Asymmetric Synthesis of α-Functionalized Primary Sulfonamides

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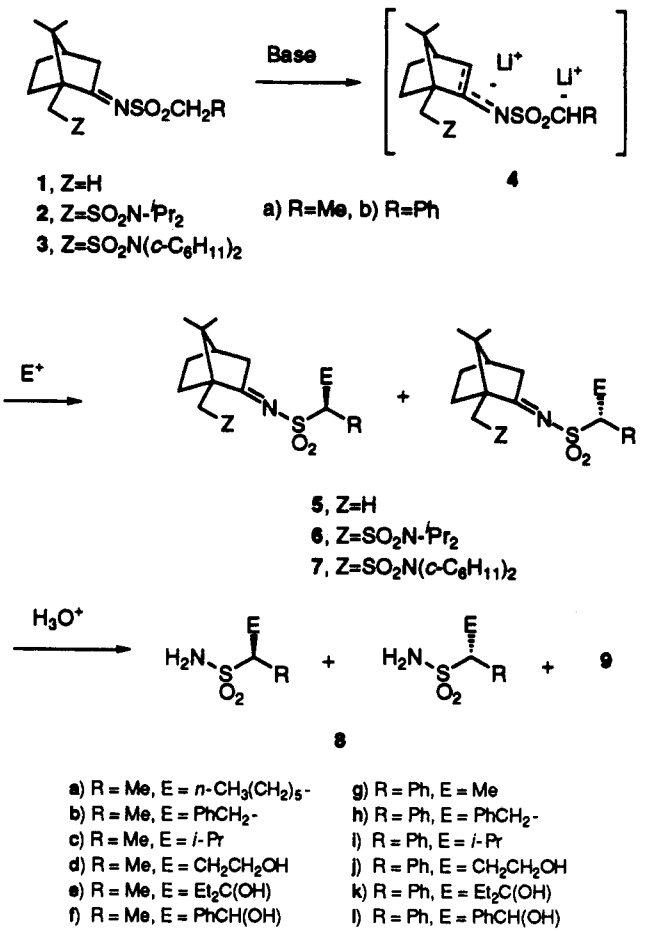
α-Functionalized primary sulfonamides **8** are prepared in good to excellent yields by treatment of the dianions of *N*-sulfonylcamphorimines **1–3** with electrophiles and hydrolysis of the resulting imines **5–7**. Alkylation of the anions of *N*-sulfonyl-10-camphorsulfonamide imines **2** and **3** with primary and secondary alkyl iodides and with ethylene oxide, following removal of the chiral auxiliary with aqueous acid, gave primary sulfonamides with ee's in the range of 66–95%.

Many important applications of sulfonamides have emerged in pharmaceutical and other areas of industrial chemistry.[1] Primary sulfonamides (RSO_2NH_2) are precursors of numerous intermediates used in organic synthesis including sulfonyl isocyanates,[2] *N*-sulfinyl sulfonamides,[3] and sulfonylimines used in the synthesis of *N*-sulfonyloxaziridines.[4] Most of these examples utilize arenesulfonamides ($ArSO_2NH_2$) because they are commercially available or are easily prepared from the sulfonyl chloride. Racemic α-functionalized primary sulfonamides can be prepared by the treatment of *N*-*tert*-butyl primary alkanesulfonamide dianions[5] with electrophiles, but this requires removal of the *tert*-butyl group with trifluoroacetic acid.[6,7]

Enantiopure primary sulfonamides are rare. The only readily available examples are derivatives of camphorsulfonic acids where the stereocenters are separated from the sulfonamide by a methylene group.[8] Apart from the difficulties encountered in preparing chiral sulfonyl chlorides, their conversion to sulfonamides is complicated by competing sulfene formation which epimerizes the α-carbon.[9,10] In connection with our interest in using sulfur–nitrogen reagents[11–14] in asymmetric synthesis, we describe methodology for the synthesis of enantiomerically enriched primary sulfonamides. This procedure involves the diastereoselective C-alkylation of *N*-sulfonylcamphorimine dianions **4** derived from **1–3** and acid-catalyzed hydrolysis of the resulting diastereomeric *N*-sulfonylcamphorimines **5–7** (Scheme I).[15]

Scheme I



1, Z=H
2, Z=SO_2N-^{i}Pr$_2$
3, Z=$SO_2N(c\text{-}C_6H_{11})_2$

4

a) R=Me, b) R=Ph

5, Z=H
6, Z=SO_2N-^{i}Pr$_2$
7, Z=$SO_2N(c\text{-}C_6H_{11})_2$

8

9

a) R = Me, E = n-$CH_3(CH_2)_5$-
b) R = Me, E = $PhCH_2$-
c) R = Me, E = i-Pr
d) R = Me, E = CH_2CH_2OH
e) R = Me, E = $Et_2C(OH)$
f) R = Me, E = PhCH(OH)
g) R = Ph, E = Me
h) R = Ph, E = $PhCH_2$-
i) R = Ph, E = i-Pr
j) R = Ph, E = CH_2CH_2OH
k) R = Ph, E = $Et_2C(OH)$
l) R = Ph, E = PhCH(OH)

(1) For reviews on sulfonamides, see: Andersen, K. K. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., series Eds.; Pergaman Press: New York, 1979; Vol. 3, Chapter 11. *The Chemistry of Sulphonic Acids, Esters and their Derivatives*; Patai, S., Ed.; John Wiley & Sons, Ltd.: New York, 1991; Chapters 10, 11, 18.

(2) For reviews, see: McFraland, J. W. *Int. J. Sulfur CHem. B* **1971**, *7*, 319. Ulrich, H. *Chem. Rev.* **1965**, *65*, 369.

(3) For reviews, see: Weinreb, S. M. *Acc. Chem. Res.* **1988**, *21*, 313.

(4) For reviews on the synthesis and applications of enantiopure *N*-sulfonyloxaziridines, see: (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. (c) Davis, F. A.; Chen, B.-C. Asymmetric Oxygenation of Enolates. In *Stereoselective Synthesis of Organic Compounds*; Houben-Weyl: Methoden der Organischen Chemie, in press.

(5) For an excellent review on the chemistry of dianions including sulfonyl dianions, see: Thompson, C. M.; Green, D. L. C. *Tetrahedron* **1991**, *47*, 4223.

(6) Thompson, M. E. *J. Org. Chem.* **1984**, *49*, 1700.

(7) For related studies using α,*N*-alkanesulfonamide dianions see: Graham, S. L.; Scholz, T. H. *J. Org. Chem.* **1991**, *56*, 4260. Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 509. Grunder-Klotz, E.; Ehrhardt, J.-D. *Synlett* **1991**, 800.

(8) For leading references, see: Davis, F. A.; Jenkins, R. H., Jr.; Awad, S. B.; Stringer, O. D.; Watson, W. H.; Galloy, J. *J. Am. Chem. Soc.* **1982**, *104*, 5412. Davis, F. A.; Billmers, J. M. *J. Org. Chem.* **1983**, *48*, 2672.

(9) Cram, D. J.; Trepka, R. D.; Janiak, P. St. *J. Am. Chem. Soc.* **1966**, *88*, 2749.

(10) For a discussion of the chemistry of sulfenes, see: King, J. F.; Rathore, R. In *The Chemistry of Sulphonic Acids, Esters and their Derivatives*; Patai, S., Ed.; John Wiley & Sons, Ltd.: New York, 1991; Chapter 17.

(11) Asymmetric hydroxylation of enolates: ref 4.

(12) Chiral sulfinimines: Davis, F. A.; Thimma Reddy, R.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387.

(13) Asymmetric oxidation of sulfides to sulfoxides: Davis, F. A.; Thimma Reddy, R.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428.

(14) Asymmetric oxidation of selenides to selenoxides: Davis, F. A.; Thimma Reddy, R. *J. Org. Chem.* **1992**, *57*, 2599.

(15) Some aspects of this work have been published in preliminary form: Davis, F. A.; Zhou, P.; Lal, G. S. *Tetrahedron Lett.* **1990**, *331*, 1653.

0022-3263/93/1958-4890$04.00/0

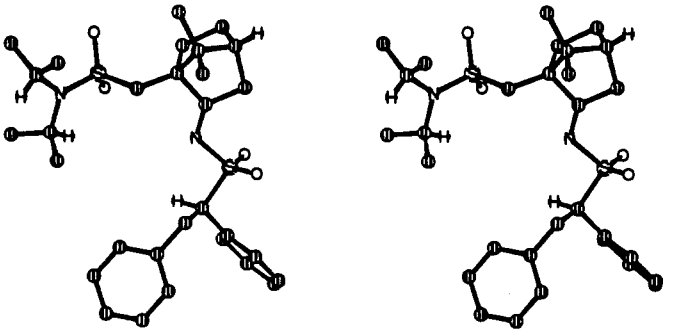
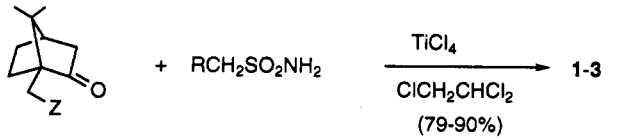


Figure 1. Computer-generated stereoview of *N*-sulfonylcamphorimine (−)-**6h**.

Table I. Synthesis of (−)-*N*-Sulfonylcamphorimines Using $TiCl_4$



9a, Z=H
b, Z=SO_2N-^{i}Pr$_2$
c, Z=$SO_2N(c\text{-}C_6H_{11})_2$

10a, R=CH_3
b, R=Ph

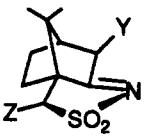
Z in 9	R in 10	amine 1–3 (% isolated yield)
9a (Z = H)	CH_3	(−)-**1a** (87)
	Ph	(−)-**1b** (82)
9b [Z = $SO_2N^iPr_2$]	CH_3	(−)-**2a** (79)
	Ph	(−)-**2b** (81)
9c [Z = $SO_2N(c\text{-}C_6H_{11})_2$]	CH_3	(−)-**3a** (90)
	Ph	(−)-**3b** (86)

Results

(−)-*N*-Sulfonylcamphorimines (camphorsulfonimines) **1–3** were prepared, as previously described,[13] by refluxing equimolar amounts of the appropriate camphor derivative **9**, ethanesulfonamide (**10a**) or phenylmethanesulfonamide (**10b**), and titanium tetrachloride in 1,1,2-trichloroethane for 14–16 h. Yields were 79–90% after purification by flash chromatography (Table I). Sulfonimines **1–3** gave satisfactory elemental analyses and exhibited diagnostic C=N bond absorptions in infrared at 1590–1680 cm^{-1} and at δ 175–200 in the ^{13}C NMR.

Earlier studies with the (camphorsulfonyl)imine **11** had shown that treatment with bases affords the aza enolate **12** which reacts with electrophilic halogen sources (X) to give the (α-halocamphorsulfonyl)imines **12** (Y = halogen).[16,17] Carbon electrophiles, however, react with difficulty at the aza enolate nitrogen to give *N*-alkyl enamines.[17] On the other hand, excess base gave the (camphorsulfonyl)imine dianion **13**, which reacts smoothly with carbon electrophiles to give products resulting from alkylation α to the sulfonyl group, reflecting its higher charge density.[17,18] As expected the dianions of **1–3** gave diastereoisomers **5–7**, indicating that mono C-alkylation at the carbon atom adjacent to the sulfonyl group was exclusive.

N-Sulfonylcamphorimine dianions **4** were generated by treatment of the corresponding imines **1–3** with 3 equiv



11, Y=Z=H
12, Y=Li, Z=H
13, Y=Z=Li

of lithium diisopropylamide (LDA) or 2 equiv of *n*-butyllithium at the appropriate temperature (Table II). After being cooled to −78 °C, the designated electrophile (E) was added and the diastereomeric products **5–7** were isolated by preparative TLC on silica gel. Hydrolysis was accomplished simply by refluxing **5–7** for 2–8 h in 18% ethanolic HCl to afford the respective sulfonamides **8** in near quantitative yield (90–98%). The 10-camphorsulfonamides **9b,c** were isolated in 85–90% for recycling. Highly efficient methodology for the general synthesis of α-functionalized primary sulfonamides is demonstrated by these results.

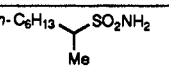
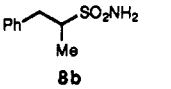
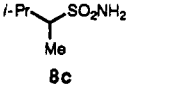
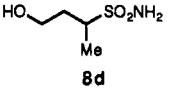
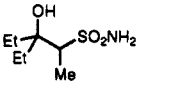
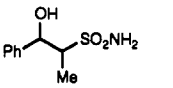
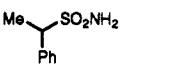
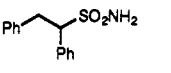
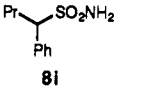
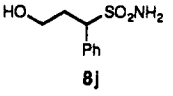
The de's of the *N*-sulfonyl-10-camphorsulfonamide diastereoisomers **6** and **7** were determined by ^1H NMR (Table II, entries 18, 19, 27, 29, 32, 34, 35, 36, and 37), but **5** required addition of the shift reagent PrFOD (Table II, entries 5, 9, and 12). The ee's of sulfonamides **8b**, **8e**, **8g**, and **8i** were established using the chiral shift reagent Eu(hfc)$_3$. It was necessary to transform sulfonamides **8a**, **8d**, **8h**, and **8j** into their *N,N*-dimethyl derivatives by refluxing with iodomethane/K_2CO_3 prior to determining the asymmetric induction with Eu(hfc)$_3$. The absolute configuration of (−)-*N,N*-dimethyl-2-octanesulfonamide (**8a**, NH_2 = NMe_2) has previously been determined as *S* by Cram and co-workers.[9,19] The configuration of the newly formed stereocenter in N-sulfonylcamphorimine (−)-**6h** was confirmed as *R* by X-ray analysis (Figure 1), and therefore, the absolute configuration of (−)-1,2-diphenylethane-2-sulfonamide (**8h**) is also *R* (Table II, entry 32).[20] Analogous to these known configurations and the model discussed below, the structures of sulfonamides (*R*)-(+)-**8a**, (*R*)-(+)-**8b**, and (*R*)-(−)-**8e** derived from **1a** (R = Me) and (*S*)-(−)-**8g** and (*S*)-(+)-**8h** derived from **2a** (R = Ph) were proposed. In a similar manner, the configurations of the sulfonamides (*S*)-(−)-**8a** and (*S*)-(−)-**8b** obtained from **2a** and **3a** (R = Me) and (*R*)-(+)-**8g**, (*R*)-(−)-**8h**, (*R*)-(+)-**8i**, and (*R*)-(−)-**8j** from **2b** and **3b** (R = Ph) were suggested.

Discussion

A number of trends are revealed by the results summarized in Table II. LDA generally gave higher yields of products than did *n*-BuLi, but 3 equiv vs 2 equiv was necessary (Table II, compare entries 28 and 29). This may be an example of the "hidden proton" effect where diisopropylamine, formed in the deprotonation of **1–3**, quenches **4** prior to alkylation.[21] This proposal is supported by the fact that 2 equiv of *n*-BuLi give the product

(16) Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Thimma Reddy, R.; Chen, B.-C. *J. Org. Chem.* **1992**, *57*, 7274.
(17) Davis, F. A.; Weismiller, M. C.; Lal, G. S.; Chen, B.-C.; Przeslawski, R. M. *Tetrahedron Lett.* **1989**, *30*, 1613.
(18) Chen, B.-C.; Weismiller, M. C.; Davis, F. A.; Boschelli, D.; Empfield, J. R.; Smith, A. B., III. *Tetrahedron* **1991**, *47*, 173.
(19) This was established for the *N,N*-dimethyl-(−)-2-octane-2-*d*-sulfonamide. Octanesulfonyl chloride and 2-octane-2-*d*-sulfonyl chloride had identical specific rotations.[9] Furthermore the absolute configuration of **8a** is consistent with predictions based on the model.
(20) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
(21) For discussion of this phenomenon, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

Table II. Asymmetric Synthesis of α-Functionalized Primary Sulfonamides 8 from *N*-Sulfonylcamphorimines 1–3

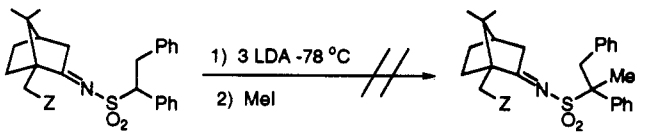
entry	sulfonimine 1–3, R =	E^+ =	reaction conditions: eqiv, base, °C, time	sulfonimine 5–7: % de [% yield][a]		sulfonimine 8: % ee (config) [% yield][a]	$[\alpha]_D$, deg (c, solvent)
1	**1a** (R = Me)	n-$C_6H_{13}I$	3 LDA, 0, 2 h	**5a**	[85]	 10[b] (*R*) [95]	+0.7 (1.0, $CHCl_3$)
2	**2a** (R = Me)		3 LDA, −78 to 20, 9 h	**6a**	[62]		−3.0 (4.0, EtOH)
3	**3a** (R = Me)		3 LDA, −78 to 20, 9 h	**7a**	[61]	42[b] (*S*)[c] [93]	−4.4 (3.8, EtOH)
						8a	
4	**1a** (R = Me)	$PhCH_2Br$	3 LDA, 0, 2 h	**5b**	[89]	 2[e] [95]	
5			2 n-BuLi, −78, 2 h		13[d] [76]	13[e] (*R*) [95]	+1.0 (1.0, $CHCl_3$)
6	**2a** (R = Me)		3 LDA, −78 to 20, 9 h	**6b**	[30]	22[e] (*S*) [88]	−13.9 (0.5, $CHCl_3$)
						8b	
7	**2a** (R = Me)	Me_2CHI	3 LDA, −78 to 20, 9 h	**6c**	n.r.[n]		
8			2 n-BuLi, −78, 2 h		n.r.		
						8c	
9	**1a** (R = Me)	oxirane	3 LDA, 0, 3 h	**5d**	[73]	 11[b] [77]	
10			2 n-BuLi, −78, 4 h		12[d] [60]	12[b] (*S*) [62]	−1.1 (1.0, Me_2CO)
11	**2a** (R = Me)		3 LDA, −78 to 20, 9 h	**6d**	[0]		
						8d	
12	**1a** (R = Me)	Et_2CO	3 LDA, 0, 3 h	**5e**	[82]	 5[e] [96]	
13			2 n-BuLi, −78, 4 h		12[d] [70]	12[e] (*R*) [94]	−7.3 (1.0, $CHCl_3$)
14	**2a** (R = Me)		3 LDA, −78 to 20, 9 h	**6e**	[0]		
						8e	
15	**1a** (R = Me)	PhCHO	3 LDA, 0, 3 h	**5f**	[80][f]	 [96][f]	
16			2 n-BuLi, −78, 3 h		[70][f]	[91][f]	
17	**2a** (R = Me)		3 LDA, −78 to 20, 9 h	**6f**	[0]		
						8f	
18	**1b** (R = Ph)	MeI	3 n-BuLi, −78, 1 h	**5g**	32[g] [94]	 32[e] (*S*) [91]	−6.0 (1.2, $CHCl_3$)
19	**2b** (R = Ph)		3 LDA, −78, 3 h	**6g**	77[g] [89]	75[e] [90]	+14.3 (1.4, $CHCl_3$)
20			3 LDA, −100, 3 h		75 [86]		
21			3 LDA, 0[h]		dec		
22			3 LDA, −78, 3 h, HMPA[i]		71 [80]		
23			2 n-BuLi, −78, 3 h		60 [87]		
24			2 n-BuLi, −78, 3 h, NaH[j]		n.r.		
25			2 n-BuLi, −78, 3 h, Et_2O[k]		61 [87]		
26			2 n-BuLi, −78, 3 h, HMPA[i]		67 [73]		
						8g	
27	**3b** (R = Ph)		3 LDA, −78, 3 h	**7g**	68[g] [91]	66[e] (*R*) [90]	+12.8 (1.2, $CHCl_3$)
28	**1b** (R = Ph)	$PhCH_2Br$	2 LDA, 0, 3 h		n.r.		
29			3 LDA, 0, 3 h	**5h**	11[g] [84]	11[b] [96]	
30			2 n-BuLi, −78, 1 h		34 [82]		
31			3 n-BuLi, −78, 1 h		34 [93]	32[b] (*S*) [93]	+18.6 (0.9, $CHCl_3$)
32	**2b** (R = Ph)		3 LDA, −78, 1 h	**6h**	74 [84] >95[g] [68][l]	95[b] (*R*)[m] [94]	−54.2 (1.0, $CHCl_3$)
33			2 n-BuLi, −78, 1 h		64 [71]		
34	**3b** (R = Ph)		3 LDA, −78, 1 h	**7h**	71 [86] >95[g] [67][l]	93[b] (*R*) [92]	−50.6 (1.0, $CHCl_3$)
						8h	
35	**2b** (R = Ph)	Me_2CHI	3 LDA, −78, 3 h	**6i**	90[g] [68]	 90[e] (*R*) [89]	+40.8 (1.2, $CHCl_3$)
36	**3b** (R = Ph)			**7i**	87[g] [64]	90[e] (*R*) [91]	+41.1 (1.2, $CHCl_3$)
						8i	
37	**2b** (R = Ph)	oxirane	3 LDA, −78 to 0, 9 h	**6j**	66[g] [34]	 66[b] (*R*) [91]	−4.5 (1.1, Me_2CO)
			3 n-BuLi, −78 to 0, 9 h		36 [39]		
						8j	
38	**2b** (R = Ph)	Et_2CO	3 LDA, −78 to 0, 7 h	**6k**	[0]	**8k**	
39	**2b** (R = Ph)	PhCHO	3 LDA, −78 to 0, 7 h	**6l**	tar	**8l**	

[a] Isolated yields. [b] Determined on the corresponding *N*,*N*-dimethyl sulfonamides using $Eu(hfc)_3$. [c] Based on the sign of rotation, see ref 8. [d] Resolve-Al PrFOD used. [e] $Eu(hfc)_3$ used. [f] Complex mixture of diastereomers obtained. [g] Determined by ^1H NMR. [h] Warmed to 0 °C for 30 min before cooling to −78 °C. [i] THF:HMPA 7:3. [j] 0.1 equiv of NaH added and warmed to 0 °C before cooling to −78 °C. [k] Ether solvent. [l] After two crystallizations from EtOH. [m] Based on the X-ray crystal structure of **6h**. [n] n.r. = no reaction.

in good yield (Table II). Furthermore, treatment of **1b** with 2 equiv of LDA, quenched with D_2O, resulted in the incorporation of only one deuterium atom at the α-imino site. Evidence that the dianion species **4** is actually generated under these conditions is supported by the fact that treatment of **2b** with 3 equiv of LDA or 2 equiv of *n*-BuLi, quenched with D_2O, resulted in quantitative recovery of **2b** with incorporation of two deuterium atoms at the α-imino and α-sulfonyl carbons. Even with 6 equiv of LDA or 3 equiv of *n*-BuLi, only two deuterium atoms are incorporated into **2b**.

Attempts to generate the "thermodynamic" dianion by warming **4** to 0 °C or addition of NaH resulted in decomposition or no reaction, respectively (entries 21 and 24). The dianions resulting from deprotonation of the *N*-sulfonylcamphorimine **1** appear to be more reactive than those derived from *N*-sulfonyl-10-camphorsulfonamide imines **2** and **3** as evidenced by the fact that the latter failed to react with benzaldehyde or 3-pentanone (entries 14, 17, 38, and 39). Generation of tertiary primary sulfonamides by treatment of the LDA-generated dianions of **5h** and **6h** with iodomethane failed, resulting in recovery of starting material.

Poor diastereoselectivities were observed for the reaction of electrophiles with *N*-sulfonylcamphorimine **1a** (R = Me) and **1b** (R = Ph) dianions. The α-benzyl sulfonyl



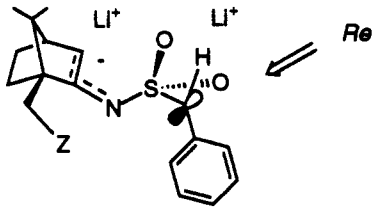
5h, Z=H
6h, Z=$SO_2N^iPr_2$

anion gave somewhat higher de's than did the α-ethyl derivative; 32% vs 11%. A dramatic improvement in the de's was seen with the dianions of *N*-sulfonyl-10-camphorsulfonamide imines **2** and **3** with the α-benzyl sulfonyl anion giving the best results. For example, the de's for the reaction of the dianion of **2b** (R = Ph) with iodomethane, benzyl bromide, isopropyl iodide, and ethylene oxide were 77, 74, 90, and 66%, respectively (entries 19, 32, 35, and 37). Sulfonylimine **6h** was obtained diastereomerically pure after recrystallization from ethanol (entry 32), but similar attempts to upgrade **6g**, **6i**, **7i**, and **6j** were unsuccessful. Higher de's were generally observed for the LDA-generated dianions of **2b** and similar de's were observed for **2b** (Z = $SO_2N^iPr_2$) and **3b** [Z = SO_2N-(c-$C_6H_{11})_2$]. Attempts to improve the asymmetric induction by variation of solvent (entry 25), lowering the temperature (entry 20), or addition of HMPA (entry 22 and 26) either had no effect or resulted in a slight lowering of the diastereoselectivity. The Zn and Mg anions, prepared by addition of $ZnCl_2$ and $MgBr_2$ to the *n*-BuLi-derived dianion of **2b**, gave no reaction on treatment with iodomethane.

As mentioned earlier, the removal of the camphor auxiliaries from **5–7** with HCl gave excellent yields of the corresponding sulfonamides **8**. Significantly, this occurred without epimerization at the chiral α-sulfonyl carbon as evidenced by the similarities in the de's and ee's of **5–7** and the sulfonamides **8**. For example, hydrolysis of **6h** (>95% de) or **7h** (>95% de) gave 1,2-diphenylethanesulfonamide (**8h**) in 93–95% ee and 92–94% isolated yield (entries 32 and 34). Likewise, the hydrolysis of **6i** (90% de) gave 3-(2-methyl-3-phenyl)ethanesulfonamide (**8i**) in 90% ee and 89% yield (entry 35).

The reactions and properties of α-sulfonyl carbanions have generated considerable interest and controversy in part because some of the anions derived from optically active precursors retain their configuration on protonation.[22] Crystallographic and NMR studies indicate that α-alkyl sulfonyl anions are largely pyramidal while the α-phenyl anions are planar.[22,23] The lithium cation is not associated with the carbanion but rather with one of the sulfonyl oxygens. In the solid state the carbanion lone pair is *gauche* to the two sulfonyl oxygen atoms and periplanar to the S–C carbon bond.[23a] A similar minimum energy conformation is predicted by *ab initio* calculations.[24] The configurational stability of α-sulfonyl carbanions is generally attributed to restricted Cα–S bond rotation which is ascribed to negative hyperconjugation (n_c–σ^*_{SR}) as well as Coulombic interactions.[22,23]

On the other hand, the origin of the diastereoselectivity in the alkylation of *N*-sulfonylcamphorimine dianions **4** is not readily apparent due to the lack of structural information concerning the dianion. However, a plausible hypothesis is that the resulting α-sulfonyl carbanions of **1–3** (e.g. **4**) are planar and have a *gauche* configuration with respect to the two sulfonyl oxygens as shown in **14**. The necessary conformational preference for the phenyl group in **14** being "down" rather than "up" can be attributed to an unfavorable steric interaction between the bridge methyl group and/or the Li cation and its ligands associated with the imino sulfone group. The much higher asymmetric induction observed for the *N*-sulfonyl-10-camphorsulfonamide imines **2b** and **3b** (R = Ph) vs the *N*-sulfonylcamphorimines **1b** was consistent with the expected preferential shielding of the *si* face by the bulky sulfonamide groups in the former. This hypothesis finds support in the X-ray structure of (–)-**6h** which suggests *si* facial shielding (Figure 1). Similar facial shielding has been proposed by Oppolzer for the high asymmetric induction observed for the related 10-sulfonamide–isoborneol chiral auxiliaries.[25–27] Increased rigidity of **2** and **3** vs **1** as a result of intramolecular chelation of the dianion with the 10-camphorsulfonamide may also play a role. Highly ordered rigid transition-state geometries are prerequisites for most asymmetric transformations which occur with high stereoselectivities. However, the addition of HMPA, known to disrupt metal chelation, has little effect on the asymmetric induction (Table II, entries 22 and 26), suggesting that intramolecular chelation as a factor enhancing rigidity and stereoinduction is probably minor.



14

The considerably higher selectivity observed for the benzyl vs the methyl derivatives of **1–3** requires additional comment. The two protons adjacent to the sulfonyl group in **2b** and **3b** are diastereotopic, and selective deprotonation would result in a chiral α-sulfonyl carbanion which could then undergo stereospecific alkylation. Indeed seminal studies by Gais and co-workers indicate that at low temperatures racemization of such carbanions is slow.[23e] However, treatment of **6h** (95% de) with 3 equiv of LDA at –78 °C and quenching at this temperature resulted in complete racemization. Alternatively, the greater steric bulk of phenyl vs methyl or the fact that α-benzyl sulfonyl carbanions are more planar than α-ethyl sulfonyl carbanions may also be factors in the former's higher de's.

Summary. α-Functionalized primary sulfonamides are readily prepared by the reaction of electrophiles (E^+) with

(22) For reviews on the chemistry and properties of α-sulfonyl carbanions, see: (a) Oae, S.; Uchida, Y. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons Ltd.: 1988; Chapter 12, pp 583–664. (b) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277.

(23) (a) Gais, H.-J.; Volhardt, J.; Lindner, H. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 939. (b) Gais, H.-J.; Hellmann, G.; Gunther, H.; Lopez, F.; Lindner, H. J.; Braun, S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1025. (c) Gais, H.-J.; Hellmann, G.; Lindner, H. J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 100. (d) Gais, H.-J.; Muller, J.; Volhardt, J. *J. Am. Chem. Soc.* **1991**, *113*, 4002. (e) Gais, H.-J.; Hellmann, G. *J. Am. Chem. Soc.* **1992**, *114*, 4439.

(24) Bors, D. A.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 1397.

(25) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.

(26) Oppolzer, W.; Chapuis, C.; Kelly, M. J. *Helv. Chim. Acta* **1983**, *66*, 2358. Oppolzer, W.; Dudfield, P. *Tetrahedron Lett.* **1985**, *26*, 5037.

(27) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Tetrahedron Lett.* **1984**, *25*, 5885.

the dianions of *N*-sulfonylcamphorimines **1–3** and hydrolysis. The advantages of this methodology over earlier methods include its high yields, lack of polyalkylation, and ease of protecting group removal. Furthermore, this method affords enantiomerically enriched α-functionalized sulfonamides **8** in up to 95% ee by alkylation of the dianions of *N*-sulfonyl-10-camphorsulfonamide imines **2** and **3**.

Experimental Section

Details concerning the recording of spectra, the analytical instruments used, the determination of melting points, elemental analyses, and the purification of solvents (freshly distilled) have been previously reported.[16] LDA (1 mmol/mL) was prepared by treatment of 1.4 mL of diisopropylamine in 4.6 mL of THF by addition of 4.0 mL of 2.5 M of *n*-butyllithium (Aldrich) at 0 °C. All reactions were performed under an argon/nitrogen atmosphere. *n*-Butyllithium and (+)-camphor (**9a**) were purchased from Aldrich. *N,N*-Diisopropyl-(1*S*)-(+)-10-camphorsulfonamide (**9b**) and *N,N*-dicyclohexyl-(1*S*)-(+)-10-camphorsulfonamide (**9c**) were prepared as previously described.[27]

Preparation of Ethanesulfonamide (10a). Ethanesulfonyl chloride (20 g, 14.7 mL) was added dropwise *via* a dropping funnel to a stirring solution of 150 mL of ammonium hydroxide in 200 mL of $CHCl_3$ cooled to 0 °C in an ice bath. After the addition was complete the mixture was brought to room temperature and stirred for 2 h. Evaporation of the solvent gave a residue which was placed in a Soxhlet extractor connected to a 1-L, round-bottomed flask containing 500 mL of $CHCl_3$. After the solution was refluxed overnight, removal of solvent gave a yellowish solid, 15.0 g (88%), mp 57–60 °C [lit.[28] mp 58–60 °C]. The product can be used without further purification.

Phenylmethanesulfonamide (10b) was prepared in a similar manner. After the reaction was completed the product was isolated by extraction with $CHCl_3$ (5 × 100 mL). Removal of the solvent gave **10b** as a white solid (89%), mp 102–104 °C [lit.[29] mp 104 °C].

General Procedure for the Preparation of (-)-Camphor *N*-(Alkylsulfonyl)imines 1–3. In 250-mL, 3-necked, round-bottomed flask equipped with a condenser connected to a mineral oil bubbler, magnetic stir bar, and rubber septum were placed the appropriate camphor derivative **9** (30 mmol) and sulfonamide **10** (30 mmol) in 150 mL of 1,1,2-trichloroethane. The solution was cooled to 0 °C under an argon atmosphere and 30 mL (30 mmol) of $TiCl_4$ in CH_2Cl_2 was added dropwise via syringe over 5 min. The rubber septum was replaced by a glass stopper, and the reaction mixture was refluxed for 14–16 h at which time the solution was cooled to room temperature and filtered. Removal of the solvent via a rotary evaporator gave the crude camphorsulfonimines **1–3** which were purified by flash chromatography on silica gel eluting with ether/*n*-pentane (3:7).

(-)-Camphor *N*-(ethylsulfonyl)imine (1a): yield 70%; mp 40–2 °C; $[\alpha]_D$ -39.0° (*c* 3.0, $CHCl_3$); IR (KBr, cm^{-1}) 1630, 1330, 1297, 1140; ^1H NMR ($CDCl_3$) δ 3.20 (q, *J* = 6.7 Hz, 2H), 3.05 (m, 1H), 2.52 (d, *J* = 20.1 Hz, 1H), 1.25–2.15 (m, 5H), 1.44 (t, *J* = 6.7 Hz, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 200.5, 56.8, 47.9, 43.5, 39.37, 31.1, 29.5, 26.2, 19.1, 18.5, 10.2, 7.6. Anal. Calcd for $C_{12}H_{21}NO_2S$: C, 59.23; H, 8.70. Found: C, 59.06, H, 8.52.

(-)-Camphor *N*-(benzylsulfonyl)imine (1b): yield 64%; mp 60–1 °C; $[\alpha]_D$ -32.4° (*c* 2.6, $CHCl_3$); IR (KBr, cm^{-1}) 1630, 1590, 1323, 1146; ^1H NMR ($CDCl_3$) δ 7.30–7.58 (m, 5H), 4.39 (q, *J* = 11.2 Hz, 2H), 2.85 (m, 1H), 3.32 (d, *J* = 20.1 Hz, 1H), 1.05–2.05 (m, 5H), 0.93 (s, 3H), 0.91 (s, 3H), 0.58 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 201.4, 130.4, 128.6, 127.7, 127.7, 59.1, 57.2, 43.3, 30.9, 26.6, 26.0, 18.9, 18.4, 10.3. Anal. Calcd for $C_{17}H_{23}NO_2S$: C, 65.49; H, 7.90. Found: C, 65.34; H, 7.63.

(-)-10-[(*N,N*-Diisopropylamino)sulfonyl]camphor *N*-(ethylsulfonyl)imine (2a): yield 79%; mp 124–125 °C; $[\alpha]_D$ -12.0° (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 1650, 1337, 1118; ^1H NMR ($CDCl_3$) δ 3.78 (m, 2H), 3.39 (d, *J* = 14.3 Hz, 1H), 3.16 (q, *J* = 7.4 Hz, 2H), 3.00 (m, 1H), 2.12 (m, 2H), 1.00–2.10 (m, 5H), 1.44 (t, *J* = 7.4 Hz, 3H), 1.33 (d, *J* = 6.8 Hz, 6H), 1.31 (d, *J* = 6.8 Hz, 6H), 1.13 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.7, 57.8, 51.8, 48.8, 48.3, 48.1, 43.7, 39.2, 27.1, 26.3, 22.15, 22.1, 19.5, 19.4, 7.7. Anal. Calcd for $C_{18}H_{34}N_2O_4S_2$: C, 53.17; H, 8.43. Found: C, 52.69; H, 8.17.

(-)-10-[(*N,N*-Diisopropylamino)sulfonyl]camphor *N*-(benzylsulfonyl)imine (2b): yield 81%; mp 109–111 °C; $[\alpha]_D$ -15.1° (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 1638, 1600, 1333, 1113; ^1H NMR ($CDCl_3$) δ 7.27–7.44 (m, 5H), 4.40 (q *J* = 13.8 Hz, 2H), 3.77–3.87 (m, 2H), 3.41 (d, *J* = 14.4 Hz, 1H), 3.68–2.91 (m, 3H), 2.26 (d, *J* = 19.8 Hz, 1H), 1.19–1.94 (m, 4H), 1.38 (m, 12H), 1.12 (m, 12H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 199.6, 130.7, 128.5, 128.4, 128.3, 59.6, 58.5, 52.0, 48.7, 48.4, 43.7, 39.6, 26.9, 26.3, 22.5, 22.2, 19.7, 19.4. Anal. Calcd for $C_{23}H_{36}N_2O_4S_2$: C, 58.94; H, 7.74. Found: C, 58.87; H, 7.56.

(-)-10-[(*N,N*-dicyclohexylamino)sulfonyl]camphor *N*-(ethylsulfonyl)imine (3a): yield 90%; mp 167–169 °C; $[\alpha]_D$ -5.3° (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 1651, 1343, 1143; ^1H NMR ($CDCl_3$) δ 3.40 (d, *J* = 14.2 Hz, 1H), 3.30 (m, 2H), 3.19 (q, *J* = 7.4 Hz, 2H), 3.0 (m, 1H), 2.85 (d, *J* = 14.2 Hz, 1H), 2.12 (m, 2H), 1.00–2.15 (m, 24H), 1.47 (t, *J* = 7.4 Hz, 3H), 1.14 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.2, 63.8, 57.6, 57.1, 52.3, 48.6, 48.2, 43.5, 39.0, 32.4, 32.2, 27.0, 26.1, 24.8, 19.3, 19.1, 7.7. Anal. Calcd for $C_{24}H_{42}N_2O_4S_2$: C, 59.22; H, 8.70. Found: C, 59.01; H, 8.56.

(-)-10-[(*N,N*-dicyclohexylamino)sulfonyl]camphor *N*-(benzylsulfonyl)imine (3b): yield 86%; mp 120–122 °C; $[\alpha]_D$ -5.4° (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 1650, 1595, 1327, 1144; ^1H NMR ($CDCl_3$) δ 7.30–7.55 (d, 5H), 4.39 (AB q, *J* = 13.4 Hz, 2H), 1.20–3.50 (m, 31H), 1.14 (s, 3H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 199.4, 130.5, 128.3, 128.2, 128.1, 63.8, 59.4, 58.3, 57.3, 52.8, 48.5, 43.5, 39.3, 32.7, 32.4, 26.8, 26.3, 26.1, 25.0, 19.5, 19.2. Anal. Calcd for $C_{29}H_{44}N_2O_4S_2$: C, 63.47; H, 8.08. Found: C, 63.57; H, 8.53.

General Procedure for the Alkylation of Camphor *N*-(Alkylsulfonyl)imines 1–3. Sulfonylimines **1–3** (1 mmol) in 5 mL of dry THF were cooled to the appropriate temperature and 2–3 equiv of LDA or *n*-BuLi (Table II) was added dropwise via syringe over 2–5 min. After the mixture was stirred for 1 h, 3 mmol of the designated electrophile was added, and stirring was continued for an additional 2–3 h (see Table II). To the reaction mixture was added 50 mL of ether, and the solution was washed with 25 mL of saturated NH_4Cl. After the solution was dried over anhydrous $MgSO_4$, removal of solvent gave crude **5–7** which were purified by preparative TLC on silica gel.

Camphor *N*-[(1-methylheptyl)sulfonyl]imine (5a): elution with ether/*n*-pentane 3:7; yield 85% (oil mixture of diastereomers); $[\alpha]_D$ 29.3° (*c* 2.2, $CHCl_3$); IR (neat, cm^{-1}) 1640, 1310, 1140; ^1H NMR ($CDCl_3$) δ 3.20–3.00 (m, 2H), 2.60–2.45 (d, *J* = 25.0 Hz, 1H), 2.20–2.00 (m, 1H), 2.00–1.75 (m, 2H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.70–1.25 (m, 12H), 1.05 (s, 6H), 0.90 (t, 3H), 0.85 (s, 3H). Anal. Calcd for $C_{18}H_{33}NO_2S$: C, 66.05; H, 10.16. Found: C, 66.33; H, 10.16.

Camphor *N*-[(1-methyl-2-phenylethyl)sulfonyl]imine (5b): elution with ether/*n*-pentane 3:7; yield 76% (oil mixture of diastereomers); $[\alpha]_D$ -32.8° (*c* 3.5, $CHCl_3$); IR (neat, cm^{-1}) 1640, 1610, 1310, 1140; ^1H NMR ($CDCl_3$) δ 7.15–7.38 (m, 5H), 3.48–3.60 (m, 1H), 3.29–3.45 (m, 1H), 2.96–3.14 (m, 1H), 2.60–2.75 (m, 1H), 2.46–2.60 (m, 1H), 2.04–2.11 (m, 1H), 1.34–198 (m, 4H), 2.30 (d, *J* = 7.9 Hz, 3H), 0.96 (s, 6H), 0.81 (s, 3H). Anal. Calcd for $C_{19}H_{27}NO_2S$: C, 68.43; H, 8.16. Found: C, 68.34; H, 8.44.

Camphor *N*-[(1-methyl-3-hydroxypropyl)sulfonyl]imine (5d): elution with ether/*n*-pentane 7:3; yield 73% (oil mixture of diastereomers); $[\alpha]_D$ -31.6° (*c* 2.7, $CHCl_3$); IR (neat, cm^{-1}) 1640, 1310, 1140; ^1H NMR ($CDCl_3$) δ 3.67–4.00 (m, 2H), 3.30–3.50 (m, 1H), 2.95–3.14 (m, 1H), 1.20–2.10 (m, 12H), 0.96 (s, 6H), 0.82 (s, 3H). Anal. Calcd for $C_{14}H_{25}NO_3S$: C, 58.50; H, 8.77. Found: C, 58.41; H, 8.78.

Camphor *N*-[(1-methyl-2-ethyl-2-hydroxybutyl)sulfonyl]imine (5e): elution with ethyl acetate/*n*-hexane 2:8; yield 82% (oil mixture of diastereomers); $[\alpha]_D$ -30.93° (*c* 1.8, $CHCl_3$); IR (neat, cm^{-1}) 1640, 1380, 1140; ^1H NMR ($CDCl_3$) δ 4.24–4.30 (m, 1H), 3.42–3.50 (m, 1H), 3.00–3.14 (m, 1H), 2.50–2.62 (m, 1H), 0.7–2.15 (m, 27H). Anal. Calcd for $C_{17}H_{31}NO_3S$: C, 61.97; H, 9.48. Found: C, 61.93; H, 9.64.

Camphor *N*-[(1-methyl-2-hydroxy-2-phenylethyl)sulfonyl]imine (5f): elution with ethyl acetate/*n*-hexane 3:7; yield 80% (oil mixture of diastereomers); $[\alpha]_D$ -26° (*c* 2.0, $CHCl_3$); IR

(28) Field, L.; Grunwald, F. A. *J. Am. Chem. Soc.* **1953**, *75*, 934.
(29) Khorgami, M. H. *Synthesis* **1972**, 574.

(neat, cm^{-1}) 1640, 1310, 1140; ^{1}H NMR ($CDCl_3$) δ 7.25–7.50 (m, 5H), 5.78 (s, 1H), 4.50 (d, 1H), 2.98–3.40 (m, 3H), 2.48–2.70 (m, 1H), 0.8–2.2 (m, 16H). Anal. Calcd for $C_{19}H_{27}NO_3S$: C, 65.30; H, 7.79. Found: C, 65.70; H, 8.09.

Camphor *N*-[(1-phenylethyl)sulfonyl]imine (5g): elution with ether:*n*-pentane 3:7; yield 94% (oil mixture of diastereomers); $[\alpha]_D$ −8.9° (*c* 1.1, $CHCl_3$); IR (neat, cm^{-1}) 1645, 1314, 1128; ^{1}H NMR ($CDCl_3$) δ 7.29–7.52 (m, 5H), 4.38–4.48 (m, 1H), 2.72–2.94 (m, 1H), 2.21–2.37 (m, 1H), 1.60–2.00 (m, 5H), 1.05–1.40 (m, 3H), 0.54–0.98 (m, 9H). Anal. Calcd for $C_{18}H_{25}NO_2S$: C, 67.68; H, 7.89. Found: C, 67.43; H, 7.67.

Camphor *N*-[(1,2-diphenylethyl)sulfonyl]imine (5h): elution with ether:*n*-pentane 3:7; yield 84% (solid mixture of diastereomers); $[\alpha]_D$ −14.0° (*c* 2.3, $CHCl_3$); IR (KBr, cm^{-1}) 1640, 1310, 1140; ^{1}H NMR ($CDCl_3$) δ 7.0–7.45 (m, 10H), 4.45–4.55 (m, 1H), 3.78–3.88 (m, 1H), 3.34–3.50 (m, 1H), 2.74–2.96 (m, 1H), 2.25–2.43 (m, 1H), 1.58–2.00 (m, 3H), 0.35–1.45 (m, 11H). Anal. Calcd for $C_{24}H_{29}NO_2S$: C, 72.8; H, 7.39. Found: C, 72.56; H, 7.57.

10-[(*N*,*N*-Diisopropylamino)sulfonyl]camphor *N*-[(1-methylheptyl)sulfonyl]imine (6a): elution with ether:*n*-pentane 3:7; yield 82% (oil mixture of diastereomers); $[\alpha]_D$ −12.8° (*c* 1.1, $CHCl_3$); IR (neat, cm^{-1}) 1650, 1335, 1136; ^{1}H NMR ($CDCl_3$) δ 3.70–3.88 (m, 2H), 3.40 (d, *J* = 14.3 Hz, 1H), 2.52–3.20 (m, 5H), 1.20–2.20 (m, 19H), 1.12 (s, 3H), 0.82–0.95 (m, 6H). Anal. Calcd for $C_{24}H_{46}N_2O_4S_2$: C, 58.74; H, 9.45. Found: C, 58.66; H, 9.16.

10-[(*N*,*N*-Diisopropylamino)sulfonyl]camphor *N*-[(1-methyl-2-phenylethyl)sulfonyl]imine (6b): elution with ether:*n*-pentane 4:6; yield 30% (oil mixture of diastereomers); $[\alpha]_D$ −7.9° (*c* 1.2, $CHCl_3$); IR (neat, cm^{-1}) 1646, 1332, 1132; ^{1}H NMR ($CDCl_3$) δ 7.15–7.40 (m, 5H), 3.80 (m, 2H), 3.61 (m, 1H), 3.46 (d, *J* = 16.1 Hz, 1H), 3.38 (m, 1H), 3.05 (m, 1H), 2.86 (d, *J* = 16.1 Hz, 1H), 1.40–2.80 (m, 7H), 1.25–1.39 (m, 15H), 1.18 (s, 3H), 0.91 (s, 3H). Anal. Calcd for $C_{25}H_{40}N_2O_4S_2$: C, 60.45; H, 8.11. Found: C, 60.20; H, 7.86.

10-[(*N*,*N*-Diisopropylamino)sulfonyl]camphor *N*-[(1-phenylethyl)sulfonyl]imine (6g): elution with ether:*n*-pentane 3:7; yield 89% (solid mixture of diastereomers); $[\alpha]_D$ −12.3° (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) 1640, 1321, 1137; ^{1}H NMR ($CDCl_3$) δ 7.28–7.55 (m, 5H), 4.41 (q, *J* = 7.2 Hz, 1H), 3.75–3.92 (m, 2H), 3.49 (d, *J* = 15.6 Hz, 1H), 2.25–2.95 (m, 3H), 2.18 (d, *J* = 18.7 Hz, 1H), 0.80–2.00 (m, 4H), 1.85 (d, *J* = 7.2 Hz, 3H), 1.38 (d, *J* = 6.7 Hz, 6H), 1.36 (d, *J* = 6.7 Hz, 6H), 1.10 (s, 3H), 0.77 (s, 3H). Anal. Calcd for $C_{24}H_{38}N_2O_4S_2$: C, 59.72; H, 7.93. Found: C, 59.61; H, 7.69.

10-[(*N*,*N*-Diisopropylamino)sulfonyl]camphor *N*-[(1,2-diphenylethyl)sulfonyl]imine (6h): elution with ether:*n*-pentane 3:7; yield 84% (single isomer after recrystallization from ethanol); mp 180–182 °C; $[\alpha]_D$ −56.0° (*c* 2.0, $CHCl_3$); IR (KBr, cm^{-1}) 1629, 1335, 1124; ^{1}H NMR ($CDCl_3$) δ 6.98–7.45 (m, 10H), 4.49 (dd, *J* = 2.9, 12.1 Hz, 1H), 3.72–3.92 (m, 3H), 3.33–3.48 (m, 2H), 2.53–2.98 (m, 3H), 1.00–2.35 (m, 5H), 1.30–1.40 (m, 12H), 1.11 (s, 3H), 0.82 (s, 3H). Anal. Calcd for $C_{30}H_{42}N_2O_4S_2$: C, 64.48; H, 7.58. Found: C, 64.75; H, 7.32.

10-[(*N*,*N*-Diisopropylamino)sulfonyl]camphor *N*-[(1-phenyl-2-methylpropyl)sulfonyl]imine (6i): elution with ether:*n*-pentane 3:7; yield 68% (oil mixture of diastereomers); $[\alpha]_D$ −12.9° (*c* 1.5, $CHCl_3$); IR (KBr, cm^{-1}) 1643, 1332, 1138; ^{1}H NMR ($CDCl_3$) δ 7.25–7.50 (m, 5H), 4.06 (d, *J* = 7.8 Hz, 1H), 3.70–3.84 (m, 2H), 3.23 (d, *J* = 14.6 Hz, 1H), 2.70–2.90 (m, 1H), 2.40–2.60 (m, 1H), 2.30 (d, *J* = 19.7 Hz, 1H), 0.75–1.95 (m, 6H), 1.34 (d, *J* = 6.8 Hz, 6H), 1.33 (d, *J* = 6.8 Hz, 6H), 1.23 (d, *J* = 6.7 Hz, 3H), 1.11 (s, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.82 (s, 3H). Anal. Calcd for $C_{26}H_{42}N_2O_4S_2$: C, 61.14; H, 8.29. Found: C, 60.86; H, 8.03.

10-[(*N*,*N*-Diisopropylamino)sulfonyl]camphor *N*-[(1-phenyl-3-hydroxypropyl)sulfonyl]imine (6j): elution with ethyl acetate:*n*-pentane 4:6; yield 34% (oil mixture of diastereomers); $[\alpha]_D$ −18.7° (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) 1636, 1318, 1137; ^{1}H NMR ($CDCl_3$) δ 7.26–7.50 (m, 5H), 4.52 (dd, *J* = 2.8, 12.0 Hz, 1H), 3.68–3.80 (m, 3H), 3.31–3.42 (m, 1H), 3.30 (d, *J* = 16.0 Hz, 1H), 2.85 (d, *J* = 16.0 Hz, 1H), 1.40–2.90 (m, 10H), 1.25–1.38 (m, 12H), 1.08 (s, 3H), 0.80 (s, 3H). Anal. Calcd for $C_{25}H_{40}N_2O_5S_2$: C, 58.51; H, 7.86. Found: C, 58.15; H, 8.07.

10-[(*N*,*N*-Dicyclohexylamino)sulfonyl]camphor *N*-[(1-methylheptyl)sulfonyl]imine (7a): elution with ether:*n*-pentane 3:7; yield 61% (oil mixture of diastereomers); $[\alpha]_D$ −6.2° (*c* 1.2, $CHCl_3$); IR (neat, cm^{-1}) 1650, 1326, 1144; ^{1}H NMR ($CDCl_3$) δ 2.51–3.50 (m, 6H), 2.05–2.15 (m, 1H), 0.90–2.00 (m, 41H), 0.86 (s, 3H), 0.84 (s, 3H). Anal. Calcd for $C_{30}H_{54}N_2O_4S_2$: C, 63.12; H, 9.53. Found: C, 62.79; H, 9.17.

10-[(*N*,*N*-Dicyclohexylamino)sulfonyl]camphor *N*-[(1-phenylethyl)sulfonyl]imine (7g): elution with ether:*n*-pentane 3:7; yield 91% (solid mixture of diastereomers); $[\alpha]_D$ −4.2° (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 1638, 1320, 1135; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 4.35–4.48 (m, 1H), 2.05–3.55 (m, 7H), 0.60–2.05 (m, 33H). Anal. Calcd for $C_{30}H_{46}N_2O_4S_2$: C, 64.02; H, 8.24. Found: C, 63.74; H, 7.99.

10-[(*N*,*N*-Dicyclohexylamino)sulfonyl]camphor *N*-[(1,2-diphenylethanyl)sulfonyl]imine (7h): elution with ether:*n*-pentane 3:7; yield 82% (single isomer after recrystallization from ethanol); mp 184–186 °C; $[\alpha]_D$ −44.0° (*c* 1.8, $CHCl_3$); IR (KBr, cm^{-1}) 1632, 1326, 1144; ^{1}H NMR ($CDCl_3$) δ 6.98–7.45 (m, 5H), 4.48 (dd, *J* = 2.9, 15.8 Hz, 1H), 3.89 (dd, *J* = 2.9, 13.2 Hz, 1H), 3.22–3.50 (m, 4H), 2.52–2.95 (m, 3H), 1.00–2.30 (m, 30H), 1.11 (s, 3H), 0.83 (s, 3H). Anal. Calcd for $C_{36}H_{50}N_2O_4S_2$: C, 67.67; H, 7.89. Found: C, 67.33; H, 7.74.

10-[(*N*,*N*-Dicyclohexylamino)sulfonyl]camphor *N*-[(1-phenyl-2-methylpropyl)sulfonyl]imine (7i): elution with ether:*n*-pentane 3:7; yield 64% (oil mixture of diastereomers); $[\alpha]_D$ −20.4° (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) 1637, 1329, 1148; ^{1}H NMR ($CDCl_3$) δ 7.25–7.50 (m, 5H), 4.05 (d, *J* = 7.7 Hz, 1H), 0.80–3.40 (m, 32H), 1.24 (d, *J* = 7.4 Hz, 3H), 1.12 (s, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.81 (s, 3H). Anal. Calcd for $C_{36}H_{50}N_2O_4S_2$: C, 65.05; H, 8.53. Found: C, 64.95; H, 8.35.

General Procedure for the Hydrolysis of Sulfonylimines 5–7 to Sulfonamides 8. In a 100-mL, single-necked flask equipped with a magnetic stirring bar and reflux condenser was placed 0.5 mmol of the appropriate sulfonimine **5–7** (0.5 mmol) in 30 mL of EtOH followed by the addition of 30 mL of 18% HCl. After the oxidation was refluxed for 2–8 h, monitoring the reaction by TLC, the ethanol solvent was evaporated and 10 mL of saturated K_2CO_3 solution added to neutralize the acid. The solution was extracted with ethyl acetate (3 × 50 mL) and dried over $MgSO_4$. Evaporation of the solvent under vacuum gave the crude sulfonamide **8** which was purified by preparative TLC.

(*S*)-(−)-1-Methylheptanesulfonamide (8a): yield 93%; 42% ee; mp 44.0–45.0 °C; $[\alpha]_D$ −4.4° (*c* 3.8, EtOH); IR (KBr, cm^{-1}) 3350, 3248, 3108, 2978, 1601, 1312, 1161; ^{1}H NMR ($CDCl_3$) δ 4.70 (s, 2H), 3.01 (m, 1H), 1.38 (d, *J* = 8.6 Hz, 3H), 1.60–1.18 (m, 10H), 0.88 (m, 3H). Anal. Calcd for $C_8H_{19}NO_2S$: C, 49.70, H, 9.91. Found: C, 49.73; H, 9.76.

(*S*)-(−)-1-Methyl-2-phenylethanesulfonamide (8b): yield 88%; 22% ee; mp 85–6 °C; $[\alpha]_D$ −13.9° (*c* 0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3350, 3248, 3108, 2978, 1601, 1312, 1161; ^{1}H NMR ($CDCl_3$) δ 7.17–7.41 (m, 5H), 4.65 (s, 2H), 3.42–3.55 (m, 1H), 3.26–3.42 (m, 1H), 2.62–2.78 (m, 1H), 1.32 (d, *J* = 8.8 Hz, 3H). Anal. Calcd for $C_9H_{13}NO_2S$: C, 54.25; H, 6.58. Found: C, 54.03; H, 6.35.

(*S*)-(−)-1-Methyl-3-hydroxypropanesulfonamide (8d): yield 77%; 12% ee; oil; $[\alpha]_D$ −1.1° (*c* 1.0, acetone); IR (neat, cm^{-1}) 3489, 3342, 3260, 2978, 1601, 1310, 1137; ^{1}H NMR ($CDCl_3$) δ 6.07 (s, 2H), 3.88–3.96 (m, 1H), 3.61–3.75 (m, 2H), 3.15–3.27, (m, 1H), 2.18–2.34 (m, 1H), 1.55–1.22 (m, 1H), 1.36 (d, *J* = 6.6 Hz, 3H). Anal. Calcd for $C_4H_{11}NO_3S$: C, 31.36; H, 7.24. Found: C, 31.00; H, 6.92.

(*R*)-(−)-1-Methyl-2-ethyl-2-hydroxybutanesulfonamide (8e): yield 94%; 12% ee; mp 100–1 °C; $[\alpha]_D$ −7.3° (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3492, 3350, 3186, 2968, 1601, 1312, 1122; ^{1}H NMR ($CDCl_3$) δ 4.96 (s, 2H), 3.42 (q AB, *J* = 8.8 Hz, 1H), 3.28 (s, 1H), 1.50–2.00 (m, 4H), 1.45 (d, *J* = 8.8 Hz, 3H), 0.93 (t, *J* = 5.3 Hz, 6H). Anal. Calcd for $C_7H_{17}NO_3S$: C, 43.06; H, 8.77. Found: C, 43.38; H, 8.74.

(−)-1-Methyl-2-hydroxy-2-phenylethanesulfonamide (8f): yield 96% (solid, mixture of diastereomers); $[\alpha]_D$ = 1.7° (*c* 0.6, acetone); IR (KBr, cm^{-1}) 3472, 3410, 3322, 1313, 1145; ^{1}H NMR ($CDCl_3$) 7.30–7.50 (m, 5H), 6.15 (s, 2H), 5.18 (s, 1H), 4.80–4.90 (m, 1H), 3.30–3.45 (m, 1H), 1.00 (d, *J* = 7.9 Hz, 3H). Anal. Calcd for $C_9H_{13}NO_3S$: C, 53.71; H, 6.51. Found: C, 53.43; H, 6.45.

(*R*)-(−)-1-Phenylethanesulfonamide (8g): yield 91%; 75% ee; mp 105–7 °C; $[\alpha]_D$ +14.3° (*c* 1.4, $CHCl_3$); IR (KBr, cm^{-1}) 3273, 1653, 1329, 1162; ^{1}H NMR ($CDCl_3$) δ 7.36–7.50 (m, 5H), 4.33 (AB

q, J = 6.8 Hz, 1H), 2.44 (s, 2H), 1.83 (d, J = 6.8 Hz, 3H). Anal. Calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99. Found: C, 51.49; H, 5.75.

(*R*)-(−)-1,2-Diphenylethanesulfonamide (8h): yield 93%; 95% ee; mp 106–8 °C; $[\alpha]_D$ −53.2° (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3372, 3252, 3067, 2925, 1601, 1312, 1133; ^1H NMR ($CDCl_3$) δ 7.00–7.45 (m, 10H), 4.30–4.45 (m, 3H), 3.68–3.82 (m, 1H), 3.30–3.45 (m, 1H). Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79. Found: C, 64.09; H, 5.96.

(*R*)-(+)-1-Phenyl-2-methylpropanesulfonamide (8i): yield 89%; 90% ee; mp 78–80 °C; $[\alpha]_D$ +41.1° (*c* 1.2, $CHCl_3$); IR (KBr, cm^{-1}) 3347, 3258, 3124, 1317, 1135; ^1H NMR ($CDCl_3$) δ 7.30–7.60 (m, 5H), 4.32 (br, 2H), 3.91 (d, J = 9.8 Hz, 1H), 2.58–2.82 (m, 1H), 1.72 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H). Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09. Found: C, 55.97; H, 6.94.

(*R*)-(−)-3-Hydroxy-1-phenylpropanesulfonamide (8j): yield 91%; 66% ee; oil; $[\alpha]_D$ −4.5° (*c* 1.1 acetone); IR (neat, cm^{-1}) 3350, 3266, 3018, 1325, 1148; ^1H NMR ($CDCl_3$) δ 7.30–7.50 (m, 5H), 6.02 (s, 2H), 4.36 (dd, J = 2.7, 12.2 Hz, 1H), 3.79 (m, 1H), 3.60 (m, 1H), 3.28 (m, 1H), 2.58 (m, 1H), 2.25 (m, 1H). Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.21; H, 6.08. Found: C, 49.83; H, 5.95.

D_2O Quench. To the stirred solution of imine **2b** (0.06 g, 0.125 mmol) in 3 mL of THF was added dropwise 0.375 mL (0.375 mmol) of LDA at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and then the reaction was quenched by addition of 1.0 mL of D_2O. The mixture was diluted with 20 mL of EtOAc and 10 mL of H_2O, the organic phase was separated, and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. Removal of solvent gave an oil which solidified on standing, 57.3 mg (97%) of **2d**. The deuterium content was determined by integration of the α-sulfonyl protons at δ 4.33–4.48 (m, 1H) and the α-imino protons at δ 2.26 (s, 1H) using RD = 5 s. Similar results were observed using 2 and 3 equiv of *n*-BuLi and 6 equiv of LDA.

Racemization of 6h. To the stirred solution of 0.040 g (0.06 mmol) of imine **6h** ($[\alpha]_D$ −56.0°) in 3 mL of THF was added dropwise 0.18 mL (0.18 mmol) of LDA at −78 °C. The reaction mixture was stirred for 1 h, and the reaction was quenched by addition of 1.0 mL of saturated NH_4Cl. The mixture was diluted with 20 mL of EtOAc and 10 mL of water, the organic phase was separated, and the aqueous phase was extracted with 20 mL of EtOAc. The combined organic layers were washed with 20 mL of brine and dried over $MgSO_4$. Removal of solvent gave 0.04 g (100%) of **6h**; $[\alpha]_D$ −17.9° (*c* 1.0, $CHCl_3$). ^1H NMR indicated that this material had racemized.

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