added aqueous sodium hydroxide (4 mL, 1 N). The resulting mixture was heated for 5 h at 60 °C. After extraction with dichloromethane the ester **44** (116 mg, 92%) was isolated: IR 1740; ^{1}H NMR 7.38 (m, 5 H), 6.27 (m, 1 H), 6.07 (m, 1 H), 4.88 (d, J = 8, 1 H), 3.77 (m, 2 H), 3.10 (br s, 1 H), 2.77 (d, J = 8, 1 H), 1.17 (d, J = 7, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 0.80 (s, 3 H, CH_3).

Hydrolysis of Ester 44. A solution of ester **44** (35 mg, 0.089 mmol) in methanol (1.5 mL) and aqueous sodium hydroxide (2.5 mL, 1.5 N) was stirred at 80 °C for 2 days. After dilution with water the resulting mixture was extracted with dichloromethane. After evaporation of the organic layer, the residue was purified by preparative TLC and afforded amino alcohol **6** (12.9 mg, 56%), $[\alpha]_D$ = −52° (c = 1.29).

The alkaline aqueous layer was acidified with hydrochloric acid (10%) and extracted with dichloromethane. The residue was purified by preparative TLC (ethyl acetate–heptane 70:30) and afforded the acid **45** (7 mg, 52%): $[\alpha]_D$ = +134° (c = 0.7 in $CHCl_3$); $[\alpha]_D$ = +119° (c = 0.56 in 95% EtOH) (lit.[27b] $[\alpha]_D$ = −151° (in 95% EtOH)).

Treatment of Oxazolines 24 and 28 with Benzyl Chloroformate. Preparation of Esters Carbamates 46 and 47. To a stirred solution (2 M) of oxazoline and sodium bicarbonate (2.2 equiv) in a mixture of dichloromethane–water (50:50) and benzyl chloroformate (1.1 equiv) was added dropwise at room temperature. The resulting mixture was stirred for 6 h and extracted with dichloromethane. After usual treatment the residue was purified by column chromatography. **46**: 93%; mp 84–85 °C (pentane); IR 3450, 2950, 1780, 1720, 1500, 1450, 1180; ^{1}H NMR (two conformers) 7.28 (m, 5 H), 6.23 (m, 1 H), 6.03 (m, 1 H), C_5-H and C_6-H, 5.12 (2 s, 2 H, CH_2-Ar), 4.95 (br s, 1 H, NH), 4.83 (d, J = 8, 1 H, C_3-H), 3.97 (2 d, J = 8, 1 H, C_2-H), 3.06 (m, 1 H), 2.45 (br s, 1 H), 2.33 (m, 1 H), 1.75 (d, J = 5, 1 H), 1.70 (m, 3 H), 1.60 and 1.30 (2 m, 4 H), 1.15 (d, J = 7, 3 H, C_3-CH_3), 1.02 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3), 0.82 (s, 3 H, CH_3); MS m/z 477 ($M^{\bullet+}$), 371, 328, 287, 286, 242, 196, 194, 135, 92, 91 (100); $[\alpha]_D$ = +25° (c = 1). Anal. Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06. Found: C, 74.38; H, 8.06. **47**: 82%; IR 3450, 2950, 1740, 1720, 1500, 1450, 1150; ^{1}H NMR (two conformers) 7.38 (m, 5 H), 6.13 and 5.92 (2 m, 1 H), C_5-H and C_6-H, 5.10 (2 H, 2 s, CH_2Ar), 4.95 (s, 1 H, NH), 4.83 (d, J = 8, 1 H, C_3-H), 3.93 (2 d, J = 8, 1 H, C_2-H), 312 (br s, 1 H), 2.87 (m, 3 H), 1.71 (d, J = 5, 1 H), 1.97–1.62 (m, 3 H), 1.40 and 1.23 (2 m, 4 H), 0.99 (s, 3 H, CH_3), 0.87 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3); MS m/z 423 ($M^{\bullet+}$) 196, 194, 135, 92, 91 (100); $[\alpha]_D$ = +28° (c = 4.77). Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85. Found: C, 73.62; H, 7.88.

Hydrolysis of Ester Carbamates 46 and 47. To a solution of esters carbamates **46** or **47** (0.3 mmol) in methanol (3.5 mL) was added an aqueous solution of sodium hydroxide (1.5 mL, 2.5 N). The reaction mixture was heated at 80 °C for 14 h and diluted with water. After extraction with dichloromethane the organic layer was washed with water, dried with magnesium sulfate, and evaporated under vacuum. The residue, dissolved in xylene and evaporated under vacuum in order to distill benzylic alcohol, afforded amino alcohol **7** (90%), $[\alpha]_D$ = −44° (c = 1.5). The aqueous layer after acidification with hydrochloric acid was extracted with ether. After usual treatment pure acids **45** and **48** were isolated, respectively. **45**: 96%; IR 3300, 2950, 1710, 1110; ^{1}H NMR 6.27 and 6.03 (2 m, 2 H, C_5-H and C_6-H), 3.12 (br s, 1 H, C_2-H), 2.48 (br s, 1 H, C_1-H), 2.40 (m, 1 H, C_3-H), 1.80 (m, 1 H, C_4-H), 1.55 and 1.48 (2 m, 2 H, C_7-H_2), 1.18 (d, J = 7, 3 H, C_3-CH_3); $[\alpha]_D$ = +131° (c = 3.14 in 95% EtOH) (Lit.[27b] $[\alpha]_D$ = −151° (in 95% EtOH)) (enantiomer of **45**). **48**: 89%; IR 3300, 2950, 1710, 1110; ^{1}H NMR 6.22 and 5.98 (2 m, 2 H, C_5-H and C_6-H), 3.32 (br s, 1 H, C_2-H), 2.95 (m, 2 H, C_3-H_2), 1.90 (m, 2 H, C_1-H and C_4-H), 1.33 (m, 2 H, C_7-H_2); $[\alpha]_D$ = +144° (c = 0.85, 95% EtOH) (Lit.[27a] $[\alpha]_D$ = +144° (95% EtOH)).

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Chemistry of Oxaziridines. 14.[1] Asymmetric Oxidation of Ketone Enolates Using Enantiomerically Pure (Camphorylsulfonyl)oxaziridine

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Abstract: The reagent-controlled asymmetric oxidation of tri- and tetrasubstituted ketone enolate anions **4** and **8** by enantiomerically pure (camphorylsulfonyl)oxaziridine **2** has been investigated. The stereoselectivities for oxidation of trisubstituted enolates **4a–d** are good to excellent, 60–95% ee, while those for tetrasubstituted enolates **4e** and **8** are lower; i.e., 21–30% ee. Isolated chemical yields for both types of enolate anions are good to excellent. The sodium enolate anions of **4a–d**, which could be oxidized at −78 °C, gave both higher yields and stereoselectivities than the corresponding lithium or zinc enolates, which required warming to higher temperatures for complete oxidation. The presence of HMPA generally had a deleterious effect on the stereoinduction. However, for oxidation of (*E*)- and (*Z*)-**4d** the highest ee's were observed in the presence of this additive. Investigation of the stereoselective trends reveals that the enolate substitution pattern and the enolate solution structure are the most important stereocontrol elements. The role that the enolate geometry has in the stereoinduction is less clear although *Z* enolates seem to exhibit higher stereoselectivities than the *E* enolates. The results obtained in this study have been formulated into a mechanistic rational involving an S_N2-type substitution of the enolate anion on oxaziridine **2** via an "open" transition state.

The α-hydroxy carbonyl structural unit is commonly found in many biologically active natural products such as sugars, pheromones, antibiotics, terpenes, and alkaloids. Enantiomerically pure α-hydroxy carbonyl compounds are also important synthons for the asymmetric synthesis of natural products[2] and are useful stereodirecting groups.[3] Consequently, numerous studies have

(1) Davis, F. A.; Towson, J. C.; Vashi, D. B.; ThimmaReddy, R.; McCauley, J. P., Jr.; Harakal, M. E.; Gosciniak, D. *J. Org. Chem.* **1990**, *55*, 1254.

(2) Hannessian, S. *Total Syntheis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983; Chapter 2.

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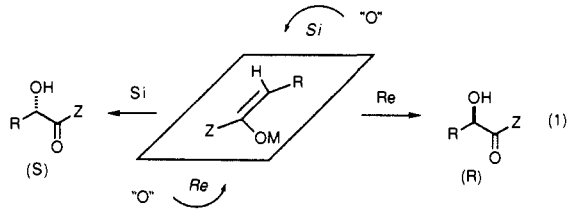
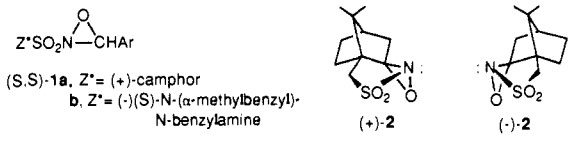
been aimed at developing methodology for the synthesis of this structural unit in chiral nonracemic form.[4]

One of the simplest and most direct methods for introducing a hydroxyl moiety adjacent to a carbonyl group is the enolate oxidation protocol using an aprotic oxidizing reagent, eq 1.[5] Good



to excellent stereoselectivities have been reported for the diastereoselective oxidation of chiral enolates using Vedejs' MoOPH reagent,[6] dibenzyl peroxy dicarbonate,[7] and *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine.[8] However, a disadvantage of any chiral auxiliary based asymmetric synthesis is the necessity for preparing and eventually removing the auxiliary reagent.

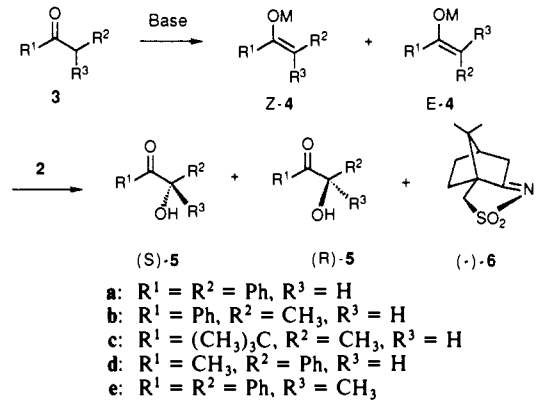
The inherent difficulties of chiral auxiliary based asymmetric synthesis can be avoided by using an enantiomerically pure reagent to control the introduction of chirality into the substrate molecule. In principle the reagent can be "tailored" to induce the desired level of stereoselectivity (i.e., >95% ee). Masamune has termed this approach *reagent-controlled asymmetric synthesis*.[3c] The oxidation of prochiral enolates to optically active α-hydroxy carbonyl compounds requires an aprotic, asymmetric oxidizing reagent. Enantiomerically pure *N*-sulfonyloxaziridines **1** and **2**



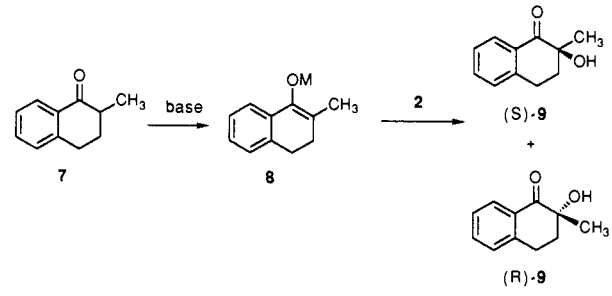
have only recently been introduced for the asymmetric oxidation of enolates.[9,10] To date the (+)- and (-)-(camphorylsulfonyl)-oxaziridines **2** are the most useful of these reagents because they are stable, easily prepared, and commercially available.

In this paper our progress in developing methodology for the reagent-controlled enantioselective oxidation of prochiral ketone enolates to optically active α-hydroxy ketones is described.[11]

Scheme I



Scheme II



Possible reaction parameters responsible for the stereoinduction are identified and analyzed in terms of transition-state models.

Results

The reaction parameters likely to be the principal transition-state control elements for the asymmetric oxidation of enolates include (i) the geometry of the enolate, (ii) the enolate substitution pattern, and (iii) the structure of the enolate in solution. The enolate solution structure will be determined by the counterion, the nature of the solvent, and the presence of various additives such as HMPA. Pioneering studies by Heathcock[12-14] and others[15] have identified similar parameters as important stereocontrol elements in the aldol reaction and base-promoted Michael reactions. To evaluate these reaction parameters, the asymmetric oxidation of acyclic enolates **4a–d** to α-hydroxy ketones **5** by enantiomerically pure **2** was examined (Scheme I). Two tetrasubstituted ketone enolates derived from 1,2-diphenylpropanone (**3e**) and 2-methyl-1-tetralone (**7**) were also examined (Schemes I and II).

Asymmetric Oxidations. In a typical experiment, a solution of the (camphorylsulfonyl)oxaziridine **2** (1.5–2 equiv) was added dropwise to the preformed enolate **4** at −78 °C. The kinetic enolate anions were formed by the slow, dropwise addition of the ketone **3** to a solution of the appropriate base at −78 °C.[14] Enough hexamethylphosphoramide (HMPA) was added to the base, prior to addition of ketone, to afford a 20:1 ratio of THF to HMPA.[16] In control experiments, the reaction progress was monitored by GLC and TLC to determine the optimal temperature for oxidation. For most oxidations of **4** at −78 °C, the reaction was complete

(3) (a) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47. (b) Mukaiyama, T.; Yura, T.; Iwasawa, N. *Chem. Lett.* **1985**, 809. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (d) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876. (e) Evans, D. A.; Bender, S. L. *Tetrahedron Lett.* **1986**, *799*. (f) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, 2653. (g) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629. (h) Dolence, E. K.; Adamczyk, M.; Watt, D. S.; Russell, G. B.; Horn, D. H. S. *Tetrahedron Lett.* **1985**, 1189. (i) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422. (j) Samuels, W. D.; Nelson, D. A.; Hallen, R. T. *Tetrahedron Lett.* **1986**, 3091. (k) Reetz, M. T.; Hullmann, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1600. (l) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(4) For leading references, see: Lohray, B. B.; Enders, D. *Helv. Chim. Acta* **1989**, *72*, 980.

(5) (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. G.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. (b) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203. (c) Vedejs, E.; Larsen, S. *Org. Synth.* **1985**, *64*, 127, and references cited therein. (d) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

(6) Aamboni, R.; Mohr, P.; Waespe-sarcevic, N.; Tamm, C. *Tetrahedron Lett.* **1985**, *26*, 203. Evan, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346. Asmboni, R.; Tamm, C. *Tetrahedron Lett.* **1986**, *27*, 3999. Aamboni, R.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 615.

(7) Gore, M. P.; Vederas, J. C. *J. Org. Chem.* **1986**, *51*, 3700.

(8) (a) Davis, F. A.; Vishwakarma, L. C. *Tetrahedron Lett.* **1985**, 3539. (b) Evans, D. A.; Morrissey, M. M.; Dorrow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346. (c) Enders, D.; Bhushan, V. *Tetrahedron Lett.* **1988**, 2437. (d) Djuric, S. W.; Miyashiro, J. M.; Penning, T. D. *Tetrahedron Lett.* **1988**, 3459. (e) Baker, R.; Castro, J. L. *J. Chem. Soc. Perkin Trans. 1* **1989**, 190. Taschner, M. J.; Aminbhavi, A. S. *Tetrahedron Lett.* **1989**, 1029.

(9) Davis, F. A.; McCauley, J. P., Jr.; Chattopadhyay, S.; Harakal, M. E.; Towson, J. C.; Watson, W. H.; Tavanaiepour, I. *J. Am. Chem. Soc.* **1987**, *109*, 3370.

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

(11) Portions of this work have been reported in preliminary form: (a) Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986**, *51*, 4083. (b) Davis, F. A.; Sheppard, A. C.; Lal, S. G. *Tetrahedron Lett.* **1989**, 779.

(12) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, **1984**, Vol. 3, pp 111–206.

(13) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227. Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. A. *J. Org. Chem.* **1990**, *55*, 132. Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.

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

(15) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(16) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959.

Table I. Oxidation of Ketone Enolates **4** and **8** Using (Camphorylsulfonyl)oxaziridines (**2**) at −78 °C (Unless Otherwise Noted in THF)

entry	ketone[a]	oxaziridine[b]	base[c] (equiv)		additive	oxidation time, min	$R^1COCH(OH)R^2$ **5** % ee (config)	% yield	enolate *Z*/*E*
1	**3a**	(+)-**2**	NHMDS	(1.5)[f]		30	93.8[g] (*S*)	80	100:0
2				(1.5)		30	95.4 (*S*)	78	
3				(1.2)		30	94.0 (*S*)	80	
4				(1.3)		2.5 h	60 (*S*)	64	
5				(1.3)[h]		30	2 (*S*)	35	
6				(1.5)	HMPA	15	63 (*S*)	78	100:0
7			LDA	(1.5)[h]		10	68 (*S*)	65	83:17
8				(1.5)[h]	HMPA	10	6 (*S*)	60	100:0
9			KHMDS	(1.5)		15	93 (*S*)	73	*i*
10		(−)-**2**	NHMDS	(1.5)		30	93 (*R*)	80	100:0
11	**3b**	(+)-**2**	NHMDS	(1.5)		30	62 (*S*)	73	100:0
12				(1.5)		15	60 (*S*)	75	
13				(1.2)		15	59 (*S*)	76	
14				(1.2)[j]	HMPA	20	50 (*S*)	77	100:0
15				(1.2)[k]	HMPA	20	50 (*S*)	78	
16				(1.5)	DME	15	37 (*S*)	72	
17				(1.5)	Et_2O	15	47 (*S*)	76	
18				(1.5)	toluene	15	62 (*S*)	67	
19			LDA	(1.5)[h]		5	40.3 (*S*)	45[l]	100:0
20				(1.5)[h]		20	39 (*S*)	50	
21				(1.5)[m]		1 h	37.5 (*S*)	43	
22				(1.2)[h]		10	39 (*S*)	45	
23				(1.5)[h]	HMPA	10	10.8 (*S*)	47	100:0
24				(1.2)[h]	HMPA	10	13.5 (*S*)	40	
25				(1.5)[h]	DME	15	4 (*R*)	50	
26				(1.5)[h]	Et_2O	15	25 (*S*)	54	
27				(1.5)	toluene	15	52 (*S*)	40	
28			$LDA/ZnCl_2$	(2.0)[h]		10	32 (*S*)	64	100:0
29			KHMDS	(1.5)		5	47 (*S*)	85	*i*
30		(−)-**2**	NHMDS	(1.5)		15	58.2 (*R*)	80	100:0
31	**3c**	(+)-**2**	NHMDS	(1.2)		20	89 (*R*)	71	100:0
32				(1.2)	HMPA	20	76 (*R*)	73	
33			LDA	(1.2)[h]		10	32 (*R*)	55	100:0
34				(1.2)[h]	HMPA	10	12 (*R*)	50	
35	**3d**	(+)-**2**	NHMDS	(1.2)		15	40.4 (*S*)	70	60:40
36				(1.2)	HMPA	15	76 (*R*)	76	94:6
37			LDA	(1.2)[h]		10	3 (*S*)	41	11:89[n]
38				(1.2)[h]	HMPA	15	61 (*R*)	60	95:5
39	**3e**	(+)-**2**	NHMDS	(1.2)		60	3.0 (*S*)	31	80:20
40				(1.2)[h]		30	21 (*S*)	62	76:24
41				(1.2)	HMPA	30	12 (*S*)	59	69:31
42			LDA	(1.2)[h]		30	9 (*S*)	71	31:69
43				(1.2)	HMPA	30	20 (*R*)	57	35:65
44	**7**	(+)-**2**	LDA	(1.2)[o,h]		15	30 (*R*)	90	
45				(1.2)[o,h]	HMPA	15	4 (*S*)	80	
46				(1.5)[o]	toluene	15	64 (*R*)	41	
47			$LDA/ZnCl_2$	(2.0)[h]		10	14.5 (*R*)	77	
48			NHMDS	(1.2)[o,h]		15	16 (*R*)	90	

[a] Typically 0.5-mmol scale. [b] Typically 1.25 equiv based on ketone. [c] Equivalents based on ketone. [d] A total of 3.5 equiv HMPA/ketone added prior to enolization. Ratio THF/HMPA of 20:1. [e] Isolated yields of pure ketone. [f] Oxidation at −90 °C. [g] Percent ee determined with a Daicel Chiral Pak OT(+) HPLC column. [h] Oxidation mixture warmed to 0 °C before quenching. [i] Not determined. [j] Ratio THF/HMPA of 20:1, 3.5 equiv of HMPA/ketone. [k] Ratio THF/HMPA of 60:1, 1.15 equiv of HMPA/ketone. [l] A 20–25% recovery of **3b** for entries 19–24. [m] Reaction at −45 °C. [n] A 1:1 mixture of enolate **4d** (*Z*/*E* 11:89) and the nonconjugated enolate **12**. [o] Enolate was warmed to 0 °C for 5 min before oxidation.

within 15–30 min. Alternatively, the mixtures were warmed to −45 or 0 °C for 2 min after addition of the oxaziridine was complete. Oxidation of tetrasubstituted enolates **8** and **4e** at −78 °C failed or were incomplete and required warming to 0 °C for several minutes prior to quenching. After the oxidation was complete, the reaction mixture was quenched at −78 °C by addition of aqueous NH_4I to effect the reduction of oxaziridine **2** to the camphorsulfonimine **6**. This procedure facilitates chromatographic isolation of the α-hydroxy ketones **5** and **9** that have R_f's similar to those of **2**. These results are summarized in Table I.

Product Enantiomeric Purity and Absolute Configuration. The enantiomeric purity (percent ee) of benzoin (**5a**) was determined by using a chiral HPLC column while **5b–e** and **9** were evaluated by using the chiral shift reagent $Eu(hfc)_3$ and/or optical rotation measurements. The stereochemistry of **5a**,[17] 1-hydroxy-1-phenyl-2-propanone (**5d**),[18] 2-hydroxy-1,2-diphenylpropanone (**5e**),[18] and 2-hydroxy-2-methyl-1-tetralone (**9**)[19] have been previously reported. The absolute configurations of 2-hydroxy-1-phenyl-1-propanone (**5b**) and 4-hydroxy-2,2-dimethyl-3-pentanone (**5c**) were established by independent synthesis as described below.

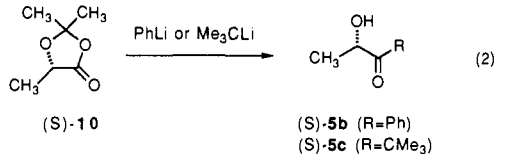
Addition of either phenyl or *tert*-butyllithium to (*S*)-2,2,5-trimethyl-4-dioxolanone (**13**),[20] under a variety of conditions, resulted in complex mixtures and low isolated yields (10–17%) of the desired (*S*)-α-hydroxy ketones **5b–c** (eq 2). Attempts to increase the yields of **5b,c** by altering the reaction conditions or using Grignard reagents failed. ^1H NMR shift reagent experi-

(17) Kenyon, J.; Patel, R. *J. Chem. Soc.* **1965**, 435.

(18) (a) Roger, A. *Biochem. Z.* **1931**, *230*, 320; *Chem. Abstr.* **1931**, *25*, 2426. (b) Mckenzie, A.; Ritchie, A. *Ber. Dtsch. Chem. Ges.* **1937**, *70B* 23; *Chem. Abstr.* **1937**, *31*, 2199. (c) Brewster, J. H. *J. Am. Chem. Soc.* **1956**, *78*, 4061. (d) Leithe, W. *Ber. Dtsch. Chem. Ges.* **1932**, *65*, 660. (e) Sayre, L. M.; Jin, S.-J. *J. Org. Chem.* **1984**, *49*, 3498. (f) Fierz, A.; McGarrity, J. S.; Dahn, H. *Helv. Chim. Acta* **1975**, *58*, 1058.

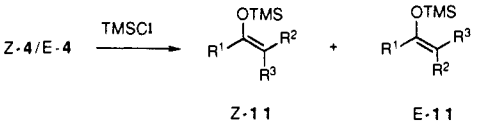
(19) Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* **1988**, 2835.

(20) (a) Oeda, H. *Bull. Chem. Soc. Jpn.* **1935**, *10*, 187. (b) Farines, M.; Soulier, J. *Bull. Soc. Chim. Fr.* **1970**, 332.



ments verified that **5b,c** had not racemized under the reaction conditions. After completion of this work, the assignment of the absolute configuration to (*S*)-**5b** was confirmed independently by Tsuchihashi and co-workers.[21]

Determination of Enolate Geometries. The geometries of the acyclic enolates **4** generated in these studies were determined by trapping with trimethylsilyl chloride [(TMS)Cl] to give the corresponding *E* and *Z* enol silanes **11** as previously described.[22] The ratios of the (*Z*)- and (*E*)-**11** were determined by ^{1}H NMR or ^{13}C NMR analysis of the crude reaction mixtures.



1-Phenyl-1-[(trimethylsilyl)oxy]propene (**11b**) and 2,2-dimethyl-3-[(trimethylsilyl)oxy]-3-pentene (**11c**), obtained on LDA enolization of ketones **3b** and **3c**, respectively, were assigned the *Z* geometry by using ^{13}C NMR spectroscopy.[14] These stereochemical assignments were based on the fact that allylic carbons in *cis*-alkenes resonate at higher field than those in the *trans*-alkenes, with the same trend being observed in **11**. The geometry of **4c**, produced by using sodium bis(trimethylsilyl)amide (NHMDS) with or without HMPA, is expected to be *Z* because these conditions favor equilibration to the thermodynamically favored *cis*-enolate anion.[16]

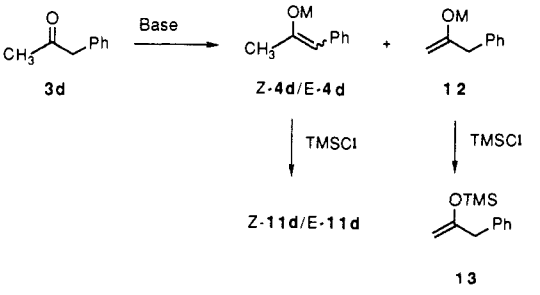
The *Z*/*E* ratios of 1,2-diphenyl-1-[(trimethylsilyl)oxy]ethylene (**11a**) were measured by ^{1}H NMR. The vinylic hydrogens in benzene-d_6 appear at δ 6.20 and 6.26 ppm with the higher field absorption corresponding to the major isomer. Analogous to the enolization of 1-phenyl-1-propanone (**3b**),[14] it was anticipated that the *Z* enolate would also be kinetically favored on enolization of **3a** using LDA (Table I, entry 7, *Z*/*E* ratio of 83:17). The use of HMPA[16] or a less reactive base such as NHMDS[23] is also expected to favor the thermodynamic *Z* enolate anion (Table I, entries 1 and 3).[14,16,24]

Enolate anion formation from 1-phenyl-2-propanone (**3d**) is complicated by the fact that three enolates (*Z*)-**4d**/(*E*)-**4d** and **12** are produced giving enol silanes **11** and **13**, respectively (Scheme III). The geometries of (*Z*)-**4d**/(*E*)-**4d** were determined by ^{1}H NMR in benzene as described by House.[22a] The increasing amounts of (*Z*)-**11d** observed when NHMDS and HMPA were used were consistent with conditions favoring equilibration and leading to the more thermodynamically stable *Z* enolate anion (Table I, compare entry 37 with entries 35, 36 and 38).

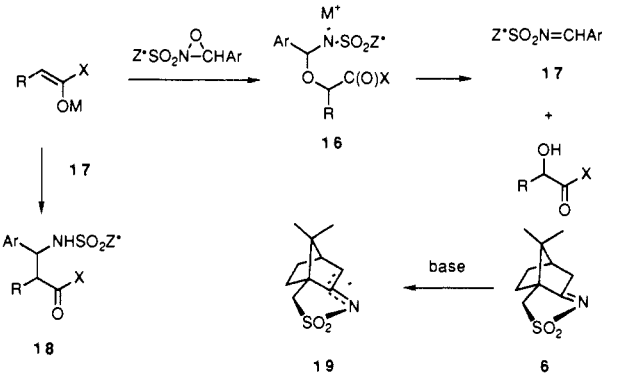
Corey reported that 1-phenyl-2-propanone (**3d**) gives only the thermodynamically favored regioisomer **4d** upon treatment with LDA.[24] In the present study, trapping enolate under Corey's conditions, invariably led to a 1:1 mixture of enol silanes **11d** (*Z*/*E* ratio 11:89) and **13** (Table I, entry 37). Under equilibrium conditions (NHMDS or HMPA), the thermodynamically stable *Z* enolate **4d** was formed exclusively (Table I, compare entry 37 with entries 35, 36 and 38).

An 80:20 mixture of enol silanes **11e** was obtained on trapping the sodium enolate of 1,2-diphenylpropanone (**3e**) with (TMS)Cl. In these compounds the trimethylsilyl protons appear at δ −0.22 and 0.05 ppm, with the higher field protons corresponding to the

Scheme III

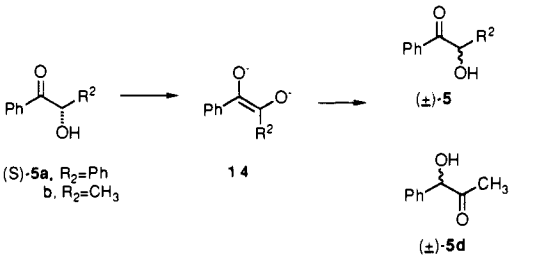


Scheme IV



Z enol silane, confirmed by an NOE experiment.

Enantiomeric Stability of α-Hydroxy Ketones. α-Hydroxy carbonyl compounds on treatment with strong bases are known to afford enediolates **14**.[25] This suggests that **5** could potentially racemize under the reaction conditions. Indeed, (−)-(*S*)-2-hydroxy-1-phenyl-1-propanone (**5b**) is reported to slowly racemize in aqueous base.[26] To examine the possible racemization of **5** the base-promoted racemizations of (+)-(*S*)-**5a** and (−)-(*S*)-**5b** were explored by treatment with NHMDS and LDA. These results are summarized in Table II.



The results in Table II show that racemization of (*S*)-benzoin (**5a**) by NHMDS is slow at −78 °C, with only a small loss of enantiomeric purity (i.e., 98–92% ee after 30 min; Table II, entry 1). The ee is lowered from 95 to 60% when the oxidation is continued for 2.5 h (Table II, entry 2). *The importance of keeping the oxidation temperature below −78 °C and quenching at this temperature is emphasized by the fact that warming to 0 °C for 30 min prior* to *quenching gave racemic* **5a** (see Table I, entry 5).

(*S*)-1-Phenyl-1-propanone (**5b**) is also only slowly racemized at −78 °C by NHMDS. However, with LDA, followed by warming to 0 °C, **5b** not only undergoes racemization, but also isomerizes to ketone **5d** (Table II, entries 4 and 5).

Although this study suggests that α-hydroxy ketones **5** can be racemized in the presence of base, the rate of racemization under controlled conditions (−78 °C for 15–30 min) is slow for several reasons. First, less base is present during oxidation than the amount used in the base-promoted racemization studies (Table

(21) Honda, Y.; Ori, A.; Tsuchihashi, G. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1027.
(22) (a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (b) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462, 4464.
(23) Wannagat, U.; Niederprum, H. *Chem. Ber.* **1961**, *94*, 1540.
(24) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, 495.
(25) For leading references, see: Davis, F. A.; Haque, M. S.; Prezeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021.
(26) Chenevert, R.; Thiboutot, S. *Chem. Lett.* **1988**, 1191.

Table II. Base-Promoted Racemization of Optically Active α-Hydroxy Ketones (*S*)-**5** in THF

entry	R^2	temp, °C (time, min)[a]	base (equiv)		**5b**/**5d**[b]	% ee	yield[c]
1	Ph[d] (**5a**)	−78 (30)	NHMDS	(1.3)		92	75
2		−78 (2.5 h)		(1.3)		60	66
3	Me[e] (**5b**) (63% ee)	−78 (30)		(1.3)		57	78
4		0 (15)	LDA	(1.5)	52:48		70
5		0 (15)		(1.5)[f]	41:59		66

[a] The hydroxy ketone was added to a −78 °C solution of base. [b] Ratio determined by ^1H NMR. [c] Recovered yield of **5**. [d] (+)-(*S*)-**5a** was 97.7% ee. [e] (−)-(*S*)-**5b** was 63% ee. [f] Reaction carried out in a 20:1 (v/v) mixture of THF/HMPA.

II). Second, if the camphorsulfonimine **6** is prsent, it will quench excess base by forming the corresponding, highly stable aza enolate (see Scheme IV).[27] Finally, the α-hydroxy ketone **5** may not even be present until quenching and workup (vide supra). Consistent with the small amount of racemization of **5**, under the conditions of oxidation, are the high enantioselectivities obtained for **5a** and **5c** (89–95% ee) and the fact that ketone **5d** is not detected in the oxidation of **3b**.

Before discussing how the stereoselectivity trends summarized in Table I are influenced by the reaction parameters, relevant information on the solution structure of enolates will be briefly discussed.

Solution Structures of Enolates. The pioneering studies of Jackman,[28] Seebach,[29] Arnett,[30] and Williard[31-33] have left little doubt that enolates exist and react as molecular aggregates in solution. It is also known that there is a strong similarity between the X-ray crystallographic structures of enolates and their aggregation state in solution.[28,30,32] In the solid state, the lithium enolates of pinacolone and cyclopentanone exist as tetrameric aggregates with each Li^+ ion bonded to three enolate oxygens and an O atom of a THF solvent molecule.[34] In the absence of THF, the former enolate aggregates as an unsolvated hexamer.[31] Williard and Carpenter reported that the sodium enolate of pinacolone aggregates as a tetramer solvated by an unenolized ketone molecule, while the potassium derivative exists as a hexamer solvated by THF.[31] A dimeric lithium ketone enolate complex with LDA has recently been characterized.[32]

Ketone enolates are known to exist as molecular aggregates in solution as determined by NMR studies and osmometic measurements.[28,29] Complexation numbers of between 1 and 4 (and in some cases higher) have been observed for a number of ketone enolates, and the degree of aggregation or complexation is highly dependent on the solvent and temperature.[28] For example, the Li enolate of cyclopentanone in THF gives an aggregation number of 2.6–2.8, corresponding to a tetramer/dimer mixture of 1:2.[34] In THF, the Li enolate of pinacolone gives an aggregation number of 4, in good agreement with the solid-state structure.[30] A detailed ^1H and ^{13}C NMR study of the lithium enolate of propiophenone, **4b**, in solution has recently been described.[35] These studies revealed that there is an equilibrium between the dimeric and the tetrameric forms and that the dimer appears to be more reactive than the tetramer. The former, but not the latter, forms mixed complexes with LDA. Finally, the addition of HMPA to **4b** appears not to destroy the dimeric or tetrameric aggregates.

Because the structure of the reacting enolate species in solution is not known with certainty, relating its aggregation state with its reactivity continues to be problematic. Nevertheless, the

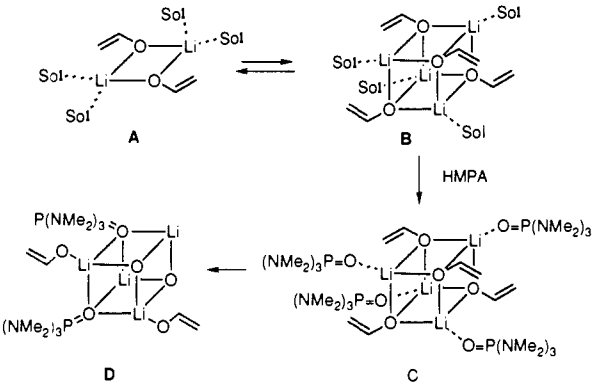


Figure 1. Seebach model for the reaction of enolates in solution.

Seebach model,[29,34] for the reaction of enolates with electrophiles, continues to receive credibility for its value in rationalizing enolate reactivity increases (Figure 1). In this model, the higher reactivity of the dimeric enolate A is attributed to less steric hindrance. Seebach suggested that the effect of HMPA, long known to increase enolate reactivity,[36] is believed to result from its ability to displace the enolate from the aggregate structure, becoming part of the complex nucleus (D). The enolate is not only more accessible to the electrophile, but should be more nucleophilic because the enolate oxygen is now coulombicly attached to only one Li^+ atom. Similar arguments can be applied to the other alkali metal enolates.

Discussion

Several trends are evident from the results summarized in Table I for the asymmetric oxidation of enolates by (camphoryl-sulfonyl)oxaziridine **2**. First, as observed for other asymmetric oxidations using enantiomerically pure *N*-sulfonyloxaziridines, the configuration of the oxaziridine three-membered ring controls the product stereochemistry.[37] For example, oxidation of the sodium enolates of deoxybenzoin (**3a**) and 1-phenyl-1-propanone (**3b**) with (+)-**2** gave the corresponding (*S*)-α-hydroxy ketones **5a,b**, while oxidation with (−)-2 gave (*R*)-**5a,b** (Table I, compare entries 2 and 11 with 10 and 30). Thus, either α-hydroxy ketone optical isomer is readily available simply by selecting the proper *N*-sulfonyloxaziridine oxidizing reagent.

Sodium enolates were generally more reactive than corresponding lithium or zinc enolates and were completely oxidized by **2** at temperatures of −78 to −40 °C. Both the highest chemical yields (71–90%) and the highest enantioselectivities (95.4–16% ee) were obtained under these conditions. By contrast, the less reactive lithium and zinc enolates required warming to 0 °C for oxidation. Lower chemical and optical yields resulted, and 15–25% of the starting ketone **3** was typically recovered. Longer reaction times failed to increase the yields. The lower yields under these conditions may be an example of the "hidden proton" effect where diisopropylamine, formed on deprotonation of **3**, quenches the enolate.[29]

(27) Davis, F. A.; Weismiller, M. C.; Lal, G. S.; Chen, B. C.; Przeslawski, R. M. *Tetrahedron Lett.* **1989**, 1613.
(28) For a review, see: Jackman, L M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737.
(29) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624, and references cited therein.
(30) Arnett, E. M.; Fisher, F. J.; Nichols, M. A.; Ribeiro, A. A. *J. Am. Chem. Soc.* **1989**, *111*, 748.
(31) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462.
(32) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539.
(33) Williard, P. G.; MacEwan, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 7671.
(34) Amstuz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617.
(35) Humma, R. R.; Cloux, R.; Haider, A., unpublished results as reported in ref 28.
(36) (a) Kackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494. (b) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622. (c) Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764.
(37) For a review on the chemistry of *N*-sulfonyloxaziridines, see: Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

The sodium enolates of 1,2-diphenylpropanone (**3e**) and 1-methyl-2-tetralone (**7**) were not completely oxidized at −78 °C and required warming to 0 °C. At the higher temperatures, yields were good to excellent (70–90%), but the stereoselectivities were low (Table I, entries 39–43 and 44–48, respectively). These results were not unexpected considering the fact that these tetrasubstituted enolates are more sterically hindered than the other enolates.

Progressing down the series lithium, sodium, and potassium enolates of ketones, House reported that increasing ion-pair separation occurs.[38] Thus, the greater reactivity of the sodium and potassium enolates compared to their lithium counterparts toward oxidation by **2** was attributed to greater ion-pair separation. It is worth noting that, except for phenylacetone (**3d**), all of the lithium enolates failed to react with **2** at −78 °C even in the presence of HMPA, which is known to increase the reactivity of lithium enolates in alkylation reactions (see Figure 1, structures D).[29] We speculate that the higher reactivity of the sodium (potassium) enolates may result from a larger concentration of the more reactive dimeric enolate being present (Figure 1, structure A). The higher stereoselectivities observed for the sodium enolates may simply be related to the fact that they are oxidized at a lower temperature than the lithium or zinc enolates.

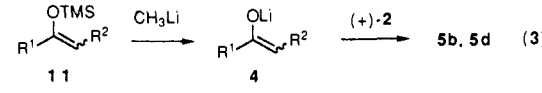
The order of increasing solvent polarity is toluene < Et_2O < THF < DME < THF/HMPA.[36a,38-40] The results summarized in Table I give no clear correlation between the stereoselectivities and the coordinating ability or polarity of the solvent. As already mentioned, addition of HMPA, a good coordinating solvent, generally gave lower stereoselectivities. In toluene, the least polar and poorest coorinating solvent, there was a significant increase in the stereoinduction for the oxidation of the lithium enolates of **3b** and **7**. In these examples, the percent ee improved from 40 and 30% to 52 and 64%, respectively, in THF and toluene (Table I, compare entries 19 and 44 with 27 and 46). It is worthwhile noting that in toluene it was possible to oxidize these enolates at −78 °C. One of the problems with toluene as a solvent for enolate oxidations is that ketone reduction[41] competes with enolization when LDA is used as the base. Thus, enolization of propiophenone (**3b**) with LDA at −78 °C in toluene gave ~35% 1-phenyl-1-propanol under all conditions. Reduction of 2-methyl-1-tetralone (**7**) under these conditions was not detected.

The results summarized in Table I suggest that the enolate substitution pattern has a strong influence on the stereoselectivities of the oxidation. For oxidations under similar conditions (sodium enolates at −78 °C), the enolate of deoxybenzoin, **4a**, gave the highest stereoselectivity (i.e., 95% ee). Replacement of phenyl in **4a** by methyl to give the propiophenone enolate, **4b**, lowered the enantioselectivity to 62%. Replacement of the phenyl group in **4b** by a *tert*-butyl group increased the stereoinduction for oxidation of **4c** to 89%, but the configuration of the product changes from *S* to *R*. Transposing the methyl and phenyl groups in **4b** to give enolate **4d** diminished the percent ee from 62 to 40%. The largest effect was observed for the tetrasubstituted enolate **4e**, where replacing hydrogen by methyl in **4a** lowers the percent ee from 95 to 3%.

Influence of Enolate Geometry. Studies of the aldol and Michael reactions reveal that there is often a strong correlation between the enolate geometry and the stereochemistry of the product.[12,13] Generally *Z* enolates exhibit higher selectivity than the *E* enolates, although this trend varies with the structure of the enolate. Examination of the data in Table I suggests that the enolate geometry also plays a role in establishing the stereostructure of the α-hydroxy ketone **5**.

For the asymmetric oxidation of an enolate anion, it is possible to evaluate only the *E*/*Z* selectivity for the lithium enolates of **4** because all of the sodium enolates have the *Z* geometry. *Z* enolates seem to exhibit higher selectivity than the *E* enolates for asymmetric oxidation (Table I, compare entries 7, 19, 33, and 38 with 37). However, this interpretation is clouded by the seemingly contradictory effect that HMPA has on the stereoselectivity. For enolates **4a–c**, HMPA influences the percent ee without apparently changing the enolate geometry (Table I, compare entries 7 and 8 as well as entries 19 and 23). On the other hand, enolization of phenylacetone (**3d**) in the presence of HMPA results in a change of enolate geometry from *E* to *Z* and formation of (*R*)-**5d** (Table I, compare entries 37 and 38). Therefore, it is unclear whether the effect that HMPA has on the percent ee is due to higher selectivity for the *Z* enolate or to a fundamental change in the enolate solution structure.

To determine the influence of the enolate geometry on the asymmetric oxidation of enolates, it is necessary to have the pure *E* and *Z* enolates and then to oxidize them under identical conditions. This was accomplished by generating the *E* and *Z* enolates of **4b** and **4d** by treating the corresponding *E* and *Z* enol silanes **11** with MeLi followed by oxidation with (+)-**2** (eq 3).



Enol silanes (*Z*)-**11d**, (*E*)-**11d**, and (*Z*)-**11b** were prepared by trapping the related enolates **4** with trimethylsilyl chloride. The *E* enol silane of propiophenone **3b** had previously been prepared in low yield by Heathcock and co-workers by HPLC separation of a 70:30 mixture of *Z* and *E* isomers of **11b**.[42] We recently reported a more convenient method for the synthesis of (*E*)-**11b** and stereodefined enol silanes in general, involving the stereospecific oxidation of vinyl anions using bis(trimethylsilyl) peroxide.[43] Indeed, oxidation of (*E*)-1-lithio-1-phenyl-1-propene afforded a 70% isolated yield of **11b** as an 93:7 mixture of the *E* and *Z* isomer.

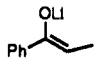
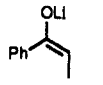
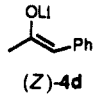
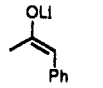
Enol silanes **11b** and **11d** were cleaved at 0 °C with 0.95 equiv of methyllithium. After 1 h, the mixture was cooled to −78 °C, and the enolates were oxidized with (+)-**2** as previously described. When HMPA used, it was added at −78 °C after cleavage of the enol silane. If more than 0.95 equiv of methyllithium are used to generate enolate anion **4b** from 1-phenyl-1-[(trimethylsilyl)oxy]propene (**11b**), the isomerized 1-hydroxy-1-phenyl-2-propanone (**5d**) is detected in addition to **5b** after oxidation (Table III, entries 2 and 4–6). The amount of **5d** increases in the presence of HMPA and with increasing amounts of MeLi. These results are summarized in Table III.

Examination of the data in Tables I and III reveals several important facts. First, the stereoselectivity for oxidation of the *Z* enolates is identical whether the enolate is generated by using LDA or from **11** by using MeLi (compare entries 1, 3, and 8 in Table III with entries 22, 24, and 37 in Table I, respectively). This suggests that the presence or absence of the amine/amide has little effect on the stereoselectivity. The association of amine and amide bases with enolates in solution can, in other cases, influence their reactivity.[29,44,45]

Second, (*Z*)-**4b** exhibits higher stereoselectivity than the (*E*)-**4b**, 35 vs 4% ee, respectively (Table III, compare entries 1 and 6). Addition of HMPA to (*Z*)-**4b** lowers the stereoinduction (entries 1 and 3), but has little effect on the *E* enolate (entries 6 and 7). Quite different results are observed for the *E* and *Z* enolates of phenylacetone (**4d**). In the absence of HMPA, 1-hydroxy-1-phenyl-2-propanone (**5d**) is obtained in 6–9% ee while oxidation in the presence of HMPA improves the enantioselectivity to 56–68%. Significantly, oxidation of both (*E*)- and (*Z*)-**4d** in the presence of HMPA, gave **5d** having the *R* configuration.

(38) (a) House, H. O.; Auerbach, R. A. *J. Org. Chem.* **1973**, *38*, 514. (b) House, H. O.; Prabhu, A. V.; Philips, W. V. *J. Org. Chem.* **1976**, *41*, 1209.
(39) Jackman, L. M.; Szeverenji, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954.
(40) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.
(41) Kowalski, C.; Creary, X.; Rolin, A. J.; Burke, C. M. *J. Org. Chem.* **1978**, *43*, 2601. Wittig, G.; Reiff, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 7.
(42) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027.
(43) Davis, F. A.; Lal, G. S.; Wei, J. *Tetrahedron Lett.* **1988**, 4269.
(44) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373.
(45) Strazewski, P.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 1041.

Table III. Oxidation of the *Z* and *E* Lithium Enolates of Ketones **3b** and **3d** Using (+)-**2**

entry	enolate	MeLi, equiv	additive[a]	*Z*/*E*	% yield[b]	**5b**/**5d**[c]	% ee[d] (config)
1		0.95		97:3	45	100:0	35 (S)
2		1.1			48	95:5	
3		0.95	HMPA		40	100:0	11 (S)
4	(*Z*)-**4b**	1.1	HMPA		36	75:25	
5		1.25	HMPA		50	67:33	
6		1.0		7:93	45	97:3	4 (*R*)
7		0.95	HMPA		37	100:0	0
	(*E*)-**4b**						
8		0.95		95:5	51	0:100	6 (*S*)
9		0.95[h]			58	0:100	10 (*R*)
10		0.95	HMPA[g]		68	0:100	68 (*R*)
	(*Z*)-**4d**						
11		0.95[e]		11:89	42[f]	0:100	9 (*S*)
12		0.95	HMPA[g]		31[f]	0:100	56 (*R*)
	(*E*)-**4d**						

[a] Reaction mixtures were warmed to 0 °C unless indicated otherwise. (a) Ratio of THF/HMPA 20:1 when additive was present. [b] Isolated yields. [c] Ratio determined by ^{1}H NMR. [d] % ee determined using the chiral shift reagent Eu(hfc)$_3$ and/or by rotation. [e] 1:1 mixture of 4d and the nonconjugated enolate 12. [f] Yield based on total enolate content. [g] Oxidation at −78 °C. [h] Oxidation at −45 °C to −50 °C.

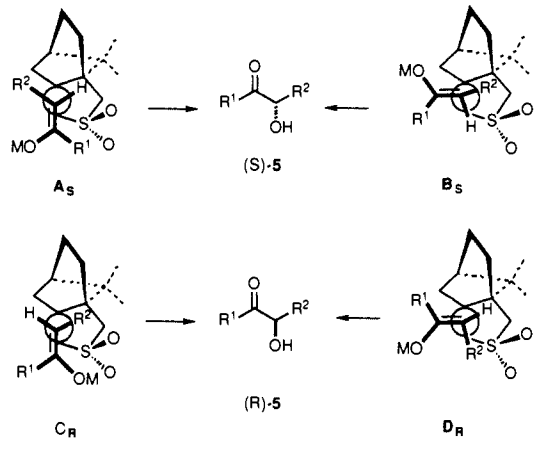


Figure 2. Proposed transition-state structures for the asymmetric oxidation of the (*Z*)-**4a–d** by (+)-**2**.

While equilibration of (*E*/*Z*)-**4d** under the reaction conditions could explain these results, we feel, for several reasons, that enolate equilibrium is not significant. First, House and co-workers previously demonstrated that the isomerization of enolates does not take place on cleavage of enol silanes with MeLi.[22] Second, oxidation is fast, even at −78 °C, and similar results are observed for the LDA-derived enolates. Third, mechanisms for *Z*/*E* equilibrium of enolates generally involve aldol reactions[16] and/or proton transfer from amine bases[40] and carbonyl compounds.[22] Since carbonyl compounds and amines are absent under our conditions, equilibration via these mechanisms is not important. Finally, if excess base were present, **5d** should have been detected in experiments starting with **3b**.

Interpretation of the influence that HMPA has on the oxidation of enolate (*Z*)- and (*E*)-**4d** is complicated by the fact that the temperatures of oxidation are −50 to 0 °C in the absence of HMPA and −78 °C in the presence of HMPA (Table III, compare entries 9 and 11 with 10 and 12). However, as is evident from Table I, HMPA has a dramatic effect on the enolate oxidation stereoselectivities for (*Z*)-**4a–c** and HMPA may bring about a fundamental change in the aggregation state or solution structure of the enolate (Figure 1).

The results summarized in Tables I and III suggest that, like the aldol and Michael reactions, the stereoinduction for asymmetric oxidation of enolates is influenced by the enolate geometry, with *Z* enolates being somewhat more stereoselective than *E* enolates. However, the enolate geometry appears to have a relatively minor influence on the stereoinduction. Of much greater importance is the enolate substitution pattern where a change of R^1 in ketone **3** from phenyl to alkyl results in a change in configuration from *S* to *R* (Table I, compare entries 11 and 31). Equally important is the enolate solution structure as illustrated by the counterion effects and the influence that HMPA has on the stereoselectivity.

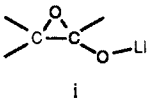
Mechanism of Oxygen Transfer. Theoretical[46,47] and experimental[48] studies have suggested an S$_N$2-type mechanism for the transfer of oxygen from *N*-sulfonyloxaziridines to nucleophiles. Despite the fact that the early part of the reaction coordinate is dominated by the four-electron repulsion of the nucleophile and the lone pair on oxygen, the "electrophilic" nature of oxaziridines is attributed to the presence of a low-lying empty Walsh orbital (LUMO) that rapidly decreases in energy during the C–O and N–O bond elongation induced by the attacking nucleophile. Recent MP4SDTQ/4-31G(d)-level calculations for the oxidation of sulfides to sulfoxides by oxaziridines indicate that 50% of the net charge transferred to the oxaziridine resides in an oxygen σ^* orbital in the transition state.[46b] It was noted in these and earlier studies on the epoxidation of alkenes[46] that the energy differences between planar and spiro transition states is too small to support enantiomeric selectivity based on electronic effects. It was concluded the observed stereochemistry derives from steric interactions in the transition state.

In the present case, the HOMO of an enolate anion is considerably higher than that of the neutral reactants studied previously.[46] Consequently, the mixing of this orbital with both filled and empty orbitals of the oxygens will be facilitated, resulting in a lower activation barrier. Following the Hammond postulate, this will correspond to an earlier or more reactant-like transition state.

A similar type of S$_N$2 mechanism can be proposed for the oxidation of enolate anions (carbanions) by oxaziridines (Scheme

(46) (a) Bach, R. D.; Wolber, G. *J. Am. Chem. Soc.* **1984**, *106*, 1410. (b) Bach, R. D.; Coddens, B. A.; McDouall, J. J. W.; Schlegel, H. B.; Davis, F. A. *J. Org. Chem.* **1990**, *55*, 3325.

(47) An alternative mechanistic pathway involves the initial formation of an anionic epoxy ketal intermediate i, which rearranges to the α-hydroxy ketone. While there is, at present, no experimental evidence supporting this possibility, it would be in analogy to the epoxidation of alkenes and silyl enol ethers by *N*-sulfonyloxaziridines.[37]



i

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

IV).[47] The enolate anion attacks at the oxaziridine oxygen atom to give hemiaminal intermediate **16**, which fragments to the sulfonimine **17** and the α-hydroxy ketone. Although there is no direct evidence implicating **16** in the oxidation of enolates by (+)-**2**, such evidence exists for the oxidation of enolates and carbanions (RM) by *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine **1** (Z* = Ar = Ph).[48,49] For example, oxidation of lithium enolates by **1** gives, in addition to the α-hydroxy carbonyl compound, the imino–aldol product **18** resulting from addition of the enolate to the sulfonimine **17**.[8b,49,50] Sodium enolates do not give **18**, implying that **16** has a relatively long lifetime. On the other hand, when the counterion is lithium, **16** is short-lived and rapidly collapses to **17**, which then gives **18**. Additional evidence in support of this scheme is that in the hydroxylation of lithium and Grignard reagents (RM) by **1** (Z* = Ph), **16** has been isolated as well as being observed in solution.[49]

Whether or not a stable hemiaminal intermediate **16** is involved in the oxidation of enolates by (+)-**2** is unclear, because carbanions and enolates do not add to the C–N double bond in the camphorsulfonimine **6**. Carbanions (bases) react with **6** to form the corresponding aza enolate **19**.[27] In an attempt to demonstrate that if **6** was present during the oxidation, it would quench the enolate, equivalent amounts of (+)-**2** and **6** were added to the sodium enolate of deoxybenzoin (**3a**) under standard conditions. Benzoin (**5a**) was isolated in 85% yield and in high optical purity (95% ee), demonstrating that proton transfer from **6** to the enolate is slow compared to oxidation. Similar yields and stereoselectivities were observed on addition of **6** to the sodium enolate of **4a** prior to addition of (+)-**2**. Aza enolate **19** is apparently not basic enough to generate **4a**, as evidenced by the fact that no reaction occurred on treatment of deoxybenzoin (**3a**) with **19** followed by oxidation with (+)-**2** at −78 °C.

One of the reasons that (camphorylsulfonyl)oxaziridines **2** are recommended for the oxidation of enolates (or for that matter carbanions) whether or not a chiral product is desired, is that imino–aldol addition products, such as **18**, are not formed.[37,50] Not only does this result in improved yields, but product isolation and purification is much easier.

Transition-State Models. Because information is lacking on the structure of actual enolate species reacting in solution, it is not possible to provide a comprehensive model that explains all of the results summarized in Table I. Only when the change in stereoinduction is large, it is reasonable to give a transition-state rationale.[51]

In the development of a model to explain the various transition-state control elements for the asymmetric oxidation of enolates by (+)-**2**, a number of assumptions are necessary. First, we assume an "open" transition state where there is little, if any, chelation between the metal enolate and the oxaziridine. NMR lithium salt and shift reagent experiments support this assumption, suggesting that (+)-**2** has only very weak Lewis base sites.[10,52,53] In (+)-**2**, the site of greatest Lewis basicity appears to be the sulfonyl oxygen furthest from the active site.[10] Consequently, we believe that the primary transition-state control element, as observed for other enantioselective oxidations by *N*-sulfonyloxaziridines,[37] is largely steric in origin. Contributions due to intermolecular attractive forces such as dipole–dipole association or van der Waals or polarization effects are not treated explicitly, because we know of no way to evaluate these forces for enolate reactions at this time.

For simplicity, we next assume that the attack trajectory of the oxaziridine on the enolate carbon is 90° (Figure 2). Studies by Dunitz and Burgi on the reaction of nucleophiles with carbonyl compounds[54,55] and ab initio calculations by Houk and co-workers,[56,57] however, suggest that the transition state is much more likely to be product-like (i.e., the oxaziridine approaches in the plane of the enolate double bond at an angle of 105°). If this is correct, reduced nonbonded interactions in our model should result (vide supra).

X-ray analysis and structure–reactivity correlations for the asymmetric oxidation of sulfides to sulfoxides by (+)-**2** suggest that the norbornane C–C bridge is the sterically most demanding region in the vicinity of the active-site oxygen.[10,11] Based on these considerations, transition-state structures A–D are analyzed for their nonbonding interactions in the oxidation of *Z* enolates **4a–d** by (+)-**2** (Figure 2). Finally, we make the reasonable assumption that regardless of the actual solution structure of the enolate (i.e., A–D, Figure 1) the sterically most demanding region in the vicinity of the enolate C–C bond is enolate–oxygen metal aggregate.

From these considerations and assumptions, structures A_S and D_R are the most favorable because there are fewest nonbonded interactions. In these structures it is also possible to have an essential bonding stabilizing interaction between the metal cation and the nitrogen anion leaving group. Structure D_R appears to be lowest in energy and is in accord with the observation that oxidation of **4c** ($R^1 = Me_3C$, $R^2 = Me$) gives (*R*)-**5c** (89% ee). However, replacement of *tert*-butyl by phenyl in **4a,b** gives (*S*)-**5a,b** with the highest stereoselectivity, 95% ee, observed for **4a** ($R^1 = Ph$, $R^2 = Ph$). In series **4a,b** ($R^1 = Ph$), structure A_S must now be favored and is possible only if there is little adverse nonbonded interactions between the phenyl group (R^1) and the sulfonyl oxygen in (+)-**2**. This might occur if the phenyl group were coplanar with the enolate C–C double bond. Indeed, Heathcock et al. have suggested that the phenyl group in (*Z*)-**4b** maintains a coplanar relationship with the double bond in the transition state.[14,42] Such an orientation could also be favored by π conjugation and/or by intramolecular π coordination between the metal cation and the phenyl π system.[58]

Changing R^2 and R^1 in **4a** from phenyl to methyl to give enolate **4b** and **4d**, respectively, is expected to lower the energies of structures C_R and D_R compared to A_S and B_S and result in lower stereoselectivities. Similarly, replacing H in **4a** by a methyl, affording tetrasubstituted enolate **4e**, raises the energy of structure A_S and lowers the ee's. Note however, that the lower stereoselectivities in this case can also be attributed to the fact that mixtures of *Z*/*E* enolates are involved (Table I, entries 39–43).

In the enolate oxidations, addition of HMPA generally resulted in lower enantioselectivities and an increase in enolate reactivity (Table I). HMPA is known to disrupt metal chelation and would be expected to significantly alter the aggregation state of the enolate (Figure 1). The reasonable suggestion by Seebach is that HMPA makes the enolate more accessible to the oxidation by altering the aggregate structure, which increases its reactivity (Figure 1, structure D). This may also make the effective size

(49) Davis, F. A.; Wei, J.; Sheppard, A. C.; Gubernick, S. *Tetrahedron Lett.* **1987**, 5115.

(50) Smith, A. B., III; Dorsey, B. D.; Obha, M.; Lupo, A. T., Jr.; Malamas, M. S. *J. Org. Chem.* **1988**, *53*, 4314.

(51) The difference in energy of the two diastereomeric transition states of only 0.050 kcal/mol corresponds approximately to 5% ee at 20 °C.

(52) 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.

(53) Oppolzer has demonstrated that chelation involving a sulfonyl oxygen and a carbonyl group is responsible for the high diastereoselectivities observed in the Lewis acid catalyzed inter- and intramolecular Diels–Alder reactions of *N*-enoylbornane-10,2-sultams: Opolzer, W.; Rodriguez, I.; Blagg, J.; Bernardinelli, G. *Helv. Chim. Acta* **1989**, *72*, 123.

(54) Burgi, H.-B.; Shefter, E.; Dunitz, J. D. *Tetrahedron* **1975**, *31*, 3089.

(55) Burgi, H.-B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153, and references cited therein.

(56) Houk, K. N.; Paddon-Row, M. N. *J. Am. Chem. Soc.* **1986**, *108*, 2659.

(57) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3684. Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481.

(58) For examples of intramolecular coordination between cations and aromatic groups in π systems, see: (a) Dietrich, H.; Mahdi, W.; Knorr, R. *J. Am. Chem. Soc.* **1986**, *108*, 2462. (b) Barr, D.; Clegg, W.; Mulvey, R. E.; Snaith, R.; Wright, D. S. *J. Chem. Soc., Chem. Commun.* **1987**, 716. (c) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934. (d) McIntosh, J. M.; Leavitt, R. K.; Mishra, P.; Cassidy, K. C.; Drake, J. E.; Chadha, R. *J. Org. Chem.* **1988**, *53*, 1947. (e) Morel, G.; Foucaud, A. *Bull. Soc. Chim. Fr.* **1969**, 4123.

of the enolate–oxygen metal aggregate smaller, reducing the energy of structure C_R (Figure 2) and lowering the ee's. Note however that addition of HMPA to either the *E* or *Z* enolates of **4d** results in higher stereoselectivities for (*R*)-**5d** changing the configuration from *S* to *R* (Table I, entries 36 and 38).

Although not shown here, similar transition-state structures and arguments can be made for oxidation of the corresponding *E* enolates **4** by transposing R^1 and OM in Figure 2. Such considerations predict that the lowest energy structure would be D_R leading to α-hydroxy ketone (*R*)-**5**. This is consistent with the fact that oxidation of enolate *E*/*Z* mixtures generally gave **5** with low levels of stereoinduction.

The "working model" developed in Figure 2 is useful for predicting the stereochemistry of the products for the asymmetric oxidation of ketone enolates **4** to α-hydroxy ketones **5** by (camphorylsulfonyl)oxaziridine **2**. Furthermore, this model satisfactorily rationalizes the effects of counterion on the reactivity as well as the effects of enolate geometry and substitution pattern on the stereoselectivity. However, as discussed earlier, care needs to be exercised in using this model for the interpretation of small differences in percent ee, in adapting it to other types of enolates and to enolate oxidations in the presence of additives such as HMPA. The difficulty in interpreting the effects of HMPA on the enolate asymmetric oxidation stereoselectivities is undoubtedly related to a paucity of information on the solution structure of enolates in the presence of this additive.

Conclusions. Useful levels of stereoinduction, 60–95% ee are observed for the asymmetric oxidation of the sodium enolates of trisubstituted ketone enolates **4a–d** by (camphorylsulfonyl)oxaziridine **2**. The stereoselectivities for the oxidation of tetrasubstituted enolates **4e** and **8** by this reagent are lower (i.e. 21–30% ee). Chemical yields for these oxidations of both types of enolates are good to excellent. The stereoselectivities are influenced by the enolate geometry, the enolate substitution pattern, and the enolate solution structure. The enolate substitution pattern and the enolate solution structure, which is influenced by the counterion and solvent, appear to be the most important stereocontrol elements. The structure–reactivity trends were analyzed in terms of an "open" transition-state model where minimization of nonbonded interactions is primarily responsible for the stereoinduction. In this model the O–metal aggregate is considered to be the sterically most demanding group in the region of the enolate C–C double bond.

Experimental Section

General Information. Unless otherwise noted, materials were obtained from commerical sources and were used without further purification. All glassware was oven-dried and cooled in a desiccator prior to use. Manipulations involving air-sensitive materials were performed under argon. Diethyl ether, tetrahydrofuran (THF), and dimethoxyethane (DME) were distilled from sodium/benzophenone under nitrogen atmosphere prior to use. Toluene, diisopropylamine, triethylamine, hexamethylphosphoramide (HMPA), and trimethylchlorosilane [(TMS)Cl] were distilled from calcium hydride under an inert atmosphere.

Sodium bis(trimethylsilyl)amide (NHMDS, 1.0 M in THF), lithium bis(trimethylsilyl)amide (LHMDS, 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.[59] Fresh solutions of lithium diisopropylamide (LDA) in THF or toluene were prepared as needed. Unless indicated otherwise, reagents were transferred via syringe.

Infrared spectra were recorded on a Perkin-Elmer 467 grating spectrometer, NMR spectra were recorded on a JEOL FX90Q (90MHz) or on a Bruker 250 (250 MHz), and ^{13}C NMR spectra were determined with complete proton decoupling. Proton and carbon chemical shifts are reported in ppm (δ) downfield from tetramethylsilane. 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 Varian CDS 111 integrator or on a Perkin-Elmer 8310. OV-17 (3%) (6 ft × $^1/_8$ in. 80/100 Supelcoport) and SPB-35 (30 m × 0.75 mm, borosilicate glass) columns were used for the GLC analysis. Analytical high-pressure liquid chromatography (HPLC) was performed on a Varian 5000 LC using a Varian Var-Chrom 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 **2** was prepared as previously described.[11] Benzoin (**3a**), propiophenone (**3b**), and 2-methyl-1-tetralone (**7**) were purchased from Aldrich. 2,2-Dimethyl-3-pentanone (**3c**)[14], 1-phenyl-2-propanone (**3d**),[60] and lithium diisopropylamide (LDA) in THF[61] and in toluene[62] were prepared as previously described.

1,2-Diphenylpropanone (3e). In a 100-mL oven-dried three-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 2.94 g (15 mmol) of deoxybenzoin (**3a**) in 40 mL of dry THF. The reaction mixture was cooled to −78 °C and 16 mL (16 mmol) of NHMDS solution was added dropwise followed by stirring for 30 min. Iodomethane (5 mL) was added dropwise and the reaction mixture was stirred for an additional 30 min at −78 °C. After being warmed to room temperature, the solution was stirred for 8 h and then quenched by addition of 10 mL of water. The reaction mixture was extracted with ether (2 × 15 mL) and dried over anhydrous $MgSO_4$ and the solvent removed to afford an oil, which was purified by silica gel flash chromatography (ether/*n*-pentane 1:1) to give 2.9 g (93%) of a white solid, mp 49–50 °C (lit.[63a] mp 50–51 °C) whose spectral properties were identical with those recorded in the literature.[63b]

Determination of α-Hydroxy Ketone 5 Optical Purity. The optical purity of benzoin (**5a**)[17] was determined by using a Daicel Chiral Pak OT(+) HPLC column (25 × 0.46 cm i.d.) and a UV detector set at 254 nm. A sample of racemic benzoin (Aldrich) was separated into its enantiomers by eluting with methanol at a flow rate of 0.3 mL/min. Coinjection of optically pure (*S*)-(+)-benzoin (Aldrich) established that the *R*-(−) isomer eluted first. Each analysis was run at least twice and the results were averaged. The optical purity of the other α-hydroxy ketones was determined by optical rotation and/or chiral shift reagent experiments[64] using $Eu(hfc)_3$ (Aldrich). Good correlation of the optical purities was observed by either method.

Procedure for ^1H NMR Chiral Shift Reagents Experiments. In an NMR tube was placed approximately 10 mg of the appropriate α-hydroxy ketone **5** or **7** in 0.3 mL of $CDCl_3$. The solvent was filtered through dried 4-Å molecular sieves prior to use to minimize the water content. An NMR spectrum was taken to establish the initial chemical shifts of the protons and the purity of the hydroxy ketone. Tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) derivative [$Eu(hfc)_3$] was added to the NMR tube in successive increments until base-line separation of the absorptions for the enantiomers was obtained. The optical purity (percent ee) was obtained by subtracting the percentages calculated for each enantiomer from the integration data.

NMR shift experiments using $Eu(hfc)_3$ were performed in racemic samples of the α-hydroxy ketones to identify the absorptions. Separation of the enantiomeric absorptions for the methyl groups adjacent to the hydroxyl function was observed for hydroxy ketones **5b**, **5c**, and **9**. The absorption at lower field corresponded to the *S* isomer for hydroxy ketones **5b** and **5c**, and to the *R* isomer for **9**. Base-line separation of the enantiomeric absorptions for the methyl group adjacent to the carbonyl function was observed for hydroxy ketone **5d**. The absorption at lower field corresponded to the *R* isomer. Base-line separation of the enantiomeric absorptions for the methyl group adjacent to the carbonyl function was observed for hydroxy ketone **5e**.

Synthesis of (*S*)-(+)-2,2,5-Trimethyl-4-dioxolanone (10). This compound was prepared by a modification of the method previously reported

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

(60) Desai, D. A.; Mane, R. B. *Indian J. Chem., Sect. B* **1981**, *20B*, 504.

(61) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(62) Ludwig, J. W.; Newcomb, M.; Bergbreiter, D. E. *Tetrahedron Lett.* **1986**, 2731.

(63) (a) Swaki, Y.; Ogata, Y. *J. Am. Chem. Soc.* **1975**, *97*, 6983. (b) Alvarez-Ibarra, C.; Arjona, O.; Prees-Ossorio, R.; Prerez-Rubalcaba, P.; Ouiroga, M. L.; Santesmases, M. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1645.

(64) For reviews on shift reagents, see: Cockerill, A. F.; Davies, G. L. O.; Harden, R. C.; Rackhman, D. M. *Chem. Rev.* **1973**, *73*, 553. Kime, K. A.; Sievers, R. E. *Aldrichimica Acta* **1977**, *10*, 54.

for the racemic material.[20] In a 250-mL oven-dried three-necked round-bottomed flask fitted with an argon bubbler, a thermometer, a magnetic stirring bar, and a 50-mL addition funnel was placed 10 g (111 mmol) of (*S*)-(+)-lactic acid (Aldrich) in 40 mL (544 mmol) of reagent-grade acetone. The reaction mixture was stirred vigorously and cooled to −10 °C (ethylene glycol/dry ice bath) and 17 mL (308 mmol) of 98% H_2SO_4 was added dropwise over 2 h using the addition funnel. The internal temperature was kept between −10 and −5 °C during the addition time. After an additional 0.5 h, 400 mL of reagent-grade benzene was added. The reaction mixture was warmed to room temperature after 1 h, layers were separated, and the lower phase was extracted with 2 × 100 mL of benzene. The combined benzene extracts were stirred over K_2CO_3 for 8 h; the mixture was filtered, concentrated in vacuo, and distilled to give 7.0 g (49%) of **10**: bp 50–53 °C (20 mm Hg) [lit.[20b] bp 54–55 °C (20 mmHg)]; $[\alpha]^{20}_D$ +33.26° (*c* 1.98, $CHCl_3$); ^1H NMR and IR data were consistent with reported values.

Synthesis of (*S*)-(+)-4-Hydroxy-2,2-dimethyl-3-pentanone (5c). In a 50-mL oven-dried three-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, a magnetic stirring bar, and an addition funnel were placed 15 mL of freshly distilled THF and 577 mg (4.43 mmol) of (*S*)-(+)-2,2,5-trimethyl-4-dioxolanone (**10**). The solution was cooled to −78 °C (dry ice/acetone bath) and 2.3 mL (4.0 mmol, 0.9 equiv based on **10**) of a 1.7 M solution of *t*-BuLi in hexane (Aldrich) was added dropwise. After 45 min, an aliquot was withdrawn and quenched with water. GC analysis using a SPB-35 capilliary column showed a mixture of several components containing some of the desired α-hydroxy ketone **5c** and starting material.

The reaction mixture was quenched with 2 mL of water after 1.5 h at −78 °C and warmed to room temperature. The aqueous layer was extracted with 5 mL of diethyl ether and the combined ether extracts were washed with 2 × 10 mL of brine and dried over anhydrous $MgSO_4$. After filtration and removal of solvent, the residue was purified by flash chromatography (pentane/Et_2O 3:1) to give 98 mg (17%) of **5c**: TLC, R_f 0.24 (pentane/Et_2O 3:1); ^1H NMR and IR data were in agreement with reported values;[65] $[\alpha]^{20}_D$ +61.5° *c* 2.01, $CHCl_3$); an NMR shift reagent using Eu(hfc)$_3$ confirmed that **5c** had not racemized under the reaction conditions.

Synthesis of (*S*)-(−)-2-Hydroxy-1-phenyl-1-propanone (5b). This compound was synthesized in the manner described for (*S*)-(+)-**5c** except that 2.0 equiv of a 1.7 M solution of PhLi in hexane (Aldrich) was used and the reaction was quenched after 0.5 h at −78 °C. Purification by flash chromatography (pentane/Et_2O 3:1) gave 66 mg (10%) of (*S*)-(−)-**5b**: ^1H NMR and IR data were consistent with reported values;[65] $[\alpha]^{20}_D$ −86.7° (*c* 2.0, $CHCl_3$) [lit.[21] $[\alpha]^{20}_D$ +81° for the *R* isomer of 99% optical purity (*c* 1.5, $CHCl_3$)]; a ^1H NMR shift experiment using Eu(hfc)$_3$ confirmed that **5b** had not racemized under the reaction conditions.

Determination of Enolate Geometry—General Procedure for Enolate Trapping. 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 (0.60 mmol, 1.2 equiv based on ketone) of a preformed 1.0 M solution of LDA in THF was added. The appropriate ketone **3** (0.5 mmol) in 3 mL of THF was added dropwise while the internal temperature was kept below −70 °C. After 0.5 h, 0.1 mL (0.73 mmol) of (TMS)Cl was added dropwise and the reaction mixture was kept at −70 °C for an additional 30 min. TLC analysis (pentane/diethyl ether 80:20) showed that silylation was complete. The reaction mixture was warmed to room temperature and 0.12 mL (0.83 mmol) of dry triethylamine was added. The mixture was diluted with 30 mL of pentane, washed with cold saturated aqueous $NaHCO_3$ (3 × 10 mL) and cold brine (2 × 10 mL), and dried over anhydrous Na_2SO_4. Filtration and vacuum concentration gave enol silane **11**.

A similar procedure was employed to trap the enolates formed with NHMDS. For reactions in the presence of HMPA, 0.3 mL of HMPA was added to the base solution prior to enolization (THF/HMPA ratio 20:1). Results are summarized in Table I.

Benzoin (**3a**) gave 1,2-diphenyl-1-[(trimethylsilyl)oxy]ethylene (**11a**): bp 132–136 °C (1 mmHg) [Lit.[66] bp 135 °C, 1.3 (mmHg)]; ^1H NMR in $CDCl_3$ and C_6D_6 showed two absorptions for the vinylic hydrogen that were assigned[22a] to the *E* and *Z* isomers of **11a**. (*Z*)-**11a**: ^1H NMR ($CDCl_3$) δ 0.06 (s, 9 H, $SiCH_3$)3), 6.14 (s, 1 H, CHAr), 7.0–7.7 (m, 10 H, Ar); ^1H NMR (C_6D_6) δ 0.02 (s, 9 H, $Si(CH_3)_3$), 6.20 (s, 1 H, CHPh), 7.0–7.8 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 0.86 ($Si(CH_3)_3$), 110.46 (CHPh), 125.96, 126.08, 127.96, 128.55, 136.53, 139.58 (Ph), 150.74 (PhC(O(TMS))). (*E*)-**11a**: ^1H NMR ($CDCl_3$) δ 0.22 (s, 9 H, $Si(CH_3)_3$), 6.08 (s, 1 H, CHPh); ^1H NMR (C_6D_6) δ 0.15 (s, 9 H, $Si(CH_3)_3$), 6.26 (s, 1 H, CHPh); ^{13}C NMR ($CDCl_3$) δ 0.56 ($Si(CH_3)_3$), 114.46 (CHPh), 125.50, 128.14, 128.72, 129.01, 136.71, 139.58 (Ph), 151.50 (PhC(O(TMS))).

Propiophenone (**3b**) gave 1-phenyl-1-[(trimethylsilyl)oxy]propene (**11b**):[14] The *Z*/*E* ratio was determined by comparison of the ^{13}C NMR ($CDCl_3$) with data reported by Heathcock.[14,42] (*Z*)-**11b**: ^{13}C NMR ($CDCl_3$) δ 0.1 ($Si(CH_3)_3$), 11.6 (Me), 105.2 (CHMe), 127.0, 127.4, 128.0, 137.01 (Ph), 149.0 (PhC(OTMS)). No absorption for the allylic carbons of (*E*)-**11b** (δ 13.0 ppm) was observed. The ratios were confirmed by GLC analysis using a SPB-35 capilliary column.

Phenyl-2-propanone (**3d**) gave 95% of a 1:1 mixture of 1-phenyl-2-[(trimethylsilyl)oxy]propene (**11d**)[22a] (*Z*/*E* ratio of 11:89) and 3-phenyl-2-(trimethylsiloxy)propene (**13**)[24,66] as determined by ^1H NMR analysis in C_6D_6.[22a] The *Z*/*E* ratio for **11d** was measured by integration of the absorptions for the vinylic hydrogens as described by House for this enol silane.[22a] **11d**: ^1H NMR (C_6D_6) δ 5.42 (*Z* isomer, s, CHPh); 6.00 (*E* isomer, s, CHPh), Δδ 0.58 (lit.[22a] Δδ 0.55). **13**: ^1H NMR (C_6H_6) δ 0.05 (s, $Si(CH_3)_3$), 3.27 (s, $PhCH_2CO(TMS)$), 4.11 (s, (TMS)OCCH), 4.17 (s, (TMS)OCCH). GC analysis of the mixture (OV-17 column) showed two peaks of about equal intensity, GC–MS *m*/*e* 206 for both compounds (M^+ calcd for $C_{12}H_{18}OSi$, 206.36).

1,2-Diphenyl-1-propanone (**3e**) gave 93% 1,2-diphenyl-1-(trimethylsiloxy)propene (**11e**). The *E*/*Z* ratio was determined by integration of the Me and/or $SiMe_3$ group absorptions by ^1H NMR. (*Z*)-**11e**: ^1H NMR ($CDCl_3$) δ −0.22 (s, 9 H, $SiMe_3$) 1.99 (s, 3 H, Me) 7.05–7.55 (m, 10 H, Ar). (*E*)-**11e**: ^1H NMR ($CDCl_3$) δ 0.05 (s, 9 H, $SiMe_3$) 2.13 (s, 3 H, Me) 7.05–7.55 (m, 10 H, Ar). The assignments were confirmed by an NOE difference experiment.

General Procedure for the Asymmetric Oxidation of Ketone Enolates 4 Using (+)- and (−)-(Camphorylsulfonyl)oxaziridine 2. 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 a 1.0 M solution of NHMDS in THF was added. A solution of the appropriate ketone **3** (0.5 mmol) in 3 mL of THF was added dropwise and the resultant mixture was stirred for 30 min. A solution of 187 mg (0.75 mmol, 1.25 equiv based on amide base) of (+)-(camphorylsulfonyl)oxaziridine **2** 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 pentane and filtered to remove the camphorsulfonimine **6** byproduct. Purification of the residue by preparative TLC or flash chromatography (pentane/Et_2O 3:1) gave the α-hydroxy ketone **5**.

For oxidations at −90 °C, the reaction mixture was cooled (dry ice/ethyl ether bath) prior to oxidation. Reactions using more than 1.2 equiv of base were carried out with typically 1.25 equiv (based on amide base) of oxaziridine. The potassium enolates were oxidized as described above except that 0.6 mL of a 1.0 M solution of KHMDS in THF was used.

The lithium and zinc enolates failed to react at −78 °C with (+)-**2** and were warmed to 0 °C (ice/water bath) for 2 min after addition of the oxaziridine. The reaction mixtures were quenched in the usual way after 10 min. Oxidation of the lithium enolate at −45 to −50 °C was carried out using a cyclohexanone/dry ice bath and the reaction was quenched after 1 h.

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. Oxidations of the sodium and lithium enolates in solvents other than THF were carried out as described above, except that the enolization time was extended to 1 h for reactions in toluene. For oxidations in Et_2O the oxaziridine was dissolved in a mixture of 1 mL of THF and 4 mL of Et_2O.

General Procedure for GLC Monitoring of Enolate Oxidations. In a small vial (4 mL capacity) were 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 pipet, 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 pipet into a clean vial and analyzed by GLC.

(65) Bowlus, S. B.; Katzenellenbogen, J. A. *J. Org. Chem.* **1974**, *39*, 3309.
(66) Simchen, G.; Kober, W. *Synthesis* **1976**, 259. Miyano, S.; Hokari, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 534.
(67) Yamakawa, K.; Satoh, T.; Ohba, N.; Sakagushi, R.; Takita, S.; Tamura, N. *Tetrahedron* **1981**, *37*, 473.

In all the above reactions, the enolization and oxidation progress was monitored by GLC (bibenzyl as internal reference added with the ketone **3**) and TLC in independent experiments.

(*S*)-(+)-2-Hydroxy-2-phenylacetophenone (5a). 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.[17] $[\alpha]^{20}_D$ −118.4° (*c* 2.4, acetone)]. **(*S*)-(−)-2-Hydroxy-1-phenyl-1-propanone (5b).** Oxidations were carried out as described above: R_f 0.23 (pentane/Et_2O 3:1); IR and ^1H NMR were consistent with reported values; 62% ee; $[\alpha]^{20}_D = -58.3°$ (*c* 2.0, $CHCl_3$). **(*R*)-(−)-4-Hydroxy-2,2-dimethyl-3-pentanone (5c).** 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;[65] 89% ee; $[\alpha]^{20}_D = -54.9°$ (*c* 1.96, $CHCl_3$). **(*S*)-(+)-1-Hydroxy-1-phenyl-2-propanone (5d).** Oxidations were carried out as described above: R_f 0.24 (pentane/Et_2O 3:1); IR data was in agreement with reported data;[18f] 37.1% ee; $[\alpha]^{20}_D = +57.5°$ (*c* 2.0, EtOH) [lit.[18c,d] $[\alpha]^{20}_D = +157°$ (*c* EtOH)]; ^1H NMR ($CDCl_3$) δ 2.09 (s, 3 H, CH_3), 4.31 (d, 1 H, OH, *J* = 4.1 Hz), 5.11 (d, 1 H, CH, *J* = 4.2 Hz), 7.34–7.45 (m, 5 H, Ar). **(*S*)-(−)-2-Hydroxy-1,2-diphenylpropanone (5e).** Oxidations were carried out as described above: R_f 0.44 (*n*-pentane/Et_2O 7:3); IR and NMR were consistent with reported values;[18e] 21% ee; $[\alpha]_D = -54.6°$ (*c* 1.2, acetone) [lit.[18b] $[\alpha]^{20}_D = -260.1°$ (*c* 3.103, acetone)].

Asymmetric Oxidation of the Enolate of 2-Methyl-1-tetralone (7) to (*R*)-(+)-2-Hydroxy-2-methyl-1-tetralone (9) in Toluene. 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 toluene. The reaction flask was cooled to −78 °C (dry ice/acetone bath) and 0.97 mL (0.75 mmol, 1.5 equiv based on ketone) of a 0.77 M solution of LDA in toluene was added. A solution of 80 mg (0.5 mmol) of 2-methyl-1-tetralone (**7**) in 2 mL of toluene was added dropwise, and after 5 min the reaction mixture was warmed to 0 °C for 15 min and cooled to −78 °C. A solution of 214 mg (0.93 mmol, 1.25 equiv based on amide base) of (+)-**2** in 5 mL of toluene was added dropwise. The reaction mixture was quenched after 30 min by addition of 3 mL of a saturated aqueous NH_4I solution, diluted with 10 mL of diethyl ether, and warmed to room temperature. The aqueous layer was extracted with 2 × 5 mL of diethyl ether and the combined organic extracts were washed with 2 × 15 mL of saturated aqueous $Na_2S_2O_3$ solution and 2 × 10 mL of brine, filtered, and dried over $MgSO_4$. Concentration in vacuo gave an oil that was stirred with three portions of 3 mL of pentane/Et_2O (4:1) and filtered to remove the camphorsulfonimine **6** byproduct. Purification of the residue by preparative TLC or flash chromatography (pentane/Et_2O 3:1) gave 36 mg (41%) of **9**: R_f 0.20 (pentane/Et_2O 3:1); the IR and ^1H NMR were in agreement with reported data;[67] 64% ee; $[\alpha]^{20}_D = +67°$ (*c* 1.04, $CHCl_3$).

Oxidations of **7** in THF were carried out as described above except that the enolate failed to oxidize at −78 °C. In these cases, the reaction mixture was warmed to 0 °C after addition of oxaziridine (+)-**2**, quenched after 10 min, and worked up as described for oxidations in toluene. For oxidations of the lithium enolate in the presence of HMPA, 0.3 mL (1.73 mmol, 3.5 equiv based on ketone) of this cosolvent was added to the LDA solution at −78 °C and addition of the ketone followed after 5 min. Oxidation was carried out as described above.

Base-Promoted Racemization of α-Hydroxy Ketones 5a and 5b. In a 25-mL oven-dried two-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar were placed 0.61 mL (0.6 mmol) of a 1 M solution of LDA and 3 mL of freshly distilled THF. The reaction flask was cooled to −78 °C (dry ice/acetone bath) and a solution of the appropriate ketone **5a** or **5b** (0.406 mmol) in 3 mL of THF was added dropwise. After 2 min, the reaction mixture was warmed to 0 °C (ice/water bath), quenched after 15 min with 1 mL of a saturated NH_4Cl solution, diluted with 10 mL of diethyl ether, and warmed to room temperature. The aqueous layer was extracted with 5 mL of diethyl ether, and the combined extracts were washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo.

For reactions in the presence of HMPA, 0.3 mL of this cosolvent was added to the THF solution of LDA before addition of the α-hydroxy ketone.

Benzoin (**5a**) was purified as described above. α-Hydroxy ketone **5b** was purified by preparative TLC (pentane/Et_2O 3:1) to give 44.3 mg (70%) of a mixture of 2-hydroxy-1-phenyl-1-propanone (**5b**)[19] and 1-hydroxy-1-phenyl-2-propanone (**5d**)[18d] in a ratio of 52:48 as determined by ^1H NMR: $[\alpha]^{20}_D$ −23.49° (*c* 2.0, $CHCl_3$); see Table II.

Synthesis of (*E*)-1-Phenyl-1-(trimethylsiloxy)propene (11b). 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 365 mg (1.85 mmol) of (*E*)-1-phenyl-1-bromopropene[68] in 2 mL of THF. The reaction mixture was cooled to −78 °C and 1.42 mL (1.85 mmol) of a 1.3 mol solution of *sec*-butyllithium (Aldrich) was added dropwise. After stirring for 10 min, 661 mg (3.70 mmol) of bis(trimethylsilyl) peroxide[69] in 1 mL of THF was added dropwise. After being stirred for 10 min, the solution was warmed to room temperature, stirred for 30 min, diluted with 10 mL of *n*-pentane, and washed with saturated $NaHCO_3$ solution. Removal of the solvent under vacuum gave an oil, which was purified by flash chromatography on silica gel (eluting with *n*-pentane) to give 267 mg (71%) yield of **11b** (*E*/*Z* ratio of 93:7): ^1H NMR ($CDCl_3$) δ −0.036 (s, 9 H, Me_3Si) 1.63 (d, *J* = 7 Hz, 3 H, Me), 5.3 (q, *J* = 7 Hz, 1 H), 7.1–7.3 (m, 5 H); the CH_3 in (*Z*)-**11b** appears at δ 2.1 ppm.

Oxidation of Lithium Ketone Enolates Generated from Silyl Enol Ethers and CH_3Li. 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 the appropriate enol silane **11** (0.5 mmol) in 7 mL of freshly distilled THF. The reaction flask was cooled to 0 °C (ice/water bath) and 0.34 mL (0.475 mmol, 0.95 equiv based on enol silane) of a 1.4 M solution of CH_3Li in diethyl ether (Aldrich) was added 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 137 mg (0.6 mmol, 1.2 equiv based on enol silane) of (+)-**2** in 3 mL of THF was added dropwise. After 2 min, the reaction mixture was warmed to 0 °C for 10 min, quenched by addition of 3 mL of a saturated aqueous NH_4I solution, diluted with 10 mL of diethyl ether, and warmed to room temperature. The aqueous layer was extracted with diethyl ether (2 × 5 mL) and the combined extracts were washed successively with saturated aqueous $Na_2S_2O_3$ and brine (2 × 15 mL) and dried over anhydrous $MgSO_4$. Concentration in vacuo gave an oil that was stirred with three portions of pentane (3 mL) and filtered to remove the (camphorsulfonimine **6** byproduct. Purification of the residue by preparative TLC or flash chromatography (pentane/Et_2O 3:1) gave the α-hydroxy ketone **5**.

For reactions using HMPA as cosolvent, 0.35 mL (2.0 mmol, 4 equiv based on silyl enol ether) of HMPA was added to the solution at −78 °C after cleavage of the silyl enol ether. Addition of (+)-**2** followed after 5 min. Reactions using more than 0.95 equiv of base were carried out with typically 1.15 equiv (based on CH_3Li) of (+)-**2**. When mixtures of **5b** and **5d** were present the ratios were measured by ^1H NMR analysis of the chromatographed mixtures; integration of the corresponding absorptions for the methyl groups determined the **5b**/**5d** ratios. **5b**: ^1H NMR ($CDCl_3$) δ 1.46 (d, 3 H, Me). **5d**: ^1H NMR ($CDCl_3$) δ 2.09 (s, 3 H, Me). Compounds **5b** and **5d** were not separable by flash chromatography (R_f 0.24 in pentane/Et_2O). Analysis of crude reaction mixtures by GC (SPB-35 column) showed the same ratios of the α-hydroxy ketones as those obtained by ^1H NMR analysis.

Enolization and Reduction of 1-Phenyl-1-propanone (3b) in Toluene. Formation of 1-Phenyl-1-propanol. 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 4 mL of dry toluene. The reaction flask was cooled to −78 °C (dry ice/acetone bath) and 0.97 mL (0.75 mmol, 1.5 equiv based on ketone) of a 0.77 M solution of LDA in toluene was added. To the stirred solution was added dropwise a solution of 67 mg (0.5 mmol) of **3b** and 38 mg of bibenzyl (Aldrich, internal standard) in 4 mL of toluene. The reaction mixture was quenched after 1 h by addition of 2 mL of saturated aqueous NH_4Cl solution, warmed to room temperature, and diluted with 10 mL of diethyl ether. The aqueous layer was further extracted with 2 × 5 mL of diethyl ether, and the combined organic extracts were washed with 2 × 10 mL of brine and dried over anhydrous $MgSO_4$. After filtration, the reaction mixture was analyzed and quantified by GLC (OV-17 column). The mixture contained 40 mg (60% recovered yield) of 1-phenyl-1-propanone (**3b**) and 25 mg (37%) of 1-phenyl-1-propanol[70] as determined by comparison with authentic samples. The ratio was confirmed by ^1H NMR analysis of this mixture (**5b**/1-phenyl-1-propanol 62:38).

Oxidation of Deoxybenzoin (3a) Using (+)-2 in the Presence of (−)-Camphorsulfonimine 6. 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 and 0.6 mL (0.6 mmol, 1.2 equiv based on ketone) of a 1.0 M solution of NHMDS in THF was added followed by dropwise addition of 105 mg (0.5 mmol) of **3a** in 3 mL of THF. After the reaction mixture was stirred for 30 min, a mixture of 172 mg of (+)-**2** (0.75 mmol) and 162 mg of (−)-**6** (0.75 mmol) in 10 mL of THF was added dropwise. After stirring for an additional 30 min, 3 mL of saturated NH_4I solution was added to quench the reaction.

(68) Kernaghan, G. F. D.; Hoffmann, H. M. R. *J. Am. Chem. Soc.* **1970**, *92*, 6988.
(69) Taddei, M.; Ricci, A. *Synthesis* **1986**, 633.
(70) Krishanmurthy, S.; Vogel, F.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2534.

Workup and product isolation were as described above to give 90 mg (85%) of **5a** (93% ee).

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Diastereoselectivity in the Reduction of Sterically Unbiased 2,2-Diarylcyclopentanones

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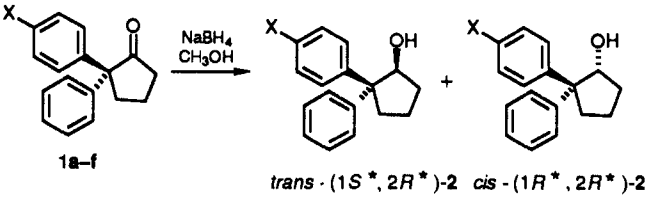
Abstract: Reduction of sterically unbiased 2-phenyl-2-(4-X-phenyl)cyclopentanones **1** (X = NO_2, Br, Cl, OCH_3, OH, NH_2) with either sodium borohydride in methanol or lithium borohydride in tetrahydrofuran at 0 °C produced diastereomeric cyclopentanols **2** in cis/trans ratios varying from 79:21 to 30:70 as determined by ^1H and ^{13}C NMR spectroscopy. These ratios correspond to an overall energy difference of 1.3 kcal/mol. In all cases the hydride was added opposite the more electron rich aromatic ring in support of Cieplak's theory for explaining stereoelectronic control in ketone reductions. A Hammet plot of log (cis/trans) versus the σ para parameter produced a linear relationship with a correlation coefficient of 0.98. An efficient synthesis of the diarylcyclopentanones is described. The diastereomeric alcohols were separable by preparatory thin layer chromatography. The stereochemistry of the products was determined by 2D NOE (NOESY) spectroscopy, ^{13}C NMR chemical shift data, and direct chemical correlation between different products.

The selective formation of one stereoisomer in organic reactions that can produce multiple isomers continues to be a general goal for synthetic chemists.[1] The selectivity in many organic transformations is thought to arise from the interplay of steric interactions, e.g. the addition of a bulky reagent to the least hindered side of a substrate. The control of stereoselective reactions by stereoelectronic effects is invoked less often and is understood much less.[2,3] Due to the paucity of suitable experimental evidence we do not know which reactions are governed by stereoelectronic effects and how strong such effects can be. Isolating stereoelectronic effects by minimizing competing steric factors should provide experimental evidence for the magnitude of stereoelectronic control in asymmetric reactions.[3] Stereoelectronic control in the reduction of ketones has been supported by results obtained with adamantanone[3] and cyclohexanone substrates.[2] As our entry into the study of stereoelectronic control of reactions, we have examined the stereoselective reduction of a functionalized 2,2-diarylcyclopentanone containing an unsubstituted phenyl group and a para-substituted phenyl group. By observing a systematic and predictable change in the selectivity for the reduction of substituted 2,2-diarylcyclopentanones in our initial study, we have found further evidence for the presence of a stereoelectronic effect in reductions of sterically nonbiased ketones and obtained an indication that our cyclopentanone system was more sensitive to stereoelectronic effects than the adamantanone[3] case.

We have chosen to study the stereoselectivity in the reduction of 2,2-diphenylcyclopentanones for several reasons. The electronically variable but sterically similar phenyl groups are located next to the carbonyl bond undergoing reaction rather than several



X = NO_2 (**a**), Cl (**b**), Br (**c**), OCH_3 (**d**), OH (**e**), NH_2 (**f**)

bonds away as in the case of le Noble's adamantanones.[3] Since the two possible donating (or withdrawing) bonds are both carbon–carbon, we avoid the disputed question in the case of Cieplak and Johnson's cyclohexanones of whether C–C or C–H bonds are better donors/acceptors.[2b,4] The geometric equivalence of the competing transition states may be achieved due to the conformational flexibility of the cyclopentanone ring.[5] The transition state for addition of a hydride to the carbonyl in this system can readily adopt a conformation in which the adding hydride is antiperiplanar to a pseudoaxial phenyl group. This reduction of geometric concerns contrasts strongly to earlier studies with substituted cyclohexanones where approach of nucleophiles to the carbonyl is not geometrically equivalent.[2] A final reason for investigating the reduction of diarylcyclopentanones is the ease of synthesizing the needed substrates and the applicability of this synthesis to related substrates needed for the study of stereoelectronic factors in a broader range of stereoselective reactions.

Synthesis of 2,2-Diarylcyclopentanone. The syntheses of the ketone substrates **1** proceed from either a monosubstituted benzophenone or diphenylacetic acid. The synthesis of **1b** (X = Cl)

(1) For a collection of reviews on stereoselective reactions see: Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic: New York, 1984–1985; Vols. 1–5.

(2) (a) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447 and references cited therein. (b) Cieplak, A. S. *Ibid.* **1981**, *103*, 4540.

(3) (a) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598. (b) Chung, W.-S.; Turro, N. J.; Srivastava, S.; Li, H.; le Noble, W. J. *Ibid.* **1988**, *110*, 7882. (c) Srivastava, S.; le Noble, W. J. *Ibid.* **1987**, *109*, 5874.

(4) (a) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908. (b) Rozeboom, M. D.; Houk, K. N. *Ibid.* **1982**, *104*, 1189. (c) Mukherjee, D.; Wu, Y.-D.; Fronczek, F. R.; Houk, K. N. *Ibid.* **1988**, *110*, 3328. (d) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Houk, K. N. *Ibid.* **1981**, *103*, 2436. (e) Houk, K. N. *Pure Appl. Chem.* **1983**, *55*, 277.

(5) Buchs, B. *Top. Stereochem.* **1968**, *10*, 1. Legon, A. C. *Chem. Rev.* **1980**, *80*, 231. Lambert, J. B.; Papay, J. J.; Khan, S. A.; Kappauf, K. A.; Magyar, E. S. *J. Am. Chem. Soc.* **1974**, *96*, 6112. Adams, W. J.; Geise, H. J.; Bartell, L. S. *Ibid.* **1970**, *92*, 5013.

0002-7863/90/1512-6690$02.50/0