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Stereocontrolled Reactions Mediated by Remote Sulfoxides: Formation and Reactivity of Enantiomerically Pure Benzylic Centers

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ABSTRACT: *Reactions of different electrophiles (alkyl halides, aldehydes, N-sulfinylimines, imines, etc) with (S)-2-p-toluenesulfinyl toluene and their alkyl, triisopropylsilyloxy, and methylthio derivatives at benzylic position, in the presence of LDA, allow the synthesis of a variety of enantiomerically pure benzylic centers, whose configuration is efficiently controlled by the γ-sulfinyl group, according to 1,4-asymmetric induction processes. With prochiral electrophiles, the 1,5-asymmetric induction processes can also be controlled either by modifying their steric or electronic features or by incorporating an additional chiral center at the electrophiles.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:537–548, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20342

Nearly 20 years ago we initiated a research program focused on methodological aspects related to the use of chiral sulfoxides in asymmetric synthesis. During these years we have worked in two main types of reactions using the sulfinyl group as a chiral auxiliary: cycloadditions (mainly Diels–Alder [1] and 1,3-dipolar reactions [2]) and nucleophilic additions. Concerning the latter ones, we initially focused on evaluating the efficiency of the sulfinyl group in the control of the stereoselectivity of reactions of β-ketosulfoxides and their corresponding iminoderivatives with different nucleophiles [3]. All these reactions are 1,3-asymmetric induction processes, whose stereoselectivities depend on the ability of the sulfinyl group to associate with any acidic center at the reagent or the catalyst, determining that reactions evolve through cyclic six-membered transition state with severe steric restrictions (Scheme 1). More recently we began investigating other nucleophilic additions controlled by remote sulfinyl groups, that is to say, with the sulfur separated by three or more covalent bonds from the reaction center. These reactions involve 1,4- and 1,5-asymmetric induction processes. In this field we have studied the hydrocyanation of the 2-*p*-toluenesulfinyl benzaldehyde [4] and different reactions of 2-*p*-toluenesulfinylphenyl acetaldehyde such as reduction [5], hydrocyanation [6], and Mukayama reactions [7], which evolve with very high stereoselectivities in the presence of $Yb(OTf)_3$ due to of the formation of chelated species containing seven- or eight-membered rings. In all these reactions, the sulfinyl group is located at the substrate, which acts as the electrophile (Scheme 1).

Another important group of nucleophilic additions involves the use of sulfinylated nucleophilic reagents. Most of these reactions use α-sulfinyl carbanions and involve 1,2- or 1,3-asymmetric induction processes evolving with good selectivity [8]. The use of prochiral carbanions in nucleophilic addition reactions, which leads to the simultaneous formation of two chiral centers in one step, is much less successful, unless an additional chiral center is also present at the electrophile; therefore, these reactions involve double asymmetric induction processes. In

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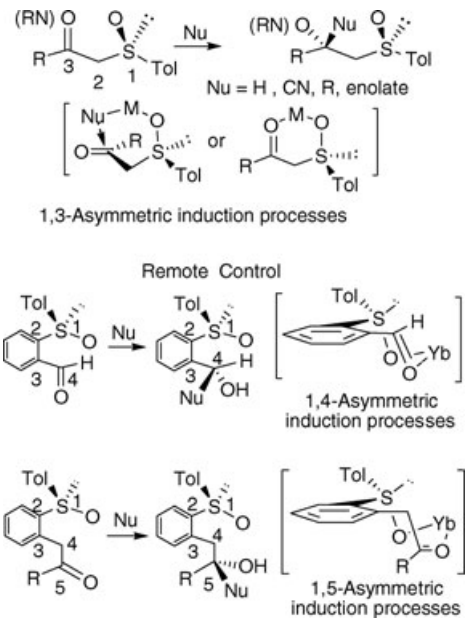

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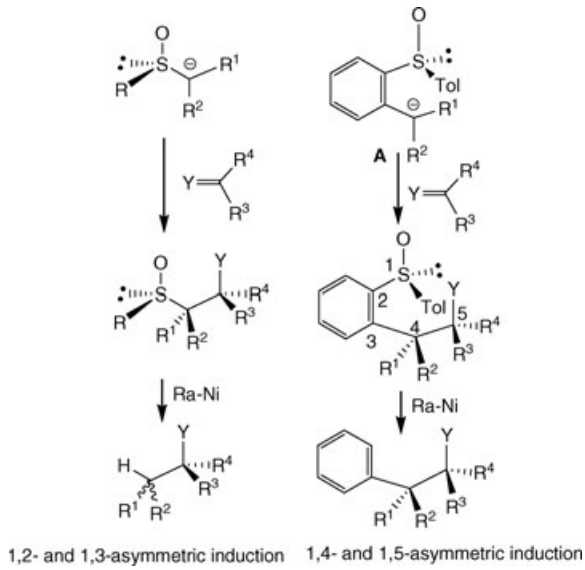
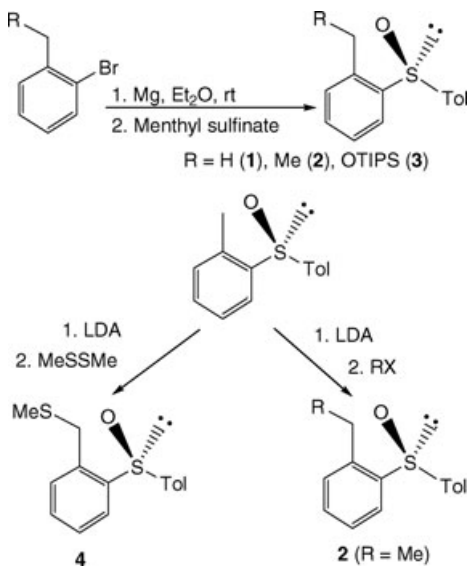


SCHEME 2

this sense, we obtained very high diastereomeric excesses in the addition of prochiral α-sulfinyl carbanions to *N*-sulfinyl imines [9]. One of the main problems inherent to reactions of prochiral α-sulfinyl carbanions is related to the fact that the chiral center vicinal to the sulfur atom is usually destroyed at the end of the synthetic sequence due to the need of removing the sulfur function, usually performed by hydrogenolysis (Scheme 2). In some cases, this problem could be circumvented by the stereoselective transformation of the sulfinyl group [9], but in most of the cases, this situation seriously restricts the synthetic applicability of these reactions.

The possibility of controlling the stereoselective evolution of carbanions by means of sulfinyl groups located at remote positions of the reaction centers emerges as a possible solution to these problems, because the elimination of the sulfinyl group would not have any consequence on the configuration at the chiral center generated in the reaction of the carbanion. In this context, we focused our attention on 2-*p*-toluenesulfinyl benzyl carbanions (**A** in Scheme 2), which are γ-sulfinylcarbanions, with the position of the double bond fixed by an aromatic ring, thus avoiding the regioselectivity problems found in sulfinylated allyl carbanions [10]. Interestingly, reactions of these anions would provide chiral benzylic centers, widely spread among natural products and not always easily obtained by other methodologies.

Compounds **1–4** were used as the precursors of the *ortho*-sulfinyl benzylcarbanions. They were prepared from commercially available 2-bromoderivatives, by reaction with magnesium and further treatment with enantiomerically pure menthyl sulfinate (Scheme 3) [11]. When the bromoderivatives are not commercially available, for example, **2** (when R is larger than Me) and **4**, precursors were prepared by reaction of **1** with LDA and further treatment with primary halides [12] or dimethyldisulfide [13], respectively (Scheme 3).



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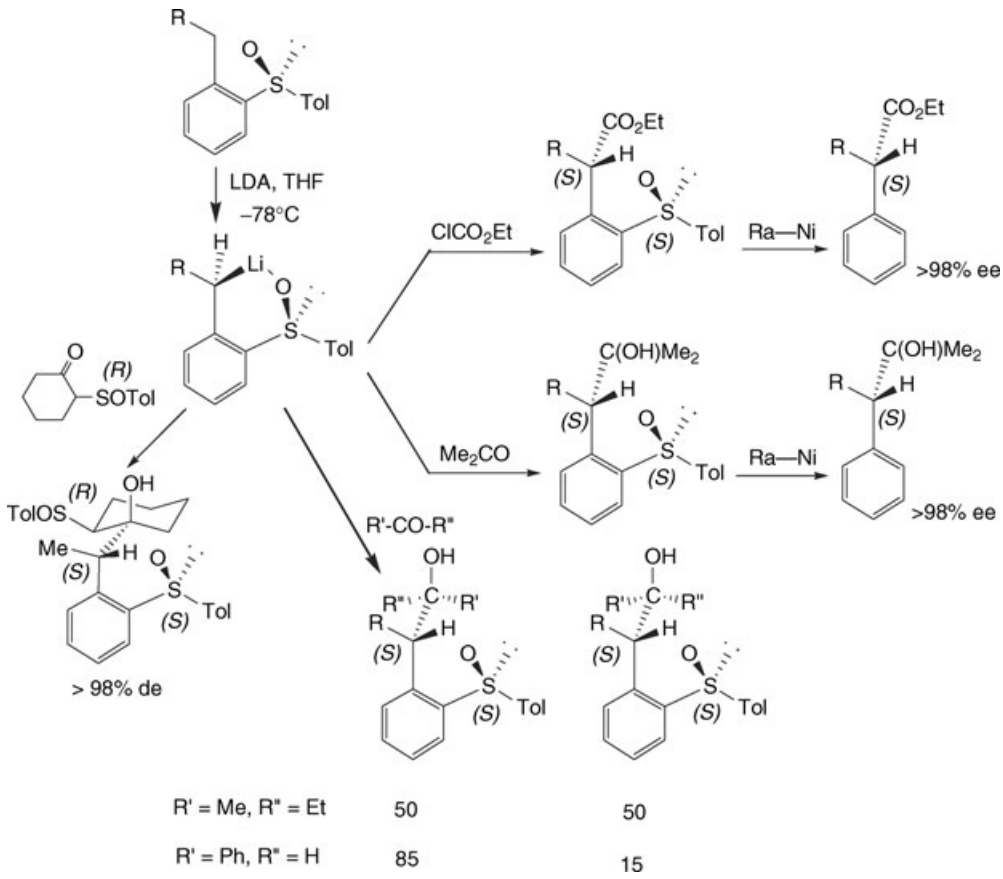
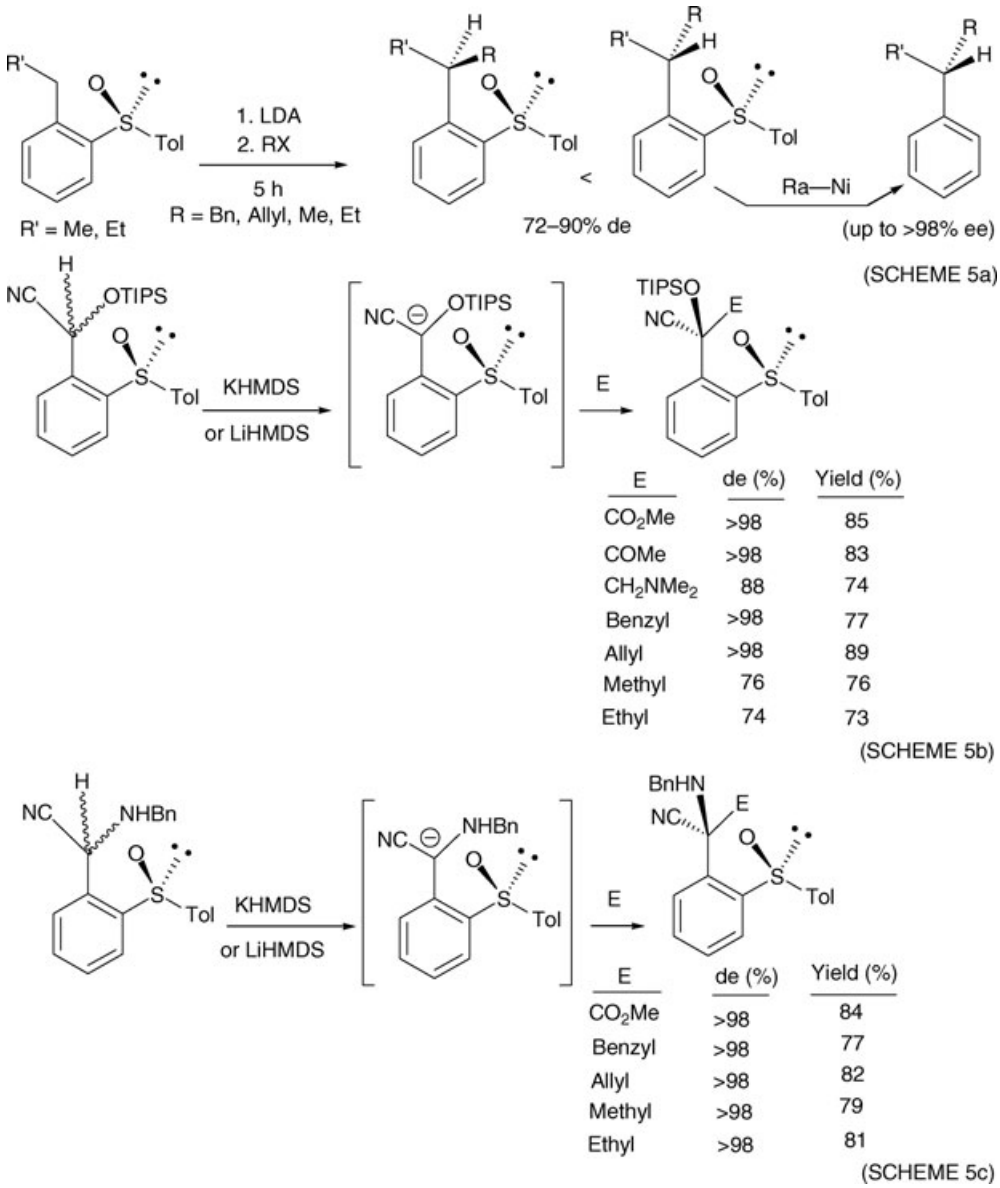


SCHEME 4

The behavior of the carbanions in their reactions with different electrophiles demonstrated that the *ortho*-sulfinyl group completely controlled the configuration at its benzylic position. Precursors were transformed into benzylcarbanions with LDA, which reacted with different electrophiles, such as ethoxycarbonyl chloride or acetone, in a completely stereoselective way, affording only one diastereoisomer with de's above 98% [11]. The elimination of the sulfinyl group with Raney niquel provided the esters or alcohols containing optically pure benzylic centers (Scheme 4). In the reactions with nonsymmetric carbonyl compounds, where two chiral centers were formed in one step, complete control of the stereoselectivity at the benzylic position could also be confirmed, but a rather low control of the configuration at the hydroxylic carbon was detected. Thus, the reaction with butanone afforded an equimolecular mixture of two epimers at the hydroxylic carbon, whereas an 85:15 mixture was obtained in the reaction with benzaldehyde (Scheme 4). The complete control of the 1,5-asymmetric processes was also achieved by incorporating the sulfinyl group at the electrophile. Thus, the reaction with 2-*p*-toluenesulfinyl cyclohexanone yielded only one isomer as a result of a double asymmetric induction process [11].

Alkylation reactions were slower than nucleophilic additions. They were satisfactory only with highly reactive halides. Benzyl and allyl halides afforded mixtures of diastereoisomers with up to 90% de's [14]. Methyl and ethyl halides or triflates also provided good de's. Although the separation of these mixtures was not easy, the hydrogenolysis of the C—S bond at the isolated major diastereoisomer afforded arenes with benzylic chiral centers in high optical purities (Scheme 5a).

The formation of quaternary centers starting from alkylated tertiary carbanions was not possible, presumably due to the low stability of these carbanions. However, if they are additionally stabilized by some electron-withdrawing group, the quaternization is feasible. Thus, the reactions of the corresponding silylated cyanohydrins with lithium or potassium HMDS, generated a benzylic carbanion that reacted with different electrophiles, both acylating and alkylating reagents, to form quaternary chiral centers in an almost complete stereoselective

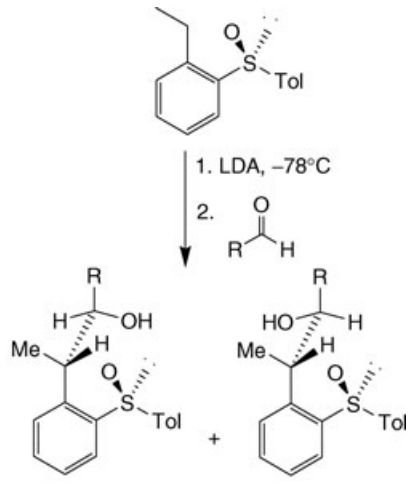


SCHEME 5

way and very high yields (Scheme 5b) [15]. Even better results were obtained starting from *N*-benzyl-α-amino nitriles, [16] which provided optically pure compounds containing quaternary carbons at C-α (Scheme 5c).

Aromatic aldehydes (R = Ph, 4-MeO, 2-Naph, 1-Naph) afforded mixtures of only two diastereoisomers, *syn* and *anti*, both epimers at the oxygenated center, the *anti* isomer being the major one (Scheme 6). Diastereoisomeric excesses were *ca.* 70% and the isomers could be separated. Stereoselectivity significantly decreased (34% de) for 2,6-disubstituted aldehydes, whereas aldehydes containing electron-withdrawing groups yielded complex mixtures (Scheme 6) [17]. Finally, the reactions with aliphatic aldehydes (R = *n*-Bu, *i*-Pr, *t*-Bu) also yielded mixtures containing only two alcohols, *syn* and *anti*, but the stereoselectivity was the opposite to that observed with aromatic aldehydes, the *syn* isomer being the major product.

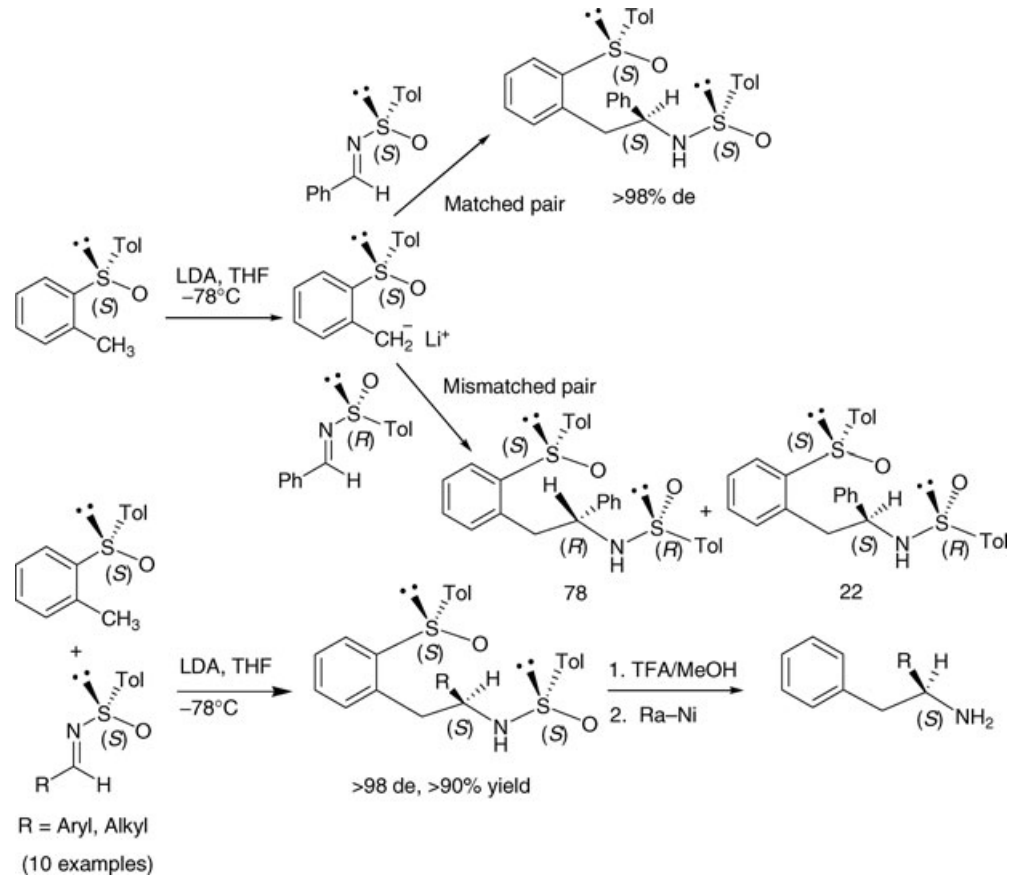
The most interesting results of this research were obtained in the reactions with imines. They provide 2-arylethylamines, which are relevant structural subunits because of their frequent occurrence in natural products and their importance as valuable synthetic intermediates. The nucleophilic addition of many alkyl and arylmetals to *N*-sulfinylimines is one of the most straightforward and attractive routes to prepare chiral amines in high yields with good stereoselectivities. However, benzylation of the



SCHEME 6

N-sulfinylimines usually proceeded with moderate and erratic stereoselectivity [18], always lower than 75% de's from *N*-*p*-toluenesulfinylimines and slightly higher in some cases with *N*-*t*-butanesulfinyl derivatives. Moreover, there was no report on the use of prochiral benzyl carbanions, which would provide 2-arylethylamines with the simultaneous formation of two chiral centers. The efficiency of the *ortho*-sulfinyl group to control the stereoselectivity of the reactions of benzyl carbanions with different electrophiles made us consider that its application to the benzylation of *N*-sulfinylimines could improve the stereoselectivity, as a consequence of a double asymmetric induction process. This would provide a new general procedure for the highly stereoselective benzylation of imines.

Initially we studied the reactions of the simplest sulfinyl benzyl carbanion with both enantiomers of the *N*-sulfinylimine derived from benzaldehyde [19]. When both reagents exhibited the opposite configuration at their sulfur atoms, a 78:22 mixture of the



SCHEME 7

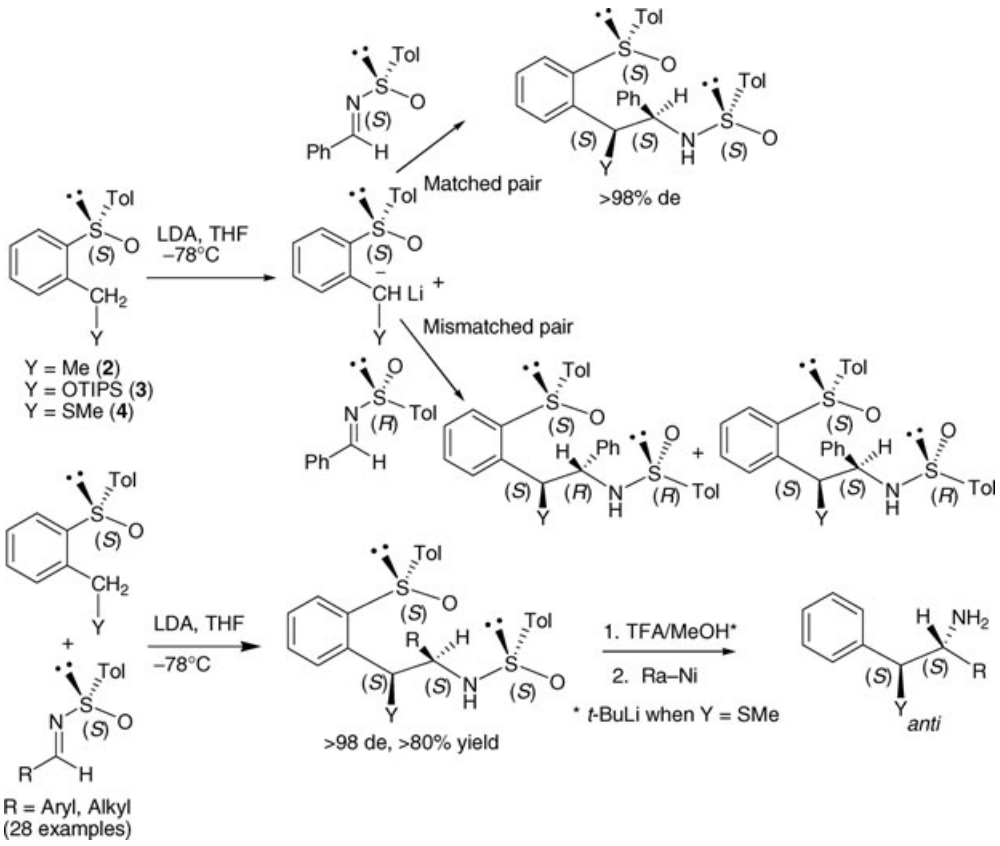
two epimers at the aminic carbon was obtained. On the contrary, when both reactants had the same (*S*) configuration the stereoselectivity control was complete and only the amine with (*S*) configuration at the chiral aminic carbon was obtained (Scheme 7). These results indicate that both sulfinyl groups play a significant role in stereoselectivity control, and when they favor the same epimer, as is the case for the matched pair, the benzylation of the imines is achieved in a completely stereoselective way.

Next we studied the reactions of our (*S*)-benzyl carbanion with a variety of (*S*)-*N*-sulfinylimines. Diastereoisomeric excesses were always higher than 98% and the isolated yields exceeded 90%, regardless the aliphatic or aromatic nature of the imine and the electronic effect of the substituent at the aromatic ring, which evidences the general scope of the reaction. Hydrogenolysis of the N—S bond with TFA and the C—S bond with Ra—Ni afforded optically pure amines (Scheme 7).

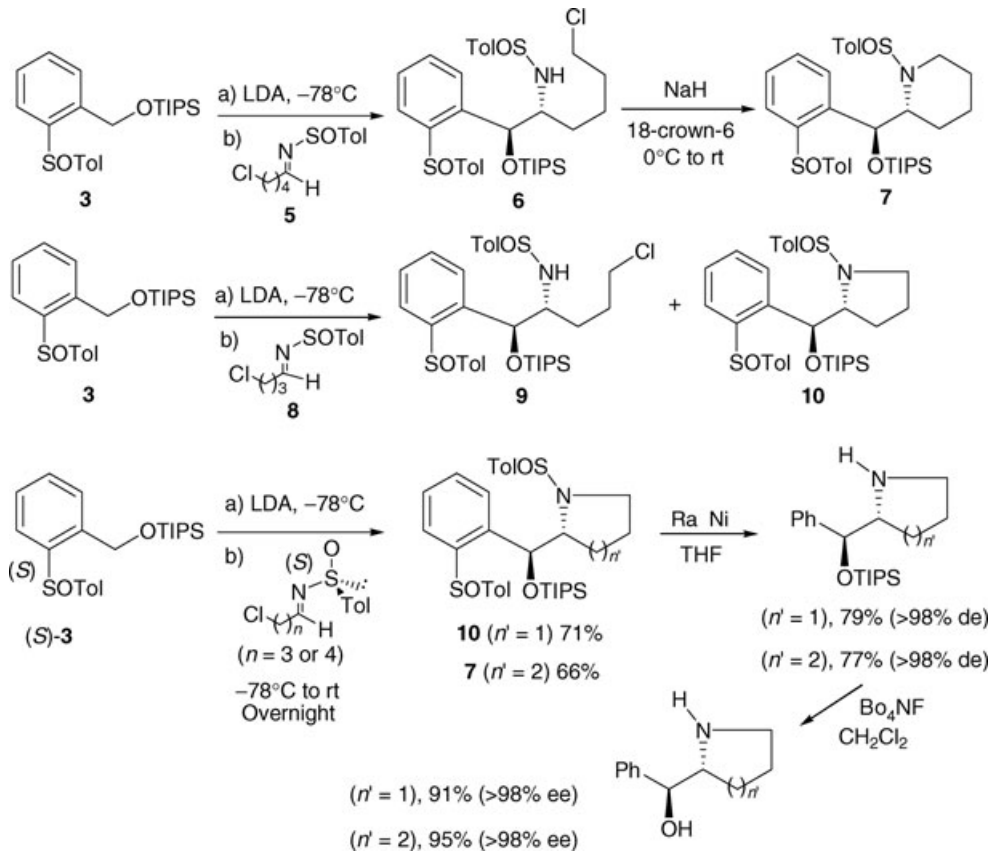
Then we investigated the reactions of prochiral carbanions derived from 2-*p*-toluenesulfinyl ethylbenzene (**2**) [19], its triisopropylsilyloxy derivative (**3**) [20], and its methylthio derivative (**4**) [13]. When the reactants exhibited the opposite configuration, which conforms the mismatched pair once again, a mixture of *syn* and *anti* epimers, both exhibiting the same configuration at the benzylic carbon, was obtained. On the contrary, starting from the reagents with the same configuration (matched pair), a complete control of the stereoselectivity at both chiral centers was observed, yielding only the *anti* diastereoisomers (Scheme 8).

Reactions of (*S*)-**2**, (*S*)-**3**, and (*S*)-**4** with different (S)-*N*-sulfinylimines afforded yields usually higher than 80%. The stereoselectivity remained complete in almost all the cases, and desulfinylation with TFA and Raney nickel in THF afforded a variety of amines in high yields with no loss of optical purity. The wide range of sulfinylimines compatible with this method, along with a facile desulfinylation protocol, provide an easy access to optically pure 1,2-diaryl (and 1-alkyl-2-aryl) propylamines, ethanolamines, and amino sulfides in a three-step sequence from 2-*p*-toluenesulfinyl alkylbenzenes and *N*-sulfinylimines (Scheme 8).

One application of these reactions developed by us is the synthesis of enantiomerically pure β-hydroxypyrrolidines and piperidines [21], interesting subunits present at many biologically active



SCHEME 8

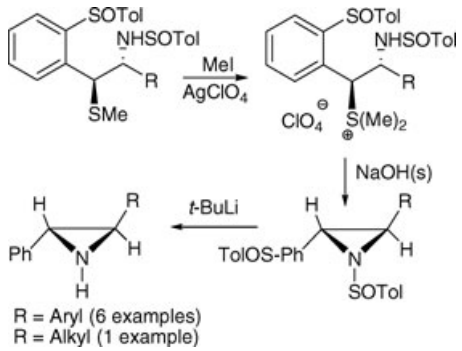


SCHEME 9

alkaloids and azasugar analogues. As they are *anti*-1,2-aminoalcohol derivatives, these compounds could be prepared by reaction of the oxygenated carbanion with the appropriate imines. The reaction of δ-chloroimine **5** with the sulfinylated benzylcarbanion derived from **3** in the presence of LDA afforded *anti*-1,2-aminoalcohol derivative **6** in 77% yield as a single diastereoisomer (Scheme 9). It reacted with sodium hydride in the presence of 18-crown-6 ether, resulting in the formation of the substituted piperidine **7** in 78% yield with no significant racemization at any of their chiral centers. Surprisingly, when we used γ-chloroimine **8** as the electrophile under identical conditions, the expected *anti* amino alcohol derivative **9** was obtained along with the corresponding pyrrolidine **10**, which indicated that partial cyclization had taken place and suggested the possibility of performing a one-pot two-step sequence without using the basic catalyst. After a detailed study of the experimental conditions, we found that heterocycles **7** and **10** could be directly obtained in 66% and 71% isolated yields, respectively, when the reactions were initiated at -78°C and then left overnight at room temperature. The sulfinyl groups can be simultaneously removed in good yields by using Ra—Ni under mild conditions without epimerization at their chiral carbons. Desilylation with TBAF in CH_2Cl_2 yielded the desired β-hydroxy pyrrolidine and piperidine (Scheme 9).

Another interesting application was the synthesis of aziridines starting from the amino sulfides resulting from these reactions. Methylation at nitrogen with methyl iodide and silver perchlorate followed by reaction of the corresponding sulfonium salt with NaOH afforded only the *trans*-aziridine derivative. The double desulfinylation with *t*-BuLi provided optically pure *trans*-1,2-aziridine (Scheme 10) [22].

The use of ketimines as electrophiles in asymmetric synthesis has been restricted seriously due to their low reactivity (specially for enolizable ketimines) and stereoselectivity (due to their facile *E,Z* isomerization). All these problems were solved by Ellman using *N-tert*-butanesulfinyl ketimines as electrophiles and Me_3Al as the catalyst in reactions with organometallics, thus providing a general method for synthesizing α,α-dibranched amines [23]. However, this method has never been used with benzylmetals nor applied to prochiral carbanions in order to obtain β-substituted α,α-dibranched amines with the simultaneous formation of two

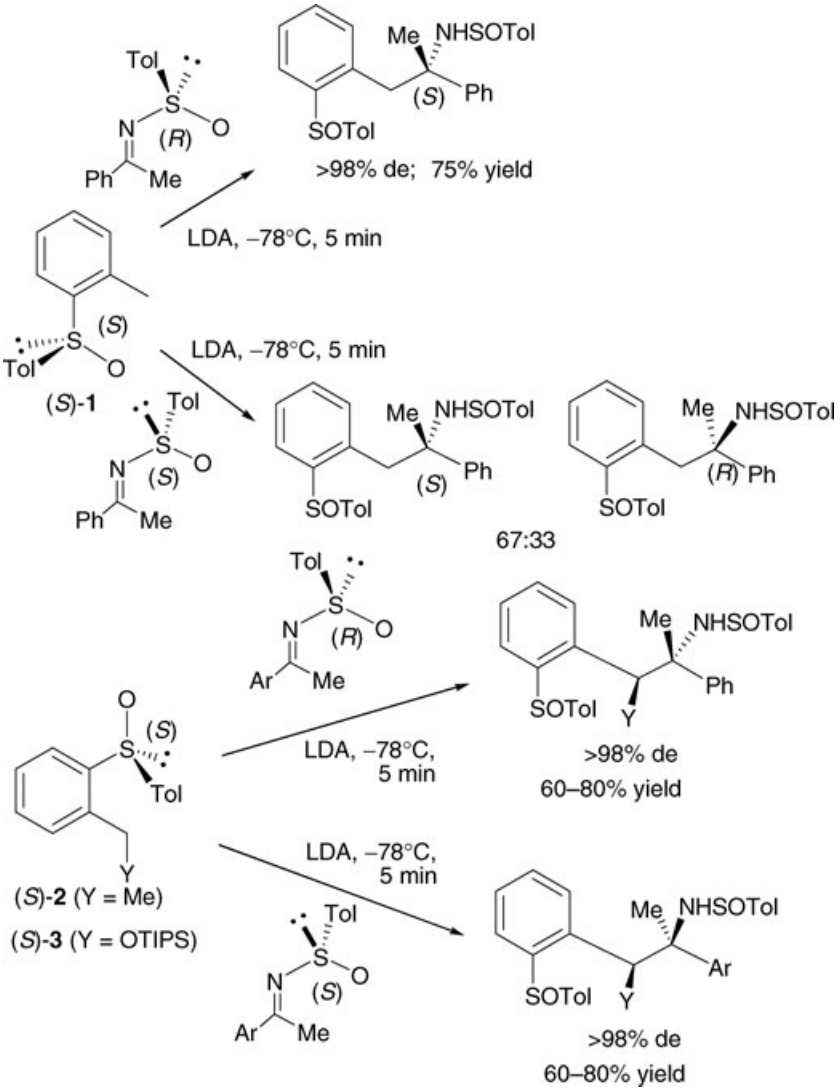


SCHEME 10

chiral centers in a single step. Therefore, we decided to investigate the reactions of 2-*p*-toluenesulfinyl benzyl carbanions derived from **1, 2,** and **3** with ketimines to check the efficiency of the sulfinyl group in solving these two questions, so far never considered.

N-Sulfinyl methylbenzylidenimines react with both enantiomers of the sulfinyl carbanions derived from **1**, with different results depending on the configuration at the *N*-sulfinyl group. When both reactants have the (*S*) configuration, a 67:33 mixture of two diastereoisomers was obtained with a moderate conversion degree. On the contrary, when starting from reactants with a different configuration at sulfur, only one diastereoisomer was obtained in very high yield. The addition of Me_3Al was not required for the reaction to reach completion (Scheme 11).

Next we studied the reaction of (*S*)-**2** with both enantiomeric *N*-*p*-toluenesulfinyl derivatives of methyl phenyl ketimines. Both reactions were completely stereoselective, yielding the *anti* and *syn* diastereoisomers when the starting imine had the (*S*)



SCHEME 11

and the (*R*) configuration, respectively. It is evident that the configuration at the quaternary carbon vicinal to nitrogen is controlled basically by the *N*-sulfinyl group, whereas the configuration at the tertiary benzylic carbon is only dependent on the configuration at the sulfinyl sulfur [24]. Similar results were obtained from the oxygenated carbanion (*S*)-**3**. This behavior was also observed with other *N*-sulfinyl aryl methyl ketimines bearing electron-donating groups or weakly electron-withdrawing groups at the ring. The yields of all these reactions ranged between 60% and 80% (Scheme 11) and the optical purity of the amines obtained after desulfinylation was complete. Ketimines containing strongly electron-withdrawing groups at the aromatic ring evolved with significantly lower yields and stereoselectivities. Aliphatic *N*-*p*-toluenesulfinylketimines did not react under these conditions, but required those used by Ellman (catalysis with Me_3Al, starting from the *N*-tert-butanesulfinyl derivative). Similar good results were obtained in the synthesis of β-amino alcohols.

Stereochemical results obtained in all the reactions with sulfinylimines were explained by assuming the initial formation of the benzyllithium intermediate **A** (Fig. 1), stabilized by the *ortho*-sulfinyl oxygen. It adopts the half-chair conformation that minimizes the allylic strain of the substituents at sulfur and carbon with their respective *ortho* protons. According to our proposal, the association of the lithium to the lone electron pair at the imine takes place as a previous step to the formation of the C—C bond (**B** in Fig. 1), which is produced through a cyclic four-membered transition state with retention of the configuration at the carbanionic center (**C** in Fig. 1). Accordingly, the configuration at the benzylic position is completely controlled by the sulfinyl group regardless the nature of the electrophile. By steric reasons, the only possible approaches of the imine are those orientating the lone electron pair at sulfur towards the chelated carbanion. On these assumptions the different behavior of the matched and mismatched pairs can be explained by steric reasons. In the first case, the approach **D′** yielding the *syn*-isomer is destabilized by the Me/Y and $(Tol/H)_{1,3\text{-syndiaxial}}$ interactions, and therefore it will be much more unstable than the approach **D** affording the *anti* isomers, lacking in any of the abovementioned interactions (Fig. 1). On the contrary, in the mismatched pair, each one of the two possible approaches, **E** and **E′**, exhibits one of these destabilizing interactions and, therefore, their energy difference is not so large and the reactions are not completely stereoselective.

This stereochemical proposal also accounts for the results obtained with ketimines (R′ = Me, in Fig. 1). The main difference derives from the strongly destabilizing character of the $(Tol/Me)_{1,3\text{-p}}$ interaction, which allows to discard the approaches **D′** and **E** (Fig. 1). Thus, when the reactants have the same configuration, the reaction can evolve only through **D** yielding the *anti* amino alcohol, whereas from

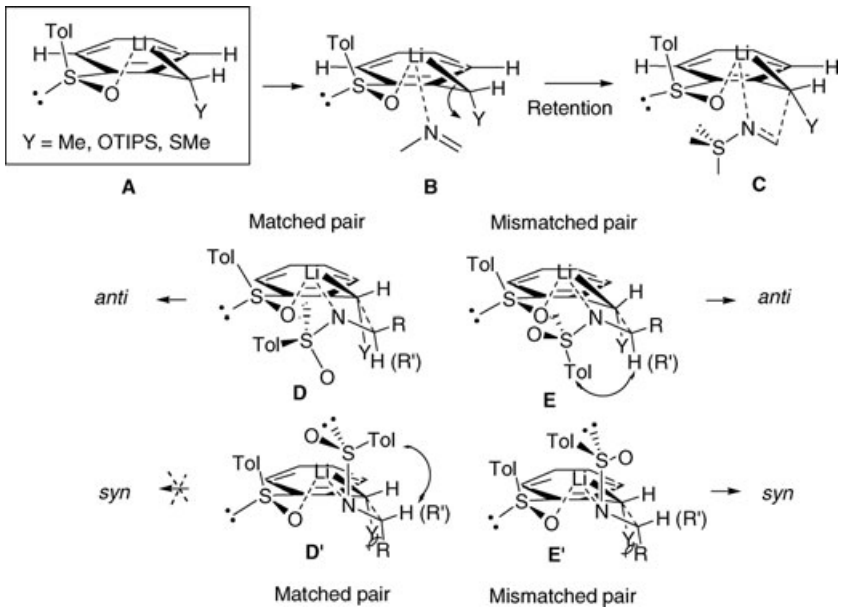
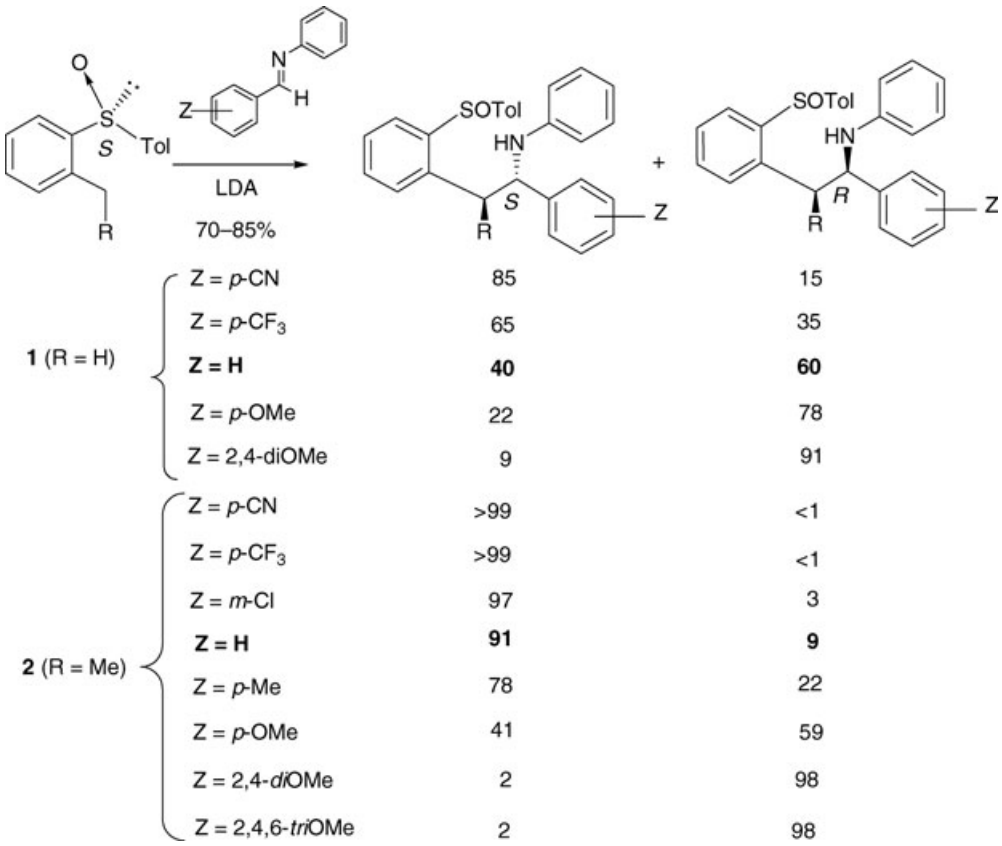


FIGURE 1 Stereochemical pathway for the reaction with sulfinylimines.



1 (R = H)	Z = *p*-CN	85	15
	Z = *p*-CF_3	65	35
	Z = H	**40**	**60**
	Z = *p*-OMe	22	78
	Z = 2,4-diOMe	9	91
2 (R = Me)	Z = *p*-CN	>99	<1
	Z = *p*-CF_3	>99	<1
	Z = *m*-Cl	97	3
	Z = H	**91**	**9**
	Z = *p*-Me	78	22
	Z = *p*-OMe	41	59
	Z = 2,4-*di*OMe	2	98
	Z = 2,4,6-*tri*OMe	2	98

SCHEME 12

reactants exhibiting different configurations the *syn* isomer will be exclusively obtained from the **E′** approach.

Finally, the reactions of the sulfinyl carbanions with *N*-arylimines will be commented. The reaction of **1** with LDA and *N*-phenyl benzylideneimine afforded a 40:60 mixture of the two possible diastereoisomers, which evidences a scarce ability of the sulfinyl group to control the configuration at the iminic carbon in accordance with a 1,5-asymmetric induction process (Scheme 12). Reactions with other *N*-phenyl aldimines derived from substituted benzaldehydes took place under mild conditions in yields ranging between 65% and 84%. Electron-withdrawing groups favor the formation of the diastereoisomers with (*S*) configuration at the iminic carbon, whereas the (*R*) epimer is favored by electron-donating groups. In the most favorable cases the observed stereoselectivity becomes very high in both senses [25].

Reactions of (*S*)-**2** with these imines, which involve the simultaneous formation of two new chiral centers, exhibited a similar behavior. They afforded mixtures of only two compounds, with the same *S* configuration at the alkylated benzylic carbon in *ortho* position to the sulfinyl group and the two possible configurations at the aminic carbon. Once again the sulfinyl group completely controls the 1,4-asymmetric induction process. The reaction of the unsubstituted *N*-phenyl benzylideneimine (Z = H) afforded a 91:9 mixture of epimers at the aminic carbon (Scheme 12). As in the previous case, electron-withdrawing groups increase the proportion of *anti* isomers, with (*S*) configuration at the aminic carbon, whereas *syn* epimers are favored by electron-donating groups. The reactions are highly stereoselective when the electron density at the ring is reduced or strongly increased.

The main conclusion that can be deduced from these results is that the electronic interactions are quite important in the stereoselectivity control, which is not compatible with the above-mentioned mechanism based only on steric interactions. Thus, a new stereochemical model has been postulated to explain the results obtained from *N*-aryl imines. As the largest stabilization of the benzylic carbanions will occur when the p orbital containing the lone electron pair is coplanar with the aromatic π-system, the most stable structure of the organometallic species

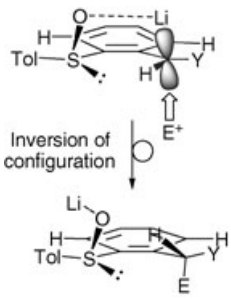


FIGURE 2 Stereochemical proposal through a boat-like TS.

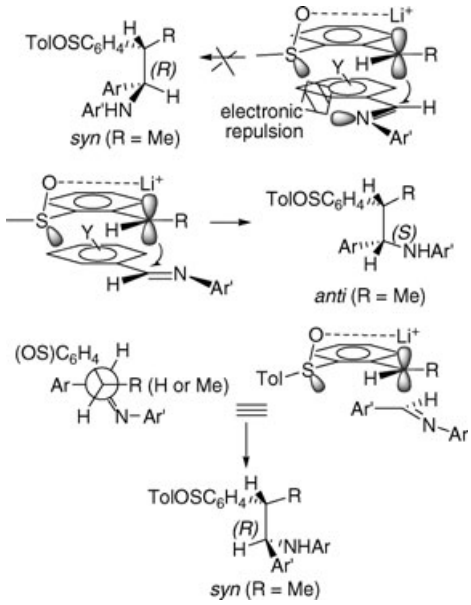


FIGURE 3 Influence of electronic and steric effects in the TS.

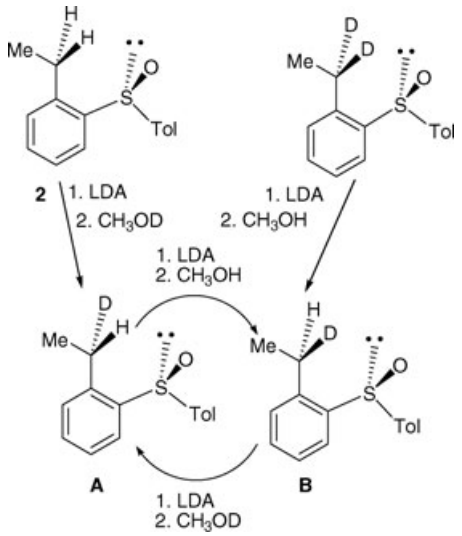
could be that depicted in Fig. 2, where the metal is additionally stabilized by the sulfinyl oxygen. The chelated species adopts a boat-like conformation, with the H at carbon and the lone electron pair at sulfur occupying the flagpoles of the boat and therefore being orientated inwards. As it determines that the metal is blocking one of the faces of the carbanion, the attack of the electrophile must take place to the opposite face with inversion of the configuration at the nucleophilic center. Differences with the previously proposed stereochemical model (Fig. 1) that involved a half-chair conformation of the reagent and retention of the configuration at the nucleophile, are evident.

Concerning the influence of the electronic effects of the substituents at the arylidene imine ring on the stereoselectivity, the stereochemical model depicted at Fig. 2 accounts for the obtained results by assuming strong donor-acceptor π-interactions between the aromatic rings of the reagents, that is to say the aromatic ring bonded to the carbanionic center acting as the donor, and that bonded to the iminic carbon, that acts as the acceptor (Fig. 3). In such a case, both interacting rings would adopt an almost eclipsed arrangement (π-stacking interaction). Although two feasible approaches of the reagents exhibit this interaction, the one yielding the *syn* isomers is destabilized by the repulsion between the lone electron pairs at sulfur and nitrogen, which would be strongly increased in the TS, where the charge at nitrogen is even larger. Therefore, the approach exhibiting the π-stacking interaction would afford the isomers with the *S* configuration at the iminic carbon (*anti* isomer when R is a methyl group). On the other hand, when no π-stacking interaction is possible, steric factors would dictate alternate approaches. Out of the three possible alternate conformations in the TS, only that corresponding to the Newman projection depicted in Fig. 3, leading to isomers with the (*R*) configuration (*syn* isomers when R is a methyl group), would be operative because it exhibits only two destabilizing interactions.

According to this description, electron-withdrawing groups at the ring enhance the donor–acceptor interactions and favor the formation of the isomers with (*S*) configuration. On the contrary, electron-donating groups decrease the acceptor character of the iminic ring and make easier the approaches favored by steric factors yielding a larger proportion of the isomers with (*R*) configuration.

Theoretical calculations [25] support the higher stability of the boat-like structure postulated in Fig. 2 with respect to the half-chair conformation of Fig. 1. They also suggest that deprotonation of these systems with bases similar to LDA must be highly stereoselective, the sulfur configuration determining the stereoselectivity as a consequence of the association of the lithium to the sulfinyl oxygen as a previous step to the abstraction of the nearest hydrogen. Both the stability of the TS and that of the resulting carbanion are larger for the abstraction of the proton, resulting in the formation of the anion shown in Fig. 2.

We have recently obtained experimental evidences of both the stereoselective deprotonation of ethyl *ortho*-sulfinyl benzene and the inversion of the configuration of the nucleophilic center by studying deuteration reactions at the benzylic position. Reaction of **2** with LDA and further treatment with



SCHEME 13

deuterated methanol yielded only one monodeutero derivative (**A** in Scheme 13), which means that the reaction is highly stereoselective. The same applies to the protonation of the dideutero derivative, in its reaction with LDA and then with normal methanol, which yields only diastereoisomer **B**. In turn, **B** is the only product formed in the protonation of **A**, which demonstrates that the reaction is taking place with inversion of the configuration at the benzylic position. The same inversion is observed in the deuteration of **B**, that mainly yields **A**. In the latter reaction the isotopic effects determined that the results were not so easily explained.

In conclusion, we have demonstrated that the *ortho*-sulfinyl group is very efficient in the control of 1,4-asymmetric induction processes, which has allowed the synthesis of a variety of benzylic centers with very high optical purities. In addition, although its influence on the stereoselectivity control of 1,5-asymmetric induction processes is not large, when it reacts with prochiral electrophiles, stereocontrol can be achieved by introducing a second chiral auxiliary at the electrophile or, in some cases, by modifying the electronic properties of the substrates.

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