+$; HRMS (ESI^+) calcd for $C_{23}H_{20}F_3N_2OS$ $(M + H)^+$: 429.1242; found: 429.1249. Diastereoisomer [2*R*,(S)*S*]-**13** was characterized from a **13** + **13′** mixture; ^1H NMR: δ 7.81 (dd, J = 3.3 and 5.8, 1H), 7.75−7.65 (m, 2H), 7.50−7.35 (m, 4H), 7.27−7.05 (m, 4H), 6.96 (d, J = 7.1 Hz, 1H), 4.87 (s, 1H), 4.03−3.85 (m, 2H), 2.37 (s, 3H), 1.95 (bs, 1H); ^{13}C NMR (representative parameters): δ 143.4, 141.0, 140.7, 137.2, 133.3, 131.2, 130.5, 129.6 (2C), 128.4 (2C), 128.1, 127.5, 127.2, 125.1 (2C), 117.4, 51.0, 50.1, 21.1.

[2*S*,(S)*S*]- and [2*R*,(S)*S*]-[(4-Methoxybenzyl)amino]{2-[(4-methylphenyl)sulfinyl]phenyl} acetonitrile (14 + 14′). It was prepared as a diastereoisomeric 40:60 mixture from imine **7** following **method A** using 4 equiv of Et_2AlCN (reaction time: 2 h). It was used in further reactions without any purification. Crystallization from $CHCl_3$/hexane gave [2*R*,(S)*S*]-**14′** as a pure diastereoisomer. Yield: 42%; yellow solid; mp 123−125 °C; $[\alpha]^{20}_D$ −87.3 (*c* 1.0, $CHCl_3$); IR (KBr): 2224, 1247, 1018, 1007, 810 cm^{-1}; ^1H NMR: δ 7.80 (dd, J = 3.4 and 5.9 Hz, 1H), 7.74 (dd, J = 3.4 and 5.8 Hz, 1H), 7.56 and 7.21 (AA′BB′ system, 4H), 7.53−7.48 (m, 2H), 7.15 and 6.81 (AA′BB′ system, 4H), 5.42 (s, 1H), 3.97 and 3.88 (AB system, J = 12.0 Hz, 2H), 3.79 (s, 3H), 2.37 (s, 3H), 1.78 (bs, 1H); ^{13}C NMR: δ 159.2, 145.0, 141.6, 141.2, 133.6, 131.7, 130.7, 130.0 (2C), 129.9 (2C), 129.2, 127.9, 127.6, 125.3 (2C), 117.7, 113.9 (2C), 55.3, 51.3, 50.6, 21.3; MS (FAB^+) *m*/*z* 391 $(M + H)^+$; HRMS (FAB^+) calcd for $C_{23}H_{23}N_2O_2S$ $(M + H)^+$: 391.1480; found: 391.1481. Diastereoisomer [2*R*,(S)*S*]-**14** was characterized from a **14** + **14′** mixture; ^1H NMR: δ 8.09−8.06 (m, 1H), 7.75−7.68 (m, 2H), 7.65−7.11 (m, 8H), 6.95−6.88 (m, 2H), 4.81 (s, 1H), 4.00−3.73 (m, 2H), 3.81 (s, 3H), 2.35 (s, 3H), 1.88 (bs, 1H); ^{13}C NMR: δ 159.3, 143.7, 142.3, 141.0, 132.4, 131.4, 130.3, 130.2 (2C), 130.1 (2C), 129.4, 127.9, 126.3, 126.2 (2C), 117.6, 114.0 (2C), 55.2, 50.7, 50.2, 21.4.

[2*S*,(S)*S*]- and [2*R*,(S)*S*]-(Isobutylamino){2-[(4-methylphenyl)-sulfinyl]phenyl}acetonitrile (15 + 15′). It was prepared as a diastereoisomeric 49:51 mixture from imine **8** following **method A** using 4 equiv of Et_2AlCN (reaction time: 16 h). It was used in further reactions without any purification. Yield: 74%; white oil; ^1H NMR (**15** + **15′** mixture): δ 8.06 (dd, J = 1.4 and 7.8 Hz, 1H), 7.82−7.76 (m, 1H), 7.74−7.68 (m, 2H), 7.61−7.54 (m, 1H),

7.56 and 7.23 (AA′BB′ system, 4H), 7.53−7.49 (m, 3H), 7.43 and 7.26 (AA′BB′ system, 4H), 5.42 (s, 1H), 4.84 (s, 1H), 2.69−2.61 (m, 1H), 2.60−2.50 (m, 2H), 2.45−2.37 (m, 1H), 2.35 (s, 3H), 2.34 (s, 3H), 1.75 (sept, J = 6.5 Hz, 1H), 1.64 (sept, J = 6.5 Hz, 1H), 1.63 (bs, 2H), 0.96 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H); ^{13}C NMR (**15** + **15′** mixture): δ 144.8, 143.6, 142.2, 141.6, 141.2, 140.9, 133.9, 132.7, 131.7, 131.3, 130.6, 130.2 (2C), 130.1, 129.8 (2C), 128.1, 127.9, 127.5, 126.6, 126.2 (2C), 125.2 (2C), 118.0, 117.9, 55.4, 54.9, 51.6, 51.5, 28.3, 28.2, 21.4, 21.2, 20.7, 20.6, 20.5, 20.4; MS (ESI$^+$) *m*/*z* 327 (M + H)$^+$; HRMS (ESI$^+$) calcd for $C_{19}H_{23}N_2OS$ (M + H)$^+$: 327.1535; found: 327.1525.

[2*S*,(S)*S*]- and [2*R*,(S)*S*]-*N*-(Cyano{2-[(4-methylphenyl)sulfinyl]-phenyl}methyl) methanesulfonamide (16 + 16′). It was prepared as a diastereoisomeric 58:42 mixture from imine **9** following **method A** using 2 equiv of Et_2AlCN (reaction time: 2 h). It was used in further reactions without any purification. Yield: 86%; white solid; ^{1}H NMR (**16** + **16′** mixture): δ 7.91−7.75 (m, 1H), 7.77−7.71 (m, 2H), 7.67−7.62 (m, 1H), 7.61−7.47 (m, 8H), 7.34−7.25 (m, 3H), 7.21−7.15 (m, 2H), 6.71 (bs, 2H), 6.07 (s, 1H), 5.89 (s, 1H), 3.05 (s, 3H), 3.04 (s, 3H), 2.38 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (**16** + **16′** mixture): δ 143.0, 142.9, 142.7, 142.3, 139.6, 139.5, 132.6, 132.1, 131.2, 131.0, 130.6, 130.5 (2C), 130.4 (3C), 130.2, 129.6, 128.2, 126.6, 126.1 (2C), 125.3 (2C), 116.7, 116.5, 44.8 (2C), 41.9, 41.7, 21.4, 21.3; MS (ESI$^+$) *m*/*z* 349 (M + H)$^+$; HRMS (ESI$^+$) calcd for $C_{16}H_{17}N_2O_3S_2$ (M + H)$^+$: 349.0675; found: 349.0673.

[2*S*,(S)*S*]- and [2*R*,(S)*S*]-*N*-(Cyano{2-[(4-methylphenyl)sulfinyl]-phenyl}methyl)-4-methylbenzenesulfonamide (17 + 17′). It was prepared as a diastereoisomeric 90:10 mixture from imine **10** following **method A** using 2 equiv of Et_2AlCN (reaction time: 2 h). It was used in further reactions without any purification. Crystallization from $CHCl_3$/hexane gave [2*S*,(S)*S*]-**17** as a pure diastereoisomer. Yield: 76%; white solid; mp 186−188 °C; $[\alpha]^{20}_D$ −43.8 (*c* 1.0, $CHCl_3$); IR (KBr): 2401, 1341, 1216, 1063, 755 cm^{-1}; ^{1}H NMR: δ 7.79 (dd, J = 1.5 and 7.8 Hz, 1H), 7.76 and 7.30 (AA′BB′ system, 4H), 7.60−7.50 (m, 3H), 7.47 and 7.27 (AA′BB′ system, 4H), 6.20 (bs, 1H), 5.72 (s, 1H), 2.42 (s, 3H), 2.38 (s, 3H); ^{13}C NMR: δ 144.5, 143.0, 142.9, 140.2, 136.2, 131.9, 130.9, 130.7, 130.5 (2C), 129.9 (2C), 127.4 (2C), 126.7, 126.2 (2C), 125.7, 115.6, 45.0, 21.6, 21.4; MS (FAB$^+$) *m*/*z* 425 (M + H)$^+$; HRMS (FAB$^+$) calcd for $C_{22}H_{21}N_2O_3S_2$ (M + H)$^+$: 425.0993; found: 425.0977. Diastereoisomer [2*R*,(S)*S*]-**17′** was characterized from a **17** + **17′** mixture; ^{1}H NMR: δ 7.91−7.84 (m, 1H), 7.79−7.20 (m, 11H), 6.67 (bs, 2H), 6.07 (s, 1H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C NMR: δ 144.1, 143.2, 142.4, 141.9, 139.6, 139.2, 132.2, 131.7, 129.6 (2C), 129.5, 129.2, 127.5, 127.2 (2C), 126.1 (2C), 125.2 (2C), 115.8, 44.3, 21.5, 21.3.

2-Benzylamino-2-{2-[(4-methylphenyl)sulfinyl]phenyl}-acetamide (18). To 40 mg (0.11 mmol) of a 38:62 diastereoisomeric mixture **12** + **12′** cooled at 0 °C was added a saturated solution of HCl(g) in HCO_2H (2 mL). The resulting mixture was stirred at 0 °C for 10 h. The solvent was evaporated at reduced pressure, and the residue was treated with a saturated aqueous solution of $NaHCO_3$ (2 mL) for 30 min at room temperature. The product was extracted with $CHCl_3$ (3 × 5 mL), and the organic layers were combined and dried (Na_2SO_4). The solvent was evaporated at reduced pressure, and the product was purified by flash column chromatography (eluent EtOAc/hexane, 2:1). Yield: 76%; white solid; mp 129−131 °C (EtOAc/hexane); IR (KBr): 3318, 3179, 1659 cm^{-1}; ^{1}H NMR: δ 7.44 (d, J = 7.2 Hz, 1H), 7.34−7.20 (m, 8H), 7.16 and 7.09 (AA′BB′ system, 4H), 6.92 (bs, 1H), 5.83 (bs, 1H), 4.85 (s, 1H), 3.72 and 3.66 (AB system, J = 13.1 Hz, 2H), 2.50 (bs, 1H), 2.31 (s, 3H); ^{13}C NMR: δ 174.6, 139.8, 139.2, 137.2, 135.2, 133.5, 132.1, 130.7 (2C), 130.1 (2C), 128.8, 128.6, 128.4 (2C), 128.2 (2C), 128.1, 127.2, 63.6, 52.3, 21.0; MS (ESI+) *m*/*z* 363 [M + H]$^+$ (40), 318 (11), 211 (21); HRMS (ESI+) calcd for $C_{22}H_{23}N_2OS$: 363.1525; found: 363.1541.

2-Benzylamino-2-phenylacetamide (19). A solution of 30 mg (0.083 mmol) of 2-benzylamino-2-(*p*-tolylsulfenyl)phenylacetamide (**18**) in THF (1 mL) was added onto a suspension of Raney-Ni (∼0.5 g) in EtOH (5 mL). The mixture was stirred at rt for 4 h. Then, the supernatant liquid was decanted, and the Raney-Ni was treated with 5 mL of NH_3 (7 M in methanol). The mixture was boiled for 20 min, and the supernatant liquid was filtered throught a small Celite pad. The Raney-Ni was extracted two more times. The organic layers were combined, and the solvent was evaporated al reduced pressure. The residue was purified by flash column chromatography (eluent EtOAc/hexane, 3:1); Yield: 89%; white solid; $[\alpha]^{20}_D$ −16.6 (*c* 0.5, $CHCl_3$) [for **19** obtained from **12** + **12′** (24% de) in two steps] [lit.[13] $[\alpha]^{20}_D$ +71 (*c* 1.0, $CHCl_3$) for (*S*)-enantiomer]; ^{1}H NMR: δ 7.43−7.27 (m, 9H), 6.96 (bs, 1H), 5.70 (bs, 1H), 4.24 (s, 1H), 3.80 (s, 2H).

General Procedure for Quaternization of Benzylic Carbons. To a solution of amino nitrile **12**−**15** (0.5 mmol) in THF (5 mL) at −78 °C under argon was added 1.1 mmol of KHMDS (0.5 M in toluene). The mixture was stirred at −78 °C for 10 min, and then 1.5 mmol of the corresponding electrophile was added dropwise. The reaction was monitored by TLC. Upon transformation of the starting material, the reaction was hydrolyzed with saturated aqueous NH_4Cl (2.5 mL). The mixture was extracted with Et_2O (3 × 2.5 mL) and dried (Na_2SO_4), and the solvent was evaporated. The product was purified by flash column chromatography or Redisep normal phase column in an automated flash chromatography.

[2*S*,(S)*S*]-2-(Benzylamino)-2-{2-[(4-methylphenyl)sulfinyl]-phenyl}propanenitrile (22). Amino nitriles **12** + **12′** were used as the starting material. Iodomethane was used as the electrophile, and the reaction was stirred at −78 °C for 1 h to give compound [2*S*,(S)*S*]-**22**, which was purified in an automated flash chromatography (5:95 to 100:0 EtOAc/hexane gradient). Yield: 81%; white solid; mp 48−50 °C; $[\alpha]^{20}_D$ +134.7 (*c* 1.0, $CHCl_3$); IR (KBr): 2223, 1494, 1013, 755 cm^{-1}; ^{1}H NMR: δ 8.28 (dd, J = 1.5 and 7.4 Hz, 1H), 7.79 (dd, J = 1.5 and 7.4 Hz, 1H), 7.65−7.51 (m, 4H), 7.43−7.34 (m, 3H), 7.37 and 7.17 (AA′BB′ system, 4H), 3.98−3.78 (m, 2H), 2.33 (s, 3H), 1.80 (dd, J = 2.8 and 9.6 Hz, 1H), 1.33 (s, 3H); ^{13}C NMR: δ 143.3, 142.8, 141.5, 137.8, 137.2, 131.3, 129.9, 129.8 (2C), 128.9 (2C), 128.8 (2C), 127.9, 127.8, 127.7, 127.0 (2C), 121.0, 62.4, 50.4, 29.9, 21.4; MS (FAB$^+$) *m*/*z* 375 (M + H)$^+$; HRMS (FAB$^+$) calcd for $C_{23}H_{23}N_2OS$ (M + H)$^+$: 375.1531; found: 375.1537.

[2*S*,(S)*S*]-2-(Benzylamino)-2-{2-[(4-methylphenyl)sulfinyl]-phenyl}butanenitrile (23). Amino nitriles **12** + **12′** were used as the starting material. Ethyl trifluoromethanesulfonate was used as the electrophile, and the reaction was stirred at −78 °C for 1 h to give compound [2*S*,(S)*S*]-**23**, which was purified in an automated flash chromatography (5:95 to 100:0 EtOAc/hexane gradient). Yield: 79%; white solid; mp 49−50 °C; $[\alpha]^{20}_D$ −113.0 (*c* 1.0, $CHCl_3$); IR (KBr): 2224, 1494, 1014, 754 cm^{-1}; ^{1}H NMR: δ 8.16 (dd, J = 1.5 and 7.5, 1H), 7.77 (dd, J = 1.5 and 7.5 Hz, 1H), 7.60−7.48 (m, 4H), 7.42−7.31 (m, 3H), 7.39 and 7.20 (AA′BB′ system, 4H), 3.98−3.75 (m, 2H), 2.35 (s, 3H), 1.85 (dd, J = 2.4 and 10.1 Hz, 1H), 1.70−1.59 (m, 2H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR: δ 143.2, 143.1, 141.3, 137.9, 136.0, 130.9, 130.0, 129.7 (2C), 128.9 (2C), 128.8, 128.7 (2C), 128.5, 127.7, 126.4 (2C), 119.9, 67.8, 50.3, 34.9, 21.3, 9.0; MS (FAB$^+$) *m*/*z* 389 (M + H)$^+$; HRMS (FAB$^+$) calcd for $C_{24}H_{25}N_2OS$ (M + H)$^+$: 389.1688; found: 389.1694.

[2*S*,(S)*S*]-2-(Benzylamino)-2-{2-[(4-methylphenyl)sulfinyl]-phenyl}-3-phenylpropanenitrile (24). Amino nitriles **12** + **12′** were used as the starting material. Benzyl bromide was used as the electrophile, and the reaction was stirred at −78 °C for 1 h to give compound [2*S*,(S)*S*]-**24**, which was purified in an automated flash chromatography (5:95 to 100:0 EtOAc/hexane gradient). Yield: 77%; white solid; mp 76−78 °C; $[\alpha]^{20}_D$ −136.9 (*c* 1.0, $CHCl_3$); IR (KBr): 2402, 1215, 1009, 773 cm^{-1}; ^{1}H NMR: δ 8.45 (d, J = 7.7, 1H), 7.63−7.55 (m, 1H), 7.55−7.24 (m, 9H), 7.19−

7.12 (m, 5H), 6.78 (dd, J = 1.4 and 7.7 Hz, 2H), 3.91−3.82 (m, 2H), 2.67 and 2.52 (AB system, J = 13.2 Hz, 2H), 2.33 (s, 3H), 1.85 (dd, J = 2.7 and 9.9 Hz, 1H); ^{13}C NMR: δ 143.6, 142.3, 141.9, 137.8, 135.7, 132.8, 130.9, 130.5 (2C), 130.0 (2C), 129.9, 129.2, 128.8 (2C), 128.6 (2C), 128.5 (2C), 128.1, 127.7, 127.5 (2C), 127.4, 119.5, 67.4, 50.2, 47.2, 21.4; MS (FAB$^+$) m/z 451 (M + H)$^+$; HRMS (FAB$^+$) calcd for $C_{29}H_{27}N_2OS$ (M + H)$^+$: 451.1844; found: 451.1843.

[2*S*,(S)*S*]-2-(Benzylamino)-2-{2-[(4-methylphenyl)sulfinyl]-phenyl}pent-4-enenitrile (25). Amino nitriles **12** + **12′** were used as the starting material. Allyl bromide was used as the electrophile, and the reaction was stirred at −78 °C for 1 h to give compound [2*S*,(S)*S*]-**25**, which was purified in an automated flash chromatography (5:95 to 100:0 EtOAc/hexane gradient). Yield: 82%; white solid; mp 51−53 °C; $[\alpha]^{20}_D$ −117.2 (*c* 1.0, $CHCl_3$); IR (KBr): 2225, 1216, 1014, 773 cm^{-1}; ^{1}H NMR: δ 8.41 (dd, J = 1.4 and 7.8, 1H), 7.77 (dd, J = 1.4 and 7.8 Hz, 1H), 7.67 (td, J = 1.4 and 7.8 Hz, 1H), 7.61−7.49 (m, 3H), 7.47−7.31 (m, 3H), 7.35 and 7.18 (AA′BB′ system, 4H), 5.82−5.65 (m, 1H), 5.16 (d, J = 10.1 Hz, 1H), 4.70 (d, J = 16.8 Hz, 1H), 2.97−2.78 (m, 2H), 2.37−2.23 (m, 1H), 2.34 (s, 3H), 1.83 (dd, J = 1.7 and 10.8 Hz, 1H), 1.77−1.61 (m, 1H); ^{13}C NMR: δ 143.8, 142.4, 141.6, 137.7, 136.0, 131.1, 130.3, 129.9 (2C), 128.9 (2C), 128.8 (2C), 128.7, 127.8, 127.4 (2C), 122.8, 119.5, 65.8, 50.3, 45.9, 21.4; MS (FAB$^+$) m/z 401 (M + H)$^+$; HRMS (FAB$^+$) calcd for $C_{25}H_{25}N_2OS$ (M + H)$^+$: 401.1687; found: 401.1696.

[2*S*,(S)*S*]-Methyl (benzylamino)(cyano){2-[(4-methylphenyl)-sulfinyl]phenyl}acetate (26). Amino nitriles **12** + **12′** were used as the starting material. Methyl chloroformate was used as the electrophile, and the reaction was stirred at −78 °C for 1 h to give compound [2*S*,(S)*S*]-**26**, which was purified in an automated flash chromatography (5:95 to 100:0 EtOAc/hexane gradient). Yield: 84%; white solid; mp 50−52 °C; $[\alpha]^{20}_D$ −91.1 (*c* 1.0, $CHCl_3$); IR (KBr): 2401, 1755, 1216, 1015, 757 cm^{-1}; ^{1}H NMR: δ 8.14 (dd, J = 1.3 and 7.7, 1H), 7.87 (dd, J = 1.3 and 7.7 Hz, 1H), 7.67 (td, J = 1.3 and 7.7 Hz, 1H), 7.58 (td, J = 1.3 and 7.7 Hz, 1H), 7.45 and 7.07 (AA′BB′ system, 4H), 7.25−7.17 (m, 3H), 6.84−6.78 (m, 2H), 3.97 (s, 3H), 3.84 (dd, J = 2.9 and 12.1 Hz, 1H), 3.15−2.89 (m, 2H), 2.32 (s, 3H); ^{13}C NMR: δ 166.6, 144.5, 141.7, 141.3, 136.7, 133.2, 131.2, 131.1, 129.8 (2C), 128.9, 128.4 (2C), 128.3, 128.0 (2C), 127.5, 126.2 (2C), 115.6, 67.2, 55.1, 48.5, 21.3; MS (FAB$^+$) m/z 419 (M + H)$^+$; HRMS (FAB$^+$) calcd for $C_{24}H_{23}N_2O_3S$ (M + H)$^+$: 419.1429; found: 419.1419.

[2*S*,(S)*S*]-2-{2-[(4-Methylphenyl)sulfinyl]phenyl}-2-{[4-(trifluoromethyl)benzyl]amino}propanenitrile (28). Amino nitriles **13** + **13′** were used as the starting material. Iodomethane was used as the electrophile, and the reaction was stirred at −78 °C for 30 min to give compound [2*S*,(S)*S*]-**28**, which was purified by flash column chromatography (EtOAc/hexane, 1:3). Yield: 57%; yellow oil; $[\alpha]^{20}_D$ −87.5 (*c* 1.0, $CHCl_3$); IR (KBr): 2224, 1326, 1125, 758 cm^{-1}; ^{1}H NMR: δ 8.11 (dd, J = 1.5 and 6.9 Hz, 1H), 7.83 (dd, J = 1.5 and 6.9 Hz, 1H), 7.70 and 7.65 (AA′BB′ system, 4H), 7.62−7.50 (m, 2H), 7.39 and 7.22 (AA′BB′ system, 4H), 4.04 (dd, J = 3.1 and 11.8 Hz, 1H), 3.93−3.81 (m, 1H), 2.39 (s, 3H), 1.90 (dd, J = 3.1 and 9.8 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR: δ 143.3, 142.7, 141.7, 141.5, 137.3, 131.6, 130.2, 129.9 (2C), 129.8 (q, ^2J = 32.3 Hz, *C*-CF_3), 129.1 (2C), 128.7, 127.8, 127.2 (q, ^1J = 272.0 Hz, CF_3), 126.5 (2C), 125.7 [q, ^3J = 3.9 Hz, (*C*H)$_2$C−CF_3], 120.7, 62.5, 49.9, 30.2, 21.4; MS (FAB$^+$) m/z 443 (M + H)$^+$; HRMS (FAB$^+$) calcd for $C_{24}H_{22}F_3N_2OS$ (M + H)$^+$: 443.1405; found: 443.1397.

[2*S*,(S)*S*]-2-[(4-Methoxybenzyl)amino]-2-{2-[(4-methylphenyl)-sulfinyl]phenyl}propanenitrile (30). Amino nitriles **14** + **14′** were used as the starting material. Iodomethane was used as the electrophile, and the reaction was stirred at −78 °C for 1 h to give compound [2*S*,(S)*S*]-**30**, which was purified by flash column chromatography (EtOAc/hexane, 1:3). Yield: 56%; yellow oil; $[\alpha]^{20}_D$ −74.5 (*c* 1.5, $CHCl_3$); IR (film): 2228, 1514, 1303, 1014, 760 cm^{-1}; ^{1}H NMR: δ 8.28 (dd, J = 1.6 and 7.8 Hz, 1H), 7.79 (dd, J = 1.5 and 7.7 Hz, 1H), 7.62 (td, J = 1.4 and 7.4 Hz, 1H), 7.54 (td, J = 1.5 and 7.5 Hz, 1H), 7.49 and 7.17 (AA′BB′ system, 4H), 7.37 and 6.93 (AA′BB′ system, 4H), 3.93−3.86 (m, 1H), 3.82 (s, 3H), 3.81−3.72 (m, 1H), 2,34 (s, 3H), 1.80 (d, J = 9.6 Hz, 1H), 1.32 (s, 3H); ^{13}C NMR: δ 159.2, 143.4, 142.8, 141.5, 137.3, 131.3, 130.2 (2C), 130.0, 129.9, 129.8 (2C), 127.9, 127.7, 127.0 (2C), 121.0, 114.2 (2C), 62.4, 55.3, 49.9, 30.0, 21.4; MS (FAB$^+$) m/z 405 (M + H)$^+$; HRMS (FAB$^+$) calcd for $C_{24}H_{25}N_2O_2S$ (M + H)$^+$: 405.1643; found: 405.1636.

***N*-((*E*,*S*)-1-{2-[(4-Methylphenyl)sulfinyl]phenyl}ethylidene)-1-phenylmethanamine (27).** Amino nitriles **12** + **12′** were used as the starting material. Iodomethane was used as the electrophile, and the reaction was stirred at −78 °C for 1 h to give compound **27** as a byproduct. It was purified in an automated flash chromatography (5:95 to 100:0 EtOAc/hexane gradient). Yield: 15%; white solid; mp 86−88 °C; $[\alpha]^{20}_D$ −113.6 (*c* 1.0, $CHCl_3$); IR (KBr): 2401, 1642, 1494, 1216, 1020, 770 cm^{-1}; ^{1}H NMR: δ 8.35 (d, J = 7.4 Hz, 1H), 7.70−7.62 (m, 2H), 7.59−7.50 (m, 1H), 7.34−7.17 (m, 5H), 7.28 and 7.04 (AA′BB′ system, 4H), 4.70 and 4.60 (AB system, J = 7.4 Hz, 2H), 2.28 (s, 3H), 2.23 (s, 3H); ^{13}C NMR: δ 164.3, 145.3, 144.9, 140.0, 139.4, 138.9, 130.1, 130.0, 129.3 (2C), 128.3 (2C), 128.0 (2C), 127.6, 126.7, 126.4, 126.1 (2C), 55.5, 21.2, 16.5; MS (FAB$^+$) m/z 348 (M + H)$^+$; HRMS (FAB$^+$) calcd for $C_{22}H_{22}NOS$ (M + H)$^+$: 348.1422; found: 348.1419.

***N*-((*E*,*S*)-1-{2-[(4-Methylphenyl)sulfinyl]phenyl}ethylidene)-1-[4-(trifluoromethyl)phenyl]methanamine (29).** Amino nitriles **13** + **13′** were used as the starting material. Iodomethane was used as the electrophile, and the reaction was stirred at −78 °C for 1 h to give compound **29** as a byproduct, which was purified by flash column chromatography (EtOAc/hexane, 1:3). Yield: 10%; yellow oil; $[\alpha]^{20}_D$ −93.7 (*c* 0.8, $CHCl_3$); IR (KBr): 1679, 1325, 1126, 1019, 759 cm^{-1}; ^{1}H NMR: δ 8.33 (d, J = 7.44 Hz, 1H), 7.96−7.83 (m, 2H), 7.65 and 6.99 (AA′BB′ system, 4H), 7.60−7.51 (m, 2H), 7.47 and 6.21 (AA′BB′ system, 4H), 4.72 and 4.60 (AB system, J = 16.3 Hz, 2H), 2.27 (s, 3H), 2.26 (s, 3H); ^{13}C NMR: δ 165.0, 145.2, 144.7, 140.1, 139.3, 130.4, 130.2, 129.3 (q, ^2J = 31.3 Hz, *C*-CF_3), 129.2 (2C), 128.2 (2C), 127.7, 126.7, 126.1 (2C), 125.2 [q, ^3J = 3.3 Hz, (*C*H)$_2$C−CF_3], 124.5 (q, ^1J = 271.1 Hz, CF_3), 55.1, 21.1, 16.7; MS (FAB$^+$) m/z 416 (M + H)$^+$; HRMS (FAB$^+$) calcd for $C_{23}H_{21}NOF_3S$ (M + H)$^+$: 416.1295; found: 416.1311.

1-(4-Methoxyphenyl)-*N*-((*E*,*S*)-1-{2-[(4-methylphenyl)sulfinyl]-phenyl}ethylidene)methanamine (31). Amino nitriles **14** + **14′** were used as the starting material. Iodomethane was used as the electrophile, and the reaction was stirred at −78 °C for 1 h to give compound **31** as a byproduct, which was purified by flash column chromatography (EtOAc/hexane, 1:3). Yield: 27%; yellow oil; $[\alpha]^{20}_D$ −137.1 (*c* 0.7, $CHCl_3$); IR (film): 1511, 1248, 1027, 760 cm^{-1}; ^{1}H NMR: δ 8.37−8.32 (m, 1H), 7.68−7.58 (m, 2H), 7.56−7.47 (m, 1H), 7.29 and 7.02 (AA′BB′ system, 4H), 7.11 and 6.79 (AA′BB′ system, 4H), 4.64 and 4.53 (AB system, J = 14.8 Hz, 2H), 3.79 (s, 3H), 2.28 (s, 3H), 2.20 (s, 3H); ^{13}C NMR: δ 163.8, 158.4, 145.2, 144.9, 139.9, 139.4, 131.1, 130.0, 129.9, 129.2 (2C), 129.1 (2C), 127.6, 126.3, 126.1 (2C), 113.7 (2C), 55.2, 54.8, 21.2, 16.3; MS (FAB$^+$) m/z 378 (M + H)$^+$; HRMS (FAB$^+$) calcd for $C_{23}H_{24}NO_2S$ (M + H)$^+$: 378.1528; found: 378.1544.

2-Methyl-*N*-((*E*,*S*)-1-{2-[(4-methylphenyl)sulfinyl]phenyl}-ethylidene)propan-1-amine (33). Amino nitriles **15** + **15′** were used as the starting material. Iodomethane was used as the electrophile, and the reaction was stirred at −78 °C for 1 h to give compound **33** as a byproduct, which was purified by flash column chromatography (EtOAc/hexane, 1:2). Yield: 56%; yellow oil; $[\alpha]^{20}_D$ −89.9 (*c* 1.4, $CHCl_3$); IR (film): 1640, 1026, 763 cm^{-1}; ^{1}H NMR: δ 8.21 (dd, J = 1.7 and 6.8 Hz, 1H), 7.62−7.51 (m, 3H), 7.48 and 7.14 (AA′BB′ system, 4H), 3.23 (m, 2H), 2.32 (s, 3H), 2.16 (s, 3H), 1.92 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR: δ 162.8, 145.3, 145.1, 140.0, 139.9, 130.0,

129.9, 129.2 (2C), 127.3, 126.3, 126.0 (2C), 60.2, 29.6, 21.2, 21.1, 21.0, 16.3; MS (FAB$^+$) *m*/*z* 314 (M + H)$^+$; HRMS (FAB$^+$) calcd for $C_{19}H_{24}NOS$ (M + H)$^+$: 314.1528; found: 314.1563.

Acknowledgment. We thank CAICYT (Grant BQU2003-04012) and UAM-CM (Grant CCG06-UAM/PPQ-0275) for financial support. F.T. thanks Comunidad Autónoma de Madrid for a predoctoral fellowship. We also thank the Centro de Computación Científica (UAM) for computation time and Dr. M. Alcamí (UAM) for helpful discussions.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for imines **2**−**10**, α-amino nitriles **11**−**17** + **11′**−**17′**, quaternization products **22**−**26**, **28** and **30** and retrohydrocyanation ketimines **27**, **29**, **31**, and **33**. X-Ray crystal structures for **13′**, **17**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0705519