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Asymmetric Synthesis of Benzylic Quaternary Difunctionalized Carbons Mediated by a Remote Sulfinyl Group

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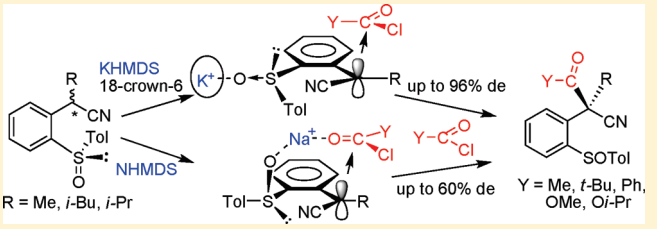
Supporting Information

ABSTRACT: Enantiomerically enriched α-aryl α-cyanoacetates and α-aryl α-acylacetonitriles bearing a benzylic quaternary stereocenter have been readily synthesized by stereoselective reaction of 2-alkyl-2-[2-(*p*-tolylsulfinyl)phenyl]acetonitriles with different acylating and alkoxycarbonylating reagents under basic conditions. The stereoselectivity of the reactions proved closely dependent on the nature of the intermediate carbanionic species, the evolution of which was effectively controlled by a sulfinyl group as a remote chiral auxiliary.



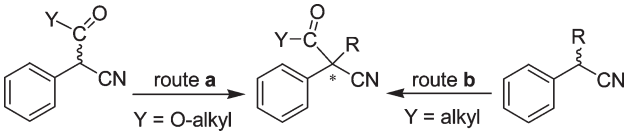
Nonracemic α-aryl α-cyanoacetates and α-aryl α-acylacetonitriles have been profusely used as building blocks for the stereoselective preparation of numerous natural products and pharmaceuticals containing chiral benzylic all-carbon quaternary centers, with the cyano group playing an important role in their biological activities.[1] Despite their potential synthetic interest, the number of methodologies applied for synthesizing them is rather limited. Over the last years two synthetic strategies have been reported for the asymmetric synthesis of these structural frameworks (Scheme 1) based either on the alkylation of α-aryl α-cyanocarboxylates (route a) or on the carbonyl group incorporation on α,α-disubstituted acetonitriles (route b).

Route a summarizes most of the procedures used in the preparation of α,α-disubstituted α-cyanoacetates, which are based on the use of chiral auxiliaries or, more frequently, catalysts as the source of chirality in allylation,[2] alkylation,[3] or conjugate addition[4] reactions of α-cyanocarboxylates. However, these reactions, which proceed with enantioselectivities ranging from moderate to good, have been scarcely used for preparing α,α-disubstituted α-acylacetonitriles, the only reported examples having been restricted to a number of structurally limited α-substituted cyclic α-acylacetonitriles.[3a]

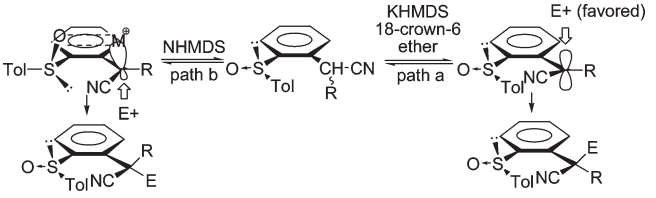
By contrast, the few reported examples involving the carbonylation of α-arylacetonitriles (route b) are based on acylation processes because the alkoxycarbonylation has proved to be unsuccessful. In this sense, the nucleophile-catalyzed asymmetric acylation of silyl ketene imines appears as one of the best reported methods for preparing enantiomerically enriched α-aryl α-acylacetonitriles containing all-carbon quaternary benzylic stereocenters.[5]

We have reported the highly stereoselective generation of stereogenic quaternary benzylic carbons in their two possible configurations, by reaction of benzyl carbanions derived from α-alkyl 2-*p*-tolylsulfinylphenylacetonitriles with alkyl halides in the presence of different bases (KHMDS/18-crown-6 ether or

Scheme 1. Reported Asymmetric Strategies for α-Aryl α-Cyanoacetates and α-Aryl α-Acylacetonitriles



Scheme 2. Stereodivergent Quaternization of 2-Alkyl-2-*p*-tolylsulfinylacetonitriles Dependent on the Basic Conditions



NHMDS).[6] Stereochemical results were rationalized by assuming a different structure for the carbanion (planar or pyramidal) depending on the reaction conditions (Scheme 2), which could be supported by NMR experiments. Encouraged by these excellent results as well as by the potential synthetic interest of α-alkyl α-aryl acetonitriles bearing alkoxycarbonyl or acyl groups at C-α, we decided to apply our above-mentioned methodology to the stereoselective preparation of these enantiomerically enriched building blocks. We report herein the results of the reactions of the benzyl carbanions, derived from the monoalkylated

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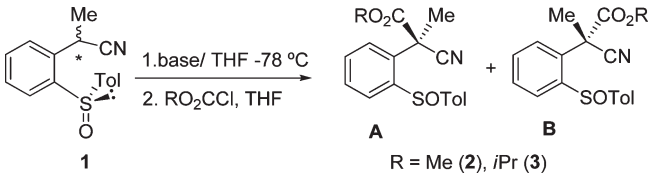
Table 1. Alkoxycarbonylation of 2-[2-(*p*-Tolylsulfinyl)phenyl]propanenitrile (1) under Different Conditions



entry	electrophile	base (additive)	product	A:B ratio	yield (%)
1	$ClCO_2Me$	LHMDS, −98 °C	**2**	42:58	n.d.
2	$ClCO_2Me$	LHMDS	**2**	44:56	64
3	$ClCO_2Me$	NHMDS	**2**	67:33	73
4	$ClCO_2Me$	KHMDS	**2**	52:48	62
5	$ClCO_2Me$	KHMDS (18-crown-6-ether)[a]	**2**	87:13	76
6	$ClCO_2Me$	KHMDS, −98 °C (18-crown-6 ether)[a]	**2**	90:10	76
7	$ClCO_2Me$	KHMDS (18-crown-6 ether)[b]	**2**	86:14	75
8	$ClCO_2Me$	LHMDS[c]	**2**	46:54	n.d.
9	$ClCO_2i$-Pr	KHMDS (18-crown-6 ether)[a]	**3**	>98:<2	77
10	$ClCO_2i$-Pr	LHMDS	**3**	45:55	n.d.

[a] 1.1 equiv. [b] 2.4 equiv. [c] Toluene was used as the solvent.

2-*p*-tolylsulfinylphenyl acetonitriles,[6] with chloroformates (affording cyanoacetates) and acyl halides (yielding acylacetonitriles), which provide enantiomerically enriched all-carbon quaternary centers.

The initial experiments consisted of the study of the behavior of 2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (**1**), as a 50:50 mixture of 2*R*,(S)*S* and 2*S*,(S)*S* diastereoisomers, in their reactions with alkyl chloroformates. The results obtained in the presence of different bases under diverse experimental conditions are collected in Table 1.[7]

We first assayed the quaternization reaction with methyl chloroformate by using LHMDS, NHMDS, or KHMDS as the base, in THF at −78 °C (Table 1, entries 2−4). Easily separable mixtures of the two possible diastereoisomers, [2*R*,(S)*S*]-**2A** and [2*S*,(S)*S*]-**2B**, were obtained in all the cases, with dr values ranging between 44:56 and 67:33, which evidence a low stereoselectivity control, slightly dependent on the metal and concentration of the reagents. Much better results were achieved when the reaction was conducted under KHMDS in the presence of 18-crown-6 ether (Table 1, entry 5), which provided a 87:13 mixture of **2A** and **2B**. No improvement in the stereochemical results was detected on increasing the amount of additive in the reaction media (entry 7). We next studied the influence of a decrease in the temperature on those two conditions which had given the most disparate results. It favored the formation of **2A** in reactions performed under KHMDS/18-crown-6 (**2A**:**2B** = 90:10 at −98 °C, entry 6), but had scarce influence in reactions with LHMDS (**2A**:**2B** = 42:58 at −98 °C, entry 1). As the use of toluene as solvent had been reported to improve the stereoselectivity in alkylation reactions of phenylacetonitriles with NHMDS,[6] we also explored the influence of this solvent in the reactions of **1** with $ClCO_2Me$ (entry 8). The reactivity significantly decreased (2 h were required for completion, as compared with the 10 min needed in THF) but the stereoselectivity was scarcely modified. Remarkably, the use of NHMDS did not invert the sense of the stereoselectivity with respect to that observed with KHMDS in the presence of 18-crown-6 ether, as had been reported for the alkylation processes.[6] Finally, we investigated the influence of the steric size of the reagent on the stereoselectivity under those two reaction conditions which had afforded the largest predominance of **2A** (entry 5) and **2B** (entry 2), respectively. To this end, isopropyl chloroformate was chosen as the reagent. Under KHMDS/18-crown-6 ether, the steric influence was significant and the stereoselectivity was complete, epimer **3A** being the only obtained adduct (**3B** was not detected in the reaction mixture, entry 9). By contrast, with LHMDS an increase in the steric size had little or no influence and the **3B**:**3A** ratio was 45:55 (entry 10), similar to that of **2A**:**2B** formed with $ClCO_2Me$ under the same basic conditions (entry 2).

We next studied the acylation of the anion generated from **1**, a process which would provide an easy access to α-aryl α-acylacetonitriles. All these reactions proceeded very rapidly (10−15 min were required for completion). The obtained results are collected in Table 2.[7] As was the case of reactions performed with methyl chloroformate, the highest proportion of diastereoisomers **A** was obtained with KHMDS/18-crown-6 ether (conditions a), whereas LHMDS (conditions b) provided the highest proportion of epimers **B**. Other conditions were assayed, but no relevant results were obtained. Reactions with acetyl chloride at −78 °C under conditions a afforded an easily separable 84:16 mixture of diastereoisomers **4A** and **4B** (entry 1), whereas an equimolecular mixture of the same compounds was obtained with LHMDS (entry 6).

The use of bulkier acyl chlorides improved the stereoselectivity of reactions with KHMDS/18-crown-6, which became almost complete with *t*-BuCOCl (**5A**:**5B** = 96:4, entry 3). Benzoyl chloride afforded a 90:10 mixture of **6A**:**6B** (entry 5), as was expected from the relative size of the R group at electrophile (Me < Ph < *t*-Bu). This dependence of dr on the steric size of the reagent is also observed in reactions conducted under conditions b (compare entries 6−8), but the stereoselectivity is not good in any case. As expected, the stereoselectivity improved as the temperature decreased (entries 2 and 5).

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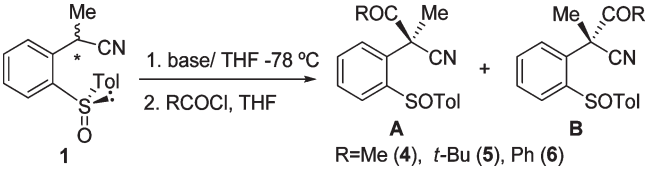
Table 2. Reactions of 2-[2-(*p*-Tolylsulfinyl)phenyl]propanenitrile (1) with Different Acylating Agents under Different Conditions



entry	electrophile	conditions[a]	product	A:B ratio	yield (%)
1	MeCOCl	a	**4**	84:16	72
2	MeCOCl	a (−98 °C)	**4**	88:12	80
3	*t*-BuCOCl	a	**5**	96:4	70
4	PhCOCl	a	**6**	90:10	84
5	PhCOCl	a (−98 °C)	**6**	93:7	73
6	MeCOCl	b	**4**	49:51	n.d.
7	*t*-BuCOCl	b	**5**	77:23	55[b]
8	PhCOCl	b	**6**	57:43	n.d.

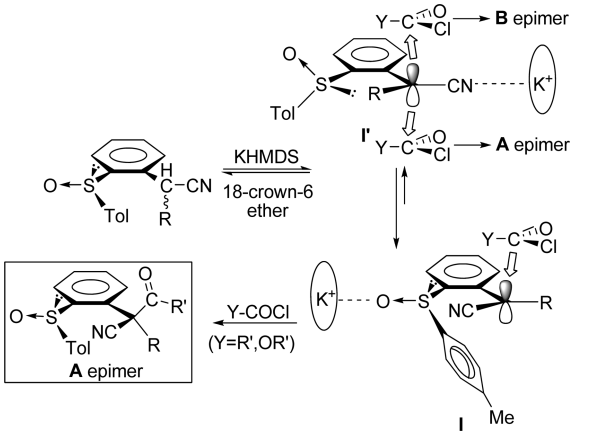
[a] Conditions: (a) KHMDS/18-crown-6 ether; (b) LHMDS. [b] 70% of conversion with 3 equiv of *t*-BuCOCl.

Finally, we investigated the dependence of the observed stereoselectivity on the size of the R group present at the substrate. In Table 3 are collected the results obtained by using KHMDS/18-crown-6 ether or NHMDS (the observed effects under other different conditions are similar but they have been omitted for being scarcely relevant). The stereoselectivity increased with the size of the R group, both in alkoxycarbonylation and acylation reactions. Thus, the 87:13 ratio of **2A** and **2B** obtained from **1** under KHMDS/18-crown-6 ether (R = Me, entry 1) increased to 96:4 of **10A** and **10B** starting from **8** (R = *i*-Bu, entry 3) and reached 97:3 of **11A** and **11B** starting from **9** (R = *i*-Pr, entry 5). Analogous results were obtained with NHMDS, although the dr values were lower. A similar tendency was observed in acylation reactions (entries 7−11). Isolated yields of the resulting diastereoisomeric mixtures were good in all cases, ranging between 70% and 78%, and the major isomers **A** were readily purified by flash column chromatography.

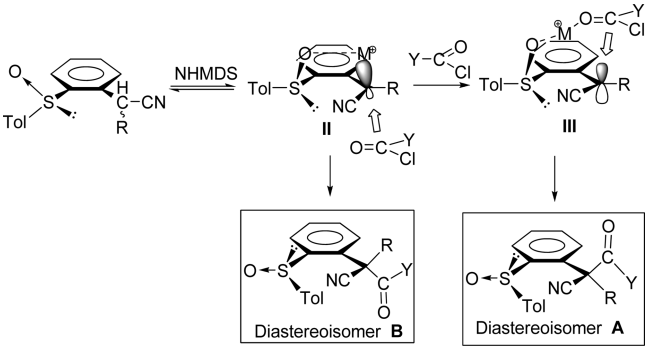
The absolute configuration of diastereoisomer **4A**, formed as the major product of the reaction of 2-[2-(*p*-tolylsulfinyl)phenyl]-propanenitrile (**1**) with KHMDS/18-crown-6 ether and acetyl chloride, was unequivocally determined as 2*R*,(S)*S* by X-ray diffraction studies.[8] From this configurational assignment, and from the assumption that all the herein reported acylation and alkoxycarbonylation reactions follow the same stereochemical pathway under the described conditions, the absolute configuration 2*R*,(S)*S* has been assigned to all the α-cyanoacetates and α-acetylacetonitriles obtained as the major products **A**. Consequently, minor isomers **B** will be the corresponding epimers at the benzylic carbon.

The stereochemical results reported in this paper should be explained taking into account the structure of the sulfinylated benzylcarbanions acting as the nucleophiles, which had been previously established by NMR studies.[6] The results obtained with KHMDS/18-crown-6 ether, herein described, are quite similar to those previously reported for the alkylation reactions of the same carbanions,[6] which suggests a similar stereochemical

Scheme 3. Proposed Planar sp^2 Carbanions Accounting for the Stereoselectivity of the Carbonylation under KHMDS/18-Crown-6 Ether



Scheme 4. Proposed Carbanionic Intermediates Accounting for the Stereoselectivity of the Carbonylation under NHMDS



course for both processes. The naked carbanion formed with KHMDS/18-crown-6 ether (K^+ should be sequestered by the crown ether) will adopt the planar sp^2 structures **I** (major) and **I**′ (minor) depicted in Scheme 3, with the potassium joined to the sulfinyl oxygen or to the nitrogen, respectively. The approach of the electrophile to the upper face of carbanion **I**, which would afford diastereoisomers **A**, is clearly favored because its steric interactions with the tolyl group are avoided. By contrast, the evolution of **I**′ should be less stereoselective because the substituents differentiating both faces of the anion are not too close to the approaching way of the electrophile. Therefore, the stereoselectivity must derive from the shifting of the equilibrium toward either carbanion. The **I**:**I**′ ratio, determined as 4:1 for **2A** by NMR studies,[6] suggests the formation of a ca. 9:1 diastereoisomeric mixture, which is in good agreement with the experimental results (entries 1 and 4, Table 3). An increase in the size of the R group would destabilize **I**′ increasing the proportion of **I** and therefore that of the **A** diastereoisomers, as can be seen in Table 3. An increase in the size of the reagent must produce a decrease in its reactivity and, therefore, enhance the stereoselectivity, which would explain the changes observed in Table 2.

One of the main differences between the results described in this paper (acylation) with respect to those reported in ref 6 (alkylation) is the behavior of the benzyl carbanions derived from

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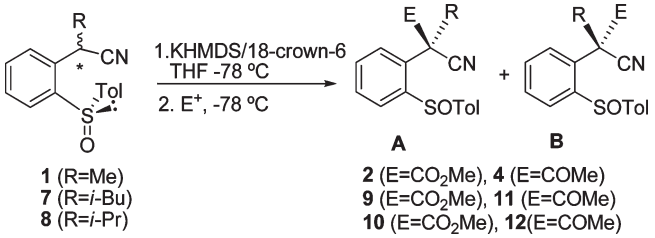
Table 3. Influence of the R Group on the Stereoselectivity of Acylation and Alkoxycarbonylation Reactions under Different Basic Conditions



entry	R	E^+	base (additive)	substrate	product	time (min)	**A**:**B** ratio	yield (%)
1	Me	$ClCO_2Me$	KHMDS (18-crown-6 ether)	**1**	**2**	5	87:13	76
2	Me	$ClCO_2Me$	NHMDS	**1**	**2**	5	67:33	73
3	*i*-Bu	$ClCO_2Me$	KHMDS (18-crown-6 ether)	7	**9**	15	96:4	72
4	*i*-Bu	$ClCO_2Me$	NHMDS	7	**9**	15	79:21	69
5	*i*-Pr	$ClCO_2Me$	KHMDS (18-crown-6 ether)	**8**	**10**	15	97:3	77
6	*i*-Pr	$ClCO_2Me$	NHMDS	**8**	**10**	20	80:20	73
7	Me	ClCOMe	KHMDS (18-crown-6 ether)	**1**	**4**	15	84:16	72
8	*i*-Bu	ClCOMe	KHMDS (18-crown-6 ether)	7	**11**	15	90:10	78
9	*i*-Bu	ClCOMe	NHMDS	7	**11**	15	78:22	64
10	*i*-Pr	ClCOMe	KHMDS (18-crown-6 ether)	**8**	**12**	30	90:10	70
11	*i*-Pr	ClCOMe	NHMDS	**8**	**12**	30	74:26	65

2 in the presence of NHMDS. Reactions with alkyl halides mainly afforded **B** diastereoisomers[6] (a stereodivergent behavior was therefore detected as compared to that observed with KHMDS/18-crown-6 ether), whereas chloroformates and acylchlorides yielded the **A** isomers predominantly, but the stereoselectivity was much lower than that observed with KHMDS/18-crown-6 ether (compare entries 2, 4, 6, 9, and 11 with entries 1, 3, 5, 7, 8 and 10, respectively, at Table 3). This can be explained by assuming that the associated pyramidal sp^3 carbanions **II**, formed in the absence of a crown ether,[6] only exhibit the lower face accessible to the attack of the electrophile, thus yielding the **B** isomers. However, in the presence of the acylating reagent, anionic species **II** can easily evolve into the planar sp^2 species **III** by association of the metal with one of the lone electron pairs at the carbonylic oxygen, displacing the benzylic carbon (this does not happen with alkyl halides). The newly formed species **III** will be preferently transformed into **A** isomers by intramolecular acylation (Scheme 4). The evidence that acylation is much faster when reactions are conducted with NHMDS than with the system KHMDS/18-crown-6 ether could be a consequence of the proposed intramolecular evolution with NHMDS. This proposal, based on the intramolecular transfer of the associated electrophile in the presence of NHMDS, was supported by the results obtained when an external sodium source was added to the reaction.[9]

From the above results we can conclude that the experimental conditions developed for the acylation and alkoxycarbonylation of 2-alkyl-2-[2-(*p*-tolylsulfinyl)phenyl]acetonitriles are a convenient synthetic methodology for the stereoselective preparation of a wide variety of differently substituted chiral α-alkyl α-aryl α-acylacetonitriles and α-cyanoacetates. As the sulfinyl group is acting as a remote chiral auxiliary in these reactions, the suitable choice of the sulfur configuration at the starting compound makes it possible to obtain the desired configuration at the quaternary carbon.

EXPERIMENTAL SECTION

General Procedures. NMR spectra were registered (300 and 75 MHz for ^1H and ^{13}C NMR, respectively) in $CDCl_3$ solutions. Melting points were measured in open capillary tubes. Mass spectra (MS) were determined by EI, FAB, and ESI, as indicated in each case. All reactions were carried out in anhydrous solvents under argon atmosphere. Commercially available anhydrous tetrahydrofuran (THF) and ethyl ether (Et_2O) were dried over 4 Å molecular sieves. Flash column chromatography was performed with use of silica gel (230−400 mesh).

General Procedure for the Synthesis of 2-Alkyl-2-[2-(*p*-tolylsulfinyl)phenyl]acetonitriles (1, 8, and 9). To a solution of (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile (255.3 mg, 1 mmol) in anhydrous THF (10 mL) at rt under argon was added LHMDS (1 M in THF) (1.2 mL, 1.2 mmol). The mixture was stirred at rt for 10 min and then 1.4 mmol of the corresponding electrophile was added dropwise. The reaction was monitored by TLC. Upon transformation of the starting material, the reaction was hydrolyzed with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with Et_2O (3 × 5 mL) and dried (Na_2SO_4) and the solvent was evaporated. The diastereoisomeric mixture was purified by automated column chromatography, using a 5:95 to 100:0 EtOAc−hexane gradient as the eluent.

[2*S*,(S)*S*]- and [2*R*,(S)*S*]-2-[2-(*p*-Tolylsulfinyl)phenyl]propanenitrile (1): The diastereoisomeric mixture **1** was obtained by using iodomethane as the electrophile. The reaction mixture was stirred at rt for 15 min. Yield 76%; colorless oil; ^1H NMR [diastereoisomeric mixture (50:50)] δ 7.93−7.83 (m, 2H), 7.62−7.49 (m, 6H), 7.46 and 7.29 (AA′BB′ system, 4H), 7.42 and 7.28 (AA′BB′ system, 4H), 4.55 (q, J = 7.1 Hz, 1H), 4.50 (q, J = 7.1 Hz, 1H), 2.38 (s, 6H), 1.58 (d, J = 7.1 Hz, 3H), 1.37 (d, J = 7.1 Hz, 3H) ppm; ^{13}C NMR [diastereoisomeric mixture (50:50)] δ 142.1 (3C), 141.6, 140.9, 140.6, 136.6, 135.8,

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132.4, 132.3, 130.4 (2C), 130.3 (2C), 129.5, 129.1 (2C), 128.2, 127.1, 126.4, 125.7 (2C), 125.3 (2C), 120.9, 120.7, 26.7, 26.3, 21.4 (2C), 21.3, 21.2 ppm; MS (EI+) m/z 269 $[M]^+$ (12), 225 (100), 211 (20); HRMS (EI+) calcd for $C_{16}H_{15}NOS$ $[M]^+$ 269.0874, found 269.0871.

[2*S*,(S)*S*]- and [2*R*,(S)*S*]-4-Methyl-2-[2-(*p*-tolylsulfinyl)phenyl]pentanenitrile (7): The diastereoisomeric mixture **7** was obtained by using 1-iodo-2-methylpropane as the electrophile. The reaction mixture was stirred at rt for 1 h. Yield 75%; colorless oil; ^{1}H NMR [diastereoisomeric mixture (50:50)] δ 7.95−7.82 (m, 2H), 7.61−7.48 (m, 6H), 7.45 and 7.29 (AA′BB′ system, 4H), 7.42 and 7.29 (AA′BB′ system, 4H), 4.49 (dd, J = 4.9 and 11.0 Hz, 1H), 4.38 (dd, J = 5.0 and 10.1 Hz, 1H), 2.38 (s, 6H), 1.97−1.57 (m, 4H), 1.35−1.16 (m, 2H), 1.01 (d, J = 6.5 Hz, 3H), 1.00 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR [diastereoisomeric mixture (50:50)] δ 142.3, 142.2, 141.9, 141.5, 140.8, 140.7, 136.3, 134.7, 132.3, 132.1, 130.3 (2C), 130.2 (2C), 129.6, 129.4, 128.9, 128.3, 127.6, 125.9, 125.7 (2C), 125.5 (2C), 120.1, 119.8, 44.5, 44.2, 31.0, 30.6, 26.6, 26.4, 22.9, 22.7, 21.3, 21.2, 21.2, 20.9 ppm; MS (FAB+) m/z 312 $[M + H]^+$ (100), 289 (12), 268 (7), 221 (10); HRMS (FAB+) calcd for $C_{19}H_{22}NOS$ 312.1422, found 312.1425.

[2*S*,(S)*S*]- and [2*R*,(S)*S*]-3-Methyl-2-[2-(*p*-tolylsulfinyl)phenyl]butanenitrile (8): The diastereoisomeric mixture **8** was obtained by using 2-iodopropane as the electrophile. The reaction mixture was stirred at rt for 1 h. Yield 81%; colorless oil; ^{1}H NMR [diastereoisomeric mixture (60:40)] δ 7.96−7.93 (m, 1H), 7.81−7.79 (m, 1H), 7.60−7.51 (m, 6H), 7.45 and 7.30 (AA′BB′ system, 4H), 7.43 and 7.30 (AA′BB′ system, 4H), 4.44 (d, J = 6.6 Hz, 1H), 4.20 (d, J = 6.6 Hz, 1H), 2.40 (s, 3H), 2.39 (s, 3H), 2.34−2.22 (m, 1H), 2.06−1.95 (m, 1H), 1.12 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR [diastereoisomeric mixture (60:40)] δ 143.0, 142.5, 142.2, 141.8, 140.8, 140.7, 135.4, 133.4, 131.9, 131.6, 130.3 (2C), 130.1 (2C), 129.9, 129.5, 129.0, 128.7, 128.0, 125.8, 125.4 (2C), 125.3, 119.0, 118.8, 40.5, 39.7, 33.7, 33.4, 21.3, 21.2, 20.8, 20.7, 18.7, 18.4 ppm; MS (FAB+) m/z 298 $[M + H]^+$ (100), 289 (9), 253 (11), 229 (7); HRMS (FAB+) calcd for $C_{18}H_{20}NOS$ 298.1265, found 298.1268.

General Procedure for Carbonylation of 2-Alkyl-2-[2-(*p*-tolylsulfinyl)phenyl]acetonitriles. To a solution of corresponding 2-alkyl-2-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile (1.0 mmol) and 18-crown-6 ether (1.1 mmol) in anhydrous THF (5 mL) at −78 °C under argon was added KHMDS (0.5 M in toluene) (1.1 mmol). The mixture was stirred at −78 °C for 10 min and then 1.1 mmol of the corresponding electrophile was added dropwise. The reaction was monitored by TLC. Upon transformation of the starting material, the reaction was hydrolyzed with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and dried (Na_2SO_4) and the solvent was evaporated. The diastereoisomeric mixture was purified by flash column chromatography, using as the eluent a mixture of AcOEt/hexane as indicated in each case.

[2*R*,(S)*S*]- and [2*S*,(S)*S*]-Methyl 2-cyano-2-[2-(*p*-tolylsulfinyl)phenyl]propanoate (2A + 2B): A 50:50 diastereoisomeric mixture of 2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (**1**) was used as the starting material. Methyl chloroformate (1.1 equiv) was used as the electrophile and the reaction was stirred at −98 °C for 15 min to give a 90:10 diastereoisomeric mixture of **2A** + **2B** which were separated and purified by flash column chromatography (eluent AcOEt/hexane 1:1). Yield (for both diastereoisomers) 76%. Diastereoisomer [2*R*,(S)*S*]-**2A**: colorless oil; $[\alpha]^{20}_D$ −123.9 (c 1.9, $CHCl_3$); IR (film) 2954, 2235, 1745, 1593, 1252, 1144 cm^{-1}; ^{1}H NMR δ 7.67−7.62 (m, 2H), 7.57 and 7.27 (AA′BB′ system, 4H), 7.55−7.49 (m, 2H), 3.88 (s, 3H), 2.38 (s, 3H), 2.24 (s, 3H) ppm; ^{13}C NMR δ 168.8, 145.5, 141.4, 140.2, 135.1, 132.4, 130.9, 129.8 (2C), 126.7, 125.5 (2C), 119.3, 54.6, 47.3, 25.4, 21.3 ppm; MS (ESI+) m/z 328 $[M + H]^+$ (100); HRMS (ESI+) calcd for $C_{18}H_{18}NO_3S$ 328.1003, found 328.1001. Diastereoisomer [2*S*,(S)*S*]-**2B**: colorless oil; $[\alpha]^{20}_D$ −80.3 (c 1.2, $CHCl_3$); ^{1}H NMR δ 7.79−7.76 (m, 1H), 7.58−7.51 (m, 3H), 7.46 and 7.27 (AA′BB′ system, 4H), 3.88 (s, 3H), 2.38 (s, 3H), 2.07 (s, 3H) ppm; ^{13}C NMR δ 168.6, 144.7, 141.6, 140.8, 135.3, 132.3, 130.7, 129.9 (2C), 129.5, 127.1, 125.8 (2C), 118.9, 54.5, 47.3, 26.2, 21.3 ppm; MS (ESI+) m/z 328 $[M + H]^+$ (100); HRMS (ESI+) calcd for $C_{18}H_{18}NO_3S$ 328.1003, found 328.1002.

[2*R*,(S)*S*]- and [2*S*,(S)*S*]-Isopropyl 2-Cyano-2-[2-(*p*-tolylsulfinyl)phenyl]propanoate (3A + 3B): A 50:50 diastereoisomeric mixture of 2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (**1**) was used as the starting material. Isopropyl chloroformate (1.4 equiv) was used as the electrophile and the reaction was stirred at −78 °C for 10 min to give a >98:<2 diastereoisomeric mixture of **3A** + **3B**, from which **3A** was isolated and purified by flash column chromatography (eluent AcOEt/hexane 1:3). Yield 77%. Diastereoisomer [2*R*,(S)*S*]-**3A**: colorless oil; $[\alpha]^{20}_D$ −134.2 (c 0.6, $CHCl_3$); IR (film) 2242, 1727, 1643, 1473, 1082 cm^{-1}; ^{1}H NMR δ 7.64−7.56 (m, 4H), 7.54−7.45 (m, 2H), 7.27 (d, J = 8.4 Hz, 2H), 5.17 (sp, J = 6.3 Hz, 1H), 2.38 (s, 3H), 2.23 (s, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.34 (d, J = 6.1 Hz, 3H) ppm; ^{13}C NMR 167.9, 145.9, 141.2, 140.5, 135.1, 132.2, 130.8, 129.9, 129.8 (2C), 126.7, 125.5 (2C), 119.6, 72.5, 47.6, 25.3, 21.3, 21.2 (2C) ppm; MS (FAB+) m/z 356 $[M + H]^+$ (100); HRMS (FAB+) calcd for $C_{20}H_{22}NO_3S$ 356.1326, found 356.1320.

[2*R*,(S)*S*]- and [2*S*,(S)*S*]-2-Methyl-3-oxo-2-[2-(*p*-tolylsulfinyl)phenyl]butanenitrile (4A + 4B): A 50:50 diastereoisomeric mixture of 2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (**1**) was used as the starting material. Acetyl chloride (1.1 equiv) was used as the electrophile and the reaction was stirred at −98 °C for 15 min to give a 88:12 diastereoisomeric mixture of **4A** + **4B** which were separated and purified by flash column chromatography (eluyent AcOEt/hexane 2:1). Yield (for both diastereoisomers) 73%. Diastereoisomer [2*R*,(S)*S*]-**4A**: yellow solid, mp 165−167 °C (CH_2Cl_2−hexane); $[\alpha]^{20}_D$ −145.5 (c 0.8, $CHCl_3$); IR (KBr) 2236, 1727, 1643, 1083 cm^{-1}; ^{1}H NMR δ 7.71−7.69 (m, 1H), 7.59 and 7.28 (AA′BB′ system, 4H), 7.58−7.55 (m, 3H), 2.51 (s, 3H), 2.38 (s, 3H), 2.10 (s, 3H) ppm; ^{13}C NMR δ 199.6, 145.6, 141.6, 140.2, 134.8, 132.4, 130.9, 129.9 (2C), 129.7, 127.1, 125.7 (2C), 120.4, 52.8, 26.1, 23.7, 21.3 ppm; MS (ESI+) m/z 312 $[M + H]^+$ (100); HRMS (ESI+) calcd for $C_{18}H_{18}NO_2S$ 312.1037, found 312.1052. Diastereoisomer [2*S*,(S)*S*]-**4B**: colorless oil; $[\alpha]^{20}_D$ −117.3 (c 1.5, $CHCl_3$); IR (film) 2236, 1727, 1640, 1081 cm^{-1}; ^{1}H NMR δ 7.74−7.72 (m, 1H), 7.59−7.45 (m, 3H), 7.41 and 7.27 (AA′BB′ system, 4H), 2.56 (s, 3H), 2.38 (s, 3H), 1.98 (s, 3H) ppm; ^{13}C NMR δ 199.9, 144.8, 141.6, 140.6, 135.4, 132.5, 130.8, 129.9, 129.8 (2C), 127.5, 125.8 (2C), 119.8, 52.8, 26.6, 24.4, 21.3 ppm; MS (ESI+) m/z 312 $[M + H]^+$ (100); HRMS (ESI+) calcd for $C_{18}H_{18}NO_2S$ 312.1037, found 312.1014.

[2*R*,(S)*S*]- and [2*S*,(S)*S*]-2,4,4-Trimethyl-3-oxo-2-[2-(*p*-tolylsulfinyl)phenyl]pentanenitrile (5A + 5B): A 50:50 diastereoisomeric mixture of 2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (**1**) was used as the starting material. Pivaloyl chloride

(1.5 equiv) was used as the electrophile and the reaction was stirred at −78 °C for 20 min to give a 96:4 diastereoisomeric mixture of **5A** + **5B**, from which **5A** was isolated and purified by flash column chromatography (eluent AcOEt/hexane 1:3). Yield 73%. Diastereoisomer [2*R*,(S)*S*]-**5A**: colorless oil; $[\alpha]^{20}_{D}$ −100.2 (*c* 0.6, $CHCl_3$); IR (film) 2236, 1727, 1643, 1083 cm^{-1}; ^1H NMR δ 8.09 (dd, *J* = 7.8 and 1.5 Hz, 1H), 7.58 and 7.27 (AA′BB′ system, 4H), 7.60−7.40 (m, 2H), 7.15 (dd, *J* = 7.9 and 1.3 Hz, 1H), 2.37 (s, 3H), 1.70 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C NMR 205.6, 144.5, 142.1, 141.3, 136.7, 132.4, 131.6, 130.3, 130.1 (2C), 129.9, 128.1, 127.1, 127.0 (2C), 125.6, 120.6, 50.3, 47.1, 29.1, 26.1, 21.4 ppm; MS (FAB+) *m*/*z* 354 $[M + H]^+$ (100); HRMS (FAB+) calcd for $C_{21}H_{24}NO_2S$ 354.1524, found 354.1528. Diastereoisomer [2*S*,(S)*S*]-**5B** (representative signals from a 96:4 **6A** + **6B** mixture): ^1H NMR δ 7.88−7.85 (m, 1H), 1.71 (s, 3H), 1.32 (s, 9H) ppm

[2*R*,(S)*S*]- and [2*S*,(S)*S*]-2-Benzoyl-2-[2-(*p*-tolylsulfinyl)-phenyl]propanenitrile (6A + 6B): A 50:50 diastereoisomeric mixture of 2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (**1**) was used as the starting material and benzoyl chloride (1.1 equiv) was used as the electrophile. The reaction was stirred at −98 °C for 15 min to give a 93:7 diastereoisomeric mixture of **6A** + **6B**, from which **6A** was isolated and purified by flash column chromatography (eluent AcOEt/hexane 1:2). Yield 73%. Diastereoisomer [2*R*,(S)*S*]-**6A**: colorless oil; $[\alpha]^{20}_{D}$ −139.2 (*c* 0.8, $CHCl_3$); IR (film) 2320, 1727, 1643, 1083 cm^{-1}; ^1H NMR δ 7.91−7.85 (m, 3H), 7.65−7.50 (m, 6H), 7.48−7.45 (m, 2H), 7.09 and 7.05 (m, 2H), 6.90−6.88 (m, 2H), 2.38 (s, 3H), 2.20 (s, 3H) ppm; ^{13}C NMR 190.5, 143.8, 141.4, 139.5, 137.8, 133.7, 133.1, 132.9, 130.7 (2C), 130.5, 130.0, 129.6 (2C), 128.7 (2C), 127.3, 125.7 (2C), 119.9, 51.6, 27.0, 21.3 ppm; MS (FAB+) *m*/*z* 374 $[M + H]^+$ (100); HRMS (FAB+) calcd for $C_{23}H_{20}NO_2S$ 374.1208, found 374.1215. Diastereoisomer [2*S*,(S)*S*]-**6B** (representative signals from a 93:7 **6A** + **6B** mixture): ^1H NMR δ 8.01−7.99 (m, 1H), 7.75−7.73 (m, 1H), 2.39 (s, 3H), 1.95 (s, 3H) ppm.

[2*R*,(S)*S*]- and [2*S*,(S)*S*]-Methyl 2-Cyano-4-methyl-2-[2-(*p*-tolylsulfinyl)phenyl]pentanoate (9A + 9B): A 50:50 diastereoisomeric mixture of 4-methyl-2-[2-(*p*-tolylsulfinyl)phenyl]pentanenitrile (**7**) was used as the starting material. Methyl chloroformate (1.1 equiv) was used as the electrophile and the reaction was stirred at −78 °C for 15 min to give a 96:4 diastereoisomeric mixture of **9A** + **9B**, from which **9A** was isolated and purified by flash column chromatography (eluent AcOEt/hexane 1:2). Yield 72%. Diastereoisomer [2*R*,(S)*S*]-**9A**: colorless oil; $[\alpha]^{20}_{D}$ −108,2 (*c* 1.0, $CHCl_3$); IR (film) 2242, 2092, 1747, 1727, 1643, 1470, 1083 cm^{-1}; ^1H NMR δ 7.81 (dd, *J* = 7.8 and 1.3 Hz, 1H), 7.62−7.42 (m, 3H), 7.47 and 7.26 (AA′BB′ system, 4H), 3.80 (s, 3H), 2.67 (dd, *J* = 14.4 and 5.2 Hz, 1H), 2.55 (dd, *J* = 14.4 and 5.2 Hz, 1H), 2.38 (s, 3H), 1.69 (sp, *J* = 6.6 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR δ 168.5, 145.2, 141.3, 140.5, 134.5, 132.1, 130.6, 130.2, 129.8 (2C), 128.2, 125.6 (2C), 118.6, 54.4, 52.6, 45.8, 25.7, 23.4, 22.8, 21.3 ppm; MS (FAB+) *m*/*z* 370 $[M + H]^+$ (100); HRMS (FAB+) calcd for $C_{21}H_{24}NO_3S$ 370.1488, found 370.1477. Diastereoisomer [2*S*,(S)*S*]-**9B** (representative signals from a 96:4 **9A** + **9B** mixture): ^1H NMR δ 7.87−7.84 (m, 3H), 3.90 (s, 3H), 2.37 (s, 3H) ppm.

[2*R*,(S)*S*]- and [2*S*,(S)*S*]-Methyl 2-Cyano-3-methyl-2-[2-(*p*-tolylsulfinyl)phenyl]butanoate (10A + 10B): A 50:50 diastereoisomeric mixture of 3-methyl-2-[2-(*p*-tolylsulfinyl)phenyl]butanenitrile (**8**) was used as the starting material. Methyl chloroformate (1.1 equiv) was used as the electrophile and the reaction was stirred at −78 °C for 15 min to give a 97:3 diastereoisomeric mixture of **10A** + **10B**, from which **10A** was isolated and purified by flash column chromatography (eluent AcOEt/hexane 1:2). Yield 77%. Diastereoisomer [2*R*,(S)*S*]-**10A**: colorless oil; $[\alpha]^{20}_{D}$ −151.2 (*c* 1.1, $CHCl_3$); IR (film) 2243, 1747, 1642, 1469, 1396, 1216, 1081 cm^{-1}; ^1H NMR δ 7.80−7.74 (m, 2H), 7.54−7.27 (m, 2H), 7.48 and 7.25 (AA′BB′ system, 4H), 3.71 (s, 3H), 3.42 (sp, *J* = 6.7 Hz, 1H), 2.37 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR 167.7, 146.1, 141.4, 141.1, 133.4, 132.0, 130.6, 130.2, 129.7 (2C), 128.6, 125.8 (2C), 117.2, 59.9, 54.0, 34.5, 21.2, 19.5, 18.6 ppm; MS (FAB+) *m*/*z* 356 $[M + H]^+$ (100); HRMS (FAB+) calcd for $C_{20}H_{22}NO_3S$ 356.1325, found 356.1320. Diastereoisomer [2*S*,(S)*S*]-**10B** (representative signals from a 97:3 **10A** + **10B** mixture): ^1H NMR δ 7.87−7.84 (m, 1H), 7.65−7.62 (m, 1H), 3.75 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H) ppm.

[2*R*,(S)*S*]- and [2*S*,(S)*S*]-4-Methyl-2-(1-oxoethyl)-2-[2-(*p*-tolylsulfinyl)phenyl]pentanitrile (11A + 11B): A 50:50 diastereoisomeric mixture of 4-methyl-2-[2-(*p*-tolylsulfinyl)phenyl]pentanitrile (**7**) was used as the starting material. Acetyl chloride (1.1 equiv) was used as the electrophile and the reaction was stirred at −78 °C for 15 min to give a 90:10 diastereoisomeric mixture of **11A** + **11B**, from which **11A** was isolated and purified by flash column chromatography (eluent AcOEt/hexane 1:2). Yield 78%. Diastereoisomer [2*R*,(S)*S*]-**11A**: colorless oil; $[\alpha]^{20}_{D}$ −125,4 (*c* 1.0, $CHCl_3$); IR (film) 2246, 1747, 1645, 1470, 1083 cm^{-1}; ^1H NMR: δ 7.80 (dd, *J* 7.8 and 1.4 Hz, 1H), 7.72 (dd, *J* = 7.5 and 1.5 Hz, 2H), 7.60−7.46 (m, 2H), 7.48 and 7.27 (AA′BB′ system, 4H), 2.70 (dd, *J* = 14.3 and 4.8 Hz, 1H), 2.38 (s, 3H), 2.36 (dd, *J* = 14.3 and 4.8 Hz, 1H), 1.63 (sp, *J* = 6.5 Hz, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR 198.9, 145.4, 141.6, 140.1, 133.5, 133.2, 130.6, 129.9, 129.8 (2C), 129.0, 125.9 (2C), 119.4, 59.6, 44.2, 26.4, 26.0, 23.5, 22.7, 21.3 ppm; MS (FAB+) *m*/*z* 354 $[M + H]^+$ (100); HRMS (FAB+) calcd for $C_{21}H_{24}NO_2S$ 354.1534, found 354.1528. Diastereoisomer [2*S*,(S)*S*]-**11B** (representative signals from a 90:10 **11A** + **11B** mixture): ^1H NMR δ 7.86−7.83 (m, 1H), 2.40 (s, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.64 (d, *J* = 6.6 Hz, 3H) ppm.

[2*R*,(S)*S*]- and [2*S*,(S)*S*]-3-Methyl-2-(1-oxoethyl)-2-[2-(*p*-tolylsulfinyl)phenyl]butanenitrile (12A + 12B): A 50:50 diastereoisomeric mixture of 3-methyl-2-[2-(*p*-tolylsulfinyl)phenyl]butanenitrile (**8**) was used as the starting material. Acetyl chloride (1.1 equiv) was used as the electrophile and the reaction was stirred at −78 °C for 30 min to give a 90:10 diastereoisomeric mixture of **12A** + **12B**, which was purified by flash column chromatography (eluent AcOEt/hexane 1:1). Yield 70%. Diastereoisomer [2*R*,(S)*S*]-**12A** (from a 90:10 mixture of **12A** + **12B**): IR (film) 2243, 1749, 1632, 1470, 1081 cm^{-1}; ^1H NMR δ 7.93−7.90 (m, 1H), 7.83−7.80 (m, 1H), 7.63−7.46 (m, 2H), 7.47 and 7.26 (AA′BB′ system, 4H), 3.44 (sp, *J* = 6.6 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H), 1.26 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR 198.6, 146.3, 141.5, 141.2, 132.5, 131.4, 130.6, 130.4, 129.9 (2C), 129.8, 126.0 (2C), 118.4, 66.5, 33.2, 28.2, 21.3, 19.5, 18.6 ppm; MS (FAB+) *m*/*z* 340 $[M + H]^+$ (100); HRMS (FAB+) calcd for $C_{20}H_{22}NO_2S$ 340.1190, found 340.1188. Diastereoisomer [2*S*,(S)*S*]-**12B** (representative signals from a 90:10 **12A** + **12B** mixture): ^1H NMR δ 2.99 (m, 1H), 2.05 (s, 3H), 1.33 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR 21.2. 18.9, 18.8 ppm.

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■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR for quaternary difunctionalized compounds **2**−**6** and **9**−**12**, and X-ray ORTEP and crystallographic data for compound **4A** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Thus, when NaI or sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF)] was added to the reaction, the stereoselectivity was much lower as a consequence of an increase in the proportion of diastereoisomer **B**, presumably resulting from the evolution of the boat-like species **II**, as was the case for reactions with alkyl halides. Unfortunately, this experimental modification, although clarifying from a mechanistic viewpoint, did not allow us to invert the stereoselectivity.