Additions of Enantiopure α-Sulfinyl Carbanions to (*S*)-*N*-Sulfinimines: Asymmetric Synthesis of *β*-Amino Sulfoxides and *β*-Amino Alcohols

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The addition of the lithium anions derived from (*R*)- and (*S*)-methyl and -ethyl *p*-tolyl sulfoxides to (*S*)-*N*-benzylidene-*p*-toluenesulfinamide provides an easy access route to enantiomerically pure *β*-(*N*-sulfinyl)amino sulfoxides. Stereoselectivity can be achieved when the configurations at the sulfur atoms of the two reagents are opposite (matched pair), thus resulting in only one diastereoisomer, even for the case in which two new chiral centers are created. The *N*-sulfinyl group primarily controls the configuration of the carbon bonded to the nitrogen, whereas the configuration of the α-sulfinyl carbanion seems to be responsible for the level of asymmetric induction, as well as for the configuration of the new stereogenic C−SO carbon in the reactions with ethyl *p*-tolyl sulfoxides. An efficient method for transforming the obtained *β*-(*N*-sulfinyl)amino sulfoxides into optically pure *β*-amino alcohols, based on the stereoselective non-oxidative Pummerer reaction, is also reported.

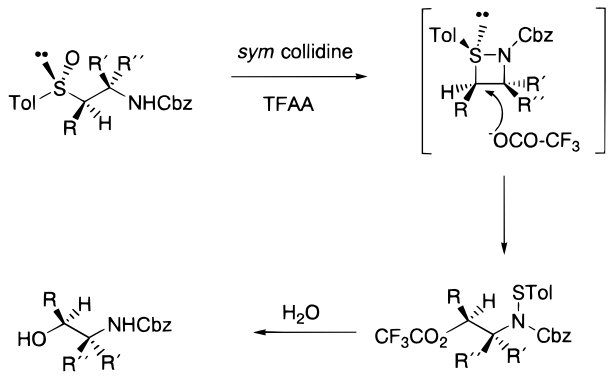
Introduction

The importance of enantiomerically pure *β*-amino alcohols as chiral auxiliaries in asymmetric synthesis[1] or as ligands in asymmetric catalysis[2] is currently well recognized, and thus, the search for new methods for the asymmetric synthesis of these compounds is highly interesting. Bravo et al.[3] have recently reported that certain fluorine-containing *β*-amino sulfoxides submitted to Pummerer conditions (TFAA, *sym*-collidine) are converted into the *β*-amino alcohols (Scheme 1) in high optical purity, thereby showing the utility of amino sulfoxides as chiral targets.

To extend this methodology as a general procedure for the asymmetric synthesis of *β*-amino alcohols, it is necessary to have an efficient method for preparing enantiomerically pure *β*-amino sulfoxides, as well as for determining whether the conditions reported by Bravo et al. can be utilized with substrates lacking fluoroalkyl substituents. Both questions have been investigated, and the results are reported in this paper.

The nucleophilic addition of organometallic reagents to the C=N double bond of imines[4] provides an attractive route to chiral amine derivatives. The sulfoxides have proven to be efficient chiral auxiliaries when bonded to either a nucleophile or an electrophile. Thus, the reaction of achiral imines with enantiomerically pure α-sulfinyl carbanions[5] allows the asymmetric synthesis of *β*-amino sulfoxides with moderate to high diastereomeric excess. Diastereoselectivities range between 14 and 84% depending on factors such as the nature of the imine, the substituent at the sulfur, and, particularly, the reaction conditions (kinetically or thermodynamically controlled). The best results were obtained in the reactions of lithiomethyl *p*-tolyl sulfoxide with fluoroalkyl aldimines,[3b]

Scheme 1



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which proceeded with 84−88% *de* (diastereomeric excess). Reactions with ketimines were much less satisfactory.[6]

Low reactivity and poor stereoselectivity, usually associated with the use of enantiopure imines, can be substantially improved by using enantiopure *N*-sulfinylimines.[7] Stereoselectivity of these reactions is high in a few cases. Thus, the reaction of (*S*)-*N*-benzylidene-*p*-toluenesulfinamide (**1**) with the lithium enolates of methyl acetate provided high *de* (72−80%),[8,9] which could be increased by adding HMPA[10] (96% *de*) or by using the sodium enolates in THF (>98% *de*).[10] Nevertheless, even in these last optimal conditions, (*R*)-*N*-(3-pyridylmethylidene)-*p*-toluenesulfinamide provides lower stereoselectivity (76% *de*).[11] The additions of phosphites,[12] α-phosphonate carbanions,[13] and sulfonium or oxosulfonium ylides[14] to *N*-sulfinimines take place with *de*'s ranging between 70 and 97%, depending on the substrate. Finally, the addition of Grignard reagents to *N*-sulfinimines and *N*-sulfenimines derived from camphor[15] gives high *de* only in the cases of allylmagnesium bromide and *tert*-butylmagnesium bromide. Similar results were reported by Hua.[16] All of these results suggest a high efficiency of the sulfinamidic sulfur configuration in controlling the stereoselectivity of the addition of carbon nucleophiles.

The evolution of reactions with the simultaneous formation of two new chiral centers, as a consequence of the prochirality of the carbon nucleophile, has not been extensively explored. To our knowledge, only reactions of the enantiopure benzyl *p*-tolyl sulfoxide with achiral fluoroalkyl aldimines have been reported.[3b] These reactions are not highly stereoselective and give a mixture of the four possible diastereoisomers. By contrast, the behavior of enantiopure sulfinimines with enolates derived from α-substituted esters, as well as that of enantiopure alkyl sulfoxides (*p*-Tol-SO-R, R ≠ Me) with imines, has not been reported.[17] In a recent paper,[18] we reported that reactions of the *N*-benzylidene-*p*-toluenesulfinamide **1** with ethyl butanoate anion yielded significant amounts of the four possible diastereoisomers.

Scheme 2

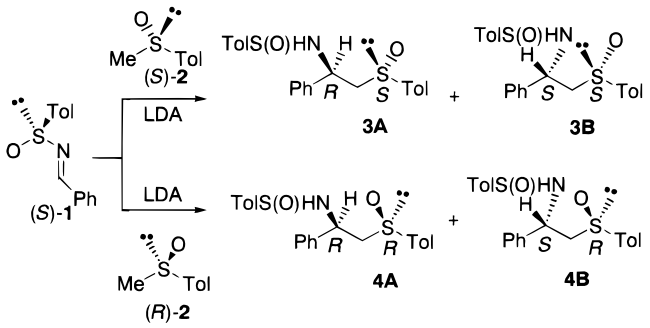

Table 1. Reaction of (*S*)-1 with (*R*)- and (*S*)-Methyl *p*-Tolyl Sulfoxide, 2

entry	sulfoxide	*T* (°C)	products (relative ratio, %)	*de*	yield (%)
1	(*S*)-**2**	−78	**3A** (90) + **3B** (10)	80	96
2	(*S*)-**2**	0	**3A** (83) + **3B** (17)	66	97
3	(*R*)-**2**	−78	**4A**	>98	99
4	(*R*)-**2**	0	**4A** (90) + **4B** (10)	80	98

To control the stereoselectivity of these reactions and, thus, achieve good stereoselectivity in the generation of two new chiral centers, we decided to evaluate the influence of incorporating the sulfinyl group in both the electrophile and nucleophile. The additions of α-sulfinyl carbanions derived from (*R*)- and (*S*)-methyl and -ethyl *p*-tolyl sulfoxide, (*R*)-**2**, (*S*)-**2**, (*R*)-**5**, and (*S*)-**5**, to (*S*)-*N*-benzylidene-*p*-toluenesulfinamide, **1**, are reported in this paper. Because inherent diastereofacial preferences of chiral sulfoxide anions and *N*-sulfinylimines may reinforce or oppose one another in the crossed condensation (matched or mismatched pair), this study should provide the proper combination (matched pair) for obtaining optically pure β-(*N*-sulfinyl)amino sulfoxides.

Results and Discussion

Products formed in the reaction of *N*-sulfinylimine (*S*)-**1**, easily prepared by the Davis method,[14a] with both enantiomers of methyl *p*-tolyl sulfoxide, **2** (Scheme 2), are shown in Table 1. Reaction with (*S*)-**2** at −78 °C yielded a 90:10 mixture of the two possible diastereoisomers **3A** and **3B** (entry 1), whereas reaction with (*R*)-**2**, under identical conditions, only afforded **4A** (entry 3). When the temperature was increased to 0 °C, the stereoselectivity of both reactions eroded (compare entries 2 and 4 with entries 1 and 3, respectively). At 0 °C, the reactions were instantaneous, but a rapid decomposition of the products was observed. To avoid this problem, the reactions were immediately quenched once the addition of the anion had finished. In this way, yields were almost quantitative in all cases. Configuration assignments of the obtained β-amino sulfoxides were made by ^{1}H NMR.

Diastereoisomers **3A** and **4A**, the major products in these reactions, have identical configurations at the new stereogenic carbons (*R* in both cases), despite the opposite configuration of the sulfoxide used as the nucleophile in each case. This fact reveals that the stereoselectivity is primarily controlled by the sulfur configuration of the starting electrophilic sulfinamide **1**. However, the results are rather surprising because the induced configuration

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(17) Reactions of racemic benzyl *tert*-butyl sulfoxide with several *N*-phenylimines are highly stereoselective (see ref 6e). A similar behavior was observed in the synthesis of aziridines from racemic α-halosulfoxides and imines (Satoh, T.; Oohara, T.; Yamakawa, K. *Tetrahedron Lett*. **1988**, *29*, 4093). Racemic fluoromethyl phenyl sulfoxide reacts with *N*-phenyl arylimines with moderate to very high selectivity, depending on the nature of the aryl group (Mahidol, C.; Reutrakul, V.; Prapansiri, V.; Panyanchotipun, C. *Chem. Lett*. **1984**, 969).
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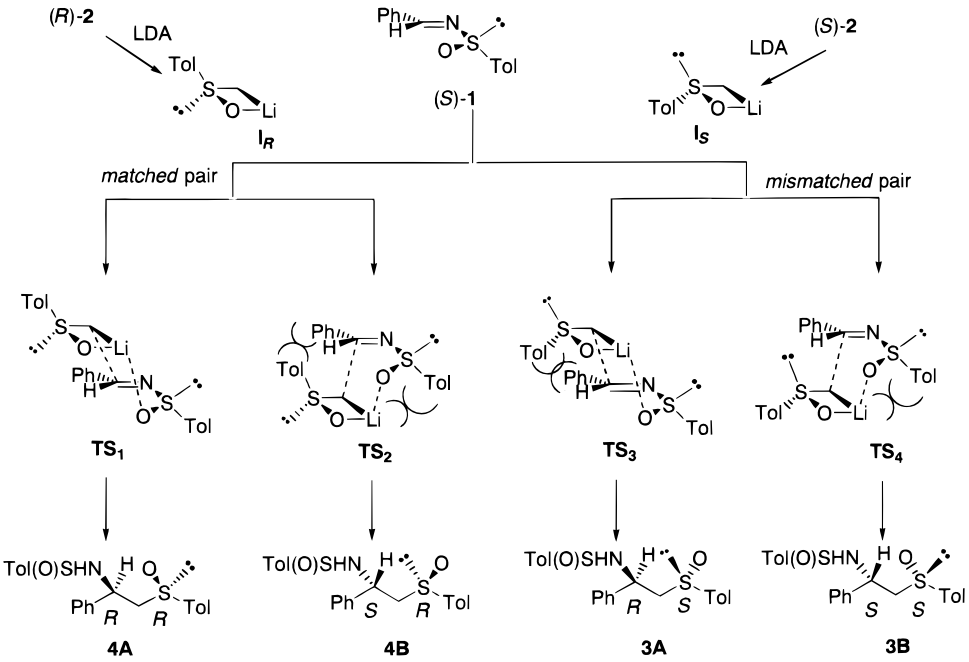


Figure 1. Reaction of (*S*)-**1** with (*R*)-**2** and (*S*)-**2** lithium derivatives.

is the opposite of that obtained in reactions of **1** with ester enolates[8,9] and other nucleophiles.[10−14] Therefore, the reactions of compound (*S*)-**1** with the sulfinyl carbanions derived from (*R*)-**2** and (*S*)-**2** must proceed through a stereochemical course different from that proposed for the other reactions. The chelating ability of the lithium cation could play an essential role in controlling product stereochemistry. This result is just the opposite of that found in reactions of (*S*)-**1** with the lithium enolate derived from ethyl acetate.[10]

We postulate that the α-sulfinyl carbanion acting as the nucleophile could be stabilized by lithium because of the presence of the sulfinyl oxygen, which allows the formation of species such as $\mathbf{I_R}$ and $\mathbf{I_S}$ (Figure 1). The association of the sulfinyl oxygen of the substrate (*S*)-**1** with the lithium of the reagents **I** would yield species able to suffer intramolecular nucleophilic attack of the α-sulfinyl carbanion on the C=N bond. Taking into account that this attack must take place from the plane normal to that defined by the Ph−C=N−S grouping (which contains the C=N bond), only the s-cis arrangement of the *N*-sulfinyl oxygen is able to fix the attacking carbanion at the suitable position, which will be the position that is forming an angle close to 104° with the C=N bond, as is required for C=O groups.

In the case of the matched pair [(*S*)-sulfinamide/(*R*)-sulfoxide], $\mathbf{TS_1}$ is clearly favored with respect to $\mathbf{TS_2}$ (Figure 1), because the steric interactions of the two sulfinyl groups destabilize the latter. This would justify the high or complete stereoselectivity observed in these reactions, with a favored attack of the (*R*)-sulfoxide from the upper *Si* face of the imine. In contrast, stability differences between the two possible transition states $\mathbf{TS_3}$ and $\mathbf{TS_4}$ for the mismatched pair [(*S*)-sulfinamide/(*S*)-sulfoxide] must be significantly lower. The approach from the *Si* face will be destabilized by the steric repulsion between the phenyl group of the substrate and the *p*-tolyl group of the reagent, whereas the attack from the *Re* face will be hindered by the orientation of the *p*-tolyl group at the substrate (Figure 1). The fact that the major isomer obtained in the reaction of the mismatched pair has the *R* configuration at the carbon indicates that the favored approach takes place from the *Si* face, and, therefore, $\mathbf{TS_3}$ must be more stable than $\mathbf{TS_4}$ (Figure 1).[19]

The results obtained in the reaction of (*S*)-**1** with (*R*)- and (*S*)-ethyl *p*-tolyl sulfoxide, **5** (Scheme 3), are shown in Table 2.[20] The reactions occurred in 15 min at −78 °C, and very high yields were obtained in all of the conditions used. The addition of (*S*)-**5** to (*S*)-**1** yielded a diastereoisomeric mixture containing three compounds, **6A**, **6B**, and **6C** (entries 1 and 2), in different ratios depending on the temperature. Starting from (*R*)-**5**, only **7A** was obtained when the reaction took place at 0 °C (entry 4), but a mixture of three diastereoisomers, **7A**, **7B**, and **7D**, could be detected at −78 °C (entry 3). Configurational assignments of compounds **6** and **7** were made by ^{1}H NMR and chemical correlation (as described below). These results indicate that the matched pair is formed by the reaction of the (*R*)-sulfoxide, (*R*)-**5**, and the (*S*)-sulfinylimine, (*S*)-**1**, which yields only one diastereoisomer, **7A**, in the optimal reaction conditions. Surprisingly, the stereoselectivity of the reactions with both enantiomers of compound **5** decreases when the temperature is lowered (compare entries 2 and 4 with entries 1 and 3, respectively), and the most favorable product

(19) The interaction Tol/Ph, depicted in Figure 1 for $\mathbf{TS_3}$, seems to be stronger than the interaction Tol/Li, depicted for $\mathbf{TS_4}$, thus suggesting the lower stability of $\mathbf{TS_3}$. Nevertheless, we must take into account that these reactions must be strongly exothermic. Thus, according to the Hammond postulate, one must expect a reactant-like transition state, involving a greater distance for the incipient new C−C bond and thus resulting in a weaker repulsive interaction (Ph/Tol) because of the long distance between the two groups.

(20) The behavior of ethyl *p*-tolyl sulfoxides, **5**, was first studied on the achiral *N*-phenylbenzylidene imine. The reaction of this imine with (*R*)-**5** yielded a mixture containing significant amounts of the four possible diastereoisomeric β-amino sulfoxides. This result contrasted with that obtained for the reaction of (*R*)-**2** with the same imine, which proceeded in an almost completely stereoselective manner (96% *de*)[5] and which evidenced a strong decrease in the stereoselectivity of reactions of achiral imines with alkyl *p*-tolyl sulfoxides.

Scheme 3

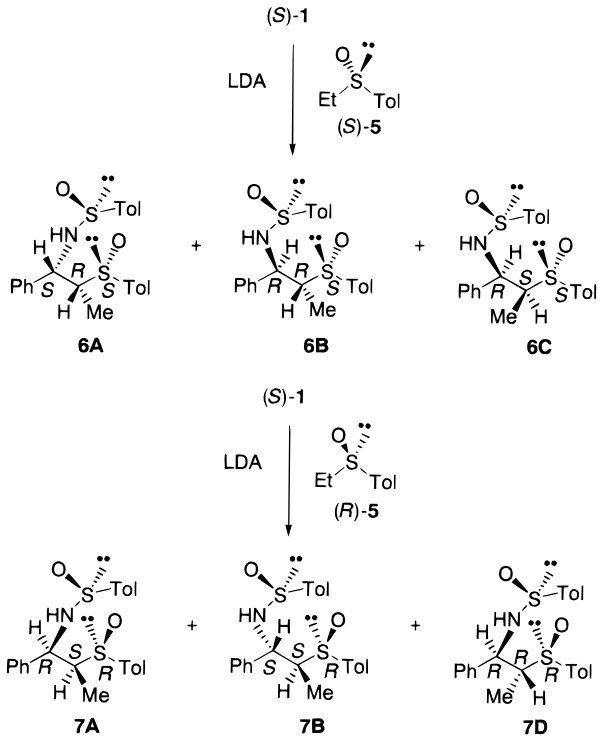


Table 2. Reaction of (*S*)-1 with (*R*)- and (*S*)-Ethyl *p*-Tolyl Sulfoxide, 5

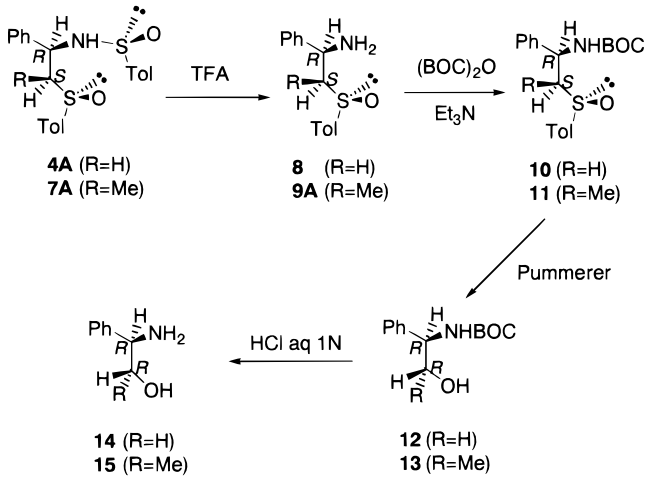
entry	sulfoxide	*T* (°C)	products (relative ratio, %)	yield (%)
1	(*S*)-**5**	−78	**6A** (35) + **6B** (57) + **6C** (8)	91
2	(*S*)-**5**	0	**6A** (25) + **6B** (63) + **6C** (12)	89
3	(*R*)-**5**	−78	**7A** (89) + **7B** (3) + **7D** (8)	80
4	(*R*)-**5**	0	**7A**	97

diastereoselection was observed under equilibrium-controlled conditions. Additionally, when the reaction of (*R*)-**5** with (*S*)-**1** was initiated at −78 °C and then the mixture was allowed to warm to 0 °C, only **7A** was detected.

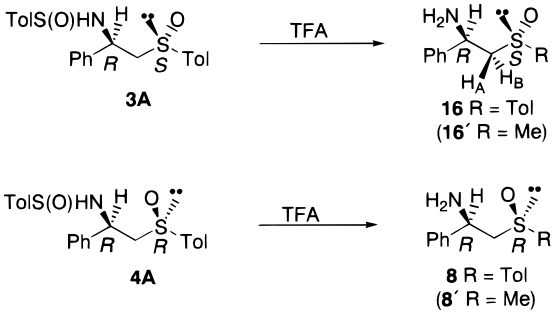
These stereochemical results suggest that the reaction is thermodynamically controlled and that **7A** is the thermodynamically more stable product. The precise reason for the thermodynamic preference of **7A** over the other diastereomers, however, is not clear.

Once the conditions for obtaining *β*-amino sulfoxides with almost complete control of the stereoselectivity were known, it was necessary to investigate the ability of the obtained substrates to be transformed into *β*-amino alcohols. In a first trial, compounds **4A** and **7A** were treated with TFA and *sym*-collidine to determine whether the NH-SOTol group could be transformed, as reported by Bravo et al. for the corresponding carbamates,[3] via a stereoselective non-oxidative Pummerer reaction. Unfortunately, the reaction gave a complex mixture of compounds, suggesting that the *N*-sulfinyl group was not stable to TFA. Therefore, compounds **4A** and **7A** were first *N*-desulfinylated, by TFA hydrolysis, to afford compounds **8** and **9**, respectively, and then the amino group was reprotected as N-BOC, yielding **10** and **11**, respectively. These compounds were transformed into the corresponding hydroxycarbamates, **12** and **13**, respectively, by reaction with TFA and *sym*-collidine (Scheme 4). The deprotection of the *N*-*tert*-butoxycarbonyl group

Scheme 4



Scheme 5



of these compounds, followed by the treatment of the resulting ammonium salts with Dowex resin, afforded the optically pure (*R*)-2-amino-2-phenylethanol, **14**,[21] and (1*R*,2*R*)-1-amino-1-phenyl-2-propanol, **15**.[22] Two conclusions can be drawn from these results. The first is that the conditions reported by Bravo et al.[3] for converting *β*-amino sulfoxides, bearing fluoralkyl substituents, to their corresponding *β*-amino alcohols can be successfully applied to alkyl derivatives and, therefore, that the presence of fluoroalkyl substituents is not strictly required. These reactions take place with complete inversion of the configuration at the carbon supporting the sulfinyl group, yielding optically pure *β*-amino alcohols. The second conclusion concerns the configurational assignment of compound **7A**. The chemical transformation depicted in Scheme 4, connecting compound **7A** with (1*R*,2*R*)-1-amino-1-phenyl-2-propanol, **15**, unequivocally demonstrates that the starting aminosulfinyl derivative must have a 1*R*,2*S* configuration at its chiral carbons, as was also evidenced by its coupling constant values (as discussed below).

Configurational Assignments. The configurational assignments of **3A** and **4A**, epimers at sulfur because they were obtained as major components in reactions of (*S*)-**1** with (*S*)-**2** and (*R*)-**2**, respectively, were established as follows. The TFA hydrolysis of their *N*-sulfinyl moieties yielded the corresponding free amines **16** and **8**, respectively (Scheme 5). The ^{1}H NMR study of these compounds revealed substantial differences between them, primarily related to the relative values of their

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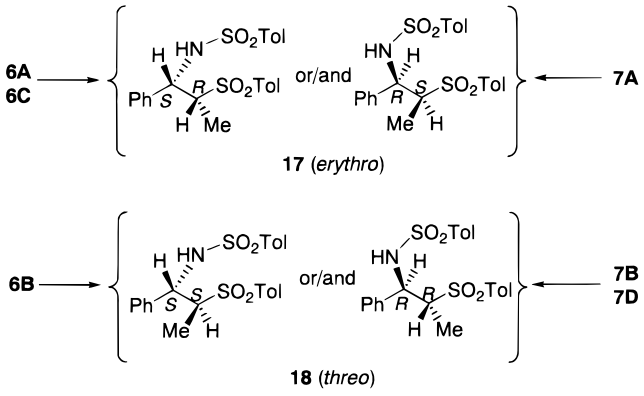
Table 3. ^{1}H NMR Parameters of 16 and 8 and Their *S*-Methyl Analogues 16′ and 8′ (Scheme 5)

compd	solvent	J_{AX} (Hz)	J_{BX} (Hz)	δ_A (ppm)	δ_B (ppm)	δ_X (ppm)
16 (**16′**)[a]	$CDCl_3$	8.4 (8.0)	4.9 (5.9)	3.15 (3.12)	2.86 (2.87)	4.52 (4.51)
	DMSO-d_6	7.4 (7.6)	6.8 (6.5)	3.10 (3.01)	2.95 (2.95)	4.15 (4.25)
8 (**8′**)[a]	$CDCl_3$	9.2 (10.5)	4.1 (3.3)	3.02 (2.97)	2.94 (2.92)	4.52 (4.59)
	DMSO-d_6	10.5 (10.8)	3.3 (3.3)	3.15 (2.99)	2.82 (2.81)	4.25 (4.21)

[a] Data from ref 24.

Scheme 6



vicinal coupling constants in different solvents (Table 3). Similar differences had allowed for the configurational assignment of diastereomeric sulfoxides **16′** and **8′**, Ph−CH(NH_2)−CH_2−SOMe,[23] which differ from **16** and **8** only in the nature of the group joined to sulfur (methyl instead *p*-tolyl). A comparison of the ^{1}H NMR parameters of both pairs of compounds (Table 3) allowed us to unambiguously assign the relative configurations of **16** and **8**. The latter would have identical configurations at its two chiral centers (*RR* or *SS*), whereas the former must have opposite configurations (*RS* or *SR*). As the configurations at the sulfinyl sulfur of **3A** and **4A** were known to be *S* and *R*, respectively, the absolute configuration of all of these compounds could be assigned as indicated in Table 3.

The configurational assignment of the different diastereoisomers of **6** and **7** was deduced from the following facts. The mixtures obtained under the conditions of entries 2 and 3 of Table 2 were oxidized into the corresponding *N*-sulfonyl sulfones (Scheme 6). Treatment of the mixture **6A** + **6B** + **6C** (25:63:12) with MCPBA yielded a new mixture of only two sulfones, **17** and **18** (36:64). The relative proportion of the latter suggests that **6A** and **6C** have been transformed into enantiomeric *N*-sulfonyl sulfones **17** (with identical ^{1}H NMR spectra), whereas the major component, **6B**, has produced **18**. Oxidation of the mixture **7A** + **7B** + **7D** (89:3:8) (entry 3, Table 3) with MCPBA yielded a mixture of the same sulfones **17** and **18** (89:11) (Scheme 6). This suggests that the relative configuration of the chiral carbons of **7A** must be correlated with that of **17**, and similarly for **7B** and **7C** with **18**.

The ^{1}H NMR study of compounds **17** and **18** reveals very different values for their vicinal coupling constants $^3J_{CH,CH}$ (2.9 Hz for **17** and 8.6 Hz for **18**). To our knowledge, the conformational behavior of *β*-amino sulfoxides and *β*-amino sulfones with a 1-phenyl-2-methylethane skeleton has never been studied. However, similarly functionalized substrates with 1-phenylethane skeletons have proved to exhibit a behavior very similar to that of their corresponding oxygenated compounds.[24] In this sense, different series of *erythro* and *threo* *β*-oxygenated sulfones derived from 1,2-diphenyl- and 1,2-dimethylethane had been studied in detail.[25] Such a study demonstrated that *erythro* compounds exhibited a low ^3J value (<4 Hz), whereas the *threo* compounds showed clearly higher values of such constants (^3J > 8 Hz). By assuming that this behavior would be similar for the nitrogenated compounds **17** and **18**, we could assign the *erythro* configuration (*RS* or *SR*) to **17** ($^3J_{CH,CH}$ = 2.9 Hz) and the *threo* configuration (*RR* or *SS*) to **18** ($^3J_{CH,CH}$ = 8.6 Hz). On the basis of Scheme 6, we can deduce that sulfoxides **6A**, **6C**, and **7A** have opposite configurations at their chiral carbons (*RS* or *SR*), whereas **6B**, **7B**, and **7D** have identical configurations there (*RR* or *SS*).

The TFA hydrolysis of the *N*-sulfinyl groups of the diastereoisomeric mixtures of **6** and **7**, obtained according to entries 1 and 3 of Table 2, afforded diastereoisomeric mixtures of amino sulfoxides **19** and **9**, respectively, which are identical in composition to the starting *N*-sulfinyl derivatives (Scheme 7). The ^{1}H NMR spectra of compounds **19A** and **19B** are respectively identical to those of **9A** and **9B** (which is only possible if they are enantiomers, because compounds **19** and **9** have different configurations at the sulfur), but those of **19C** and **9D** are clearly different. Significant ^{1}H NMR parameters of all of these compounds, obtained from the spectra of the mixtures, are depicted in Scheme 7. A conformational study of the four possible *β*-oxygenated (OH, OR, and OAc) sulfoxides with 1,2-dimethyl- and 1,2-diphenylethane skeletons revealed that *erythro* and *threo* sulfoxides with different configurations at sulfur and C-*β* (the carbon supporting the oxygenated function) show, respectively, the lowest and highest $^3J_{CH,CH}$ values (see Figure 2). Moreover, these coupling constants were barely dependent on the solvent polarity,[26] thus contrasting with those of the *erythro* and *threo* sulfoxides with identical configurations at sulfur and C-*β*, which are substantially modified by the solvent. By assuming that our nitrogenated compounds **19** and **9** would exhibit a similar behavior, their configurational assignment could be easily completed, on the basis of their ^3J values, as indicated in Scheme 7, taking into account that they derive from (*S*)-**5** and (*R*)-**5**, respectively.

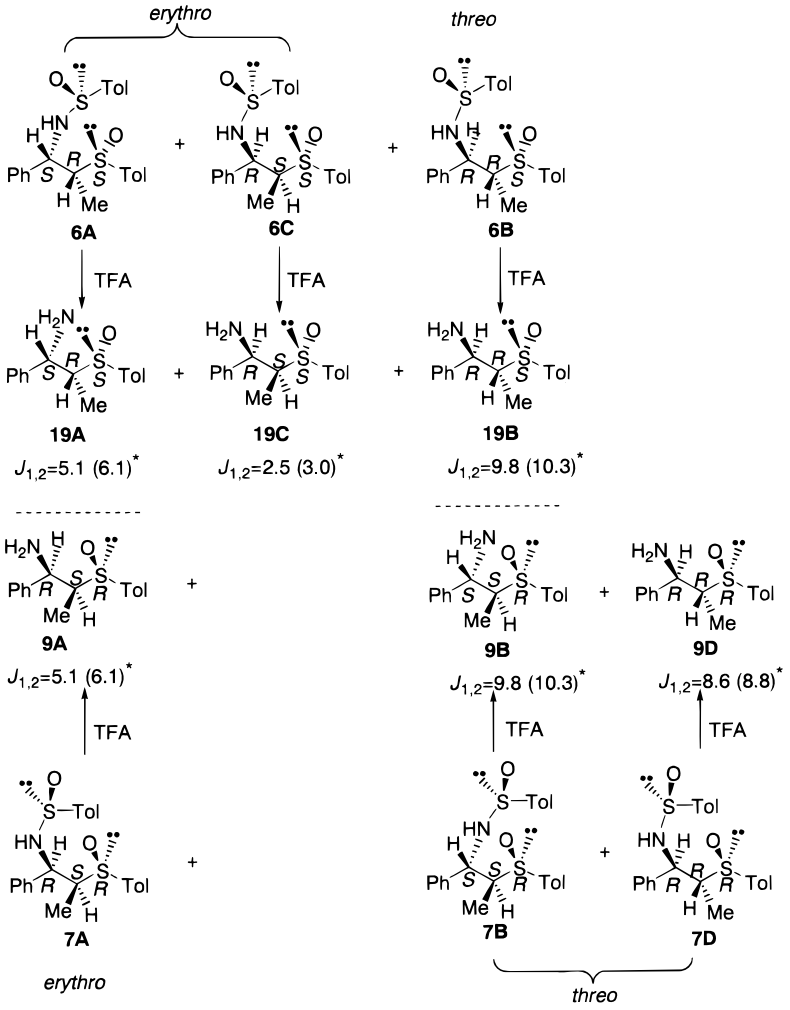
(23) Brunet, E.; Gallego, M. T.; García Ruano, J. L.; Alcudia, F. *Tetrahedron* **1986**, *42*, 1423.

(24) This similarity was established from a detailed conformational study of compounds Ph−CHX−CH_2−SO_nMe (n = 1 or 2). A comparison of the oxygenated series with X = OH and OMe (Alcudia, F.; Brunet, E.; García Ruano, J. L.; Hoyos, M. A.; Prados, P.; Rodríguez, J. H. *Org. Magn. Reson.* **1983**, *21*, 643) with the corresponding nitrogenated series with X = NHPh, NH_2, and NR_2 (Alcudia, F.; Brunet, E.; Carreño, M. C.; Gallego, M.; García Ruano, J. L. *J. Chem. Soc., Perkin Trans. 2* **1983**, 937) showed that the interactions controlling the conformational behavior were similar in both series.

(25) Carretero, J. C.; García Ruano, J. L.; Martínez, M. C.; Rodríguez, J. H. *Tetrahedron* **1985**, *41*, 2419.

(26)) A detailed discusion of the conformational behavior of these substrates appears in ref 25.

Scheme 7[a]



[a] ^{1}H NMR coupling constants in $CDCl_3$ and DMSO-d_6 (in parentheses).

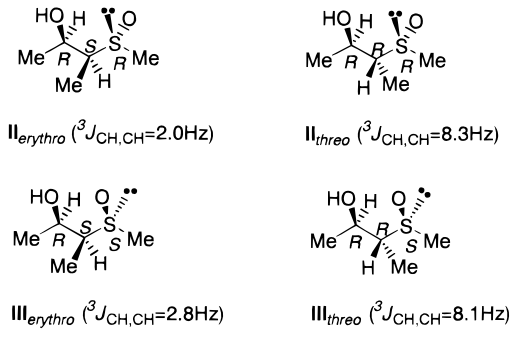


Figure 2. Coupling constants ($^3J_{CH,CH}$) of the *erythro* and *threo* sulfoxides used as models for the configurational assignment of the nitrogenated compound **9** and **19**.

Conclusion

In summary, we have developed a practical and efficient synthesis of enantiomerically pure *β*-amino alcohols from enantiopure *N*-sulfinylimines. The key steps are the asymmetric addition of enantiopure alkyl *p*-tolyl sulfoxide anions to compound (*S*)-**1** and the stereospecific non-oxidative Pummerer reaction of the resulting *β*-amino sulfoxide. The first reaction is a double asymmetric induction process, with the couple (*R*)-sulfoxide/(*S*)-sulfinimine as the matched pair, which occurs with almost quantitative yield and a very high control of the stereoselectivity in all of the new stereogenic centers. It emerges as one of the best methods for obtaining enantiomerically pure *β*-amino sulfoxides. The accessibility of the chiral reagents and the crystallinity of many of the starting materials and products make the reported procedure amenable to large-scale processes.

Experimental Section

Addition of Enantiopure Alkyl *p*-Tolyl Sulfoxide Anions to *N*-Sulfinylimines. General Procedure. To a solution of diisopropylamine (3.43 mL, 24.3 mmol) in dry THF (100 mL) at −78 °C under argon was added a 2.4 M solution of butyllithium in hexane (10.12 mL, 24.3 mmol). After 20 min, a solution of the alkyl sulfoxide (24.3 mmol) in THF (120 mL) was added dropwise. After the mixture was stirred for 30 min at −78 °C, a solution of (+)-(*S*)-(*E*)-*N*-benzylidene-*p*-toluenesulfinamide (**1**) (2.77 g, 12.1 mmol) in THF (160 mL) was added. After the reaction finished (15 min), a saturated aqueous NH_4Cl solution (50 mL) was added; the organic phase was extracted with ethyl acetate (3 × 200 mL), dried over anhydrous sodium sulfate, and evaporated in vacuo. The crude product was treated with hot ethyl *tert*-butyl ether (5 × 25 mL) to eliminate the excess sulfoxide, affording the corresponding *N*-(*β*-sulfinylalkyl)sulfinamide.

(*S*)-*N*-[(2*R*,*R*$_S$)-1-Phenyl-2-*p*-tolylsulfinylethyl]-*p*-toluenesulfinamide (4A). The product was obtained as a white crystalline solid from (*S*)-**1** and (*R*)-**2**: yield 98%; mp 161−

162 °C; $[\alpha]^{25}_D = +216.5$ (*c* 0.9, acetone); ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H), 2.37 (s, 3H), 3.23 (AB fragment of an ABX system, 2H, $J = 6.4$, 8.2, 13.2 Hz, $\Delta\nu = 82$ Hz), 4.93 (m, 1H), 5.26 (d, 1H, $J = 5.1$ Hz), 7.13−7.56 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 141.9, 141.2, 140.8, 140.5, 141.0, 130.0, 129.2, 128.7, 128.0, 127.0, 125.7, 124.1, 64.9, 53.1, 21.4, 21.2. Anal. Calcd for $C_{22}H_{23}NO_2S_2$: C, 66.46; H, 5.83; N, 3.52. Found: C, 66.37; H, 5.99; N, 3.51. HRMS calcd for $C_{22}H_{23}NO_2S_2$, 397.1170; found, 397.1166 (0.8 ppm).

(*S*)-*N*-[(1*R*,2*S*,*R*$_S$)-1-Phenyl-2-*p*-tolylsulfinylpropyl]-*p*-toluenesulfinamide (7A). The product was obtained as a white crystalline solid: yield 85%; mp 177−179 °C; $[\alpha]^{25}_D = +154.4$ (*c* 0.9, methanol); ^{1}H NMR ($CDCl_3$) δ 1.00 (d, 3H, $J = 6.7$ Hz), 2.32 (s, 6H), 2.36 (s, 1H), 3.12 (m, 1H), 4.53 (d, 1H, $J = 9.1$ Hz), 7.51−6.93 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 137.0, 136.9, 136.7, 134.9, 134.7, 125.4, 124.9, 124.1, 123.4, 122.7, 121.2, 120.0, 61.4, 54.1, 16.9, 16.8, 1.2. Anal. Calcd for $C_{23}H_{25}NO_2S_2$: C, 67.12; H, 6.12; N, 3.40. Found: C, 67.00; H, 6.24; N, 3.25.

Desulfinylation of *N*-(*β*-Sulfinylalkyl)sulfinamides. General Procedure. To a stirred solution of the *N*-(*β*-sulfinylalkyl)sulfinamide (12.4 mmol) in methanol (124 mL) was added TFA (4.7 mL, 61.8 mmol). After the mixture was stirred for 15 h at room temperature, the solvent was evaporated, CH_2Cl_2 (100 mL) was added, and the organic phase was extracted with a 10% HCl aqueous solution (3 × 150 mL). The aqueous phase was neutralized, at 0 °C, with solid Na_2CO_3 and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under vacuo to yield the free *β*-amino sulfoxide.

(1*R*,*R*$_S$)-1-Phenyl-2-*p*-tolylsulfinylethylamine (8). The product was obtained as a yellow powder from **4A**: yield 95%; mp 46−48 °C; $[\alpha]^{25}_D = +110.9$ (*c* 0.6, methanol); ^{1}H NMR ($CDCl_3$, D_2O) δ 2.36 (s, 3H), 3.00 (AB fragment of an ABX system, 2H, $J = 5.0$, 8.4, 13.0 Hz, $\Delta\nu = 58.0$ Hz), 4.5 (dd, 1H, $J = 5.0$, 8.4 Hz), 7.52−7.26 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 143.4, 141.2, 140.5, 129.6, 128.4, 127.4, 126.0, 123.6, 66.1, 52.5, 21.0. Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.60; N, 5.40. Found: C, 69.39; H, 6.62; N, 5.36. HRMS calcd for $C_{15}H_{17}NOS$, 259.1030; found, 259.1037 (−2.5 ppm).

(1*R*,2*S*,*R*$_S$)-1-Phenyl-2-*p*-tolylsulfinylpropylamine (9A). The product was obtained as a white crystalline solid from **7A**: yield 96%; mp 113−115 °C; $[\alpha]^{25}_D = +110.0$ (*c* 0.7, methanol); ^{1}H NMR ($CDCl_3$, D_2O) δ 1.02 (d, 3H, $J = 6.9$ Hz), 2.34 (s, 3H), 2.69 (dq, 1H, $J = 5.1$, 6.9 Hz), 4.50 (d, 1H, $J = 5.1$ Hz), 7.40−7.24 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 142.9, 140.9, 139.0, 129.6, 128.5, 127.5, 126.5, 124.1, 66.5, 56.6, 21.2, 4.1. Anal. Calcd for $C_{16}H_{19}NOS$: C, 70.29; H, 7.00; N, 5.12. Found: C, 70.31; H, 7.12; N, 5.20. HRMS calcd for $C_{16}H_{19}NOS$, 273.1187; found, 273.1192 (−1.9 ppm).

BOC Protection of *β*-Sulfinylamines. General Procedure. To a solution of the free *β*-amino sulfoxide (12 mmol) in acetonitrile (180 mL) and Et_3N (4.2 mL, 30 mmol) was added $(t\text{-BuOCO})_2O$ (3.4 g, 15.6 mmol). After the mixture was stirred for 15 h at room temperature (the mixture turned brown), the reaction was quenched with 10% HCl aqueous solution (20 mL), and the organic phase was extracted with ethyl acetate (4 × 100 mL). The organic layer was dried over Na_2SO_4, evaporated under vacuum, and purified by column chromatography on silica gel (ether/hexane, 2:1) to give the corresponding carbamate.

***tert*-Butyl *N*-[(1*R*,*R*$_S$)-1-Phenyl-2-*p*-tolylsulfinylethyl]-carbamate (10).** The product was obtained as a white crystalline solid from **8**: yield 91%; mp 132−134 °C; $[\alpha]^{25}_D = +47.38$ (*c* 0.5, methanol); ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.38 (s, 3H), 3.14 (AB fragment of an ABX system, 2H, $J = 5.1$, 9.6, 13.3 Hz, $\Delta\nu = 48.0$ Hz), 5.01 (m, 1H), 5.49 (br s, 1H), 7.24−7.40 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 154.7, 141.4, 140.5, 139.9, 129.6, 128.3, 127.3, 126.0, 124.0, 79.0, 63.9, 50.6, 27.9, 21.0. Anal. Calcd for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.00; N, 3.89. Found: C, 66.65; H, 7.28; N, 3.88.

***tert*-Butyl *N*-[(1*R*,2*R*,*R*$_S$)-1-Phenyl-2-*p*-tolylsulfinylpropyl]carbamate (11).** The product was obtained as a white crystalline solid from **9A**: yield 93%; mp 164−166 °C; $[\alpha]^{25}_D = +76.5$ (*c* 0.6, methanol); ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3H, $J = 7.0$ Hz), 1.41 (s, 9H), 2.38 (s, 3H), 2.94 (m, 1H), 5.07 (m, 1H), 5.36 (d, 1H, $J = 7.7$ Hz), 7.50−7.37 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 155.0, 141.4, 139.4, 129.8, 128.7, 127.7, 126.4, 124.5, 65.3, 55.6, 28.3, 21.4, 5.5. Anal. Calcd for $C_{21}H_{27}NO_3S$: C, 67.53; H, 7.29; N, 3.75. Found: C, 67.42; H, 7.68; N, 3.69.

Pummerer Reaction and Deprotection of *β*-Sulfinylcarbamates. General Procedure. To a stirred solution of the *β*-sulfinylcarbamate (11.4 mmol, 1 equiv) and *sym*-collidine (2.67 mL, 34.2 mmol, 3 equiv) in acetonitrile (50 mL) at 0 °C was added TFAA (7.0 mL, 56.9 mmol, 5 equiv), dropwise. The reaction mixture was maintained for 15 min at 0 °C under stirring before the addition of water (5 mL) and solid K_2CO_3 until pH 7 was reached. The mixture was warmed to room temperature; after 5 min, the reaction was quenched with saturated NH_4Cl aqueous solution (50 mL), and the organic phase was extracted with ethyl acetate (5 × 100 mL). The organic layers were treated with 10% HCl aqueous solution (50 mL) to remove the excess *sym*-collidine, dried over Na_2SO_4, and evaporated under vacuo. The crude material was treated with a mixture of 1 N HCl aqueous solution (25 mL) and THF (4 mL). After 48 h of vigorous stirring, the crude product was extracted with CH_2Cl_2 (20 mL), and the aqueous layer was evaporated under vacuo. The residue was treated with a Dowex 1X8-200 ion-exchange resin, affording the corresponding *β*-amino alcohol.

(*R*)-2-Amino-2-phenylethanol (14).[22] This product was obtained from **10**: yield 94%; $[\alpha]^{25}_D = -31$ (*c* 0.76, 1 N HCl); ^{1}H NMR ($CDCl_3$, D_2O) δ 3.52 (AB fragment of an ABX system, 2H, $J = 4.6$, 8.0, 10.7 Hz, $\Delta\nu = 32.0$ Hz), 3.85 (dd, 1H, $J = 8.0$, 4.6 Hz), 7.30−7.12 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 143.4, 129.5, 128.3, 127.9, 68.9, 58.7.

(1*R*,2*R*)-1-Amino-1-phenylpropan-2-ol (15). This product was obtained from **11**: yield 94%; ^{1}H NMR ($CDCl_3$, D_2O) δ 0.82 (d, 3H, $J = 6.2$ Hz), 3.45 (d, 1H, $J = 3.4$ Hz), 3.63 (dq, 1H, $J = 3.4$, 6.2 Hz), 7.28−7.11 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 143.8, 129.5, 128.6, 127.8, 73.2, 64.2, 20.7. **(1*R*,2*R*)-1-Amino-1-phenylpropan-2-ol hydrochloride:**[23] mp 192−193 °C; $[\alpha]^{25}_D = -26$ (*c* 0.9, water).

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