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The Formyl C–H--O Hydrogen Bond as a Critical Factor in Enantioselective Reactions of Aldehydes, Part 4. Aldol, Ethylation, Hydrocyanation and Diels-Alder Reactions Catalyzed by Chiral B, Ti and Al Lewis Acids.

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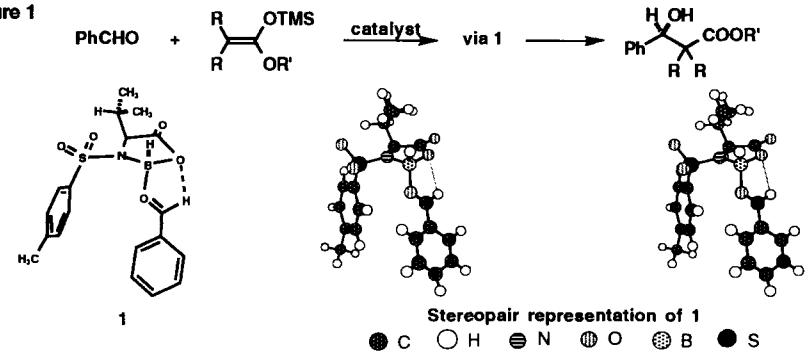
Abstract: *Formyl C–H--O hydrogen bonding provides a rational explanation of several diverse catalytic enantioselective addition reactions of aldehydes, as outlined in Figures 1-5.*

One of the most significant areas of research in the field of enantioselective catalysis is the study of the detailed mechanistic basis of enantioselectivity in terms of transition-state structure. Research in this area is crucial to the rational development of new synthetic methodology and to the successful application and/or extension of enantioselective reactions. Indeed, highly enantioselective catalytic reactions provide an unparalleled opportunity to discern the fine details of transition-state structure for many key synthetic processes. Earlier papers of this series have provided evidence for the importance of the formyl C–H--O hydrogen bond as an organizing factor in various enantioselective chiral Lewis acid-catalyzed reactions of aldehydes, including Diels-Alder, aldol and allylation reactions.[1-3] In each of thirteen different reactions, the rational use of strongly precedented structural principles and the formyl C–H--O hydrogen bond has led to a transition-state assembly which predicts the observed absolute configuration of the predominating enantiomer. In this paper we show that this analysis can be extended successfully to seven additional reactions. As was the case for previous examples, all these reactions are highly exothermic and proceed via early transition states which resemble the initial catalyst-substrate complex. Under these circumstances, the major reaction channel will be via the most stable complex since the rate constant from that complex will be comparable to those from less stable species, or possibly even greater to the extent that tighter coordination leads to greater substrate activation, i.e. an even earlier transition state.

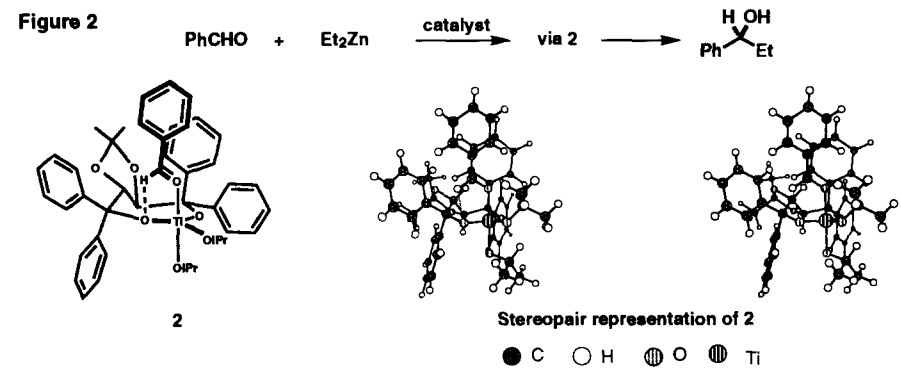
Kiyooka and coworkers[4] have studied enantioselective Mukaiyama aldol reactions of aldehydes with various silyl enol ethers using an *N*-arylsulfonylvaline-derived oxazaborolidine catalyst. Figure 1 illustrates a proposed partial transition-state assembly (silyl enol ether not included) where the isopropyl and arylsulfonyl appendages are disposed *trans* to one another about the oxazaborolidine ring and in the sterically most stable conformation as shown in **1**. The aldehyde can coordinate to the face of boron *trans* to isopropyl, thereby minimizing steric repulsion and providing for the necessary hydrogen bonding between the formyl hydrogen and the oxazaborolidine oxygen. An early transition state with preferential attack of the nucleophilic enol ether at the *si* face of the formyl group (corresponding to the front face in **1**) is predicted, in agreement with the experimental findings.[4] Figure 1 also includes a stereopair representation of **1**[5] which provides a clear picture of the three-

Figure 1



dimensional arrangement. Kiyooka *et al.*[4a] have proposed a transition state which is the same as **1** with respect to the Lewis acid moiety, but which differs with regard to the absence of a formyl C–H--O hydrogen bond and the rotational orientation of the complexed aldehyde about the B–O bond (arbitrarily assumed by them).[6]

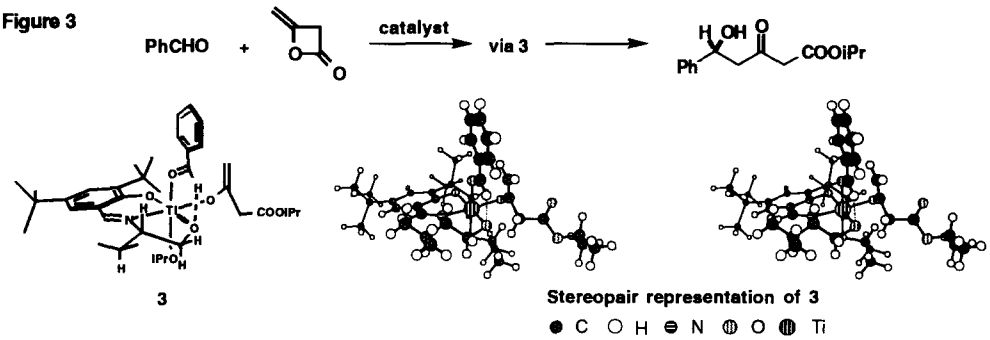
Seebach, Narasaka and coworkers have pioneered the use of titanium alkoxide catalysts containing a chiral tartrate-derived tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) bidentate ligand as a promoter of reactions of aldehydes with diethylzinc[7] and trimethylsilyl cyanide.[8] The reaction with diethylzinc is depicted in Figure 2. The partial transition-state assembly shown in the stereopair representation **2** possesses the following features: (1) the pentacoordinate Ti has trigonal bipyramidal geometry with the TADDOL ligand bound to basal positions, both to minimize angle strain and to allow access to the Lewis acidic Ti by the aldehyde; (2) coordination of the aldehyde to Ti occurs through one of the two symmetry equivalent apical bonds (apical binding of the aldehyde is favored because it is preferred for the least basic ligand[9] and because it allows formyl C–H--O hydrogen bonding); (3) the orientation of the complexed aldehyde is fixed by a stereoelectronically favorable formyl C–H--O hydrogen bond and avoidance of steric repulsion with the axial phenyl group; (4) attack on the formyl group by the nucleophile EtZnX occurs at the more open *si* face of the formyl carbon, leading to the observed predominant product shown in Figure 2. The hydrocyanation of the benzaldehyde is also proposed to proceed via **2** with attack of cyanide ion on the *si* face of the formyl carbon, again in accord with experiment.[7,8] These models for the TADDOL-catalyzed ethylation and hydrocyanation of aldehydes are consistent with the less specific scheme proposed by Seebach and coworkers,[7] which does not contain the key formyl C–H--O hydrogen bond but which assumes a similar orientation of the complexed aldehyde. It should be pointed out that in the event that the



aldehyde were coordinated to Ti in a basal position (unlikely because it is the most electronegative ligand[9]) the formyl C–H--O hydrogen bond would not be possible and little or no enantioselectivity would result.

Oguni and coworkers have introduced a chiral reagent which is derived from the reaction of titanium tetraisopropoxide with the Schiff base of 3,5-di-*t*-butyl-salicylaldehyde and (*S*)-valinol for the catalyzed reaction of aldehydes with diketene (aldol)[10] or trimethylsilyl cyanide.[11] The aldol reaction is illustrated in Figure 3; the same absolute stereochemical course is favored for the hydrocyanation reaction, i.e. *si* face attack on the coordinated aldehyde. The mechanistic basis for enantioselectivity in these cases has been unclear. Our analysis of the Oguni enantioselective diketene aldol reaction of aldehydes has led unequivocally to the favored partial transition-state assembly which is shown in **3**. In this structure there is octahedral hexacoordination to titanium with the three donor groups of the Oguni ligand in plane with the metal and with the five-membered chelate ring puckered to allow an equatorial[12] isopropyl group. Axial coordination of the aldehyde so as to allow the best formyl C–H--O hydrogen bond occurs at the top face of Ti in Figure 3 (hydrogen bond to the axial lone pair on O). The enolate ligand is coordinated *cis* to the aldehyde to allow carbonyl addition via a six-membered chair transition state; the remaining isopropoxy ligand is *trans* to the coordinated aldehyde. In the model shown in Figure 3 attack by the enolate occurs at the *si* face of the aldehyde as required to produce the (*S*) aldol enantiomer, as observed.[10] Switching the aldehyde and enolate ligands of **3** does not allow good formyl C–H--O hydrogen bonding because each of the two lone pairs on the valinol oxygen of the tridentate chiral ligand is poorly positioned to interact with the formyl hydrogen.

Figure 3



Hydrocyanation of aldehydes using the (*S*)-Oguni catalyst, which also occurs by attack at the *si* face of the coordinated aldehyde, can be explained by a transition-state structure similar to **3** but with isopropoxy replacing the enolate ligand. Rearward (*si* face) attack by CN^- then occurs on the rigidly held formyl group to give the observed (*R*) cyanohydrin derivative.[11]

Kagan and coworkers have reported a Lewis acid system derived from (*S*)-1,1-diphenyl-1,2-dihydroxypropane and $EtAlCl_2$ (1 : 1) which catalyzes the Diels-Alder reaction of 2-methylacrolein and 1,3-cyclopentadiene to form the (2*R*)-adduct (exo formyl diastereomer) as shown in Figure 4.[13] A linear relationship was demonstrated for ln R_e vs 1/T where R_e is the ratio of enantiomeric products (*R*/*S*) and T is the Kelvin temperature, and values were obtained for $\Delta\Delta G^{\ddagger}$ (-0.74 kcal mole^{-1}), $\Delta\Delta H^{\ddagger}$ (-2.46 kcal mole^{-1}) and $-T\Delta\Delta S^{\ddagger}$ (+1.73 kcal mole^{-1}). The enthalpic barrier is lower for formation of the predominating enantiomer, but this is partly counterbalanced entropically due to the more ordered transition state for the major pathway. The most likely structure for the effective catalyst is the dioxaaluminolidine shown in Figure 4. Steric repulsion between the adjacent phenyl and methyl substituents fixes the conformation of the five-membered dioxaaluminolidine ring and thus orients one of the four oxygen lone pairs suitably for hydrogen bonding. This complex also minimizes steric repulsion between the aldehyde and the phenyl or methyl substituent and allows for a favorable π,π-attractive interaction between the positive formyl carbon and the neighboring phenyl group (spacing ca. 3Å). The *s-trans* arrangement of the complexed dienophile can be expected to lead to a lower energy transition state than the *s-cis* form, because in the former there will be less repulsion between the α-methyl substituent of the dienophile and the phenyl of the catalyst in the transition state.[14] As shown in **4**, the α-methyl group remains clear of the neighboring phenyl group as Cα goes from sp^2 to sp^3 hybridization (this is especially obvious in the 3-D stereopair diagram). Diene addition to the *si* face of **4** produces the observed[13] predominating enantiomer (2*R*), as shown. The high degree of organization in the transition state corresponding to **4** is consistent with the observed greater loss of entropy for the pathway leading to the major enantiomer.[13]

A highly enantioselective Diels-Alder reaction using a catalyst derived from diethylaluminum chloride and

Figure 4

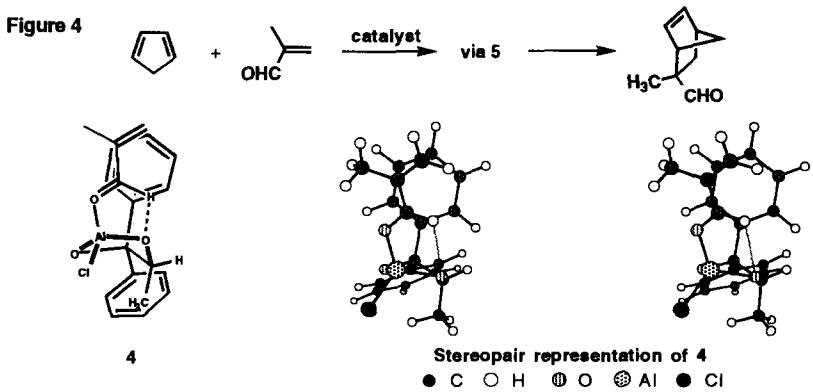
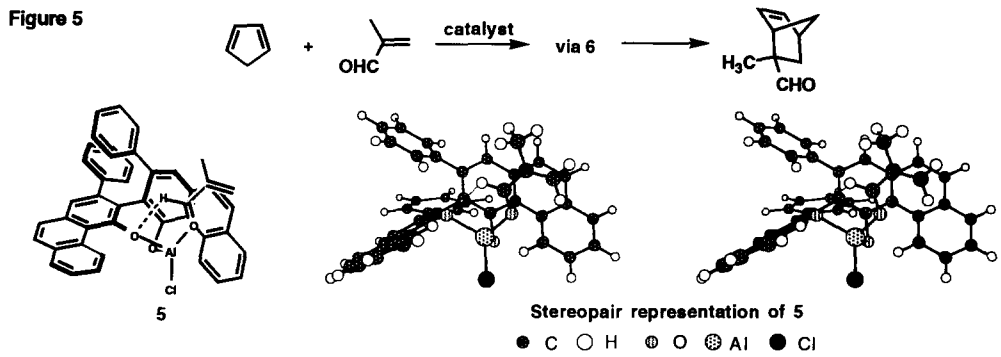


Figure 5



a substituted 2,2'-bi-1-phenanthrol has been described by Wulff *et al.* (see Figure 5).[15] No transition-state structure was proposed, and indeed it is difficult to understand the absolute stereochemical course of this reaction without the organizing influence of a formyl C–H--O hydrogen bond. A favorable hydrogen bond is only possible in the arrangement depicted in **5**. The addition of cyclopentadiene to the accessible *si* (front) face of the coordinated *s-cis* 2-methylacrolein leads to the correct (2*R*) configuration of the observed major enantiomer.[15] In this case the α-methyl substituent of the dienophile is clear of the neighboring π-aromatic group in the *s-cis* but not in the *s-trans* rotamer,[14] leading to faster reaction via the *s-cis* form.

The understanding of the catalytic enantioselective reactions which are shown in Figures 1-5 would be very difficult without some restriction of rotation of the bond between the catalytic Lewis acidic metal and the carbonyl group of the aldehyde. The formyl C–H--O hydrogen bond restricts that rotation and provides the organization which leads in each of the examples discussed herein to the correct absolute configuration of the major reaction product. We believe that the occurrence of formyl C–H--O hydrogen bonding in the transition states of enantioselective reactions of aldehydes with chiral Lewis acid catalysts provides a unique and simple explanation of a large body of important synthetic chemistry and a useful guide for catalyst design.[16]

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5. Stereopair diagrams **1-6** were generated with CSC Chem3D Plus™ (standard bond distances and angles).
6. An analysis similar to that summarized in Figure 1 can be used to explain the results of Masamune *et al.* for enantioselective aldol reactions of related oxazaborolidine catalysts. See (a) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365. (b) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Letters* **1992**, *33*, 1729.
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