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Facile Synthesis of Optically Pure 1,2-Diaryl (and 1-Alkyl-2-aryl) Ethyl and Propylamines

José L. García Ruano,* José Alemán, and José F. Soriano

Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain

joseluis.garcia.ruano@uam.es

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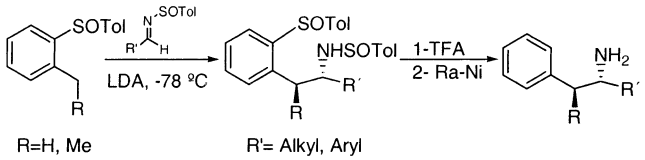
ABSTRACT



A concise high-yielding route to synthetically useful 1,2-diaryl (and 1-alkyl-2-aryl) ethyl and propylamines in high enantiomeric purity is described. The key step of this route is the completely stereoselective addition of lithium (*R*)-*ortho*-(*p*-toluenesulfinyl)benzylic carbanions to (*S*)-*N*-*p*-toluenesulfinylimines, which takes place in very high or quantitative yields. N-Desulfinylation and C-desulfinylation of the resulting adducts can be achieved with no loss of optical purity employing conventional methods (TFA and Raney-Ni, respectively).

Enantiomerically pure 2-arylethyl and propylamines are relevant structural subunits because of their frequent occurrence in natural products and their importance as valuable synthetic intermediates.[1] The nucleophilic addition of organometallic reagents to iminic C═N double bonds[2] is a synthetically attractive route to chiral amine derivatives. Moderate reactivity and stereoselectivity, usually observed when using imines, can be substantially improved by using enantiopure *N*-sulfinylimines.[3] The diastereoselectivity of these reactions is usually high, as has shown by several authors, the most significant contributions being those from Davis'[4] and Ellman's groups.[5] Despite the success of these approaches, the benzylation of *N*-sulfinylimines, which affords 2-arylethylamines, remains elusive because it usually proceeds with only moderate stereoselectivity. The first systematic study of these reactions was performed in 1997 by Moreau,[6] who reported the reaction of BnMgCl with different *N*-*p*-tolylsulfinyl aromatic aldimines. These reactions evolved with 60−74% des. Davis and co-workers[7] observed better diastereoselectivities (up to 88% de) by using *N*-*t*-butanesulfinylimines derived from glyoxylic esters.[8] Some of the results recently reported by Davis' group could suggest that the use

(1) Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, pp 27−29.

(2) (a) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 1.12, p 355. (b) Risch, N.; Arend, M. In *Methods of Organic Chemistry* (Houben-Weyl): *Stereoselective Synthesis;* Helmechen, G., Hoffmann, R. W., Mulzer, J., Schauman, E., Eds.; Georg Thieme Verlag: Stutgart, 1995, E21b; D.1.4, p 1833. (c) Enders, D.; Reinhold, U. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1895. (d) Pridgen, L. N. *Adv. Asymm. Synth.* **1997**, *2*, 55.

(3) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555.

(4) (a) Davis, F. A.; Zhou, P.; Chen, B. C. *Chem. Soc. Rev.* **1998**, *27*, 13 and references therein. (b) Recent references; Davis, F. A.; Prasad, K. R.; Carroll, P. J. *J. Org. Chem.* **2002**, *67*, 7802. (c) Davis, F. A.; Deng, J.; Zhang, Y.; Haltiwanger, R. C. *Tetrahedron* **2002**, *58*, 7135. (d) Davis, F. A.; Chao, B.; Andemichael, Y. W.; Mohanty, P. K.; Fang, T.; Burns, D. M.; Rao, A.; Szewczyk, J. M. *Heteroat. Chem.* **2002**, *13*, 486.

(5) (a) Liu, G.; Cogan, D. A.: Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278. (b) Cogan, D. A.; Liu, G.; Kim, K.: Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011. (c) Cogan, D. A.; Liu. G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883. (d) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12. (e) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. (f) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.

(6) Moreau, P.; Essiz, M.; Merour, J.-Y.; Bouzard, D. *Tetrahedron*: *Asymmetry* **1997**, *8*, 591.

(7) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396.

(8) However, *N*-*t*-butanesulfinylimines with alkoxy groups at C-α afforded poorer stereoselectivity in the attack of benzylic anions (0−55% de); see: Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051.

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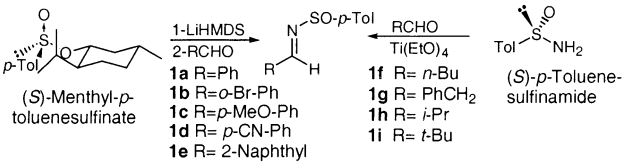
of *ortho*-substituted benzyl carbanions would improve the stereoselectivity. Thus, one diastereomer was almost exclusively formed in reactions of *ortho*-carboxamide[9,11] and *ortho*-cyano[10] benzyl carbanions with *N*-sulfinylalkylaldimines. Nevertheless, the lower de (76−80%) observed for the addition of *ortho*-cyano benzyl carbanion to *N*-*p*-tolylsulfinylarylaldimines pointed out that this tendency was not general.[11] Bearing in mind these antecedents, the development of a new general procedure for the highly stereoselective benzylation of imines remained a synthetic challenge. The fact that optically pure substituted 2-arylethylamines have been widely used in the synthesis of tetrahydroisoquinolines, as well as other more elaborated structures containing such a skeleton,[11,12] increases the interest of the development of new methods for the preparation of 2-arylethylamines. Additionally, to the best of our knowledge there are no reported highly stereoselective approaches to 2-aryl propylamines containing chiral centers at both C-1 and C-2.

We have recently reported that α-sulfinyl carbanions derived from ethyl *p*-tolyl sulfoxides react with *N*-*p*-tolylsulfinylimines derived from aromatic aldehydes with complete control of the stereoselectivity at the two newly created chiral centers.[13] Since some problems associated with the use of benzyl α-sulfinyl carbanions as nucleophiles were to be expected,[14] we decided to investigate the behavior of benzyl carbanions bearing the sulfinyl group at the *ortho* position, which had already been successfully used in reactions with carbonyl compounds.[15] We reasoned that the stereoselectivity of the benzylation of *N*-sulfinylimines could be sharply increased by using *ortho*-sulfinyl benzyl carbanions, as a consequence of a double asymmetric induction process. Additionally, the use of methyl benzyl carbanions would allow the exploration of the scope of these reactions in the simultaneous control of two chiral centers. In this paper, we report the results obtained in the completely stereoselective reactions of different *N*-*p*-tolylsulfinylimines (**1a**−**i**), derived from aromatic and aliphatic aldehydes, with 2-*p*-tolylsulfinyl toluene (**2**) and 2-*p*-tolylsulfinyl ethylbenzene (**4**). Application of this method to the preparation of 1,2-diaryl (and 1-alkyl-2-aryl) ethyl and propylamines through a facile desulfinilation protocol is also described.

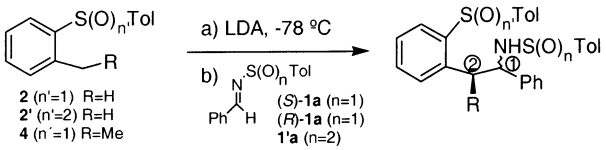
Enantiopure sulfinylimines **1** were prepared in good yields according to Davis' procedures (Scheme 1) starting from (*S*)-menthyl sulfinate[16] (for aryl aldehydes) or *p*-toluenesulfinamide[17] (for alkyl aldehydes). Aryl imines were isolated by crystallization[18] and alkyl imines by chromatography. The configurational assignment of compounds **1b** and **1d**, which had not been previously described, was based on the generally accepted reaction pathway involved in their preparation.

Scheme 1



To determine whether the sulfinyl group at the nucleophile played any role in the stereochemical course of the addition reaction and to identify, in such a case, the matched pair, we first studied the reactions of (*S*)-*ortho*-2-*p*-tolylsulfinyl toluene[19] (**2**) with (*R*)-**1a**, (*S*)-**1a**, and their corresponding sulfone **1′a**. In this context, the reaction of sulfone **2′** with (*S*)-**1a** (Table 1) was also investigated.

Table 1. Reaction of **2** and **4** with *N*-Thioderivative Imines from Benzaldehyde



entry	reagents	sulfoxide configuration	imine configuration	de (%) (configuration of C-1)
1	**2′** + (*S*)-**1a**		*S*	64 (*S*)
2	**2** + **1′a**	*S*		38 (*S*)
3	**2** + (*R*)-**1a**	*S*	*R*	56 (*R*)
4	**2** + (*S*)-**1a**	*S*	*S*	>98 (*S*)
5	**4** + (*S*)-**1a**	*S*	*S*	>98 (*S*)
6	**4** + (*R*)-**1a**	*S*	*R*	4 (*S*)

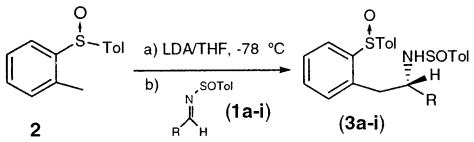
The sulfonyl group at the *ortho* position of the benzyl carbanion (generated by treatment of **2′** with LDA) has scarce influence on the stereoselectivity of its addition to (*S*)-**1a** (64% de, entry 1), which is identical to that observed for reaction of (*S*)-**1a** with BnMgCl.[5] On the other hand, we focused our attention on finding whether there is any significant influence of the sulfinyl group at the nucleophile on the stereoselectivity of the addition to the C═N bond. In

(9) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*, 3902.
(10) Davis, F. A.; Andemichael, Y. W. *Tetrahedron Lett.* **1999**, *49*, 3099.
(11) In this work, the use of the sterically more demanding *N*-naphalenesulfinyl arylimine was required to increase the de up to 96%. See: Davis, F. A.; Pradyudmna, K. M. *J. Org. Chem.* **2002**, *67*, 1290.
(12) Recent references: (a) Cutter, P. S.; Miller, R. B.; Schore, N. E. *Tetrahedron* **2002**, *58*, 1471. (b) Laumer, J. M.; Kim, D. D.; Beak, P. *J. Org. Chem.* **2002**, *67*, 6797. (c) Katritzky, A. R.; Suzuki, K.; He, H.-Y. *J. Org. Chem.* **2002**, *67*, 8224.
(13) García Ruano, J. L.; Alcudia, A.; Prado, M.; Barros, D.; Maestro, M. C.; Fernandez, I. *J. Org. Chem.* **2000**, *65*, 2856.
(14) Moderate configurational stability of benzyl sulfoxides due to the sulfoxide−sulfenate rearrangement and, mainly, low thermal stability of the amines resulting from their reactions with *N*-sulfinylimines, prone to desulfinylation, should be expected.
(15) García Ruano, J. L.; Aranda, M.; Carreño, M. C.; Toledo, M. A.; *Angew. Chem., Int. Ed.* **2000**, *39*, 2736.
(16) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S., *Tetrahedron Lett.* **1993**, *34*, 6229.
(17) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.
(18) This allowed for the rapid preparation of these compounds on a multigram scale, with no chromatographic separation being needed.
(19) See Supporting Information for experimental details concerning the synthesis of this compound.

this sense, the reaction of (*S*)-**2** with achiral sulfonamide **1′a** evolved with a 38% de (entry 2), the (1*S*)-amine being favored.[20] On the basis of this influence, the results we obtained in reactions of the sulfoxide **2** with the imines **1a** were not unexpected. The reaction with (*R*)-**1a** (entry 3) afforded a mixture of amines with 56% de ((1*R*)-isomer being predominant), lower than that observed in reactions with benzyl Grignard.[5] However, to our delight, the exclusive formation of the disulfinylated 1,2-diphenyl ethylamine **3a** (>98% de, measured by ^{1}H NMR) in almost quantitative yield was observed when (*S*)-**2** reacted with (*S*)-**1a** (entry 4) under the same conditions (LDA; THF at −78 °C for 10 min).[21] These results indicated that reagents with identical configurations at the sulfur atoms conform with the matched pair.

With these results in hand, the reactions of (*S*)-**2** with a variety of imines **1b**−**i**, all of them with the (*S*)-configuration, were studied. De values higher than 98% (measured by ^{1}H NMR) and almost quantitative isolated yields were obtained in all cases, regardless of the aliphatic or aromatic nature of the imine and the electronic effect of the substituent on the aromatic ring (Table 2).

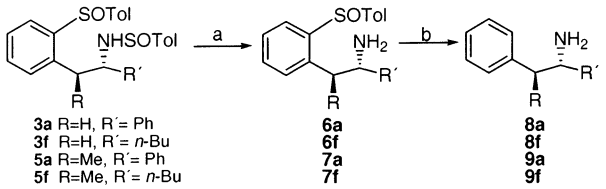
Table 2. Reactions of **2** with *N*-Sulfinylimines (*S*)-**1a**−**i**



entry	products	isolated yield (%)	de (%)
1	(R = Ph) **3a**	quantitative	>98
2	(R = *o*-BrC_6H_4) **3b**	91	>98
3	(R = *p*-MeOC_6H_4) **3c**	quantitative	>98
4	(R = *p*-CNC_6H_4) **3d**	88	>98
5	(R = Naph) **3e**	quantitative	>98
6	(R = *n*-Bu) **3f**	95	>98
7	(R = Ph-CH_2) **3g**	93	>98
8	(R = *i*-Pr) **3h**	94	>98
9	(R = *t*-Bu) **3i**	91	>98

The absolute configuration of **3i** was unequivocally established by X-ray analysis (see Supporting Information), whereas that of **3a** was assigned by chemical correlation with **8a** (see Scheme 2), whose enantiomer had been previously reported.[5] The configuration at C-1 of **8f**, obtained from **3f** after N- and C-desulfinylation (Scheme 2), was established as (*R*)[22] by studying its corresponding Mösher amides.[23] We

Scheme 2[a]



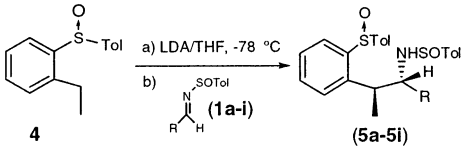
[a] Reaction conditions: (a) TFA, MeOH (>90%). (b) Raney-Ni, THF (72−78%).

proposed the configuration depicted in Table 2 for compounds **3a**−**i** by assuming identical stereochemical evolution for all the imines.

To investigate the possibilities of these reactions to achieve the simultaneous control of the configurations at C-1 and C-2 when both are chiral centers, we studied the reactions of (*S*)-2-*p*-toluenesulfinyl ethylbenzene (**4**) with (*R*)-**1a** and (*S*)-**1a**. Once again, the mismatched pair is that formed by (*S*)-**4** and (*R*)-**1a**, yielding an almost equimolecular mixture of two isomers (4% de, entry 6) that exhibit the same configuration at the benzyl carbon. This indicates that both sulfinyl groups generate a similar level but an opposite sense of asymmetric induction at C-1, whereas that at C-2 is exclusively controlled by the sulfinyl group at the nucleophile. Complete control of the stereoselectivity at both chiral centers is also observed in reaction of (*S*)-**4** and (*S*)-**1a**, which represent the consonant pair, only yielding one diastereomer (>98% de, entry 5, Table 1).

Then we studied the reactions of compound **4** with imines **1b**−**i** in the presence of LDA. The results are collected in Table 3. As expected, the reactivity of **4** was slightly lower

Table 3. Reactions of **4** with *N*-Sulfinylimines (*S*)-**1a**−**i**



entry	products	isolated yield (%)	de (%)
1	(R = Ph) **5a**	82	>98
2	(R = *o*-BrC_6H_4) **5b**	87	>98
3	(R = *p*-MeOC_6H_4) **5c**	84	>98
4	(R = *p*-CNC_6H_4) **5d**	60	>98
5	(R = Naph) **5e**	75	78
6	(R = *n*-Bu) **5f**	85	>98
7	(R = Ph-CH_2) **5g**	88	>98
8	(R = *i*-Pr) **5h**	88	>98
9	(R = *t*-Bu) **5i**	89	>98

than that of **2**,[24] and the yields ranged between 60 and 89%. The stereoselectivity remained complete in all cases (>98% de) except for the reaction of **1e**, affording a 89:11 mixture of two propylamines, **5e** and **5′e**, presumably epimers at C-1.[25]

(20) From the results obtained in reactions of **4** with other achiral *N*-aryl aldimines, we have checked that the level of the asymmetric induction depends on the group joined to the iminic nitrogen. De values become higher than those achieved by benzylation of *N*-sulfinylimines in ref 5. These results will be published in due course.

(21) Reactions of **2** and **4** with (*S*)-**1a** could be successfully performed on a gram scale (see Supporting Information for experimental details).

(22) The (*R*) or (*S*) stereochemical notation assigned to C(1) in compounds **3** and **5**−**9** depends on the nature of the R group.

(23) Kusumi, T.; Fukushima, T.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2939.

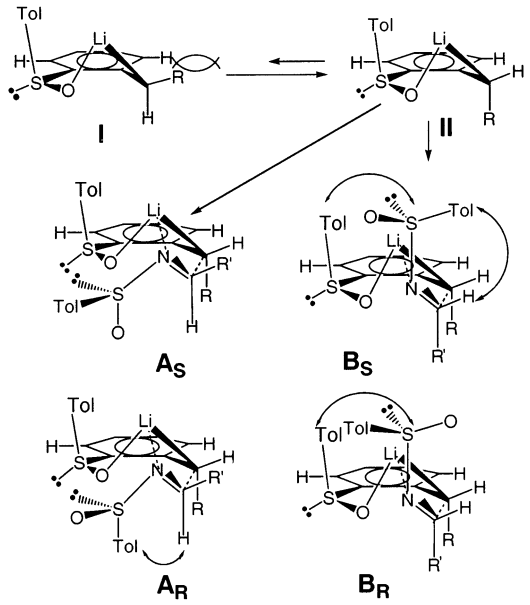


Figure 1. Stereochemical model explaining the reactions of **2** and **4** with *N*-sulfinylimines **1**.

The absolute configurations of **5h** and **5i** were assigned by X-ray crystallography as (1*R*,2*S*) and (1*S*,2*S*),[22] respectively (see Supporting Information).[26] The configuration at C-1 of **9f**, obtained from **5f** by N and C-desulfinylation (Scheme 2), was established as (*R*)[22] by studying its Mösher amides.[23] The amine **5a** was chemically correlated with **9a** (Scheme 2), whose enantiomer had been previously reported.[27]

The initial formation of a benzyllithium intermediate, stabilized by the *ortho*-sulfinyl oxygen, allows us to explain the stereochemical results. This species must exhibit the *p*-tolyl group at the sulfur atom in a pseudo *axial* arrangement (**I** and **II** in Figure 1) in the half-chair conformation of the six-membered ring, thus avoiding any allylic strain with the aromatic *ortho* proton.[15] The approaches of the imine could take place according to an almost concerted mechanism through a four-membered cyclic transition state involving the simultaneous formation of the C−C and Li−N bonds, the first one being more developed (Figure 1).

Each (*R*)- or (*S*)-imine may approach the benzyllithium intermediate in two different ways[28] (**A** and **B**, in Figure 1). In reactions of **2** (R = H, **I** and **II** are identical) with (*S*)-**1**, $\mathbf{A_S}$ must be strongly favored with respect to $\mathbf{B_S}$ (Figure 1), the latter being destabilized by the steric interactions $(Tol/H)_{1,3-diaxial}$ and (Tol/SOTol) (adopting an almost 1,3-diaxial arrangement) and dipolar repulsion between the C=N and S−O dipoles (lower in $\mathbf{A_S}$ with the sulfinyl oxygen in an s-cis arrangement). This model would account for the exclusive formation of compounds **3** (Table 2) in all these reactions. According to the same model, a higher stereoselectivity could be expected from **4** (R = Me, **II** would be clearly favored with respect to **I** due to the allylic strain), where $\mathbf{B_S}$ would be additionally destabilized by the interaction between the almost eclipsed Me and R′ groups.[29] The lower de observed in reactions of the mismatched pair, **2** and (*R*)-**1a** (entry 3, Table 1), can be explained with the same stereochemical model. In this case, the stability differences between $\mathbf{A_R}$ and $\mathbf{B_R}$ are not as large as in the matched pair [C=N/S−O dipolar repulsion and steric $(Tol/H)_{1,3-diaxial}$ interaction destabilize $\mathbf{A_R}$ with respect to $\mathbf{A_S}$ but stabilize $\mathbf{B_R}$ with respect to $\mathbf{B_S}$], which accounts for the decrease in the de, as shown in Table 1. According to the experimental results, $\mathbf{A_R}$ is seemingly less stable than $\mathbf{B_R}$ in the case of **2** (entry 3, Table 1) but slightly more stable in the case of **4** (entry 6, Table 1), where the interaction between the Me group at the nucleophile and R′ at the imine would cause an additional destabilization of $\mathbf{B_R}$.

Hydrolysis of the N−S bond of compounds **3** and **5** with TFA/methanol followed by C-desulfinylation of the resulting free amines **6** and **7** with Raney Ni in THF[30] afforded a wide variety of 1,2-diaryl (and 1-alkyl-2-aryl) ethyl and propylamines. The reaction took place in high yields for compounds **3a**, **3f**, **5a**, and **5f** with no loss of optical purity.[31]

In conclusion, the benzylation of *N*-*p*-toluenesulfinylimines can be achieved under smooth conditions in a completely stereoselective manner by introduction of a sulfinyl group with the proper configuration at the *ortho* position of the benzyl carbanion. The broad 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) ethyl and propylamines.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1b**, **1d**, **2**, **3**, and **5**−**9** and X-ray data for **3i**, **5i**, and **5h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Reactions of compound **4** required 30−40 min for completion, whereas less than 20 min were required for the reactions of compound **2**.

(25) Stereochemistry for **5′e** has not been unequivocally established.

(26) Atomic coordinates for **5h**, **5i**, and **3i** have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers CCDC 197 388, 197 389, and 197 390, respectively). The coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge Cb2 1EZ, UK.

(27) Berova, N. D.; Kurtev, B. J. *Tetrahedron* **1969**, *25*, 2301.

(28) Favored conformations around the N−S bond in these approaches are those displaying the lone electron pair at sulfur oriented towards the anion, thus minimizing the interactions between both SOTol groups.

(29) $\mathbf{A_S}$ approach will be relatively destabilized in the case of the reaction of **4** with **1e** because of the orientation of the naphthalene ring, which would strongly interact with the methyl group at benzyl carbanion. This would explain the lower de observed in the entry 5 of Table 3.

(30) Lower yields of some unidentified amine derivatives are obtained by using EtOH as the solvent.

(31) De values higher than 98% were determined for **8f** and **9f** by using the Mösher amides protocol. The same conclusion could be deduced for **8a** and **9a** from their specific rotations (see Supporting Information).