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New Strategy for the Asymmetric Synthesis of Phenyl Ketone Cyanohydrins: Quaternization of Cyanohydrins Derived from 2-*p*-Tolylsulfinyl Benzaldehyde

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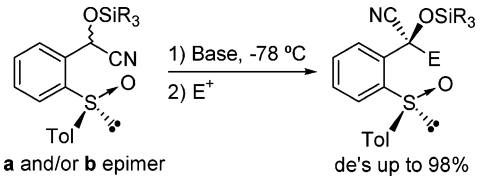

Optically pure functionalized cyanohydrins derived from 1-[2-(*p*-tolylsulfinyl)phenyl] ethanone can be obtained by the reaction of 2-*p*-tolylsulfinyl benzaldehyde derived cyanohydrins with bases and further treatment with suitable electrophiles. High yields and excellent stereoselectivities (up to de >98%) were obtained for these remote 1,4-asymmetric induction processes controlled by a sulfinyl chiral inductor.

Introduction

The interest of optically pure cyanohydrins is closely connected to that of α-hydroxy acids,[1] frequently involved in the synthesis of peptides, α-hydroxy ketones,[2] α-halonitriles,[3] and a number of natural products.[4] Many efforts have been done in the field of the asymmetric synthesis of cyanohydrins, most of them involving hydrocyanation processes of the carbonyl precursors. In this sense, the number of efficient methods for obtaining aldehyde derivatives is rather large.[5] By contrast, the success in the asymmetric hydrocyanation of ketones is much more restricted, although several good procedures have been reported in the last years.[6] This fact suggests that any method allowing the stereocontrolled quaternization of the hydroxylic carbon at cyanohydrins derived from aldehydes would mean a new strategy to obtain ketone cyanohydrins and, therefore, would significantly widen the scope of the alternatives for obtaining these compounds.

The sulfinyl group has shown its efficiency in controlling the stereoselectivity of reactions of β-ketosulfoxides with Et_2AlCN, giving rise to diastereomerically pure sulfinylcyanohydrins.[7] More recently, we also demonstrated that the hydrocyanation of 2-*p*-tolylsulfinyl benzaldehyde **1**[8] (a γ-carbonyl sulfoxide) also evolved in a completely stereoselective way in its reaction with

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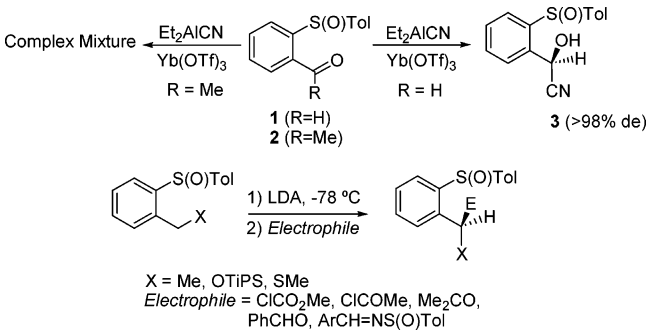
SCHEME 1



Et_2AlCN under $Yb(OTf)_3$ catalysis to afford cyanohydrin **3** (Scheme 1). However, when we tried to obtain the cyanohydrins derived from 2-*p*-tolylsulfinyl acetophenone **2** under similar conditions, the reaction was unsuccessful. All attempts yielded complex mixtures of products where the presence of the cyanohydrins was not easily detected (Scheme 1).

The scarce efficiency shown by the sulfinyl group at **2** to control the stereoselectivity of the hydrocyanation at the carbonyl group at the benzylic position contrasts with the excellent control exerted in reactions of 2-*p*-tolylsulfinyl substituted benzyl carbanions with different electrophiles (Scheme 1).[9] The results in the latter field allowed us to infer that the sulfinyl group controls much more efficiently the stereoselectivity at the nucleophilic rather than at the electrophilic centers when they are separated by three bonds from the chiral sulfur (1,4-asymmetric induction). On the basis of these results, we reasoned that benzyl carbanions obtained from cyanohydrin **3** could also be stabilized by an *o*-sulfinyl group and, therefore, further transformed stereoselectively into cyanohydrins derived from ketones or even more complex compounds, by a reaction with suitable electrophiles. This prompted us to explore the stereoselective quaternization of the benzyl carbon in **3** as a convenient indirect method for the preparation of highly functionalized optically enriched molecules containing ketone cyanohydrin moieties. We report herein the results obtained in this research.

Results

Initially, we studied the behavior of carbanions derived from the OTMS derivative **4** in the presence of MeI. Ketone **2** was isolated, whereas the expected methylation product **5** was not detected under any of the tested conditions (different bases, reaction times, and temperatures, as well as the addition mode). The formation of **2**, which could only be explained by assuming deprotection of the oxygen at **5** and subsequent elimination of the cyano group (Scheme 2),[10] suggested that the methylation of **4** had taken place under experimental conditions used in these experiences.

When the more stable OTBDMS cyanohydrin **6** was used as the substrate, the reactions with $ClCO_2Me$ afforded the desired cyanohydrins **7a** and **7b** in high yields. As we can see in Table 1, diastereoselectivity was dependent on the base and solvent employed. The poorest diastereomeric ratio was achieved with *n*-BuLi (entries 1−3), and THF proved to be the most efficient solvent. The ready separation of the resulting cyanohydrins allowed us to obtain the major one, **7a**, in an 82% isolated yield (entry 6).

The highest levels of diastereoselectivity were obtained starting from OTIPS cyanohydrins **8**, which bear the bulkiest O-protecting group. We first tried independently the reaction of **8a** and **8b**, epimers at the benzylic carbon, with $ClCO_2Me$, and the results obtained from both substrates were identical. Therefore, a 1:1 mixture of diastereoisomers **8a** and **8b** (Table 2), obtained by hydrocyanation of **1** with TIPSCN under $Yb(OTf)_3$ catalysis (refluxing CH_2Cl_2, 5 h),[8] was used as the starting material for the rest of the experiences. It is noteworthy that the 1,4-asymmetric induction at the newly created chiral center is not dependent on the diastereomeric excess of the starting compound, which indicates that the applicability of these reactions is independent of the stereochemical outcome achieved in the previous hydrocyanation step. Reaction of $ClCO_2Me$ with the anion produced by treatment of **8** with KHMDS (entry 1) proceeded in an excellent yield with a complete diastereoselectivity affording **9a**. A similar result was obtained with acetyl chloride (entry 2), which also yielded **10a** as the only diastereoisomer. By contrast, the reaction of **8** with Eschenmoser's salt afforded a 70:30 mixture of diastereoisomers **11a** and **11b** (entry 3), which were readily separated. Analogous results were obtained in the reactions with MeOTf, MeI, and EtOTf (entries 4−6), which required longer reaction times to reach completion, whereas EtI did not react under the same experimental conditions. A higher although not complete diastereoselectivity (70% de) was observed with allyl bromide (entry 8), whereas with benzyl bromide (entry 7), it was not so good (40% de), and in contrast with the other results, **14b**

SCHEME 2

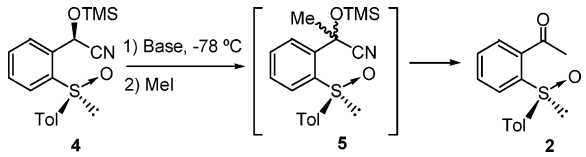
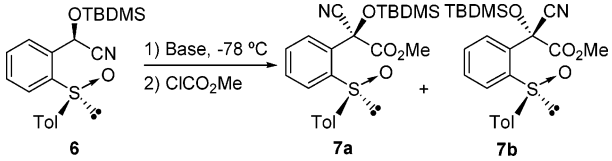


TABLE 1. Reactions of OTBDMS Cyanohydrins with $ClCO_2Me$



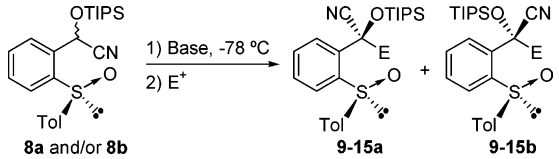
entry	base	solvent	time (min)	**7a**:**7b**
1	*n*-BuLi	toluene	40	47:53
2	*n*-BuLi	Et_2O	60	60:40
3	*n*-BuLi	THF	60	73:27
4	LiHMDS	THF	60	80:20
5	NaHMDS	THF	20	83:17
6	KHMDS	THF	20	89[a]:11

[a] Isolated yield 82% (major diastereoisomer **7a**).

(9) García Ruano, J. L.; Carreño, M. C.; Toledo, M. A.; Aguirre, J. M.; Aranda, M. T.; Fischer, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2736. García Ruano, J. L.; Alemán, J.; Soriano, J. F. *Org. Lett.* **2003**, *5*, 677. García Ruano, J. L.; Alemán, J. *Org. Lett.* **2003**, *5*, 4513. García Ruano, J. L.; Aranda, M. T.; Aguirre, J. M. *Tetrahedron.* **2004**, *60*, 5383.

(10) A similar result was achieved when methyl chloroformate was used as the electrophile.

TABLE 2. Reactions of OTIPS Cyanohydrins (8a and 8b) with Different Electrophiles



8a and/or **8b** **9-15a** **9-15b**

entry	base	electrophile	time	product	*dr* (yield[a] %)
1	KHMDS	$ClCO_2Me$	30 min	**9a** + **9b**	>98:<2 (85)
2	KHMDS	ClCOMe	30 min	**10a** + **10b**	>98:<2 (83)
3	KHMDS	$CH_2{=}N^+Me_2\ I^-$	30 min	**11a** + **11b**	70:30
4	KHMDS	MeOTf	2 h	**12a** + **12b**	70:30
5	KHMDS	MeI	2 h	**12a** + **12b**	70:30
6	KHMDS	EtOTf[b]	4 h	**13a** + **13b**	70:30
7	KHMDS	$PhCH_2Br$	1 h	**14a** + **14b**	30:70
8	KHMDS	$CH_2{=}CH{-}CH_2Br$	1 h	**15a** + **15b**	85:15
9	LiHMDS	$ClCO_2Me$	1 h	**9a** + **9b**	>98:<2
10	LiHMDS	ClCOMe	1 h	**10a** + **10b**	>98:<2
11	LiHMDS	$CH_2{=}N^+Me_2\ I^-$	1 h	**11a** + **11b**	94:6 (74)
12	LiHMDS	MeOTf	3 h	**12a** + **12b**	60:40
13	LiHMDS	MeI	3 h	**12a** + **12b**	77:23
14	LiHMDS	EtOTf[b]	3 h	**13a** + **13b**	70:30
15	LiHMDS	$PhCH_2Br$	2 h	**14a** + **14b**	>98:<2 (77)
16	LiHMDS	$CH_2{=}CHCH_2Br$	2 h	**15a** + **15b**	>98:<2 (89)
17	K/18-crown-6	MeOTf	3 h	**12a** + **12b**	76:24
18	K/18-crown-6	MeI	3 h	**12a** + **12b**	88:12 (76)
19	K/18-crown-6	EtOTf	3 h	**13a** + **13b**	87:13 (73)
20	Li/12-crown-4	MeOTf	3 h	**12a** + **12b**	76:24
21	Li/12-crown-4	MeI	3 h	**12a** + **12b**	87:13
22	Li/12-crown-4	EtOTf	3 h	**13a** + **13b**	87:13

[a] Yield of major **a** diastereoisomer. [b] Reaction with EtI did not evolve under the assayed conditions.

was now the major isomer, which could be isolated in 61% yield. These two latter electrophiles required shorter reaction times than those described for the alkylating reagents but longer than those required by the acylating ones.

We next used LiHMDS as the base. Reaction with $ClCO_2Me$ also afforded **9a** as the only diastereoisomer (entry 9), but the reaction time was longer than that of entry 1, which indicates that the reactivity of the benzyllithium derivative was lower than that of the corresponding potassium derivative. Similarly, the reaction with ClCOMe evolved with a complete stereoselectivity into **10a** but required a longer reaction time than in the presence of KHMDS (compare entries 2 and 10). When **8** reacted with Eschenmoser's salt in the presence of LiHMDS, the stereoselectivity dramatically increased, and an 88% de (entry 11) was obtained, which allowed us to obtain diastereomerically pure **11a** in 72% yield.[11] Even better results were obtained in the reactions with benzyl and allyl bromides, which yielded **14a** and **15a**, respectively, as the only diastereoisomers (entries 15 and 16), thus evidencing complete control of the stereoselectivity. The use of LiHMDS instead of KHMDS in the reactions of **8** with MeOTf, MeI, and EtOTf did not have any significant consequence, the yields and stereoselectivities being quite similar (compare entries 12−14 with 4−6). Reaction with EtI in the presence of LiHMDS was also unsuccessful, the unaltered starting material **8** having been recovered.

We have also studied the role of suitable crown ethers (12-crown-4 and 18-crown-6), able to capture the Li^+ or K^+ cations, respectively, in the reaction course because their influence could be of interest from both a synthetic and a mechanistic point of view. In Table 2 are collected the results obtained in the reactions of **8** with some electrophiles (those having given an incomplete stereoselectivity in the reactions with KHMDS) in the presence of KHMDS/18-crown-6 (entries 17−19) and LiHMDS/12-crown-4 (entries 20−22). The best stereochemical results were obtained under these conditions, as compared with the assays performed in the absence of any crown ether. The reactions with MeOTf (entries 17 and 21), MeI (entries 18 and 22), and EtOTf (entries 19 and 23) afforded mixtures of epimers with higher de values than those observed in the absence of crown ethers. Reactions with EtI were unsuccessful. Finally, the addition of *n*-Bu_4I to the potassium carbanion in the reaction with MeI gave a stereochemical outcome similar to that exerted by 18-crown-6 ether due to the ability of the iodide to capture the potassium.[12] Some other electrophiles were also studied in the presence of a crown ether. When the reactions with allyl bromide, benzyl bromide, and Eschenmoser's salt were performed in the presence of a suitable crown ether, as a rule, an increase in the diastereoselectivity (ca. 40% de) was detected as compared with the results obtained with KHMDS in the absence of any additive (entries 3, 7, and 8), whereas a slight decrease in the diastereomeric excess (<10%) could be observed in comparison with the results with LiHMDS for benzyl bromide and Eschenmoser's salt (entries 11 and 15).

The absolute configuration of the minor diastereoisomer from the reaction with Eschenmoser's salt (**11b**) was

(11) To obtain the yields and the stereoselectivity indicated in Table 2 for reactions with Eschenmoser's salt, it was necessary to dry the salt prior to its use.

(12) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195.

unequivocally determined as *S* by X-ray diffraction studies.[13] We have assigned a similar stereochemistry (configurational notation is different depending on the electrophile) to all **b** minor epimers, whereas the **a** diastereoisomers, obtained as the major or exclusive products of these reactions, exhibited the opposite configuration at the quaternary chiral carbon. This has been postulated from the assumption that the stereochemical course of the nucleophilic addition is identical in all cases. The reversal of the asymmetric induction with benzyl bromide in the presence of KHMDS (entry 7) is consistent with the X-ray diffraction analysis for **14a** (absolute configuration *S*).[13]

Any plausible mechanistic proposal must account for the formation of diastereoisomers **a** as the major or exclusive products of the reactions of (*S*)-sulfoxides. Moreover, it must be consistent with the following facts: (a) the stereochemical results are independent of the configuration at the benzyl carbon of the starting cyanohydrin; (b) the observed stereoselectivity with LiHMDS is higher than with KHMDS in the reactions with alkylating reagents; and (c) the stereoselectivity decreases in the order ClCOR (or $ClCO_2R$) > $C{=}NR_2$ > Bn−X ∼ allyl−X > R−X, that is to say when the reactivity of the electrophile became lower.

The stereoselectivity was higher with LiHMDS than in the presence of KHMDS. This was initially attributed to the formation of a chelate by association of the *C*-metalated species with the sulfinyl oxygen, and this chelate species would be more stable with lithium, suchs as has been reported by our group to rationalize the stereoselectivity of the reaction of carbanions at benzyl positions.[14] However, this chelate would lead to the opposite configuration at the quaternary chiral centers of the compounds derived from **8** (**b** isomers). Additionally, the high stereoselectivity in the presence of crown ethers was not compatible with this proposal. The structure of the lithium and potassium benzyl carbanions derived from phenylacetonitrile by reaction with LiHMDS and KHMDS, respectively,[15] seems to be dependent on the nature of the positive counterion. Lithium carbanions have been reported to be planar, bearing the metal coordinated with the nitrogen, this moiety being additionally stabilized by a molecule of $(Me_3Si)_2NH$ (**A**, Figure 1). By contrast, potassium prefers to attach to carbon, and the resulting *C*-metalated species adopts a

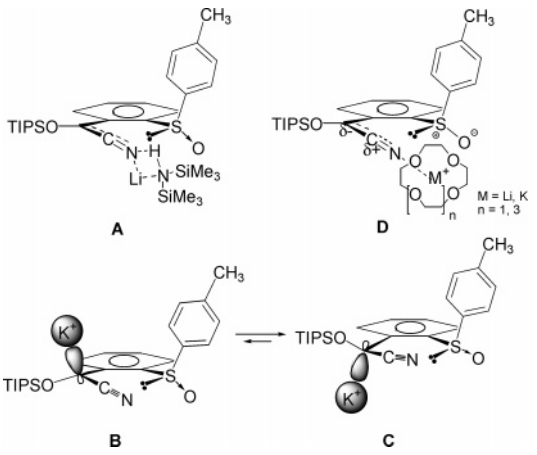


FIGURE 1. Structures of metalated O-protected cyanohydrins.

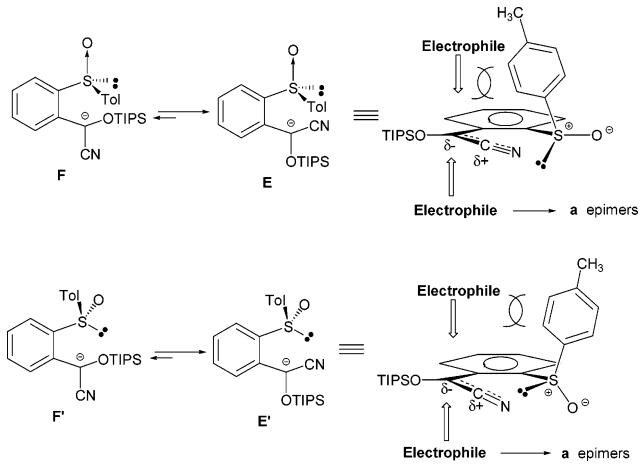


FIGURE 2. Differently favored approaches of the electrophile to the planar cyanohydrin anion.

pyramidal structure in their two possible configurations **B** and **C** (Figure 1), the latter being presumably more populated on steric grounds (interactions Tol/K^+). In the presence of the suitable crown ether, the degree of pyramidalization of the potassium carbanions gradually decreases through to a planar structure[15h−j] because K^+ (as is also the case with Li^+), stabilized by the crown ether, also coordinates with the nitrogen (**D**, Figure 1).

If we assume that this is the structure of the carbanions involved in our reactions, the stereochemical results suggest that the planar intermediates, presumably formed with LiHMDS (**A**) and KHMDS/18-crown-6 (**D**), should evolve in a higher stereoselective manner than the pyramidal intermediates (**B** and **C**), presumably formed with KHMDS.

The stereoselectivity observed for planar carbanions can be explained as depicted in Figure 2. Four possible conformations around the Ar−C and Ar−S bonds can be considered. **E** and **F** are the presumably most stable ones from an electrostatic point of view (the negatively charged sulfinyl oxygen adopts an anti-arrangement with respect to the carbanionic carbon), whereas **E′** and **F′** must be those conformations favored by steric grounds (the smallest size of the lone electron pair allows it to interact with the benzyl carbon). On the basis of the steric and electronic interactions between the OTIPS and the SOTol

(13) Crystallographic data (excluding structure factors) for **11b** and **14b** have been deposited with the Cambridge Crystallographic Data Centre as suplementary publication numbers CCDC 272154 and 277177, respectively.

(14) Similar intermediates had been proposed to explain the stereochemical evolution of other 2-*p*-tolylsulfinyl carbanions (see ref 9)

(15) Stork, G.; Maldonado, L. *J. Am. Chem. Soc*. **1974**, *96*, 5272. Croisat, D.; Seyden-Penne, T. S.; Wartski, L. *J. Org. Chem.* **1992**, *57*, 6435. Abbotto, A.; Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1993**, *58*, 449. Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 11602. Strzalko, T.; Seyden-Penne, J.; Wartski, L. *J. Org. Chem.* **1998**, *63*, 3287. Naota, T.; Tannna, A.; Murahashi, S.-I. *J. Am. Chem. Soc*. **2000**, *122*, 2960. Naota, T.; Tannna, A.; Kamuro, S.; Murahashi, S.-I. *J. Am. Chem. Soc*. **2002**, *124*, 6842. Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 2885. Carlier, P. R.; Madura, J. D. *J. Org. Chem.* **2002**, *67*, 3832. Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1. Fleming, F. F.; Zhang, Z.; Wei, G.; Steward, O. W. *Org. Lett*. **2005**, *7*, 447. Fleming, F. F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200. Reich, H. J.; Biddle, M. M.; Edmonston, R. J. *J. Org. Chem.* **2005**, *70*, 3375. Fleming, F. F.; Gudipati, S.; Zhang, Z.; Liu, W.; Steward, O. W. *J. Org. Chem.* **2005**, *70*, 3845.

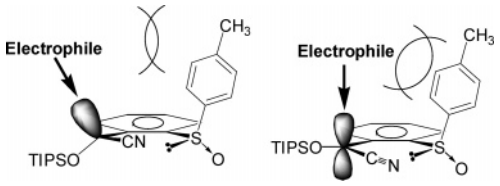


FIGURE 3. Proposed model accounting for the different stereoselectivities observed with KHMDS with respect to LiHMDS.

groups, we can assume that **E** and/or **E′** should be the clearly favored rotamers. The approach of the electrophile to the lower face of any of these rotamers, affording **a** epimers, is favored by steric interactions. This model also explains that the configuration at the benzyl carbon of the starting cyanohydrin (**8a** or **8b**) has no influence on the stereochemical results because of the configurational unstability of the resulting carbanions.

The lower stereoselectivity observed with KHMDS with respect to LiHMDS can be explained as indicated in Figure 3, where the less favored approaches to the upper face have been represented for both types of carbanions (planar and pyramidal). Steric interactions are stronger for planar carbanions, and therefore, a more stereoselective evolution favoring the approach to the lower face could be expected. This explanation could also account for the increase in the stereoselectivity when the reactions with KHMDS were performed in the presence of 18-crown-6 ether.

A final question to be considered is the unexpected increase in the stereoselectivity when the reactivity of the electrophiles becomes higher. Corey[16] has recently explained a similar situation by assuming differences in the location of the TS on the reaction coordinate. In the case of the early TS, carbanions must retain their original structure because the new bond is scarcely developed. This situation is typical of the most reactive electrophiles. On the contrary, for late TS, the new bond must be formed in large extension, and therefore, the structure of the involved carbons must be pyramidal. This situation is typical of the poorest nucleophiles. The stereoselectivity observed with LiHMDS, as well as that observed in the presence of the crown ethers, which is higher for the more reactive electrophiles and poorer for the less reactive alkylating agents, was in agreement with this explanation. The only discrepancy is the complete stereoselectivity observed in the reactions with acyl chlorides and KHMDS because of the supposedly pyramidal structure for the organopotassium species (entries 1 and 2, Table 2). However, with these electrophiles containing oxygens with lone electron pairs, the weak association C−K^+ can be disrupted, and the carbanion adopts a planar structure. Finally, some aspects concerning the stereoselectivity of the reactions with benzyl bromide remained to be explained.

Conclusions

From the previous results, we can conclude that 2-triisopropylsilyloxy-2-(*p*-tolylsulfinyl)acetonitrile (**8**) reacts with different electrophiles in the presence of LiHMDS or KHMDS/18-crown-6, with very high levels of diastereoselectivity controlled by the sulfinyl group, to afford α-substituted cyanohydrins derived from benzaldehyde. These reactions illustrate a new strategy for obtaining optically pure ketone-derived cyanohydrins starting from those much more available aldehyde-derived cyanohydrins. Reactions with prochiral electrophiles, resulting in the simultaneous formation of two chiral centers, are in progress.

Experimental Procedures

General Procedures for Quaternization of Benzylic Carbons. To a solution of silylcyanohydrin (1 mmol) in THF (10 mL) at −78 °C under argon was added 1.3 mmol of KHMDS (0.5 M in toluene). The mixture was stirred at −78 °C for 30 min and then 4 mmol of the corresponding electrophile dropwise was added. 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. All the reported yields were calculated from reactions performed with KHMDS. The same procedure was used when the base was LiHMDS.

(*S*)-1-[2-(*p*-Tolylsulfinyl)phenyl]ethanone (2). *O*-TMS cyanohydrin **4** was used as the starting material. Iodomethane was used as the electrophile, and the reaction was stirred at −78 °C for 2 h to give compound **9,** which was purified by flash column chromatography (AcOEt/hexane 1:2). Yield: 34%; white solid; mp: 143−146 °C; $[\alpha]^{20}_D$ −240.3 (*c* 1, $CHCl_3$); IR (KBr): 2401, 1620 cm^{-1}; ^1H NMR: δ 8.57 (dd, *J* 1.0 and 8.0 Hz, 1H), 7.90 (dd, *J* 1.4 and 7.6 Hz, 1H), 7.85 (dt, *J* 1.4 and 7.6 Hz, 1H), 7.58 (dt, *J* 1.4 and 7.6 Hz, 1H), 7.58 and 7.14 (AA′BB′ system, 4H), 2.54 (s, 3H), 2.28 (s, 3H); ^{13}C NMR: δ 197.5, 148.5, 143.6, 140.9, 133.8, 130.6, 130.2, 129.5, 126.6, 125.1, 26.9, 21.3; MS (FAB+) *m/z* 258; HRMS Calcd for $C_{15}H_{14}O_2S$: 258.0714; found: 258.0706.

(2*S*,(*S*)*S*)- and (2*R*,(*S*)*S*)-Methyl 2-(*t*-butyldimethylsilyloxy)-2-cyano-2-[2-(*p*-tolylsulfinyl)phenyl]acetate (7a and 7b). *O*-TBDMS cyanohydrin **6** was used as the starting material. Methyl chloroformate was used as the electhophile, and the reaction was stirred at −78 °C for 2 h to give an 89:11 mixture of diastereoisomers **7a** and **7b**. They were separated by flash column chromatography (AcOEt/hexane 1:6). Diastereoisomer **(2*S*,(*S*)*S*)-7a**: Yield: 75%; colorless oil; $[\alpha]^{20}_D$ −142.5 (*c* 1.0, $CHCl_3$); IR (film): 2271, 1764, 1216, 756 cm^{-1}; ^1H NMR: δ 7.94−7.90 (m, 1H), 7.87−7.84 (m, 1H), 7.61−7.58 (m, 2H), 7.44 and 7.26 (AA′BB′ system, 4H), 3.92 (s, 3H), 2.40 (s, 3H), 0.91 (s, 9H), 0.41 (s, 3H), 0.33 (s, 3H); ^{13}C NMR: δ 168.0, 144.6, 141.5, 141.2, 135.8, 131.7, 131.2, 129.8, 129.0, 126.8, 125.8, 117.8, 75.0, 54.9, 25.6, 21.3, 18.6, −3.8, −4.3. Anal. Calcd for $C_{23}H_{29}NO_4SSi$: C, 62.27; H, 6.59; N, 3.16; S, 7.23; found: C, 62.00; H, 6.47; N, 3.17; S, 7.21. Diastereoisomer **(2*R*,(*S*)*S*)-7b**: Yield: 7%; colorless oil; $[\alpha]^{20}_D$ −141.1 (*c* 1.0, $CHCl_3$); IR (film): 2271, 1767, 1229, 756 cm^{-1}; ^1H NMR: δ 7.90−7.94 (m, 1H), 7.86−7.82 (m, 1H), 7.61−7.57 (m, 2H), 7.51 and 7.29 (AA′BB′ system, 4H), 3.83 (s, 3H), 2.41 (s, 3H), 1.04 (s, 9H), 0.42 (s, 3H), 0.36 (s, 3H); ^{13}C NMR: δ 168.4, 145.0, 142.4, 140.9, 135.5, 131.7, 131.4, 129.7, 129.0, 127.2, 125.7, 117.5, 77.2, 54.6, 25.7, 21.3, 18.7, −3.6, −3.8. MS (FAB+) *m/z* 444 (M + 1); HRMS Calcd for $C_{23}H_{30}NO_4SSi$ (M + 1): 444.1665; found: 444.1679.

(2*S*,(*S*)*S*)-Methyl 2-cyano-2-[2-(*p*-tolylsulfinyl)phenyl]-2-(triisopropylsilyloxy)acetate (9a). A 50:50 diastereoisomeric mixture of *O*-TIPS cyanohydrins **8a** + **8b** was used as the starting material. Methyl chloroformate was used as the electrophile, and the reaction was stirred at −78 °C for 30 min to give diastereoisomer **9a** as the only reaction product. It was purified by flash column chromatography (AcOEt/hexane 1:4). Yield: 85%; white solid; mp: 101−102 °C; $[\alpha]^{20}_D$ −132.1 (*c* 1.0, $CHCl_3$); IR (KBr): 2271, 1773, 1463, 1255, 756 cm^{-1}; ^1H

(16) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5387.

NMR: δ 8.01−7.98 (m, 1H), 7.85−7.82 (m, 1H), 7.61−7.57 (m, 2H), 7.51 and 7.29 (AA′BB′ system, 4H), 3.79 (s, 3H), 2.41 (s, 3H), 1.55−1.41 (m, 3H), 1.17 (d, *J* 7.5 Hz, 9H), 1.15 (d, *J* 7.5 Hz, 9H); ^{13}C NMR: δ 166.9, 144.6, 141.3, 141.2, 136.2, 131.6, 131.2, 129.8, 129.2, 127.0, 125.8, 117.8, 74.8, 54.2, 21.3, 18.0, 17.9, 12.9; Anal. Calcd for $C_{26}H_{33}NO_4SSi$: C, 64.29; H, 7.26; N, 2.88; S, 6.60; found: C, 64.21; H, 7.10; N, 2.86; S, 6.53.

(2*S*,(*S*)*S*)-3-Oxo-2-[2-(*p*-tolylsulfinyl)phenyl]-2-(triisopropylsilyloxy)butane Nitrile (10a). A 50:50 diastereoisomeric mixture of *O*-TIPS cyanohydrins **8a** + **8b** was used as the starting material. Acetyl chloride was used as the electrophile, and the reaction was stirred at −78 °C for 30 min to give diastereoisomer **10a** as the only reaction product. It was purified by flash column chromatography (AcOEt/hexane 1:6). Yield: 83%; white solid; mp: 138−140 °C; $[\alpha]^{20}_D$ −70.8 (*c* 1.0, $CHCl_3$); IR (KBr): 2271, 1735, 1449, 1142, 756 cm^{-1}; ^{1}H NMR: δ 7.95 (dd, *J* 1.7 and 6.0 Hz, 1H), 7.64−7.48 (m, 3H), 7.61−7.57 (m, 2H), 7.45 and 7.26 (AA′BB′ system, 4H), 2.50 (s, 3H), 2.37 (s, 3H), 1.53−1.28 (m, 3H), 1.09 (d, *J* 7.4 Hz, 9H), 1.07 (d, *J* 7.4 Hz, 9H); ^{13}C NMR: δ 200.5, 144.9, 141.2, 140.7, 136.8, 131.8, 131.5, 130.1, 129.8, 127.7, 125.3, 117.4, 80.2, 24.4, 21.3, 18.0, 13.0; Anal. Calcd for $C_{27}H_{37}NO_3SSi$: C, 66.48; H, 7.51; N, 2.98; S, 6.83; found: C, 66.47; H, 7.36; N, 3.01; S, 6.78.

(2*R*,(*S*)*S*)- and (2*S*,(*S*)*S*)-3-(*N*,*N*-Dimethylamino)-2-[2-(*p*-tolylsulfinyl)phenyl]-2-(triisopropyls ilyloxy) Propanenitrile (11a and 11b). A 50:50 diastereoisomeric mixture of *O*-TIPS cyanohydrins **8a** + **8b** was used as the starting material. Eschenmoser's salt was used as the electrophile, and the reaction was stirred at −78 °C for 30 min to give a 70:30 diastereoisomeric mixture of **11a** and **11b**. These were separated by flash column chromatography (AcOEt/hexane 1:6). Diastereoisomer (2*R*,(*S*)*S*)-**11a**: Yield: 59%; white solid; mp: 94−96 °C; $[\alpha]^{20}_D$ −155.8° (*c* 1.0, $CHCl_3$); IR (KBr): 2271, 1464, 1107, 756 cm^{-1}; ^{1}H NMR: δ 7.88−7.82 (m, 2H), 7.63 and 7.29 (AA′BB′ system, 4H), 7.52−7.48 (m, 2H), 3.31 and 2.71 (AB system, *J* 13.7 Hz, 2H), 2.40 (s, 3H), 2.27 (s, 6H), 1.57−1.42 (m, 3H), 1.18 (d, *J* 7.1 Hz, 9H), 1.15 (d, *J* 7.1 Hz, 9H); ^{13}C NMR: δ 146.0, 143.3, 140.5, 138.3, 130.8, 130.2, 129.7, 128.5, 126.0, 125.5, 122.4, 77.2, 71.6, 46.7, 21.3, 18.3, 18.2, 13.0; Anal. Calcd for $C_{27}H_{40}N_2O_2SSi$: C, 66.90; H, 8.32; N, 5.78; S, 6.61; found: C, 66.80; H, 8.10; N, 5.63; S, 6.51. Diastereoisomer (2*S*,-(*S*)*S*)-**11b**: Yield: 21%; white solid; mp: 71−73 °C; $[\alpha]^{20}_D$ −106.9° (*c* 1.0, $CHCl_3$); IR (KBr): 2271, 1464, 1107, 756 cm^{-1}; ^{1}H NMR: δ 7.95−7.91 (m, 1H), 7.84−7.81 (m, 1H), 7.55−7.53 (m, 2H), 7.46 and 7.27 (AA′BB′ system, 4H), 3.26 and 3.16 (AB system, *J* 13.7 Hz, 2H), 2.41 (s, 3H), 2.27 (s, 6H), 1.36−1.23 (m, 3H), 1.11 (d, *J* 7.1 Hz, 9H), 1.08 (d, *J* 7.1 Hz, 9H); ^{13}C NMR: δ 144.3, 142.3, 140.9, 138.7, 131.1, 130.3, 129.5, 128.9, 127.9, 126.6, 120.9, 76.6, 71.1, 46.9, 21.3, 18.3, 13.1; Anal. Calcd for $C_{27}H_{40}N_2O_2SSi$: C, 66.90; H, 8.32; N, 5.78; S, 6.61; found: C, 66.82; H, 8.21; N, 5.63; S, 6.48.

(2*S*,(*S*)*S*)- and (2*R*,(*S*)*S*)-2-[2-(*p*-Tolylsulfinyl)phenyl]-2-(triisopropylsilyloxy)propanenitrile (12a and 12b). A 50:50 diastereoisomeric mixture of *O*-TIPS cyanohydrins **8a** + **8b** was used as the starting material. Methyl trifluoromethanesulfonate was used as the electrophile, and the reaction was stirred at −78 °C for 2 h to give a 70:30 diastereoisomeric mixture of **12a** and **12b**. These were separated by flash column chromatography (AcOEt/hexane 1:6). Diastereoisomer (2*S*,(*S*)*S*)-**12a**: Yield: 62%; white solid; mp: 122−123 °C; $[\alpha]^{20}_D$ −125.8 (*c* 1.0, $CHCl_3$); IR (KBr): 2271, 1462, 1116, 756 cm^{-1}; ^{1}H NMR: δ 7.90−7.87 (m, 2H), 7.82−7.79 (m, 2H), 7.55 and 7.31 (AA′BB′ system, 4H), 7.54 (dd, *J* 2.0 and 5.2, 1H), 7.51 (dd, *J* 1.6 and 4.8, 1H), 7.31 (d, *J* 7.7 Hz, 2H), 2.42 (s, 3H), 2.16 (s, 3H), 1.53−1.41 (m, 3H), 1.19 (d, *J* 7.3 Hz, 9H), 1.18 (d, *J* 7.3 Hz, 9H); ^{13}C NMR: δ 143.6, 141.4, 141.2, 141.1, 131.7, 130.4, 129.9, 129.3, 125.6, 125.1, 122.3, 70.6, 33.7, 21.3, 18.2, 13.0; Anal. Calcd for $C_{25}H_{35}NO_2SSi$: C, 67.98; H, 7.99; N, 3.17; S, 7.26; found: C, 67.55; H, 7.76; N, 3.16; S, 7.19. Diastereoisomer (2*R*,(*S*)*S*)-**12b**: Yield: 17%; white solid; mp: 75−76 °C; $[\alpha]^{20}_D$ −136.9° (*c* 1.0, $CHCl_3$); IR (KBr): 2271, 1463, 1114, 756 cm^{-1}; ^{1}H NMR: δ 7.85−7.82 (m, 1H), 7.81−7.78 (m, 1H), 7.56−7.52 (m, 2H), 7.51 and 7.29 (AA′BB′ system, 4H), 2.42 (s, 3H), 2.16 (s, 3H), 1.39−1.27 (m, 3H), 1.14 (d, *J* 7.3 Hz, 9H), 1.12 (d, *J* 7.3 Hz, 9H); ^{13}C NMR: δ 144.4, 142.1, 141.0, 140.7, 131.5, 130.5, 129.7, 129.5, 126.0, 125.2, 121.6, 70.7, 32.3, 21.3, 18.2, 13.2. MS (FAB+) *m/z* 442 (M + 1); HRMS Calcd for $C_{25}H_{36}NO_2SSi$ (M+1): 442.2236; found: 442.2231.

(2*S*,(*S*)*S*)- and (2*R*,(*S*)*S*)-2-[2-(*p*-Tolylsulfinyl)phenyl]-2-(triisopropylsilyloxy)butanenitrile (13a and 13b). A 50:50 diastereoisomeric mixture of *O*-TIPS cyanohydrins **8a** + **8b** was used as the starting material. Ethyl trifluoromethanesulfonate was used as the electrophile, and the reaction was stirred at −78 °C for 4 h to give a 70:30 diastereomeric mixture of **13a** and **13b**. These were separated by flash column chromatography (AcOEt/hexane 1:6). Diastereoisomer **(2*S*,(*S*)-*S*)-13a**: Yield: 61%; colorless oil, $[\alpha]^{20}_D$ −149.6 (*c* 1.0, $CHCl_3$); IR (film): 2271, 1463, 1215, 755 cm^{-1}; ^{1}H NMR: δ 7.85−7.82 (m, 2H), 7.56−7.49 (m, 2H), 7.54 and 7.31 (AA′BB′ system, 4H), 2.58 (dq, *J* 7.4 and 14.0 Hz, 1H), 2.42 (s, 3H), 2.36 (dq, *J* 7.4 and 14.0 Hz, 1H), 1.53−1.41 (m, 3H), 1.15 (d, *J* 7.4 Hz, 9H), 1.14 (d, *J* 7.4 Hz, 9H), 0.91 (t, *J* 7.4 Hz, 3H); ^{13}C NMR: δ 143.9, 141.9, 141.1, 138.9, 131.1, 130.4, 129.9, 129.5, 126.9, 125.5, 121.4, 75.3, 38.9, 21.3, 18.2, 13.0, 8.2; MS (FAB+) *m/z* 456 (M + 1); HRMS Calcd for $C_{26}H_{38}NO_2SSi$ (M + 1): 456.2393; found: 456.2404. Diastereoisomer **(2*R*,(*S*)*S*)-13b**: Yield: 21%; colorless oil; $[\alpha]^{20}_D$ −79.6 (*c* 1.0, $CHCl_3$); IR (film): 2271, 1463, 1215, 758 cm^{-1}; ^{1}H NMR: δ 7.84−7.79 (m, 2H), 7.54−7.46 (m, 2H), 7.50 and 7.28 (AA′BB′ system, 4H), 7.28 (d, *J* 7.9 Hz, 2H), 2.56 (dq, *J* 7.3 and 14.3 Hz, 1H), 2.42 (s, 3H), 2.33 (dq, *J* 7.3 and 14.3 Hz, 1H), 1.39−1.27 (m, 3H), 1.13 (d, *J* 7.3 Hz, 9H), 1.10 (d, *J* 7.3 Hz, 9H), 0.88 (t, *J* 7.3 Hz, 3H); ^{13}C NMR: δ 143.4, 142.0, 141.2, 138.8, 131.2, 130.3, 129.7, 129.3, 127.5, 126.5, 120.7, 75.8, 38.5, 21.3, 18.3, 13.0, 8.4; MS (FAB+) *m/z* 456 (M + 1); HRMS Calcd for $C_{26}H_{38}NO_2SSi$ (M + 1): 456.2393; found: 456.2397.

(2*S*,(*S*)*S*)- and (2*R*,(*S*)*S*)-3-Phenyl-2-[2-(*p*-tolylsulfinyl)-phenyl]-2-(triisopropylsilyloxy) Propanenitrile (14a and 14b). A 50:50 diastereoisomeric mixture of O-protected cyanohydrins **8a** + **8b** was used as the starting material. Benzyl bromide was used as the electrophile, and the reaction was stirred at −78 °C for 1 h to give a 30:70 diastereoisomeric mixture of **14a** and **14b**. These were separated by flash column chromatography (acetone/hexane 1:10). Diastereoisomer **(2*S*,-(*S*)*S*)-14a**: Yield: 5%; colorless oil, $[\alpha]^{20}_D$ −93.5 (*c* 0.75, $CHCl_3$); IR (film): 2234, 1465, 1103, 757 cm^{-1}; ^{1}H NMR: δ 7.91−7.86 (m, 1H), 7.51−7.43 (m, 1H), 7.48 and 7.27 (AA′BB′ system, 4H), 7.33−7.26 (m, 2H), 7.16−7.10 (m, 3H), 6.97−6.90 (m, 2H), 3.64 and 3.41 (AB system, *J* 13.3 Hz, 2H), 2.39 (s, 3H), 1.34−1.16 (m, 3H), 1.03 (d, *J* 7.4 Hz, 9H), 1.02 (d, *J* 7.4 Hz, 9H); ^{13}C NMR: δ 143.4, 141.7, 141.5, 138.8, 132.9, 130.8, 130.3, 129.8, 128.6, 128.0, 127.9, 127.4, 126.9, 120.2, 77.2, 51.1, 21.4, 18.4, 18.3, 13.1; MS (FAB+) *m/z* 518 (M + 1); HRMS Calcd. for $C_{31}H_{40}NO_2SSi$ (M + 1): 518.2549; found: 518.2568. Diastereoisomer **(2*R*,(*S*)*S*)-14b**: Yield: 61%; white solid; mp: 95−96 °C; $[\alpha]^{20}_D$ −142.9 (*c* 1.0, $CHCl_3$); IR (KBr): 2234, 1465, 1103, 757 cm^{-1}; ^{1}H NMR: δ 7.98−7.95 (m, 1H), 7.67 and 7.33 (AA′BB′ system, 4H), 7.54−7.49 (m, 1H), 7.42−7.37 (m, 2H), 7.25−7.16 (m, 3H), 7.03−7.00 (m, 2H), 3.64 and 3.45 (AB system, *J* 13.4 Hz, 2H), 2.42 (s, 3H) 1.56−1.43 (m, 3H), 1.11 (d, *J* 7.4 Hz, 9H), 1.08 (d, *J* 7.4 Hz, 9H); ^{13}C NMR: δ 143.6, 141.7, 141.4, 138.8, 132.8, 131.1, 130.8, 130.5, 130.0, 128.6, 127.9, 127.5, 127.0, 126.0, 121.2, 76.3, 51.2, 21.4, 18.3, 18.2, 13.0; MS (FAB+) *m/z* 518 (M + 1); HRMS Calcd for $C_{31}H_{40}$-NO_2SSi (M+1): 518.2549; found: 518.2552.

(2*S*,(*S*)*S*)- and (2*R*,(*S*)*S*)-2-[2-(*p*-Tolylsulfinyl)phenyl]-2-(triisopropylsilyloxy)pent-4-enenitrile (15a and 15b). A 50:50 diastereoisomeric mixture of *O*-TIPS cyanohydrins **8a** + **8b** was used as the starting material. Allyl bromide was used as the electrophile, and the reaction was stirred at −78 °C for 1 h to give a 85:15 diastereoisomeric mixture of **15a** and **15b**. These were separated by flash column chromatography (AcOEt/hexane 1:8). Diastereoisomer (2*S*,(*S*)*S*)-**15a**: Yield: 78%; colorless oil, $[\alpha]^{20}_D$ −132.2 (*c* 1.0, $CHCl_3$); IR

(film): 2271, 1643, 1463, 1108, 757 cm^{-1}; ^1H NMR: δ 7.90−7.87 (m, 1H), 7.79−7.76 (m, 1H), 7.55 and 7.31 (AA′BB′ system, 4H), 7.53−7.50 (m, 2H), 5.66−5.52 (m, 1H), 5.14 (dd, *J* 1.3 and 9.1 Hz, 1H), 5.10 (dd, *J* 1.3 and 19.9 Hz, 1H), 3.20 (dd, *J* 7.6 and 14.1 Hz, 1H), 2.99 (dd, *J* 7.6 and 14.1 Hz, 1H), 2.41 (s, 3H) 1.57−1.42 (m, 3H), 1.15 (d, *J* 7.6 Hz, 9H), 1.14 (d, *J* 7.6 Hz, 9H); ^{13}C NMR: δ 143.7, 141.7, 141.2, 138.7, 131.1, 130.4, 129.9, 129.4, 129.2, 126.9, 125.7, 121.5, 121.0, 74.6, 49.7, 21.3, 18.2, 12.9; MS (FAB+) *m/z* 468 (M + 1); HRMS Calcd for $C_{27}H_{38}NO_2SSi$ (M + 1): 468.2393; found: 468.2378. Diastereoisomer **(2***R*,(*S*)*S*)-**15b**: Yield: 9%; colorless oil, $[\alpha]^{20}_D$ −55.5 (*c* 1.0, $CHCl_3$); IR (film): 2271, 1643, 1463, 1108, 757 cm^{-1}; ^1H NMR: δ 7.93−7.90 (m, 1H), 7.81−7.78 (m, 1H), 7.57−7.53 (m, 2H), 7.45 and 7.29 (AA′BB′ system, 4H), 7.29 (d, *J* 8.3 Hz, 2H), 5.59−5.45 (m, 1H), 5.10 (dd, *J* 1.6 and 10.6 Hz, 1H), 5.03 (dd, *J* 1.9 and 17.3 Hz, 1H), 3.19 (dd, *J* 6.7 and 13.8 Hz, 1H), 2.95 (dd, *J* 6.7 and 13.8 Hz, 1H), 2.42 (s, 3H) 1.38−1.28 (m, 3H), 1.12 (d, *J* 7.5 Hz, 9H), 1.09 (d, *J* 7.5 Hz, 9H); ^{13}C NMR: δ 143.2, 141.9, 141.4, 138.8, 131.2, 130.4, 129.7, 129.6, 128.9, 127.4, 126.6, 121.3, 120.3, 75.0, 49.4, 21.3, 18.3, 13.1; MS (FAB+) *m/z* 468 (M + 1); HRMS Calcd for $C_{27}H_{38}NO_2SSi$ (M + 1): 468.2393; found: 468.2397.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **2**, **7a**, **7b**, **9a**−**15a**, and **11b**−**15b** and X-ray crystal structures for **11b** and **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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