Asymmetric Synthesis

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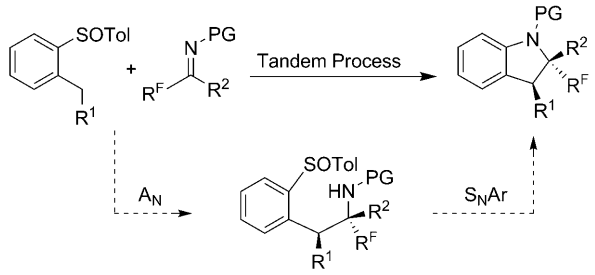
Anionic–Anionic Asymmetric Tandem Reactions: One-Pot Synthesis of Optically Pure Fluorinated Indolines from 2-*p*-Tolylsulfinyl Alkylbenzenes**

José Luis García Ruano, José Alemán, Silvia Catalán, Vanesa Marcos, Silvia Monteagudo, Alejandro Parra, Carlos del Pozo, and Santos Fustero**

The indoline skeleton is a ubiquitous scaffold found in the structures of several alkaloids[1] and other natural products which have diverse biological activity.[2] Indolines are considered to be "privileged structures"[3] which accounts for their widespread use not only as building blocks in the total synthesis of natural products, but also as a common motif in the design of new biologically significant compounds. Indolines have also been successfully employed as chiral auxiliaries in asymmetric synthesis.[4] Consequently, a number of multistep strategies have been developed for synthesizing these compounds.[5] However, no short and efficient methods for the preparation of enantiomerically pure substituted indolines have been developed to date, therefore the search for new methods for synthesizing them remains a challenge. Surprisingly, no examples of fluorinated indolines have been reported despite the fact that the inclusion of fluorinated fragments, such as the trifluoromethyl group,[6] in organic molecules has contributed significantly to the development of new pharmaceuticals.[7]

Our research group has recently reported that reactions of 2-(*p*-tolylsulfinyl) benzylcarbanions with different electrophiles take place with almost complete control of the configuration at the benzylic position, thus providing one of the best methods for creating optically pure benzylic carbon centers.[8] In particular, the use of imines as electrophiles has allowed us to synthesize 2-phenylethyl (and propyl) amines with complete control of the configuration at the two stereogenic centers that are created simultaneously. [9] We hypothesized that amines resulting from nucleophilic addition (A_N) could serve as substrates for the synthesis of optically pure indolines—once the optimal reaction conditions for the displacement of the sulfinyl group by the nitrogen center are determined, an intramolecular nucleophilic aromatic substitution (S_NAr) could take place (Scheme 1).[10] We also felt that



Scheme 1. Synthesis of fluorinated indolines. $R^F = CF_3$ or CF_2Cl. PG = protecting group, Tol = tolyl.

both processes (A_N and S_NAr) could occur in a tandem fashion to afford optically pure indolines from 2-(*p*-tolylsulfinyl) alkylbenzenes and imines. As part of our continuing study towards the development of new fluorinated compounds,[11] we set out to determine suitable reaction conditions for the preparation of these previously unreported optically pure fluorinated indolines, by using fluorinated imines as electrophiles. Herein, we present optimized nucleophilic addition (A_N) and the intramolecular nucleophilic aromatic substitution (S_NAr) reactions, each separately and in a tandem protocol. This approach constitutes a new strategy for synthesizing enantiomerically pure fluorinated indolines (Scheme 1).

Deprotonation of sulfoxide (*S*)-**1A**[8] at its benzylic position with LDA at −78 °C and subsequent treatment with fluorinated imines **2a–d** and then protonation at −78 °C gave mixtures of the two diastereoisomers **3** (major) and **4** (Table 1, entries 1–4). Aldimines **2a** and **2b** afforded a 70:30 diastereoisomeric mixture (**3Aa**/**3Ab** and **4Aa**/**4Ab**, respectively) that were easily separable (Table 1, entries 1 and 2).[12] The use of ketimines **2c** and **2d** as electrophiles led to a significant increase in the selectivity (80% and 92% *de*). The major products **3Ac** and **3Ad** were isolated in 60% and 77% yield, respectively (Table 1, entries 3 and 4). The results were

[*] Prof. Dr. J. L. García Ruano, Dr. J. Alemán, V. Marcos, A. Parra
Departamento de Química Orgánica (C-I)
Universidad Autónoma de Madrid
Cantoblanco, 28049 Madrid (Spain)
Fax: (+34) 91-497-466
E-mail: joseluis.garcia.ruano@uam.es
Dr. S. Catalán, S. Monteagudo, Dr. C. del Pozo, Prof. Dr. S. Fustero
Departamento de Química Orgánica
Universidad de Valencia, Burjassot, 46100 Valencia (Spain)
E-mail: santos.fustero@uv.es
Prof. Dr. S. Fustero
Laboratorio de Moléculas Orgánicas
Centro de Investigación Príncipe Felipe, 46013 Valencia (Spain)
E-mail: sfustero@cipf.es

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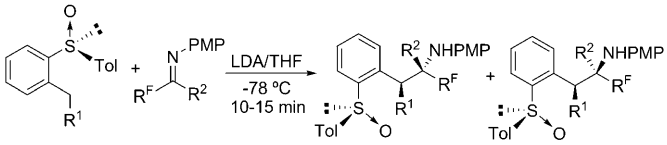
Table 1: Addition of sulfinyl carbanions derived from (*S*)-**1** to fluorinated imines **2**. LDA = lithium diisopropylamide, PMP = *p*-methoxyphenyl.



(*S*)-**1** **2** **3** **4**

Ent	Sulfoxide (R^1)	Imine (R^2, R^F)	d.r. **3**/**4**[a]	Product (yield [%])
1	(*S*)-**1A** (H)	**2a** (H, CF_3)	69:31	**3Aa** (51)[b] + **4Aa** (23)
2	(*S*)-**1A** (H)	**2b** (H, CF_2Cl)	70:30	**3Ab** (56) + **4Ab** (24)
3	(*S*)-**1A** (H)	**2c** (Ph, CF_3)	90:10	**3Ac** (60) + **4Ac**
4	(*S*)-**1A** (H)	**2d** (Me, CF_3)	96:4	**3Ad** (77) + **4Ad**
5	(*S*)-**1B** (Me)	**2a** (H, CF_3)	>98:<2	**3Ba** (71)
6	(*S*)-**1B** (Me)	**2b** (H, CF_2Cl)	>98:<2	**3Bb** (69)[b]
7	(*S*)-**1B** (Me)	**2c** (Ph, CF_3)	>98:<2	**3Bc** (60)
8	(*S*)-**1B** (Me)	**2d** (Me, CF_3)	>98:<2	**3Bd** (86)[b]
9	(*S*)-**1B** (Me)	**2e** (2-furyl, CF_3)	>98:<2	**3Be** (65)
10	(*S*)-**1C** (Et)	**2a** (H, CF_3)	>98:<2	**3Ca** (60)
11	(*S*)-**1C** (Et)	**2d** (Me, CF_3)	>98:<2	**3Cd** (40)
12	(*S*)-**1D** (Allyl)	**2a** (H, CF_3)	>98:<2	**3Da** (51)
13	(*S*)-**1D** (Allyl)	**2d** (Me, CF_3)	>98:<2	**3Dd** (52)
14	(*S*)-**1E** (Bn)	**2a** (H, CF_3)	>98:<2	**3Ea** (74)
15	(*S*)-**1E** (Bn)	**2d** (Me, CF_3)	>98:<2	**3Ed** (68)

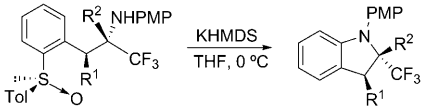
[a] Diastereomeric ratio was determined by ^{19}F and ^1H NMR spectroscopy. [b] Absolute configuration was determined by X-ray analysis. Bn = benzyl.

much better when substituted benzylcarbanions such as (*S*)-**1B–E** were used.[8,9] The reactions evolved in a completely stereoselective fashion to yield products **3** as single diastereoisomers with aldimines **2a** and **2b** (Table 1, entries 5, 6, 10, 12, and 14) and ketimines **2c–e** (Table 1, entries 7–9, 11, 13, and 15). The complete stereoselective control of the quaternary centers observed in the reactions with ketimines is remarkable (even with the enolizable **2d**).

The absolute configuration of the final products obtained from sulfoxide (*S*)-**1B** was unequivocally established by X-ray analysis of **3Bb** and **3Bd**,[13] which were derived from aldimine **2b** and ketimine **2d**, respectively. Since these compounds exhibit the *S* configuration at the two stereogenic centers created during the reaction,[14] we have assigned the same configuration to all the amines that were obtained as exclusive products in the reactions of (*S*)-**1B** (**3Ba–3Be**), (*S*)-**1C** (**3Ca** and **3Cd**), (*S*)-**1D** (**3Da** and **3Dd**), and (*S*)-**1E** (**3Ea** and **3Ed**). The *S* configuration for the only stereogenic center of the major isomers obtained in the reaction of (*S*)-**1A** was determined by X-ray analysis of **3Aa**,[13] and we again assume the same stereochemical outcome for **3Ab**, **3Ac**, and **3Ad**.

Next, we focused our attention on the transformation of **3** into indolines in the presence of base. For some of the experiments listed in Table 1 we isolated small amounts of a new product, which was identified as the indoline **5** (Table 2). Detection of this by-product clearly indicated that intramolecular aromatic substitution of the sulfinyl group by the nitrogen center could take place under the right reaction conditions. After trying different bases (LDA, LiHMDS, NaHMDS) and temperatures, we found that the best reaction

Table 2: Preparation of fluorinated indolines **5**. HMDS = hexamethyldisilazane.



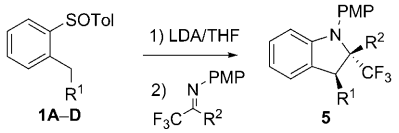
3 **5**

Entry	R^1	R^2	Product	Yield [%]
1	H	H	**5Aa**	64
2	H	Me	**5Ad**	67
3	Me	H	**5Ba**	66
4	Me	Ph	**5Bc**	83
5	Me	Me	**5Bd**	71
6	Allyl	Me	**5Dd**	60

conditions for the transformation of **3** into **5** involved the use of KHMDS in THF at 0 °C.[15] The cyclization of different aminosulfoxides **3**, derived from both aldimines (Table 2, entries 1 and 3) and ketimines (Table 2, entries 2 and 4–6), was also studied. Yields ranged from between 60 % and 83 %.

Asymmetric tandem processes that generate one or more stereogenic centers in a selective fashion have undeniable benefits in the field of synthetic organic chemistry.[16] Thus, we then evaluated the tandem process starting from sulfoxides (*S*)-**1** and imines **2** without isolation of the addition products **3** (Table 3). Initially KHMDS was used (the base that provided the best results in the cyclization reaction), but it was unsuccessful.[17] However, we found that when the reaction mixture of (*S*)-**1** and **2** was allowed to reach room temperature in the presence of LDA (before protonation), the intramolecular cyclization took place smoothly in about one

Table 3: One pot synthesis of indolines **5** through addition and S_NAr.



1A–D **2a–e** **5**

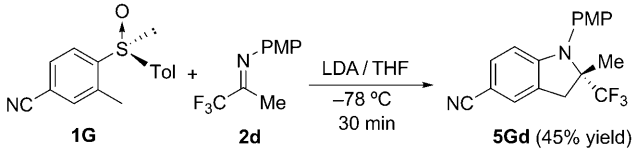
Ent	Reagents	Indoline (R^1, R^2)	d.r.[a]	Yield [%][b]
1	(*S*)-**1A** + **2a**	**5Aa** (H, H)	–[c]	61[d]
2	(*S*)-**1B** + **2a**	**5Ba** (Me, H)	>98:<2	61[e]
3	(*S*)-**1C** + **2a**	**5Ca** (Et, H)	>98:<2	61
4	(*S*)-**1D** + **2a**	**5Da** (Allyl, H)	>98:<2	60
5	(*S*)-**1E** + **2a**	**5Ea** (Bn, H)	>98:<2	71
6	(*S*)-**1B** + **2c**	**5Bc** (Me, Ph)	>98:<2	55
7	(*S*)-**1C** + **2c**	**5Cc** (Et, Ph)	>98:<2	35
8	(*S*)-**1D** + **2c**	**5Dc** (Allyl, Ph)	>98:<2	46
9	(*S*)-**1A** + **2d**	**5Ad** (H, Me)	–[c]	67
10	(*S*)-**1B** + **2d**	**5Bd** (Me, Me)	>98:<2	70
11	(*S*)-**1C** + **2d**	**5Cd** (Et, Me)	>98:<2	40[f]
12	(*S*)-**1D** + **2d**	**5Dd** (Allyl, Me)	>98:<2	52
13	(*S*)-**1E** + **2d**	**5Ed** (Bn, Me)	>98:<2	55[f]
14	(*S*)-**1B** + **2e**	**5Be** (Me, 2-Furyl)	>98:<2	60

[a] Diastereomeric ratio was determined by ^{19}F and ^1H NMR spectroscopy. [b] Yield of isolated products. [c] Enantiomers were obtained in this case. [d] 16 % of (*S*)-**1A** was recovered. [e] 28 % of (*S*)-**1B** was recovered. [f] Cyclization was also possible at −78 °C in 90 min.

hour to give indolines **5** in moderate yields (35–71%; Table 3).

The reactions were completely stereoselective and thus fluorinated indolines **5** containing one or two stereogenic centers were obtained as single compounds, even those bearing quaternary carbon atoms. Initially, **5Aa** and **5Ad** were obtained as indicated in Table 2, entries 1 and 2 (the starting amines were obtained as a diastereoisomeric mixture of **3** and **4** which required separation before cyclization), however, the reaction of (*S*)-**1A** with **2a** or **2d** under the tandem process reaction conditions afforded **5Aa** (61%, along with 16% of recovery sulfoxide; Table 3, entry 1) or **5Ad** (67%; Table 3, entry 9) as the only indolines. Cyclization of sulfoxides where $R^1 \neq H$ were faster, and took place at −78 °C, although they were still slower than the cyclization required for the preparation of amine **3** (Table 1). Thus, reactions of **2d** with (*S*)-**1B** or (*S*)-**1E** at −78 °C and subsequent protonation after 10 min afforded **3Bd** and **3Ed**, respectively, (Table 1, entries 8 and 15) whereas **5Bd** and **5Ed** were obtained exclusively after one hour at low temperature (Table 3, entries 10 and 13).

The results obtained for the above reactions point to an intramolecular substitution of the sulfinyl group by the nitrogenated anion, thus suggesting an S_NAr process. However, since reactions involving the sulfinyl functionality as the leaving group and a nitrogen center as the nucleophile have yet to be described[10] we set out to demonstrate unequivocally that an S_NAr process was involved in the conversion of **3** into **5** (most of the references regarding intramolecular S_NAr reactions entail strongly deactivated rings bearing F or NO_2 leaving groups).[18] We carried out several experiments which resulted in the exclusion of a radical mechanism and supported the nucleophilic character of the reaction on the basis of the substituent effects at the aromatic ring. Thus, electron-donating groups preclude the reaction, whereas electron-withdrawing groups accelerate it considerably (Scheme 2; see the Supporting Information for details).



Scheme 2. Influence of the substituents on the tandem reaction.

In conclusion, we have outlined a new strategy for the preparation of optically pure fluorinated indolines containing one or two stereogenic centers. Our approach involves the direct reaction of *N*-PMP-fluorinated imines[19] with 2-(*p*-toluenesulfinyl) alkylbenzenes in the presence of LDA. Almost complete stereoselectivity and mild conditions are the key features of these tandem processes, which include the unusual intramolecular nucleophilic aromatic substitution of a *p*-tolylsulfinyl group by the amide anion as the key reaction. Moreover, we have demonstrated that reactions of sulfinylated benzylcarbanions with fluorinated aldimines and ketimines lead to the synthesis of fluorinated amines with two vicinal stereogenic centers (one of them quaternary when starting from a ketimine). Additional interest in the mechanism of this nucleophilic addition stems from the high levels of selectivity achieved, and deserves further in-depth investigation.

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[12] Notably, the corresponding *N*-PMP-ethylideneimine derivatives do not react under similar reaction conditions, which is evidence for the increase in reactivity provided by the fluorinated substituent.

[13] CCDC 689575 (**3Bb**), 689576 (**3Bd**) and 690716 (**3Aa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] When R^2 = Ph or 2-furyl, in compounds **3Ac**, **3Bc**, and **3Be**, the priority of the substituents in the nitrogen containing stereogenic center was reverse, and these compounds exhibit the *R* configuration at this center.

[15] The use of LDA as the base provided lower yields in most cases.

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[19] Non-fluorinated indolines can also be obtained in high yields by the reaction of KHMDS with the amines obtained in reactions of lithiated (*S*)-**1B** with *N*-PMP derivatives of benzylideneimine and *p*-cyanobenzylidene imine under the reaction conditions outlined in Table 2. Reactions are slower that those of the fluorinated amines. Direct treatment of (*S*)-**1B** with *N*-PMP-benzylideneimine under the reaction conditions outlined in Table 3 afforded the product in low yield (see the Supporting Information).

