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Asymmetric Synthesis of Indolines through Intramolecular Shifting of Aromatic Sulfinyl Groups. Role of the π,π-Stacking Interactions in these Unusual S_NAr Processes

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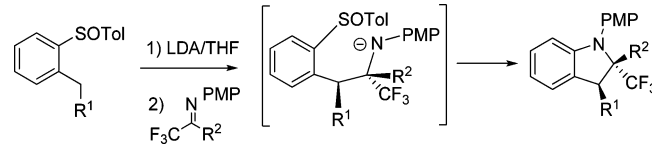
Abstract: Cyclization of *N*-aryl substituted 1-aryl-2[2-*p*-tolylsulfinyl]phenyl propylamines under LDA, LHMDS, or KHMDS provides a new approach for synthesizing optically pure 2,3-disubstituted indolines. Both the scope and the limitations of this method have been investigated. The π,π-stacking interactions are crucial for these unprecedented intramolecular S_NAr processes, in which a sulfinyl group located on a slightly deactivated ring is substituted by amide anions under mild conditions. X-ray and NMR proofs supporting these π,π-stacking interactions are presented.

Introduction

The importance of the indoline skeletons, present in the structure of alkaloids[1] and other natural products with diverse biological activities[2] and considered as privileged structures[3] due to their widespread use as building blocks and as chiral auxiliaries in asymmetric synthesis,[4] has determined that numerous synthetic multistep strategies[5] have been developed. However, the lack of short and efficient methods for obtaining optically pure substituted indolines has left researchers with the challenge of finding new, simpler methods for their preparation.

Scheme 1



We have recently reported that reactions of 2-*p*-tolylsulfinyl benzylcarbanions with *N*-*p*-methoxyphenyl (PMP) fluorinated imines produce indolines with almost complete control of the stereoselectivity[6] (Scheme 1). These reactions involve a tandem A_N/S_NAr process. The first step, the nucleophilic addition of the sulfinylated benzylcarbanion to the fluorinated imine, takes place in a completely stereoselective manner as previously observed with other imines.[7] Subsequent intramolecular cyclization appears to involve a nucleophilic aromatic substitution of the amide anion intermediate in which the sulfinyl group acts as the leaving group.

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(1) (a) Gan, Z.; Reddy, P. T.; Quevillon, S.; Couve-Bonaire, S.; Arya, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1366. (b) Nicolaou, K. C.; Rao, P. B.; Hao, J.; Reddy, M. V.; Rassias, G.; Huang, X.; Chen, D. Y.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1753. (c) Ori, M.; Toda, N.; Takami, K.; Tago, K.; Kogen, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2540.

(2) (a) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. (b) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *J. Org. Culghem.* **2006**, *71*, 8316, and references cited therein. (c) Ontoria, J. M.; Marco, S. D.; Conte, M.; Di Francesco, M. E.; Gardelli, C.; Koch, U.; Matassa, V. G.; Poma, M.; Steinkühler, C.; Volpari, C.; Harper, S. *J. Med. Chem.* **2004**, *47*, 6443. (d) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (e) Hesse, M. *Alkaloide*; Verlag Helvetica Chimica Acta Zürich, Wiley-VCH: Weinheim, 2000.

(3) The concept of privileged structures was first introduced by Evans and recently updated by Patchett. (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; Dipardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirschfield, J. J. *J. Med. Chem.* **1988**, *31*, 2235. (b) Patchett, A. A.; Nargund, R. P. *Annu. Rep. Med. Chem.* **2000**, *35*, 289.

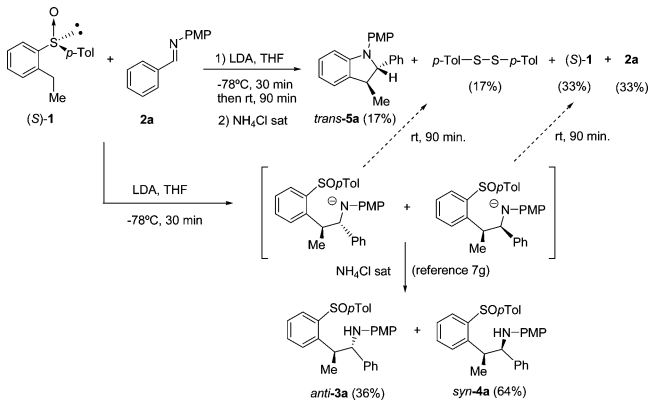
(4) Andersson, F.; Hedenström, E. *Tetrahedron: Asymmetry* **2006**, 1952, and references cited therein.

(5) Recent references representative of the different strategies used for preparing indolines: (a) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255. (b) Yamamoto, H.; Pandey, G.; Asai, Y.; Nakano, M.; Kinoshita, A.; Namba, K.; Imagawa, H.; Nishizawa, M. *Org. Lett.* **2007**, *9*, 4029. (c) Benniaza, R.; Dunet, J.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2007**, *9*, 3913. (d) Wang, Z.; Wan, W.; Jiang, H.; Hao, J. *J. Org. Chem.* **2007**, *72*, 9364. (e) Jin, W.; Trzupek, J. D.; Rayl, T. J.; Broward, M. A.; Veilhauer, G. A.; Weir, S. J.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2007**, *129*, 15391. (f) Fuwa, H.; Sasaki, M. *Org. Lett.* **2007**, *9*, 3347. (g) Zhang, G.; Catalano, V. J.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 11358. (h) Snyder, B. B.; Wu, X. *Org. Lett.* **2007**, *9*, 4913. (i) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, *9*, 279. (j) Matsuda, Y.; Katahima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125. (k) Silva-López, C.; Pérez-Valado, C.; Rodríguez-Graña, C.; de Lera, A. R. *Org. Lett.* **2008**, *10*, 77.

(6) García Ruano, J. L.; Alemán, J.; Catalán, S.; Marcos, V.; Monteagudo, S.; Parra, A.; del Pozo, C.; Fustero, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7941.

 10.1021/ja8096527 CCC: $40.75

Scheme 2



Considering the interest in new methods for generating enantiomerically pure substituted indolines, it was necessary to determine whether our method was applicable to the synthesis of nonfluorinated indolines, as well as to delimit its possible structural restrictions. We were also interested in examining two mechanistic aspects of the S_NAr step in more depth. First, nucleophilic substitution of a sulfinyl group is seldom exploited in this type of process;[8] what enables this transformation in our work? Second, the sulfinyl group is a moderately deactivated α-alkylaryl ring; how can the mild conditions[9] employed in these transformations be explained? In this paper, we report on the results of the reactions of different (2-*p*-tolylsulfinyl)phenyl ethylamines with bases to provide a new entry for the asymmetric synthesis of enantiomerically pure 2,3-disubstituted indolines on the basis of the direct formation of the N−C(aromatic) bond according to a S_NAr process. After establishing the structural requirements needed for the success of this cyclization, we proposed a significant role for π,π-stacking interactions to better understand the evolution of these unusual S_NAr reactions.

Results and Discussion

When sulfoxide (*S*)-**1** reacted with LDA and the *N*-PMP benzylideneimine **2a** for 30 min at −78 °C and the resulting reaction mixture was then protonated at the same temperature, a 36:64 mixture of *anti*-**3a** and *syn*-**4a** amines was obtained[7g] (Scheme 2). In contrast, when the reaction was maintained at −78 °C for 30 min and then left for 90 min at room temperature (rt) before protonation (conditions that are commonly used in the direct synthesis of indolines from fluorinated imines), a mixture of four easily isolated products was obtained (Scheme 2). These included the two starting products, (*S*)-**1** and **2a**, in similar amounts (66% combined yield), along with two new compounds in the same ratio (34% combined yield). The two latter compounds, identified with the aid of spectroscopic methods as *p*-tolyl disulfide and *trans*-**5a** indoline (Scheme 2), both seem to result from the intramolecular substitution at rt of the *p*-Tol-SO- group by the amide anion derived from *anti*-**3a** (the sulfinyl moiety is eliminated as *p*-tolenesulfenic acid, which is then readily converted into *p*-Tol−S−S−*p*-Tol[10]). The amount of the recovered starting products (*S*)-**1** and **2a** suggests that they are formed from the amide anion derived from *syn*-**4a**, which indicates that the nucleophilic addition is reversible at rt and that, in the case of *syn*-**4a**, this reversal is preferred over its indoline cyclization.

To confirm this hypothesis, we first studied the behavior of *anti*-**3a** (prepared in accordance with the method outlined in ref 7g) with LDA and LHMDS (easier to handle) at rt. In both cases, a complete conversion to *trans*-**5a** and *p*-Tol−S−S-*p*-Tol was observed after 90 min. This result indicates that intramolecular substitution of the sulfinyl group is possible from *anti*-**3a** despite slight deactivation of the aromatic ring. In order to evaluate the scope of this reaction, we reacted various *N*-aryl derivatives of *anti*-1,2-diarylpropylamines (**3b**−**3n**) with LHMDS (Table 1). Starting from the *N*-**PMP** derivatives **3a**−**3e**, the reactions took place under mild conditions (only **3e** required reflux in THF to produce a 34% conversion). Reaction time increases were necessary when the electronic density of the ring joined to C-1 decreased. Thus, the *N*-phenyl derivatives (**3f**−**3h**) showed the same tendency (entries 6−8), but their reactivity was lower than that of the PMP derivatives (all of these reactions were performed at 70 °C). *N*-*p*-Chlorophenyl derivatives **3j**−**3l** required even longer reaction times in refluxing THF to evolve into the corresponding indolines (entries 10−12), with **3l** giving a conversion of only 40%. Finally, we found that *N*-*p*-cyanophenyl derivatives were not able to react under similar conditions, even after 48 h in refluxing THF. In all cases in which the reaction did not take place or the conversion was incomplete, starting amine **3** was not recovered, but precursor (*S*)-**1** and imine **2** were, a finding that points to the reversible character of the nucleophilic addition under these conditions and the higher stability of the starting products.

When the reactions were performed with KHMDS as base, the reactivity increased substantially, especially when 18-crown-6 ether was added (Table 1). Thus, compound **3a** reacted almost instantaneously under these conditions (entry 3) while **3e** required 24 h for its conversion to *trans*-**5e** (entry 5). Anilines **3g** and **3h** reacted in less than 5 min at rt (entries 7 and 8) and **3l** required just 3 h for complete conversion at 70 °C. Compound **3m**, which did not react with LHMDS, evolved with KHMDS in 24 h (entry 13), but **3n** was recovered unaltered after 48 h at 70 °C with KHMDS (entry 14). This substantial increase in reactivity in the presence of a different base had previously been observed in the cyclization of fluorinated amines.[6] These results indicate that reactions of amines *anti*-**3** with the indicated bases constitute a good general method for obtaining *trans*-**5** indolines. We have also studied the behavior of the amines *anti*-**3o** and *anti*-**3p**, derived from 3,4-dimethoxyaniline (see Supporting Information), with KHMDS, in order to check that their reactivity was respectively higher than that of **3a** and **3e**

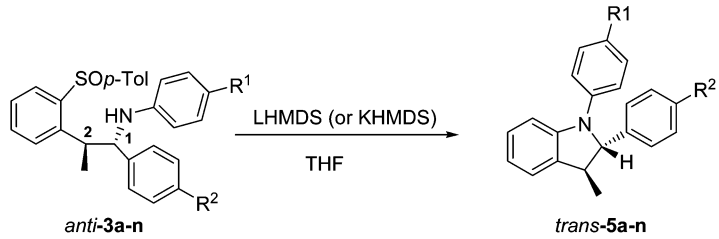
(7) (a) García Ruano, J. L.; Alemán, J.; Soriano, J. F. *Org. Lett.* **2003**, *5*, 677. (b) García Ruano, J. L.; Alemán, J. *Org. Lett.* **2003**, *5*, 4513. (c) García Ruano, J. L.; Alemán, J.; Parra, A. *J. Am. Chem. Soc.* **2005**, *127*, 13048. (d) Arroyo, Y.; Meana, A.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; García Ruano, J. L. *J. Org. Chem.* **2005**, *70*, 3914. (e) García Ruano, J. L.; Aleman, J.; Cid, M. B. *Synthesis* **2006**, 687. (f) Arroyo, Y.; Meana, A.; Rodriguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; Garcia Ruano, J. L. *J. Org. Chem.* **2006**, *62*, 8525. (g) García Ruano, J. L.; Aleman, J.; Alonso, I.; Parra, A.; Marcos, V.; Aguirre, J. *Chem.—Eur. J.* **2007**, *13*, 6179.

(8) Rossi, R. A.; Pierini, A. B.; Peñeñory, A. B. *Chem. Rev.* **2003**, *103*, 71.

(9) The low number of references on intramolecular S_NAr (see ref 8) always deal with strongly deactivated rings bearing very good leaving groups (−F or $-NO_2$). See: (a) Jawdosiuk, M.; Kmiotek-Skarzinska, I.; Czarnecka, E. *Pol. J. Chem.* **1978**, *52*, 1837. (b) Fekner, T.; Gallucci, J.; Chan, M. K. *Org. Lett.* **2003**, *5*, 4795. (c) Buttero, P.; del; Molteri, G.; Papagni, A.; Pilati, T. *Tetrahedron* **2003**, *59*, 5259. (d) Domingos, J. B.; Longhinotti, E.; Bunton, C. A.; Faruk, N. *J. Org. Chem.* **2003**, *68*, 7051. (e) Bowman, W. R.; Heaney, H.; Smith, P. H. G. *Arkivoc* **2003**, 434. (f) Crowley, B. M.; Mori, Y.; McComas, C. C.; Tang, D.; Boger, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 4310.

(10) Davis, F. A.; Arthur, J. F.; Upender, K. N. *J. Am. Chem. Soc.* **1978**, *78*, 2844.

Table 1. Results Obtained in the Cyclization of the Amines *anti*-**3a**−**3q**

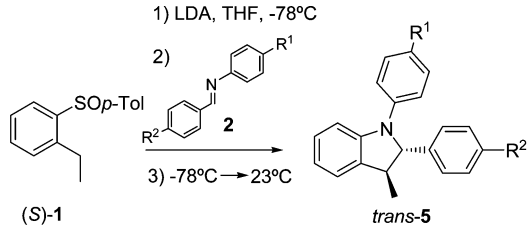


anti-**3a-n** *trans*-**5a-n**

Entry	Start. Comp.	R^1	R^2	Reaction Time (h) LiHMDS	Reaction Time (h) KHMDS[a]	Temperature(ºC) LiHMDS	Temperature(ºC) KHMDS[a]	Indoline	Yield (%) LiHMDS	Yield (%) KHMDS[a]
1	*anti*-**3b**	MeO-	MeO-	0.5	---	Rt		*trans*-**5b**	80	---
2	*anti*-**3c**	MeO-	CH_3-	1.0	---	Rt		*trans*-**5c**	72	---
3	*anti*-**3a**	MeO-	H-	1.5	<0.1	Rt	Rt	*trans*-**5a**	75	79
4	*anti*-**3d**	MeO-	Cl-	2.5	---	Rt		*trans*-**5d**	68	---
5	*anti*-**3e**	MeO-	CN-	24	24	70	70	*trans*-**5e**	34	82
6	*anti*-**3f**	H-	MeO-	1.0	---	70		*trans*-**5f**	71	---
7	*anti*-**3g**	H-	H-	3.0	<0.1	70	Rt	*trans*-**5g**	75	81
8	*anti*-**3h**	H-	Cl-	4.0	<0.1	70	Rt	*trans*-**5h**	76	76
9	*anti*-**3i**	H-	CN-	24	---	70		*trans*-**5i**	n.r	---
10	*anti*-**3j**	Cl-	MeO-	18	---	70		*trans*-**5j**	75	---
11	*anti*-**3k**	Cl-	H-	24	---	70		*trans*-**5k**	71	---
12	*anti*-**3l**	Cl-	Cl-	48	3.0	70	70	*trans*-**5l**	40	84
13	*anti*-**3m**	CN-	MeO-	48	24	70	70	*trans*-**5m**	n.r	57
14	*anti*-**3n**	CN-	H-	48	48	70	70	*trans*-**5n**	n.r	n.r
15	*anti*-**3o**	3,4-diMeO-	H-	---	<0.1	Rt		*trans*-**5o**	---	83
16	*anti*-**3p**	3,4-diMeO-	CN-	---	24	70		*trans*-**5p**	---	81
17	*anti*-**3q**	H-	CF_3-	---	48	70		*trans*-**5q**	---	n.r.

[a] In the presence of 18-crown-6

Table 2. Results Obtained in the Tandem-Cyclization of the Amines *anti*-**3a**−**3m**



(*S*)-**1** *trans*-**5**

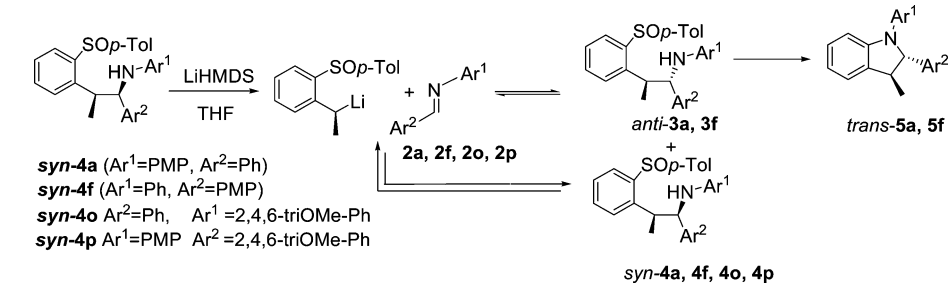
Entry	R^1	R^2	Product	Reaction Time (h)	Yield (%)
1	H-	H-	*trans*-**5g**	5	54
2	MeO-	H-	*trans*-**5a**	2	62
3	H-	MeO-	*trans*-**5f**	3.5	59
4	MeO-	Cl-	*trans*-**5d**	8	58
5	MeO-	CN-	*trans*-**5e**	48	25
6	3,4-diMeO-	CN-	*trans*-**5p**	48	41

(containing a 4-$MeOC_6H_4$ group). Reaction of *anti*-**3o** was almost instantaneous at rt (entry 15) whereas *anti*-**3p** required 24 h at reflux (entry 17) to be converted in their corresponding indolines. These results were similar to those obtained from **3a** (entry 3) and **3e** (entry 5). However, when the reaction of a 1:1 mixture of *anti*-**3e** and *anti*-**3p** with more than 2.0 equiv of KHMDS was followed by ^{1}H NMR it could be confirmed that reactivity of *anti*-**3p** is around 1.8 times higher than that of the *anti*-**3e**. Finally, reaction of *anti*-**3q** with KHMDS was unsuccessful (entry 17), indicating that the negative influence of the $-CF_3$ group is similar to that of the −CN group (entry 9). The synthesis of the anti amines derived from 4-trifluoromethyl benzaldehyde and 4-methoxy or 3,4-dimethoxy anilines was not possible (reactions only yield compounds with the syn stereochemistry, see Supporting Information).

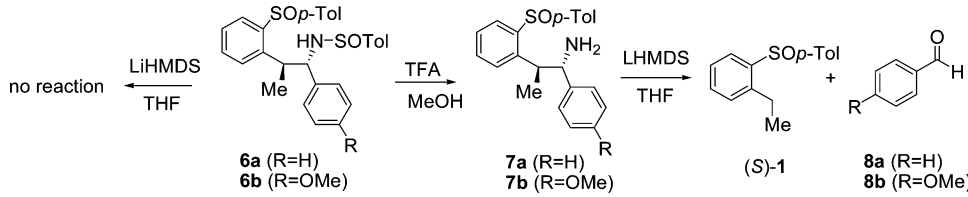
In order to study the role of substrate relative configuration on the course of the reaction, we next examined the behavior of **4a** (the syn isomer of **3a**) in the presence of LHMDS (Scheme 3). After 1.5 h at rt (which was the time required for complete evolution of *anti*-**3a**; see entry 3, Table 1), *syn*-**4a** had completely disappeared and a mixture of the starting products (*S*)-**1** and **2a**, along with a small amount of the indoline *trans*-**5a**, had been formed. When the reaction time was increased to 5 h, compound *trans*-**5a** was the only product isolated in the reaction (70% yield). Identical results were obtained with *syn*-**4f** at 40 °C after 10 h, which afforded *trans*-**5f** as the only product (67% isolated yield). These results indicate that the *syn* isomers **4a** and **4f** cannot cyclize into their corresponding cis indolines. In contrast, they must reach an equilibrium with their corresponding *anti*-**3** isomers (through the starting imines **2a** or **2f** and the carbanion derived from (*S*)-**1**), which in turn would be converted into the trans indolines **5a** or **5f**. This provokes a shift of the equilibrium between *anti*-**3** and *syn*-**4** toward the former, which finally leads to complete conversion of *syn*-**4** to indolines *trans*-**5** (Scheme 3).

This behavior is highly interesting because reactions of (*S*)-**1** with *N*-arylimines are not usually completely stereoselective, yielding instead a mixture of syn and anti diastereoisomers. As both evolve into the same trans indoline through treatment with

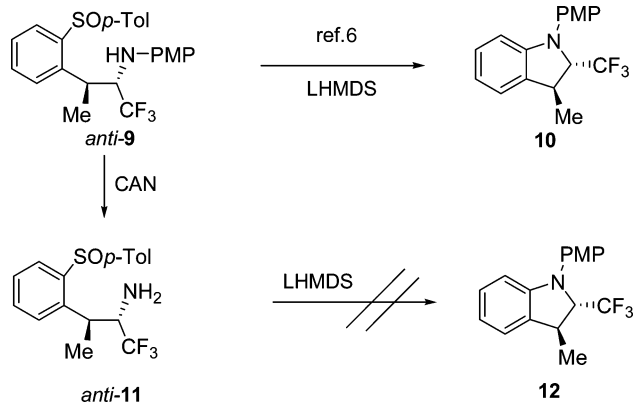
Scheme 3



Scheme 4



Scheme 5



LHMDS, the reaction mixture, without previous separation, could be stereoselectively transformed into only one indoline.

This was confirmed starting from the mixture *syn*-**4a** + *anti*-**3a**, which was obtained through reaction of **2a** with (*S*)-**1**. After 5 h with LHMDS, only compound *trans*-**5a** was obtained. Moreover, these results suggest that the tandem A_N/S_NAr processes used for synthesizing fluorinated indolines (the A_N in these reactions is usually completely stereoselective, yielding only anti imines) can also be applied to the synthesis of nonfluorinated indolines, despite the fact that the first step, which entails nucleophilic addition, affords mixtures of syn and anti amines. To corroborate this hypothesis, we reacted (*S*)-**1** with the *N*-phenyl benzylideneimine **2g**, as well as with other imines bearing electron-donating (**2a** and **2f**) and electron-withdrawing (**2i**) groups at their aromatic rings. All of these reactions gave satisfactory results (Table 2), which indicates that optically pure *N*-aryl trans indolines can be prepared through direct reaction of the imines with (*S*)-**1**, involving A_N/S_NAr tandem processes. It is remarkable that the yield of *trans*-**5p** is higher than that of *trans*-**5e**, which could also be a consequence of the relative reactivity of their corresponding precursors (see above).

When we studied the behavior of the *N*-(2,4,6-trimethoxyphenyl) amino sulfoxides *syn*-**4o** and *syn*-**4p** in their reactions with LHMDS, we observed that only imines **2o** and **2p** were obtained along with (*S*)-**1** (Scheme 3). The trans indolines **5o** and **5p**, which presumably arise in the cyclization of the anti isomers **3o** and **3p**, were not detected. These results were not wholly unexpected, since the reactions of **2o** and **2p** with (*S*)-**1** are completely stereoselective, yielding only the *syn*-**4o** and *syn*-**4p** isomers.[11] The anti isomers required for cyclization are never formed.[7g]

Reaction of the syn isomers **4a** or **4f** with KHMDS, which had proven to be more efficient for cyclization than LHMDS, were also unsuccessful. However, in the presence of this base, the starting aminosulfoxides were recovered unaltered. Cis indolines and the products resulting in the retro-addition were never detected, even when the reaction was halted before it had finished. The same absence of reactivity was observed when the syn amines obtained in reactions of 4-trifluoromethyl benzaldehyde and 4-methoxy or 3,4-dimethoxy anilines were treated with KHMDS. These results not only confirm that cis indolines cannot be formed by means of this procedure but also indicate that equilibrium between isomers **3** and **4** does not take place in the presence of KHMDS.[12]

Once we had clarified that substrate need to have an *anti* configuration for successful intramolecular S_NAr to indolines, we examined the role of other structural features. We first studied the behavior of anti *N*-sulfinyl amines **6a** and **6b**, which were easily prepared through the reaction of Li-(*S*)-**1** with N-sulfinylimines,[7a−f] in the presence of LHMDS (Scheme 4. Both amines were recovered unaltered after 10 h, which indicates that no reactions take place, probably due to the stable and consequently less nucleophilic character of the *N*-sulfinyl amide anions with respect to the *N*-aryl amide anions. We then studied reactions of primary amines **7a** and **7b**, which were obtained by means of N−S cleavage of **6a** and **6b** with TFA/MeOH,[7a] in analogous conditions, but the results were similarly

(11) We have also tried to obtain unsuccessfully the indolines containing *p*-CF_3-C_6H_4 groups at C-2 by reaction with KHMDS of the syn amines obtained from 4-trifluoromethyl benzaldehyde and 4-methoxy or 3,4-dimethoxy anilines.

(12) The reversibility of the nucleophilic addition in the presence of lithium bases (LDA or LHMDS) could be due to the higher stability of the lithium benzylcarbanions, which form chelated species that are scarcely stabilized for potassium benzylcarbanions.

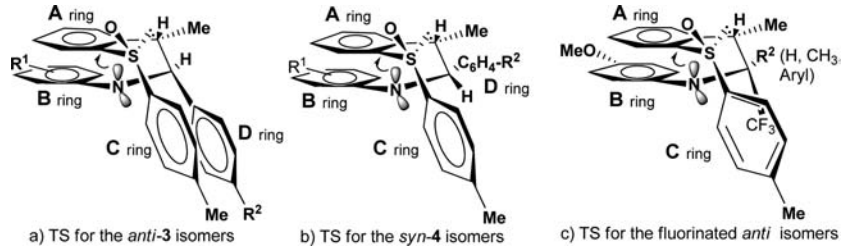
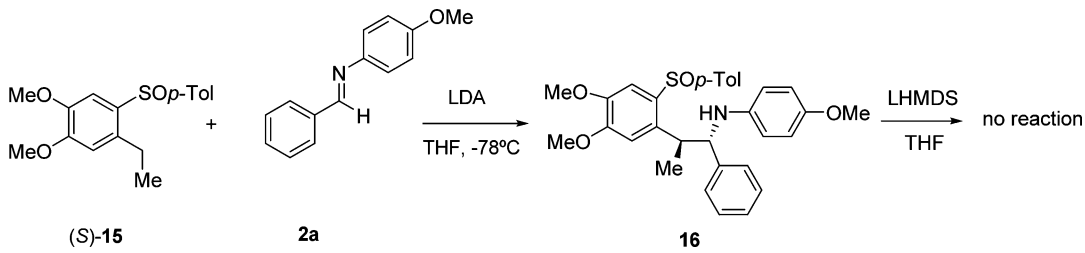


Figure 1. Structural preorganization in the TS leading to indolines.

Scheme 6



unsuccessful. This time, mixtures of compound (*S*)-**1** with aldehydes **8a** or **8b**, which arise from the hydrolysis of imines **2a** or **2b**, were isolated (Scheme 4), but indolines were not detected even after adding TMDA or 12-crown-4 to increase the reactivity of the lithium anion amide. Reactions with KHMDS (or KHMDS/18-crowm-4) were also unsuccessful, even at refluxing THF, with recovery of the starting products **7a** and **7b** unaltered.

Taking into account that the nucleophilic power of the amide anion derived from free amines **7a** and **7b** must be higher than that of the *N*-aryl derivatives **3a** and **3b**, the different reactivity of both types of substrates seems to be related to the presence of the aryl group at the nitrogen. In order to confirm this, we studied the reaction of fluorinated amines **9** and **11** with KHMDS (Scheme 5). Whereas compound **9** was transformed into the indoline under mild conditions,[6] compound **11**, obtained from **9** through CAN oxidation, was recovered unaltered after several hours at 70 °C. This finding indicates that indoline **12** cannot be obtained from free amine **11**, which further suggests that the presence of the *N*-aryl group is required for the success of this cyclization.

Taken together, these results suggest an S_NAr mechanism.[13] The influence of the substituents at the N-aryl ring on the reactivity, which is generally higher for compounds with electron-donating groups, can be explained by taking into account their effect on the nucleophilic strength of the amide ion, which is lowered by electron withdrawing groups. In this sense, the lack of reactivity observed for the *N*-sulfinyl amides derived from **6** is also understandable. However, several facts point to a more complex situation. For example, the lack of reactivity of the amide anions **7** cannot be attributed to their nucleophilic features, which are more propitious than those of the *N*-aryl derivatives *anti*-**3** from both an electronic and steric perspective, but rather to the absence of the *N*-aryl group, which seems to be required for cyclization. This suggests that *N*-aryl groups are involved in some sort of interaction able to stabilize the transition state of the reaction.

In addition, the syn or anti stereochemistry of the starting amides is crucial for the success of the reaction, as can be seen from the fact that the syn isomers **4** do not react, although this feature is not related to the nucleophilic power of the amide anion. This, too, indicates the existence of a stabilizing interaction in the transition states involving the *anti*-**3** isomers, which are not there when the relative stereochemistry is altered. The magnitude of this interaction is larger when the electronic density of the ring joined to C-1 increases, thus explaining the significant reactivity differences observed when the substituents at this ring are changed (Table 2).[14]

To account for all these experimental results, we propose that the double π,π-stacking interaction shown in Figure 1 is responsible for the efficiency of this S_NAr reaction for compounds *anti*-**3**. The ortho-disubstituted ring (**A** in Figure 1), which is deactivated by the sulfinyl group and therefore acts as an acceptor, interacts with the *N*-aryl group (**B** in Figure 1), which is usually activated and therefore acts as the donor. Moreover, the deactivated *p*-tolyl ring joined to the sulfur (**C** in Figure 1) can interact favorably with the ring joined to C-1 (**D** in Figure 1) only in the case of the anti isomers **3**. In contrast, *syn*-**4** causes the ring **D** to be arranged in a gauche position with respect to the methyl and ring **A** (Figure 1), which is not overly favored.

The ready cyclization observed in fluorinated anti amines[6] suggests that $-CF_3$ is also able to interact favorably with the *p*-methylphenyl group joined to the sulfur (**C** ring in Figure 1). Taking into account the electronic deficiency of this ring and the fact that the $-CF_3$ is an electron-rich group; a donor−acceptor interaction between both (similar to π,π-stacking) can be postulated to explain the experimental results (Figure 1).

According to the theoretical calculations performed by Uneyama,[15] the electrostatic interaction of a CF_3 functionality with aryl groups is repulsive when the rings are negatively charged, but it becomes attractive when their electronic density

(13) Two additional tests were made to corroborate this mechanism. The first test involved reacting *anti*-**3b** with LHMDS in the presence of TEMPO. The results obtained were identical to those shown in entry 1 of Table 1, indicating that the radical inhibitor has no influence, which thus excludes a radical process. In contrast, the reaction of (*S*)-**15** (Scheme 6) with LHMDS did not work, as could be expected from the negative influence of the methoxy groups on the course of the S_NAr reaction.

(14) As this aryl group is not directly joined to the nitrogen, the influence of its electronic density on the nucleophilic strength of the amide anion should be very low.

(15) Katagiri, T.; Yamaji, S.; Handa, M.; Irie, M.; Uneyama, K. *Chem. Commun* **2001**, 2054.

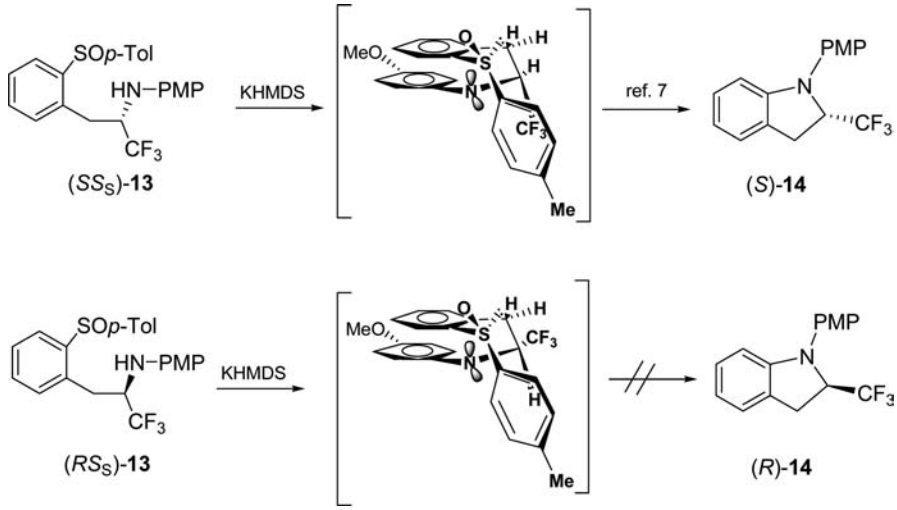


Figure 2. Evolution of (SS_S)-**13** and (RS_S)-**13** with KHMDS.

is decreased by electron-withdrawing substituents, an observation that supports our proposal. Thus, syn-fluorinated amines should not evolve into the corresponding cis indolines. Unfortunately, we were unable to prove this because reaction of (*S*)-**1** with fluorinated aldimines and ketimines yielded only anti amines. We were, however, able to establish the importance of the stabilizing CF_3/aryl interactions in the course of the cyclization by studying the behavior of amines syn (RS_S)-**13** and anti (SS_S)-**13** (Figure 2), obtained as a mixture in the reaction of 2-*p*-tolylsulfinyl toluene and the *N*-*p*-methoxyphenyl imine derived from CF_3−CHO.[6] These compounds differ in their configuration at the aminic carbon. Compound (SS_S)-**13** reacts with KHMDS in less than 1 h, affording the corresponding indoline (*S*)-**14**, whereas the isomer syn (RS_S)-**13** remained unaltered after 24 h under similar conditions. As can be seen in Figure 2, this behavior can be attributed to the CF_3/*p*-tolyl interaction, which stabilizes the TS from anti (SS_S)-**13**, but which is absent in the TS from syn (RS_S)-**13**.

At this point it was necessary to find some proofs supporting the π,π-stacking interactions we have proposed to explain the experimental results. A combined experimental and theoretical approach was adopted, using X-ray diffraction, NMR experiments, and molecular mechanics calculations. We first studied in detail the X-ray data obtained for compound *anti*-**1**.[6,16] Inspection of Figure 3 reveals that the *p*-OMe aniline ring (**B**) and the ortho-disubstituted ring (**A**) exhibit an almost parallel (face-to-face) geometry with an average separation of ca. 3.9 Å, which strongly suggests the presence of an attractive π,π-interaction. An anti-type arrangement for the torsion angle value between the CHs protons at the aliphatic chain was observed in the solid state. Also, an intramolecular S═O···H−N hydrogen bond was evidenced, although its role to favor the stacked orientation of the aromatic rings was negligible (see below).

In a parallel manner, these observations found support by NMR studies performed on diluted samples of *anti*-**15** at 223 and 273 K in THF-d_8. These experimental conditions were chosen to minimize any possible intermolecular stacking. Moreover, the choice of this polar solvent could favor hydrophobic interactions, as well as disfavor the intramolecular S═O···H−N hydrogen bond present in the solid state. Weak NOE contacts among the hydrogens of the PMP ring (**B**) and those of the orthosulfinylated ring (**A**) were clearly detected (see Supporting Information). The ^3J vicinal coupling value between the CHs protons at the aliphatic chain is 10 Hz, also suggesting a major anti-type conformation at the corresponding torsion angle, as that deduced in the crystal structure. The strong NOEs between the CH(NH) and the aromatic protons adjacent to the aliphatic linker, in both PMP (H1 of ring **B**) and orthosulfinylated (H4 of ring **A**) aromatic moieties, also indicated their proximity in space. Nevertheless, the simultaneous existence of medium intensity NOEs between the aliphatic $CH(CH_3)$ and the same H1 of ring **B** and H4 of ring **A** hydrogens indicated that, in THF solution, there is certain mobility around the torsional degress of freedom of the molecule. In any case, these NMR evidence mostly agree with the X-ray structure and suggest that, although not unique, the molecule in solution displays a major conformation, with the PMP-containing ring and the ortho-disubstituted ring, containing the sulfinyl moiety, stacked in space.

We have also tried to find evidence of these interactions in the non fluorinated compounds which are described in this paper. Thus, the X-ray diffraction study of compound *anti*-**3a** was performed.[16] However, in contrast to the observations for the CF_2Cl analogue, the aromatic rings in the solid state structure of *anti*-**3a** do not adopt the π,π-stacked geometry (Figure 4), although the intramolecular S═O···H−N hydrogen bond was also present, as well as the anti-type geometry at the CH−CH aliphatic segment. An intermolecular π,π-stacking interaction of the **A** and **D** rings of different molecules can be observed in the crystal structure (see Supporting Information). Thus, the different chemical nature at one of the segments of the molecule gives rise to the presence of a significantly different geometry, at least in the solid state.

NMR studies were then performed using experimental conditions similar to those described above, using diluted samples of *anti*-**3a** and THF-d_8 as solvent. The ^{1}H NMR spectrum at 195 K was fairly similar to that of *anti*-**17**, with a J_{CH-CH} vicinal coupling constant value about 10 Hz. Only a very minor shielding of the protons at ring **B** was observed.

(16) CCDC 730583 and CCDC 689575 contain the supplementary crystallographic data of compound *anti*-**3a** and *anti*-**17**, respectively. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK; fax: (int.) +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk).

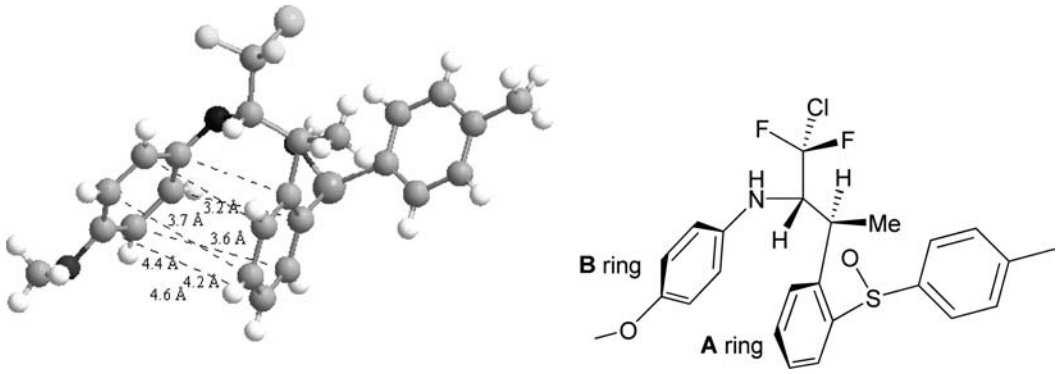


Figure 3. View of the X-ray structure of compound *anti*-**17** showing the almost parallel geometry of the rings **A** and **B** and the interatomic distances of some significant nuclei.

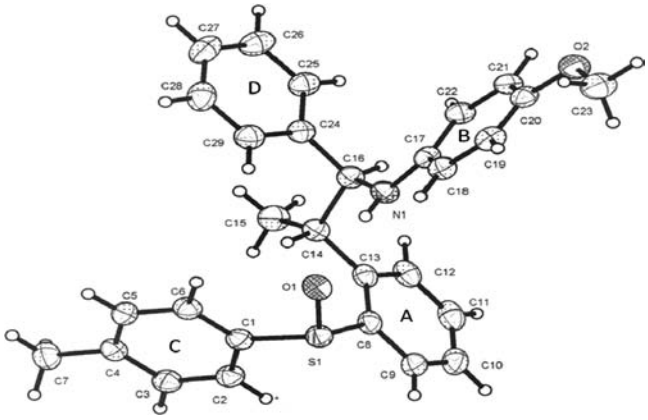


Figure 4. ORTEP of compound *anti*-**3a**.

The analysis of the NOESY experiment performed under these conditions permitted to detect several NOE crosspeaks between different hydrogens at the molecule, including aromatic and aliphatic protons, with somehow different intensities to those detected for the CF_2Cl analogue (see Table 1 in the Supporting Information). These experimental evidence pointed out that the aromatic ring **B** in *anti*-**3a** could be involved in different or additional interactions than those described above for *anti*-**17**.

No crystals were obtained for *anti*-**3b** and *anti*-**3f**, but the NMR data permitted deduction of the existence of a strikingly different behavior for these molecules under analogous experimental conditions (diluted samples in THF-d_8 and 195 K). Strong shielding of the protons at rings **A** and **C** with respect to those in *anti*-**3a** (and *anti*-**17**) was observed, when the *p*-methoxy group was attached to ring **D**, *anti*-**3b** and *anti*-**3f**. This behavior was independent of the presence of a *p*-methoxy group at ring **B** (as in *anti*-**3b**), or not (as in *anti*-**3f**). Also, for both *anti*-**3b** and *anti*-**3f**, the ^3J vicinal coupling value between the CHs protons at the aliphatic chain was much smaller than for *anti*-**3a** and *anti*-**17** (6.5 Hz) strongly suggesting the presence of a conformational equilibrium at the corresponding torsion angle. Again, several NOE contacts among the hydrogens of the different aromatic rings were observed, but the presence of additional nontrivial NOEs all around the molecule could obviously not been explained by one unique geometry.

Interestingly, despite the presence of different substitutions at ring **B** of *anti*-**3f** and *anti*-**3b**, their NOE crosspeaks, and their relative intensities were fairly similar, indicating an analogous conformational behavior for both compounds. As example, it is possible to identify a weak (but reliable) NOE contact among the hydrogens at the orthosulfinylated ring (**A** in Figure 4) with those at the **B** ring, as well as a medium-intensity peak between the hydrogens at **A** and those at the aromatic **D** moiety (see figure 4). Therefore, the discussion will only be focused on the *anti*-**3b** analogue.

As a further step, and since all these experimental data could not be accounted for any single structure, a conformational search was performed with the aim of scanning the possible energy minima available for *anti*-**3b**. Twenty three conformers were found by the MM3* force field by random rotation around all the torsional degrees of freedom of the molecule. The 10 geometries within a 5 kcal/mol threshold were analyzed on the basis of the experimental NMR data (Table 1 in the Supporting Information). In particular, the 6.5 Hz value for the vicinal $J_{CH,CH}$ coupling is in agreement with a ca. 50:50 equilibrium between gauche-type and anti-type rotamers at the CH−CH aliphatic linkage.

The two lowest energy geometries (*conf1* and *conf2*, Figure 6) are anti-type geometries at the CH−CH section of the molecule, and display a satisfactory agreement with the experimental X-ray geometry described above for *anti*-**3a**. They are extended structures with no stacking between the aromatic rings. They slightly differ at the position of the sulfur atom, although no S═O···H−N hydrogen bond is formed. Both geometries can explain the strong observed NOE peak between the CH(NH) and the ortho **A**-ring proton.

Additionally, there are also two low energy geometries (*conf6* and *conf10*) with a gauche-type conformation at the CH−CH fragments which, in turn, can explain the medium intensity NOE crosspeak between the ortho protons at **A** and **D** rings. These conformers display a π,π-stacking interaction between rings **D** and **C** (Figure 6). The combination of conformers *conf1* and/or *conf2* with conformers *conf6* and/or *conf10,* in a ca. 50:50 ratio, can satisfactorily explain the experimental NOE and *J* NMR data for *anti*-**3f** and *anti*-**3b**.

On the observation of the geometries of the alternative conformers predicted by the MM3* calculations, the minor conformers contributing to the conformational equilibria of compounds *anti*-**3a** and *anti*-**17** could be deduced. In particular, *conf3* for *anti*-**3a** could explain the observed **A**4-**B**1 NOE for this molecule, while a minor presence of *conf4* for *anti*-**17** could support the observed medium **A**4-CH(CH_3) NOE. Moreover, *conf7* is probably also contributing in both molecules and may account for the experimental **B**1-CH(CH_3) NOE observed for both *anti*-**3a** and *anti*-**17**. These three conformers also display the anti geometry at the CH−CH linkage, required to enlighten the experimental value of 10 Hz for the corre-

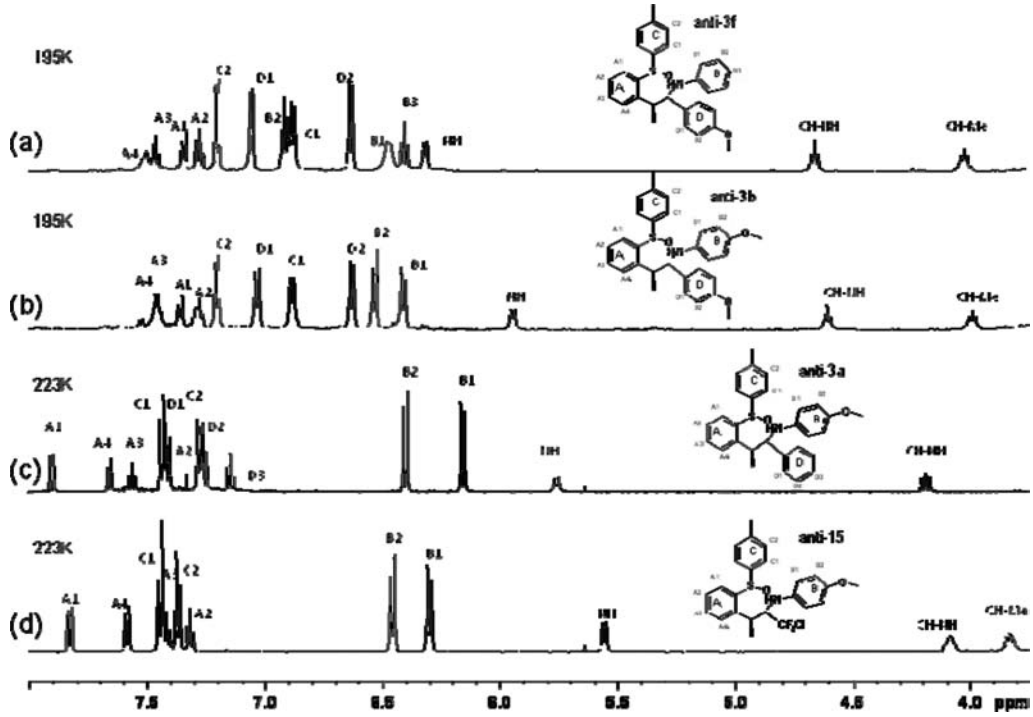


Figure 5. Section of the ^{1}H NMR spectra of the (a) *anti*-**3f**, (b) *anti*-**3b**, (c) *anti*-**3a**, and (d) *anti*-**15** compounds showing the differences in chemical shift in the aromatic rings for each compound.

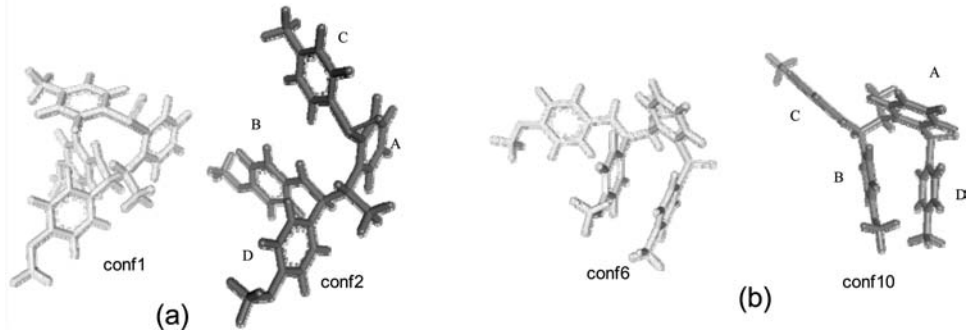


Figure 6. Low-energy conformers used to explain the experimental results. (a) Anti-type conformers, *conf1* and *conf2*. (b) Gauche-type conformers, *conf6* and *conf10*.

sponding coupling constant. A more complete description of the different geometries is given in the Supporting Information.

Then, although subtle structural and chemical differences may modify the existing conformational equilibrium for this type of molecules, the X-ray and NMR data support the presence of conformers exhibiting π,π-stacking between rings **A** and **B** (for *anti*-**15**) or **C** and **D** (for *anti*-**3f** and *anti*-**3b**). Therefore, the proposed TS to explain the evolution of the anti isomers into indolines (Figure 1) could be stabilized by two π,π-stacking interactions (**A/B** and **C/D** rings) and therefore would be favored with respect to that TS in which only the **A/B** interaction were present, as is the case for the syn isomers. This different stabilization can account for the observed different behavior for the anti and syn isomers in the unusual S_NAr reaction reported in this paper.

Conclusion

In conclusion, we have described a new entry for the preparation of enantiomerically pure trans indolines containing two chiral centers which entails treating the amines resulting from reactions between 2-*p*-tolylsulfinylphenyl ethane and N-aryl arylideneimines with LHMDS or KHMDS. After a detailed study of this unusual intramolecular S_NAr on mildly deactivated rings under very mild conditions, we have established the scope and limitations of this method, which seems to require a double π,π-stacking donor−acceptor interaction to stabilize the transition states that lead to the desired indolines. These interactions have been evidenced from X-ray and NMR studies.

Experimental Section

General Method. ^{1}H NMR spectra were acquired at either 200 or 300 MHz and ^{13}C NMR were acquired at either 50 or 75 MHz unless otherwise indicated. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (7.26 and 77.0 ppm). Low-temperature and 2D NMR studies were performed at 500 MHz. Mass spectra (MS) were determined by FAB. Melting points were determined in open capillary tubes. All reactions were carried out in anhydrous solvents and under argon atmosphere. THF was distilled from sodium−benzophenone under argon. Toluene was dried under metallic sodium. Molecular sieves (4 Å) were activated at 110 °C for 4 days. *i*-Pr_2NH

was distilled from KOH. Flash silica gel column chromatography was performed with silica gel Merk-60 (230−400 mesh). *n*-BuLi (2.5 M solution in hexane), LHMDS (1 M in THF), KHMDS (0.5 M in Toluene), and compound **2g** (imine, PhCH=N−Ph) were purchased from Aldrich. Compounds (*S*)-**1**, **2b**, **2c**, **2e**, **2f**, **2i**, **2j**, **2k**, **2n**, **6a**−**b**, **7a**−**b**, *anti*-**9**, **10**, (*S*,S_S)-**13**, (*S*,S_R)-**13**, (*S*)-**14**, and (*S*)-**15** were previously synthesized.[6,7]

General Procedure for Cyclization of Amines *anti*-3a−n. Synthesis of the Indolines *trans*-5a−n (Table 1). Either LHMDS or KHMDS (0.55 mmol) was added to a solution of the corresponding amine **3a**−**n** (0.5 mmol) in THF (2 mL) at 0 °C. When the reaction was complete (see Table 1), the resulting reaction mixture was hydrolyzed (1 mL of H_2O), extracted (3 × 10 mL Et_2O), washed (2 × 10 mL sat. NaCl), and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Compounds were purified by means of flash silica gel column chromatography with hexane as the eluent in each case. Yields are indicated in all cases.

Compounds Listed in Table 1. (2*S*,3*S*)-1-(4-Methoxyphenyl)-3-methyl-2-phenylindoline (*trans*-5a).[6] By means of the process described above at rt, *trans*-**5a** was obtained as a white solid; mp: 152−154 °C, in 79% yield from amine *anti*-**3a** in a step-by-step process and in 62% yield with a tandem procedure. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.41 (d, J = 6.8 Hz, 3H), 3.29−3.20 (m, 1H), 3.74 (s, 3H), 4.60 (d, J = 9.1 Hz, 1H), 6.81−6.71 (m, 4H), 7.11−7.05 (m, 4H), 7.31−7.22 (m, 3H), 7.39 (dd, J = 6.8, 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): 17.5, 46.2, 55.3, 78.2, 107.8, 114.3, 118.8, 123.2, 124.2, 127.3, 127.4, 127.6, 128.4, 133.4, 137.1, 142.1, 149.9, 155.8. $[\alpha]_D^{20}$ +151.1 (c = 1, $CHCl_3$). HRMS (M + H)$^+$ calcd for $C_{22}H_{21}NO$: 315.1616; Found: 315.1623.

(2*S*,3*S*)-1-(4-Methoxyphenyl)-3-methyl-2-(4-methoxyphenyl)indoline (*trans*-5b). By means of the process described above at rt, *trans*-**5b** was obtained as a yellow oil in 80% yield from amine *anti*-**3b** in a step-by-step process. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.40 (d, J = 6.8 Hz, 3H), 3.20−3.29 (m, 1H), 3.74 (s, 3H), 3.77 (s, 3H), 4.55 (d, J = 9.1 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 6.77−6.84 (m, 5H), 7.04−7.12 (m, 4H), 7.32 (d, J = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): 17.2, 46.1, 55.2, 55.3, 77.7, 107.7, 113.8, 114.3, 118.3, 123.1, 124.4, 127.5, 128.5, 133.4, 133.9, 139.9, 150.1, 155.8, 158.9. $[\alpha]_D^{20}$ −57.1 (c = 0.89, $CHCl_3$). HRMS (M + H)$^+$ calcd for $C_{23}H_{23}NO_2$: 345.1728; Found: 345.1728.

(2*S*,3*S*)-1-(4-Methoxyphenyl)-3-methyl-2-(4-methylphenyl)indoline (*trans*-5c). By means of the process described above at rt, *trans*-**5c** was obtained as a yellow oil in 72% yield from amine *anti*-**3c** in a step-by-step process. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.35 (d, J = 6.8 Hz, 3H), 2.26 (s, 3H), 3.15−3.21 (m, 1H), 3.68 (s, 3H), 4.53 (d, J = 9.2 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 6.72−6.99 (m, 2H), 7.01−7.06 (m, 6H), 7.06−7.25 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 17.4, 21.1, 46.2, 55.3, 77.9, 107.7, 114.3, 118.7, 123.1, 124.2, 127.2, 129.1, 133.4, 136.9, 137.1, 143.5, 150.1, 155.8, 159.4. $[\alpha]_D^{20}$ −55.4 (c =1.1, $CHCl_3$). HRMS (M + H)$^+$ calcd for $C_{23}H_{23}NO$: 329.1779; Found: 329.1781.

(2*S*,3*S*)-1-(4-Methoxyphenyl)-3-methyl-2-(4-chlorophenyl)indoline (*trans*-5d). By means of the process described above at rt, *trans*-**5d** was obtained as a yellow oil in 68% yield from amine *anti*-**3a** in a step-by-step process and in 58% yield with a tandem procedure. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.32 (d, J = 6.8 Hz, 3H), 3.07−3.17 (m, 1H), 3.66 (s, 3H), 4.53 (d, J = 9.2 Hz, 1H), 6.60 (d, J = 7.8 Hz, 1H), 6.69−6.71 (m, 3H), 6.95−7.02 (m, 5H), 7.16−7.32 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 17.3, 155.8. $[\alpha]_D^{20}$ −87.2 (c = 0.78, $CHCl_3$). HRMS (M + H)$^+$ calcd for $C_{23}H_{20}N_2O$: 340.1278; Found: 340.1225.

(2*S*,3*S*)-1-(4-Methoxyphenyl)-3-methyl-2-(4-cyanophenyl)indoline (*trans*-5e). By means of the process described above at rt, *trans*-**5e** was obtained as a yellow oil in 82% yield from amine *anti*-**3e** in a step-by-step process and in 25% yield with a tandem procedure. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.39 (d, J = 6.8 Hz, 3H), 3.17−3.27 (m, 1H), 3.72 (s, 3H), 4.54 (d, J = 9.2 Hz, 1H), 6.69−6.79 (m, 4H), 7.03−7.09 (m, 4H), 7.24−7.28 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 17.4, 21.1, 46.2, 55.4, 107.7, 114.3, 118.7, 123.1, 124.3, 127.3, 127.5, 129.2, 133.5, 136.9, 136.9, 137.1, 139.1, 150.1, 46.2, 55.4, 77.9, 107.9, 114.6, 118.9, 123.2, 124.4, 127.7, 128.6, 128.7, 129.8, 133.1, 136.8, 140.7, 149.9, 156.1. $[\alpha]_D^{20}$ +100.2 (c = 1.0, $CHCl_3$). HRMS (M + H)$^+$ calcd for $C_{22}H_{20}ClNO$: 349.1233; Found: 349.1232.

(2*S*,3*S*)-1-Phenyl-3-methyl-2-(4-methoxyphenyl)indoline (*trans*-5f). By means of the process described above at rt, *trans*-**5f** was obtained as a yellow oil in 71% yield from amine *anti*-**3f** in a step-by-step process and in 59% yield with a tandem procedure. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.40 (d, J = 6.8 Hz, 3H), 3.14−3.24 (m, 1H), 3.76 (s, 3H), 4.68 (d, J = 9.2 Hz, 1H), 6.78−6.83 (m, 2H), 6.93−7.01 (m, 2H), 7.08−7.11 (m, 4H), 7.13−7.29 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): 18.3, 29.7, 46.4, 55.2, 108.1, 113.9, 119.3, 120.9, 122.4, 123.6, 127.4, 127.9, 128.9, 134.0, 134.3, 143.6, 148.2, 158.9. $[\alpha]_D^{20}$ −76.6 (c = 1.0, $CHCl_3$). HRMS (M + H)$^+$ calcd for $C_{22}H_{21}NO$: 315.2034; Found: 315.2190.

(2*S*,3*S*)-1-Phenyl-3-methyl-2-phenylindoline (*trans*-5g). By means of the process described above at rt, *trans*-**5g** was obtained as a yellow oil in 81% yield from amine *anti*-**3g** in a step-by-step process and in 54% yield with a tandem procedure. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.43 (d, J = 6.8 Hz, 3H), 3.18−3.27 (m, 1H), 4.74 (d, J = 7.6 Hz, 1H), 6.80 (t, J = 1.1 Hz, 1H), 6.85 (t, J = 1.1 Hz, 1H), 6.91−7.30 (m, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): 18.7, 46.4, 77.1, 108.3, 119.4, 120.6, 122.3, 123.7, 126.7, 127.3, 127.5, 128.6, 128.9, 134.0, 142.4, 143.6, 148.0 $[\alpha]_D^{20}$ −66.6 (c = 0.3, $CHCl_3$). HRMS (M + H)$^+$ calcd for $C_{21}H_{19}NO$: 285.1508; Found: 285.1518.

(2*S*,3*S*)-1-Phenyl-3-methyl-2-(chlorophenyl)indoline (*trans*-5h). By means of the process described above at rt, *trans*-**5h** was obtained as a yellow oil in 76% yield from amine *anti*-**3h** in a step-by-step process. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.41 (d, J = 6.8 Hz, 3H), 3.15−3.22 (m, 1H), 4.71 (d, J = 9.2 Hz, 1H), 6.83 (t, J = 6.6 Hz, 1H), 6.96−7.02 (m, 2H), 7.09−7.14 (m, 4H), 7.14−7.32 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): 18.3, 46.4, 76.4, 108.3, 119.3, 120.8, 122.6, 123.6, 127.6, 128.1, 128.8, 129.1, 133.0, 133.6, 140.9, 143.3, 147.9. $[\alpha]_D^{20}$ −90.2 (c = 1.0, $CHCl_3$). HRMS (M + H)$^+$ calcd for $C_{22}H_{21}NO$: 315.2034; Found: 315.2190.

(2*S*,3*S*)-1-(4-Chlorophenyl)-3-methyl-2-(4-methoxyphenyl)indoline (*trans*-5j). By means of the process described above at rt, *trans*-**5j** was obtained as a yellow oil in 75% yield from amine *anti*-**3j** in a step-by-step process. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.40 (d, J = 6.8 Hz, 3H), 3.16−3.226 (m, 1H), 3.77 (s, 3H), 4.62 (d, J = 9.2 Hz, 1H), 6.81−6.86 (m, 2H), 6.93−6.96 (m, 2H), 7.03−7.18 (m, 6H), 7.24−7.27 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): 18.1, 46.3, 55.2, 76.2, 108.0, 114.0, 119.7, 122.3, 123.7, 127.3, 127.5, 128.0, 129.0, 133.6, 134.0, 142.1, 147.8, 159.0. $[\alpha]_D^{20}$ −21.0 (c = 0.7, $CHCl_3$). HRMS (M + H)$^+$ calcd for $C_{22}H_{20}ClNO$: 349.1235; Found: 349.1224.

(2*S*,3*S*)-1-(4-Chlorophenyl)-3-methyl-2-phenylindoline (*trans*-5k). By means of the process described above at rt, *trans*-**5k** was obtained as a yellow oil in 71% yield from amine *anti*-**3k** in a step-by-step process. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.34 (d, J = 6.8 Hz, 3H), 3.10−3.20 (m, 1H), 4.61 (d, J = 9.2 Hz, 1H), 6.74 (t, J = 6.6 Hz, 1H), 6.79−7.13 (m, 5H), 7.10−7.27 (m, 7). ^{13}C NMR ($CDCl_3$, 75 MHz): 18.3, 46.4, 55.2, 108.1, 119.3, 121.9, 123.7, 126.7, 127.6, 128.7, 129.0, 129.2, 130.5, 133.9, 141.8, 142.1, 147.7. $[\alpha]_D^{20}$ −85.3 (c = 1.0, $CHCl_3$). HRMS (M + H)$^+$ calcd for $C_{21}H_{18}Cl$: 319.1137; Found: 319.1128.

(2*S*,3*S*)-1-(4-Chlorophenyl)-3-methyl-2-(4-chlrophenyl)indoline (*trans*-5l). By means of the process described above at rt, *trans*-**5l** was obtained as a yellow oil in 84% yield from amine *anti*-**3l** in a step-by-step process. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.40 (d, J = 6.8 Hz, 3H), 3.13−3.23 (m, 1H), 4.65 (d, J = 9.2 Hz, 1H), 6.81 (t, J = 6.6 Hz, 1H), 6.86 (d, J = 1.1 Hz, 1H), 6.93−7.25 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): 14.1, 22.7, 31.6, 75.8, 108.2, 120.0, 122.1, 123.7, 127.7, 128.1, 129.0, 129.1, 133.3, 133.6, 141.9, 147.7 $[\alpha]_D^{20}$ −88.9 (c = 0.8, $CHCl_3$). HRMS (M + H)$^+$ calcd for $C_{21}H_{17}Cl_2N$: 353.0734; Found: 353.0738.

(2*S*,3*S*)-1-(4-Cyanophenyl)-3-methyl-2-(4-methoxyphenyl)indoline (*trans*-5m). By means of the process described above at rt, *trans*-**5m** was obtained as a yellow oil in 57% yield from amine *anti*-**3m** in a step-by-step process. Compound *trans*-**5m** was obtained together with *p*-tolyldisulfide (50%). ^{1}H NMR ($CDCl_3$, 300 MHz): 1.43 (d, J = 6.9 Hz, 3H), 3.17−3.22 (m, 1H), 3.64 (s, 3H), 3.73 (s, 3H), 4.52 (d, J = 9.1 Hz, 1H), 6.60−6. (m, 4H), 6.96−6.98 (m, 5H), 7.00−7.22 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 17.4, 21.1, 46.2, 55.3, 79.9, 107.7, 114.3, 118.7, 123.1, 124.2, 127.2, 127.5, 129.2, 133.4, 137.0, 139.0, 150.0. $[\alpha]_D^{20}$ −71.9 (c = 0.8, $CHCl_3$).

(2*S*,3*S*)-1-(3,4-Dimethoxyphenyl)-3-methyl-2-phenylindoline (*trans*-5o). By means of the process described above at rt, *trans*-**5o** was obtained as a yellow oil in 83% yield from amine *anti*-**3o** in a step-by-step process. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.35 (d, J = 6.7 Hz, 3H), 3.19−3.12 (m, 1H), 3.67 (s, 3H), 3.33 (s, 3H), 4.58 (d, J = 8.9 Hz, 1H), 6.62−6.73 (m, 4H), 7.04−7.21 (m, 6H), 7.33 (d, J = 9.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): 17.4, 21.1, 46.2, 55.3, 56.3, 107.7, 114.3, 118.7, 123.1, 124.2, 126.3, 126.7 (2C), 127.2, 127.5, 129.2, 133.4, 135.3, 137.0, 139.0, 150.0. $[\alpha]_D^{20}$ −88.9 (c = 0.6, $CHCl_3$).

4-((2*S*,3*S*)-1-(3,4-Dimethoxyphenyl)-3-methylindolin-2-yl)benzonitrile (*trans*-5p). By means of the process described above at rt, *trans*-**5o** was obtained as a yellow oil in 81% yield from amine *anti*-**3p** in a step-by-step process. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.33 (d, J = 6.8 Hz, 3H), 3.10−3.20 (m, 1H), 3.66 (s, 3H), 4.51 (d, J = 9.2 Hz, 1H), 6.49−6.53 (m, 2H), 6.61−6.67 (m, 4H), 6.71−6.78 (m, 2H), 6.78−7.54 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 17.6, 29.7, 46.3, 55.9, 56.0, 107.2, 108.3, 111.5, 111.7, 114.9, 119.5, 123.7, 126.1, 126.7, 126.9 (2C), 127.9, 132.4, 132.8, 136.9, 147.9, 149.4. $[\alpha]_D^{20}$ −35.6 (c = 0.5, $CHCl_3$).

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Supporting Information Available: Experimental procedures, spectroscopic data for synthesis of imines **2d**, **2h**, **2j**, **2l**, **2m** and the compounds **3a**−**n**, and NMR and X-ray data used to support the π,π-stacking interactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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