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Stereodivergent Quaternization of 2-Alkyl-2-*p*-tolylsulfinylacetonitriles: NMR Spectroscopic Evidence of Planar and Pyramidal Benzylic Carbanions

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Dedicated to Professor Antonio García Martinez on the occasion of his 70th birthday

Abstract: Enantiomerically enriched α,α-disubstituted phenylacetonitriles have been readily prepared by stereoselective quaternization of 2-alkyl-2-[2-(*p*-tolylsulfinyl)phenyl]acetonitriles with different alkylating electrophiles in the presence of bases. The use of potassium hexamethyldisilazane (KHMDS)/[18]crown-6 ether and NHMDS with alkyl halides afforded S,S_S and R,S_S diastereoisomers, respectively, in high enantiomeric purities, thus providing stereodivergent processes for synthesizing both isomers. The dependence of the stereochemical course of the reactions on the experimental conditions (mainly on the counterion) has been rationalized by assuming a planar or pyramidal structure for the benzylic carbanions. This hypothesis has been supported by NMR spectroscopic studies, which permit one to assign a chelated pyramidal structure to the sodium benzylic carbanions and an almost planar naked carbanionic structure to the potassium benzylic carbanions generated in the presence of [18]crown-6 ether.

Keywords: asymmetric synthesis · carbanions · chirality · diastereoselectivity · NMR spectroscopy

Introduction

The stereoselective construction of C−C bonds has been profusely studied in recent decades due to its frequent application to the synthesis of many natural and biologically active products. Among them, compounds bearing chiral quaternary carbon centers are numerous. The development of synthetic strategies for the asymmetric formation of such chiral centers, especially those bearing only carbon substituents, has been an attractive though difficult challenge to organic chemists in recent years.[1] Both the stoichiometric use of chiral auxiliaries and enantioselective catalytic methods have been investigated for the asymmetric synthesis of molecules containing a quaternary carbon center, which in many cases occupies a benzylic position.[2] In this context, the chiral α,α-dialkyl phenylacetonitrile fragment has been found present in highly active molecules of the azole family of fungicides and herbicides,[3] such as fenbuconazole or myclobutanyl, and calcium channel blockers,[4,5] (verapamil, norverapamil, gallopamil, emopamil, or E2050), which have emerged as important and useful agents for treating hypertension, angina pectoris, migraines, and arrhythmias.

2-*p*-Tolylsulfinyl benzyl carbanions[6] (derived from **1** by treatment with lithium diisopropylamide (LDA)) have shown a very high stereoselective nucleophilic behavior in their reactions with different electrophiles such as alkyl halides,[7] carbonyl compounds,[8] *N*-sulfinyl imines,[9] and *N*-aryl imines.[10] In all these reactions, chelated structures, with the counterion (Li^+) joined to the benzylic carbon and stabilized by the sulfinyl oxygen, have been postulated to account for the stereoselectivity [Scheme 1, Eq. (1)]. Additionally, carbanions formed from *O*-protected cyanohydrins[11] (**2**, Y = OP) and their corresponding N-protected α-aminoni-

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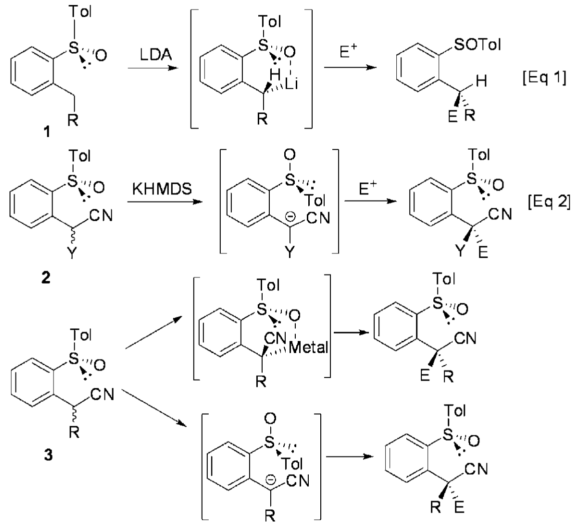
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903521. It includes ^{1}H and ^{13}C NMR spectra for starting materials **5–6**, tertiary α-alkylphenylacetonitriles **3a–g**, quaternary α,α-dialkylphenylacetonitriles **7–10**, chemical correlation products **11–13**, and subproducts **14–16** (ref. [21]), as well as the 2D NMR spectra of anions derived from **3a**.



Scheme 1.

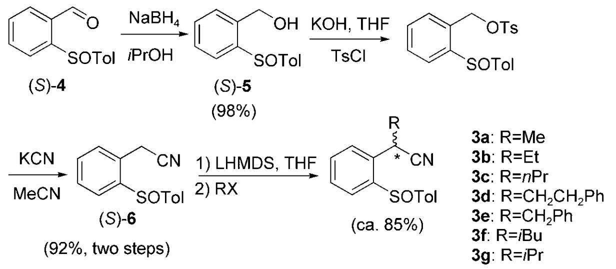
triles[12] (**2**, Y = NHBn) and potassium hexamethyldisilazane (KHMDS) also evolved in a highly stereoselective way [Scheme 1, Eq. (2)] allowing the creation of chiral benzylic quaternary centers with high optical purities. In these cases, planar nonchelated carbanions stabilized by the CN group, in which the counterion (K$^+$, less prone to the association) is not joined to the benzylic carbon, have been proposed as the intermediates.

These results suggested the possibility of achieving both types of intermediates starting from the same substrate, simply by choosing the reaction conditions, mainly the base containing the appropriate metal. To verify the viability of such a proposal, we decided to study the alkylation of 2-alkyl-2-[(2-*p*-tolylsulfinyl)phenyl]acetonitriles **3** (Scheme 1) under different conditions, which would provide a ready access to the α,α-dialkylphenylacetonitrile fragment, present in biologically active molecules, in either of its two possible configurations. Compounds **3**, with intermediate structures between those of **1** and **2**, were chosen for this study because marked conformational constrains of differently metalated nitriles have been reported recently as responsible for their stereodivergent evolution in intramolecular[13] and intermolecular[14] alkylation processes. Results obtained in this study are herein reported.

Results and Discussion

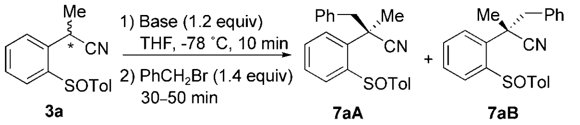
The synthesis of the starting sulfinyl phenylacetonitriles **3a**–**d** was performed by quantitative NaBH$_4$ reduction of (*S*)-**4**,[15] substitution of the OH at the resulting alcohol (*S*)-**5** by CN, and final alkylation of nitrile (*S*)-**6** (Scheme 2). Compounds **3a**–**g** were obtained as inseparable mixtures of diastereoisomers (< 36 % *de*) under all the assayed conditions (different bases, solvents, and temperatures).

Quaternization reactions were initially assayed on a diastereoisomeric 1:1 mixture of **3a** by treatment with benzyl bromide as the electrophile. The effect of different bases (LHMDS, NHMDS, KHMDS), additives, solvents, and temperatures was investigated (Table 1). When LHMDS was used as the base in THF at −78 °C, the reaction evolved with moderate stereoselectivity yielding a 74:26 diastereoisomeric mixture of **7aA** and **7aB** (Table 1, entry 1).[16] The use of CH$_2$Cl$_2$ as the solvent determined a decrease in the stereoselectivity (Table 1, entry 2), whereas the addition of [12]crown-4 ether had scarce influence on the diastereoisomeric ratio (d.r.) (Table 1, entry 3). More interesting results were obtained when KHMDS was employed as the base (Table 1, entries 4–6), mainly in the presence of [18]crown-6 ether, which provided a very high proportion of compound **7aA** (entries 5 and 6). As expected, the d.r. improved when the temperature was lowered (compare entries 5 and 6), although such an improvement was rather low and it did not compensate for the higher experimental difficulties and the decrease in the yield. Interestingly, the use of NHMDS afforded a 10:90 mixture of **7aA** and **7aB** (Table 1, entry 7), with the stereoselectivity being opposite to that detected with KHMDS and LHMDS. The addition of [15]crown-5 ether substantially decreased the stereoselectivity (Table 1, entry 8) and the conversion (30 %).



Scheme 2. Synthesis of the starting materials.

Table 1. Stereodivergent behavior of **3a** with benzyl bromide under different conditions.



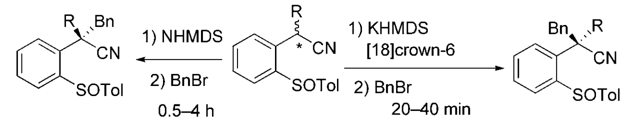
Entry	Base (additive)	Solvent	*T* [°C]	**7aA**/**7aB**[a]	Yield [%][b]
1	LHMDS	THF	−78	74:26	77
2	LHMDS	CH$_2$Cl$_2$	−78	64:36	[c]
3	LHMDS ([12]crown-4)	THF	−78	80:20	79
4	KHMDS	THF	−78	57:43	84
5	KHMDS ([18]crown-6)	THF	−78	87:13	86
6	KHMDS ([18]crown-6)	THF	−98	89:11	86
7	NHMDS	THF	−78	10:90	84
8	NHMDS ([15]crown-5)	THF	−78	68:32	[c,d]

[a] Determined by integration of well-separated signals in the ^{1}H NMR spectra of the crude reaction. [b] Combined yield for both diastereoisomers. [c] Not determined. [d] 30 % conversion.

From these results we can conclude that quaternization of **3a** with benzyl bromide proceeds with good yields and diastereomeric excess (*de*) values in a completely stereodivergent process closely dependent on the experimental basic conditions; **7aB** is favored with NHMDS and **7aA** with KHMDS/[18]crown-6 ether.

Then we investigated the benzylation reactions of substrates **3b**–**3d**, **3f**, and **3g**, which differ in the R group, under the experimental conditions of entries 5 and 7 of Table 1 (Table 2). Regardless the nature of R, reactions conducted with KHMDS/[18]crown-6 ether yielded diastereoisomers **A** as the major ones with 74–80% *de*, whereas epimers **B** were mainly obtained in those reactions performed with NHMDS, with 70–80% *de*, except for **7fB** (52% *de*). Reaction times under the former conditions were shorter than under the latter ones, thus providing evidence of the higher reactivity of potassium carbanions. All the reactions proceeded in high yields.

Table 2. Stereodivergent benzylation of substrates **3a**–**3d**, **3f**, and **3g**.

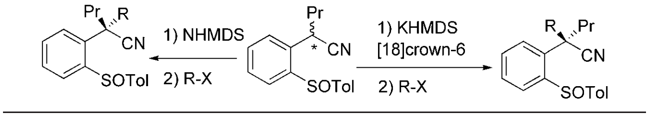


Compound (*de* [%])	Yield [%]	Compound (R)	Yield [%]	Compound (*de* [%])
7aB (80)[a]	84	**7a** (Me)	86	**7aA** (74)
7bB (70)	79	**7b** (Et)	82	**7bA** (76)
7cB (76)	78	**7c** (Pr)	83	**7cA** (76)
7dB (78)	81	**7d** (CH_2Bn)	90	**7dA** (80)
7fB (52)[b]	85	**7f** (*i*Bu)	91	**7fA** (76)[b]
7gB (80)	77	**7g** (*i*Pr)	79	**7gA** (74)

[a] In toluene, $de>98\%$, yield = 71%. [b] In toluene, $de=80\%$, yield = 10%.

Next we investigated the behavior of other alkylating reagents under the optimum conditions favoring the stereodivergence. The study was performed on **3c** and furnished similar results (Table 3) to those obtained for benzylation reactions (Table 2). Thus, stereodivergence was observed for all the alkylation reactions with isomers **A** being predominant with KHMDS/[18]crown-6 ether, whereas isomers **B** were preferentially formed with NHMDS. Under the former conditions the reactivity was higher (shorter reaction times were needed for the reaction to reach completion). As expected, the use of alkyl iodides instead of alkyl bromides decreased the reaction times and sometimes provided slightly better yields, but the stereoselectivity remained almost identical (only one example has been included in Table 3). These results confirm the stereodivergent behavior of the carbanions derived from **3** depending on the counterion and indicate that the synthesis of any of the epimers can be performed by tuning the experimental conditions, in particular, the base used in the reaction.

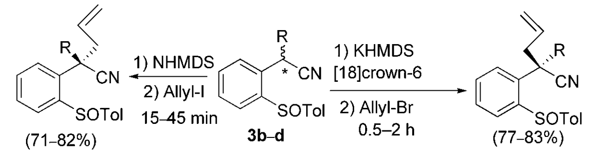
Table 3. Stereodivergent behavior of **3c** with different electrophiles.



Compound (*de* [%])	Yield [%]	Time [h]	R–X	Time [h]	Yield [%]	Compound (*de* [%])
8cB (86)	79	1	MeI	0.5	83	**8cA** (46)
9cB (70)	56	8	EtI	2.5	71	**9cA** (66)
7cB (76)	78	3	BnBr	0.5	83	**7cA** (76)
10cB (54)	74	3	allyl-Br	0.5	79	**10cA** (84)
10cB (58)	81	0.2	allyl-I	–	–	–

Two facts are noteworthy from Table 3. The first one is the marked differences in stereoselectivity observed for the methylation reaction, which exhibits the lowest *de* values with KHMDS but the highest ones with NHMDS. The other remarkable data is the higher *de* values observed for allylations (84%) with KHMDS/[18]crown-6 ether as compared with those observed with other alkylating reagents. These results induced us to study these two reactions thoroughly. The results obtained from the allylation reactions are collected in Table 4.

Table 4. Stereodivergent evolution of allylation reactions.



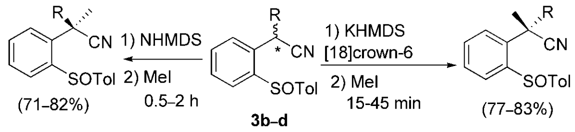
Compound	Yield [%]	*de* [%]	(*de* [%], yield [%])[a]	R	Yield [%]	Compound (*de* [%])
10aB	78	80	(96, 80)	Me (**3a**)	82	**10aA** (86)
10bB	79	74	(96, 66)	Et (**3b**)	83	**10bA** (88)
10cB	81	58	(86, 65)	Pr (**3c**)	77	**10cA** (84)
10dB	84	66	–	$BnCH_2$ (**3d**)	83	**10dA** (88)
10eB	71	34	(84, 60)	Bn (**3e**)	77	**10eA** (90)
10fB	81	−24	(96, 8)	*i*Bu (**3f**)	76	**10fA** (96)
10gB	81	78	–	*i*Pr (**3g**)	74	**10gA** (90)

[a] Toluene was used as the solvent.

The observed stereoselectivity with KHMDS/[18]crown-6 ether was very high with all the assayed electrophiles (84–90% *de*). By contrast, reactions conducted in the presence of NHMDS, which once again evolved with the opposite selectivity, exhibited a stereoselectivity dependent on the nature of the R group present in the starting material, ranging between 34% for **10eB** (R = Bn) and 80% for **10aB** (R = Me). This behavior seems to be related to the steric size of the R group (the selectivity decreases as the size increases), which would explain the completely unexpected result obtained from **3f**, which yielded **10fA** as the major diastereoisomer in the presence of NHMDS. However, the high stereoselectivity observed in the reaction of **3g** (R = *i*Pr) with NHMDS, which is not compatible with this tendency, suggests a more complex dependence. Most of these reactions were performed starting from allyl bromides and iodides. The reactivity of the iodides was higher (shorter reaction times were necessary) in all cases but the stereoselectivity remained almost unaltered.

Results obtained in the methylation reactions of different substrates are collected in Table 5. As we can see, the stereoselectivity of the reactions conducted with KHMDS/[18]crown-6 ether (ca. 50 % *de*) is scarcely dependent on the size of R in the starting material and lower than that observed for other alkylation reactions (for example, compare Tables 4 and 5). On the contrary, reactions with NHMDS are highly stereoselective (78–86 % *de*), with the exception of **3 f** (R = *i*Bu), which afforded a 19:81 mixture of **8 fA** and **8 fB**.

Table 5. Stereodivergent evolution of methylation reactions.

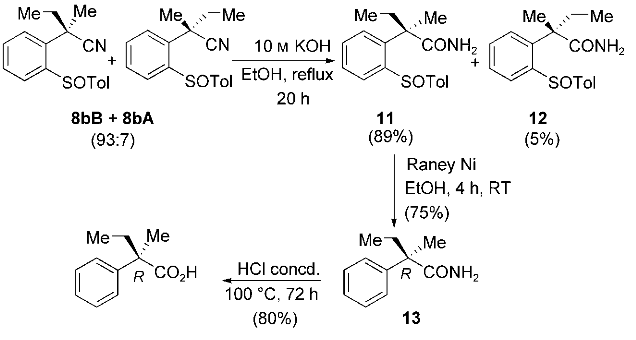


Compound	Yield [%]	*de* [%]	(*de* [%], yield [%])[a]	R	Yield [%]	Compound (*de* [%])
8bB	86	86	–	Et (**3b**)	84	**8bA** (46)
8cB	79	86	(98, 65)	Pr (**3c**)	83	**8cA** (46)
8dB	81	86	–	BnCH$_2$ (**3d**)	86	**8dA** (56)
8eB	78	82	–	Bn (**3e**)	86	**8eA** (44)
8fB	76	62	(84, 20)	*i*Bu (**3f**)	79	**8fB** (50)
8gB	83	84	–	*i*Pr (**3g**)	84	**8gA** (46)

[a] Toluene was used as the solvent.

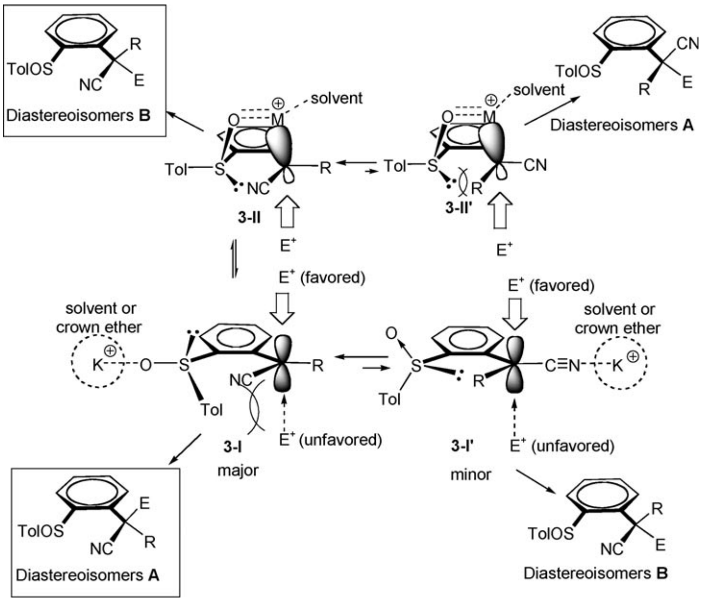
Chromatographic purification and separation of the diastereoisomeric mixtures obtained in most of these reactions afforded the major diastereoisomers. All the attempts to achieve good crystals of the nitriles proved unsuccessful and therefore chemical correlation with configurational assignment was necessary.

Thus, **8bB** (R = Me, R′ = Et) was chemically correlated with (*R*)-2-methyl 2-ethyl phenyl acetic acid (Scheme 3). Hydrolysis of a 93:7 mixture of nitriles **8bB** and **8bA** followed by desulfinylation of the major diastereoisomeric sulfinyl carboxamide **11** and additional hydrolysis of the resulting amide **13** produced nonracemic 2-methyl-2-phenylbutanoic acid, the [α] value of which was of a similar magnitude and opposite sign to that previously reported for (*S*)-2-methyl-2-phenylbutanoic acid (94 % *ee*).[17] Consequently, the *R* configuration could be assigned to our 2-methyl-2-phenylbutanoic acid and, therefore, to the benzylic carbon atom at the major diastereoisomeric nitrile **8bB**.



Scheme 3. Chemical correlation of compound **8bB**.

The stereodivergent behavior of benzylic carbanions derived from **3a–g** can be explained by assuming that they adopt a different structure dependent on the nature of the base (NHMDS or KHMDS) used in their generation. Two types of carbanionic species can be conceived. Carbanions **3-I** and **3-I′** have the metal detached from the planar sp^2 benzylic carbanion[18]—the charge will delocalize throughout the ring and the CN group—and stabilized by association to the sulfinyl oxygen (**3-I**) or to the nitrogen (**3-I′**), as well as by molecules of coordinating solvents (THF). The higher electronic density at the sulfinyl oxygen as compared with that at the nitrogen atom suggests that the association O···M$^+$ must be stronger and, therefore, **3-I** would be predominant in its equilibrium with **3-I′** (steric factors also support this preference, Scheme 4). Chelated species **3-II** and **3-II′**, with the metal joined to both the sulfinyl oxygen and the sp^3 benzylic carbon and additionally stabilized by solvent molecules (THF), are also plausible. These species will adopt a boatlike conformation (it allows for a significant charge delocalization throughout the ring) with the lone electron pair at sulfur orientated towards one of the flagpole positions of the boat.[19] The second flagpole position could be occupied either by the CN (**3-II**) or by the R group (**3-II′**) at the benzylic carbon (Scheme 4), but the latter situation must be less stable since the size of the alkyl groups hinders them from adopting the flagpole position in a boatlike structure.



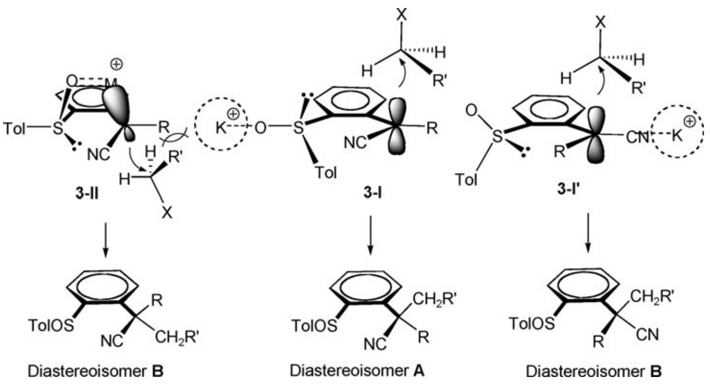
Scheme 4. Proposed carbanions accounting for the stereodivergence of quaternization reactions.

In the presence of NHMDS, a mixture of carbanionic species will be formed, chelated **3-II** being the major one and, therefore, responsible for the observed stereoselectivity. By contrast, the larger K^+ will not adapt well in chelated **3-II** and **3-II′** structures. Hence the addition of [18]crown-6 ether would determine the easy capture of the cation, which would increase its relative size. As a consequence, its presence in a chelated species will be practically forbidden on steric grounds and the equilibrium will be completely shifted towards the singly associated species. Thus, the stereoselectivity of the reactions with KHMDS/[18]crown-6 ether must be rationalized by taking into account the evolution of species **3-I** (presumably more stable than **3-I′**,[20] see above). The electrophiles can approach only the opposite face to that occupied by the metal at species **II** (Scheme 4). Accordingly, the evolution of carbanion **3-II** (predominant when the reaction was conducted under NHMDS) will mainly afford diastereoisomers **B**. By contrast, carbanion **3-I** (generated as the major one with KHMDS/[18]crown-6-ether) will mainly evolve into diastereoisomers **A** due to the steric repulsion of the tolyl group with the electrophile approaching the bottom face (Scheme 4). This would justify the stereodivergence observed with the change of the base. Another point to be explained concerns the reactivity, which is significantly higher (shorter reaction times were needed for the reaction to reach completion) for reactions performed with KHMDS. The smaller steric hindrance and the higher electronic density associated to the nonassociated carbanions **II** could account for their higher reactivity.

Other significant changes in the stereoselectivity, deduced from Tables 2–5, are the following:

1) The increase in the size of the electrophile seemingly improves the stereoselectivity of reactions performed with KHMDS/[18]crown-6-ether (methylation is the less stereoselective process), whereas the opposite tendency is observed with NHMDS (methylation is the most stereoselective process).
2) The increase in the size of the R group at the substrate decreases the stereoselectivity in reactions with NHMDS, whereas it has a scarce influence in reactions with KHMDS/[18]crown-6 ether.

The equilibrium between species **3-II** (major) and **3-I** for reactions with NHMDS, and between **3-I** (major) and **3-I′** for reactions with KHMDS/[18]crown-6 ether, permit an explanation of the above observations. As can be deduced from Scheme 5, the steric repulsion (R/R′) in the evolution of tetracoordinated **3-II** is higher than that of tricoordinated **3-I** due to the smaller steric hindrance of the nucleophilic center in **3-I**. Consequently, an increase in the size of the R or R′ will cause a decrease in the stereoselectivity in reactions conducted with NHMDS. Therefore, methylation will produce the highest proportion of diastereoisomers **B** and the increase in the size of R will afford larger amounts of diastereoisomers **A**. By contrast, in reactions conducted with KHMDS/[18]crown-6 ether, in which only **3-I** and **3-I′** species are involved, evolution through **3-I** will be clearly favored due to the large size of the K-coordinated CN group in **3-I′**. However, in these reactions the small size of R′ at the electrophile may permit the approach of the reagent to **3-I** from the anion face that exhibits the *p*-tolyl group, thus affording the minor isomer **B**.



Scheme 5. Influence of the steric size on the stereoselectivity.

To confirm this hypothesis, we reasoned that the use of toluene as the solvent, less polar than THF and, therefore, unable to stabilize the metal, would increase the proportion of chelated **3-II** with respect to singly associated **3-I**, thus favoring the formation of diastereoisomers **B** and improving the stereoselectivity of the reactions performed with NHMDS. As the reactions in toluene were much slower, probably due to solubility problems, these conditions were mainly assayed in allylation processes. The results of reactions conducted in toluene are collected in Table 4. The stereoselectivity substantially increased in all the cases and became almost complete in allylations of **3a** and **3b**. Improvements were noteworthy starting from **3c** and **3e**, which is synthetically relevant because the yields obtained in toluene were similar to those of reactions conducted in THF. Methylation of **3c** in toluene also evolved with higher stereoselectivity than in THF (Table 5). We have also studied different alkylation reactions in toluene starting from **3f**, which is the substrate that provides the poorest stereoselectivities in reactions with NHMDS in THF. In all the cases, the stereoselectivity substantially increased, thus reinforcing our mechanistic proposal, but these reactions are not synthetically useful because of the low conversions detected in all of them: allylation, 8% (Table 4); methylation, 20% (Table 5), and benzylation, 10% (Table 2).[21]

NMR spectroscopic studies of carbanion intermediates: To support the mechanistic proposal depicted in Scheme 4, it would be highly interesting to find some experimental evidence that supports the different structures of the proposed carbanions. We reasoned that a detailed analysis of the carbanion NMR spectroscopic data could be suitable for this purpose because chemical shifts are highly sensitive to the electronic delocalization, which in turn must be dependent on the structure of the carbanion. Thus, we performed an NMR spectroscopic study of the carbanions generated by reaction of **3a** (as a diastereoisomeric mixture) with NHDMS and KHDMS/[18]crown-6 ether, respectively, under experimental conditions similar to those previously used in the synthetic work, that is, −50 °C in [D$_8$]THF (see the Supporting Information).

We started our study generating the sodium carbanion by treating the diastereoisomeric mixture **3a** with NHMDS. A new species **3a-II** was detected, with total conversion of the starting material at the previously described experimental conditions. On the other hand, when the anion was formed by treating **3a** with KHMDS in the presence of [18]crown-6 ether, a complex mixture was obtained. In fact, an equilibrium of four species in chemical exchange was detected by NMR spectroscopy (see Figure 1), which corresponds to the two diastereoisomeric starting materials **3a** (21 and 24 %) and another two anionic species, **3a-I** (44 %) and **3a-I′** (11 %), the NMR spectroscopic data of which are different to those of **3a-II** (see Table 6).

The analysis of the ^{1}H and ^{13}C NMR spectroscopic resonances of the new species generated from **3a** and bases, by using 2D-COSY, HSQC, HMBC, and NOESY (mixing time: 300 ms) experiments, permitted us to demonstrate that a strong shielding in the signals that corresponds to the *ortho*-disubstituted aromatic ring, with respect to those of **3a**, was taking place. It can be satisfactorily explained by assuming the formation of three different benzylic carbanionic species able to delocalize the charge onto the π-aromatic system. This delocalization is particularly significant on the aromatic NMR-spectroscopy-sensitive nuclei at *ortho* (6′ and 2′) and *para* (4′) positions, with respect to the benzylic fragment. Indeed, it is even more evident for the ^{13}C NMR spectroscopic resonances, as deduced from the HSQC and HMBC experiments. Hence, the carbanionic species show important variations of the chemical shifts of the nuclei at the *para* position (Δδ(C-4) ranging between −23.3 and −24.9 ppm and Δδ(H-4) ranging between −1.8 and −2.0 ppm). Also significant are the variations of the chemical shifts at the *ortho* positions (Δδ(C-6) and Δδ(C-2) range between −6.6 and −20 ppm and Δδ(H$_{ortho}$-6) between −0.8 and −1.8 ppm) with respect to the starting product (Table 6). The larger range observed for nuclei at the *ortho* position is due to the influence of the substituents (vide infra). In addition to these variations, there are other ones that are clearly indicative of the formation of benzylic carbanions. This is the case of the ^{13}C NMR spectroscopic signal of the benzylic carbon atoms (Figure 2), which resonate at much lower field (δ = 40.0–46.6 ppm) than the equivalent signal for **3a** (δ = 26.8–27.1 ppm), and the strong deshielding of the CN group (Δδ ranging between +12.3 and +17.3 ppm) and the *ipso* carbon C-1′ (Δδ ranging between +8.0 and +12.0 ppm). Taking into account the above-mentioned precedents, these variations allow us to conclude that species **3a-II**, **3a-I**, and **3a-I′** have a carbanionic structure.

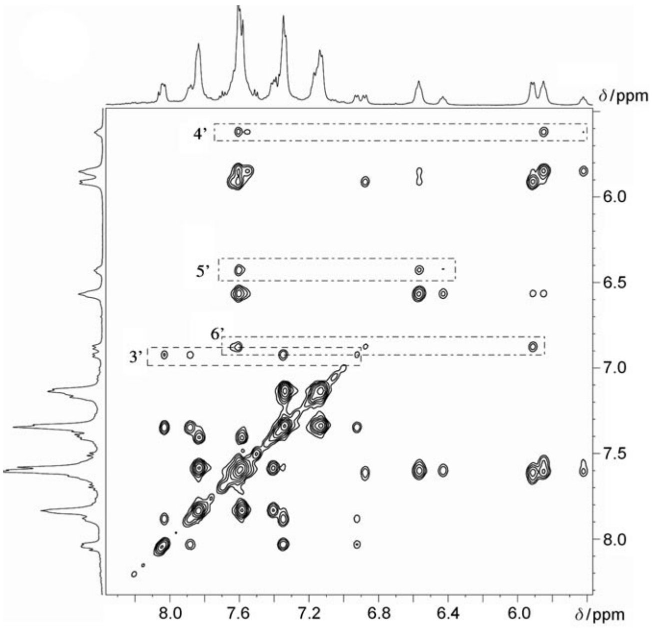
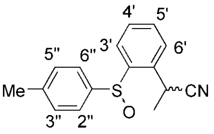


Figure 1. Section of the 2D-NOESY/EXSY spectrum of the compound **3a** treated with KHMDS/[18]crown-6 ether at −50 °C in [D$_8$]THF, showing the chemical exchange among the starting products and the two anions in the aromatic rings zone. Some NOE cross peaks are observed. The key aromatic exchange peaks are shown within boxes.

Table 6. ^{1}H and ^{13}C NMR spectroscopic chemical shifts of compounds **3a** (diastereoisomeric mixture), and anions **3a-II** (Na), **3a-I** (K/[18]crown-6 ether, major), and **3a-I′** (K/[18]crown-6 ether, minor).



3a

	3a ^{1}H	**3a** ^{13}C[a]	**3a-I** ^{1}H	**3a-I** ^{13}C[a]	**3a-I′** ^{1}H	**3a-I′** ^{13}C[a]	**3a-II** ^{1}H	**3a-II** ^{13}C[a]
1-CN	–	121.7	–	137	–	134	–	139
2 (anion)	4.6/4.9	26.8/27.1	–	40.6	–	46.6	–	40
3-Me	1.1/1.4	21.1/21.3	1.66	18.4	1.99	21.2	1.69	16.9
Ar-1′	–	137	–	145	–	149	–	149
Ar-2′	–	144	–	129	–	125	–	124
Ar-3′	8.1/7.9	126/126.5	7.35	124.2	6.9	128.3	6.38	129.9
Ar-4′	7.6/7.5	129.7/130	5.8	108.4	5.6	108.1	5.71	109.7
Ar-5′	7.6/7.5	132.6	6.6	129.3	6.4	128.7	6.61	130
Ar-6′	7.7/7.5	129.6/129.7	5.9	116	6.9	123	6.16	117
Tol-2″/6″	7.6	125/126	7.84	126.5	7.4	125.5	7.37	125.4
Tol-3″/5″	7.3	131	7.13	129	7.17	130.7	7.16	129
Me-Tol	2.24	21.1/21.3	2.22	n.d.[b]	2.16	21.16	2.25	20.2

[a] ^{13}C data from HSQC and HMBC experiments. [b] n.d. = not detected.

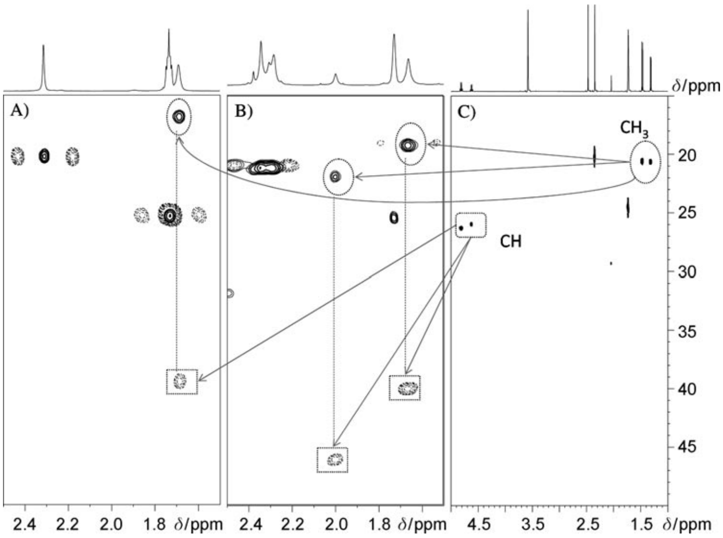


Figure 2. HSQC (solid lines)/HMBC (broken lines) superimposition of the aliphatic region showing the correspondence between the methyl moieties (dotted circles) and the related anionic nonprotonated carbons (dotted squares) for A) the product obtained by reaction of **3a** with NHDMS and B) the reaction mixture obtained by reaction of **3a** with KHDMS/[18]crown-6 ether. C) HSQC spectrum of the corresponding region for the diastereoisomeric mixture **3a** (500 MHz, −50 °C, [D$_8$]THF).

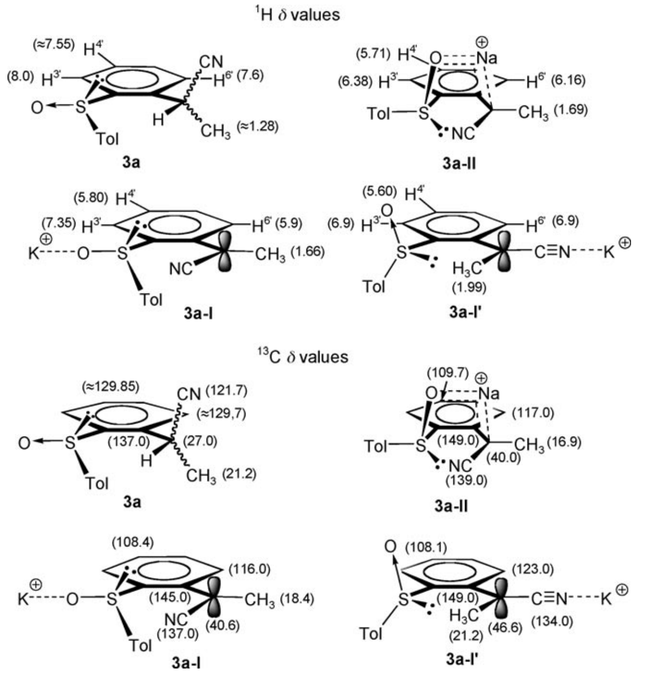
To get the charge delocalized through the aromatic ring, benzyl carbanions must be able to arrange their lone electron pairs in an orientation parallel to that of the aromatic π system. The three species depicted in Scheme 4 fulfill this requirement: benzylmetals **II** (**3a-II** when generated from **3a**) with the sp^3 orbital that contain the lone electron pair adopting an almost parallel arrangement to the π cloud because of the boatlike structure, and free carbanions **I** and **I′** (**3a-I** and **3a-I′** when they derive from **3a**) with sp^2 hybridization, in which the conjugation of the p orbital with the π orbital of the aromatic ring could be slightly distorted by steric interactions of either the R or CN groups with the sulfinyl group. Delocalization must be similarly effective in the three species, maybe slightly higher for the planar carbanions **3a-I** and **3a-I′**, which is in agreement with the values of Δδ for the nuclei at the *para* position (Table 6), at which no additional electronic influence of the substituents is present. To elucidate the structures of the different carbanions it is necessary to take into account other factors. The new species obtained with NHMDS (**3a-II**) is characterized by the existence of NOE cross peaks between the methyl group bonded to the anionic carbon and the *ortho* proton (H-6′), as well as additional contacts between the tolyl ring and the *ortho* proton with respect to the sulfur function (H-3′). These facts suggest that these groups are located very close each other, which agrees with the proposed structure (and geometry) for the boatlike **3a-II** (Figure 1).

On the other hand, the NOE cross peaks between the tolyl ring and H-3′ are absent in **3a-I** and **3a-I′**, whereas those of Me group and H-6′ are involved in a complex system due to the dynamics of the system and the existing chemical exchange. When cross peak intensities are calculated relative to their corresponding diagonal peaks, the cross peak with the largest relative intensity always corresponds to the H6′ (any of the species in solution) and Me (**3a-I**, major anion) interaction (see the Supporting Information). This indicates that the H6′/Me moieties are close in space in the **3a-I** anionic compound and that this is the primary NOE contact, thereby supporting the structural assignment of these carbanionic species.

To confirm this assignment, the following differences in chemical shifts are worth mentioning:

1) In **3a-I′**, the electronic density of the anion must be delocalized through the cyano group more efficiently than in **3a-I**, because the electron-demanding character of the CN in the former one must be enhanced by its association to K$^+$. It agrees with the higher ^{13}C δ value of the carbanionic carbon observed for **3a-I′** ($\delta = 46.6$ ppm) than for **3a-I** ($\delta = 40.6$ ppm). In turn, the observed ^{13}C δ value for the cyano carbon signal of **3a-I′** resonates at higher field ($\delta = 134.0$ ppm) than that of **3a-I** ($\delta = 137.0$ ppm), as expected by the electron-withdrawing effect of the K$^+$ on the electronic cloud of the cyano moiety.
2) The observed relative low-field chemical shift for the *ortho* proton H-6′ in **3a-I’** ($\delta = 6.9$ ppm) with respect to that observed in **3a-I** ($\delta = 5.9$ ppm) can be explained by the anisotropic effect of the quasi-ketenimine moiety that results from charge delocalization of the anion through the cyano group. Additionally, as far as ^{13}C δ(C-6′) values for **3a-I** and **3a-II** are concerned, their high-field chemical shifts, relative to that for **3a-I′**, may be a consequence of their 1,3-parallel interaction with the methyl group in their presumably proposed more stable conformation[22] (see Figure 1).
3) The relatively low-field chemical shift of H-3′ ($\delta = 7.35$ ppm) in **3a-I**, relative to that of **3a-I′** ($\delta = 6.90$ ppm), can also be accounted for by the anisotropic effect of the S−O bond, which is coplanar to the aromatic ring in **3a-I**. In the same sense, the low δ value observed for H-3′ in **3a-II** ($\delta = 6.38$ ppm) is consistent with the anisotropic shielding effect of the tolyl group in this compound (see Scheme 6).
4) Finally, the higher value of the chemical shift of the CH_3 group (^{13}C: $\delta = 21.2$ ppm; ^{1}H: $\delta = 1.99$ ppm) for **3a-I′**, relative to those for **3a-I** (^{13}C: $\delta = 18.4$ ppm; ^{1}H: $\delta = 1.66$ ppm) could be a consequence of the association of the potassium to the nitrogen in **3a-I′**, thereby increasing the electron-withdrawing power of the cyano group, although the formation of a weak intramolecular hydrogen bond of the CH_3 with the lone electron pair at sulfur could also play some role in these differences.

Therefore, as a conclusion from the NMR spectroscopic analysis, two different types of geometries for the herein reported carbanionic species can be claimed. The first one is a cyclic geometry, closer to a pyramidal state, with involve-



Scheme 6. ^{1}H and ^{13}C NMR spectroscopic chemical shifts relevant for structural assignments of sulfinyl benzylic carbanions.

ment of the Na$^+$ ion as contact ion pair, for **3a-II**. The second one is an almost planar and open geometry, exhibited by the species **3a-I** and **3a-I′**. In these cases, the smaller degree of coordination to the anion expected for the K$^+$/crown ether complexes, as well as their large size, would prevent the formation of the cyclic intermediate, and these systems behave as solvated-like ion pairs, thereby differing in the position at which the metal is associated to the anion (oxygen in **3a-I** and nitrogen in **3a-I′**). As the restrictions imposed by the cyclic geometry are no longer present, interconversion between the trigonal sp^2 and the pyramidal sp^3 states, with the result of an averaged planar structure, is probably taking place for the extended **3a-I** and **3a-I’** structures.[23]

Conclusion

In summary, we have demonstrated that benzylic carbanions derived from 2-alkyl-2-*p*-tolylsulfinylphenylacetonitriles show a stereodivergent behavior in their reactions with alkyl halides in the presence of KHMDS/[18]crown-6 ether or NHMDS. This stereodivergence allows the highly stereoselective generation of chiral quaternary benzylic carbon centers in their two possible configurations. This behavior seems to be associated with the planar or pyramidal structure adopted by the carbanion, which in turn is related to the conditions (solvent, additive, and mainly counterion) used in the reaction. NMR spectroscopy has proved to be a valuable instrument for determining structural differences in the carbanionic intermediates.

Experimental Section

General procedure for the synthesis of compounds 7–10

Method A: KHMDS (0.5 M in toluene; 0.24 mL, 1.2 mmol) was added to a solution of the corresponding (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile (0.1 mmol) (**3a–g**) and [18]crown-6 ether (31.7 mg, 0.12 mmol) in anhydrous THF (1 mL) cooled to −78 °C under argon. The reaction mixture was stirred at −78 °C for 10 min and then the electrophile was added. The reaction was monitored by TLC. Upon transformation of the starting material, the reaction was hydrolyzed with saturated aqueous NH$_4$Cl (5 mL). The mixture was extracted with Et$_2$O (3×5 mL), dried (Na$_2$SO$_4$), and the solvent was evaporated. The resulting diastereoisomeric mixture was purified by flash column chromatography.

Method B: NHMDS (0.5 M in toluene; 0.24 mL, 1.2 mmol) was added to a solution of the corresponding (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile (0.1 mmol) (**3a–g**) in anhydrous THF (1 mL) cooled to −78 °C under argon. The reaction mixture was stirred at −78 °C for 10 min and then the electrophile was added. The reaction was monitored by TLC. Upon transformation of the starting material, the reaction was hydrolyzed with saturated aqueous NH$_4$Cl (5 mL). The mixture was extracted with Et$_2$O (3×5 mL), dried (Na$_2$SO$_4$), and the solvent was evaporated. The resulting diastereoisomeric mixture was purified by flash column chromatography.

Compounds (2*R*,(S)*S*)-7aA and (2*S*,(S)*S*)-7bB: A diastereoisomeric 50:50 mixture of (2*R*,(*S*)*S*)- and (2*S*,(*S*)*S*)-**3a** was used as the starting material. Benzyl bromide (1.4 equiv) was used as the electrophile, and the reaction was stirred at −78 °C for 30 min to give a diastereoisomeric 87:13 mixture of **7aA+7bB**, which were separated and purified by flash column chromatography (eluent CH$_2$Cl$_2$/Et$_2$O/hexane 20:1:5). Combined yield (for both diastereoisomers): 86 %. Diastereoisomer (2*R*,(*S*)*S*)-**7aA**: colorless oil: $[\alpha]_D^{20}=-206.3$ ($c=1.9$, CHCl$_3$); ^{1}H NMR: $\delta=7.74$ (dd, $J=1.6$, 7.5 Hz, 1H), 7.67 and 7.30 (AA′BB′ system, 4H), 7.47–7.35 (m, 2H), 7.26–7.22 (m, 4H), 7.16–7.12 (m, 2H), 3.70 and 3.44 (AB system, $J=13.4$ Hz, 2H), 2.39 (s, 3H), 1.89 ppm (s, 3H); ^{13}C NMR: $\delta=146.2$, 141.1, 140.8, 138.5, 134.1, 131.8, 130.6 (2C), 130.3, 130.2, 129.9 (2C), 128.2 (2C), 127.6, 126.0, 125.5 (2C), 124.2, 47.9, 40.7, 25.0, 21.3 ppm; IR (film): 2234, 1027 cm^{-1}; MS (FAB+): *m/z* (%): 360 (100) $[M+H]^+$, 225 (8); HRMS (FAB+): *m/z* calcd for C$_{23}$H$_{22}$NOS $[M+H]^+$: 360.1422; found: 360.1407. Diastereoisomer (2*S*,(*S*)*S*)-**7bB**: colorless oil; $[\alpha]_D^{20}=-136.4$ ($c=0.4$, CHCl$_3$); ^{1}H NMR: $\delta=7.84$ (dd, $J=1.4$ and 7.7 Hz, 1H), 7.75 (dd, $J=1.4$ and 7.7 Hz, 1H), 7.70–7.64 (m, 2H), 7.53–7.33 (m, 6H), 7.33–7.08 (m, 16H), 3.67 and 3.42 (AB system, $J=13.6$ Hz, 2H), 2.38 (s, 3H), 2.02 ppm (s, 3H); ^{13}C NMR: $\delta=146.2$, 144.4, 141.4, 141.3, 141.0, 140.9, 138.6, 138.5, 134.5, 134.1, 131.9, 131.8, 130.5 (2C), 130.3, 130.2, 130.1, 130.0 (2C), 129.9, 129.8, 128.2 (3C), 127.6, 127.5, 126.0, 125.7 (2C), 125.5 (2C), 124.2, 122.7, 47.9, 46.9, 45.0, 40.7, 29.0, 25.0, 21.3 ppm; IR (film): 2234, 1027 cm^{-1}; MS (ESI+): *m/z* (%): 360 (51) $[M+H]^+$, 225 (9); HRMS (ESI+): *m/z* calcd for C$_{23}$H$_{22}$NOS: 360.1422; found: 360.1416.

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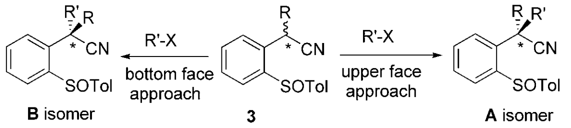
[16] The notation used for the alkylation products throughout the text consists of one number and two letters. The number indicates the reaction that is taking place: **7** for benzylation, **8** for methylation, **9** for ethylation, and **10** for allylation. The lower-case letter refers the nature of the alkyl group present in the starting compound, as depicted in Scheme 1. Finally, the capital letter, **A** or **B**, indicates the configuration at the benzylic center. When compounds **3** are drawn as indicated in the figure, with the C−CN bond parallel to the C−SOTol bond, isomers **A** and **B** are generated by approach of the alkylating reagents to the upper and bottom faces of the molecule, respectively. In those cases in which the priority order of the R′ group (reagent) is lower than that of the R group (substrate), according to Cahn–Ingold–Prelog rules, **A** isomers exhibit identical configuration at both benzylic carbon and sulfinyl group (*S* in the cases herein presented), whereas this is true for those **B** isomers when the priority order of R and R′ changes.



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[18] To clarify the discussion, an sp^2 hybridization has been assigned to carbanionic centers of species **I** and **I′**. However, the rather small energetic difference between the two plausible pyramidal (sp^3) or trigonal (sp^2) states for free carbanions suggests that species **I** and **I′** should be more accurately described as flattened pyramidal structures with intermediate hybridization between sp^3 and sp^2.

[19] This structure has also been suggested for some lithium 2-*p*-tolylsulfinyl benzyl carbanions on the basis of theoretical calculations (see ref. [10]).

[20] Structures similar to **3a-I′** have been suggested for other benzylic carbanions stabilized by cyano groups and generated in the presence of [18]crown-6 ether (see ref. [11] and references therein).

[21] Reactions were considerably slower in toluene than in THF and the formation of alkyl (Et, Pr, or Bn) 2-*p*-tolylsulfinylphenyl ketones (**14**–**16**) was detected.

[22] This effect is quite analogous to the well-known influence reported for an axial methyl group on C3 and C5 positions of a cyclohexane ring.

[23] In fact, the existence of a rather small energy difference between the two possible pyramidal (sp^3) or trigonal (sp^2) states precludes the presence of a unique geometry (see: G. Vanermen, S. Toppet, M. Van Beylen, P. Geerlings, *J. Chem. Soc. Perkin. Trans. 2* **1986**, 707).

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