Asymmetric Synthesis of Chiral Sulfinate Esters and Sulfoxides. Synthesis of Sulforaphane

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Reaction of the chiral auxiliary *trans*-2-phenylcyclohexanol (1) with thionyl chloride afforded a nearly equal mixture of two diastereomeric chlorosulfite esters (6). Treatment of this mixture with an equivalent amount of a dialkylzinc reagent (Me, Et, *i*-Pr) afforded high levels of conversion of both chlorosulfite esters to (mainly) a single diastereomer of the sulfinate ester (7). Levels of absolute stereochemical induction ranged from 10:1 to 96:4 under conditions affording high chemical yields. The method was employed for the separate synthesis of both enantiomers of sulforaphane (13).

The number of possible applications of chiral sulfoxides as reagents and intermediates for the synthesis of enantiomerically enriched materials has grown substantially in recent years.[1] There have been several recent contributions to the synthesis of chiral sulfoxides from a number of groups, including Kagan,[2] Marino,[3] Evans,[4] Davis,[5] and Burgess.[6] The method of Kagan, employing the cyclic sulfinate 3, is particularly attractive because it circumvents the need for the preparation of sulfinic acid chlorides, required for the methods of Andersen and Evans (using 4 and a related oxazolidinone). By contrast, Marino has shown that 4 can be prepared by enantioselective oxidation using a modified Sharpless system and Davis has developed 5 as an oxidant for enantioselective formation of chiral sulfoxides (Figure 1). Burgess has used a bacterial lipase to effect kinetic resolution of methyl sulfinylalkanoates, affording recovered esters in greater than 95% ee. Here we wish to report a novel extension of our method using *trans*-2-phenylcyclohexanol that is the first method to provide high levels of asymmetric induction. Further, the method does not require the preparation of sulfinic acid chlorides and thus overall greatly simplifies access to chiral sulfoxides and provides a simple and general route to this class of compounds.

Recently we investigated the Andersen synthesis of chiral sulfoxides with the substitution of *trans*-2-phenylcyclohexanol (1) for menthol and found that the selectivity in the formation of the sulfinates was enhanced and that, further, the ease with which these esters could be separated, both chromatographically and, more importantly, by crystallization, was also greatly improved.[7,8] Nonetheless,

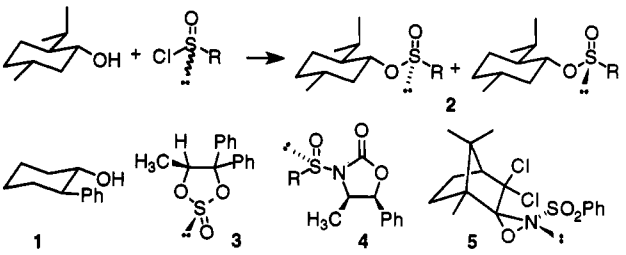

Figure 1.

this modification requires as does the original procedure, the synthesis of sulfinic acid chlorides, a serious disadvantage for our materials program which required rapid and efficient access to a number of different chiral sulfoxides. Further, stereochemical control was only moderate and separation was required to reach acceptable levels.

We thus began an investigation of possible reactions of the chlorosulfite ester of *trans*-2-phenylcyclohexanol with nucleophiles and found that the two diastereomeric chlorosulfite esters of 1 were sufficiently stable that full spectroscopic data could be obtained.[9] These diastereomers are not formed in equal amounts, although the ratio did not vary significantly from room temperature to −78 °C (1:1 and 2:1). The mixture of chlorosulfite esters (6) underwent reaction with Grignard and organolithium reagents to form sulfinate esters with diastereomer ratios similar to these of the chlorosulfinates (Table 1, entries 1–5).

On the other hand, reaction of the diastereomeric mixture of chlorosulfite esters with 0.25 equiv of commercial dimethylzinc (Figure 2) afforded the sulfinate esters in a diastereomeric ratio of 95:5 (entry 7). Further, this ratio actually improved as the amount of reagent was increased, and with 0.9 equiv, a 59% conversion to a 98:2 mixture of diastereomers was obtained (entry 9). Optimal reaction conditions from a synthetic point of view are represented by entry 10 where a 97% chemical yield with an ee of 92% was obtained.

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(2) Rebiere, F.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 3659. Rebiere, F.; Samuel, O.; Ricard, L.; Kagan, *J. Org. Chem.* **1991**, *56*, 5991.

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(5) Davis, F. A.; Reddy, R. T.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428. Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Reddy, R. T.; Han, W.; Chen, B.-C. *J. Org. Chem.* **1992**, *57*, 7274.

(6) Burgess, K.; Henderson, I.; Ho, K.-K. *J. Org. Chem.* **1992**, *57*, 1290.

(7) Whitesell, J. K.; Wong, M.-S. *J. Org. Chem.* **1991**, *56*, 4552.

(8) Alcudia has recently reported high levels of kinetic selectivity in the reactions of a variety of sulfinyl chlorides with diacetone *d*-glucose. See: Fernández, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789.

(9) Carré, P.; Libermann, D. *C. R. Acad. Sci.* **1935**, *200*, 2086. Only two citations of this article appear in the Science Citation Index, and neither details additional chemistry of chlorosulfite esters.

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Table 1. Synthesis of Chiral Sulfinate Esters by the Addition of Organometallic Reagents to a Diastereomeric Mixture of Chlorosulfinate Esters of *trans*-2-Phenylcyclohexanol

entry	organometallic reagent	solvent	equiv[a]	solvent	time (h)	diastereomeric ratio (*R*):(*S*)[b]	isolated yield (%)[c]
1	CH_3MgBr	ether	0.20	ether	2	71:29	68
2	tolylMgBr	ether	0.25	ether	2	60:40	80
3	PhMgBr	ether	0.25	ether	5	57:43	
4	ArMgBr[d]	ether	0.25	ether	2	57:43	68
5	PhLi	ether	0.25	ether	2	33:67	
6	$(CH_3)_2Zn$	toluene	0.25	ether	2	92:8	29
7	$(CH_3)_2Zn$	toluene	0.25	ether	5	95:5	90
8	$(CH_3)_2Zn$	toluene	0.50	ether	5	96:4	95
9	$(CH_3)_2Zn$	toluene	0.90	ether	5	98:2	59
10	$(CH_3)_2Zn$	toluene	0.90	ether	8	96:4	97
11	$(CH_3)_2Zn$	toluene	0.25	Skelly B	2	91:9	100
12	$(CH_3)_2Zn$	toluene	0.90	Skelly B	3	88:12	50
13	$(CH_3)_2Zn$	toluene	0.25	toluene	1	91:9	100
14	$(CH_3)_2Zn$	toluene	0.90	toluene	3	72:28	81
15	$CH_3ZnBr + MgBr_2$	THF	0.25	ether	5	97:3	42
16	$CH_3ZnBr + MgBr_2$	THF	0.90	ether	5	93:7	29
17	$(CH_3)_2Zn + MgBr_2$	ether	0.50	ether	5	93:7	100
18	$(CH_3)_2Zn + MgBr_2$	ether	0.90	ether	4	93:7	80
19	$(C_2H_5)_2Zn$	hexane	0.50	ether	100	19:1	100
20	$(C_2H_5)_2Zn$	hexane	0.25	ether	10	19:1	
21	$((CH_3)_2CH)_2Zn + MgBr_2$	ether	0.50	ether	10	77:23	
22	$((CH_3)_2CH)_2Zn$	Skelly B	0.25	ether	10	10:1	
23	PhZnBr + LiBr	THF	0.25	ether	100		no reactn
24	PhZnBr + LiBr	THF	0.25	THF	400		no reactn
25[e]	PhZnBr + LiBr	THF	0.25	ether	2	59:41	
26	$PhZnBr + MgBr_2$	THF	0.50	Skelly B	5		no reactn
27	$(Ph)_2Zn + MgBr_2$	ether	0.25	ether	5	51:49	53
28	$CH_3CdCl + MgBr_2$	THF	0.50	ether	5	96:4	41
29	$(CH_3)_2Cd + MgBr_2$	ether	0.12	toluene	2	85:15	69
30	$(CH_3)_2Cd + MgBr_2$	ether	0.12	ether	2	87:13	31
31	$(CH_3)_2Cd$	toluene	0.13	ether	2	97:3	10
32	$(CH_3)_2Cd$	toluene	0.25	ether	700	97:3	62
33	$(CH_3)_2Cd$	toluene	0.15	Skelly B	5	88:12	68
34	$(CH_3)_2Cd$	toluene	0.25	toluene	3	86:14	60
35	$(Ph)_2Cd + MgBr_2$	ether	0.50	ether	5		no reactn
36	$(Ph)_2Cd + MgBr_2$	ether	0.50	ether	2	54:46	83

[a] Equivalents of organometallic reagent used relative to *trans*-2-phenylcyclohexanol. [b] The diastereomeric ratio was determined by analytical HPLC, except entries 19 and 20 where ^{13}C NMR spectral analysis was employed. [c] Isolated yield based on the limiting organometallic reagent used. [d] Ar = *p*-isopropenylphenyl. [e] All reactions were run at −78 °C, except entries 25 and 36, run at 0 °C.

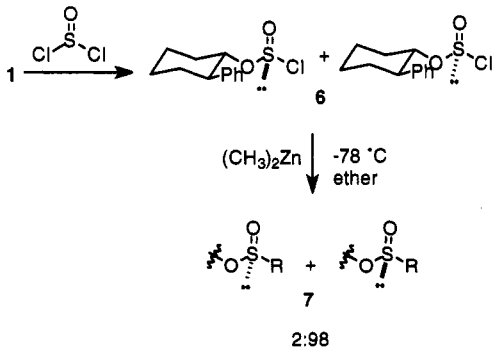

Figure 2.

We have considered two explanations for the convergence of both isomers of the chlorosulfinate intermediate to mainly a single diastereomer of the product sulfinate ester: (1) the chlorosulfinates are in rapid equilibrium relative to their reaction with the organozinc reagent and the rates of reaction of the two diastereomers are significantly different and (2) the intermediate formed upon addition of the zinc reagent to sulfur undergoes pseudorotation faster than expulsion of chloride ion to form product *and* the rate of collapse of one of the stereoisomeric adducts to product is much faster than that of the other. We currently favor the first explanation as the latter has little firm precedent in sulfur chemistry.[10] Nonetheless, attempts to raise selectivity with Grignard reagents by very slow addition (8 h) of the nucleophile to the chlorosulfinate ester mixture did not result in significant improvement in the ratio of diastereomers.

High levels of diastereomeric excess for the sulfinate esters formed by reaction of alkyl- and allylzinc reagents were obtained. Unfortunately, levels of control with arylzinc (as well as other arylmetal nucleophiles) were poor. Further, reaction of the chlorosulfite esters with alcohols and amines produced sulfinic acid derivatives in good yield but with unusably low levels of stereocontrol (<2:1).

The preparation of the mixture of sulfinate esters by this method still represents a significant improvement over their formation from sulfinic acid chlorides and affords rapid and efficient entry to a wide range of sulfoxides. Each carbon–sulfur bond is formed by the addition of a nucleophilic carbon species and the procedure is thus applicable to the synthesis of chiral and enantiomerically enriched sulfoxides where the appropriate organometallic species can be formed and at least one is an aliphatic carbon.

In order to demonstrate the utility of this methodology, we have applied it to the synthesis of sulforaphane in both the natural and unnatural configurations (Figure 3),[11] a naturally occurring sulfoxide that has been demonstrated

(10) Oae, S.; Uchida, Y. *Acc. Chem. Res.* **1991**, *24*, 202.

(11) Sulforaphane has previously been synthesized in both racemic and optically active forms. See: Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1948**, *31*, 1497.

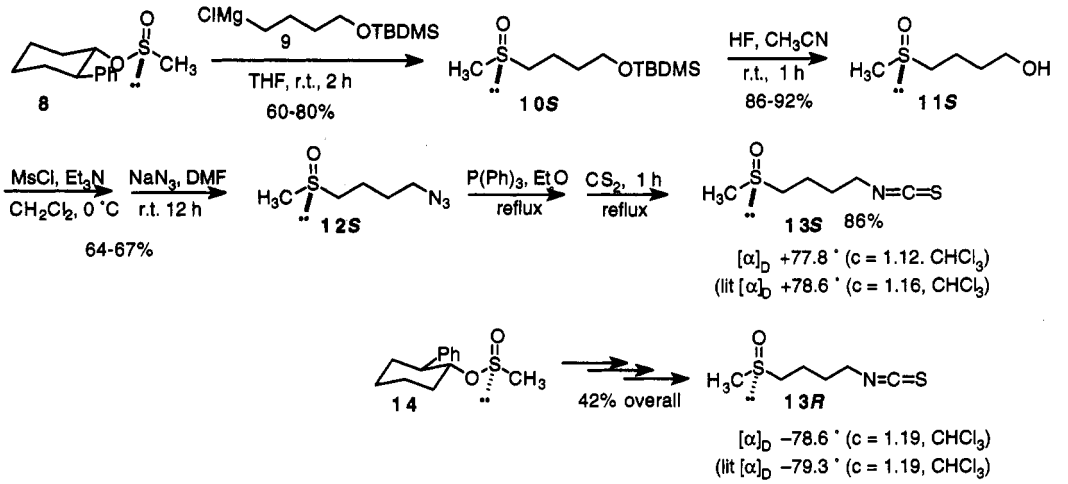

Figure 3.

to stimulate the production of carcinogen detoxifying enzymes.[12] The chiral sulfinate esters 8 and 14, prepared as described above, were reacted with the Grignard reagent 9, and removal of the *tert*-butyldimethylsiloxy protecting group afforded the alcohols 11*S* and 11*R*.[13] The alcohol was converted to the azide via the mesylate,[14] and reaction of the azide with triphenylphospine to form the iminophosphorane[15] followed by carbon disulfide[16] afforded sulforaphane.

Experimental Section

Materials. Skelly B was stirred first with concentrated sulfuric acid and then with solid sodium carbonate, filtered through alumina, and distilled before use. (Skelly B is a trade name for a hydrocarbon solvent that is greater than 95% *n*-hexane.) Ether and tetrahydrofuran (THF) were distilled prior to use from a deep blue solution resulting from benzophenone and sodium. Toluene was refluxed and distilled from calcium hydride. Thionyl chloride was distilled once before use. Zinc bromide was dried in an oven at 150 °C under vacuum for 1 day and cadmium chloride was dried in an oven at 120 °C under vacuum overnight before use. All other solvents and reagents were used as obtained from commercial sources unless stated otherwise.

Procedures. Reactions were routinely carried out under a dry nitrogen or argon atmosphere with magnetic stirring. Analytical HPLC was performed with a Waters 6000A HPLC pump with two 30-cm Porasil A silica gel analytical columns with a Waters 440 UV detector at 254 μm.

General Procedures for the Synthesis of Chiral Sulfinate Esters via Chlorosulfinates. To 0.44 mL (6.0 mmol) of $SOCl_2$ in 25 mL of ether at 0 °C was added a solution of 180 mg (1.0 mmol) of (+)-(1*S*, 2*R*)-*trans*-2-phenylcyclohexanol over 1 to 2 h. The reaction mixture was stirred for 3–4 h at 0 °C, and then excess $SOCl_2$ and ether were removed under vacuum (water aspirator) without external heating. The clear viscous residue was dissolved in 30 mL of the reaction solvent listed in Table 1 and the resulting solution was cooled to −78 °C under N_2. The organometallic reagent was then added slowly and the reaction mixture was stirred at −78 °C for the time shown. The reaction was quenched with H_2O, a saturated NH_4Cl solution was added, and the mixture was extracted twice with ether. The combined organic layers were washed with saturated Na_2CO_3 solution, dried over anhydrous $MgSO_4$, and evaporated to dryness. Diastereomeric ratios were determined on the crude products by analytical HPLC using 4:1 Skelly B/EtOAc and one μ-Porasil column. The individual sulfinate ester diastereomers were separated and purified by column chromatography. Yields were calculated on the basis of the organometallic as the limiting reagent where all of the metal exchange reactions were presumed to proceed with 100% conversion. Physical data for the product sulfinate esters were identical to those that we reported previously.[2]

Grignard Reagents. Entry 1: Methanesulfinates. The procedure above was followed with 0.08 mL (0.2 mmol) of 2.45 M of methylmagnesium bromide.

Entry 2: *p*-Toluenesulfinates. The procedure above was followed with 0.43 mL (0.25 mmol) of 0.6 M *p*-tolylmagnesium bromide, prepared from magnesium turnings and *p*-bromotoluene.

Entry 3: Benzenesulfinates. The procedure above was followed with 0.085 mL (0.25 mmol) of 3.0 M phenylmagnesium bromide and a 5-h reaction time resulting in a diastereomeric ratio of 57:43. The relative stereochemistry and therefore the absolute configuration of these diastereomers at sulfur were determined by ^{13}C NMR chemical shift correlation with authentic samples. Pure samples of each diastereomer were obtained by silica gel column chromatography using 10:1 Skelly B/EtOAc.

For the major diastereomer, (+)-(1*S*,2*R*)-*trans*-2-phenylcyclohexyl (*R*)-*p*-benzenesulfinate (15*R*), mp 93–93.5 °C: $[\alpha]^{25}_D$ +181.8° (*c* 1.0, acetone); ^{13}C NMR (75 MHz) δ 145.0 (s), 142.6 (s), 131.5 (d), 128.7 (d), 128.3 (d), 127.8 (d), 126.4 (d), 125.1 (d), 81.5 (d), 50.3 (d), 35.1 (t), 34.0 (t), 25.6 (t), 25.0 (t); ^1H NMR (300 MHz) δ 7.42–7.19 (m, 10 H), 4.31–4.23 (m, 1 H), 2.78–2.70 (m, 1 H), 2.48–2.44 (m, 1 H), 1.89–1.37 (m, 7 H); MS-CI *m/z* 301 (M^+ + H), 159, 154, 143; HRMS-CI *m/z* calcd for $C_{18}H_{21}O_2S$ 301.1262, found 301.1270.

For the minor diastereomer, (+)-(1*S*,2*R*)-*trans*-2-phenylcyclohexyl (*S*)-*p*-benzenesulfinate (15*S*), mp 117–117.5 °C: $[\alpha]^{25}_D$ +67.5° (*c* 1.0, acetone); ^{13}C NMR (75 MHz) δ 145.6 (s), 143.1 (s), 131.5 (d), 128.6 (d), 128.5 (d), 128.1 (d), 126.7 (d), 124.6 (d), 86.0 (d), 51.4 (d), 35.3 (t), 34.1 (t), 25.5 (t), 25.1 (t); ^1H NMR (300 MHz) δ 7.40–7.23 (m, 8 H), 6.91 (d, *J* = 7.8 Hz, 2 H), 4.56–4.48 (m, 1 H), 2.70–2.62 (m, 1 H), 2.38–2.32 (m, 1 H), 1.99–1.29 (m, 7 H); MS-CI *m/z* 301 (M^+ + H), 159, 143; HRMS-CI *m/z* calcd for $C_{18}H_{21}O_2S$ 301.1262, found 301.1271.

Entry 4: *p*-Isopropenylbenzenesulfinates. The procedure above was followed using 0.6 mL (0.25 mmol) of 0.43 M (*p*-isopropenylphenyl)magnesium bromide, prepared from 2-(4-bromophenyl)-1-propene and magnesium powder in THF at reflux, and a 2-h reaction time. The diastereomeric ratio was 57:43. Pure samples of the individual diastereomers were obtained by silica gel column chromatography using 10:1 Skelly B/EtOAc as elutant, affording 33.7 mg of the *R* diastereomer and 25 mg of the *S* isomer with a combined yield of 68%. The absolute configuration of these diastereomers was determined by the ^{13}C NMR chemical shift correlation with authentic samples.

For the major diastereomer, (+)-(1*S*,2*R*)-*trans*-2-phenylcy-

(12) Zang, Y. S.; Talalay, P.; Cho, C. G.; Posner, G. H. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 2399.

(13) This alcohol has been previous prepared in racemic form by a different route: Harpp, D. N.; Vines, S. M.; Montillier, J. P.; Chan, T. H. *J. Org. Chem.* **1976**, *41*, 3987.

(14) Reist, E. J.; Spencer, R. R.; Baker, B. R.; Goodman, L. *Chem. Ind. (London)* **1962**, 1794.

(15) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.

(16) Molina, P.; Alajarin, M.; Arques, A. *Synthesis* **1982**, 596.

clohexyl (*R*)-*p*-isopropenylbenzenesulfinate (**16*R***), mp 63–64 °C: $[\alpha]^{25}_D$ +172° (*c* 2.0, acetone); ^{13}C NMR (75 MHz) δ 144.4 (s), 143.7 (s), 142.7 (s), 142.3 (s), 128.3 (d), 127.8 (d), 126.3 (d), 125.8 (d), 125.0 (d), 114.4 (t), 81.2 (d), 50.3 (d), 35.3 (t), 34.1 (t), 25.6 (t), 25.0 (t), 21.7 (q); ^{1}H NMR (300 MHz) δ 7.36 (d, *J* = 8.4 Hz, 2 H), 7.24–7.19 (m, 3 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 7.04–7.01 (m, 2 H), 5.40 (s, 1 H), 5.16 (s, 1 H), 4.31–4.24 (m, 1 H), 2.76–2.68 (m, 1 H), 2.48–2.43 (m, 1 H), 2.13 (s, 3 H),1.90–1.84 (m, 2 H), 1.74–1.65 (m, 2 H) 1.52–1.30 (m, 3 H); IR 3040, 2940, 2870, 1590, 1490, 1450, 1135, 1115 cm^{-1}; MS-CI *m/z* 341(M^+ + H), 183, 159; HRMS-FAB *m/z* calcd for $C_{21}H_{25}O_2S$ (M^+ + H) 341.1575, found, 341.1566.

For the minor diastereomer, (+)-(1*S*,2*R*)-*trans*-2-phenylcyclohexyl (*S*)-*p*-isopropenylbenzenesulfinate (**16*S***), mp 92–93 °C: $[\alpha]^{25}_D$ +52.8° (*c* 2.0, acetone); ^{13}C NMR (75 MHz) δ 144.6 (s), 144.3 (s), 143.1 (s), 142.3 (s), 128.6 (d), 128.1 (d), 126.7 (d), 125.6 (d), 124.5 (d), 114.4 (t), 85.8 (d), 51.4 (d), 35.3 (t), 34.1 (t), 25.4 (t), 25.1 (t), 21.6 (q); ^{1}H NMR (300 MHz) δ 7.32–7.24 (m, 7 H), 6.87 (d, *J* = 7.8 Hz, 2 H), 5.36 (s, 1 H), 5.13 (s, 1 H), 4.56–4.49 (m, 1 H), 2.70–2.62 (m, 1 H), 2.37–2.33 (m, 1 H), 2.10 (s, 3 H), 2.00–1.31 (m, 7 H); MS-CI *m/z* 341 (M^+ + H), 211, 183, 159; HRMS-CI *m/z* calcd for $C_{21}H_{25}O_2S$ (M^+ + H) 341.1575, found 341.1561.

Organozinc Reagents. Entries 6–14: Methanesulfinates. The procedure above was followed using 2 M dimethylzinc in toluene as obtained from Aldrich.

Entries 15 and 16. Methylzinc bromide[17] was prepared by stirring with 393 mg (1.7 mmol) of zinc bromide in THF and 0.71 mL (1.7 mmol) of a 2.45 M methylmagnesium bromide solution at rt until Gilman's test[18] was negative (1 h).

Entries 17 and 18. Dimethylzinc was generated *in situ*[19] by refluxing 492 mg (2.2 mmol) of zinc bromide in 23 mL ether and 1.42 mL of 3.0 M methylmagnesium bromide for 1.5 h at which time Gilman's test was negative.

Entries 19 and 20. The procedure above was followed with 0.51 mL (0.5 mmol) of commercial 1 M diethylzinc in hexane. The diastereomers were not separable by analytical HPLC. The configuration at the sulfur atom of the major diastereomer was assigned as *R* by comparison of the ^{13}C NMR spectrum with that of an authentic sample of (+)-(1*S*,2*R*)-*trans*-2-phenylcyclohexyl (*R*)-ethanesulfinate (**16*R***):[2] ^{13}C NMR (75 MHz) δ 142.7 (s), 128.2 (s), 127.7 (d), 126.5 (d), 79.9 (d), 50.4 (d), 50.3 (t), 34.5 (t), 33.5 (t), 25.7 (t), 24.9 (t), 4.7 (q); ^{1}H NMR (300 MHz) δ 7.31–7.16 (m, 7 H), 4.35–4.26 (m, 1 H), 2.76–2.67 (m, 1 H), 2.38 (q, *J* = 7.5 Hz, 2 H), 2.33–2.28 (m, 1 H), 1.97–1.32 (br m, 7 H), 0.91 (t, *J* = 7.5 Hz, 3 H); IR 3030, 2940, 2860, 1600, 1490, 1440, 1130 cm^{-1}; MS-EI *m/z* 252 (M^+), 159, 91; HRMS-EI *m/z* calcd for $C_{14}H_{20}O_2S$ 252.1184, found 252.1196.

Entry 21. Diisopropylzinc was generated *in situ* from 942 mg (4.1 mmol) of zinc bromide and 15.4 mL (9.2 mmol) of isopropylmagnesium bromide, prepared from isopropyl bromide and magnesium powder, in ether at reflux under N_2, until Gilman's test was negative.

Entry 22. Purified diisopropylzinc was obtained by vacuum distillation after the removal of ether from the metal exchange reaction above.

Entries 23–26. Phenylzinc bromide[20] was prepared from 485 mg (2.1 mmol) of zinc bromide in 3.57 mL of THF and 1.43 mL (2.1 mmol) of a 1.44 M phenyllithium solution at rt until Gilman's test was negative (negative Gilman's test after 1.5 h).

Entry 27. Diphenylzinc was generated *in situ*[11] from 137.6 mg (0.61 mmol) of zinc bromide in 10 mL of ether and 0.44 mL (1.22 mmol) of 2.76 M phenylmagnesium bromide at reflux under argon (negative Gilman's test after 1 h).

(*S*)-4-(*tert*-Butyldimethylsiloxy)butyl Methyl Sulfoxide (10*S*). To a solution of 223 mg (0.9 mmol) (+)-(1*S*,2*R*)-*trans*-2-phenylcyclohexyl (*S*)-methanesulfinate (**8**) in 10 mL of THF at rt was added the Grignard reagent **9** derived from *tert*-butyldimethylsilyl 4-chlorobutyl ether over 10 min. The reaction mixture was stirred for 2 h at rt and then quenched with saturated NH_4Cl solution and extracted with ether twice. The combined organic layers were washed with a saturated NaCl solution and dried over $NaSO_4$. The crude sulfoxide was purified by alumina chromatography using EtOAc as elutant, affording 164 mg (70%) of a colorless liquid: $[\alpha]^{25}_D$ +43.7° (*c* 2.2, CH_2Cl_2); ^{13}C NMR (75 MHz) δ 62.3 (t), 54.5 (t), 38.5 (q), 31.6 (t), 25.9 (q), 19.3 (t), 18.2 (s), −5.34 (q); ^{1}H NMR (300 MHz) δ 3.60 (t, *J* = 6 Hz, 2 H), 2.72–2.64 (m, 2 H), 2.50 (s, 3 H), 1.87–1.75 (m, 2 H), 1.64–1.60 (m, 2 H), 0.82 (s, 9 H), 0.15 (s, 6 H); MS-CI *m/z* 251 (M^+ + H), 235, 193, 187, 119; HRMS-CI *m/z* calcd for $C_{11}H_{27}O_2SiS$ (M^+ + H) 251.1501, found 251.1509.

(*R*)-4-(*tert*-Butyldimethylsiloxy)butyl Methyl Sulfoxide (10*R*). The procedure above was followed using 203 mg (0.9 mmol) of (+)-(1*S*,2*R*)-*trans*-2-phenylcyclohexyl (*R*)-methanesulfinate (**14**). Isolation was the same as above, affording 171 mg (80%) of the pure product: $[\alpha]^{25}_D$ 46.3° (*c* 2.63, CH_2Cl_2).

(*S*)-4-Hydroxybutyl Methyl Sulfoxide (11*S*). To 120 mg (0.5 mmol) of (*S*)-4-(*tert*-butyldimethylsiloxy)butyl methyl sulfoxide (**10*S***) was added 1 mL of 5% HF in CH_3CN with stirring. After 0.5 h, CH_2Cl_2 was added to the mixture and the solution was then dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, affording 60 mg (92%) of the desired product: $[\alpha]^{25}_D$ +80.6° (*c* 1.34, CH_2Cl_2); ^{13}C NMR (75 MHz) δ 61.0 (t), 53.0 (t), 37.2 (q), 30.8 (t), 18.8 (t); ^{1}H NMR (300 MHz) δ 4.70 (bs, 1 H), 3.68 (t, *J* = 6.3 Hz, 2 H), 2.85–2.76 (m, 2 H), 2.62 (s, 3 H), 1.92–1.84 (m, 2 H), 1.76–1.65 (m, 2 H); HRMS-EI *m/z* calcd for $C_5H_{13}O_2S$ (M^+ + H) 137.0636, found 137.0644. Anal. Calcd for $C_5H_{12}O_2S$: C, 44.09; H, 8.88; S, 23.54. Found: C, 44.22; H, 8.93; S, 23.40.

(*R*)-4-Hydroxybutyl Methyl Sulfoxide (11*R*). The procedure above was followed using 171 mg (0.7 mmol) of (*R*)-4-(*tert*-butyldimethylsiloxy)butyl methyl sulfoxide (**10*R***). Isolation was the same as above, affording 73 mg (92%) of the pure product: $[\alpha]^{25}_D$ 82.8° (*c* 0.91, CH_2Cl_2).

(*S*)-4-Azidobutyl Methyl Sulfoxide (12*S*). To a solution of 200 mg (1.5 mmol) of (*S*)-4-hydroxybutyl methyl sulfoxide and 0.23 mL (1.6 mmol) of Et_3N in 20 mL of CH_2Cl_2 at 0 °C was added 0.13 mL (1.6 mmol) of mesyl chloride over 5 min. After 2 h at 0 °C, the reaction mixture was quenched with 1 mL of saturated Na_2CO_3 solution and extracted with CH_2Cl_2 twice. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. To this crude mesylated sulfoxide was added 963 mg (14.8 mmol) of NaN_3 in 5 mL of DMF. After being stirred overnight at rt, the reaction mixture was filtered through a plug of cotton. The solvent was removed under vacuum. The crude product was purified by Florisil chromatography using 9:1 EtOAc/MeOH, affording 152 mg (64%) of the azide: $[\alpha]^{25}_D$ +77.3° (*c* 1.34, CH_2Cl_2); ^{13}C NMR (75 MHz) δ 53.9 (t), 50.9 (t), 38.7 (q), 28.0 (t), 20.0 (t); ^{1}H NMR (300 MHz): δ 3.36 (t, *J* = 6.6 Hz, 2 H), 2.77–2.69 (m, 2 H), 2.59 (s, 3 H), 1.91–1.76 (m, 4 H); MS-EI *m/z* 162 (M^+), 133, 118, 115, 91, 70, 69, 68, 61, 56, 58, 47, 43, 41, 39; HRMS-EI *m/z* calcd for $C_5H_{12}NOS$ 162.0701, found 162.0710.

(*R*)-4-Azidobutyl Methyl Sulfoxide (12*R*). The procedure above was followed using 73 mg (0.5 mmol) of (*R*)-4-hydroxybutyl methyl sulfoxide (**11*R***), 0.08 mL (0.6 mmol) of Et_3N, 0.05 mL (0.6 mmol) of mesyl chloride, and 350 mg (5.4 mmol) of NaN_3. Isolation was the same as above, affording 58 mg (67%) of the pure product: $[\alpha]^{25}_D$ 80.0° (*c* 1.36, CH_2Cl_2).

(+)-1-Isothiocyanato-4(*S*)-(methylsulfinyl)butane (13*S*). To a solution of 108 mg (0.67 mmol) of (*S*)-4-azidobutyl methyl sulfoxide (**12*S***) was added 353 mg (1.3 mmol) of triphenyl phosphite in 5 mL of ether. After the reaction had been refluxed for 3 h, the solvent was removed *in vacuo*. To this residue was added 1 mL of carbon disulfide. After this mixture was refluxed for 1 h, the solvent was removed under vacuum. The crude product was purified by silica gel chromatography using 9:1 EtOAc/MeOH, affording 105 mg (86%) of a light yellow liquid: $[\alpha]^{25}_D$ +77.8° (*c* 1.12, $CHCl_3$) (lit.[10] $[\alpha]^{25D}$ +78.6° ± 1° (*c* 1.158, $CHCl_3$)); ^{13}C NMR (75 MHz) δ 53.5 (t), 44.6 (t), 38.7 (q), 29.0 (t), 20.0 (t); ^{1}H NMR (300 MHz) δ 3.62 (t, *J* = 6.3 Hz, 2 H), 2.78–2.71 (m, 2 H), 2.61 (s, 3 H), 1.98–1.89 (m, 4 H); HRMS-CI *m/z* calcd for $C_6H_{12}NOS_2$ (M^+ + H) 178.0360, found 178.0359.

(−)-1-Isothiocyanato-4(*R*)-(methylsulfinyl)butane (13*R*). The procedure above was followed using 58 mg (0.36 mmol) of (*R*)-4-azidobutyl methyl sulfoxide (**12*R***), 189 mg (0.72 mmol) of

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(18) For procedure, see: Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; p 417 and reference cited therein.

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triphenyl phosphite, and 1 mL of carbon disulfide. Isolation was the same as above, affording 55 mg (86%) of the pure product: $[\alpha]^{25}_D$ 78.6° (*c* 1.19, $CHCl_3$) (lit.[10] $[\alpha]^{25}_D$ 79.3° ± 1° (*c* 1.223, $CHCl_3$)).

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Supplementary Material Available: Experimental procedures for reactions with organolithium and organocadmium reagents and ^{13}C NMR spectra for **10*S***, **11*S***, **12*S***, **13*S***, **15*R***, **15*S***, **16*R***, **16*S***, and a 19:1 mixture of **17*R*** and **17*S*** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.