state is also *Z*. In all the samples we have purchased or prepared, some of which were reputed to give (*E*)-enol OAA, we have failed to find any evidence for the (*E*)-enol. In all probability the lower melting form of OAA that others have taken to be (*E*)-enol OAA is really (*Z*)-enol OAA contaminated with impurities which readily form in solution during recrystallization efforts and depress the melting point. Based primarily on enzymatic evidence, the form of enol OAA in aqueous solution appears to also be *Z*.

Supplementary Material Available: Crystal data for di-*tert*-butyl oxalacetate and an ORTEP plot of (*Z*)-enol oxalacetic acid (4 pages). This material is contained in many 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.

Chemistry of Oxaziridines. 18. Synthesis and Enantioselective Oxidations of the [(8,8-Dihalocamphoryl)sulfonyl]oxaziridines[1,2]

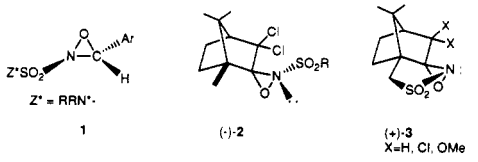
Franklin A. Davis,* Michael C. Weismiller, Christopher K. Murphy, R. Thimma Reddy, and Band-Chi Chen

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

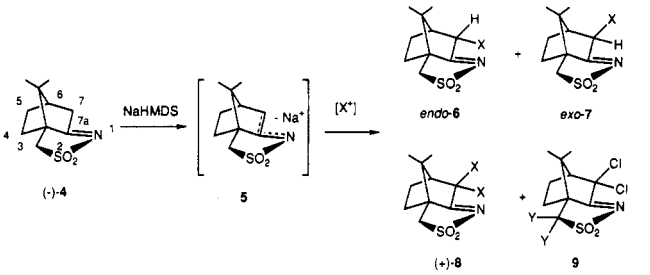
Received September 25, 1992

The synthesis and enantioselective oxidations of [(8,8-dihalocamphoryl)sulfonyl]oxaziridines [8,8-dichloro-1,7,7-trimethyl-2′-(phenylsulfonyl)spiro[bicyclo[2.2.1]heptane-2,3′-oxazinidine]] **13** are reported. These reagents are prepared in two steps from the (camphorylsulfonyl)imine **4** by treatment of the corresponding azaenolate with electrophilic halogen sources followed by biphasic oxidation of the resulting dihalo imine **6–9** with *m*-CPBA/K_2CO_3. Of these oxaziridines the dichloro reagent **13b**, available on a multigram scale, affords the highest enantioselectivities for the asymmetric oxidation of sulfides to sulfoxides (42–74%) and for the hydroxylation of enolates (often better than 95% ee). In general the molecular recognition is predicted and explained in terms of minimization of nonbonded steric interactions in the transition states. For the asymmetric oxidation of sulfides to sulfoxides, secondary electronic factors related to the polarity of the sulfide and oxaziridine also play a role. Definitive evidence for chelation of the metal enolate with the C–X bond in **13** is not found. The molecular recognition is interpreted in terms of the higher reactivity of the reagents and an active-site structure which is sterically complementary with the enolate. For the asymmetric hydroxylation of the *Z*- and *E*-enolates of propiophenone (**16a**), the *Z*-enolate exhibits much higher stereoselectivity than the *E*-enolate: >95% vs 22% ee.

Enantiopure *N*-sulfonyloxaziridines **1–3** are important asymmetric oxidants for the reagent controlled synthesis of enantiomerically enriched α-hydroxy carbonyl compounds, sulfoxides, selenoxides, and epoxides.[3] Not only is the product stereochemistry predictable, but the ee's often exceed 95%. Reflecting their dissimilar active site structures, these reagents exhibit quite different stereoselectivities in their asymmetric oxidations. Particularly useful in maximizing the efficiencies of these reagents has been the systematic modification of their active sites which has also provided important information concerning the origins of the molecular recognition. This has been especially true of the (camphorylsulfonyl)oxaziridine derivatives **3**, which are superior to types **1** and **2** for the asymmetric hydroxylation of enolates, where the dichloro and dimethoxy analogs (X = Cl, OMe) have been employed in the enantioselective syntheses (>95% ee) of biologically significant α-hydroxy carbonyl compounds.[4-8]



Scheme I



a, X = F; **b**, X = Cl; **c**, X = Br; **d**, Y = Cl

a, X = F; **b**, X = Cl; **c**, X = Br

This paper concerns the synthesis of the [(monohalocamphoryl)sulfonyl]oxaziridines **11–12** and [(dihalocamphoryl)sulfonyl]oxaziridines **13**, their stereoselective oxidations, and rationale for the molecular recognition.

Results and Discussion

Synthesis of the [(Halocamphoryl)sulfonyl]imines. The starting material for the synthesis of all the (camphorylsulfonyl)oxaziridine derivatives **3** is the (−)-(camphorsulfonyl)imine **4**, readily prepared on a large scale in two steps (>90%), from (+)-10-camphorsulfonic acid.[9,10]

(1) Taken in part from the Ph.D. Thesis of M. C. Weismiller, Drexel University, 1990.
(2) Part 17: Davis, F. A.; Reddy, R. T.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428.
(3) Reviews: (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.; Haque, S. M. Oxygen Transfer Reactions of Oxaziridines. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAL Press: Greenwich, CT, 1990; Vol 2, p 61.
(4) Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990**, *55*, 3715.
(5) Davis, F. A.; Kumar, A.; Chen, B. C. *Tetrahedron Lett.* **1991**, *32*, 867.
(6) Davis, F. A.; Kumar, A.; Chen, B. C. *J. Org. Chem.* **1991**, *56*, 1143.
(7) Davis, F. A.; Kumar, A. *Tetrahedron Lett.* **1991**, *32*, 7671.
(8) Davis, F. A.; Chen, B. C. *Tetrahedron Lett.* **1990**, *31*, 6823.

0022-3263/92/1957-7274$03.00/0

Table I. Halogenation of the (Camphorsulfonyl)imine 4

entry	equiv of Na-HMDS	halogen (equiv)	products (% isolated yields) [endo/exo ratio]
1	1.1	AcO–F (3.0)[a]	**6a/7a** (5–10) [7:3]
2	1.1	AcO–F (3.0)[a,b]	**6a/7a** (50) [7:3]
3	1.1	AcO–F (7–10)[a,b]	**6a/7a** (75) [7:3]
4	2.2	AcO–F (3.0)[a,b]	**6a/7a** (75) [7:3], **9d** (10)
5	1.1	NFOBS **10** (3.0)[c]	**6a/7a** (45) [46:54]
6	1.0	CCl_4 (1.0)	**6b/7b** (10–20) [1:1]
7	1.0	NCS (1.0	**6b/7b** (85) [8:2], **8b** (5)
8	1.2	NCS (1.0)	**6b/7b** (75) [8:2], **8b** (15)
9	2.5	NCS (2.5)[a]	**8b** (64), **9d** (8)
10	3.0	NCS (3.0)[a]	**8b** (20), **9d** (60)
11	3.0	NCS (3.0)[a,d]	**8b** (74), **4** (15)
12	1.0	CBr_4 (1.0)	**6c/7c** (85) [7:3]
13	1.0	NBS (1.0)	**6c/7c** (80) [7:3], **8c** (trace)
14	2.2	NBS (3.0)	**6c/7c** (20) [7:3], **8c** (60)
15	2.2	NBS (3.0)[a]	**8b** (80)

[a] Inverse addition. [b] THF solvent removed by distillation followed by addition of fresh THF. [c] Reference 14. [d] Quenched at −78 °C.

Our synthesis of the [(halocamphoryl)sulfonyl]imines **7–9**, outlined in Scheme I, involves the reaction of an electrophilic halogen (X^+) source with azaenolate **5**, generated by treatment of **4** with bis(trimethylsilyl)amide (NaHMDS).[11]

Addition of 1 equiv of *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) to the sodium azaenolate **5** afforded 80–85% yields of the *endo*-**6b**/*exo*-**7b** and *endo*-**6c**/*exo*-**7c** mixtures in ratios of 8:3 and 7:3, respectively (Table I, entries 7 and 13). Less than 5% of the corresponding dihalo imines **8b–c** were detected. All attempts to separate **6/7** failed. While replacing NCS with CCl_4 gave only low yields of products, CBr_4 afforded **6c/7c** exclusively (Table I, entry 12). The endo/exo ratios in these materials are readily determined by integration of the C-7 proton geminal to the chlorine or bromine atoms. The endo C-7 proton appears as a doublet at δ 4.7–4.9 ppm (J = 4.2–4.4 Hz) as a consequence of coupling with the C-6 proton whereas the exo C-7 proton is a singlet at δ 4.6–4.7 ppm. These assignments are consistent with similar results reported for borane and bromocamphor systems.[12] The imino C-7a carbon in these compounds appears in the region δ 190-196 ppm with C–N double bond absorption at 1640–1650 cm^{-1} in the infrared.

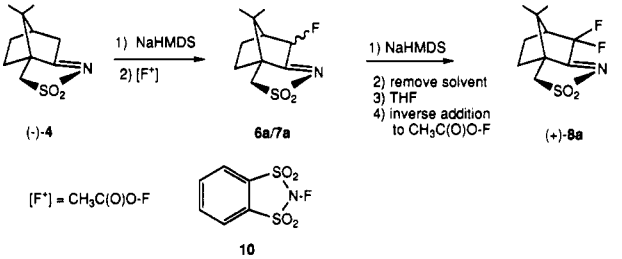
Dihalogenation was accomplished by addition of azaenolate **5**, generated by treatment of **4** with 2.2–3.0 equiv of NaHMDS, to 2–3 equiv of NCS or NBS. Direct addition of NCS or NBS to the azaenolate resulted in an incomplete reaction due likely to quenching of **5** by the acidic protons of the monohalogenated imines **6** and **7** (Table I, entry 14). With NCS mixtures of the di- and tetrachlorinated imines **8b** and **9d** resulted on warming to 0 °C prior to quenching (Table I, entries 9 and 10). Quenching at −78 °C eliminated **9d** affording the [(8,8-dichlorocamphoryl)sulfonyl]imine (**8b**) in 74% isolated yield following crystallization (Table I, entry 11). After completion of this work Gala and co-workers reported an improved synthesis of **8b** using 1,3-dichloro-5,5-dimethylhydantoin as the chlorinating agent and DBU to generate the enolate.[13]

Table II. Biphasic Oxidation of the (Camphorsulfonyl)imines to the (Camphorsulfonyl)oxaziridines with Saturated K_2CO_3

entry	imine	oxidant (equiv)	time, h	oxaziridine [% yield][a]
1	**6b/7b** (8:2)[b]	oxone (10)	2 days	**11b/12b** (2:8)[b] [76]
2	**6c/7c** (8:2)[b]	oxone (10)	2 days	(+)-**12c** [70]
3	**8a**	50% *m*-CPBA (1.5)	2	(+)-**13a** [90]
4	**8a**	95% *m*-CPBA (1.5)	<1	(+)-**13a** [91]
5	**8b**	50% *m*-CPBA (1.5)	8	(+)-**13b** [95]
6	**8b**	95% *m*-CPBA (1.5)	2	(+)-**13b** [92]
7	**8c**	oxone (10)		no reaction
8	**8c**	50% *m*-CPBA (1.5)	10	(+)-**13c** [50]
9	**8c**	95% *m*-CPBA (1.5)	3–4	(+)-**13c** [85]
10	**8c**[c]	95% *m*-CPBA (1.5)	4 days	(+)-**13c** [60]
11	**9**	95% *m*-CPBA (1.5)	3–4	(+)-**14** [82]

[a] Isolated yields. [b] Endo/exo ratio. [c] $KHCO_3$ buffer.

Attempts to prepare monofluoro imines **6a/7a** by treatment of azaenolate **5** with commercially available sources of electrophilic fluorine, *N*-fluoro-*N*-alkylsulfonamides or *N*-fluoropyridinum triflate failed, and addition of **5** to a 0 °C solution of acetyl hypofluorite ($CH_3C(O)OF$)[14] gave only trace amounts of the monofluoro compounds **6a/7a**. It was thought that the low yields resulted from preferential reaction of the fluorinating reagent with the hexamethyldisilazane byproduct. Indeed careful removal of the azaenolate solvent by distillation followed by addition of fresh, dry THF and addition to acetyl hypofluorite increased the yield of **6a/7a** to 50–75% (Table I, entries 2–4). Use of *N*-fluoro-*o*-benzenedisulfonimide [NFOBS] **10**, a more convenient stable source of "electrophilic" fluorine, gave on addition to the azaenolate **6a/7a** in 45% yield, and removal of the hexamethyldisilazane byproduct was not required (Table I, entry 4).[15] The geminal proton in *endo*-**6a** appears as a pair of doublets at δ 5.40 and 5.61 ppm as a consequence of coupling with both the fluorine and C-6 proton. In *exo*-**7a** this proton appears as a doublet at δ 5.15 (J = 52 Hz). Despite the use of a large excess of the fluorinating reagents only monofluorination was observed (Table I, entries 2–4). Difluoro imine **8a** was prepared in 50% yield by treatment of monofluoro imines **6a/7a** with NaHMDS followed by addition to 7–10 equiv of acetyl bypofluorite.



Synthesis of [(Halocamphoryl)sulfonyl]oxaziridines. Biphasic oxidation of imines **6–9** with oxone (potassium monoperoxysulfate) or *m*-chloroperbenzoic acid (*m*-CPBA) buffered with saturated K_2CO_3 affords the corresponding oxaziridines **11–14** in good to excellent yields (Table II). Oxidation of **6b/7b** (8:2) with oxone gives *endo*/*exo*-**11b/12b** with the ratios reversed, i.e. 2:8 (Table II, entry 1). All attempts to separate the oxaziridine mixtures by TLC or HPLC failed. Oxidation of **6c/7c** (7:3) with oxone gives only the *exo*-bromooxaziridine **12c** (entry

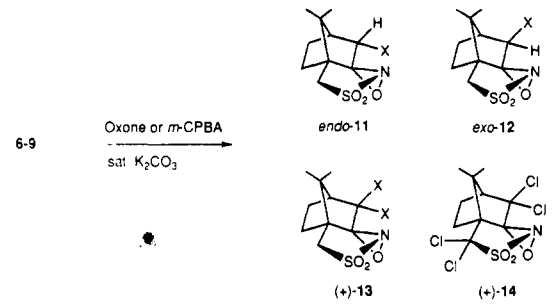
(9) Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Sheppard, A. C.; Davis, F. A. *Org. Synth.* **1990**, *69*, 158.
(10) Available from Aldrich.
(11) The chlorination and bromination of **4** has previously been described earlier. Armstrong, H. E.; Lowry, T. M. *J. Chem. Soc.* **1902**, *81*, 1441.
(12) Daniel, A.; Pavai, A. *Bull. Chem. Soc. Fr* **1971**, 1060. Beque, J.; Charpentier-Morize, M.; Pardo, C.; Sansoulet, J. *Tetrahedron* **1978**, *34*, 293.
(13) Mergelsberg, I.; Gala, D.; Scherer, D.; DiBenedetto, D.; Tanner, M. *Tetrahedron Lett.* **1992**, *33*, 161.
(14) Rozen, S.; Brand, M. *Synthesis* **1985**, 665.
(15) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1991**, *32*, 1631. Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153.

Table III. Asymmetric Oxidation of Sulfoxides by Oxaziridines 11–14 at 20 °C for 1 h[a]

entry	oxaziridine	solvent	% ee of sulfoxide (configuration)			
			p-Tol-S(O)-Me	p-Tol-S(O)-Bu-n	9-anthryl-S(O)-Me	$PhCH_2$-S(O)-Me
1	(+)-15	CH_2Cl_2	4 (S)	2 (S)	66 (S)	22 (S)
2		CCl_4	8 (S)	1 (S)	80 (S)	25 (S)
3	(+)-12c (X = Br)	CCl_4	16 (S)	2 (S)		
4	(+)-13a (X = F)	CH_2Cl_2	50 (S)	60 (S)	62 (S)	
5		CCl_4	64 (S)	75 (S)	75 (S)	
6	(+)-13b (X = Cl)	CH_2Cl_2	42 (S)	54 (S)	42 (S)	20 (S)
7		CCl_4	67 (S)	74 (S)	69 (S)	21 (S)
8	(+)-13c (X = Br)	CH_2Cl_2	59 (S)	61 (S)	24 (S)	
9		CCl_4	67 (S)	76 (S)	50 (S)	
10	(+)-14 (X = Cl)	CH_2Cl_2	20 (S)	24 (S)	31 (S)	
11		CCl_4	21 (S)	22 (S)	30 (S)	

[a] Isolated yields 85–90%.

2). Not unexpectedly the *exo*-imines **7** are oxidized at a faster rate than the *endo*-imines **6**, and apparently exclusively in the case of the more bulky bromo derivative **7c**. Under the basic oxidation conditions *endo*/*exo*-**6**/**7** are in equilibrium via their azaenolates resulting in the preferential oxidation of the *exo*-imines to the *exo*-oxaziridines. This was confirmed by treatment of pure *exo*-imine **7c**, obtained by reduction of oxaziridine **12c** with sodium thiosulfate, with saturated K_2CO_3/toluene to afford **6c**/**7c** (8:2)

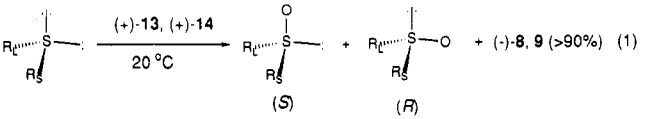


The dihalo and tetrachloro imines **8** and **9** were oxidized to oxaziridines **13** and **14** in good to excellent yield using the *m*-CPBA/saturated K_2CO_3 protocol (Table II). Good yields required the use of a K_2CO_3 buffer because the pH (9.5) is higher than that which is possible with $KHCO_3$ (pH 7.5). Use of a Morton flask ensures efficient mixing and is also necessary for good yields. Oxidation with 95% or technical grade (50%) *m*-CPBA affords good to excellent yields of the difluoro- and dichlorooxaziridines **13a** and **13b**, with the rate of oxidation being faster with 95% *m*-CPBA (Table II, entries 3–6). No reaction occurred on oxidation of the bromo imine **8c** with oxone, and with 50% *m*-CPBA the oxidation was incomplete (Table II, entries 7 and 8). It is interesting to note that Verfürth and Herrmann were unable to oxidize **8b–c** to **13b–c** using the *m*-CPBA/Na_2CO_3 system.[16] Oxaziridine **13b** has also been prepared on a larger scale by oxidation of **8b** with peracetic acid/K_2CO_3 using the phase-transfer catalyst Aliquat 336.[13]

The ^1H NMR spectra of **11**/**12** are quite similar to the starting imines in that the endo C-3 proton appears as a singlet (δ 4.0–4.57 ppm) and the exo C-3 proton in **12b** as a doublet at δ 4.89 ppm (J = 4.3 Hz). An upfield shift of the imino carbon from ca. 189–195 to 94–101 ppm in the oxaziridine is also characteristic of these materials.

Asymmetric Oxidation of Sulfides to Sulfoxides. The sulfide oxidations by **13–14** are summarized in Table III. Values for the dihydro analog (−)-(camphorylsulfonyl)oxaziridine (**15**) are also included for comparison.

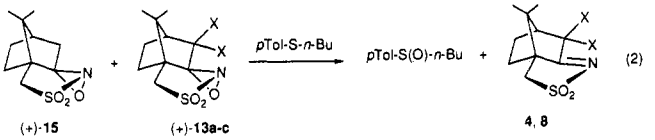
These oxidations were carried out by treating the sulfide with an equivalent amount of the oxaziridine in the appropriate solvent at 20 °C (eq 1). The sulfoxides were



(1)

separared from the corresponding sulfonimines **8** and **9** by preparative TLC in 85–95% isolated yields and the enantiomeric purity determined using the a chiral shift reagent [Eu(hfc)] and by use of a chiral Pirkle HPLC column. The absolute configurations were established by comparison with authentic samples and with the literature as previously described.[2]

The stereoselectivities for these oxidations proved to be solvent dependent, with higher ee's being observed in CCl_4 than CH_2Cl_2 (Table III). Similar results were observed for oxidations by **2**, and it was argued that the slower rates observed in the nonpolar solvents favored a later transition state (Hammond postulate) where steric effects become more important.[2] The rates of oxidation by **13–14** were considerably faster than **2**, being complete within 1 h vs 1–48 h. The relative rates of oxidation by **13a–c** are in the expected order of H < Br < Cl < F (1:3:10:>15), and were determined in a competition experiment carried out by oxidation of *n*-butyl *p*-tolyl sulfide with a mixture of 1 equiv of **15** and **13a–c** (eq 2). These results are consistent with earlier findings where electronegative groups attached to the oxaziridine carbon in *N*-sulfonyloxaziridines increased the rates of oxidation.[17]



(2)

Theoretical[18,19] and experimental[17] studies support an S_N2 type mechanism for transfer of oxygen from *N*-sulfonyloxaziridines to nucleophiles. The theoretical studies, however, failed to detect any stereoelectronic influences that might favor a particular transition state orientation (planar or spiro) for the oxidation of sulfoxides to sulfones[19] or for the epoxidation of alkenes.[18] It was concluded that molecular recognition is largely steric in origin dictated by the substituents on both the oxaziridine and substrates. These results have recently been confirmed experimentally in studies of the asymmetric oxi-

(16) Verfurth, U.; Herrmann, R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2919.

(17) Davis, F. A.; Billmers, J. M.; Gosciniak, D. J.; Towson, J. C.; Bach, R. D. *J. Org. Chem.* **1986**, *51*, 4240.

(18) Bach, R. D.; Wolber, G. *J. Am. Chem. Soc.* **1984**, *106*, 1410.

(19) Bach, R. D.; Coddens, B. A.; McDouall, J. J. W.; Schlegel, H. B.; Davis, F. A. *J. Org. Chem.* **1990**, *55*, 3325.

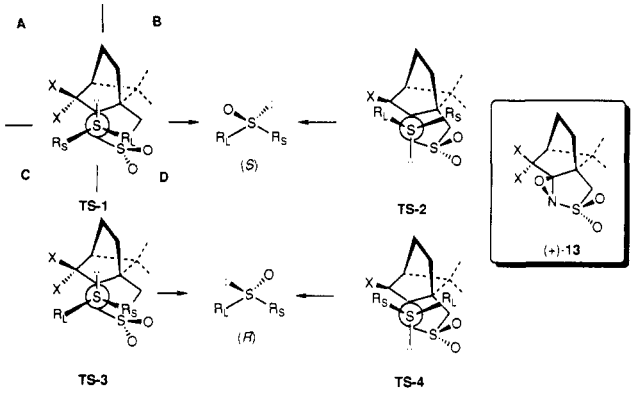


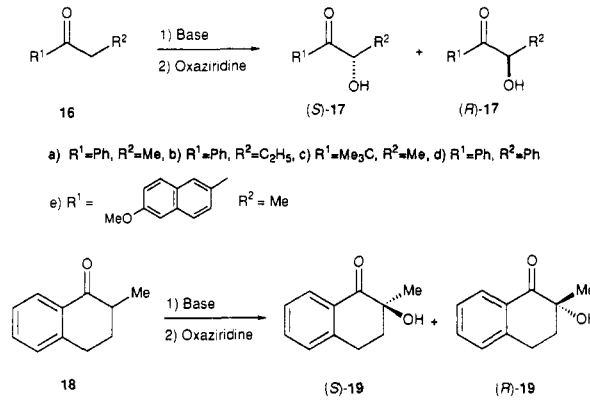
Figure 1. Transition-state structures for the oxidation of sulfides to sulfoxides by **13**.

dation of sulfides to sulfoxides by oxaziridine **2**.[2] Here it was found that the molecular recognition was predictable using a simple active-site model where the nonbonded steric interaction between the large (R_L) and small (R_S) groups of the sulfide (R_L–S–R_S) and the active-site surface of the oxaziridine are minimized in a planar transition-state structure.

The related planar transition-state structures for the oxidation of sulfides to sulfoxides by **13** are shown in Figure 1. In an earlier study of the oxidation of sulfides to sulfoxides by **15** it was concluded that only quadrant B is occupied by a large group (the 5–6 carbon–carbon bridge) based on the low ee's (Table III, entries 1 and 2).[20] Only when R_L in the sulfide is the bulky 9-anthryl group do the unfavorable nonbonded interactions in quadrant D in **TS-4** become significant, resulting in higher ee's. Not surprisingly *exo*-bromo derivative (–)-**12c**, where the bromine atom is directed away from the active site, gave results very similar to **15** (Table III, entry 2). The ee's for the oxidation of alkyl *p*-tolyl sulfides by dihalo oxaziridine **13a–c** increased significantly compared to **15**. Since the (*S*)-sulfoxides are favored, this must mean that transition states **TS-1** and **TS-2** are favored over **TS-3** and **TS-4**, with **TS-1** being the most favorable from a steric perspective. The increase in asymmetric induction due to the X substituent can in part be ascribed to an increase in the steric bulk of quadrant A which favors **TS-1** with respect to the other transition states. However, this can be only part of the answer because the van der Waals radius of the fluorine atom in **13a** is not much bigger than that of the hydrogen atom in **15** (1.35 vs 1.2) yet their ee's for **13a** are quite different (Table III). This result, as well as the solvent influence on the ee's, can be ascribed to secondary, electronic effects caused by the polarity of the oxaziridine and the aromatic sulfide. Note that solvent effects are observed only for the halo oxaziridines **13a–c** and for those sulfides where an aryl group is directly attached to sulfur. Alkyl aryl sulfides (methyl pheny sulfide) generally have higher dipole moments than dialkyl sulfides (diethyl sulfide), i.e. 5.34 vs 1.5 μ.[21]

Tetrachloro oxaziridine (–)-**14** gives low levels of asymmetric induction for the oxidation of sulfides to sulfoxides (Table III, entries 10 and 11). Increasing the size of quadrant D increases the energies of **TS-1** and **TS-2**.

Asymmetric Hydroxylation of Enolates. The asymmetric hydroxylations of acyclic ketone enolates of propiophenone (**16a**), butyrophenone (**16b**), 2,2-dimethyl-3-pentanone (**16c**), deoxybenzoin (**16d**), 1-(6-methoxy-2-naphthyl)ethanone (**16e**), and 2-methyl-1-tetralone (**18**) by (+)-**13a–c** and (+)-**15** are summarized in Table IV. Formerly we had shown that the *Z*-geometry (>95%) is preferred for the sodium and lithium enolates of **16a** and **16c**, and by analogy a similar preference is anticpated for the enolates of **16b** and **16e**. Enolate hydroxylations were carried out as previously described by addition of 1.2–1.5 equiv of the oxaziridine to the preformed enolate at –78 °C.[4,22] The progress of the reaction was monitored by TLC and quenched at –78 °C by addition of NH_4Cl solution. In general hydroxylations at this temperature were complete within 20 min. The products were isolated by preparative TLC and the ee's and absolute configurations determined by comparison with literature values and/or chiral shift reagents.



Hydroxylation of the sodium enolate of deoxybenzoin **16d** at –78 °C with **13b** was sluggish, requiring in excess of 1 h for complete reaction. In addition to the expected hydroxy ketone **17d** (25% ee) a 49% yield of 2-chloro-2-phenylacetophenone (**20**) was also obtained (Table IV, entry 27). Addition of the enolate to the oxaziridine eliminated **20** and improved the yield of **17d** from 40 to 70% (entry 27). The only other instance where an α-chloro derivative was detected was in the hydroxylation of the potassium enolate of 2-methyl-1-tetralone (**18**) giving **21** in 15% yield (entry 44). These products arose via chlorination of the enolate by the byproduct [(dichorocamphoryl)sulfonyl]imine (+)-**8b**. Indeed treatment of the enolates of 2-methyl-1-tetralone (**18**) with (+)-**8b** afforded **21** in addition to the monochloro imines **6b**/**7b** (Table V). Warming of the Li^+ and Na^+ enolates of **18** was necessary for chlorination, indicating that the reaction is quite slow relative to oxidation. Although (+)-**8b** is potentially a chiral chlorinating agent, products **20** and **21** were racemic. It is interesting to note in these examples, Table V, that small amounts of racemic 2-hydroxy-2-methyl-1-tetralone (**19**) were also formed resulting from hydrolysis of **21**; i.e. treatment of **21** under the reaction conditions affords **19**.[23]

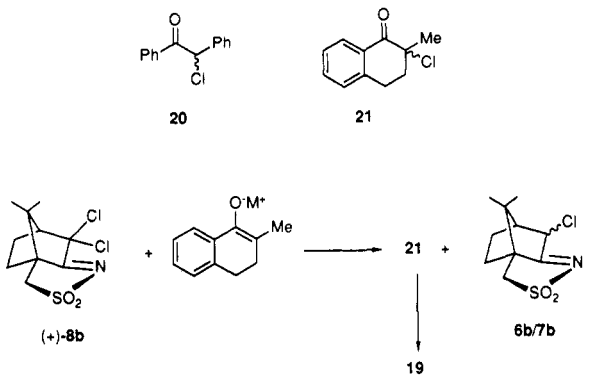
The results summarized in Table IV suggest a number of trends. First, that lithium enolates are less reactive than sodium enolates for hydroxylations by (+)-(camphorylsulfonyl)oxaziridine (**15**) [tetrahydro-9,9-dimethyl-4*H*-4a,7-methanooxazirino[3,2-*i*][2,1]benzisothiazole 3,3-dioxide] as evidenced by the fact that it was necessary to warm the mixtures to 0 °C for complete reaction in several

(20) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477.

(21) McCellan, A. L. *Tables of Experimental Dipole Moments*; W. H. Freeman: San Francisco, 1963; Vol. 1; Rahara Enterprises: El Cenito, CA, 1989; Vols. II and III.

(22) Davis, F. A.; Shappard, A. C.; Chen, B.-C.; Haque, S. M. *J. Am. Chem. Soc.* **1990**, *112*, 6679.

(23) For a discussion of α-chloro ketone hydrolysis, see: De Kimpe, N.; Verhe, R. In *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1988; Appendix to Chapter 1.



cases (Table IV, entries 1, 14, 19, and 33–36). Second, as was observed for the oxidation of sulfides to sulfoxides the dihalo oxaziridines **13a–c** were more reactive than the dihydro reagent (+)-**15** since hydroxylation occurs at −78 °C. The tetrasubstituted enolate of 2-methyl-1-tetralone (**18**) was more difficult to form than the acyclic trisubstituted enolates of **16a–e**, and warming to 0 °C was necessary.

The highest stereoselectivities for the asymmetric hydroxylation of the related lithium or sodium enolates of propiophenone (**16a**), butyrophenone (**16b**), and 1-(6-methoxy-2-naphthyl)ethanone (**16e**) were observed with (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine **13b** giving the corresponding (*S*)-hydroxy ketones **17a**, **17b**, and **17e** in better than 95% ee (Table IV, compare entries 1 and 2 with 7 and 8). Slightly lower results (80–94% ee) were noted for difluoro (+)-**13a** and dibromo (+)-**13c** oxaziridines with the enolate of propiophenone (**16a**) (entries 5, 6 and 12, 13). However, (+)-**13b** gave much poorer results for the hydroxylations of the enolates of 2,2-dimethyl-3-pentanone (**16c**), 2–16% ee, and deoxybenzoin (**16d**), 21–36% ee, where oxaziridine (+)-**15** gave the best results (90–95% ee).[22]

The dichloro oxaziridine (+)-**13b** also afforded (*R*)-2-hydroxy-2-methyl-1-tetralone (**19**) in better than 95% ee on hydroxylation of the corresponding enolate where (+)-**15** gave **19** in 16–30% ee (Table IV, compare entries 40, 42 with 33–37). This result is particularly significant considering the fact that the 2-hydroxy-1-tetralone ring system is a prototype for those found in many natural products including the anthacycline antitumor antibiotics.[3b] Indeed the asymmetric enolate oxidation protocol using **13b** has been employed in highly enantioselective syntheses of the AB rings of rhodomycinones,[6] adriamycin and daunomycin,[5] aklavinone,[7] and the homoisoflavanones.[8] It was observed in these studies that high ee's (>95%) were obtained for the hydroxylation of a variety of 2-substituted 1-tetralone enolates (Me, Et, $PhCH_2$), although substitution of a methoxy group into the 8-position of the tetralone ring lowered the stereoselectivity to 83%.[5-8]

Molecular recognition for the asymmetric hydroxylation of acyclic ketone (propiophenone, deoxybenzoin) and cyclic enolates (tetralones, chromones) by (camphorylsulfonyl)-oxaziridine derivatives **3** has been interpreted in terms of "open" or "nonchelated" transition-state structures **TS-1** to **TS-4**, respectively (Figure 2).[24] Based on the structure reactivity trends it was argued that the primary transition-state control element is steric in origin, as observed for other enantioselective oxidations by these reagents.[3] It was assumed that regardless of the actual solution structure of the enolate the enolate–oxygen metal aggegate

(24) For a discussion of the assumptions that went into this model see ref 22.

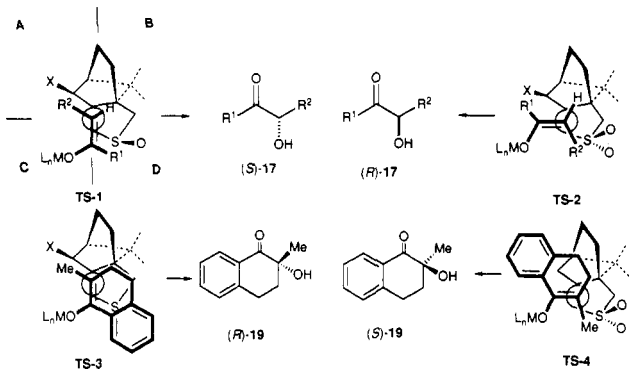
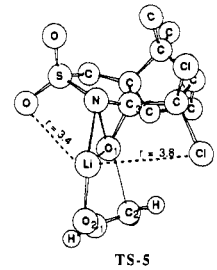


Figure 2. Transition-state structures for the hydroxylation of acyclic *Z*-ketone enolates of **16** and **18**.

was sterically the most demanding group in the vicinity of the enolate C–C bond. While these "working models" proved useful in rationalizing the molecular recognition in a number of examples (vide infra), the influence of the reaction parameters (counterion, solvent, cosolvents, etc.) on the stereoselectivities was often unpredictable.[3b,22]

Molecular orbital calculations, by Bach and co-workers, at the HF/6-31+G*//HF/4-31+G level revealed that oxidation of the monomeric lithium enolate of acetaldehyde proceeds by S_N2 attack of the β-carbon on the enolate along the O–N bond of the parent oxaziridine.[25] In this transition state, the lithium cation is coordinated not only to the enolate oxygen atom but to the oxaziridine oxygen and nitrogen atoms as well, i.e. a closed transition state. In these studies a more realistic view of the actual bonding interactions involved was estimated by appending the ab initio geometry to the X-ray geometry of **15** giving **TS-5**. In this idealized geometry the Li–Cl and Li–sulfonyl oxygen bond distances are too long to provide effective transition-state stabilization via chelation. It was argued, however, that twisting about the O_1–C_2 in **TS-5** could bring the lithium cation sufficiently close to the sulfonyl oxygen or the Cl substituent to result in significant TS stabilization.



The effects of cation variations, addition of HMPA, and inclusion of chelating groups in the oxaziridine can all be accommodated by the "closed" transition-state model. Optimal stereoselectivity should be attained by selecting a metal cation which provides maximum binding of the reactants in the transition state. A strongly coordinating solvent such as HMPA will inhibit effective chelation in the transition state and lower the ee's, as was observed experimentally.[25,26] If the metal cation in **TS-5** is also coordinated to Cl (X) or a sulfonyl oxygen, the enolate must react as a monomer; reactivity would then be independent of aggregation. The relevant energies and reaction

(25) Bach, R. D.; Andres, J. L.; Davis, F. A. *J. Org. Chem.* **1992**, *57*, 613.

(26) For recent studies on the influence of HMPA on anion aggregation see: Collum, D. B. *Acct. Chem. Res.* **1992**, *25*, 448. Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1992**, *114*, 403.

Table IV. Asymmetric Hydroxylation of Enolates Using Oxaziridines 13–15 at −78 °C in THF

entry	ketone (R^1/R^2)	oxaziridine	base	% ee (config), % isolated yield $R^1COCH(OH)R^2$ (17, 19)	% ee (config), % isolated yield $R^1COCH(Cl)R^2$ (20)
1	**16a** (Ph/Me)	(+)-**15**[a]	LDA[b]	40 (*S*), 45	
2			NaHMDS	62 (*S*), 73	
3			NaHMDS/HMPA[c]	50 (*S*), 77	
4			KHMDS	47 (*S*), 85	
5		(+)-**13a** (X = F)	LDA	90 (*S*), 68	
6			NaHMDS	94 (*S*), 71	
7		(+)-**13b** (X = Cl)	LDA[d]	95 (*S*), 69	
8			NaHMDS	95 (*S*), 70	
9			NaHMDS/HMPA[c]	62 (*S*), 38	
10			KHMDS	59 (*S*), 40	
11		(−)-**13b** (X = Cl)	NaHMDS	93 (*R*), 65	
12		(+)-**13c** (X = Br)	LDA[d]	80 (*S*), 61	
13			NaHMDS	90 (*S*), 51	
14		(+)-**14**	NaHMDS[b]	8 (*S*), 45	
15	**16b** (Ph/*n*-C_3H_7)	(+)-**15**[e]	LDA	37 (*S*),[f] 35	
16			NaHMDS	53 (*S*), 73	
17		(+)-**13b** (X = Cl)	LDA	88 (*S*), 78	
18			NaHMDS	95 (*S*), 76	
19	**16c** (Me_3C/Me)	(+)-**15**[a]	LDA[b]	32 (*R*), 55	
20			NaHMDS	89 (*R*), 71	
21			KHMDS	30 (*R*), 45	
22		(+)-**13b**[e] (X = Cl)	LDA	2 (*R*), 48	
23			NaHMDS	13 (*R*), 42	
24			KHMDS	no reaction	
25	**16d** (Ph/Ph)	(+)-**15**[a]	NaHMDS	95 (*S*), 71	
			NaHMDS/HMPA[c]	63 (*S*), 78	
26			KHMDS	93 (*S*), 73	
27		(+)-**13b** (X = Cl)	NaHMDS	25 (*S*) [31],[g] 40 [70]	49 [0][g]
28			NaHMDS/HMPA[g]	36 (*S*), 40	
29			KHMDS[g]	21 (*S*), 71	
30	**16e**	(+)-**13b** (X = Cl)	LDA		
31			NaHMDS	>95 (*S*), 56	
32			KHMDS	64 (*S*), 75	
33	**18**	(+)-**15**[a]	LDA[b,d]	30 (*R*), 82	
34			LDA/HMPA[b–d]	4 (*S*), 80	
35			NaHMDS[b,d]	16 (*R*), 90	
36			NaHMDS/HMPA[b–d]	22 (*R*), 70	
37			KHMDS	6 (*R*), 76	
38		(+)-**13a**[e] (X = F)	LDA[d]	65 (*R*), 65	
39			NaHMDS[d]	62 (*R*), 70	
40		(+)-**13b** (X = Cl)	LDA[d]	>95 (*R*), 60	
41			LDA/HMPA[b,c]	55 (*R*), 49	
42			NaHMDS[d]	>95 (*R*), 66	
43			NaHMDS/HMPA[c,d]	91 (*R*), 60	
44			KHMDS	60 (*R*), 61	14
45			NaHMDS[b,d]	56 (*R*), 68	
46		(−)-**13b** (X = Cl)	NaHMDS	>95 (*R*), 70	
44		(+)-**13c** (X = Br)	LDA[d]	75 (*R*), 70	
45			NaHMDS[b,d]	80 (*R*), 58	
46		(+)-**14**	NaHMDS[b,d]	no reaction	

[a] Ref 22. [b] Oxidation warm to 0 °C before quenching. [c] Ratio THF/HMPA of 20:1, 3.5 equiv of HMPA/ketone. [d] Enolate generated at 0 °C for 30 min and then cooled to −78 °C prior to addition of oxaziridine. [e] This work. [f] % ee determined on the acetate. [g] Inverse addition.

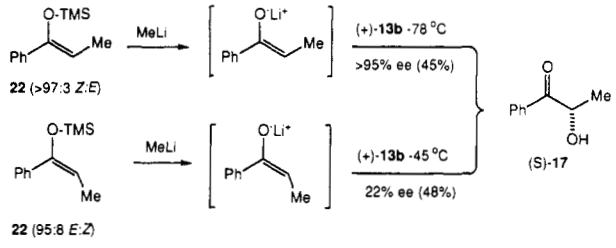
Table V. Chlorination of 2-Methyl-1-tetralone (18) by (+)-8b

enolate M^+	temp (°C)	products (% yield)
Li	−78	no reaction
	0	**21** (16), **6a/7b** (18), **19** (4)
Na	−78	no reaction
	0	**21** (34), **6a/7b** (40), **19** (4)
K	−78	**21** (20), **6a/7b** (21), **19** (5)
	0	**21** (35), **6a/7b** (43), **19** (15)

rates could favor breakdown of higher aggregates to permit reaction of enolate monomers via **TS-5**. Alternatively, reaction could occur via a less highly organized TS involving higher aggregates.

Transition-state structures **TS-1** to **TS-4** can best approximate the geometric constraints of the calculated transition state, i.e. coordination of the metal to enolate oxygen and the oxaziridine oxygen and nitrogen atoms (Figure 2). From a steric perspective **TS-1** and **TS-3** are favored giving the stereochemically observed *S* and *R* products **17a–b,d,e** and **19**, respectively. This must also mean that there are few if any adverse nonbonded interactions between the phenyl (naphthyl) group (R^1) and the aromatic tetralone ring and the sulfonyl group oxygen in **13a–c** and **15**. The aromatic rings in these compounds are considered to be coplanar with the enolate C–C double bond. However when R^1 is *tert*-butyl group, **16c**, this interaction becomes unfavorable leading to (*R*)-4,4-hydroxy-2,2-dimethyl-3-pentanone (**17c**) via the less favorably organized **TS-2**. Replacement of X in **TS-1** by a halogen apparently increases the size of quadrant A and the energy of **TS-2** and **TS-4** relative to **TS-1** and **TS-3** resulting in higher ee's for the enolates of **16a** (R^2 = Me), **16b** (R^2 = *n*-C_3H_7), and **18**. When R^2 in series **16** becomes a Ph group, **16d**, the ee's are lower as a consequence of unfavorable interactions between the X substituent and R^2 in the enolate. Likewise the lower ee's on oxidation of

Scheme II



the enolate of **16b** (R^1 = *tert*-butyl) can be explained by the adverse interaction of the bulky *tert*-butyl group and the Cl substituent in **13b**.

While the observed stereoselectivity trends summarized in Table IV can largely be accounted for in terms of nonbonded interactions, other factors undoubtedly also have a role. The remarkable increase in stereoselectivity for the hydroxylation of the propiophenone (**16a**), butyrophenone (**16b**), 1-(6-methoxy-2-naphthyl)ethanone (**16e**), and 2-methyl-1-tetralone (**18**) enolates by the dihalo oxaziridines (+)-**13a–c** cannot only be ascribed to favorable nonbonded interactions in the transition state, but also to the fact that **13a–c** are more reactive reagents compared to (+)-**15**. Indeed, hydroxylation with (+)-**13b** (X = Cl) of **18** at −78 °C affords hydroxytetralone **19** in >95% ee while at 0 °C the ee was 56% (Table IV, compare entries 40, 41 with 45).

Another factor that needs to be considered in the stabilization of **TS-1** and **TS-3** (Figure 2) is chelation of the metal enolate to the halogen X in **13a–c**, i.e. **TS-5**. Indeed there is a considerable body of information which suggests that metal chelation to carbon–halogen bonds can be important, particularly with C–F bonds.[28,29] The calculated (HF/6-31G*) lithium Me-X---Li^+ energies for MeCl and MeF are 21.6 and 35.1 kcal/mol, respectively,[25] which agrees quite well with the experimentally determined gas-phase lithium affinities of 24 and 31 kcal/mol.[27] These results suggest therefore that chelation of the metal enolate to difluoro oxaziridine (+)-**13a** should be more effective than to dichloro oxaziridine (+)-**13b** (X = Cl). Experimentally, however, the observed ee's for the hydroxylation of the sodium enolate of 2-methyl-1-tetralone (**19**) by oxaziridine **13** and **15** are in the order of Cl (>95%) > Br (80%) > F (62%) ≫ H (16%) (see Table IV). While these results certainly do not rule out the possibility of some contribution to transition-state stabilization by chelation of the metal enolate to the halogen in **13**, it is not necessary to evoke it in order the explain the enhanced stereoselectivity. *Indeed the enhanced molecular recognition exhibited by the dihalo oxaziridines 13 can best be explained in terms of higher reactivity allowing enolate hydroxylations to proceed at −78 vs 0 °C, and an optimum shape or size of the active site which is complementary to the metal enolate.*

Influence of the Metal Enolate Geometry. Initial studies with (+)-**15** suggested that the *Z*-enolate of propiophenone (**16a**) gave higher enantioselectivities than the *E*-enolate.[22] However, this conclusion remains tentative because the ee's were very low (4–35%). In this work, oxidation of the Li enolate of propiophenone with (+)-**13b** (X = Cl) gave the α-hydroxy ketone **17a** in >95% ee (Table IV, entry 7). Thus it is now possible to reexamine the asymmetric oxidation of the *E*- and *Z*-enolates of propiophenone (**16a**) with (+)-**13b** to definitely establish the influence of the enolate geometry on the stereoselectivity.

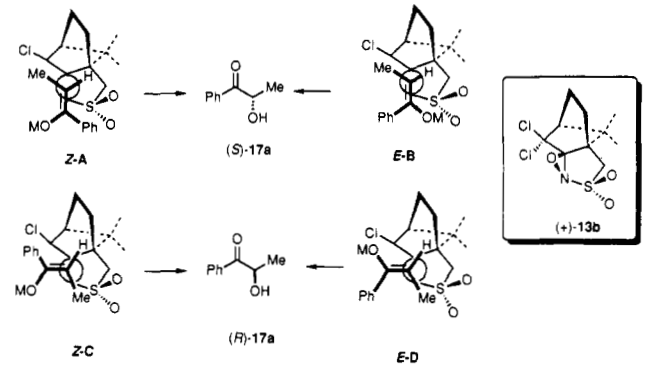


Figure 3. Transition-state structures for the hydroxylation of *E*- and *Z*-enolates. (Selected atoms have been omitted for clarity.)

The lithium *E*- and *Z*-enolates of **16a** were generated under identical kinetically controlled conditions by treatment of the pure *E*- and *Z*-silyl enol ethers **22** with 0.95 equiv MeLi (Scheme II). The *Z*-silyl enol ether of **16a** was generated by trapping the related enolate, generated by treatment of **16a** with LDA.[22] On the other hand the *E*-silyl enol ether was prepared as previously described by treatment of (*E*)-1-lithio-1-phenyl-1-propene with bis(trimethylsilyl) peroxide.[30] Hydroxylation was accomplished by addition of 1.2 equiv of (+)-**13b** to the enolate at −78 °C followed by standard work up after 30 min. The *Z*-enolate was efficiently oxidized to (*S*)-**17** in better than 95% ee at −78 °C within 20 min. By contrast the *E*-enolate was unreactive at −78 °C, but on warming on −45 °C also gave (*S*)-**17**, but this time in only 22% ee (Scheme II).

Quite clearly *Z*-enolates exhibit higher stereoselectivity than *E*-enolates and can be understood in terms of the transition-state structures in Figure 3. In ***Z*-A** not only are there the fewest nonbonded interactions, but the metal enolate is able to coordinate with both the oxaziridine oxygen and nitrogen atoms as required by the theoretical calculations. The *E*-enolate also gives a predominance of (*S*)-**17a**, suggesting that transition-state structure ***E*-B** is a major contributor. Here too there are presumably fewer nonbonded interactions than in ***E*-D**. Structure ***E*-B** may be further stabilized by chelation of the metal enolate to one of the sulfonyl oxygens. Metal chelation to sulfonyl oxygens has often been cited as an important element of transition-state control.[31] The fact that structure ***E*-D** apparently does not contribute to transition-state stabilization provides further support for the argument that there is little if any chelation of the metal enolate with the C–Cl bond in **13b**.

One final point concerns the fact that the ee's for the hydroxylation of the *Z*-enolate of propiophenone (**16a**) are the same (>95% ee) whether the enolate is generated from LDA or from the silyl enol ether **22**. This result implies that the stereoselectivity is independent of the solution

(27) Staley, R. H.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 5920.
(28) For a possible example of metal chelation to a C–Cl bond, see: Kigoshi, H.; Imamura, Y.; Yoshikawa, K.; Niwa, H.; Yamada, K. *Tetrahedron Lett.* **1991**, *35*, 4541.
(29) For examples of metal chelation to C–F bonds, see: Murray-Rust, P.; Stallings, W. C.; Monti, C. T.; Preston, R. K.; Glusker, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 3206. Carrell, H. L.; Glusker, J. P.; Piercy, E. A.; Stallings, W. C.; Zacharias, D. E.; Davis, R. L.; Astbury, C.; Kennard, C. H. L. *J. Am. Chem. Soc.* **1987**, *109*, 8067. Hanamoto, T.; Fuchikami, T. *J. Org. Chem.* **1990**, *55*, 4969. Qian, C.-P.; Nakai, T. *Tetrahedron Lett.* **1988**, *29*, 4119. Qian, C.-P.; Nakai, T.; Dixon, D. A.; Smart, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 4602.
(30) Davis, F. A.; Lal, G. S.; Wei, J. *Tetrahedron Lett.* **1988**, *29*, 4269.
(31) For examples of metal chelation involving sulfonyl oxygens, see: Trost, B. M.; Schmuff, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 396. Hellwinkel, D.; Lenz, R.; Lammerzahl, F. *Tetrahedron* **1983**, *39*, 2073. Giblin, G. M. P.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1987**, 207. Hollstein, W.; Harms, K.; Marsch, M.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1287.

structure of the enolate as required by the calculations, i.e. the enolate mostly reacts as a monomer (**TS-5**).

Summary and Conclusions. Of the dihalo oxaziridines [(8,8-dichlorocamphor)sulfonyl]oxaziridine **13b** affords the highest stereoselectivities for the asymmetric oxidation of sulfides to sulfoxides and for the hydroxylation of propiophenone- and tetralone-derived enolates (>95% ee). For the sulfide oxidations the molecular recognition was explained in terms of minimization of nonbonded steric interaction in the transition state and secondary electronic effects which are influenced by the polarity of the solvent, the oxaziridine and sulfide. Similarly, the enhanced enolate hydroxylation stereoselectivities observed for **13b** compared with the dihydro analog **15** were attributed to the higher reactivity of the oxaziridine and to an active-site structure sterically complementary to enolate. In this regard *Z*-enolates exhibited much higher stereoselectivity than *E*-enolates. Definitive evidence in support of chelation of the metal enolate with the C–X bond in **13** as a factor controlling transition-state geometry was not found.

Experimental Section

General Information. Unless otherwise noted, materials were obtained from commercial sources and were used without further purification. All glassware were oven-dried and cooled in a desiccator prior to use. Manipulations involving air-sensitive materials were performed under argon. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, and hexamethylphosphoramide (HMPA) was distilled from calcium hydride under a nitrogen atmosphere prior to use.

Sodium bis(trimethylsilyl)amide (NaHMDS, 1.0 M in THF), lithium bis(trimethylsilyl)amide (LiHMDS, 1.0 M in THF), potassium bis(trimethylsilyl)amide (KHMDS, 0.5 M in toluene), *n*-butyllithium (*n*-BuLi, 2.5 M in hexane), and halide-free methyllithium (MeLi, 1.4 M in diethyl ether) were purchased from Aldrich. The solutions were standardized by titration with diphenylacetic acid.[32] Fresh solutions of lithium diisopropylamide (LDA) in THF were prepared as needed. Unless indicated otherwise, reagents were transferred via syringe.

Infrared spectra were recorded on a Perkin-Elmer 467 grating spectrometer, and NMR spectra were recorded on a Bruker 250 (250 MHz). ^{13}C NMR spectra were determined with complete proton decoupling. Proton and carbon chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (Me_4Si). ^{19}F NMR spectra were recorded on a JOEL FX-90Q (84.6 MHz) upfield from fluorotrichloromethane ($CFCl_3$). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Mass spectra were performed on a Finnigan 4000 GC/MS at either 70 or 30 eV and recorded as m/z (intensity expressed as percent in total ion current). Gas–liquid partition chromatography (GLC) was performed on a Varian 3700 GC connected to a Shimadru Integrator or on a Perkin-Elmer 8310. A 3% OV-17 (6-ft × $^1/_8$-in., 80/100 Supelcoport) and a SPB-35 (30-m × 0.75-mm, borosilicate glass) column were used for the GLC analysis. Analytical high-pressure liquid chromatography (HPLC) was performed on a Varian 9010 LC using a Varian 9050 UV detector set at 254 nm. Analytical thin-layer chromatography (TLC) was performed using 2.5 × 10 cm (250 μm) precoated silica gel plates (Analtech). Preparative TLC was performed using 20 × 20 cm (1000 μm) silica gel plates (Analtech, Inc.). Flash chromatography was performed using 230–400-mesh silica gel (Merck and Co.). Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Micro-Analysis, Inc., of Wilmington, DE. The purity of the products on which yields are reported was determined to be ≥95% on the basis of ^1H NMR and GLC analysis.

(Camphorylsulfonyl)oxaziridine **15** and the (camphorsulfonyl)imine **4** were prepared as previously described.[9,20] Sulfides were synthesized as described earlier.[2] Propiophenone (**16a**), butyrophenone (**16b**), deoxybenzoin (**16d**), and 2-methyl-1-tetralone (**18**) were purchased from Aldrich. 2,2-Dimethyl-3-pentanone (**16c**)[33] and 1-(6-methoxy-2-naphthyl)ethanone (**16e**)[34] were prepared according to literature procedures.

Determination of Enantiomeric Purity. Sulfoxide enantiomeric purity and absolute configuration were determined as previously described by comparison of optical rotations with literature values, by chiral shift reagent experiments using tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$], and by separation on a Regis Pirkle covalent phenylglycine HPLC column.[2] The enantiomeric purity and absolute configurations of the α-hydroxy ketones were determined by comparison with literature values and by chiral shift reagent experiments using Eu(hfc)$_3$ as previously described.[22]

The [(7-*endo*- and [(7-*exo*-Fluorocamphoryl)sulfonyl]imine 6a/7a Mixture. In a 100-mL oven-dried three-necked round-bottomed flask with a magnetic stirring bar, rubber septum, and fitted with a distillation condenser having a 50-mL collecting flask (at −78 °C) and an outlet to a vacuum and argon source were placed 0.5 g (2.3 mmol) of the (−)-(camphorylsulfonyl)imine **4** and 30 mL of freshly distilled THF. The reaction flask was cooled to 0 °C, and 2.6 mL of 1 M NaHMDS (1.1 equiv) was added dropwise under a blanket of argon. After 15 min, the solvent was distilled off and collected in the receiving flask by disconnecting the argon source and slow application of a vacuum source (approximately 4–10 mmHg). The resulting thick oil was covered with a blanket of argon and dissolved in 30 mL of freshly distilled THF.

Acetyl hypofluorite was prepared using a modification of the procedure reported by Rosen and Brand.[14] In a separate oven-dried 500-mL three-necked round-bottom flask fitted with a S/T Teflon adapter with Teflon inlet and outlet tubes, the latter attached to a soda lime tower, was placed 8.2 g (0.1 mol) of NaOAc in 400 mL of freon ($CFCl_3$). The reaction flask was cooled to −78 °C, and 10% F_2 (balance N_2) gas mixture (Matheson) was bubbled through the reaction mixture for approximately 3–4 h until a concentration of 7–8 equiv of acetyl hypofluorite was obtained. The concentration of the acetyl hypofluorite was determined by removal of a 4-mL aliquot of the reaction mixture, addition of 25 mL of 3 N H_2SO_4/0.5 g of KI solution, and titration of the liberated iodine with standard 0.1 N sodium thiosulfate solution. The azaenolate **5**, prepared above, was then added to the −78 °C solution of acetyl hypofluorite via a cannula tube with stirring. After addition the reaction mixture was stirred for 30 min, quenched by adding the reaction mixture to 100 mL of 5% $Na_2S_2O_3$ in a 1-L separatory funnel, washed 1 × 50 mL of $NaHCO_3$, 1 × 50 mL of water, and 1 × 50 mL of brine, dried over anhydrous $MgSO_4$, and filtered, and solvent was evaporated in vacuo. The resulting crude solid contained 75% of an *exo*-**6a** (δ 5.5, 5.6) and *endo*-**7a** (δ 5.15) in a ratio of approximately 3:7, respectively, and 25% of **4** (by NMR). All attempts to separate **6a/7a** from **4** failed, and this mixture was used directly for the preparation of **8a**.

The (+)-[(7,7-Difluorocamphoryl)sulfonyl]imine 8a. In a 100-mL oven-dried three-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and fitted with a distillation condenser having a 50-mL collecting flask (at −78 °C) and an outlet to a vacuum and argon source was placed 0.72 g of the 75:25 **6a/7a**:4 mixture prepared above in 30 mL of freshly distilled THF. The reaction flask was cooled to 0 °C, and 3.5 mL of 1 M NaHMDS (approximately 1.1 equiv) was added dropwise under a blanket of argon. After 15 min the reaction solvent was distilled off, 30 mL of freshly distilled THF was added, and the reaction mixture was then added to 7–10 equiv of acetyl fluoride, following the procedure for the preparation of **6a/7a**. Workup afforded a solid consisting of 60% of the [(7,7-difluorocamphoryl)sulfonyl]imine **8a**, 40% of **6a/7a**, and <10% of the (camphorylsulfonyl)imine **4** (by NMR). The resulting solid was purified by flash chromatography (CH_2Cl_2/hexane, 4:6), giving 0.35 g (50% yield) of **8a**: mp 139 °C; $[\alpha]^{20}_D$ = +5.5° (c = 1.8, $CHCl_3$); TLC R_f = 0.37 using CH_2Cl_2 as the eluant and 10% molybdophosphoric acid in ethanol as the developer; ^1H NMR ($CDCl_3$) δ 1.04 (d, J = 4.5 Hz, 3 H, Me), 1.16 (s, 3 H, Me), 1.90–2.20

(32) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

(33) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(34) Shioiri, T.; Kawai, N. *J. Org. Chem.* **1978**, *43*, 2936.

(m, 4 H), 2.50–2.61 (m, 1 H), 3.20, 3.42 (both d, J = 13.7 Hz, 2 H); ^{19}F NMR ($CFCl_3$) δ −102.3, −109.9 (both d, J = 297 Hz, 2 F); IR (KBr) 2920 (CH), 1670 (CN), 1165, and 1210 (SO_2) cm^{-1}. Anal. Calcd for $C_{10}H_{13}F_2NO_2S$: C, 48.18; H, 5.25. Found: C, 48.20; H, 5.30.

The [(7-*endo*- and [(7-*exo*-Chlorocamphoryl)sulfonyl]imine 6b/7b Mixture. In a 100-mL oven-dried three-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar were placed 1.0 g (4.7 mmol) of the (−)-(camphorylsulfonyl)imine 4 and 30 mL of freshly distilled THF. The reaction mixture was cooled to 0 °C, and 5.2 mL of 1 M NaHMDS (1.0 equiv) was added dropwise. After 15 min the reaction mixture was cooled to −78 °C, 0.63 g (4.7 mmol) of recrystallized *N*-chlorosuccinimide in 10 mL of freshly distilled THF was added dropwise, and the mixture was warmed to room temperature. After 2 h, the mixture was quenched with 5 mL of water and added to 50 mL of ethyl acetate, the organic layer was separated and washed with 1 × 10 mL of 1 N HCl, 1 × 10 mL of $NaHCO_3$, 1 × 10 mL of brine, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed on a rotary evaporator to give a solid which was purified by flash chromatography (CH_2Cl_2/hexane, 4:6), affording 0.68 g (59%) of an endo/exo mixture of **6b** and **7b** in a ratio of 2:8, respectively: mp 162–163 °C; TLC R_f (pentane/ether, 3:1); ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 3 H, Me), 1.09 (s, 3 H, Me), 1.14 (s, 3 H, Me), 1.18 (s, 3 H, Me), 1.58–2.46 (m, 8 H), 3.00–3.33 (dd, 2 H), 3.12–3.31 (dd, 2 H), 4.56 (s, 1 H), 4.90 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.91, 19.85, 20.20, 20.41, 20.58, 27.04, 28.92, 47.19, 49.95, 50.77, 51.04, 55.33, 55.18, 56.12, 63.84, 190.96. Anal. Calcd for $C_{10}H_{14}ClNO_2S$: C, 48.48; H, 5.69; N, 5.65. Found: C, 48.48; H, 5.94; N, 5.99.

The (+)-[(7,7-Dichlorocamphoryl)sulfonyl]imine 8b. In a 500-mL oven-dried three-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar were placed 12.0 g (53.6 mmol) of the (−)-(camphorylsulfonyl)imine 4 and 300 mL of freshly distilled THF. The reaction flask was cooled to −78 °C (dry ice–acetone bath), and 169 mL of 1 M NaHMDS (2.2 equiv) was added dropwise. After 1.5 h the reaction mixture was added via cannula tube (reverse addition) to 22 g (165 mmol) of of recrystallized *N*-chlorosuccinimide in 500 mL of THF at −78 °C (dry ice–acetone bath) in a 2-L oven-dried three-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar. After addition, the reaction mixture was stirred at −78 °C for 2 h or until TLC indicates the absence of 4. The reaction mixture was quenched by addition of 50 mL of water, and the solution was warmed to room temperature. At this time the reaction mixture was diluted with 200 mL of ethyl acetate, washed with water, 3 × 100 mL, and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave the crude product as a 85:12 mixture of (+)-**8b** and (−)-4. Crystallization from ethanol gave 11.82 g (74%) of (+)-**8b**: mp 174 °C; $[\alpha]^{20}_D$ = +7.9° (c = 1.0, $CHCl_3$); TLC R_f = 0.42 using CH_2Cl_2 and 10% molybdophosphoric acid in ethanol as the developer; ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 3 H, Me), 1.22 (s, 3 H, Me), 1.82–2.45 (m, 4 H), 2.80 (d, J = 3.6 Hz, 1 H), 3.24, 3.42 (both d, J = 13.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 21.7, 25.3, 27.6, 48.0, 51.0, 61.4, 64.2, 81.9, 188.9; EI-MS m/z (rel abund) 286 (M^{+4}, 1), 284 (M^{+2}, 12), 282 (M^+, 18), 109 (100), 91 (13) 77 (64), 67 (45), 53 (31), 41 (90); IR (KBr) 2949 (CH), 1662 (CN), 1161 and 1345 (SO_2) cm^{-1}. Anal. Calcd for $C_{10}H_{13}Cl_2NO_2S$: C, 42.56; H, 4.65. Found: C, 42.37; H, 4.29.

The [(3,3,7,7-Tetrachlorocamphoryl)sulfonyl]imine 9d. In the preceding procedure, on a 23.5-mmol scale, when 2.5 equiv of NCS was used and the solution was kept at 0 °C prior to quenching, **9d** in addition to **8b** was obtained (15:85). The mixture was separated by flash chromatography (CH_2Cl_2/hexane, 4:6), affording 4.3 g (64%) of (+)-**8b** and 0.97 g (12%) of the (−)-[(3,3,7,7-tetrachlorocamphoryl)sulfonyl]imine **9d**: mp 191–2 °C; $[\alpha]^{20}_D$ = −10.4° (c = 1.3, $CHCl_3$); TLC R_f = 0.75 using CH_2Cl_2 as the eluant and 10% molybdophosphoric acid in ethanol as the developer; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 3 H, Me), 1.51 (s, 3 H, Me), 1.83–1.91 (m, 1 H), 2.17–2.31 (m, 2 H), 2.58–2.71 (m, 1 H), 2.75 (d, J = 4.0 Hz, 1 H); EIMS m/z (rel abund) 355 (M^{+4}, 6), 353 (M^{+2}, 14), 351 (M^+, 9), 288 (100), 252 (38), 210 (26), 162 (31), 142 (75), 115 (55); IR (KBr) 2980 (CH), 1660 (CN), 1165 and 1355 (SO_2) cm^{-1}. Anal. Calcd for $C_{10}H_{11}Cl_4NO_2S$: C, 34.21; H, 3.16. Found: C, 34.11; H, 3.20.

The [(7-*endo*- and [(7-*exo*-Bromocamphoryl)sulfonyl]imine 6c/7c Mixture. In a 100-mL oven-dried three-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar were placed 1.0 g (4.7 mmol) of the (−)-(camphorylsulfonyl)imine 4 and 30 mL of freshly distilled THF. The reaction mixture was cooled to 0 °C, and 5.2 mL of 1 M NaHMDS (1.0 equiv) was added dropwise. After 15 min, a mixture of 1.5 g (1.0 equiv) of carbon tetrabromide (CBr_4) in 10 mL of freshly distilled THF was added dropwise via cannula tube, and the mixture was warmed to room temperature. After 2 h, the mixture was quenched with 5 mL of water and added to 50 mL of ethyl acetate, the organic layer was separated, washed with 1 × 10 mL of 1 N HCl, 1 × 10 mL of $NaHCO_3$, and 1 × 10 mL of brine, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed on a rotary evaporator to give 1.2 g (87%) of an endo/exo mixture of **6c** (δ 4.90 d, J = 4.2 Hz) and **7c** (δ 4.67) in a ratio of approximately 2:8, respectively. This crude product was used without further purification for the preparation of (+)-[(8-*exo*-bromocamphoryl)sulfonyl]oxaziridine **12c**.

The (−)-[(7-*exo*-Bromocamphoryl)sulfonyl]imine 7c. In a 100-mL separatory funnel were placed 1.0 g (3.25 mmol) of (+)-[(8-*exo*-bromocamphoryl)sulfonyl]oxaziridine **12c** and 50 mL of CH_2Cl_2. The mixture was washed 4 × 25 mL with saturated sodium hydrogen sulfite, the organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed on a rotary evaporator to give 0.93 g of crude product. The resulting solid was crystallized from absolute ethanol to give 0.82 g (80%) of **7c**: mp 205–6 °C; $[\alpha]^{20}_D$ = −72.0° (c = 1.0, $CHCl_3$); TLC R_f = 0.25 using CH_2Cl_2 as the eluant and 10% molybdophosphoric acid in ethanol as the developer; ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 3 H, Me), 1.21 (s, 3 H, Me), 1.53–1.98 (m, 4 H), 2.50 (d, J = 4.6 Hz, 1 H), 3.16 and 3.31 (both d, J = 13.0 Hz, 2 H), 4.67 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.3, 20.9, 27.1, 29.9, 42.4, 48.3, 50.5, 53.0, 64.5, 191.0. Anal. Calcd for $C_{10}H_{14}Br_1NO_2S$: C, 41.10; H, 4.83. Found: C, 41.05; H, 4.80.

The (+)-[(7,7-Dibromocamphoryl)sulfonyl]imine 8c. In a 250-mL oven-dried three-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar were placed 4.0 g (18.8 mmol) (−)-4 and 150 mL of freshly distilled THF. The reaction flask was cooled to 0 °C, and 41.3 mL of 1 M NaHMDS (2.2 equiv) was added dropwise. After 15 min, the reaction mixture was added via cannula tube (reverse addition) to 8.3 g of *N*-bromosuccinimide (NBS, 2.5 equiv, recrystallized) in 300 mL of THF at 0 °C in a 500-mL oven-dried three-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a 1.5-in. egg-shaped magnetic stirring bar. Vigorous stirring was maintained to prevent a solid gel from forming. The gel, if formed, can be dissolved by shaking the flask. After addition, the reaction mixture was stirred for 1 h, quenched with 20 mL of water, and warmed to room temperature. The solvent was evaporated, the wet solid was dissolved with 100 mL of CH_2Cl_2, the mixture was washed with 1 × 20 mL of 1 N HCl, 3 × 50 mL of water, and 1 × 50 mL of brine, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated in vacuo. The resulting solid was crystallized from absolute ethanol to give 5.2 g (75%) of **8c**: mp 195–6 °C; $[\alpha]^{20}_D$ = +4.6° (c = 1.1, $CHCl_3$); TLC R_f = 0.42 using CH_2Cl_2 as the eluant and 10% molybdophosphoric acid in ethanol as the developer; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 3 H, Me), 1.28 (s, 3 H, Me), 1.82–2.55 (m, 4 H), 2.90 (d, J = 4.2 Hz, 1 H), 3.20 and 3.41 (both d, J = 13.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.7, 22.9, 27.3, 28.6, 47.9, 50.1, 53.5, 61.6, 63.8, 191.2; EI-MS m/z (rel abund) 374 (M^{+4}, 1.49), 372 (M^{+2}, 2.34), 370 (M^+,1.29) 307 (1), 290 (6), 226 (29), 146 (90), 109 (100), 62 (97); IR (KBr) 2970 (CH), 1650 (CN), 1165 and 1342 (SO_2) cm^{-1}. Anal. Calcd for $C_{10}H_{13}Br_2NO_2S$: C, 32.36; H, 3.53. Found: C, 32.62; H, 3.41.

(+)-[(8-*endo*- and [(8-*exo*-Chlorocamphoryl)sulfonyl]oxaziridine 11b/12b Mixture. In a 2-L three-necked Morton flask equipped with an efficient mechanical stirrer with a 125-mm Teflon stirring blade, a Safe Lab stirring bearing, and a 250-mL addition funnel were placed 4.0 g (16.2 mmol) of the [(7-*endo*- and [(7-*exo*-chlorocamphoryl)sulfonyl]imine **6b/7b**, 300 mL of toluene, and a solution of 39.7 g (0.29 mol, 7 equiv based on oxone) of K_2CO_3 in 250 mL of distilled H_2O. The reaction mixture was stirred vigorously, and a solution of 25.3 g (41.1 mmol, 3.0 equiv) of oxone in 200 mL of distilled H_2O was added dropwise over 30

min. After stirring for 1 day, a solution of 25.3 g (41.1 mmol, 3.0 equiv) of oxone in 200 mL of distilled H_2O was added dropwise over 30 min. The reaction mixture was stirred vigorously and monitored by TLC. Additional oxone and K_2CO_3 (to maintain the pH at approximately 9.0) was added until the oxidation was complete (normally 3 days). The reaction mixture was transferred to a 3-L separatory funnel, the toluene layer was separated, and the aqueous layer was washed 3 × 50 mL with CH_2Cl_2. Any white solids remaining in the Morton flask were washed with 50 mL of CH_2Cl_2. The organic extracts were combined, washed with 1 × 50 mL of saturated $Na_2S_2O_3$, and dried over anhydrous $MgSO_4$, the solvent was evaporated, and the crude solid was recrystallized from ethanol giving 3.2 g (76% yield) of (+)-**11b/12b**: mp 162–163 °C; TLC R_f 0.69 using CH_2Cl_2 as the eluant and 10% molybdophosphoric acid in ethanol as the developer; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3 H, Me), 1.13 (s, 3 H, Me), 1.23 (s, 3 H, Me), 1.44 (s, 3 H, Me), 1.56–2.36 (m, 8 H), 3.19 and 3.40 (both d, 2 H, J = 14.1 Hz), 3.24 and 3.40 (both d, 2 H, J = 14.0 Hz), 4.09 (s, 1 H), 4.89 (d, 1 H, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$) δ 0.11, 18.9, 19.5, 20.0, 20.2, 20.5, 21.9, 26.9, 27.4, 28.1, 46.5, 48.5, 48.7, 49.3, 52.3, 53.5, 53.9, 54.5, 56.6, 57.7; IR (KBr) 3004 (CH), 1182 and 1354 (SO_2) cm^{-1}. Anal. Calcd for $C_{10}H_{14}ClNO_3S$: C, 45.54; H, 5.35; N, 5.31. Found: C, 45.45; H, 5.4; N, 5.29.

(+)-[(8-*exo*-Bromocamphoryl)sulfonyl]oxaziridine 12c was prepared in a similar manner starting from the (+)-**6c/7c** to give 3.0 g (71%) of **12c** after crystallization from ethanol: mp 170 °C; $[\alpha]^{20}_D$ = +30.2° (c = 2.8, $CHCl_3$); TLC R_f = 0.60 using CH_2Cl_2 as the eluant and 10% molybdophosphoric acid in ethanol as the developer; ^1H NMR ($CDCl_3$) δ 1.07 (s, 3 H, Me), 1.50 (s, 3 H, Me), 1.59–1.60 (m, 1 H), 1.90–2.22 (m, 3 H), 2.43 (d, J = 4.6 Hz, 1 H), 3.20, 3.40 (both d, J = 14.0 Hz, 2 H), 4.00 (s); ^{13}C NMR ($CDCl_3$) δ 20.3, 21.8, 22.4, 27.5, 44.0, 49.2, 54.0, 55.0, 101.0. Anal. Calcd for $C_{10}H_{14}BrNO_3S$: C, 38.97; H, 4.58. Found: C, 38.87; H, 4.68.

Preparation of (+)-[(8,8-Dichlorocamphoryl)sulfonyl]oxaziridine 13b. In a 1-L three-necked Morton flask equipped with an efficient mechanical stirrer having a 125-mm Teflon stirring blade and a Safe Lab stirring bearing were placed 7.10 g (25 mmol) of (+)-**8b**, 200 mL of CH_2Cl_2, and 200 mL of saturated K_2CO_3. The mixture was stirred vigorously, to which 13.5 g (40 mmol) of technical-grade *m*-CPBA (ca. 50–60%) was added in small portions over 5 min. The reaction mixture was stirred vigorously until the oxidation was complete as indicated by TLC, typically 8 h, at which time 250 mL of water was added. The organic layer was separated and the aqueous layer extracted with methylene chloride (2 × 200 mL). The combined organic extracts were washed with saturated sodium sulfide (150 mL) and water (150 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent on a rotary evaporator gave the crude oxaziridine which was recrystallized from ethanol to give 7.3 g (98%) of (+)-**13b**: mp 160 °C; $[\alpha]^{20}_D$ = +89.4° (c = 2.1, $CHCl_3$); TLC R_f = 0.68 using CH_2Cl_2 as the eluant and 10% molybdophosphoric acid in ethanol as the developer; ^1H NMR ($CDCl_3$) δ 1.18 (s, 3 H, Me), 1.49 (s, 3 H, Me), 1.82–2.50 (m, 4 H), 2.77 (d, J = 3.5 Hz, 1 H), 3.36 (AB quartet, J = 14.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 1.1, 22.0, 23.4, 25.3, 27.0, 47.4, 49.4, 54.6, 62.6, 99.0. Anal. Calcd for $C_{10}H_{13}Cl_2NO_3S$: C, 40.28; H, 4.39. Found: C, 40.54; H, 4.31.

(-)-[(8,8-Dichlorocamphoryl)sulfonyl]oxaziridine 13b was prepared in a similar manner starting from (+)-**4**: $[\alpha]^{20}_D$ = −88.3° (c = 1.3, $CHCl_3$).

(+)-[(8,8-Difluorocamphoryl)sulfonyl]oxaziridine 13a was prepared in a manner similar to **13b** starting from (+)-**8a**: yield 91%; mp 175 °C (EtOH); $[\alpha]^{20}_D$ = +56.2° (c = 0.93, $CHCl_3$); TLC R_f = 0.67 using CH_2Cl_2 as the eluant and 10% molybdophosphoric acid in ethanol as the developer; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H, Me), 1.30 (d, J = 3.9 Hz, 3 H, Me), 1.95–2.10 (m, 4 H), 2.50 (d, J = 8.3 Hz, 1 H), 3.32 (AB quartet, J = 14.0 Hz, 2 H); ^{19}F NMR ($CFCl_3$) δ −102.5 and −114.0 (both d, J = 172 Hz, 2 F). Anal. Calcd for $C_{10}H_{13}F_2NO_3S$: C, 45.27; H, 4.94. Found: C, 45.21; H, 4.97.

(+)-[(8,8-Dibromocamphoryl)sulfonyl]oxaziridine 13c. In a 1-L three-necked Morton flask equipped with an efficient mechanical stirrer having a 125-mm Teflon stirring blade, a Safe Lab stirring bearing, and a 100-mL addition funnel were placed 3.72 g (10 mmol) of (+)-**8c**, 50 mL of CH_2Cl_2, and a solution of 50.0 mmol (5 equiv) of K_2CO_3 in 100 mL of distilled water. The reaction mixture was stirred vigorously, and a solution of 2.6 g (15 mmol) of >95% *m*-CPBA[35] in 60 mL of CH_2Cl_2 was added dropwise over 5 min. The reaction mixture was stirred vigorously for 1–3 h, monitored by TLC, and when complete transferred to a 250-mL separatory funnel. The organic layer was separated and the aqueous layer washed with 1 × 50 mL with CH_2Cl_2. The organic extracts were combined, washed 1 × 25 mL of saturated $Na_2S_2O_3$ and 1 × 25 mL of brine, and dried over anhydrous $MgSO_4$, the solvent was evaporated, and the crude solid was crystallized from ethanol to give 3.3 g (85%) of **13c** as a white solid: mp 179–80 °C; $[\alpha]^{20}_D$ = +78.6° (c = 2.3, $CHCl_3$); TLC R_f = 0.64 using CH_2Cl_2 as the eluant and 10% molybdophosphoric acid in ethanol as the developer; ^1H NMR ($CDCl_3$) δ 1.19 (s, 3 H, Me), 1.58 (s, 3 H, Me), 1.90–2.15 (m, 3 H), 2.40–2.50 (m, 1 H), 2.80 (d, J = 3.0 Hz, 1 H), 3.37 (AB quartet, J = 14.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.9, 24.3, 26.9, 28.8, 47.6, 49.7, 54.3, 59.3, 63.0, 99.4. Anal. Calcd for $C_{10}H_{13}Br_2NO_3S$: C, 31.03; H, 3.38. Found: 30.77; H, 3.19.

(+)-[(4,4,8,8-Tetrachlorocamphoryl)sulfonyl]oxaziridine 14 was prepared in a similar manner by oxidation of imine **9d**: yield 82%; mp 150–1 °C (EtOH); $[\alpha]^{20}_D$ = +133.2° (c = 1.1, $CHCl_3$); TLC R_f = 0.86 using CH_2Cl_2 as the eluant and 10% molybdophosphoric acid in ethanol as the developer; ^1H NMR ($CDCl_3$) δ 1.48 (s, 3 H, Me), 1.57 (s, 3 H, Me), 2.05–2.6 (m, 5 H), 2.70 (d, J = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.8, 24.3, 24.6, 28.7, 51.9, 61.7, 64.7, 85.0, 96.3, 96.7; IR (KBr) 3000 (CH), 1165 and 1355 (SO_2) cm^{-1}. Anal. Calcd for $C_{10}H_{11}Cl_4NO_3S$: C, 32.72; H, 3.03. Found: C, 32.82; H, 3.19.

General Procedure for Oxidation of Sulfides to Sulfoxides. In a 5-mL round-bottom flask equipped with a magnetic stirring bar and argon inlet was placed 0.25 mmol of appropriate oxaziridine in 5 mL of CH_2Cl_2 or 10 mL of CCl_4, followed by addition of 1.1 equiv of the sulfide in 5 mL of solvent. The progress of the reaction was monitored by TLC (80% CH_2Cl_2/pentane), and the sulfoxide was isolated by preparative TLC (silica gel G) by eluting with ether. The sulfoxide had the lowest R_f value.

Asymmetric Oxidation of Sulfides to Sulfoxides: Competitive Rate Study of (Camphorylsulfonyl)oxaziridine 15 vs [(8,8-Dihalocamphoryl)sulfonyl]oxaziridines 13. The rate of oxidation of *p*-tolyl *n*-butyl sulfide to the corresponding sulfoxide in $CDCl_3$ by the oxaziridines **13a** (F), **13b** (Cl), and **13c** (Br) were compared to the unsubstituted (camphorylsulfonyl)oxaziridine **15**. An example of the general procedure is given by the competition reaction between **15** and **13c**.

Into an oven-dried NMR tube were placed 12 mg (0.075 mmol, 1 equiv) of *p*-tolyl *n*-butyl sulfide in 0.5 mL of $CDCl_3$ and a premixed solution of 30 mg (0.075 mmol, 2 equiv) of **13c** in 0.5 mL of $CDCl_3$ and 17 mg (0.075 mmol, 1 equiv) of **15** in 0.5 mL of $CDCl_3$. The NMR tube was shaken for 0.5 min, and an NMR spectra of the sample was taken every 5 min until the reaction was complete (see below), as evidenced by the disappearance of the sulfide's aromatic absorptions at δ 7.10 and 7.24 (dd, 4 H, J = 10 Hz) ppm and the appearance of the sulfoxide's aromatic absorptions at δ 7.32 and 7.52 dd, 4 H, J = 10 Hz) ppm. After 40 min, the percent conversion of **13b** to the imine **8b** was calculated to be 70% by comparing the areas of the methyl peak for the dibromooxaziridine **13b** (δ 1.28 ppm) to the methyl peak for the dibromoimine **8b** (δ 1.58 ppm). Likewise, the percent conversion of the (camphorylsulfonyl)oxaziridine **15** to the (camphorylsulfonyl)imine **4** was calculated to be 20% by comparing the area of the methyl peak for the oxaziridine **15** (δ 1.04 ppm) to the methyl peak for the imine **4** (δ 0.87 ppm). Therefore, the dibromo oxaziridine **13b** reacts 3 times (70:20 = ca. 3:1) faster than the unsubstituted oxaziridine **15**.

Via the same procedure, after 15 min the percent conversion of the [(8,8-dichlorocamphoryl)sulfonyl]oxaziridine **13b** to imine **8b** was calculated to be 88% by integration of the methyl peak of the oxaziridine (δ 1.48 ppm) to the methyl peaks of the dichloro imine **8b** (δ 1.22 ppm). Likewise, the percent conversion of the oxaziridine **15** to imine **4** was calculated to be 8% by comparing the area of the methyl peak for **15** (δ 1.04 ppm) to the methyl peaks for **4** (δ 0.87 ppm). Therefore, the dichloro oxaziridine **13b** reacted 10 times (88:8 = 10.1) faster than the unsubstituted oxaziridine **15**.

(35) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976.

Via the same procedure, after 5 min the percent conversion of the [(8,8-difluorocamphoryl)sulfonyl]oxaziridine **13a** to imine **8a** was calculated to be 71% by integration of the methyl peaks for **13a** (δ 1.29 ppm, d) to the methyl peaks for the imine **8a** (δ 1.15 ppm). Similarly, the percent conversion of **15** to **4** was calculated to be ca. 5% by comparing the area of the methyl peak for the oxaziridine **15** (δ 1.18 ppm) to the methyl peak for the imine **4** (δ 0.87 ppm). Therefore, the difluoro oxaziridine **13a** reacts >15 times (71:<5 = >15:1) faster than the unsubstituted oxaziridine **15**.

General Procedure for the Asymmetric Oxidation of Ketone Enolates 4 Using [(Dihalocamphoryl)sulfonyl]oxaziridine 13. In a 25-mL oven-dried two-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 3 mL of freshly distilled THF. The reaction flask was cooled to −78 °C (dry ice–acetone bath), and 0.6 mL (0.6 mmol, 1.2 equiv based on ketone) of the base was added. A solution of the appropriate ketone **16a–e** of **18** (0.5 mmol) in 3 mL of THF was added dropwise, and the mixture was stirred for 30 min. A solution of 0.19 g (0.75 mmol, 1.25 equiv based on amide base) of appropriate oxaziridine (+)-**13** in 3 mL of THF was added dropwise. The reaction mixture was quenched after 15 min by addition of 3 mL of a saturated aqueous NH_4I solution, diluted with 10 mL of diethyl ether at −78 °C, and warmed to room temperature. The aqueous layer was extracted with diethyl ether (2 × 5 mL) and the combined organic extracts were washed successively with saturated aqueous $Na_2S_2O_3$ (2 × 15 mL) and brine (2 × 10 mL), dried over anhydrous $MgSO_4$, and filtered. Concentration in vacuo gave an oil that was stirred with three portions of 3 mL of *n*-pentane and filtered to remove the (camphorsulfonyl)imine **8** byproduct. Purification of the residue by preparative TLC (pentane/Et_2O, 3:1) or flash chromatography (pentane/EtOAc, 19:1) gave the α-hydroxy ketone **17** or **19**.

For oxidations of potassium, sodium, and lithium enolates in the presence of HMPA, 0.3 mL (1.73 mmol, 3.5 equiv based on ketone) of this cosolvent was added to the base solution at −78 °C followed by addition of the ketone after 5 min.

General Procedure for GLC Monitoring Enolate Oxidations. In a small vial (4-mL capacity) was placed 3 drops of a saturated NH_4Cl solution (saturated NH_4I solution or distilled H_2O were used in some reactions). A few drops (3–5) were withdrawn from the reaction mixture via syringe and quickly mixed with the NH_4Cl quenching solution. The mixture was diluted with ca. 0.5 mL of Et_2O, mixed, and allowed to settle. The layers were separated by pipette, the aqueous layer was extracted with some Et_2O, and the combined organic extracts were dried over Na_2SO_4 for 2–5 min in a 4-mL vial. The liquid was transferred by pipette into a clean vial and analyzed by GLC.

(*S*)-(−)-2-Hydroxy-1-phenyl-1-propanone (17a). Oxidations were carried out as described above: R_f 0.23 (pentane/Et_2O, 3:1); >95% ee; $[\alpha]^{20}_D$ = −80.9° (*c* = 2.0 $CHCl_3$).

(*S*)-(−)-2-Hydroxy-1-phenyl-1-butanone (17b).[38] Oxidations were carried out as described above: R_f 0.30 (pentane/ether, 3:1); ^1H NMR ($CDCl_3$) δ 0.94 (t, 3 H, Me, *J* = 7.42 Hz), 1.52–1.72 (m, 1 H), 1.87–2.04 (m, 1 H), 3.71 (br s, 1 H, OH), 5.07 (m, 1 H), 7.45–7.56 (m, 2 H), 7.58–7.68 (m, 1 H), 7.88–7.97 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 8.89, 28.8, 73.9, 128.3, 128.7, 133.7, 133.8, 201.8; IR (NaCl) 3475 (OH), 2967 (CH), 1969–1817, 1681 (C=O), 1450, 1406, 1244, 1133, 976, 910. Determination of % ee was made by Eu(hfc)$_3$ NMR shift reagent experiments of the acetate derivative: 95% ee $[\alpha]^{20}_D$ = −30.78° (*c* = 2.24, $CHCl_3$).

(*S*)-(+)-2-(Acetyloxy)-1-phenyl-1-butanone. In a 10-mL round-bottomed flask equipped with a magnetic stirring bar was placed 0.022 g (0.131 mmol) of **17b** in 3 mL of pyridine. To this mixture was added 0.018 g of DMAP, followed by 0.50 mL (0.196 mmol, 1.5 equiv) of acetic anhydride. The reaction was monitored by TLC until complete. At this time pyridine was removed by distillation and the product was purified by preparative TLC (CH_2Cl_2 eluent) to give the acetate 0.026 g (96%). Determination of % ee was made by Eu(hfc)$_3$ NMR shift reagent experiments: R_f 0.68 (pentane/Et_2O, 3:1); IR and ^1H NMR are in agreement with reported data;[39] $[\alpha]^{20}_D$ = +5.02° (*c* = 2.1, acetone) [lit.[40] $[\alpha]^{20}_D$ = +5.2 (*c* = 1.8, acetone)].

(*R*)-(−)-4-Hydroxy-2,2-dimethyl-3-pentanone (17c). Oxidations were carried out as described above: R_f 0.23 (pentane/Et_2O, 3:1); IR and ^1H NMR were in agreement with reported data;[22] 89% ee; $[\alpha]^{20}_D$ = −54.9° (*c* = 1.96 $CHCl_3$).

(*S*)-(+)-2-Hydroxy-2-phenylacetophenone (17d). Oxidations were carried out as described above: R_f 0.22 (pentane/Et_2O, 3:1); IR and ^1H NMR were consistent with reported values; 95% ee; $[\alpha]^{20}_D$ = +114.9° (*c* = 1.5, acetone) [lit.[36] $[\alpha]^{20}_D$ = −118.4° (*c* = 2.4 acetone)].

(*S*)-(−)-2-Hydroxy-1-(6-methoxy-2-naphthyl)-1-propanone (17e). Oxidations were carried out as described above: R_f (pentane/Et_2O, 3:1); IR and ^1H NMR were in agreement with reported data;[41] 95% ee; $[\alpha]^{20}_D$ = −93.5° (*c* = 1.10, $CHCl_3$) [lit.[41] $[\alpha]^{2-}_D$ = −98.4° (*c* = 1.01, $CHCl_3$)].

(*R*)-(+)-2-Hydroxy-2-methyl-1-tetralone (19). Oxidations were carried out as described above: R_f 0.20 (pentane/Et_2O, 3:1); IR and ^1H NMR were consistent with reported values: >95 % ee, $[\alpha]^{20}_D$ +17.3° (*c* 2.0, CH_3OH). CD spectra: Molecular ellipticity [Q] (*c* 1.7, C_2H_5OH), 21 °C; $[Q]_{295}$ −6000°, $[Q]_{308}$ 0°, $[Q]_{322}$ +2500°. IR and ^1H NMR was consistent with reported values.[37]

2-Chloro-2-phenylacetophenone (Desyl Chloride, 20). This product was isolated as a byproduct of the oxidation of **16d**: mp 62–63 °C [lit.[42] mp 63 °C]; R_f 0.82 (pentane/Et_2O, 3:1); IR and ^1H NMR were in agreement with reported data;[42] 0% ee.

2-Chloro-2-methyl-1-tetralone (21).[43] This product was isolated as a byproduct of the oxidation of **18**: R_f 0.86 (pentane/Et_2O, 3:1); ^1H NMR ($CDCl_3$) δ 1.87 (s, 3 H, Me), 2.26–2.42 (m, 1 H), 2.83–2.99 (m, 1 H), 3.31–3.50 (m, 1 H), 7.22–7.43 (m, 2 H), 7.46–7.59 (m, 1 H), 8.06–8.18 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.0, 26.7, 38.5, 67.5, 126.9, 128.6, 128.9, 129.6, 133.7, 142.9, 191.1; IR (NaCl) 3053, 2985, 2359, 1693, 1602, 1455, 1422, 1378, 1304, 896, 804, 739, 705 cm^{-1}; 0% ee.

Chlorination of the Enolate of 2-Methyl-1-tetralone (18) by (+)-8b. In an oven-dried two-necked 25-mL round-bottomed flask equipped with a magnetic stirring bar under argon was placed 3 mL of THF. The flask was cooled to −78 °C, and 0.749 mmol of the appropriate base was added, followed by dropwise addition of 0.10 g (0.624 mmol) of **18**, dissolved in 3 mL of THF. The enolate was stirred for 20 min at −78 °C, warmed to 0 °C, and stirred for an additional 20 min. The reaction was then cooled back to −78 °C, and 0.264 g (0.94 mmol, 1.25 equiv) of (+)-**8b** in 3 mL of THF was added to the reaction. Although addition of the imine was sometimes accompanied by a color change, progress of the reaction was made by TLC (3/1 pentane/ether eluent) and/or by ^1H NMR to ensure that reaction had indeed taken place. Careful identification of the chlorinated product by TLC was required since the product appears just above the starting material (R_f 0.86 vs 0.80). If no reaction was indicated by TLC at −78 °C, the flask was warmed to 0 °C, but in no case did the reaction go to completion. The reaction was quenched with 3 mL of saturated NH_4Cl and transferred to a 60-mL separatory funnel, and the layers were separated. The aqueous layer was extracted with 2 × 5 mL of ether, and the combined organic layers were washed with 2 × 10 mL of brine. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed to give the crude product, which was purified by preparative TLC (3/1 ether/pentane eluent) to give **21**.

Oxidation of *E*- and *Z*-Lithium Enolates of 16a Generated from the Silyl Enol Ethers and CH_3Li. In a 50-mL oven-dried two-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 0.2 (1.0 mmol) of the *Z*-enol silane **22** (>97:3 *Z*:*E*) in 10 mL of freshly distilled THF. The reaction flask was cooled to 0 °C (ice–water bath); and 0.67 mL (0.93 mmol, 0.95 equiv based on the enol silane) of a 1.4 M solution of CH_3Li in diethyl ether (Aldrich) was added

(36) Kenyon, J.; Patel, R. *J. Chem. Soc.* **1965**, 435.
(37) Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 2835.
(38) Collin, J.; Namy, J.-L.; Dallemer, F.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 3118.
(39) Kotani, E.; Kobayashi, S.; Adachi, M.; Tsujioka, T.; Nakamura, K.; Tobinaga, S. *Chem. Pharm. Bull.* **1989**, *37*, 606.
(40) Ohta, H.; Ikemoto, M.; Il, H.; Okamoto, Y.; Tsuchihashi, G. *Chem. Lett.* **1986**, 1169.
(41) Honda, Y.; Ori, A.; Tsuchihashi, G. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1027.
(42) Schroeter, G. *Chem. Ber.* **1909**, *42*, 2336.
(43) Stevens, C. L.; Beereboom, J. J.; Rutherford, K. G. *J. Am. Chem. Soc.* **1955**, *77*, 4590.

dropwise. Cleavage of the enol silane was monitored by GC or TLC. After 1 h the solution was cooled to −78 °C (dry ice–acetone bath), and a solution of 0.35 g (1.2 mmol, 1.2 equiv based on enol silane) of (+)-**13b** in 10 mL of THF was added dropwise. After 30 min at −78 °C the mixture was quenched by addition of 3 mL of a saturated aqueous NH_4Cl solution followed by 3 mL of saturated NH_4I solution. The solution was brought to room temperature and diluted with 20 mL of ethyl acetate. The organic layer was washed successively with saturated $Na_2S_2O_3$ solution and brine, 2 × 15 mL, and dried. Concentration in vacuo gave an oil that was stirred with three portions of *n*-pentane (3 mL) and filtered to remove the (camphorsulfonyl)imine **8b** byproduct. Purification of the residue by preparative TLC or flash chromatography (pentane/Et_2O, 60:40) gave 0.06 g (45%) of (*S*)-(+)-2-hydroxy-1-phenyl-1-propanone (**17a**): >95% ee; $[\alpha]^{20}_D$ = −79.8° (*c* = 1.3, $CHCl_3$) [lit.[22] $[\alpha]^{20}_D$ = −80.9° (*c* = 2.0, $CHCl_3$)].

Oxidation of the *E*-silyl enol ether **22** (93:7 *E*:*Z*)[30] was carried out in a similar manner except that there was no reaction at −78 °C and warming to −45 °C was required. Standard workup gave 0.76 g (51%) of (*S*)-**17a**, 23% ee $[\alpha]^{20}_D$ −20.65° (*c* = 1.8, $CHCl_3$).

Acknowledgment. We thank Professor Robert D. Bach, Wayne State University, and Robert M. Przeslawski, Drexel University, for helpful discussions. The financial support of the National Institutes of Health (Institute of General Medical Sciences) through Grant GM 34014 is gratefully acknowledged.

Total Synthesis of Montanine-Type *Amaryllidaceae* Alkaloids, Which Possess a 5,11-Methanomorphanthridine Ring System, through Cyclization with Sodium Bis(2-methoxyethoxy)aluminum Hydride: The First Stereoselective Total Syntheses of (±)-Montanine, (±)-Coccinine, (±)-*O*-Acetylmontanine, (±)-Pancracine, and (±)-Brunsvigine[1]

Miyuki Ishizaki and Osamu Hoshino*

Faculty of Pharmaceutical Sciences, Science University of Tokyo, 12, Ichigaya Funagawara-machi, Shinjuki-ku, Tokyo 162, Japan

Yoichi Iitaka

Department of Biological Sciences, Nishi Tokyo University, Uenohara-machi, Kitatsurugun, Yamanashi 409-01, Japan

Received June 3, 1992

The stereoselective total syntheses of the title alkaloids **1**–**5** from allylic chloride **31** are described. The key steps in the reaction sequences are as follows: (1) stereoselective hydroboration–oxidation of **12** by means of an intramolecular charge-transfer complex to afford alcohol **13** as a single isomer; (2) cyclization of tosylamide alcohol **21** with sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) to afford functionalized 5,11-methanomorphanthridine **22**, which possesses the basic skeleton of montanine-type alkaloids; and (3) conversion of **30a** to allylic chloride **31** by treatment with PhSeCl in MeOH under ultrasonication followed by $NaIO_4$ oxidation. A formal total synthesis of (±)-manthine (**6**) was also accomplished.

Introduction

Montanine-type alkaloids such as montanine (**1**),[2] coccinine (**2**),[2] *O*-acetylmontanine (**3**),[3] pancracine (**4**),[4] and brunsvigine (**5**)[5a] have a 5,11-methanomorphanthridine ring system unique among the *Amaryllidaceae* alkaloids.[6] Montanine-type alkaloids are attractive synthetic targets for synthetic chemists because of their unique architectures and their pharmacological promise.[7] Although there is a report[8] on synthetic studies of montanine-type alkaloids, synthesis of the 5,11-methanomorphanthridine ring system other than by conversion[2b] of haemanthamine to manthine (**6**) has been unsuccessful. However, very recently, we succeeded in a synthesis of the ring system[9] and the total syntheses[1] of (±)-montanine (**1**), (±)-coccinine (**2**), and (±)-pancracine (**4**). Concurrently, a total synthesis of (±)-pancracine (**4**) was reported by Overman and Shim.[10]

In the present paper, we describe stereoselective total syntheses of the title alkaloids, (±)-montanine (**1**), (±)-coccinine (**2**), (±)-*O*-acetylmontanine (**3**), (±)-pancracine (**4**), and (±)-brunsvigine (**5**), using as the key step reductive cyclization of tosylamide alcohol **21** with sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) to afford functionalized 5,11-methanomorphanthridine **22**. A retrosynthetic analysis for these alkaloids is depicted in Scheme I.

Results and Discussion

Synthesis of Key Compound 23a. Synthesis of key compound **23a** was carried out as follows (Scheme II). Reaction of *cis*-cyclohexenedicarboxylic acid anhydride **7** with 3,4-(methylenedioxy)phenylmagnesium bromide in tetrahydrofuran (THF) at 0 °C afforded keto acid **8** in 96% yield. Keto acid **8** was converted to the acid azide, and

(1) For preliminary communication of a part of this work, see: Ishizaki, M.; Hoshino, O.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 7079.
(2) (a) Wildman, W. C.; Kaufman, C. J. *J. Am. Chem. Soc.* **1955**, *77*, 1248. (b) Inubushi, Y.; Fales, H. M.; Warnhoff, E. W.; Wildman, W. C. *J. Org. Chem.* **1960**, *25*, 2153.
(3) Wildman, W. C.; Brown, C.; Michei, K.-H.; Bailey, D.; Heimer, N.; Walffer, R. Murphy, C. *Pharmazie* **1967**, *22*, 725.
(4) Sandberg, F.; Michel, K.-H. *Lloydia* **1963**, *26*, 78.
(5) (a) Dry, L. J.; Poynton, M.; Thompson, M. E.; Warren, F. L. *J. Chem. Soc.* **1958**, 4701. (b) Laing, M.; Clark, R. C. *Tetrahedron Lett.* **1974**, 583. (c) Clark, R. C.; Warren, F. L. *Tetrahedron* **1975**, *31*, 1855.
(6) Martin, S. F. In *The Alkaloids*; Brossi, A. R., Ed.; Academic Press: New York, 1987; Vol. 30, Chapter 2.
(7) Cf. Dictionary of Alkaloids; Southon, I. W., Buckingham, J., Eds.; Chapman and Hall: London, 1989; C-00291, M-00331.
(8) Sanchez, I. H.; Larraza, M. I.; Rojas, I.; Brena, F. K.; Flores, H. J. *Heterocycles* **1985**, *23*, 3033.
(9) (a) Hoshino, O.; Ishizaki, M. *Chem. Lett.* **1990**, 1817. (b) Hoshino, O.; Ishizaki, M.; Saito, K.; Yumoto, K. *J. Chem. Soc., Chem. Commun.* **1990**, 420.
(10) Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005.

0022-3263/92/1957-7285$03.00/0