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Stereocontrolled Reactions Mediated by a Remote Sulfoxide Group: Synthesis of Optically Pure *anti*-β-Amino Alcohols

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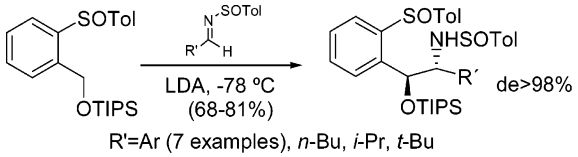
ABSTRACT



A one-step synthesis of enantiomerically pure *anti*-1,2-amino alcohol derivatives has been achieved by reaction of prochiral oxygenated 2-*p*-tolylsulfinylbenzyl carbanions with *N*-sulfinylimines bearing the same configuration at sulfur.

Enantiomerically pure β-amino alcohols are structural subunits of wide occurrence in natural products. These compounds are of importance as key synthetic intermediates for the synthesis of biologically active compounds[1] and as stationary phases in HPLC.[2] However, the main interest in these substrates is related to their use as chiral ligands or auxiliaries in asymmetric reactions.[3] There are a large number of recent publications involved in the search for new and efficient methods of synthesis. In addition to resolution methods,[4] the most common strategy for their preparation involves sequential creation of both chiral centers starting from compounds containing the α-imino carbonyl fragment (O═C−C═N) or from functional groups (α-aminocarbonyls, α-hydroxyimines or oximes, α-amino acids, etc.),[5] which are conveniently modified by reduction or nucleophilic addition. These procedures are characterized by a sequential creation of both chiral centers by the use of nonracemic chiral starting compounds. Of special mention is the Sharpless asymmetric dihydroxylation[6] (followed by regioselective amination of the resulting cyclic carbamates or cyclic sulfates) and aminohydroxylation[7] of olefins. The usefulness of these methods is often restricted by regioselectivity problems, similar to those observed in sequences that involve the ring opening of oxiranes, that arise using different catalytic systems.[8] As a consequence, the synthesis of 1,2-diaryl derivatives, with different aromatic residues, is very difficult using asymmetric catalysis. Therefore, most of the 1,2-diaryl-1,2-amino alcohols used as chiral ligands have identical aromatic residues (usually phenyl).

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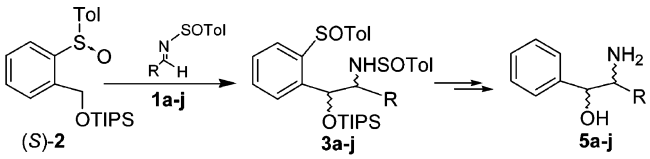
Interestingly, the C−C bond disconnection represents the most direct retrosynthetic route for simultaneously creating both chiral carbon atoms of β-amino alcohols. An interesting approach reported from the Uemura group[9] is based on a radical reductive cross-coupling of *N*-tosyl benzylideneamine with chromium complexes of benzaldehydes mediated by samarium iodide. Thus, this reaction gives *syn*-β-amino alcohols in high optical purity (90−94% de). The coupling reactions of α-metalloheteroatoms with aldehydes or imines have also been used. The most common are those in which the anion is generated adjacent to a nitrogen,[1d] but few are efficient and only produce *syn*-amino alcohols.[10] The reactions of anions α to an oxygen are less popular (also yielding the syn isomers), with imines[11] perhaps due to the paucity of suitable imines. In this sense, the use of *N*-sulfinylimines[12] as electrophiles could provide a powerful method for 1,2-amino alcohol preparation. However, their reactions with α-oxygenated carbanions have never been reported.

We have recently solved the problem regarding stereoselective benzylation of *N*-sulfinylimines by using benzylcarbanions stabilized by a *p*-tolylsulfinyl group at the ortho position.[13] This method efficiently achieved complete stereocontrol in reactions forming two chiral centers simultaneously. Such results suggested an unusual configurational stability of the benzylic carbanions, due to the stabilization by the sulfinyl group. Taking into account the positive influence of the oxygen on the configurational stability of the carbanions, we reasoned that the reactions of the *N*-sulfinylimines with the oxygenated carbanions also bearing a *p*-tolylsulfinyl at the ortho position should provide 1,2-amino alcohol derivatives. Moreover, as a similar stereochemical course should be expected for both reactions, anti products would be obtained (most of the reported methods concern the syn isomers). This procedure would provide access to diaryl derivatives with various aromatic residues, which cannot be easily obtained by chiral catalysis. In this paper we report the results obtained from the reaction of different *N*-*p*-tolylsulfinylimines (**1a**−**j**), derived from aliphatic and aromatic aldehydes with the oxygenated carbanion **2**, which produces *anti*-(1-alkyl or aryl)-2-aryl-1,2-amino alcohol derivatives (Scheme 1).

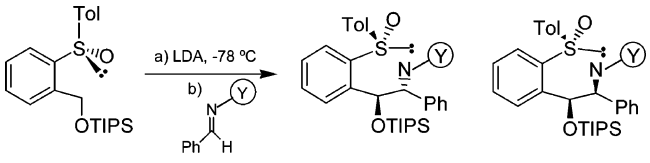
Scheme 1



R=Ph (**a**), *o*-BrPh (**b**), *p*-MeOPh (**c**) , *p*-CNPh (**d**), *p*-ClPh (**e**), 2-Py (**f**), 2-Napht (**g**), *n*-Bu (**h**), *i*-Pr (**i**), *t*-Bu (**j**)

The synthesis of the enantiopure *N*-sulfinylimines **1a**−**j**[14] as well as alcohol (*S*)-**2**[13] has been previously reported. To determine the role played by the sulfur configuration of each reagent in controlling the newly created chiral centers, we first studied the reaction of sulfoxide (*S*)-**2** with (*R*)-**1a**, (*S*)-**1a**, and the corresponding sulfone **1′a** (Scheme 2). *N*-

Scheme 2



sulfonylimine (**1′a**) yielded a 89:11 mixture of **3′** and **4′**, epimeric at C-2 (de 78%). This result demonstrates that the sulfur configuration in (*S*)-**2** completely controls the stereoselectivity at the benzylic position. It also exhibits a strong influence on the configuration created at the electrophilic center. A mixture of two compounds [(*R*)-**3a** and (*R*)-**4a**] was also obtained starting from (*R*)-**1a**, but in this case, the de was lower (50%) than that observed from the sulfone. The reaction of (*S*)-**2** with (*S*)-**1a** yielded the (*S*)-**3a** compound as a single stereoisomer (de > 98%, Scheme 2). These results indicate that changing the configuration at the sulfur of **1a** does not have any influence on the configuration of the benzyl oxygenated carbon. The configuration is completely controlled by the sulfinyl group of (*S*)-**2**. It is remarkable that the chiral sulfur is more important than the *N*-sulfinylimine in controlling the stereoselectivity at the electrophilic center.

In our reactions, the configuration of the imine only modulates the stereocontrol exerted by the sulfinyl group in (*S*)-**2**. In this sense, the stereochemical outcome of these reactions is similar to that of a double-asymmetric induction process where the matched pair is formed by reagents with the same configuration at sulfur (*S*)-**2** and (*S*)-**1a**. Another significant fact concerns the comparison of the results obtained from α-oxygenated carbanions (Scheme 2) and their corresponding alkyl carbanions.[14] The stereoselectivity of all these reactions was higher with the oxygenated substrates, in agreement with our initial analysis.

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The stereochemical results shown in Scheme 2 can be explained on the basis of the same model proposed for alkyl benzyl carbanions.[14] We assume the structure of the nucleophile is (Li^+-(*S*)-**2**) (Figure 1) where the benzyllithium is

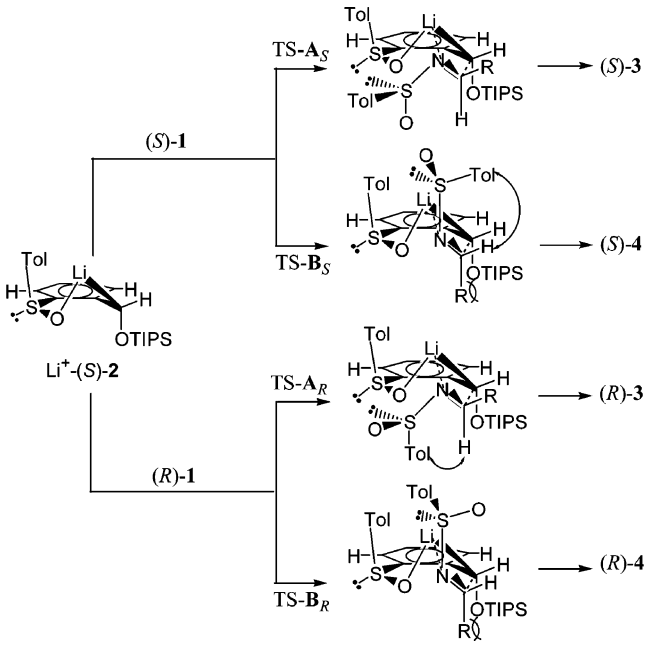


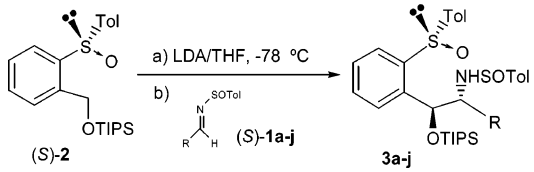
Figure 1. Stereochemical model explaining the reactions of **2** and with *N*-sulfinylimines.

stabilized by the sulfinyl oxygen atom. The preferred configuration of this intermediate is where the carbanion adopts a pseudo axial arrangement with the *p*-tolyl and OTIPS groups, thus avoiding allylic strain with the neighboring aromatic ortho protons.[13] The complete stereoselective control at the benzylic position observed in all the reactions is consistent with the assumption that nucleophilic addition to the C=N bond proceeds with total retention of stereochemistry.

After association of the lone pair of electrons at the imine nitrogen with the lithium metal, where an equatorial approach is favored, two different four-membered ring transition states (A and B in Figure 1) can be postulated. The minimized steric interactions in TS-**A** (H/OTIPS + H/R) with respect to TS-**B** (H/H + R/OTIPS) nicely explains the strong influence of the sulfinyl group at (*S*)-**2** on the stereoselectivity at the electrophilic center. Compound **3** is the major product regardless of the substituent group at nitrogen.[15] The sulfur configuration at (**1**) modifies the energetic difference between TS-A and TS-B, and this becomes higher for (*S*)-**1a** (de > 98%) and lower for (*R*)-**1a** (de = 50%).[16]

With these results in hand, the reactions of (*S*)-**2** with a variety of (*S*)-*N*-*p*-tolylsulfinylimines (**1a**−**j**) were studied. Seven of them derive from arylaldimines (**1a**−**g**) containing donor and electron-attracting groups due to the potential interest of the 1,2-diaryl-1,2-amino alcohols with different aromatic residues as chiral ligands. Alkylaldimines were also studied. The NMR spectra of the crude reaction mixtures show signals corresponding to only one diastereoisomer (**3a**−**j**). This means that the de of the reaction is greater than 98% in all of the cases studied, regardless the electronic character of the aryl groups and the size of the alkyl ones. The isolated yields were decreased, ranging from 68 to 81% (Table 1),

Table 1. Reactions of (*S*)-**2** with *N*-Sulfinylimines (*S*)-**1a**−**j**



entry	products (R)	crude yield (%)	yield (%)	de (%)
1	(Ph) **3a**	>98	81	>98
2	(o-BrC_6H_4) **3b**	90	71	>98
3	(p-MeOC_6H_4) **3c**	>98	78	>98
4	(p-CNC_6H_4) **3d**	>98	74	>98
5	(p-ClC_6H_4) **3e**	95	76	>98
6	(2-Py) **3f**	>98	77	>98
7	(2-Napht) **3g**	>98	68	>98
8	(*n*-Bu) **3h**	>98	74	>98
9	(*i*-Pr) **3i**	>98	72	>98
10	(*t*-Bu) **3j**	>98	see text	>98

because the resulting amino alcohol derivatives are not completely stable on silica gel.[17] Configurational assignments for compounds **3** were tentatively made from their NMR data and later confirmed by X-ray analysis of compound **3i**[18] (see Supporting Information). Chemical correlation of compound **3a** with compound **9**[19]of known configuration was achieved (Scheme 3).

Although the final aim of this work is the synthesis of *anti*-1,2-amino alcohols, compounds **3a**−**i** as well as their partially deprotected derivate are also interesting in the field of chiral ligands, because they contain additional coordination centers. In particular, the ability of the sulfinyl group to coordinate to several metals[20] adds interest to the sulfinylated amino alcohols. Eventually, these sulfoxides can be easily transformed into thioethers, which have also been widely

(15) The higher de observed from α-sylilated carbanions with respect to their corresponding alkyl derivatives (see ref 13) could be explained with this model by assuming the OTIPS group is larger than the Me one. However, the competence between transition states such as TS-**A** with others involving eight-membered rings cannot be disregarded and it is currently under study with other electrophiles.

(16) As the lone pair of electrons supported by the sulfur at sulfinylimine group will be oriented toward the intermediate, thus minimizing steric interactions, the relative stability of TS-**A** and TS-**B** will depend on the configuration of **1** because the interaction $(O/H)_{1,3-syndiaxial}$ is lower than $(Tol/H)_{1,3-syndiaxial}$, thus making TS-$\mathbf{B_S}$ and TS-$\mathbf{A_R}$ less stable (see Figure 1).

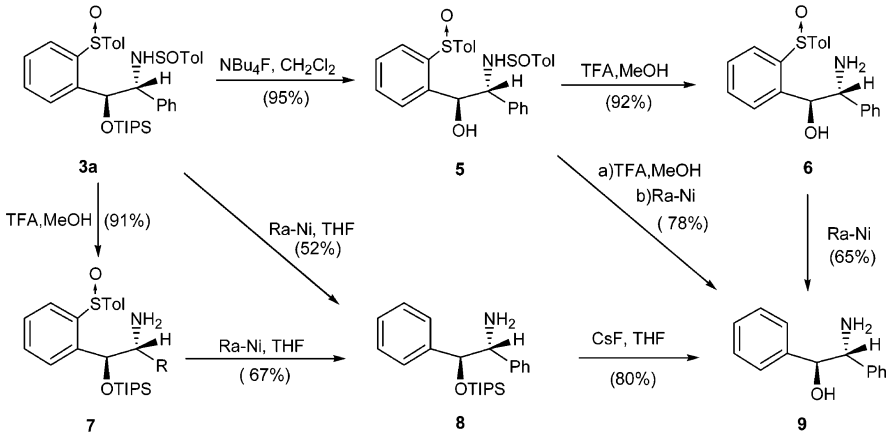
(17) NMR spectra of the reaction crude are very clean and revealed the almost quantitative conversion in all the cases, even starting from **1j**. Indeed, compound **3j** was completely destroyed during chromatographic purification

(18) The authors have deposited atomic coordinates for **3i** with the Cambridge Crystallographic Data Centre (deposition number CCDC 208928). The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge Cb2 1EZ, UK.

(19) Kanematsu, K.; Sasaki, T. *J. Med. Chem.* **1966**, 847.

(20) Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651.

Scheme 3



used as coordinating centers.[21] In this sense, an additional advantage of compounds **3** is the fact that their protecting groups are orthogonal. Different approaches to the sequential breaking in **3a** of the N−S, O−Si, and C−S bonds, which do not affect the configuration of the two newly created chiral carbons, are illustrated in Scheme 3. The TIPS group can be easily removed with Bu_4NF or CsF without affecting the other functions. Analogously, the N−S bond is easily broken with TFA. Hydrogenolysis of the C−S bond with Ra−Ni proceeds in higher yield with substrates containing a free hydroxyl group. However, the use of the OTIPS derivative can be more convenient in some cases in order to avoid epimerization[22] of the final benzylic alcohol, as was reported in some cases.[23]

In summary, the reaction between prochiral oxygenated 2-*p*-tolylsulfinylbenzyl carbanions with *N*-sulfinylimines allows formation of the C−C bond to proceed with complete stereoselective control at the two new stereogenic centers. The method allows for a one-step synthesis of enantiomerically pure 1,2-diaryl *anti*-1,2-amino alcohols with identical or different aromatic residues and 1-aryl-2-alkyl anti-1,2-amino alcohol derivatives. The orthogonal deprotection of the different functional groups yields a variety of structures potentially useful as chiral ligands. Studies directed toward adapting this procedure to the synthesis of the *syn*-1,2-amino alcohols, as well as to probing the efficiency of the obtained chiral ligands in asymmetric catalysis are in progress.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **3a**−**j** and **5**−**9** and X-ray data for **3i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Partial epimerization was not observed in the reactions from **6** and **9** indicated in Scheme 3.

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