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A Transition-State Model for the Mikami Enantioselective Ene Reaction

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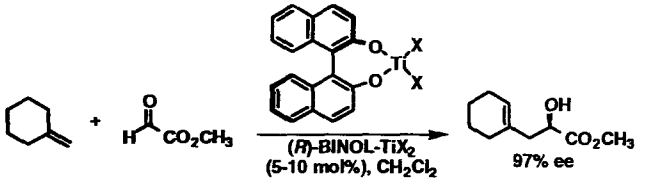
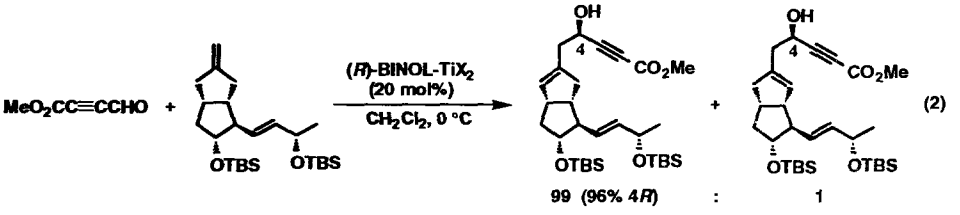
Abstract: A logically derived mechanistic model is presented for the Mikami enantioselective ene reaction which correctly describes the absolute and relative stereochemistry resulting from transition-state structures such as **3** and **5**. © 1997 Elsevier Science Ltd.

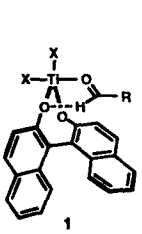
One of the most interesting findings in the field of catalytic enantioselective synthesis is the development by K. Mikami and his group of a family of enantioselective ene reactions between glyoxylic (and related) aldehydes and a series of terminal olefins under the influence of chiral Lewis acids, especially of the type BINOL–TiX_2 (derived from 1,1'-bi-2-naphthol, $TiCl_2(Oi\text{-}Pr)_2$ and 4A molecular sieves).[1] The Mikami ene reaction often proceeds with excellent enantioselectivity as is illustrated by the example shown in equation (1).[2] In addition to the high face 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 equation (2).[3] The detailed 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.[1e,4] In this paper we show that the line of analysis recently applied to explain enantioselectivity in some twenty addition reactions involving aldehydes and chiral Lewis acids (e.g. Diels-Alder, aldol, hydrocyanation, allylation and alkylation) can also provide a simple and clear understanding of the Mikami ene reactions catalyzed by BINOL–TiX_2.[5] The principles and logic of the earlier studies suffice to define a favored and highly organized transition state (i.e. reaction channel) for the enantioselective ene reaction.



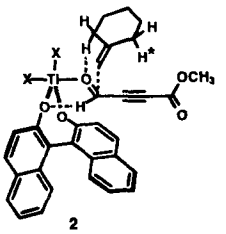
(1)



(2)



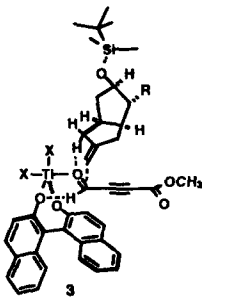
1



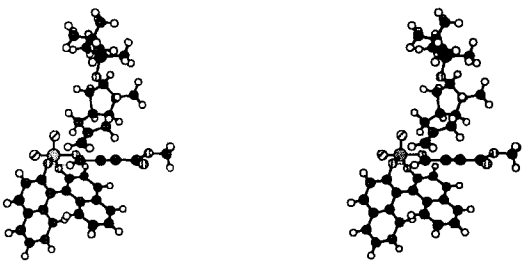
2

The exact structure of the effective Mikami catalyst is unclear. Since the presence of water in the 4A molecular sieves seems to increase catalyst effectiveness (with regard to rate and yield, but not necessarily with regard to enantioselectivity),[6] any of the following species may function as effective (and possibly functionally similar) catalytic species: BINOL–$TiCl_2$ (**A**), BINOL—Ti<(Cl, OH) (**B**), or BINOL—Ti<(O, O)>Ti—BINOL (**C**). In the following discussion catalysts **A**, **B** and **C** are referred to generically as BINOL–TiX_2.

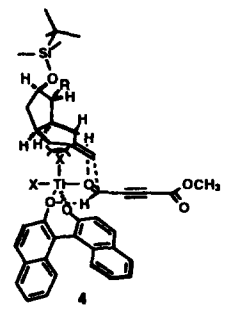
The transition-state geometry which we now propose for the Mikami ene reaction has been derived by the following logical steps. (1) The aldehyde is activated by complexation with the chiral catalyst (*R*)-BINOL–TiX_2 via the formyl lone electron pair which is syn to the formyl hydrogen to form a pentacoordinate Ti structure. The comparable behavior of glyoxylic esters (equation 1) and 3-methoxylcarbonylpropynal (equation 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 the most electronegative of the remaining ligands. This arrangement follows from the preference for the two most electronegative (i.e. weakest) ligands to



3



Stereopair representation of 3



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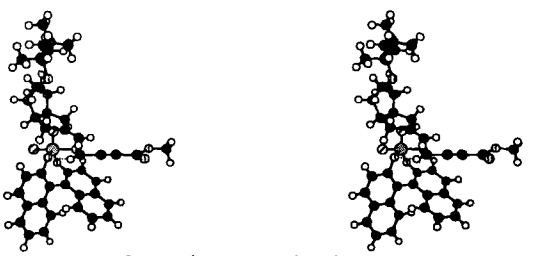
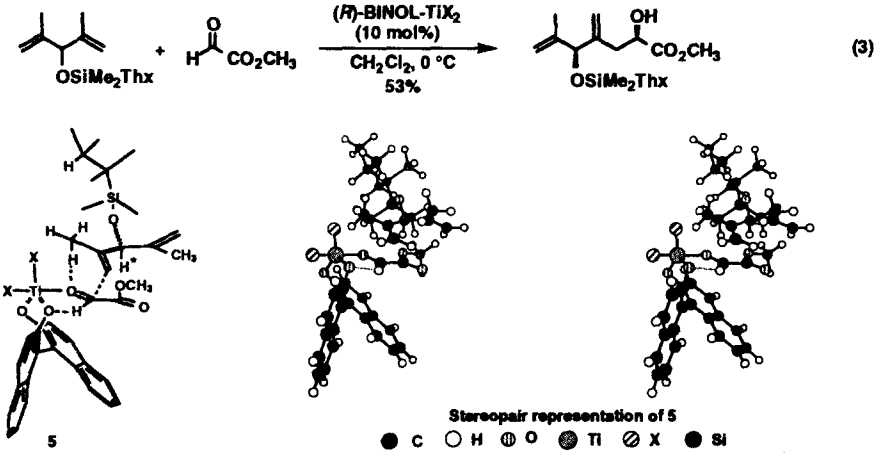


Stereopair representation of 4

● C ○ H ◍ O ◉ Ti ⊘ X ● Si

be in the apical positions for d^0 pentacoordinated structures such as Ti(IV) complexes.[7] Thus, for catalyst **A** or **B**, Cl would preferentially occupy an apical position, whereas in catalyst **C** one μ-oxo group would be apical and one basal (in the case of **C** the two μ-oxo groups clearly will not both be basal because of angle strain as well as because of electronegativity). (3) Formyl CH--O hydrogen bonding occurs to the stereoelectronically most favorable oxygen lone pair of the BINOL ligand to generate structure **1**.[5] In this structure 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 CH--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 **2** exemplifies that type of transition-state structure for the reaction described in equation (1). It also predicts the absolute configuration of the Mikami ene product as shown in equation (1) and, as well, preferential cleavage of the allylic C–H shown rather than C–H* of **2**. Cleavage of C–H* is obviously unfavorable because it necessitates a steric clash between the cyclohexane ring and the nearby basal X ligand.

The favored transition-state structure (**3**) for the ene reaction described in equation (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 **3** predicts the stereochemistry and structure of the product shown in equation (2).[8] The corresponding transition-state structure for forming the position isomeric olefin in the Mikami ene reaction is depicted in **4**. It is clearly very unfavorable because of a serious clash between the basal X substituent and the proximate five-membered ring.



Mikami and coworkers have also applied the BINOL–TiX_2 catalyzed ene reaction to desymmetrization of a symmetrical diolefinic substrate as shown in equation (3).[9] Outstanding enantio- and diastereoselectivity were observed (>99% ee and >99% de). Our analysis leads to the proposed transition-state structure **5** 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 $SiMe_2Thx$ 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 **5** for steric reasons. Transition-state structure **5** predicts the overall stereochemistry shown in equation (3).

Ene reactions such as those described herein are calculated to be exothermic by *ca.* 20 kcal/mol.[10] The reaction of the Lewis-acid coordinated aldehyde will be much more exothermic – possibly 30 kcal/mol. Therefore, the transition state for the 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. When highly organized activated reactant complexes resemble transition states, the type of analysis presented herein should be valid since the structural factors such as steric repulsions which disfavor such complexes also disfavor the corresponding transition states. A corollary of this proposition, which can guide the invention of enantioselective catalysts, is that the *rational design of such catalysts is simplified when the product-determining step from a catalyst-substrate complex is strongly exothermic.*

(*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.[11] The absolute stereochemical course of these reactions can be readily explained by the same considerations which are outlined herein for the Mikami ene reaction.[12]

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10. Standard bond energy calculation: (C–OH = 92) + (O–H = 112) + (C–C = 84) - (RCH=O = 170) - (C–H = 98) = 20 kcal/mol
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