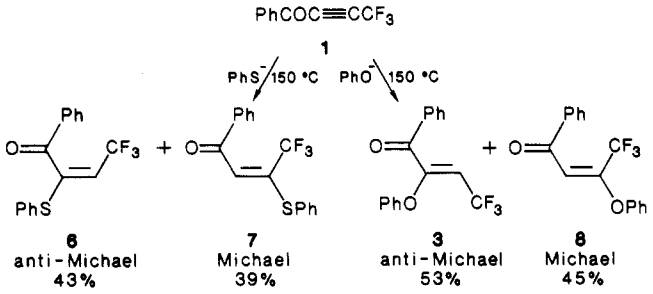
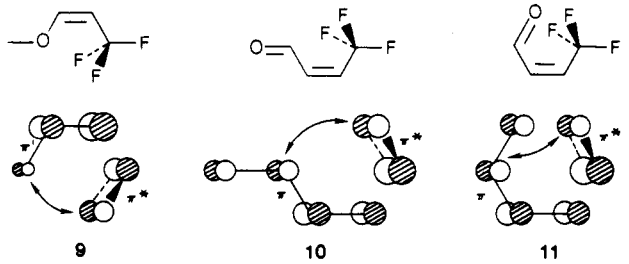


products **2** or **3** to 150 °C for 24 h with a catalytic amount of base produced essentially the same mixture as given in eq 2. Comparison of eq 1 and 2 reveals that although there is an overwhelming kinetic preference for anti-Michael addition, both the Michael and anti-Michael products are almost equally stable. The trans arrangement of CF_3 and carbonyl groups in the kinetic products **2** and **3** is a direct consequence of anti addition of nucleophile and H^+.[8] In the thermodynamic products of the reaction with PhS^-, both the Michael and anti-Michael products (**7** and **6**, respectively) have a cis arrangement of CF_3 and carbonyl groups. In the thermodynamic products of the reaction with PhO^-, however, the Michael and anti-Michael products (**8** and **3**, respectively) have cis and trans arrangements of CF_3 and carbonyl groups, respectively.

In the reactions of PhO^- and PhS^- with $PhC{\equiv}CCF_3$,[9] the thermodynamic product was found to have a cis arrangement of CF_3 and PhO groups for the PhO^- addition but a trans arrangement of CF_3 and PhS for the PhS^- addition. The preference for the cis arrangement of CF_3 and PhO is rationalized[9] in terms of secondary orbital interactions of $\pi^*_{CF_3}$ with the HOMO π' of the vinyl ether framework as shown in **9**. The secondary orbital interaction ($\pi' - \pi^*_{CF_3}$) is not significant for the case of PhS and CF_3.[9] Similarly, according to the interaction of $\pi^*_{CF_3}$ with the HOMO π of an enone framework shown in **10**, CF_3 and carbonyl groups are expected to prefer a cis arrangement as well. From eq 2 we see that indeed this preference is shown by the thermodynamic compounds **6–8**. The only exception, **3**, is accounted for if the ($\pi' - \pi^*_{CF_3}$) interaction is stronger than the ($\pi - \pi^*_{CF_3}$) interaction. Given the s-trans conformation of the enone framework, the trans



arrangement of CF_3 and carbonyl in **3** may be rationalized by simply invoking steric hindrance between the benzoyl benzene ring and the CF_3 group. This argument, however, would predict a trans arrangement of CF_3 and carbonyl for **6–8**, in disagreement with experiment. There is no need to invoke steric hindrance between the benzoyl group and the CF_3 groups, if the enone framework has a s-cis conformation. In such a case, the secondary orbital interaction of ($\pi - \pi^*_{CF_3}$) will increase the preference for a cis arrangement of carbonyl and CF_3 as depicted in **11**.

Registry No. **1**, 85694-32-2; **2**, 104322-88-5; **3**, 104322-89-6; **4**, 99048-75-6; **6**, 104322-90-9; (*E*)-**7**, 104322-91-0; (*Z*)-**7**, 104322-93-2; (*E*)-**8**, 104322-92-1; (*Z*)-**8**, 104322-94-3; PhO^-, 3229-70-7; PhS, 13133-62-5; PhSH, 108-98-5; PhOH, 108-95-2; PhCOCl, 98-88-4; $(CF_3C{\equiv}C)_2Zn$, 104322-95-4.

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Stereochemistry of the Asymmetric Oxidation of Ketone Enolates Using (Camphorylsulfonyl)oxaziridines

Summary: Asymmetric oxidation of the sodium enolates of ketones using chiral oxaziridines (+)-(2*R*,8a*S*)-**1** and (−)-(2*S*,8a*R*)-**2** affords α-hydroxy ketones **4** in high optical purity (69–95% ee). An open transition state, controlled by nonbonded steric interactions, is proposed as being responsible for the chiral recognition.

Sir: Chiral α-hydroxy carbonyl compounds are important reagents for the synthesis of complex optically active natural products and are useful stereodirecting groups.[1] Recently we reported a study of the asymmetric oxidation of ester and amide lithium enolates to α-hydroxy carbonyl compounds using (camphorylsulfonyl)oxaziridines (+)-(2*R*,8a*S*)-**1** and (−)-(2*S*,8a*R*)-**2** and oxaziridine (−)-(*S*,*S*)-**3**.[2] Both α-hydroxy carbonyl enantiomers, with enantioselectivities up to 85% ee, were accessible because the configuration of the oxaziridine three-membered ring determines the product stereochemistry.

In this paper we have extended these preliminary investigations to a detailed study of the asymmetric oxidation of ketone enolates (eq 1). From a consideration of the structure–stereoselectivity trends a transition-state hypothesis has been developed which also provides a useful probe into the solution chemistry of metal enolates.

(7) Heating the reaction mixtures described in ref 2 to 150 °C for 24 h gave, after workup and chromatography, the results shown in eq 2. Compound **6**: ^1H NMR ($CDCl_3$) δ 8.2–7.0 (m, Ar H), 5.4 (q, J = 9 Hz, vinyl H cis to PhS); ^{19}F NMR ($CFCl_3$) 56 ppm (d, J = 9 Hz, *gem* CF_3, H).[3] Compound **7**: ^1H NMR ($CDCl_3$) δ 8.2–7.1 (m, Ar H), 6.4 (s, vinyl H trans to CF_3); ^{19}F NMR ($CFCl_3$) 69 ppm (s, CF_3 trans to vinyl H).[3] Compound **8**: ^1H NMR ($CDCl_3$) δ 8.3–7.0 (m, Ar H), 6.5 (s, vinyl H trans to CF_3); ^{19}F NMR ($CFCl_3$) 67 ppm (s, CF_3 trans to vinyl H).[3] In addition from $PhCOC{\equiv}CCF_3$ and PhS^- at 150 °C for 24 h a small amount (1%) of (*Z*)-PhCOCH=C(CF_3)SPh ([^1H NMR ($CDCl_3$) δ 8.2–7.0 (m, Ar H); ^{19}F NMR ($CFCl_3$) 64 ppm (d, J = 1–2 Hz, CF_3 cis to vinyl H)] was obtained.[3] Similarly from reaction of $PhCOC{\equiv}CCF_3$ and PhO^- at 150 °C for 4 h a trace of (*Z*)-PhCOCH=C(CF_3)OPh was isolated: ^1H NMR ($CDCl_3$) δ 7.2–6.8 (m, Ar H); ^{19}F NMR ($CFCl_3$) 64 ppm (d, J = 1–2 Hz, CF_3 cis to vinyl H).[3] In both of these cases the vinyl H signal was obscured by the aromatic resonance but the coupling clearly visible in the ^{19}F spectrum permitted assignments.

(8) Albright, T. A.; Burdett, J. K.; Whangbo, M.-H. *Orbital Interactions in Chemistry*; Wiley: New York, 1985; pp 175–178. Dickstein, J. I.; Miller, S. I. *The Chemistry of the Carbon–Carbon Triple Bond*; Patai, S., Ed.; Wiley: New York, 1978; Part 2, p 826.

(9) Bumgardner, C. L.; Bunch, J. E.; Whangbo, M.-H. *Tetrahedron Lett.* **1986**, *27*, 1883.

(10) $PhCOC{\equiv}CCF_3$ was prepared from PhCOCl and $Zn(C{\equiv}CCF_3)_2$. The physical properties of the ketone agreed with those reported by: Shen, Y.; Xin, Y.; Cen. W.; Huang, Y. *Synthesis*, **1984**, 35.

(11) The substrate properties are correlated with the observed regiochemistry when the transition state for addition is early and resembles the starting material. This would be the case if the rate-determining step is exothermic, a likely possibility given the protic medium where nucleophilic attack on the triple bond can be concerted with proton attachment.

(1) For leading references on chiral α-hydroxy carbonyl compounds, see: (a) Davis, F. A.; Vishwakarma, L. C. *Tetrahedron Lett.* **1985**, 3539. (b) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346. (c) Brown, H. C.; Pai, G. G.; Jadhav, P. K. *J. Am. Chem. Soc.* **1984**, *106*, 1531. (d) Gamboni, R.; Mohr, P.; Waespe-Sarcebvic, N.; Tamm, C. *Tetrahedron Lett.* **1985**, 203. (e) Oppolzer, W.; Dudfield, P. *Helv. Chim. Acta* **1985**, *68*, 216.

(2) Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402.

0022-3263/86/1951-4083$01.50/0

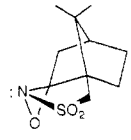
Table I Asymmetric Oxidation of Ketone Enolates Using Chiral Sulfonyloxaziridines at −78 °C in THF

				α-hydroxy ketone 5		
entry	ketone	oxaziridine	base	% ee	configuration	% yield[a]
1	**4a** (R = Me)	(+)-(2*R*,8a*S*)-**1**	LDA[b]	43.2	(−)-*S*[d]	51
2			LDA/HMPA[b,c]	12.0	(−)-*S*	54
3			NHMDS	68.5	(−)-*S*	77
4			NHMDS/HMPA[c]	41.4	(−)-*S*	80
5			KHMDS	47.0	(−)-*S*	85
6			LDA/$ZnCl_2$[b]	35.5	(−)-*S*	71
7		(−)-(2*S*,8a*R*)-**2**	NHMDS	65.0	(+)-*R*	80
8		(−)-(*S*,*S*)-**3**	NHMDS	28.0	(+)-*R*	62
9	**4b** (R = Ph)	(+)-(2*R*,8a*S*)-**1**	LDA[b]	68.0	(+)-*S*[e]	70
10			LDA/HMPA[b,c]	6.0	(+)-*S*	64
11			NHMDS	95.4	(+)-*S*	84
12			NHMDS/HMPA[c]	63.1	(+)-*S*	78
13			KHMDS	93.0	(+)-*S*	73
13		(−)-(2*S*,8a*R*)-**2**	NHMDS	95.0	(−)-*R*	88
14		(−)-(*S*,*S*)-**3**	NHMDS	54.0	(+)-*S*	77
15	**6**	(+)-(2*R*,8a*S*)-**1**	LDA[b,f]	12.3	(+)[d]	75
16			LDA/HMPA[b,c]	4.0	(−)	80
17			NHMDS	16.0	(+)	90
18			KHMDS	6.7	(+)	82
19			LDA/$ZnCl_2$[b]	14.5	(+)	77
20		(−)-(*S*,*S*)-**3**	NHMDS	23.5	(+)	74

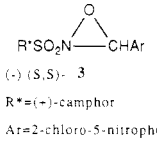
[a] Isolated yield of pure material (>98%). [b] Reaction warmed to 0 °C before quenching. [c] Ratio of THF/HMPA, 20:1. [d] % ee determined by using the chiral shift reagent Eu(hfc)$_3$. [e] % ee determined by using a Daicel Chiral Pak OT (+) HPLC column, 25 cm × 0.46 cm; solvent, MeOH; flow rate, 0.5 mL/min. First to be eluted was (+)-(*S*)-**5b**. [f] The lithium enolate was generated at 0 °C (30 min) before cooling to −78 °C for oxidation.

The lithium and sodium enolates of 1-phenylpropanone (**4a**) and deoxybenzoin (**4b**) were chosen for this study because they have, almost exclusively, the *Z* geometry (>98:2).[3,4] For structural reasons the enolate derived from 2-methyltetralone (**6**) must have the *E* geometry. Typically, enolates were preformed by addition of a THF (5–6 mL) solution of the ketone (0.5 mmol) to 1.2 equiv of lithium diisopropylamide (LDA) or sodium bis(trimethylsilyl)amide (NHMDS) in 5 mL of THF at −78 °C. After 15–20 min 1.5 equiv of the oxaziridine, dissolved in 5 mL of THF, was added dropwise and the reaction mixture quenched after 15 min with saturated NH_4Cl solution. Enolates prepared with LDA, LDA/$ZnCl_2$ failed to be oxidized at −78 °C and were warmed to 0 °C for 2 min prior to quenching. Enolates derived from 2-methyltetralone (**6**) required warming to 0 °C before quenching.

(+)(2R,8aS) **1**



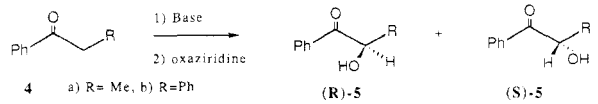
(−)(2S,8aR) **-2**



(−) (S,S)- **3**

R*=(+)-camphor

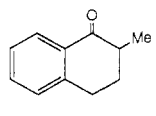
Ar=2-chloro-5-nitrophenyl



4 a) R= Me, b) R=Ph

(R)-**5**

(S)-**5**



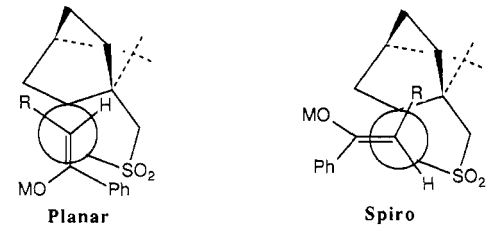
6

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

(4) The enolate geometries of the lithium and sodium enolates of deoxybenzoin and the sodium enolate of 1-phenylpropanone were determined to be >98:2 *Z* by trapping the enolates with *t*-BuMe_2SiCl according to the procedure of Ireland et al.[5]

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

Scheme I



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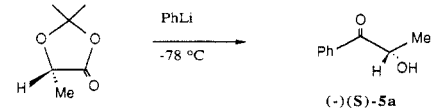
After removal of the solvent the reaction mixture was dissolved in 2 mL of ether, cooled to −78 °C, to precipitate the sulfonyl imines ($RSO_2N{=}CR_2$), and the products were isolated by preparative TLC (silica gel) eluting with 1:1 ether–pentane. Enantiomeric purities and absolute configurations of **5a,b** were established by the use of a chiral HPLC column, a chiral shift reagent and by independent synthesis.[6] These results are summarized in Table I.

The highest stereoselectivities were observed for oxidation of the sodium rather than the lithium enolates of ketones **4a,b** and **6** (Table I). The opposite trend was observed for the ester and amide enolates.[2,9] Asymmetric oxidation of **4a–b** by oxaziridine (+)-(2*R*,8a*S*)-**1** gave (−)-(*S*)-2-hydroxy-1-phenylpropanone (**5a**) and (+)-(*S*)-benzoin (**5b**) in 68.5% ee and >95% ee, respectively (entries 3 and 11). The *R* enantiomers of these hydroxy ketones were obtained by using the opposite oxaziridine

(6) (−)-(*S*)-2-Hydroxy-1-phenylpropanone (**5a**)[7] was prepared, optically pure, by treatment of the 1,3-dioxolane[8] of (−)-(*S*)-lactic acid with phenyllithium at −78 °C to give a 10–15% isolated yield of (*S*)-**5a**; $[\alpha]_D$ −86.7° (*c* 2, $CHCl_3$). A chiral shift reagent experiment, using Eu(hfc)$_3$, determined that racemaziation had not taken place.



(−)(S)-**5a**

(7) Harada, K.; Shiono, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1040.

(8) Khalaj, A.; Nahid, E. *Synthesis* **1985**, 1153.

(9) The enantioselectivities for the asymmetric oxidation of ester and amide sodium enolates were generally in the range of 16–35% ee. Unpublished results of M. S. Haque.

isomer, (−)-(2*S*,8a*R*)-**2** (entries 7 and 13). Asymmetric enolate oxidation of 2-methyltetralone (**6**) with (+)-(2*R*,8a*S*)-**1** gave much lower stereoselectivities (entries 15–19). Changing the base or solvent failed to increase the asymmetric induction. Asymmetric oxidations using (−)-(*S*,*S*)-**3** also reduced the asymmetric induction for **4a,b** (entries 8 and 14) but nearly doubled it from 16% ee to 23.5% ee for ketone **6** (compare entries 17 with 20).

The results summarized in Table I are best understood in terms of an open transition state, where nonbonded steric interactions are principally responsible for the chiral recognition.[10] Dreiding models and an X-ray crystal structure of the conformationally locked oxaziridine (+)-(2*R*,8a*S*)-**1**, suggest that in the vicinity of the active site oxygen the most sterically demanding region is the bridgehead 5–4a bond.[12] We consider, by analogy with recent studies by Heathcock and co-workers,[13] that the largest enolate group is the "OM" (M = Li, Na) solvent aggregate complex. The two extreme geometries for the oxidation of the si-faces of the metal (*Z*)-enolates of **4a,b** by (+)-(2*R*,8a*S*)-**1** are depicted in Scheme I. From a consideration of the nonbonded interactions, the planar transition-state geometry is favored over the spiro form.[14] The lower enantioselectivities noted for 2-methyltetralone (**6**) are consistent with this hypothesis because all rotational conformations of this enolate are sterically demanding. It is interesting to note that planar transition-state geometry is also preferred for asymmetric epoxidations of alkenes by chiral oxaziridines[18] and certain conformationally restricted peracids.[19]

If our assumptions concerning the factors that control the transition state geometries are correct, then it follows that "NaO" can also be considered as a large group. The higher enantioselectivities associated with sodium vs. lithium enolates of **4a,b** probably reflect the lower temperature of oxidation for the former counterion (Table I).[20] We speculate that the generally lower stereoselectivities seen in the presence of HMPA (entries 2, 4, 10, 12, 16) and for the potassium enolates (entries 5, 13, 18) are the result of a smaller effective size for "OM" group. K^+ is a poorer chelating metal than either Li^+ or Na^+, and HMPA is known to disrupt metal chelation.[21]

Attempts to extend these transition-state ideas to our previous studies of ester and amide lithium enolates are hindered by the lack of regioselective enolate formation and the seemingly contradictory effect of solvent on the stereoselectivity. Nevertheless, the available information is consistent with the spiro transition-state geometry for these enolates. We believe that the differences in the asymmetric oxidation of the ketones and the esters and amides may reflect different solution structures for their enolates.[15]

Acknowledgment. This work was supported by a research grant from the National Institutes of Health. We thank Professors P. Beak (U. Illinois) and L. M. Jackman (Penn State) for helpful discussions.

(10) No change in the ^1H or ^{13}C NMR spectra of oxaziridine (+)-(2*R*,8a*S*)-**1** and the shift reagent $Pr(fod)_3$ at 1:1 molar ratios could be detected.[11]

(11) Davis, F. A.; Towson, J. T., manuscript in preparation.

(12) Details of the X-ray structure of (+)-(2*R*,8a*S*)-**1** will be published elsewhere.[11]

(13) (a) Heathcock, C. H.; Henderson, M. A.; Oare, D. A.; Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3019. (b) Heathcock, C. H.; Oare, D. A. *J. Org. Chem.* **1985**, *50*, 3022.

(14) In analogy with other studies,[16] the enolate and oxaziridine are considered to approach in a perpendicular fashion. Recent ab initio calculations by Houk and Paddon-Row suggest that the transition state for reaction of MeF with the acetaldehyde enolate is product-like; i.e., MeF approaches the enolate at an angle of 106°.[17] Reduced steric interactions of enolates with the bridgehead bond in (+)-(2*S*,8a*R*)-**1** would be predicted with this transition-state geometry.

(15) The aggregate solution structures of enolates, as well as the actual reacting species have not been clearly established. See, for example: Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* **1985**, *107*, 2805. The solid-state enolate structures of ketones (tetramers), esters (dimers and tetramers), and amides (dimers) have been reported. See: Seebach, D.; Amstutz, R.; Laube, W.; Schweizer, B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403. Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764 and references cited therein.

(16) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435.

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

(18) Davis, F. A.; Harakal, M. E.; Awad, S. B. *J. Am. Chem. Soc.* **1983**, *105*, 3123.

(19) Rebek, J., Jr.; Marshall, L.; Wolak, R.; McManis, J. *J. Am. Chem. Soc.* **1984**, *106*, 1170.

(20) Attempts to carry out the oxidation of the sodium enolates at higher temperatures (0 °C) resulted in decomposition.

(21) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737 and references cited therein.

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The First Two-Step 1,3-Dipolar Cycloadditions: Interception of an Intermediate†

Summary: The zwitterionic intermediate **4** from thiocarbonyl ylide **2** and tetracyanoethylene undergoes competing cyclizations to give the normal cycloadduct **3** and a seven-membered ketene imine **6** in a 35/65 ratio; **6** is formed reversibly and is intercepted by water and methanol to furnish lactam **7** or lactim ether **5**.

Sir: Normal 1,3-dipolar cycloadditions being concerted,[1] we were guided in our search for transgressions by the PMO considerations[2] in Figure 1. Further strong lifting of the π-MO energies of the 1,3-dipole and lowering those of the dipolarophile should make ΔE_{II} negligibly small, i.e., ΔE_{II} can no longer defray the additional "entropy price" for the highly ordered transition state of the concerted process vs. that of *zwitterion formation* which results from *one* HO–LU interaction.

Thiocarbonyl ylides[3] are the 1,3-dipoles with the highest π-MO energies. We recently described the cycloadditions of 2,2,4,4-tetramethyl-1-oxocyclobutane-3-thione *S*-methylide (**2**) and of adamantanethione *S*-methylide to dimethyl 2,3-dicyanofumarate, an ethylene derivative with four electron-attracting substituents.[4] The *nonstereospecificity* implied a zwitterionic intermediate capable of rotation. The following experiments indicate that *two intermediates* are involved in the reaction of **2** with tetracyanoethylene (TCNE).

The extrusion of N_2 from the 1,3,4-thiadiazoline **1**[5,6] ($t_{1/2}$ = 76 min in THF, 40 °C) is a 1,3-dipolar cycloreversion furnishing **2**; in situ, **2** adds to a wide range of dipolarophiles.[6] N_2 elimination from **1** in THF + 1 vol % *water* in the presence of 1.1 equiv of TCNE at 40 °C provided 24% of **3** (mp 213–215 °C dec),[7] the normal cycloadduct of **2**, accompanied by 45% of $C_{15}H_{16}N_4OS$ (mp 171–173 °C) i.e., a compound with one additional H_2O. The reaction

†Dedicated to Professor Siegfried Hünig on the occasion of his 65th birthday.

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