

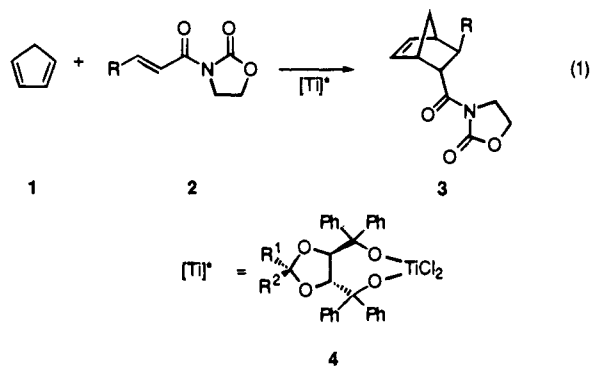
Crystal Structure of a Chiral Titanium–Catalyst–Alkene Complex. The Intermediate in Catalytic Asymmetric Diels–Alder and 1,3-Dipolar Cycloaddition Reactions

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The enantioselective synthesis of organic compounds using chiral transition-metal complexes is currently an important topic in chemistry. One of the fundamental reactions in this field is the catalytic asymmetric Diels–Alder reaction,¹ which in principle allows the formation of four contiguous asymmetric centers. The catalysts for the asymmetric Diels–Alder reaction are mainly based on chiral ligands attached to Lewis acids.^{1,2} Among these catalysts, chiral alkoxytitanium complexes have shown a remarkable diastereo- and enantioselectivity in the Diels–Alder reaction,¹ and one of the most interesting of the various catalytic enantioselective Diels–Alder reactions is probably that reported by Narasaka *et al.* (reaction 1).³



The chiral alkoxytitanium complexes **4** have also been applied as catalysts in other reactions, such as the enantioselective addition of nucleophiles to aldehydes,⁴ and more recently have been shown to catalyze the asymmetric 1,3-dipolar cycloaddition reaction between nitrones and **2**, giving the *exo* diastereomer of the isoxazolidine with a good enantiomeric excess (ee).⁵

In an attempt to elucidate the origin of the high ee observed in reaction 1, Corey *et al.*⁶ have investigated modified titanium

(1) For a recent review about catalytic asymmetric Diels–Alder reactions, see *e.g.*: Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

(2) For other catalytic asymmetric Diels–Alder reactions, see *e.g.*: (a) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. (b) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (c) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (d) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807. (e) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027. (f) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (g) Pikul, S.; Corey, E. J. *Org. Synth.* **1993**, *71*, 30. (h) Corey, E. J.; Roper, T. D.; Ishihara, K.; Sarakinos, G. *Tetrahedron Lett.* **1993**, *34*, 8399. (i) Waldmann, H. *Synthesis* **1994**, 535. (j) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623. (k) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561.

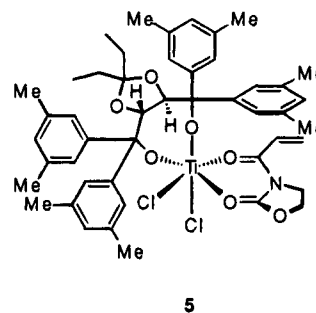
(3) (a) Narasaka, K.; Inoue, M.; Ojada, N. *Chem. Lett.* **1986**, 1109. (b) Narasaka, K.; Inoue, M.; Yamada, T. *Chem. Lett.* **1986**, 1967. (c) Narasaka, K.; Inoue, M.; Yamada, T.; Sigimori, J.; Iwasawa, N. *Chem. Lett.* **1987**, 2409. (d) Narasaka, K.; Inoue, M.; Sugimori, J.; Kawase, Y.; Narasaka, K. *Chem. Lett.* **1989**, 1947. (f) Iwasawa, N.; Hayashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **1989**, 1581. (g) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Narashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340.

(4) (a) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807. (b) Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954.

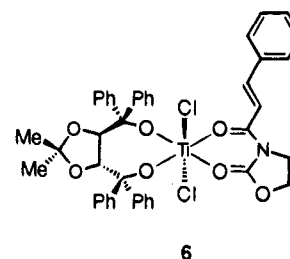
(5) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687.

(6) Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* **1991**, *32*, 6289.

catalysts. They proposed, based on a strong influence of the substituents in the meta position of the aromatic rings, that attractive π – π interactions between a donor aromatic group and the double bond of the dienophile in an *s-trans* geometry and a *cis* orientation of the two chloride ligands at the titanium atom of **5** protect one face and account for the high ee.⁶



A full characterization of the chiral titanium–alkene intermediate will be of considerable value, as it allows one to obtain information about the reaction mechanism in which this type of complexes are involved. This Communication presents the isolation and characterization of the chiral titanium–catalyst–alkene intermediate **6**.



Compound **6** was synthesized by addition of $\text{TiCl}_2(\text{O-}i\text{-Pr})_2$ ^{5,7} (0.2 mmol) in a 2 mL toluene solution to (2*R*,3*R*)-2,3-*O*-(2-propylidene)-1,1,4,4-tetra-phenyl-1,2,3,4-butanediol (93.3 mg, 0.2 mmol) under an N_2 atmosphere and stirred for 0.5 h at room temperature. The solvent was evaporated and the residue dissolved in dry CH_2Cl_2 (1 mL). To this solution was added 3-((*E*)-3-cinnamoyl)-1,3-oxazolidin-2-one (**2a**) (43.4 mg, 0.2 mmol) dissolved in dry CH_2Cl_2 (1 mL). Light petroleum ether (1–2 mL) was added, and the solution was placed in an open 5 mL flask in a desiccator with blue gel. The solvent was allowed to evaporate at room temperature at 1 bar until precipitation began. The flask was then closed, and the precipitation proceeded for 2 days at room temperature. The precipitate was filtered off to give **6** (63 mg, 39%) as small white crystals (mp = 191–195 °C dec).

The structure of **6**, determined by X-ray diffraction,⁸ is depicted in Figure 1. The X-ray structure of **6** consists of the chiral diol and **2a** in the equatorial plane and the two chloride ligands in the axial positions, *trans* to each other. The Ti–

(7) Complex **6** was first observed as a precipitate when 3-((*E*)-3-cinnamoyl)-1,3-oxazolidin-2-one (**2a**) was treated with benzylidene-phenylamine *N*-oxide (**8**) in the presence of **4** ($\text{R}^1 = \text{R}^2 = \text{Me}$) as the catalyst. Compound **2a** did not react with **8**, whereas the 3-crotonoyl- and 3-henenoxyloxazolidinones reacted smoothly when catalyzed by **4**.⁵ In the Diels–Alder reaction, **2a** needs a higher temperature than the other derivatives to react, but the steric cause is the same.^{3b} We therefore assume **6** to be representative of the intermediate in the Diels–Alder reaction, as well as in the 1,3-dipolar cycloaddition reaction.

(8) Compound **6** crystallizes in the orthorhombic system, space group $P2_12_12_1$, with $a = 13.639(8)$ Å, $b = 9.516(5)$ Å, and $c = 32.471(17)$ Å, $V = 4214$ Å³, and $\rho_{\text{calc}} = 1.39$ g cm⁻³ for $Z = 4$. By use of 1738 unique, observed reflections collected at 120 K by diffractometry using Mo $K\alpha$ ($\lambda = 0.71073$ Å) radiation out to $2\theta = 45^\circ$, the structure was solved and refined by constrained least-squares methods to a current value of the discrepancy index $R_1 = 0.074$.

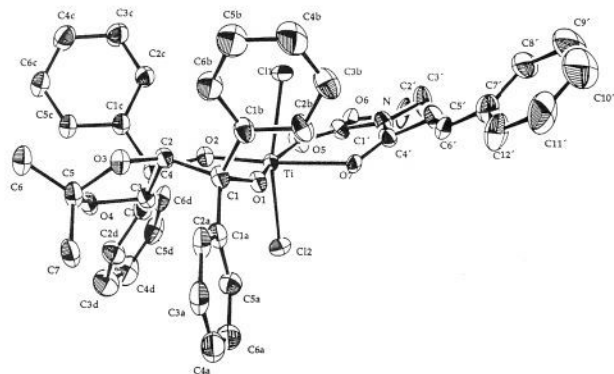


Figure 1. ORTEP drawing of **6**. For clarity, hydrogen atoms are omitted.

O(1) and Ti–O(2) bond lengths are 1.762 and 1.789 Å, respectively, while the Ti–O(5) and Ti–O(7) bond lengths are 2.168 and 2.137 Å, respectively. The Ti–Cl(1) and Ti–Cl(2) bond lengths are 2.356 and 2.355 Å, respectively, and the Cl(1)–Ti–Cl(2) bond angle is 164.3°, with the chloride atoms tilted toward **2a** as the Cl(1)–Ti–O(7) and Cl(2)–Ti–O(7) bond angles are 81.9° and 86.9°, respectively. The alkene plane of the dienophile is tilted 33° out of the plane containing the titanium atom and the four equatorial oxygen atoms.

The X-ray structure of **6** differs in two major ways from the one postulated previously to account for the asymmetric catalytic Diels–Alder reactions:^{1,6} the chloride ligands are located *trans* to each other, and the alkene in the dienophile is in an *s-cis* geometry relative to the carbonyl functionality. Previous X-ray crystallographic investigations of carbonyl compounds coordinated to Lewis acids indicate that a mono coordination leads to an *s-trans* conformation of the α,β -unsaturated carbonyl compound,⁹ whereas bidentate chelation leads to an *s-cis* geometry.¹⁰ Knowing the structure of **6**, a mechanism for the catalytic asymmetric Diels–Alder reaction is tentatively postulated. The suggested approach of cyclopentadiene to the alkene in **6** is outlined in Figure 2.

It appears from the X-ray structure of **6** that one of the phenyl substituents of the chiral ligand seems to block one face of the alkene. Cyclopentadiene approaches the alkene from the less hindered face (Figure 2a), placing the carbonyl functionality *endo* to optimize secondary orbital interactions¹¹ (Figure 2b). Complex **6** is soluble in CH₂Cl₂, and it cannot be excluded that the dissolved complex has another geometry than that in the solid state. However, **6** and similar complexes precipitate in toluene and petroleum ether (1:1), which was the solvent composition used by Narasaka *et al.*,^{3g} and we therefore assume that **6** probably represents the active catalyst in Diels–Alder reactions. The approach outlined in Figure 2 both accounts for the diastereo- and enantioselectivity in the catalytic asymmetric Diels–Alder reactions with **4** as the catalyst and agrees with the experimental results achieved by Narasaka *et al.*^{3g} The diastereo- and enantioselectivity properties of this type of catalyst are thus probably due to both electronic and steric effects.

(9) For other Lewis acid–carbonyl complexes, see: (a) Shanbayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256. (b) Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794. (c) Hawkins, J. M.; Loren, S.; Nambu, M. *J. Am. Chem. Soc.* **1994**, *116*, 1657.

(10) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112.

(11) See *e.g.*: Woodward, R. B.; Hoffmann, R. *The Conversion of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970; p 145.

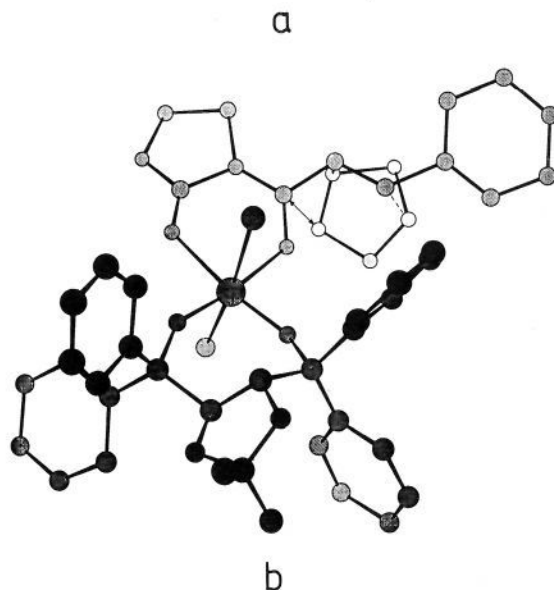
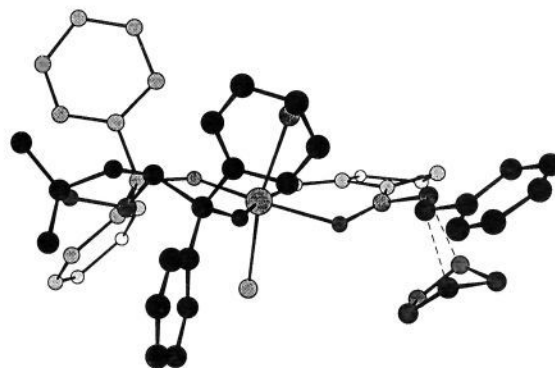


Figure 2. (a) Model for the catalytic diastereo- and enantioselective Diels–Alder reaction between **6** and cyclopentadiene. The approach of cyclopentadiene toward the alkene in **6** is depicted along the equatorial plane of **6**. The interaction of the alkene part of **6** and cyclopentadiene is outlined with dashed lines. (b) Similar approach as in (a), but viewed perpendicular to the plane in (a) showing the possible secondary orbital interaction between the carbonyl and the sp²-hybridized carbon atom in cyclopentadiene.

Further work is in progress to understand the catalytic properties of complexes similar to **6**.

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Supplementary Material Available: Tables of experimental details, atomic coordinates and isotropic parameters, bond lengths, and bond angles (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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