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The formyl C–H···O hydrogen bond as a critical factor in enantioselective Lewis-acid catalyzed reactions of aldehydes

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X-Ray crystallographic studies have provided experimental evidence for the existence of intramolecular formyl C–H hydrogen bonds to oxygen or fluorine ligands in complexes of aldehydes and boron Lewis acids. This type of hydrogen bond can be regarded as 'induced' or 'cooperative' in the sense that its strength can be expected to increase as the bonding between the formyl oxygen and the Lewis acid becomes stronger. Coplanarity of the formyl group and the metal–X subunit to which it is bound in a five-membered ring effectively restricts rotation about the donor–acceptor bond between the formyl oxygen and the metal center of the Lewis acid, thus creating an additional organizing element in these complexes. This organizing element provides a simple and logical basis for understanding the mechanistic basis for enantioselectivity in many reactions of achiral aldehydes which are catalyzed by chiral Lewis acids. These reactions include aldol, allylation and ene addition to the formyl C=O group and Diels–Alder reactions of α,β-unsaturated aldehydes with 1,3-dienes. The idea of the induced formyl C–H hydrogen bond can serve as a guide in the design of new enantioselective catalysts as well as a mechanistic principle for understanding preferred transition state assemblies.

Introduction

One important aspect of research on enantioselective catalysis is the study of the detailed mechanistic basis of enantioselectivity in terms of transition-state structure. A clear understanding of the origin of enantioselection 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.

Recent X-ray crystallographic studies[1] have provided evidence for a new kind of hydrogen bond in complexes of Lewis acids with the formyl group, exemplified generally by structures **1** and **2** (Fig. 1). The X-ray crystal structures of boron trifluoride

Fig. 1 Examples of formyl C–H···F and C–H···O hydrogen bonds.

complexes with benzaldehyde, methacrolein, 2,3-methylenedioxybenzaldehyde and dimethylformamide (DMF) show a preference for conformer **1** in which the formyl group and one of the B–F bonds are coplanar (eclipsed).[1] The H···F distances of 2.35–2.36 Å in these complexes are within the sum of the van der Waals radii of 2.67 Å (H = 1.20 Å and F = 1.47 Å).[2] Formyl C–H···O hydrogen bonding is indicated by the X-ray structures of [catecholborane·$(DMF)_2$]$^+Br^-$ (**3**) and [2-(*N*,*N*-dimethylamino)phenoxyboron·$(DMF)_2$]$^+I^-$ (**4**) (Fig. 2); the H···O distances of 2.41–2.59 Å in these complexes are well below the sum of the van der Waals radii of 2.72 Å (H = 1.20 Å and O = 1.52 Å).

Although the formyl proton of an uncomplexed substrate normally lacks the electrophilicity (*i.e.* acidity or positive charge) required for hydrogen bonding, coordination to a Lewis acid greatly enhances the positive charge at the formyl hydrogen while increasing the electron density at the oxygen or fluorine atoms attached to boron. Thus, the observed formyl hydrogen bonds shown in **1** and **2** (Fig. 1) are logical from an electronic structural point of view and in agreement with molecular orbital calculations.[3] There may also be a contribution from an anomeric effect in which electrons from the non-complexed lone pair on aldehyde oxygen delocalize into the σ* orbital of the eclipsed B–F or B–O bond (n → σ*). The authors of one study[3a] attributed a value of 6 kJ mol^{-1} to the anomeric effect and 9 kJ mol^{-1} to the formyl hydrogen bond.[4]

A recent publication[5] from this laboratory has provided the first discussion of the role of formyl hydrogen bonding in determining transition-state geometry in chiral Lewis acid-catalyzed reactions of aldehydes.[6] For instance, the highly enantioselective Diels–Alder reactions of 1,3-dienes with 2-bromoacrolein under the control of two very effective boron catalysts[7,8] can be explained in terms of the transition-state assembly shown in **5** or **6**, which contains a key formyl hydrogen bond as an organizing factor (Fig. 3). The *N*-

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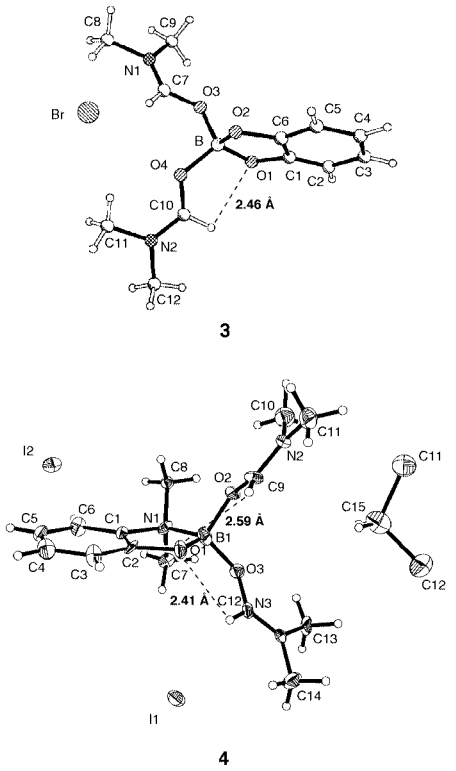


Fig. 2 X-Ray structures of [catecholborane·$(DMF)_2$]$^+Br^-$ (**3**) and [2-(*N*,*N*-dimethylamino)phenoxyboron·$(DMF)_2$]$^+I^-$ (**4**) showing formyl C–H···O hydrogen bonds.

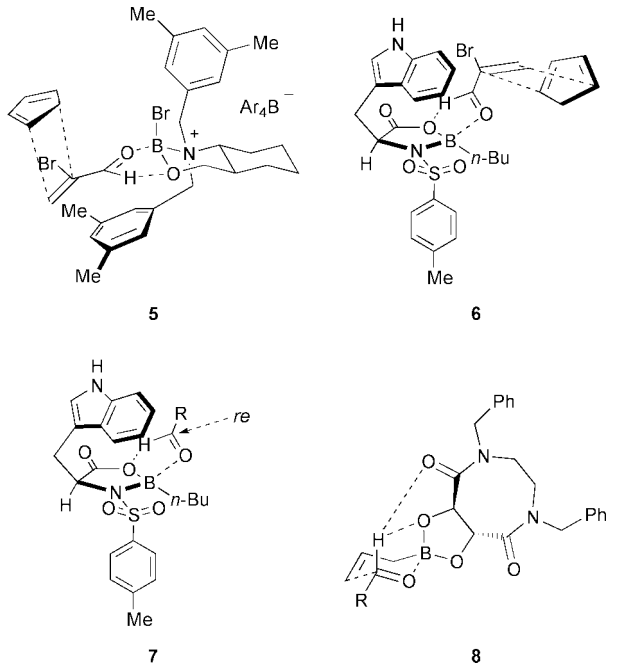


Fig. 3 Formyl hydrogen bond as an organizing element in enantioselective reactions.

tosyltryptophan-derived oxazaborolidine structure which appears in assembly **6** can also function very effectively to direct catalytic Mukaiyama aldol reactions.[9] The *re* face selectivity of these carbonyl additions can be predicted using the same line of analysis (see **7**). In addition, the Roush enantioselective allylboration of aldehydes,[10] a stoichiometric reaction for which there was no satisfactory explanation previously, can be understood in terms of a preference for the doubly hydrogen bonded structure **8**. It should be noted that the formyl hydrogen bond is only one of several structural elements contributing to the high enantioselectivities observed in these reactions.[7–10]

Pathways for enantioselective reactions of aldehydes involving formyl C–H···O hydrogen bonding

This section describes the application of the formyl hydrogen bond as an organizing stereochemical element to the understanding of a number of catalytic reactions involving aldehydes and chiral Lewis acids (*e.g.* Diels–Alder, aldol, ene reaction, hydrocyanation, allylation and alkylation) which have recently been developed and for which there has been no clear mechanistic rationale.

It has been pointed out[5] that the absolute stereochemical course of aldol reactions which are promoted by Yamamoto's chiral acyloxyborane (CAB) catalyst can be explained readily by formyl hydrogen bonding to *two* oxygens of the chiral ligand. The favored mode of binding of the (*R*,*R*)-tartrate-derived CAB catalyst with benzaldehyde as ligand is shown in **9** of Fig. 4.[11] The combination of the double (bifurcated) hydrogen bond and the π-attractive interaction of the bound formyl group 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 a preference for this structure for the complex, it is expected that an enol silyl ether would attack benzaldehyde at the *re* face of the formyl carbon to form the (*R*)-Mukaiyama aldol product, as has been observed experimentally.[12] This simple explanation of the absolute stereochemical course of the CAB-catalyzed Mukaiyama aldol reaction can also be applied to CAB-catalyzed allylations of aldehydes[12d,e] and Diels–Alder reactions of α,β-enals.[13]

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[14] and aldol[15] reactions catalyzed by a 2 : 1 complex derived from (*R*)-1,1′-bi-2-naphthol ((*R*)-BINOL) and Ti(O*i*-Pr)$_4$. The catalytic species in these reactions is probably the bis-BINOL titanate ester, $BINOL_2Ti$. In the case of catalytic allylation of an aldehyde with allyltri-*n*-butyltin, the latter reagent probably allylates Ti(IV) while the Bu_3Sn 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 **10** (Fig. 4) 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 **10** leads to the observed absolute configuration of the homoallylic alcohol adduct ((*R*) from (*R*)-BINOL; (*S*) from (*S*)-BINOL).[14] It should be noted that interchanging allyl and benzaldehyde ligands in **10** places the aldehyde in a basal site which does not allow formation of a good formyl hydrogen bond to oxygen.[16]

For the Keck catalytic aldol process using $BINOL_2Ti$, an aldehyde and $H_2C{=}C(St\text{-}Bu)OSiMe_3$ as nucleophile, a structure analogous to **10** with $H_2C{=}C(St\text{-}Bu)O$ replacing allyl leads unambiguously to the observed absolute configuration of the predominant Mukaiyama aldol adduct.[15,17]

A Ti-based system related to that of Keck for the catalytic enantioselective Mukaiyama acetate aldol reaction of aldehydes with $H_2C{=}C(OMe)OSiMe_3$ 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.[18] The Schiff base probably serves as a tridentate ligand with a coplanar arrangement of the two phenolic oxygens and the imine nitrogen, while

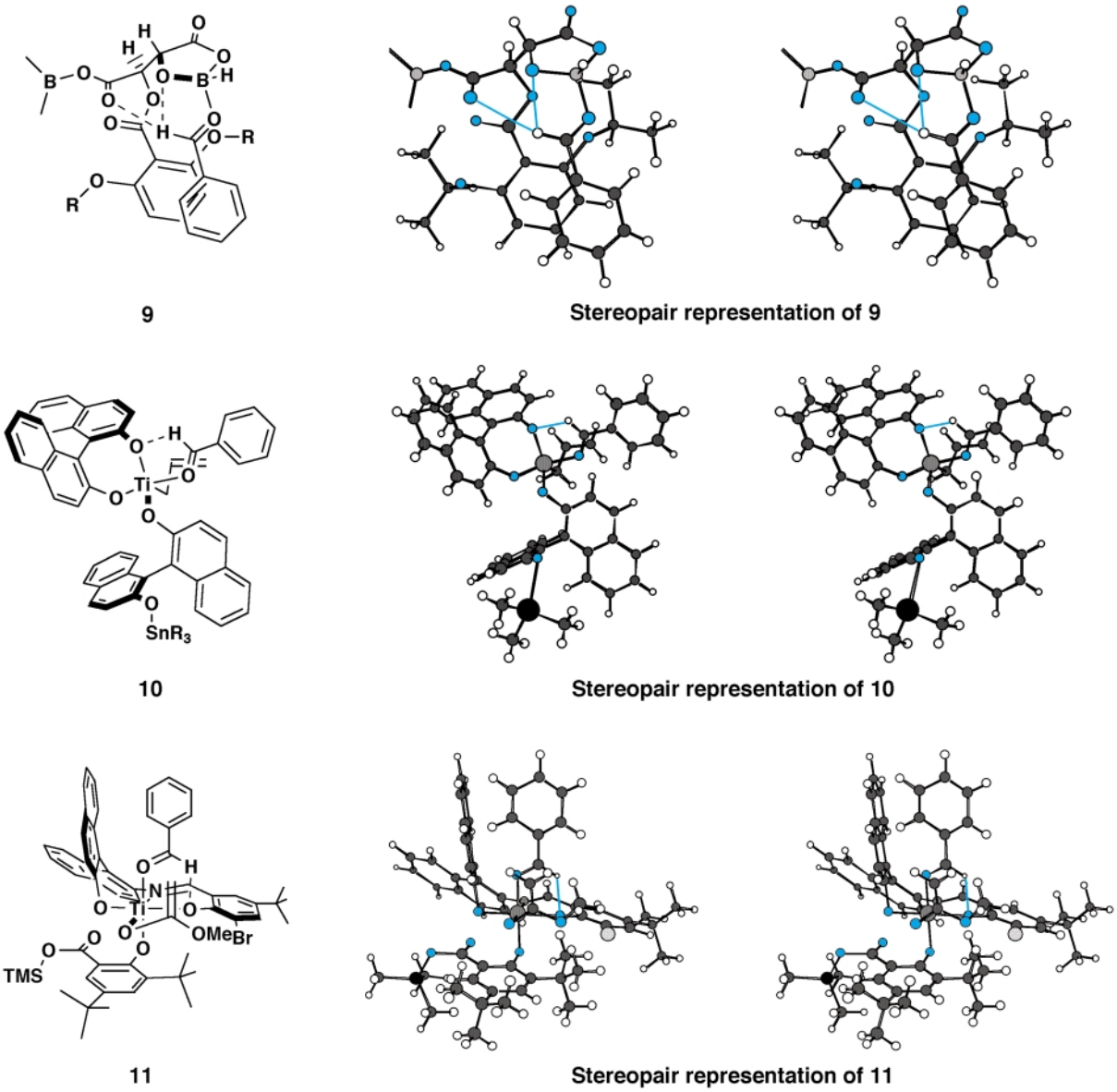


Fig. 4 Transition-state structures of Yamamoto's CAB aldol (**9**), Keck allylation (**10**) and Carreira aldol reaction (**11**). (Blue circles represent oxygen atoms and blue lines represent hydrogen bonds).

the salicylic acid acts as a bidentate ligand which is capable of accepting a trimethylsilyl group at the carboxy oxygen by reaction with $H_2C{=}C(OMe)OSiMe_3$. 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 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 **11** (Fig. 4) permits formyl C–H···O hydrogen bonding while minimizing steric repulsion involving the bulky 2,4-di-*tert*-butyl-6-trimethylsilyloxycarbonylphenoxide ligand. Structure **11** unambiguously leads to the observed enantiomeric aldol product.[18] The use of the formyl C–H···O hydrogen bond concept simplifies the analysis of the absolute stereochemical course of the Carreira aldol and, simultaneously provides a simple explanation of the effectiveness of the *bulky* substituted salicylic acid ligand.

Yamamoto has prepared a catalyst (Brønsted acid-assisted chiral Lewis acid, BLA) for enantioselective reactions of α,β-enals from trimethyl borate and (*R*)-3,3′-bis(2-hydroxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl.[19] Although a possible transition state was 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, a unique explanation of the absolute stereochemical result emerges, as shown in **12** (Fig. 5) for the (*R*)-catalyst. A favorable hydrogen bond is only possible to the terminal aryloxy oxygen as is shown in Fig. 5. In **12** 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 of **12** as viewed) 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. This steric compression factor[8a] in the transition state clearly favors reaction *via* the s-*cis*-α,β-enal in this system.

Recently, Yamamoto has described another (*R*)-BINOL-based BLA Diels–Alder system (**13** in Fig. 5) which produces adducts of opposite absolute configuration in comparison with (*R*)-BINOL-based **12**.[20] A simple explanation for this difference is provided by the formyl hydrogen bonded transition structure shown in **13**, which contains the s-*cis*-complexed α,β-

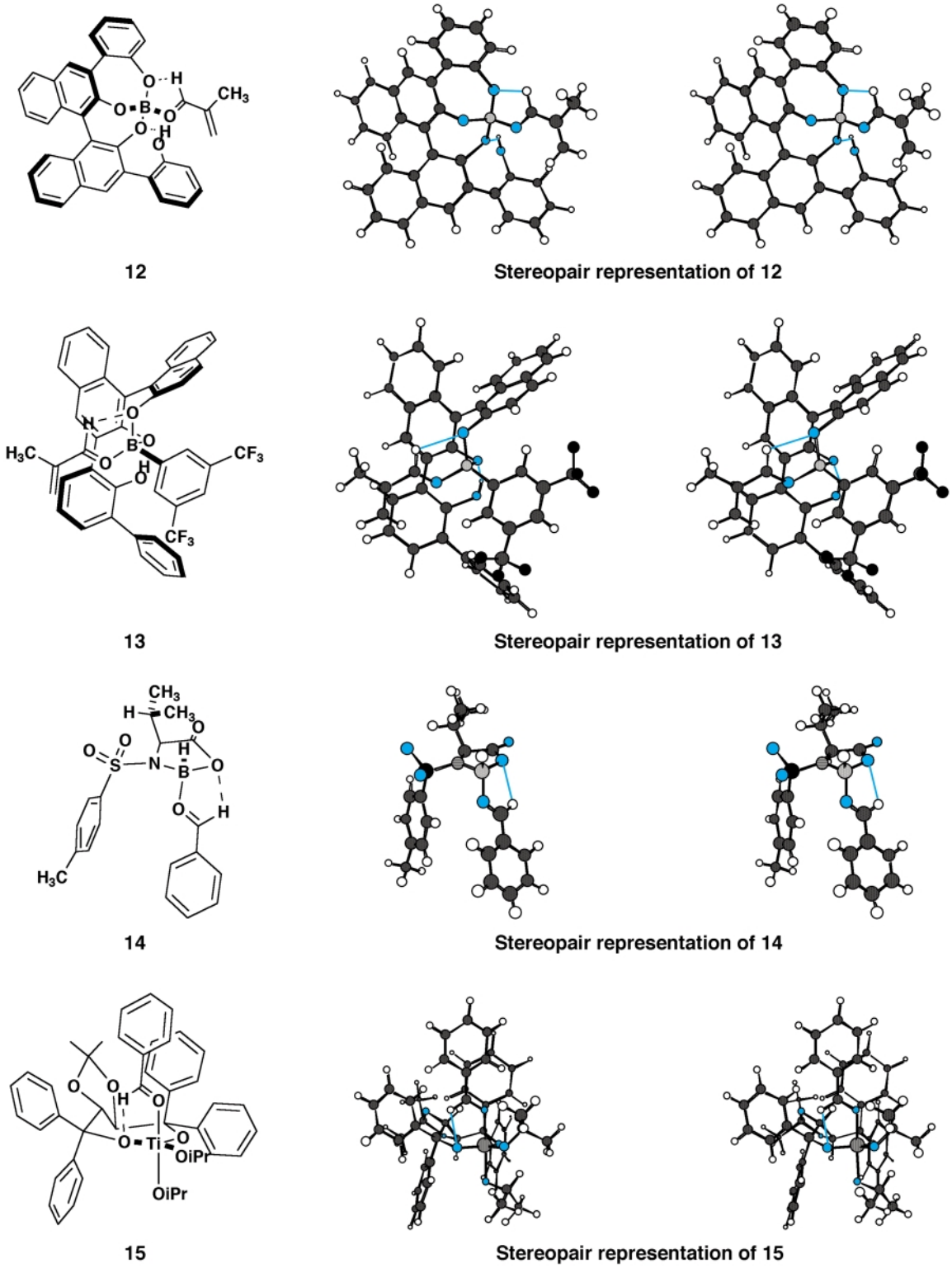


Fig. 5 Favored binding modes of Yamamoto's BLA catalysts (**12** and **13**), Kiyooka's oxazaborolidine catalyst (**14**) and Ti–TADDOL catalyst (**15**) with aldehyde substrates. (Blue circles represent oxygen atoms and blue lines represent hydrogen bonds.)

enal for the reasons described for **12**. Structure **13** is optimal with regard to favorable stereoelectronics for the hydrogen bond and conformation of the coordinated ligand.

Kiyooka and coworkers[21] have studied enantioselective Mukaiyama aldol reactions of aldehydes with various silyl enol ethers using an *N*-arylsulfonylvaline-derived oxazaborolidine catalyst. Structure **14** (Fig. 5) illustrates the proposed transition-state assembly in which the isopropyl and arylsulfonyl appendages are disposed *trans* to one another about the oxazaborolidine ring and in the sterically most stable arrangement. 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. Preferential attack of the nucleophilic enol ether at the *si* face of the formyl group (corresponding to the front face in **14**) is predicted, in agreement with the experimental findings.[21] Kiyooka *et al.*[21a] have proposed a transition state which is the same as **14** 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).[22]

Seebach, Narasaka and coworkers have pioneered the use of titanium alkoxide catalysts containing a chiral tartrate-derived tetraaryl-1,3-dioxolane-4,5-diyldimethanol (TADDOL) bidentate ligand as a promoter of reactions of aldehydes with diethylzinc[23] and trimethylsilyl cyanide.[24] The transition-state assembly shown in **15** 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 the least basic ligand[25] 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. The hydrocyanation of the benzaldehyde could also proceed *via* **15** with attack of cyanide ion on the *si* face of the formyl carbon, again in accord with experiment.[23,24] These models for the TADDOL-catalyzed ethylation and hydrocyanation of aldehydes are consistent with the less specific scheme proposed by Seebach and coworkers,[23] 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 was coordinated to Ti in a basal position (unlikely because it is the most electronegative ligand[25]) 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-*tert*-butylsalicylaldehyde and (*S*)-valinol for the catalyzed reaction of aldehydes with diketene (aldol)[26] or trimethylsilyl cyanide.[27] 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 transition-state assembly **16** which is shown in Fig. 6. In this structure there is octahedral hexacoordination to titanium with the three donor groups of the ligand coplanar with the metal, and the five-membered chelate ring is puckered to allow an equatorial[28] 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 **16** (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 **16** attack by the enolate occurs at the *si* face of the aldehyde to produce the (*S*)-aldol enantiomer, the observed product.[26] Switching the aldehyde and enolate ligands of **16** to the arrangement shown in **17**, 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.

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 **16** except for an 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.[27]

Kagan and coworkers have reported a Diels–Alder catalyst system derived from (*S*)-1,1-diphenyl-1,2-dihydroxypropane and $EtAlCl_2$ (1 : 1).[29] 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 mol^{-1}), $\Delta\Delta H^{\ddagger}$ (−2.46 kcal mol^{-1}) and $-T\Delta\Delta S^{\ddagger}$ (+1.73 kcal mol^{-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 dioxaluminolidine **18** shown in Fig. 7. Steric repulsion between the adjacent phenyl and methyl substituents fixes the conformation of the five-membered dioxaluminolidine 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.* 3.5 Å). 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. As shown in **18**, the α-methyl group remains clear of the neighboring phenyl group as C(α) goes from sp^2 to sp^3 hybridization. Diene addition to the *si* face of **18** leads to the observed[29] predominating enantiomer. The high degree of organization in the transition state corresponding

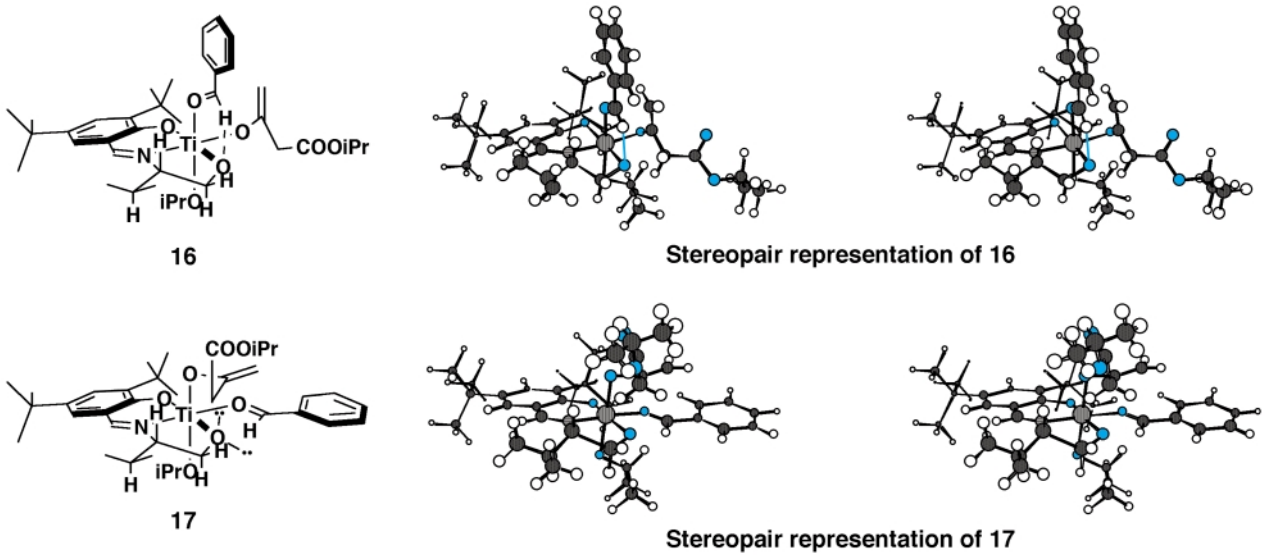


Fig. 6 Favored (**16**) and disfavored (**17**) transition-state assemblies of Oguni diketene aldol reaction. (Blue circles represent oxygen atoms and blue lines represent hydrogen bonds.)

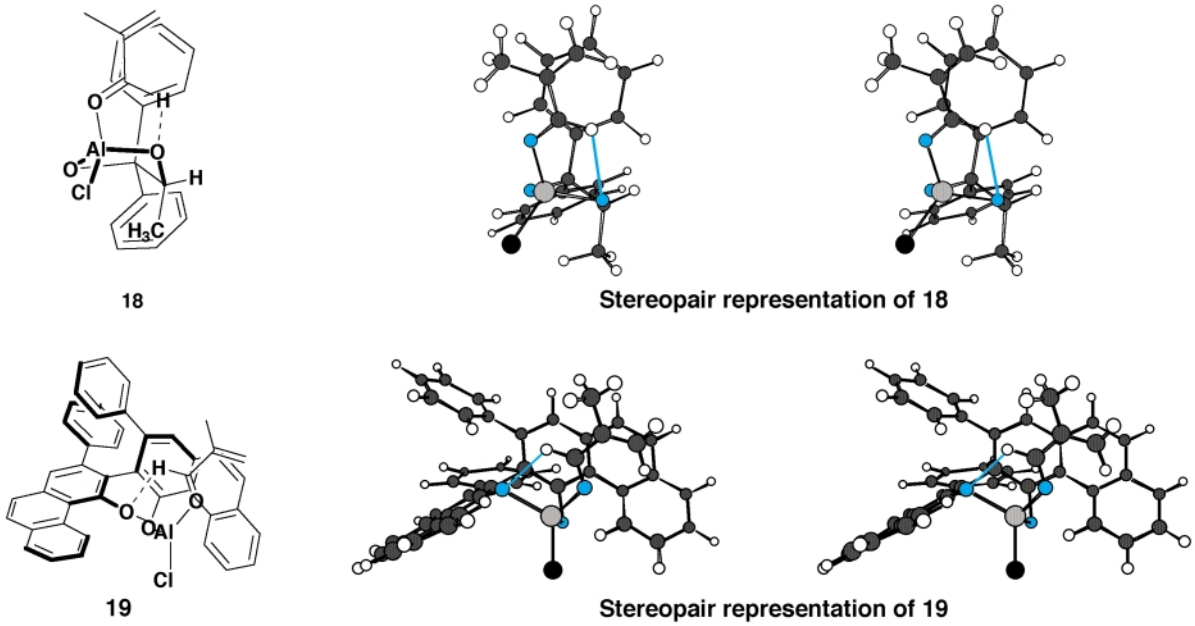
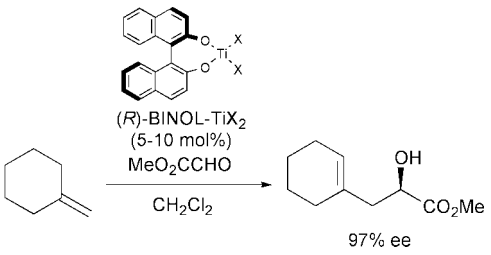


Fig. 7 Favored binding mode of Kagan's dioxaluminolidine catalyst (**18**) and Wulff's Al–VAPOL catalyst (**19**) with α-methacrolein. (Blue circles represent oxygen atoms and blue lines represent hydrogen bonds.)

to **18** is consistent with the observed greater loss of entropy for the pathway leading to the major enantiomer.[29]

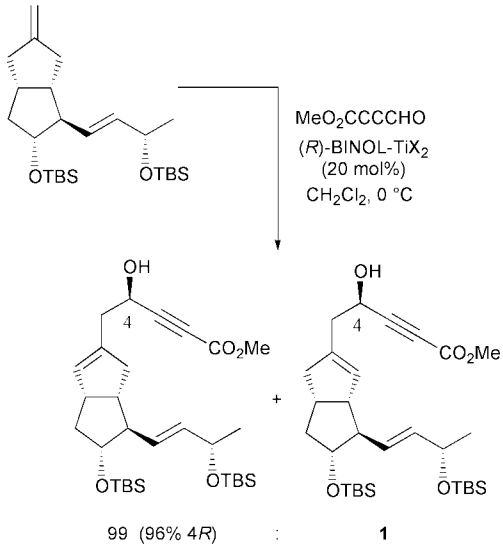
A highly enantioselective Diels–Alder reaction using a catalyst derived from diethylaluminum chloride and a substituted 2,2′-bi-1-phenanthrol (vaulted biphenanthrol, VAPOL) has been described by Wulff.[30] No transition-state structure was proposed, and indeed it is difficult to understand the absolute 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 **19** (Fig. 7). The addition of cyclopentadiene to the accessible *si* (front) face of the coordinated s-*cis*-2-methylacrolein leads to the correct absolute configuration of the observed major enantiomer.[30] 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, leading to faster reaction *via* the s-*cis* form.

One of the most interesting findings in the field of catalytic enantioselective synthesis is the development by the Mikami group of a family of enantioselective ene reactions between unusually electrophilic (*e.g.* glyoxylic) aldehydes and a series of terminal olefins under the influence of chiral Lewis acids, especially BINOL–TiX_2 (derived from 1,1′-bi-2-naphthol and $TiCl_2$(O*i*-Pr)$_2$ and 4 Å molecular sieves).[31,32] Numerous examples of the ene reaction have been described by Mikami which proceed with excellent enantioselectivity, as illustrated by the example shown in eqn. (1).[33]



(1)

In addition to the high facial selectivity of this process with regard to the aldehyde component, remarkable selectivity for the olefinic component with regard to π-facial attack and C–H cleavage has been observed, as shown in eqn. (2).[34] The detailed

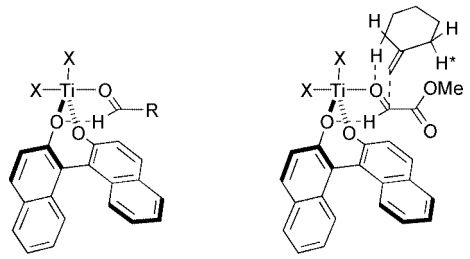


(2)

mechanistic basis for such high stereoselectivity has remained obscure, although a chair-like six-membered pericyclic transition state has been proposed for the $SnCl_4$-catalyzed diastereoselective reaction of glyoxylate esters and olefins, with the glyoxylate substrate chelated to the metal through the 1,2-dicarbonyl subunit.[31e,35]

A transition-state structure has been derived for the Mikami ene reaction by use of the following logical steps. (1) The aldehyde is activated by complexation with the chiral catalyst (*R*)-BINOL–TiX_2 *via* the formyl lone electron pair which is *syn* to the formyl hydrogen to form a pentacoordinate Ti structure. The comparable behavior of glyoxylic esters (eqn. (1)) and 3-methoxycarbonylpropynal (eqn. (2)) in the Mikami ene reaction argues against bidentate coordination of both carbonyl groups of glyoxylic esters since bidentate coordination is clearly not possible with the latter. (2) The resulting complex prefers trigonal bipyramidal geometry with the apical substituents being the coordinated aldehyde and one of the chlorines. This arrangement follows from the preference for the two most electronegative (*i.e.* weakest) ligands to be in the apical

positions for d^0 pentacoordinated structures such as Ti(IV) complexes.[25] (3) Formyl CH···O hydrogen bonding occurs to the stereoelectronically most favorable oxygen lone pair of the BINOL ligand to generate structure **20** (Fig. 8). In this structure,



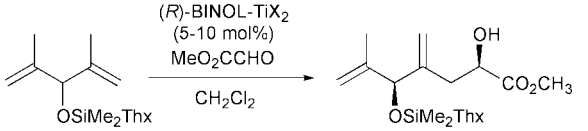
20 **21**

Fig. 8 Mechanistic rationale for the Mikami ene reactions.

the top (*re*) face of the formyl group is much more accessible to a nucleophile than the bottom (*si*) face since the latter is strongly shielded by the nearby naphthol subunit. Formyl C–H···O hydrogen bonding to the other BINOL oxygen is stereoelectronically and sterically disfavored (strong steric repulsion exists between the formyl group and the proximate naphthol ring). (4) The transition-state structure for the ene reaction is likely to involve some degree of proton transfer from the scissile allylic C–H to the formyl oxygen as the new C–C bond is being formed and the olefinic substrate is gaining positive charge β to the scissile C–H. Structure **21** exemplifies that type of transition-state structure for the reaction described in eqn. (1). It also predicts the absolute configuration of the Mikami ene product as shown in eqn. (1) and, as well, preferential cleavage of the allylic C–H shown rather than C–H* of **21**. Cleavage of C–H* is obviously unfavorable because it necessitates strong steric repulsion (clash) between the cyclohexane ring and the nearby basal chlorine ligand.

The favored transition-state structure **22** (Fig. 9) for the ene reaction described in eqn. (2) can be derived in the same way with the additional proviso that the face of the olefinic component which binds to the aldehyde is that on the convex side of the bicyclo[3.3.0]octyl ring pair. Structure **22** predicts the stereochemistry and structure of the product shown in eqn. (2).[36] The corresponding transition-state structure for forming the position isomeric olefin in the Mikami ene reaction is depicted in **23**. It is clearly very unfavorable because of a serious steric clash between the basal chlorine substituent and the proximate five-membered ring.

Mikami and coworkers have also applied the BINOL–$TiCl_2$ catalyzed ene reaction to the desymmetrization of a symmetrical diolefinic substrate as shown in eqn. (3).[37] Outstanding enantio-



(3)

>99% ee, >99% de

and diastereoselectivity were observed (> 99% ee and > 99% de). Our analysis leads to the proposed transition-state structure **24** (Fig. 10) as most favorable. In this structure the approach of the complexed aldehyde to the olefin occurs so as to minimize steric repulsion, with the bulky $SiMe_2Thx$ (Thx = thexyl, 1,1,2-trimethylpropyl) substituent remote and the small H* in proximity to the attacking electrophile, as indicated. An analogous transition state for reaction at the diastereotopic double bond is less stable than **24** for steric reasons. Transition-state structure **24** leads to the overall stereochemistry shown in eqn. (3).

Ene reactions such as those described herein are calculated to be exothermic by *ca.* 20 kcal mol^{-1}.[38] The reaction of the Lewis acid coordinated aldehyde will be much more exothermic—possibly 30 kcal mol^{-1}. Therefore, the transition state for the

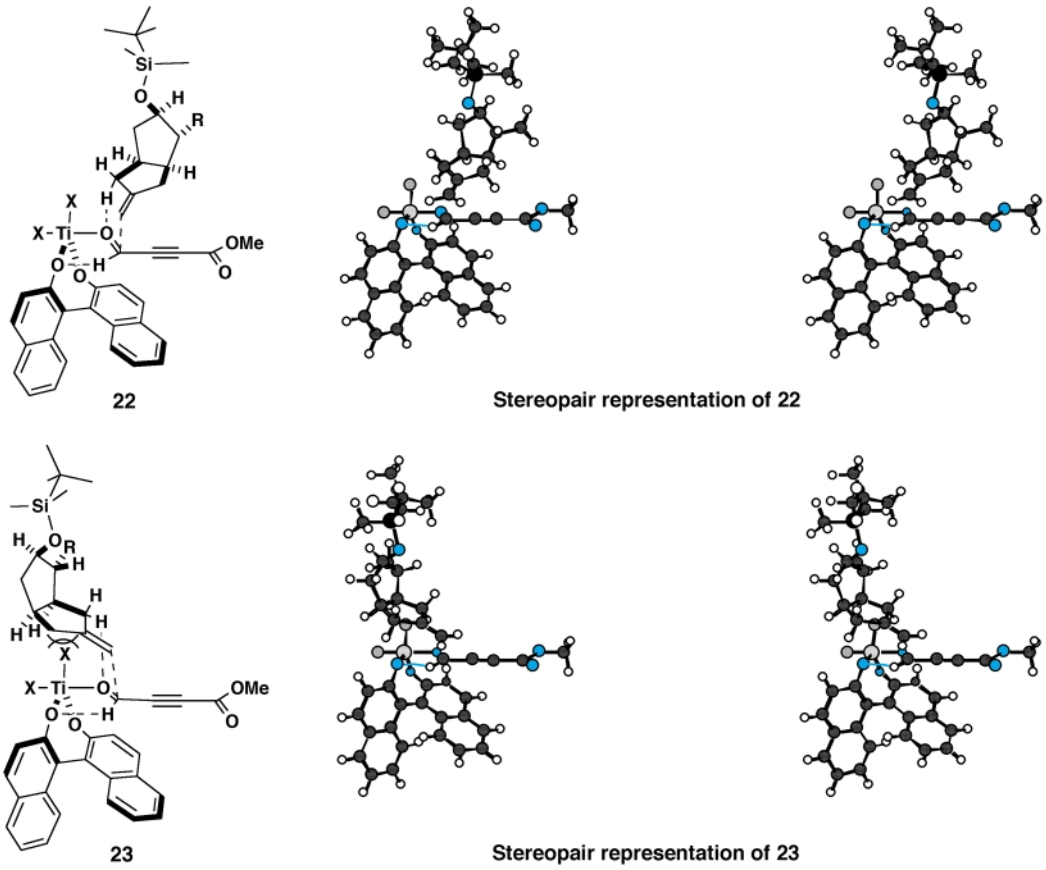


Fig. 9 Mechanistic rationale for the Mikami ene reaction shown in eqn. (2). (Blue circles represent oxygen atoms and blue lines represent hydrogen bonds.)

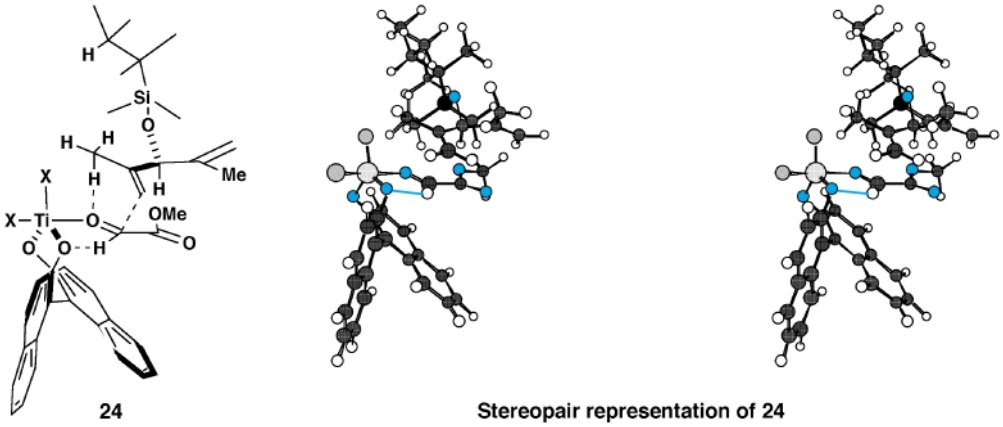


Fig. 10 Mechanistic rationale for the Mikami ene reaction shown in eqn. (3). (Blue circles represent oxygen atoms and blue lines represent hydrogen bonds.)

reaction of an unhindered olefin and a Lewis acid–aldehyde complex should be early, *i.e.* 'starting-material like', and the organizing structural elements in the complex are likely to be preserved in the transition state. Because highly organized, activated and sterically favored reactant complexes can lead to products *via* early transition states, the type of analysis presented herein should be valid since structural factors such as steric repulsions which disfavor alternative complexes also disfavor the corresponding transition states.

(*R*)- and (*S*)-BINOL–TiX_2 catalysts have also been utilized successfully to promote enantioselective Mukaiyama aldol, allylic silane mediated allylation and hetero-Diels–Alder reactions of glyoxylic esters.[39] The absolute stereochemical course of these reactions can be readily explained by the same considerations which are outlined herein for the Mikami ene reaction.

Conclusion

The understanding of the catalytic enantioselective reactions discussed in this appendix 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. In each of approximately thirty known enantioselective reactions of aldehydes under chiral Lewis acid catalysis, the rational use of the formyl C–H···O hydrogen bond and strongly precedented structural principles has led to a transition-state assembly which predicts the observed absolute configuration of the predominating enantiomer. The success of the formyl C–H···O hydrogen bond idea in clarifying and unifying such a large and varied body of reactions, together with supporting evidence from X-ray crystallographic studies of formyl-Lewis acid complexes add credence to its validity. We believe that this formyl C–H···O hydrogen bonding concept will be useful in future catalyst design.

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