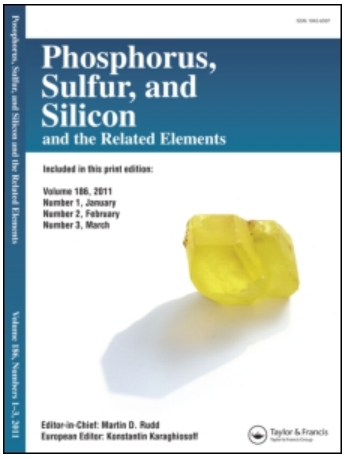

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Highly Stereoselective Reactions of γ-Sulfinyl Carbanions with Achiral Imines

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Lithium 2-p-tolylsulfinylbenzyl carbanions react with different N*-substituted imines affording 1,2-diaryl ethyl (and propyl) amines with a high stereoselectivity control at both benzyllic (only dependent of the sulfur configuration) and iminic carbons. The* anti:syn *ratio, ranging between >96:<4 and <2:>98, dependent on the electronic density at nitrogen.*

Keywords 1,4- and 1,5-Asymmetric induction; asymmetric benzylation; remote stereocontrol with sulfoxides

INTRODUCTION

There are a large number of recent publications involved in the search for new and efficient methods for synthesizing enantiomerically pure 2-arylethyl and propylamines. They are relevant structural subunits because of their frequent occurrence in natural products and their importance as valuable synthetic intermediates.[1] Otherwise enantiomerically pure β-amino alcohols are even more important as key intermediates for the synthesis of biologically active compounds,[2] as stationary phases in HPLC,[3] and as chiral ligands or auxiliaries in asymmetric reactions.[4] Interestingly, the C—C bond disconnection represents the most direct retrosynthetic route for simultaneously creating both chiral centers. In this sense, the nucleophilic addition of organometallic reagents to iminic C=N double bonds[5] is one of the most direct routes

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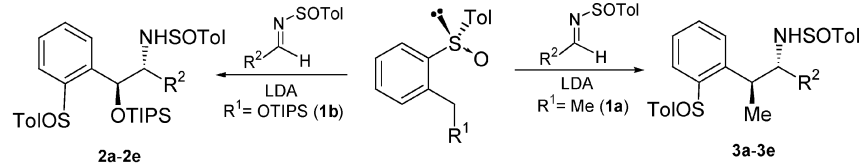
to chiral amine derivatives. Thus the use of the *N*-sulfinylimines as starting compounds has been shown to be highly efficient in the asymmetric addition of organometallic reagents, except for benzylic nucleophiles.[6] In this communication we describe different procedures to achieve the benzylation of C=N in a completely stereocontrolled manner.

RESULTS AND DISCUSSION

We first studied the benzylation of *N*-sulfinylimines by using the enantiomerically pure benzylcarbanion derived from 2-*p*-tolylsulfinyl-2-ethylbenzene (**1a**)[7] as electrophile. Reactions were completely stereoselective[8] even when two new chiral centers are simultaneously created in the formation of 2-arylethyl and propylamines (Scheme 1 and Table I).

TABLE I Yields and de Obtained for Reactions at Scheme 1

R^2	de	Yield (%)
Ph	>98	81
p-$MeOC_6H_4$	>98	78
p-CNC_6H_4	>98	74
Bu	>98	72
i-Bu	>98	89
o-BrC_6H_4	>98	71
2-Py	>98	77
Napht	>98	68
p-CIC_6H_4	>98	76
Ph	>98	82
p-$MeOC_6H_4$	>98	84
p-CNC_6H_4	>98	60
Bu	>98	85
i-Bu	>98	88
t-Bu	>98	89
$PhCH_2$	>98	88
Naph	>98	75
o-BrC_6H_4	>98	87

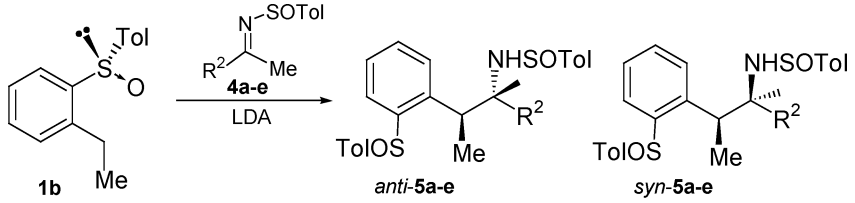


SCHEME 1

Starting from benzylcarbanions derived from 2-*p*-tolylsulfinyl benzyl alcohol (**1b**), we could also prepare the *anti* 1,2-aminoalcohols (Scheme 1), making use of the same procedure.[9] Desulfinylation with Raney–Nickel afforded the corresponding free amines.

Both reactions are good examples of double asymmetric induction processes with the sulfinyl group acting as a chiral inductor at both electrophile and nucleophile, each one controlling the configuration of their closer chiral center. The matched pairs (formed by compounds with *S* configuration) yield the *anti* compounds with diastereomeric excess (de) >98% and very high yields. The reactions are efficient from aliphatic and aromatic aldimines (Scheme 1).

The next step in this research was the study of the reactions of **1a** with *N*-*p*-tolylsulfinylketimines (**4**). The results indicate that the stereoselectivity is also completely controlled in most of the cases, yielding the *anti* compounds **5** (Scheme 2 and Table II). However, the reaction with the *N*-*p*-tolylsulfinyl methyl *p*-cyanophenylidenimine (**4e**) evolves into a 75:25 mixture of *anti*-**5e** and *syn*-**5e**, thus evidencing a significant influence of the electronic density on the stereoselectivity control.



SCHEME 2

These results prompted us to study the behavior of the anions derived from **1a** and **1b** with achiral imines. Our aim was to explore the influence of the steric and electronic factors at the electrophile on the stereochemical course of the reaction and eventually obtain the

TABLE II Results Obtained for Reaction at Scheme 2

R^2	dr (*anti*:*syn*)	Yield (%)
Ph	>99:1<	73
p-$MeOC_6H_4$	>99:1<	64
p-MeC_6H_4	>99:1<	69
p-CNC_6H_4	75:25	27
n-Bu	No reaction	—
i-Bu	No reaction	—

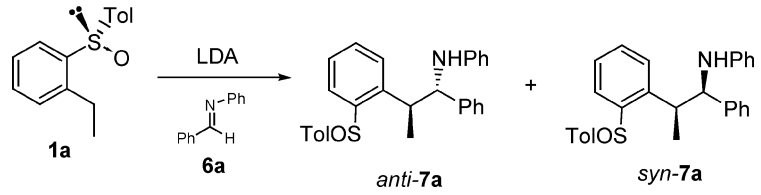
TABLE III Structure of the Studied *N*-Benzylidenanilines (Ar^1-CH=N-Ar^2)

Imine	Ar^1	Ar^2	Imine	Ar^1	Ar^2
6a	Ph	Ph	**6i**	*p*-CN-C_6H_4	Ph
6b	Ph	*p*-CN-C_6H_4	**6j**	*p*-Me-C_6H_4	Ph
6c	Ph	*p*-Cl-C_6H_4	**6k**	*p*-MeO-C_6H_4	Ph
6d	Ph	*p*-Me-C_6H_4	**6l**	3,4-di-MeO-C_6H_4	Ph
6e	Ph	*p*-MeO-C_6H_4	**6m**	2,4-di-MeO-C_6H_4	Ph
6f	Ph	3,4-di-MeO-C_6H_4	**6n**	2,4,6-tri-MeO-C_6H_4	Ph
6g	Ph	2,4-di-MeO-C_6H_4	**6o**	*p*-MeO-C_6H_4	*p*-MeO-C_6H_4
6h	Ph	2,4,6-tri-MeO-C_6H_4			

syn-compounds by modulating their features. It would make the reaction stereodivergent and much more versatile from a synthetic point of view.

We first synthesized the *N*-benzylidenaniline **6a** and their derivatives **6b–o** (Table III) containing electron-withdrawing and electron-donating groups at the two phenyl rings, by reacting substituted anilines with benzaldehydes under the presence of molecular shieves.

The reaction of **1a** with the imine **6a** yielded a 91:9 epimeric mixture of *anti*-**7a** and *syn*-**7a**, both exhibiting the same configuration at benzylic carbon (Scheme 3). It demonstrates that this is completely controlled by the sulfinyl group at **1a**, which also has a significant influence on the configuration induced at the nitrogenated center. Both compounds can be easily obtained in an optically pure form after chromatographic purification.



1a **6a** *anti*-**7a** *syn*-**7a**

SCHEME 3

At this point we evaluated the influence of the substituent at the *N*-aryl group. Electron-withdrawing substituents increased the *anti*/*syn* relationship whereas electron-donating groups decreased and even inverted it. The reaction of **1** with **6h** is completely stereoselective, only yielding compound *syn*-**7h** (Scheme 4 and Table IV).

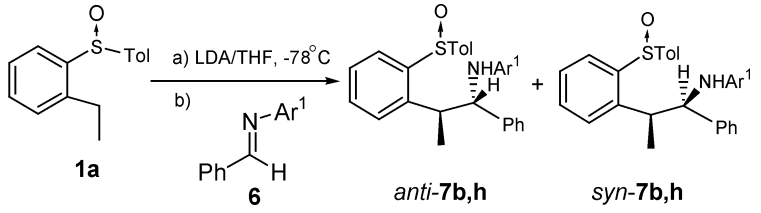
A similar influence is exerted by the substituent when they are located at the aromatic ring of the arylideneimine (Scheme 5 and Table V), except for **6n**, where the presence of two MeO groups at both

TABLE IV Results Obtained for Reaction at Scheme 4

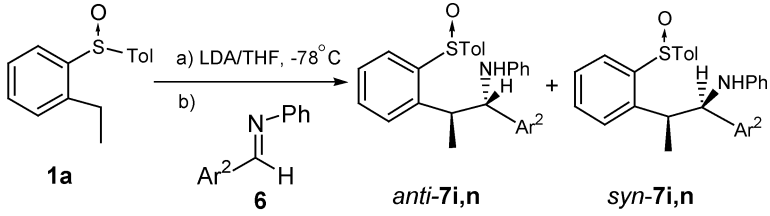
6	*anti*-**7b,h**	*syn*-**7b,h**
6b(*p*-CN)	96	4
6c(*p*-Cl)	85	15
6d(*p*-Me)	66	33
6e(*p*-MeO)	36	64
6f(3,4-di-MeO)	23	77
6g(2,4-di-MeO)	1	99
6h(2,4,6-tri-MeO)	1	99

TABLE V Results Obtained for Reaction at Scheme 5

6	*anti*-**7i,n**	*syn*-**7i,n**
6i(*p*-CN)	99	1
6j(*p*-Me)	78	22
6k(*p*-MeO)	41	59
6l(3,4-di-MeO)	33	67
6m(2,4-di-MeO)	1	99
6n(2,4,6-tri-MeO)	34	66



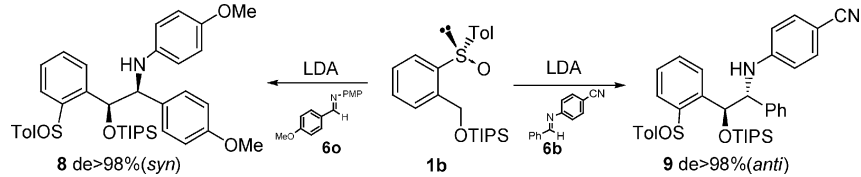
SCHEME 4



SCHEME 5

ortho positions has a negative influence on the stereoselectivity that must be due to a steric inhibition of the resonance that is not present when such groups are in the *N*-aryl ring (see **6h** in Table IV).

To illustrate the scope of this powerful methodology, we have applied it to the synthesis of the amine-alcohols starting from **1b**. Its reaction with the imine **6b** yielded only the *anti* diastereoisomer **8**, whereas the *syn*-**9** was exclusively formed in the reaction with the imine **6o**, with both aromatic rings substituted with electron donating groups (Scheme 6).



SCHEME 6

As conclusion we have found that γ-sulfinyl carbanions derived from 2-*p*-tolylsulfinyl ethyl and hydroxymethyl benzenes are quite efficient to control the stereoselectivity of the reactions with *N*-sulfinylimines, yielding the corresponding *anti* derivatives. *N*-arylimines derived from benzaldehydes yielded *syn* or *anti* isomers depending on the electronic density at iminic nitrogen.[10]

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