PhSeSePh provides the means to trap first-formed carbon radicals and thereby give insight to the mechanism of their generation.

The chemistry that is outlined in Scheme I yields phenylselenyl derivatives of C-H centers, which, upon subsequent elimination of PhSeH via oxygenation to $PhSe(O)OH$[3] yield the olefinic derivative of the substrate.[12]

With 1:1 $Fe(PA)_2$/HOOH Fenton chemistry is the dominant process, but when the mole ratio of $Fe(PA)_2$/HOOH is 1:10 or less (as well as under Gif^{III} or Gif^{IV} conditions),[1,13] the major part of the chemistry does not involve oxy radicals or reduced iron (Table IA).[4,13]

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Investigations on Transition-State Geometry in the Aldol Condensation

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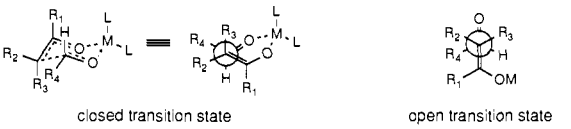
The aldol condensation has developed into one of the most important carbon–carbon bond-forming reactions used in organic synthesis today.[1] The synthetic utility of the aldol reaction stems from the high levels of internal[2] asymmetric induction that can be achieved under kinetic control. This diastereoselectivity is dependent upon the enolate geometry, metal counterion, and the bulk of the groups on the enolate and carbonyl moieties.[1c] Several transition-state hypotheses have been formulated to explain the stereochemical outcome. The most popular of these is the chairlike, chelated transition state first proposed by Zimmerman.[3-5] This hypothesis (Chart I) implies a synclinal orientation of enolate and carbonyl moieties. However, Lewis acid-catalyzed aldol reactions[1d,6] behave differently in that the product configuration is often independent of enolate geometry. In these cases open, nonchelated transition states with an antiperiplanar orientation of enolate and carbonyl moieties have been invoked (Chart I).[6]

The orientation of the enolate and carbonyl groups assumed in the transition-state hypotheses above is questionable since the intermolecular nature of these reactions makes it impossible to assign the disposition of the reactants unambiguously.[7] A

Chart I



Scheme I

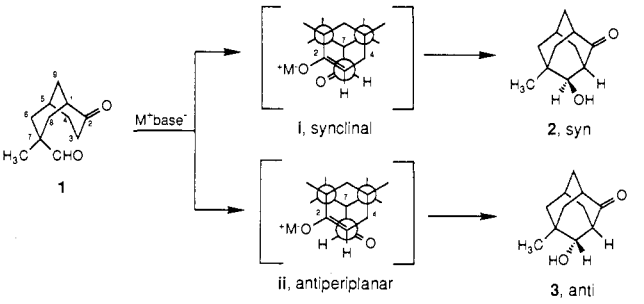
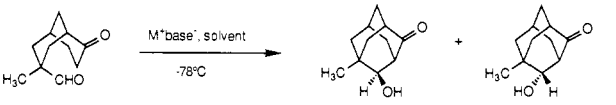


Table I. Effect of Metal Cation and Base Type in the Cyclization of **1**



entry[a]	M^+	base[b]	solvent	2/3[c,d]	yield,[d] %	$\Delta\Delta G^{\ddagger}$ (195 K)
1	K	HMDS	THF	59/41	73	0.14
2	Na	HMDS	THF	67/33	69	0.27
3	Li	HMDS	THF	87/13	87	0.74
4	MgBr	HMDS	THF	96/4	94	1.23
5	K	*t*-BuO	THF	65/35	89	0.24
6	Na	*t*-BuO	THF	67/33	91	0.27
7	Li	*t*-BuO	THF	83/17	99	0.62

[a] All cyclizations were performed with 1.1 equiv of base at −78 °C. [b] HMDS = hexamethyldisilazide. [c] Average of at least three runs within ±3%. [d] Ratios and yields were calculated based on independently determined response factors vs cyclododecane.

Table II. Effect of Solvent in the Cyclization of **1**

entry[a]	base	solvent	2/3[b,c]	yield,[c] %	$\Delta\Delta G^{\ddagger}$ (195 K)
1	$LiN(TMS)_2$	THF	87/13	87	0.74
2	$LiN(TMS)_2$	hexane	87/13	88	0.74
3	$LiN(TMS)_2$	toluene	87/13	84	0.74
4	$LiN(TMS)_2$	Et_2O	90/10	96	0.85
5	$LiN(TMS)_2$	DME	70/30	84	0.33
6	$KN(TMS)_2$	THF	59/41	73	0.14
7	$KN(TMS)_2$	toluene	89/11	90	0.81

[a] All reactions were performed with 1.1 equiv of base at −78 °C. [b] Average of at least three runs within ±3%. [c] Ratios and yields were calculated based on independently determined response factors vs cyclododecane.

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Table III. Effect of Additives in the Cyclization of **1**

entry[a]	base	solvent	additive (equiv)	**2**/**3**[b,c]	yield,[c] %	$\Delta\Delta G^{\ddagger}$ (195 K)
1	$LiN(TMS)_2$	THF	none	87/13	87	0.74
2	$LiN(TMS)_2$	THF	LiCl (5)	87/13	96	0.74
3	$LiN(TMS)_2$	THF	HMPA (5)	42/58	78	−0.13
4	$KN(TMS)_2$	THF	none	59/41	73	0.14
5	$KN(TMS)_2$	THF	Kryptofix 222(2)	9/91	79	−0.90
6	$KN(TMS)_2$	toluene	none	89/11	90	0.81
7	$KN(TMS)_2$	toluene	Kryptofix 222(2)	2/98	69	−1.51

[a] All reactions were performed with 1.1 equiv of base at −78 °C. [b] Average of at least three runs within ±3%. [c] Ratios and yields were calculated based on independently determined response factors vs cyclododecane.

knowledge of the preferences for relative orientation of reactants in the transition structure is crucial to the rational design of catalytic asymmetric aldol reactions.[8] We describe herein an investigation to probe the transition-state geometry in the aldol reaction.

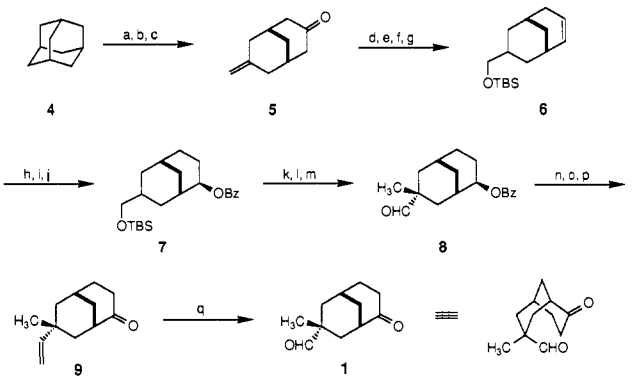
The model system **1** was designed for this study (Scheme I). Models reveal that the aldehyde is constrained to two limiting transition structures generated by rotation about the C_7–formyl bond, corresponding to synclinal (**i**) and antiperiplanar (**ii**) orientations with respect to the enolate.[9] Reaction through the different conformations leads to diastereomeric alcohols **2** and **3**, thus providing a measure of the synclinal/antiperiplanar preference in the transition structure. Steric bias is minimal due to the nearly symmetrical nature of the starting keto aldehyde. Finally, the stability of the adamantane framework in **2** and **3** should ensure kinetic control.

The synthesis of model system **1** is depicted in Scheme II[10] Model system **1** was extremely prone to cyclization and could be purified only by column chromatography at −45 °C on activity V neutral alumina.

The first series of experiments[11] addressed the effect of the metal counterion and type of base on the stereochemical course[12] of the cyclization (Table I). As the coordinating ability of the counterion increased, the syn selectivity of the reaction also increased (entries 1–4). *Use of a cation with a strong ability for chelation such as Mg^{2+} afforded a 96:4 product ratio favoring the syn diastereomer.*[13] Thus, the propensity for reaction through a closed transition state increases as the coordinating ability of the cation increases.[14] Changing the base type had little effect (compare entries 1–3 and 5–7).

We next examined the effect of solvent on the stereochemical course of cyclization, Table II. With lithium hexamethyldisilazide as the base, the product distribution was largely unaffected by a change in solvent. However, the use of DME resulted in a lowering of the syn selectivity, which is interpreted as an attenuation of the coordinating ability of the lithium cation.[15] With potassium, the solvent effect was much larger (entries 6 and 7). Toluene is less effective than THF in solvating cations and delocalizing charge. Thus, Coulombic interactions are more pronounced in toluene, and the coordinating ability of the more ionic potassium ion is increased compared to lithium.

Scheme II[a]



[a] (a) Br_2, 25 °C to 105 °C, 2 h, 78%; (b) Br_2, BBr_3, $AlBr_3$, 25 °C to 85 °C, 1.5 h, 87%; (c) 1 M NaOH, dioxane, 185 °C, 16 h, 83%; (d) BH_3·THF, 0 °C to 25 °C, 1.5 h, then 30% H_2O_2, 10% NaOH, 25 °C, 0.5 h, 64%; (e) TBSCl, imidazole, DMF, 45 °C, 16 h, 80%; (f) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 99%; (g) *t*-BuO^-K^+, THF, 25 °C, 2 h, 92%; (h) MCPBA, $NaHCO_3$, CH_2Cl_2, 25 °C, 1 h, 98%; (i) $LiBEt_3H$, THF, 45 °C, 4 h, then 30% H_2O_2, 10% NaOH, 25 °C, 0.5 h, 72%; (j) *n*-BuLi, −5 °C, 5 min, then PhCOCl, 25 °C, 0.5 h, 95%; (k) *n*-$Bu_4N^+F^-$, THF, 25 °C, 8 h, 94%; (l) $(COCl)_2$, DMSO, Et_3N, −78 °C, 75%; (m) *t*-BuO^-K^+, MeI, 25 °C, 0.5 h, 78%; (n) *n*-BuLi, Ph_3P^+-CH_3Br^-, −78 °C to 25 °C, 20 min, 92%; (o) 5% NaOH/MeOH, Et_2O, 25 °C, 19 h, 96%; (p) NCS, DMS, Et_3N, toluene, −25 °C, 2 h, 90%; (q) O_3, CH_2Cl_2, −78 °C, then $(MeO)_3P$, 25 °C, 18 h, then O_3, CH_2Cl_2, −78 °C, 67%.

We have also investigated the dependence of cyclization stereochemistry on additives, Table III. Addition of LiCl[16] had no effect on the stereochemistry of cyclization. However, addition of HMPA resulted in a large change in selectivity, now providing a slightly anti selective reaction. The cation solvating power of HMPA[17] clearly attenuates the coordinating ability of the lithium cation. An even more dramatic result was observed upon sequestering the cation with a macrobicyclic cryptand[18] (entries 5 and 7). *Cyclization of the potassium enolate in the presence of Kryptofix 222 resulted in a product ratio of 98:2 favoring the anti isomer.*[19] This result establishes the preference for cyclization of "naked" enolates through an open transition state. The preference may be due to either the smaller overall dipole moment in the transition state **ii** relative to **i** or the Coulombic repulsion of the partially negatively charged oxygens in **i**.

In summary, this study has revealed a strong preference for aldol reaction via an antiperplanar orientation of reactants in the absence of a coordinating cation. The use of a strongly coordinating cation overwhelms this preference and leads to a high selectivity for reaction through a chelated transition structure.

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(9) These orientations do not necessarily reflect the transition-state geometries in intermolecular aldol reactions.

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(12) Stereochemical assignments were made by X-ray crystallographic analysis.

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(19) This corresponds to an energy *difference* of >2.7 Kcal/mol compared to entry 4, Table I. The wide spectrum of selectivities supports our belief that the model is not inherently biased.

Acknowledgment. We gratefully acknowledge financial support for this project from the National Science Foundation (NSF CHE 8515371 and 8818147). S.E.D. acknowledges support from the National Science Foundation (Presidential Young Investigator Award, 1985-1990) and the Alfred P. Sloan Foundation (1985-1989). B.R.H. thanks the University of Illinois for a Graduate Fellowship (1984-1988).

Supplementary Material Available: Full characterization of **1**, **2**, and **3** is provided along with general experimental and cyclization procedures (5 pages). Ordering information is given on any current masthead page.

Correlated Motion Monitored by NMR Relaxation in the Rotating Frame. A Source of Structural and Dynamic Information on Macromolecules

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Nuclear magnetic cross relaxation has become a major tool for the investigation of macromolecular structure and dynamics.[1,2] In particular two-dimensional nuclear Overhauser effect spectroscopy (NOESY) proved to be quite informative.[3,4] Additionally, it has been shown that cross relaxation involving higher spin orders contains specific information on correlated motional processes,[5-15] useful for the description of segmental motion and conformational equilibria in biomolecules.

Recently a technique has been proposed for the observation of cross relaxation between one- and three-spin order in the laboratory frame,[16] however with applicability to small molecules ($\omega_0\tau_c \leq 1$) only. We propose in this communication an alternative method for the measurement of cross relaxation in a tilted rotating frame, called 3QF T-ROESY (T refers to Tilted frame), that does not suffer from this limitation.

For simplicity, we concentrate on the α and the two β protons in an amino acid residue of a protein. They form an AMX spin subsystem. We assume residues in which the feasible conformations are limited to the three staggered ones shown in Figure 1a that possibly may dynamically interconvert. Dipolar interaction among the three spins, modulated by overall molecular tumbling and intramolecular motion, causes correlated cross relaxation. We consider the transfer between one-spin and three-spin order:

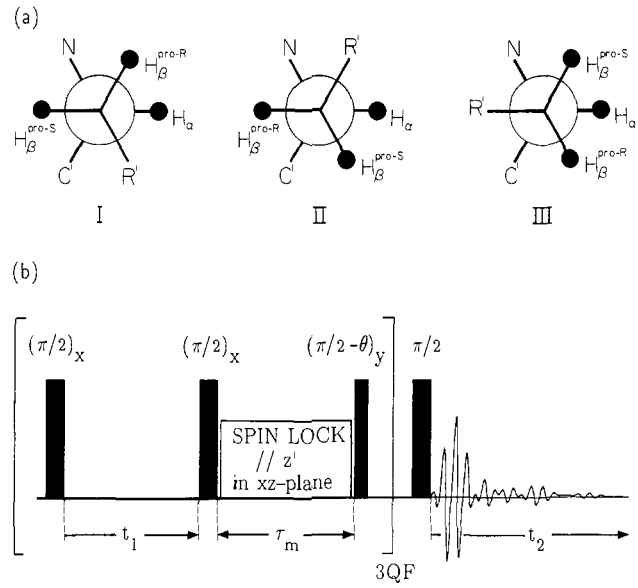

Figure 1. (a) Three staggered conformations of a $C_\alpha C_\beta$ fragment of an amino acid residue. (b) Pulse sequence for 3QF T-ROESY. The $(\pi/2)_x$ pulse before and the $(\pi/2-\theta)_y$ pulse after the spin lock sequence ensure optimal transfer of in-phase coherence to and from the lock axis.[19] The off-resonance lock during the mixing time τ_m for $\theta = 35°$ is effected by time-proportional phase incrementation with the pulse sequence $(14^{\circ}_{0}, 14^{\circ}_{-20}, 14^{\circ}_{-40}, \ldots, 14^{\circ}_{-340})_n$.

$$I_{Az'} \xrightarrow{\Gamma^{\theta}_{AMX\,A}} 4I_{Az'}\,I_{Mz'}\,I_{Xz'}$$

We assume that during cross relaxation an rf field B_1 is applied off-resonant by $\Delta\omega$ such that the effective field in the rotating frame is oriented along z' tilted by an angle $\theta = \tan^{-1}(\gamma B_1/\Delta\omega)$ with respect to the static field. The rate constant for the creation of three-spin order is[17]

$$\Gamma^{\theta}_{AMX\,A} = \left(\frac{\mu_0}{4\pi}\right)^2 \gamma^4\hbar^2\frac{3}{20}[3\sin^2\theta\cos^2\theta J_{AM\,AX}(0) + (\sin^4\theta - \sin^2\theta\cos^2\theta + 2\cos^4\theta)J_{AM\,AX}(\omega_0) + (\sin^2\theta(1+\cos^2\theta)J_{AM\,AX}(2\omega_0)] \quad (1)$$

where $J_{AM\,AX}(\omega)$ is the cross power spectral density of the two dipolar interactions AM and AX, assuming equal θ values for all spins for strong rf field B_1. The first term in eq 1 disappears for laboratory frame cross relaxation (NOESY, $B_1 = 0$, and $\theta = 0$) and for on-resonance rotating frame cross relaxation (ROESY, $\Delta\omega = 0$, and $\theta = \pi/2$) for all values of τ_c, whereas for large molecules with long correlation times τ_c ($\omega_0\tau_c \gg 1$) in addition the second and third terms vanish. For large molecules, the maximum rate constant is obtained for $\theta = 45°$. Some characteristic values for the ratio of the rates in laboratory and tilted rotating frame are $\Gamma^{0}_{AMA\,X}/\Gamma^{45°}_{AMA\,X} = 1$, 0.1, 0.01 for $\omega_0\tau_c \simeq 0$, 5, 16, respectively ($\omega_0\tau_c \simeq 13$ for BPTI at room temperature and 500 MHz). In spite of a slowdown by 10% it is advisable to set $\theta = 35°$ ($\simeq 90° - \cos^{-1}(1/\sqrt{3})$) as at this value cross-relaxation rate constant Γ^{θ}_{MA} vanishes in competitive transfers, such as in

$$I_{Az'} \xrightarrow{\Gamma^{\theta}_{MA}} I_{Mz'} \xrightarrow{\Gamma^{\theta}_{AMX\,M}} 4I_{Az'}I_{Mz'}I_{Xz'}$$

The cross power spectral density $J_{AM\,AX}(\omega)$ contains information on overall and intramolecular motional processes. We assume a random jump process between the three conformations of Figure

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