J. Org. Chem. **1997,** *62,* 3026−3027

First Enantioselective Catalytic Diels−Alder Reaction of Dienes and Acetylenic Aldehydes: Experimental and Theoretical Evidence for the Predominance of *Exo*-Transition Structure

Kazuaki Ishihara, Shoichi Kondo,
Hideki Kurihara, and Hisashi Yamamoto*

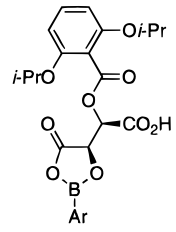
*Graduate School of Engineering, Nagoya University,
CREST, Japan Science and Technology Corporation (JST),
Chikusa, Nagoya 464-01, Japan*

Shigenori Ohashi and Satoshi Inagaki*

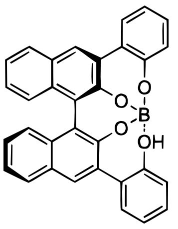
*Faculty of Engineering, Gifu University, Yanagido,
Gifu 501-11, Japan*

Received January 30, 1997

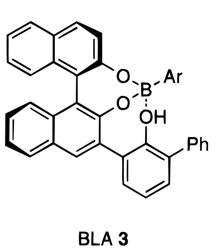
We previously reported that chiral boron catalysts **1**,[1a−c] **2**,[1d] and **3**[1e] are extremely effective for the enantioselective Diels−Alder reactions of dienes and α,β-enals.[2,3] As far as we know, however, the enantioselective reaction of dienes and acetylenic aldehydes has never been reported.[4,5] In this paper, we report not only the first example of an enantioselective reaction of dienes, which have prochiral reactive centers, and acetylenic aldehydes catalyzed by **1**−**3**, but also an *ab initio* study which supports the predominance of an exo-transition structure, thus clarifying the origin of the enantioselectivity observed upon catalysis.



CAB **1**
Ar=3,5-(CF$_3$)$_2$C$_6$H$_3$



BLA **2**



BLA **3**
Ar=3,5-(CF$_3$)$_2$C$_6$H$_3$

The four possible transition-state structures (TS) for the Lewis acid-promoted Diels−Alder reaction of cyclopentadiene with propynal are depicted in Figure 1. In the chiral Lewis acid-promoted reaction, an enantiomeric excess of an adduct originates in the enantiofacial selectivity of cyclopentadiene, which has prochiral reactive centers. The enantioselective pathway presupposes the following characteristics: (1) the chiral Lewis acid must sterically shield one enantioface of the coordinated propynal because the open acetylenic π-face in the chiral catalyst−dienophile complex approaches one face of cyclopentadiene; (2) the coordination of Lewis acid to propynal in the transition-state assembly must be either *syn*- or *anti*-selective, since its selectivity directly influences the enantiomeric excess of the products; and (3) either the *exo*- or *endo*-TS must be predominant, for the same reason as in (2).

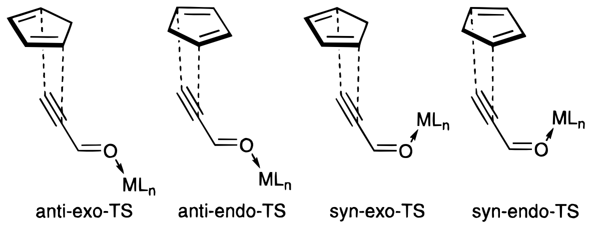
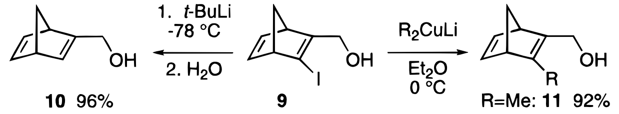


Figure 1. Four possible transition structures in the Diels−Alder reaction of propynal and cyclopentadiene promoted by Lewis acid. ML$_n$ = Lewis acid.

The results of the Diels−Alder reaction of cyclic dienes and acetylenic dienophiles catalyzed by **1**−**3** are summarized in Table 1. Overall, the reaction catalyzed by BLA (**2**) proceeded with good enantioselectivity and conversion, although the use of CAB (**1**) or BLA (**3**) gave higher enantioselectivity in some cases.[6] The absolute configurations of the adducts with **1** and **2** are opposite those with **3**. This inversion of absolute stereochemistry is analogous to the reaction of dienes and α,β-enals.[3] The optically active norbornadienes **4** and **7** are key intermediates for the synthesis of biologically active analogues of the prostaglandin endoperoxides PGH$_2$ and PGG$_2$[7] and β-santalol.[8] 3-Iodopropynal is an outstanding dienophile in these catalytic processes not only because of the observed enantioselectivity and reactivity but also because of the synthetic versatility of the resulting adducts. To illustrate, **9** can be smoothly converted into **10** and **11**, which are synthetic equivalents of adducts prepared in the reaction with dienophiles like propynal and 3-alkylpropynal.



The absolute stereochemical selectivities attained in these reactions can be explained in terms of the *anti*-*exo*-transition-state models, which are analogous to those previously proposed for the reaction of dienes and olefinic dienophiles.[1]

To determine the activated face of a carbonyl group in an acetylenic aldehyde−CAB **1** complex, an aldol reaction of acetylenic aldehydes with trimethylsilyl enol ether derived from acetophenone was carried out in the presence of 20 mol % of **1** under conditions similar to those of the Diels−Alder reaction. Good enantioselectivities were obtained, with the predominant enantiomer corresponding to *re*-face attack, as anticipated.[9] Although it

---

[1] (a) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54,* 1481. (b) Ishihara, K.; Qingzhi, G.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115,* 10412. (c) Ishihara, K.; Qingzhi, G.; Yamamoto, H. *J. Org. Chem.* **1993**, *58,* 6917. (d) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116,* 1561. (e) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118,* 3049.

[2] For a recent review, see: Ishihara, K.; Yamamoto, H. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: London, 1995; Vol. 1, pp 29−59.

[3] Hayashi, Y.; Rhode, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118,* 5502 and references cited therein.

[4] For a comprehensive review, see: Fucks, R.; Viehe, H. G. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 425−595.

[5] We previously reported the Diels−Alder reaction of cyclopentadiene and methyl propiolate catalyzed by a chiral organoaluminum reagent, giving the cycloadduct in 55% ee. Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1992**, *65,* 3501.

[6] In the reaction of propynal and cyclopentadiene, the desired reaction and the over reaction of **4** and cyclopentadiene proceed competitively.

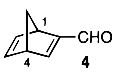
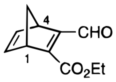
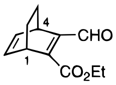
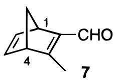
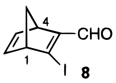
[7] Corey, E. J.; Shibasaki, M.; Nicolaou, K. C.; Malmsten, C. L.; Samuelsson, B. *Tetrahedron Lett.* **1976**, 737.

[8] (a) Sato, K.; Miyamoto, O.; Inoue, S.; Honda, K. *Chem. Lett.* **1981**, 1183. (b) Monti, H.; Corriol, C.; Bertrand, M. *Tetrahedron Lett.* **1982**, *23,* 947 and 5539.

[9] For determination of the absolute configuration of aldol adducts, see the Supporting Information.

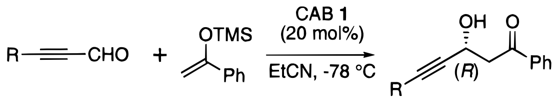
S0022-3263(97)00171-0 CCC: $14.00

Table 1. Enantioselective Diels−Alder Reaction of Dienes and Acetylenic Dienophiles Catalyzed by 1−3[a]

RC≡CCHO R	diene[b]	cat.	product	yield (%)[e]	ee (%)[h] (config)-(rotn)
H	CP	**1**[c]	 **4**	<12[—][f]	68 (1*R*,4*S*)-(−)
		2[d]		63[37]	88 (1*R*,4*S*)-(−)
		3		<28[58]	95 (1*S*,4*R*)-(+)
EtO_2C	CP	**1**[c]	 **5**	99	78 (1*R*,4*S*)-(+)
		2		97	95 (1*R*,4*S*)-(+)
		3		98	63 (1*S*,4*R*)-(−)
EtO_2C	CH	**1**[c,d]	 **6**	18	86 (−)
		2[d]		81	84 (−)
		3[d]		54	34 (+)
Me	CP	**1**[c,d]	 **7**	34	89 (1*R*,4*S*)-(+)
I	CP	**2**[d]	 **8**	72[g]	85 (1*S*,4*R*)-(−)[i]
		3		85[g]	81 (1*R*,4*S*)-(+)[i]

[a] Unless otherwise noted, Diels−Alder reaction of a dienophile (1 equiv) and a diene (4 equiv) was carried out in dichloromethane in the presence of 10 mol % of the catalyst at −78 °C for 3−66 h. [b] CP = cyclopentadiene; CH = cyclohexadiene. [c] Propionitrile was used as solvents. [d] 20 mol % of the catalyst was used. [e] Isolated yield. Yield of byproducts is indicated in parentheses. See ref 6. [f] Not isolated. [g] Overall yield of **9** *via* the Diels−Alder reaction and subsequent reduction by DIBAH. [h] For determination methods, see the Supporting Information. [i] Determined for **9**.

is essential to stress that the results of an aldol reaction cannot be directly used to explain the transition state in cycloaddition, the effective steric shielding of the *si*-face of the coordinated aldehyde is consistent with cycloaddition *via* the *anti*-*exo*-transition-state assembly.[1b,10]



R=H: 77% ee (88% yield); $R=CO_2Et$: 91% ee (91% yield)

Exo-*endo* selectivity in the Diels−Alder reaction of olefinic dienophiles has been extensively studied both experimentally and theoretically.[11] However, *exo*−*endo* selectivity of the TS in the reaction of acetylenic dienophiles has not been previously investigated since the adducts produced *via exo*- or *endo*-transition-state assembly are identical diastereomerically. We used *ab initio* molecular orbital calculations at the RHF/6-31G* level[12] to identify the TS of simple processes of this type: i.e., acid-free and BF_3-promoted reactions of cyclopentadiene and propynal (Figure 2). As expected, our calculations showed that the *exo*-TS are more stable than the *endo*-TS by 0.8 kcal/mol for the former reaction and by 2.0 and 2.4 kcal/mol for *anti* and *syn* pairs, respectively, for the latter. *These calculations strongly suggest the predominance of an exo-TS*[13,14] *and its enhancement by coordination of the Lewis acid.*[15] The *anti*-preference of the BF_3−propynal complex in transition-state assembly, as suggested by our calculations, may be adapted to complexes with bulky chiral Lewis acids such as **1**−**3**.

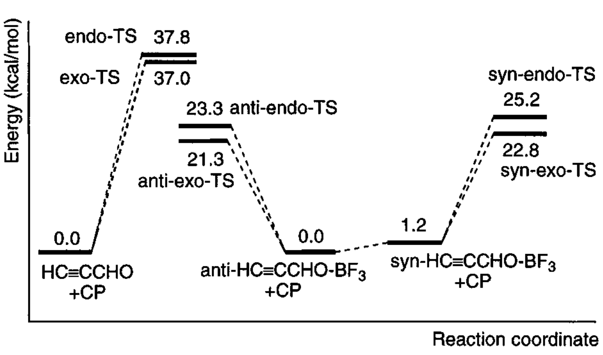


Figure 2. Potential-energy profile of Diels−Alder reactions without/with BF_3 calculated by the RHF/6-31G* method.

In summary, chiral Lewis acids **1**−**3** are effective for the enantioselective Diels−Alder reaction of dienes and acetylenic aldehydes: *a transfer of asymmetry from a chiral catalyst to a diene is efficiently originated through the asymmetric recognition of the carbonyl face of the acetylenic dienophile by the catalyst, since the preference for exo-transition-state assembly is present regardless of the steric factors of the Lewis acid.*[16]

Supporting Information Available: Experimental procedures, compound characterization data, and full geometries of all the transition structures (24 pages).

JO970171V

---

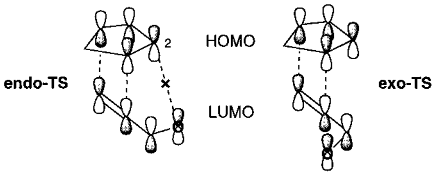
(10) Steric shielding of the *si*-face of aldehydes is consistent with other previously reported enantioselective reactions catalyzed by **1**; see: Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483. Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, 115, 11490. Gao, Q.; Ishihara, K.; Maruyama, T.; Mouri, M.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 979.

(11) For theoretical studies, see: (a) Fleming, I. *Frontier Orbitals and Organic Chemical reactions*; Wiley: New York, 1976; Chapter 4. (b) Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127. (c) Yamabe, S.; Dai, T.; Minato, T. *J. Am. Chem. Soc.* **1995**, *117*, 10994 and references cited therein.

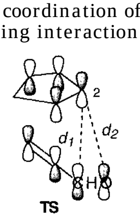
(12) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrewsky, V. G.; Ortiz, J. W.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian 94, Gaussian, Inc.: Pittsburgh, PA, 1995.

(13) As a control experiment, our calculations provided the expected *endo*-TS for the reaction of acrolein with cyclopentadiene as is observed experimentally. For further particulars, see the Supporting Information.

(14) The frontier molecular-orbital theory explains *exo* selectivity in terms of the secondary antibonding interaction between the lobes on *C*-2 of cyclopentadiene and carbonyl oxygen of propynal in *endo*-TS.



(15) According to our calculations, the distances (d_1, d_2) between *C*-2 of cyclopentadiene and the carbonyl moiety in TS shorten with the coordination of BF_3. This proximity enhances the secondary antibonding interaction (see ref 14) and the *exo*-TS-selectivity.



exo-TS (without BF_3)	d_1, d_2=3.628, 4.446 Å
endo-TS (without BF_3)	d_1, d_2=3.626, 4.023 Å
anti-exo-TS (with BF_3)	d_1, d_2=3.403, 4.165 Å
anti-endo-TS (with BF_3)	d_1, d_2=3.342, 3.511 Å

(d=distances shown by dotted lines)

(16) H.K. acknowledges a JSPS Fellowship for Japanese Junior Scientists. We thank Mr. Manabu Kubota for his helpful discussions.