Investigations on Transition-State Geometry in the Lewis Acid- (Mukaiyama) and Fluoride-Promoted Aldol Reactions

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Summary: The stereochemical course of the Lewis acid- and fluoride ion-promoted aldol reaction has been studied with model 1. Cyclizations of 1 show a modest preference for reaction via an antiperiplanar (open transition state) orientation of reactants in the presence of a wide range of Lewis acids and fluoride sources.

The directed aldol reaction between a silyl enol ether and an aldehyde is one of the most powerful and selective carbon–carbon bond forming reactions.[1] The use of Lewis acids to promote (or catalyze) this condensation has added a new dimension to the aldol reaction, which has had enormous practical and stereochemical consequences. Since Mukaiyama's initial disclosure,[1a] many different promoters and catalysts have been reported including $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, fluoride ion, aluminum salts, trimethylsilyl triflate, dimethylsilyl ditriflate, trityl salts, Sn(II)/Sn(IV) combinations, rhodium complexes, $BiCl_3$, $InCl_3$, lanthanide salts, ruthenium salts, zirconium salts, tungsten salts, and a ytterbium complex. Perhaps the most important advance in recent years has been the use of chirally modified Lewis acids for enantioselective aldol reactions.[2]

Given the diversity of reaction conditions it is unlikely that a single mechanistic pathway exists for this condensation. Furthermore, the mechanism and origins of stereogenesis under various reaction conditions are still not well understood.[3] In continuation of our studies on the origin of stereocontrol in the anionic aldol condensation,[4] we have now investigated the transition structure geometry in the Mukaiyama aldol reaction as a function of promoter and conditions.

Model system 1 (Figure 1) has been developed for the systematic examination of the preferences for double bond orientation. The design considerations, advantages, and limitations of this approach and basic system have been discussed at length previously.[4a] In the Lewis acid-induced cyclization of 1, there are two limiting reactive geometries generated by the rotation about the C_7-formyl bond: synclinal and antiperiplanar structures T_1 and T_2, respectively. The ratio of the diastereomeric aldols products 2 and 3 provides a measure of the synclinal/antiperiplanar preference for the corresponding transition structure. An antiperiplanar arrangement of the groups is the currently most popular formulation of the transition state and has been supported by an extensive survey of additions by Heathcock.[5] In the fluoride ion-promoted aldol addition reaction there are also various possibilities.[6] While initially thought to proceed by desilylation to a "naked enolate" (T_4) followed by rapid and reversible addition,[6b] Corriu has recently proposed two distinct mechanisms depending upon the fluoride source.[7] The two limiting intermediates shown in Figure 1 are the hexavalent siliconate (T_3) and "naked enolate" (T_4). Model system 1 can distinguish these intermediates since reaction via T_3 must lead to 2 while reaction via T_4 is expected to give 3 on the basis of our previous results.[4a]

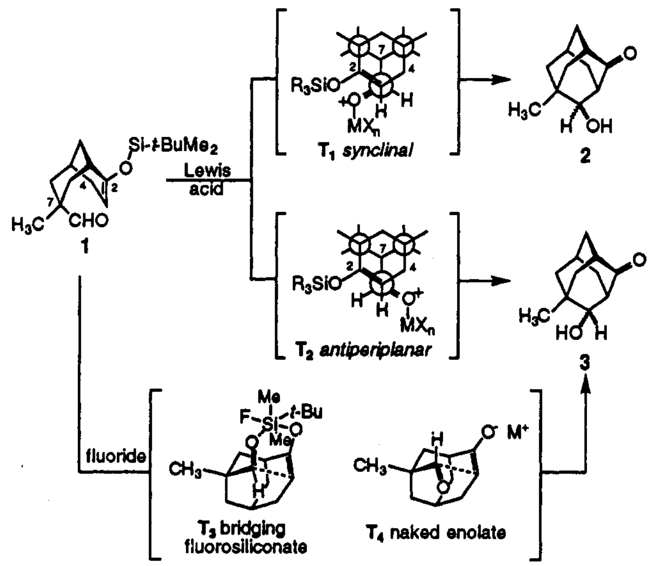

Figure 1. Transition structure analysis for cyclization of model system 1.

The synthesis of 1 is outlined in Scheme 1. The precarious juxtaposition of nucleophilic and electrophilic functions provided a considerable challenge. Strategies involving oxidation of the enolsilane–alcohol or reduction of enolsilane–carboxylic derivatives to the target enolsilane–aldehyde failed. The successful synthesis of 1 hinged on the invention of a new aldehyde protecting group

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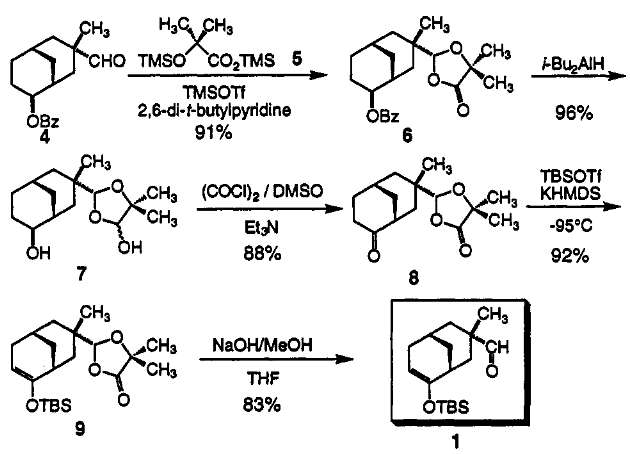
Scheme 1



that would resist reduction and enolization conditions and be removable under basic conditions. We have developed the 5,5-dimethyl-1,3-dioxolan-4-one acylal for this purpose. Thus, protection of aldehyde 4[4a,8] with the bis-silylated 2-hydroxy-2-methylpropanoate 5 in the presence of TMSOTf and 2,4-di-*tert*-butylpyridine[9] gave the 1,3-dioxolan-4-one 6[8] in 91% yield. The removal of the benzoate group was accomplished by DIBAL-H reduction. Although the dioxolanone was also reduced under these conditions, it preserved the aldehyde oxidation state and was remarkably stable, e.g., surviving silica column chromatography to afford 7[8] in high yield (96%). Oxidation of 7 with the Swern reagent afforded ketodioxolanone 8[8] in 88% yield. Treatment of 8 with KHMDS in the presence of TBSOTf at -95 °C afforded the silyl enol ether–dioxolanone 9[8] in 92% yield after cold (-78 °C) column chromatography on activity III neutral alumina. Selective removal of the dioxolanone was readily accomplished upon treatment with 5% NaOH in MeOH/THF at 0 °C to produce the target silyl enol ether–aldehyde 1[8] in 83% yield after purification by cold column chromatography at -78 °C (activity V basic alumina).

Results of the aldol condensation of 1 with several representative Lewis acids and fluoride ion sources are summarized in Table 1.[10] To vouchsafe the interpretation of *Lewis acid* versus adventitious protic acid catalysis, the experiments were also carried out in the presence of 2,6-di-*tert*-butylpyridine. In general, the Lewis acid promoted reactions showed a modest anti selectivity. Considering the wide range of Lewis acid types examined (mono- and divalent, neutral, and cationic), the narrow range of selectivities recorded is remarkable. Even protic acid catalysis (entry 7) gave a similar level of anti selection. Control experiments (entries 1, 2, 5, and 6) revealed that the anti selectivity was not the result of Bronsted acid catalysis except in the case of $SnCl_4$ which showed an unexpected reversal in selectivity.

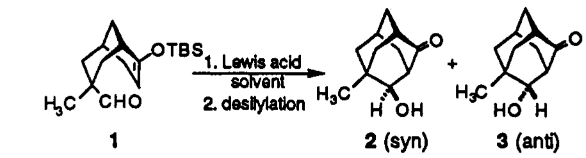
The remarkable divergence of $SnCl_4$ was further exemplified by the behavior of $SnCl_2$ which promoted a syn-selective reaction (syn/anti 79/21). The cyclizations with this Lewis acid showed little sensitivity to the amount of

(8) All new compounds have been fully characterized. See supplementary material.

(9) (a) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. (b) For the preparation of dioxanones see: Schreiber, S. L.; Reagan, J. *Tetrahedron Lett.* **1986**, 2945.

(10) Kinetic control was established in all cyclization experiments: the silyl ethers of both 2 and 3 were recovered unchanged under all cyclization conditions, and both 2 and 3 were recovered unchanged from desilylation experiments.

Table 1. Aldol Cyclizations of Model System 1[a]



entry	Lewis acid	syn/anti[b]	syn/anti[b,c]	$\Delta\Delta G^{\ddagger}$,[c] kcal/mol
1	$TiCl_4$	21/79	25/75	-0.43
2	$EtAlCl_2$	24/76	25/75	-0.43
3	$BF_3{\cdot}OEt_2$	29/71		-0.35
4	TMSBr	30/70		-0.33
5	TMSOTf	25/75	27/73	-0.39
6	$TrClO_4$[d]	27/73	28/72	-0.37
7	CF_3SO_3H	18/82		-0.59
8	$SnCl_4$	18/82	61/39	0.17
9	$SnCl_2$	78/22	79/21	0.51
10	TBAF[e]	20/80	19/81	-0.56
11	CsF[f]	10/90	10/90	-0.85
12	KF-Kryptofix[2.2.2][e]	9/91		-0.90

[a] Reactions run with 1.1 equiv of reagent in CH_2Cl_2 at -78 °C for 1 h. [b] From capillary GC analysis. Average of at least three runs within ±3%. [c] 1.1 equiv of reagent and 2,6-di-*tert*-butylpyridine. [d] 0.1 equiv of reagent used. [e] Reaction run at -78 °C in THF for 24 h. [f] Reaction run at room temperature in THF for 8 h.

Table 2. Cyclization of 1 with Tin(II) Salts[a]

Lewis acid	syn/anti[b]	syn/anti[b,c]	$\Delta\Delta G^{\ddagger}$,[c] kcal/mol
SnF_2	63/37	66/34	0.26
$SnCl_2$[d]	74/26		0.41
$SnCl_2$	78/22	79/21	0.51
$SnCl_2$[e]	64/36	72/28	0.37
$SnBr_2$	39/61	63/37	0.21
SnI_2	49/51	44/56	-0.09
$Sn(OTf)_2$	31/69	36/64	-0.22

[a–c] See Table 1. [d] 0.5 equiv used. [e] 5.0 equiv used.

reagent used ranging from 74/26 to 72/28 (syn/anti) for 0.5–5.0 equiv, Table 2. However, the selectivity was strongly influenced by the nature of the counterion. The magnitude of the syn preference decreases in the order Cl > Br > I > OTf. Stannous fluoride does not follow this trend since it behaves as both a Lewis acid and fluoride source (vide infra).

The overall anti selectivities observed in Lewis acid-induced cyclizations can be explained by the competing transition structures T_1 and T_2 (Figure 1). We assume Lewis acid complexation of the aldehyde takes place in an anti fashion.[5a,11] In that reactive complex, the synclinal transition structure T_1 experiences unfavorable dipole–dipole interaction between two carbon–oxygen bonds in synclinal disposition. The striking insensitivity of the reaction to bulk and nature of the Lewis acid (compare entries 6 and 7) underscores the absence of an intrinsic steric bias.[12] Moreover, the modest selectivity reveals a weak intrinsic preference for double bond orientation consistent with the well documented variation in selectivity with enol geometry, substitution, and aldehyde structure.[3]

The syn-selectivity observed for $SnCl_2$ can be rationalized by the balance between transition structures T_2 and T_5 (Figure 2). Given the overall anti preference for most Lewis acids, the special behavior of $SnCl_2$ must be due to (1) its attenuated Lewis acidity and (2) its ability to

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(12) An alternative explanation that the silyl electrofuge, *t*-$BuMe_2SiX$, is the actual promotor cannot be unambiguously ruled out but seems unlikely in view of the results with $SnCl_2$.

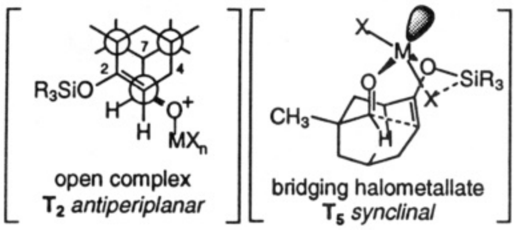

Figure 2. Transition structures of the model system **1** with Lewis acids.

coordinate both enol and aldehyde oxygens.[13] The distorted, trigonal bipyramidal coordination geometry depicted in $\mathbf{T_5}$ is supported by the X-ray structures of SnX_2(1,4-dioxane).[14] In addition, for this complex to be kinetically competent, the X group must be able to remove the silicon electrofuge, which explains the counterion dependence.

All fluoride ion sources gave anti-selective cyclization (entries 10–12). It is thus apparent that the hexacoordinate structure $\mathbf{T_3}$ is not energetically favorable under these conditions and that either the naked enolate or a pentacoordinate fluorosiliconate reacts preferentially via transition structure $\mathbf{T_4}$. This structure minimizes the Coulombic repulsion between the enolate and aldehyde oxygens and is precedented by the extremely anti-selective cyclization of the anionic aldol model as the potassium salt in the presence of Kryptofix[2.2.2].[4a]

In summary, this study has revealed a modest preference for the antiperiplanar orientation of double bonds in the Mukaiyama aldol reaction with Lewis acids and a stronger preference for the fluoride ion promoted process. With $SnCl_2$, a synclinal orientation is favored which suggests bidentate coordination. Further examination of the role of Sn(II) salts in catalytic asymmetric aldol reactions and the dependence on the silicon electrofuge is in progress.

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Supplementary Material Available: Full characterization of compounds **1** and **6–9** and a representative procedure for the cyclization experiments (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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