

STEREOCHEMISTRY OF THE FLUORIDE CATALYZED ALDOL REACTION OF ENOL SILYL ETHERS. EVIDENCE FOR ANOTHER NON-CHELATE TRANSITION STATE

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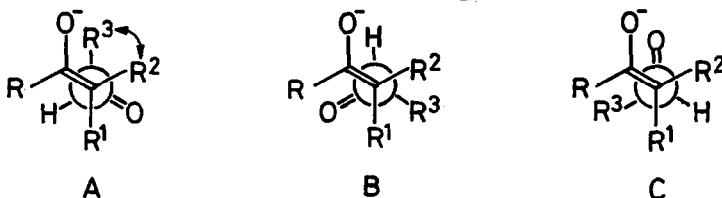
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Summary: Stereochemistry of the tetrabutylammonium fluoride catalyzed aldol reaction of enol silyl ethers was examined for both tri- and tetra-substituted enolates to find that the previous "extended, non-chelate" transition model (A) applicable only for enolates with sterically bulky substituents, and that another model (B) should also be considered for the less hindered enolates.

It is generally agreed that the aldol reaction of metal enolates proceeds via chelate (cyclic) transition states (TSs),¹ the structure of which is highly sensitive to the environment of the metal cation (e.g., ligands and solvents). By contrast, the fluoride catalyzed aldol reaction² of enol silyl ethers is considered not to proceed via such TSs because of the presumed intermediacy of metal-free enolates.² Existence of free enolate anions under the reaction conditions has been demonstrated,³ and a "non-chelate, extended" TS model A (Scheme 1) has been proposed to account for the observed diastereoselectivity.⁴ However, it has not been made clear if these previous observations actually provide a correct picture of the TS itself. We have examined this point with the aid of four experimental probes to find that the current view is largely appropriate, but must be reconciled with a new TS protocol of a broader framework, in that another non-chelate "skew" TS B should be considered as a significant contributor in certain important cases.

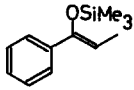
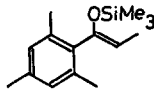
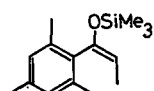
Scheme 1. Non-chelate Transition States Leading to erythro-Aldols ($R^1 > R^2 > R^3$)



The criteria we have relied on are the following: if the TS is truly "extended non-chelated",⁴ then (1) neither of the counteraction,^{5a} (2) the silyl group,^{5a} and (3) the R group (in A)^{5b} would exercise any effects on the diastereoselectivity, and (4) the reaction of tetra-substituted enolates ($R^1 = R^2 = \text{alkyl}$; e.g., 1, 2, 3) would also show erythro selectivity, the degree of which must however be only moderate.^{5c} On the basis of the tetrabutylammonium (TBA) chemistry developed earlier in these laboratories,⁶ we examined these points to find that the first two expectations were fulfilled, and the latter two not.

TBA and tris(diethylamino)sulfonium (TAS) cations differ not only in their steric but electronic properties, in that the cationic charge is delocalized in the latter.³ We have examined the TBA fluoride (TBAF)-catalyzed aldol reaction (eq 1)^{6a} for most of the combination of substrates examined earlier with TAS fluoride (TASF)³ to find that both the sense

Table 1. TBAF Catalyzed Aldol Reaction of Enol Silyl Ethers^a

entry	enol silyl ether (geometrical purity, %)		Aldehyde	time (h)	% yield (e : t) ^b	with TASF (e : t) ^b
1		R ₃ = Me ₃ Si (97)	PhCHO	2	72 (86:14) ^c	(86:14)
2		Me ₂ PhSi (93)	PhCHO	2	87 (85:15)	
3		Ph ₃ Si (91)	PhCHO	13	6 (>9:1)	
4		R ₃ = Me ₃ Si (89)	PhCHO	2	89 (44:56) ^c	(53:47)
5		Me ₂ PhSi (72)	PhCHO	2	86 (43:57)	
6		Ph ₃ Si (70)	PhCHO	13	5 (ca.1:1)	
7		(93)	PhCHO	1	89 (93: 7)	(95: 5)
8		(96)	PhCHO	4	73 (>99:1)	(ca. 95:5)
9			<i>i</i> -PrCHO	21	3 (>99:1)	(ca. 95:5)
10		(>99)	PhCHO	4	67 (>97:3)	(ca. 95:5)
11			<i>i</i> -PrCHO	21	9 (>99:1)	(ca. 95:5)
12			<i>i</i> -PrCHO	13	35 (97: 3) ^d	(100: 0)
13			<i>i</i> -PrCHO	14	50 (100: 0) ^e	(100: 0)

^aReactions were carried out with 20 mol% of TBAF at -72 °C. Data for TASF are based on those in ref 3. ^bDetermined by 200 MHz ¹H NMR analysis of the crude mixture, and the ratio was corrected on the basis of the isomeric purity of the enolate, assuming the equal reactivity of both geometrical isomers. ^c Me₃SiF did not change the diastereomeric ratio (cf. ref 4, 6a). ^dThe reaction was performed in the presence of Me₃SiF (5 equiv). ^eAt -30 °C with 2 equiv of Me₃SiF (ref 6a).

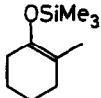
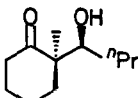
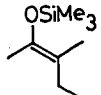
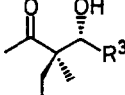
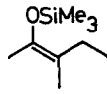
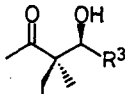
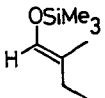
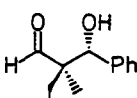
and the degree of stereoselection are identical within experimental error with those of the TASF-catalyzed reaction (Table 1). Notably, good agreement of the data has been found even for the moderately selective cases (entries 1, 4) wherein the energy difference among the diastereomeric transition states can be most accurately evaluated.

We then examined the effect of the silyl group of the enol silyl ethers, for the first time in the fluoride-catalyzed chemistry, to find that the nature of the silyl group does not affect the diastereoselectivity. Thus, the diastereomeric ratios observed for Me₃Si, Me₂PhSi, and Ph₃Si enol ethers of 3-pentanone were identical with each other within experimental error (entries 1-6).

The remarkable consistency of the selectivity against the variation of the cation and the silyl group provides a strong support of the non-chelate TS protocol. In particular, the lack of the effects of the silyl groups discounts the possible participation of a pentavalent silicon species⁷ in the TS.

The most striking feature of the diastereoselectivity found in Table 1 is the complete lack of the diastereoselectivity of the 3-pentanone *E*-enolate (entries 4-6), which stands in contrast to the high selectivity of the other bulkier enolates in entries 7-13. Importance

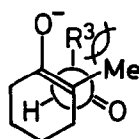
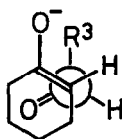
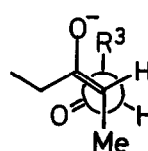
Table 2. Aldol Reaction of Tetra-Substituted Enolates^a

entry	enol silyl ether (geomet. purity, %)	aldehyde	time (h)	product ^c	% yield (e : t) ^b
1		<u>n</u> -PrCHO	2		49 (86:14)
2		<u>n</u> -PrCHO	15		30 (88:12) ^d
3		PhCHO	0.5		R ³ = Ph 68 (29:71)
4		<u>n</u> -PrCHO	2		R ³ = Pr 65 (22:78)
5		PhCHO	0.5		R ³ = Ph 97 (64:36)
6		<u>n</u> -PrCHO	2		R ³ = Pr 60 (68:32)
7		PhCHO	2		68 (35:65)

^{a,b}See footnote a,b in Table 1. ^cMajor diastereomer is indicated. ^dCarried out in the presence of Me₃SiF (2-5 equiv).

of the steric effect of the R group (cf. A) is thus evident, which has been overlooked thus far.^{3,4} Experiments described below further provided examples of such an "exceptional" properties of the enolates with small R groups.

The fourth criterion was examined for the reaction of the tetra-substituted enolates **1**, **2**, and **3**, as well as the aldehyde enolate **4** (Table 2).⁸ The reaction was carried out at -72 °C under TBAF catalysis. Appropriate control experiments indicated that the retro-aldol reaction does not occur under the reaction conditions.

**D:** disfavored erythro TS**E:** disfavored threo TS**F:** threo TS

The behavior of the erythro-producing cyclic enolate **1** (entry 1, 2) was found consistent with the extended model A: The lower degree of selectivity compared with the simple cyclohexanone enolate (Table 1, entry 12) is probably due to the additional gauche interaction caused by the 2-methyl group shown in **D**. To the contrary, the E-acyclic enolates **2** and **4** were found threo-selective, while the Z-enolate **3** still erythro-selective. The threo selectivity of the E-enolate **2**, though only moderate, sharply contradicts with the conventional TS model A, as does the behavior of the E-enolate of 3-pentanone (Table 1, entries 4-6). The erythro selectivity which has earlier been ascribed to the characteristic behavior of the enolates generated by the fluoride methodology emerges only for the enolates with a bulky R group (phenyl or mesityl) or for the cyclic enolates (termed herein category L), and not for simpler enolates with a small R group (category S).

Given the evidence for the non-chelate TS, the importance of the size of the R group, and the abnormal behavior of enolates **2** and **4**, we propose that a non-chelate "skew" TS **B**, in addition to the previous model **A**, be considered as another "non-chelate" TS. In case of the category L enolates, it can be argued that the bulky R or the cyclic bridge structure provides steric hindrance against the carbonyl oxygen (cf. **E**) and raises the energy of the TS **B**. For the category S enolates, since R is small, a threo producing "skew" TS (cf. **F**) is relatively strain-free, and should have significant contribution.

Very recent *ab initio* calculation of the aldol reaction of the metal-free enolate anion in gas phase⁹ fully supported our contention in that, of three possible TSs, **A**, **B**, and **C**, the first two are of equally low energy, and the last is disfavored by as much as 3.3 kcal/mol, owing to the oxygen-oxygen repulsion.¹⁰ Although more sophisticated level of calculation¹¹ and experimental work are needed to assess the substituent effects in each TS type, the present studies indicate that closer examination of the TS **B** is needed for better understanding of the fluoride-catalyzed aldol reaction.^{12,13}

References and Notes

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5. (a) Note that the TS **A** assumes the enolate being metal-free. (b) The experimental data have been rationalized without considering the steric effect of the R group. (c) The magnitude of the gauche interaction between R² and R³ has been assumed similar to that between R¹ and R³ in the two diastereomeric TS.
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9. Li, Y.; Padon-Row, M. N.; Houk, K. N.; manuscript submitted for publication. We thank Professor Houk for making us available the manuscript before publication.
10. It should be noted that the TS **C** is topologically related to the chelate TS..
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