Pergamon

Tetrahedron Letters, Vol. 38, No. 10, pp. 1699-1702, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00193-7

The Formyl C–H--O Hydrogen Bond As a Key to Transition-State Organization in Enantioselective Allylation, Aldol and Diels-Alder Reactions Catalyzed by Chiral Lewis Acids.

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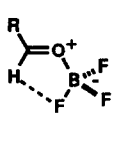
***Summary**: The occurrence of formyl C–H--O hydrogen bonding in enantioselective allylation, aldol and Diels-Alder reactions of aldehydes with chiral Lewis acid catalysts is a key to the understanding of absolute stereochemistry.* © 1997 Elsevier Science Ltd. All rights reserved.

Two recent publications have provided (1) experimental X-ray crystallographic evidence for a new kind of hydrogen bond in complexes of Lewis acids with the formyl group and (2) a discussion of the role of such an interaction in determining transition-state geometry in chiral Lewis acid-catalyzed reactions of aldehydes.[1,2] Formyl hydrogen bonds, exemplified generally by structures **1** and **2**, provide a simple explanation of enantioselectivity for a variety of highly enantioselective Diels-Alder reactions involving different catalytic systems. For instance, the highly enantioselective Diels-Alder reactions of 1,3-dienes with 2-bromoacrolein which are controlled by an oxazaborolidine catalyst derived from *N*-tosyltryptophan[3] can be explained in terms of the transition-state assembly shown in **3**, which contains a key hydrogen bond between formyl and oxygen.[2] Although the formyl proton of an uncomplexed substrate normally lacks the electrophilicity (acidity) required for hydrogen bonding to oxygen, coordination to a Lewis acid, such as in **3**, greatly enhances the positive charge at the formyl hydrogen while increasing the nucleophilicity of the oxazaborolidine oxygen. Thus, the hydrogen bond shown in **3** is logical from a chemical point of view as well as in terms of the precedent from X-ray crystallographic studies.[1] The formyl hydrogen bond in **3** is one of several structural elements contributing to a highly enantioselective (>200 : 1) reaction.[3]

This paper describes the application of the formyl hydrogen bond as an organizing stereochemical element to the understanding of a number of catalytic enantioselective aldol, carbonyl allylation and Diels-Alder reactions which have recently been developed and for which there has been no clear mechanistic rationale.

The *N*-tosyltryptophan-derived oxazaborolidine structure which appears in assembly **3** can also function very effectively to direct catalytic Mukaiyama aldol reactions.[4] These carbonyl additions take place enantioselectively to the *re* face of the formyl group,[4] as expected from the formyl hydrogen bonded structure **4**. Selective aldehyde coordination at the top face of the oxazaborolidine ring in **4** is a consequence of steric screening of one face (bottom) by the *N*-tosyl substituent and neighboring π-rich indole attraction to the complexed aldehyde (formyl carbon and indole N are located favorably for an attractive π,π-interaction).



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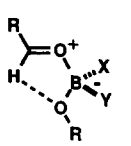

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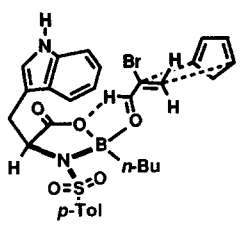

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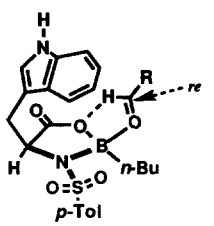

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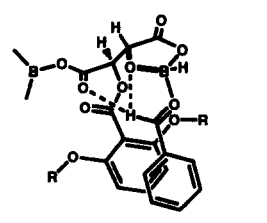
It was also pointed out in a previous paper[2] that the absolute stereochemical course of the Diels-Alder reactions of α,β-enals (e.g. 2-methylacrolein) and 1,3-dienes which are catalyzed by H. Yamamoto's chiral acyloxyborane (CAB) catalyst[5] could be explained readily by formyl hydrogen bonding to *two* oxygens of the chiral ligand. The same favored mode of binding of the (*R*,*R*)-tartrate-derived CAB catalyst with benzaldehyde as ligand is shown in **5**. The combination of the double (bifurcated) hydrogen bond and the interaction of the bound aldehyde with the neighboring substituted aromatic ring defines a unique structure which involves strong screening of the *si* face of the aldehyde formyl group. On the basis of the preference for structure **5** for the complex, it can be predicted that an enol silyl ether would attack benzaldehyde at the *re* face of the formyl carbon to form the *R*-Mukaiyama aldol product, exactly as is observed experimentally.[5] This simple explanation of the absolute stereochemical course of the CAB-catalyzed Mukaiyama aldol reaction can also be applied to CAB-catalyzed aldehyde allylation.[5d]

Formyl hydrogen bonding also seems to be a significant factor in determining the stereochemical course of reactions of aldehydes which are mediated by chiral complexes of Ti(IV). Keck and coworkers have described allylation[6] and aldol reactions[7] catalyzed by a 2 : 1 complex derived from (*R*)-1,1-binaphthol ((*R*)-BINOL, 2 equiv) and Ti(O*i*-Pr)$_4$. The catalytic species in these reactions is probably the bis-BINOL titanate ester, BINOL$_2$Ti. In the case of catalytic allylation of an aldehyde with allyltri-*n*-butyltin, the latter reagent probably allylates Ti(IV) while the Bu$_3$Sn group attaches to one of the BINOL oxygens and causes dissociation of that oxygen from Ti. Coordination of benzaldehyde to this species with formation of the trigonal bipyramidal, hydrogen bonded structure **6** should be preferred since this arrangement uniquely satisfies three conditions: (1) minimize non-bonded steric repulsion, (2) allow formation of a stereoelectronically and entropically favorable formyl hydrogen bond to one of the oxygens of the bidentate BINOL ligand, and (3) place the allyl group in the basal position and the formyl oxygen in the apical position, ideal for the allylation reaction. Structure **6** leads to the observed absolute configuration of the homoallylic alcohol adduct ((*R*) from (*R*)-BINOL; (*S*) from (*S*)-BINOL).[6] It should be noted that interchanging allyl and benzaldehyde ligands in **6** places the aldehyde in a basal site which does not allow formation of a good formyl hydrogen bond to oxygen.[8]

For the Keck catalytic aldol process using BINOL$_2$Ti, an aldehyde and H$_2$C=C(S-*t*-Bu)OTMS as nucleophile, a structure analogous to **6** with H$_2$C=C(S-*t*-Bu)O replacing allyl leads unambiguously to the observed absolute configuration of the predominant Mukaiyama aldol adduct.[7,9]

A Ti-based system related to that of Keck for the catalytic enantioselective Mukaiyama acetate aldol reaction of aldehydes with H$_2$C=C(OMe)OSiMe$_3$ using a catalyst derived from Ti(O*i*-Pr)$_4$, a Schiff base of 2-amino-2'-hydroxy-1,1'-binaphthyl and 3-bromo-5-*tert*-butylsalicylaldehyde, and 3,5-di-*tert*-butylsalicylic acid has been described by Carreira.[10] The Schiff base probably serves as a tridentate ligand with a coplanar arrangement of the two phenolic oxygens and the imine nitrogen, while the salicylic acid acts as a bidentate ligand which is capable of accepting a trimethylsilyl group at the carboxyl oxygen by reaction with H$_2$C=C(OMe)OSiMe$_3$. The reactive complex in the aldol-forming step is thus likely to have the following ligands coordinated octahedrally to Ti(IV): (1) the tridentate Schiff base, (2) an aryloxy group, (3) the aldehyde, and (4) the enol of methyl acetate. Clearly, the aldehyde and enolate ligands must be *cis* to one another (i.e. not *trans*) in the octahedral arrangement in order to react. Although there are two possible arrangements of the complex which satisfy this condition, only that which is shown in **7** permits formyl C–H--O hydrogen bonding while minimizing steric repulsion involving the bulky 2,4-di-*tert*-butyl-6-trimethylsilyloxycarbonyl-phenoxide ligand. Structure **7** unambiguously leads to the observed enantiomeric aldol product.[10] The use of the formyl C–H--O hydrogen bond concept simplifies the analysis of the absolute stereochemical course of the Carreira aldol[10] and, simultaneously provides a simple explanation of the effectiveness of the *bulky* substituted salicylic acid ligand.

Finally, we present two more examples of catalytic Diels-Alder reactions which are difficult to understand in absolute stereochemical terms without the organizing influence of a formyl C–H--O hydrogen bond. H. Yamamoto has prepared a catalyst (BLA) for enantioselective reactions of α,β-enals from trimethyl borate and (*R*)-3,3'-bis(2-hydroxyphenyl)-2,2'-dihydroxy-1,1'-binaphthyl.[11] Although a possible transition state was



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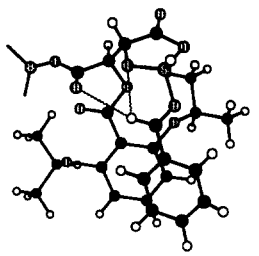

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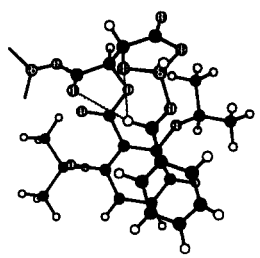

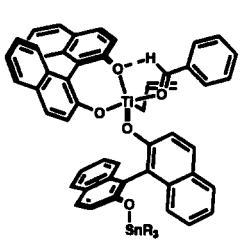

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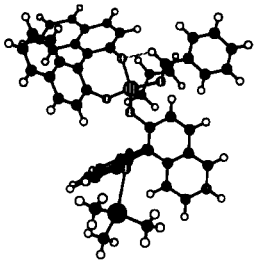

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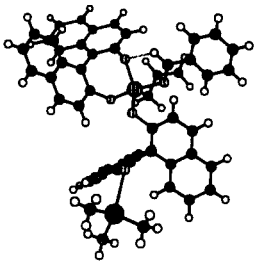

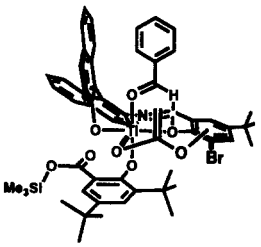

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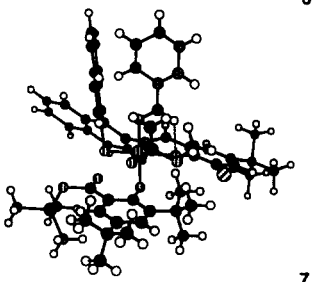

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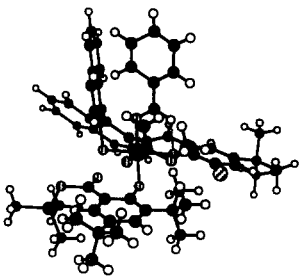

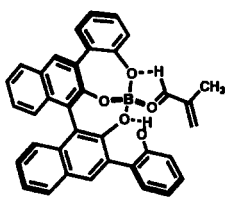

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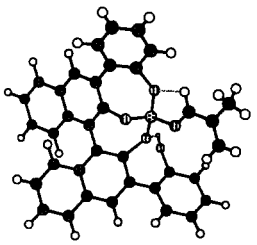

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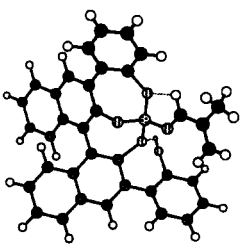

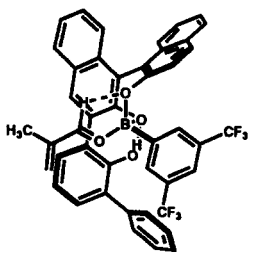

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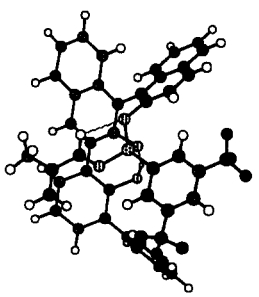

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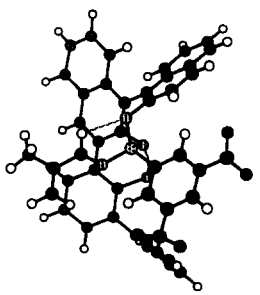

Stereopair representations

proposed for this process which involved *s-trans*-complexed α,β-enal, the corresponding structure with the *s-cis*-complexed α,β-enal seems equally plausible, even though it would lead to the enantiomer of the observed product in each case. Probably for this reason, the *s-cis*-α,β-enal transition state was ignored. If the condition of formyl C–H--O hydrogen bonding is imposed on the Yamamoto BLA system,[11] a unique explanation of the absolute stereochemical result emerges, as shown in **8** for the *R*-catalyst. A favorable hydrogen bond is only possible to the terminal aryloxy oxygen as is shown in **8**. In **8** the α,β-enal is coordinated to boron in the *s-cis* form. Addition of the diene to the unobstructed *si* face of the α,β-enal (i.e. top face as viewed in **8**) then leads to the observed Diels-Alder adduct. This mode of addition minimizes steric repulsion involving the α-substituent of the α,β-enal and the cofacial neighboring π-aromatic ring in the transition state.[2a,2b] This steric compression/transition-state factor clearly favors reaction via the *s-cis*-α,β-enal in this system.

Recently, Yamamoto has described another (*R*)-BINOL-based Diels-Alder system (**9**) which produces adducts of opposite absolute configuration in comparison with (*R*)-BINOL-based **8**.[12] A simple explanation for this difference is provided by the formyl hydrogen bonded transition structure shown in **9**, which contains the *s-cis*-complexed α,β-enal for the reasons described for **8**. Structure **9** is optimal with regard to favorable stereoelectronics for the hydrogen bond and conformation of the coordinated ligand.

The success of the formyl C–H--O hydrogen bond concept in explaining very simply the enantioselective reactions discussed in this and the earlier[2] paper suggests that this approach is of value both in the understanding of known enantioselective reactions and in the design of new ones.[13,14]

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8. Carbonyl allylation from a Ti complex in which both allyl and aldehyde ligands occupy basal sites can be expected to be relatively unfavorable since the 120° angle between apical bonds places the atoms which are required to bond at an improbably large distance (*ca.* 4.5 Å).
9. A product-forming complex analogous to **6** to explains the absolute stereochemical course of catalytic reactions analogous to those of Keck including: (1) Tagliavini aldehyde allylation with BINOL–Zr(O*i*-Pr)$_4$; Bedeschi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron Letters* **1995**, *36*, 7897. (2) Aldehyde allylation with BINOL–TiF_4–CH_3CN according to Gauthier, D. R., Jr.; Carreira, E. M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2363. (3) Mikami aldehyde aldol with BINOL–$TiCl_4$; Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077 (Cl replaces monodentate aryloxy).
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14. We are grateful to the N.S.F. for Graduate Fellowships to D.B.-S. and T.W.L. and a research grant.

(*Received in USA* 11 *December* 1996; *revised* 22 *January* 1997; *accepted* 23 *January* 1997)