Design of Brønsted Acid-Assisted Chiral Lewis Acid (BLA) Catalysts for Highly Enantioselective Diels−Alder Reactions

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Received March 26, 1998

Abstract: Brønsted acid-assisted chiral Lewis acid (BLA) was highly effective as a chiral catalyst for the enantioselective Diels−Alder reaction of both α-substituted and α-unsubstituted α,β-enals with various dienes. Hydroxy groups in optically active binaphthol derivatives and boron reagents with electron-withdrawing substituents were used as Brønsted acids and Lewis acids, respectively. Intramolecular Brønsted acids in a chiral BLA catalyst played an important role in accelerating the rate of Diels−Alder reactions and in producing a high level of enantioselectivity. In particular, excellent enantioselectivity was achieved due to intramolecular hydrogen bonding interaction and attractive π−π donor−acceptor interaction in the transition-state assembly by hydroxy aromatic groups in a chiral BLA catalyst.

Introduction

Spectacular advances have recently been achieved in enantioselective Diels−Alder reactions catalyzed by chiral Lewis acids.[1] In particular, the design of chiral metal aryloxides prepared from metal reagents and optically active binaphthol derivatives has been one of the most intensively studied areas in the development of new asymmetric Diels−Alder catalysts.[2] Nevertheless, there are still few practical procedures available which can be widely applied to various dienes and dienophiles. In most cases, asymmetric induction with chiral metal aryloxides is controlled by steric interaction between a dienophile and a chiral ligand, but this kind of interaction is insufficient to provide a high level of enantioselectivity.[2] On the other hand, Hawkins et al.,[3a] Corey et al.,[3b] and we[3c] have independently reported that the attractive π−π donor−acceptor interaction between a dienophile and a chiral ligand is highly effective for inducing asymmetry. This finding encouraged us to seek new members of this class to achieve high enantioselectivity through *the combination of intramolecular hydrogen bonding and attractive* π−π donor−acceptor interaction in the transition-state assembly by hydroxy aromatic groups in chiral Lewis acids. Thus, we developed Brønsted acid-assisted chiral Lewis acid (BLA) catalysts, **1**-**4**, which are highly effective for enantioselective Diels−Alder reactions.[4,5] This paper describes a successful and practical methodology based on this new concept, which we believe has wide implications in catalyst design and which deals specifically with catalysis of the Diels−Alder reaction.[4]

Results and Discussion

Design of BLA Using $B(OMe)_3$. (*R*)-3,3′-Di(2-hydroxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (**5a**) was synthesized from (*R*)-binaphthol using the Pd(0)-catalyzed-coupling reaction as a key step.[2f,6] Reaction of (*R*)-tetraol **5a** with $B(OMe)_3$ in dichloromethane at reflux with the removal of methanol (4 Å molecular sieves (MS 4A) in a Soxhlet thimble) gave (*R*)-**1a** as a white precipitate after 2∼3 h. To the suspension of (*R*)-**1a** in dichloromethane was added THF (1 mL per 1 mmol of **1a**) at 25 °C, and after 2 h the mixture turned to a colorless solution. The ^{1}H NMR spectrum of **1a** after the addition of D_2O showed no methanol peak. The ^{11}B NMR spectrum of a solution of **1a** in CD_2Cl_2 showed a single broad peak at 10 ppm (downfield from external BF_3-Et_2O). The ^{11}B NMR data are

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(1) For recent reviews, see: (a) Ishihara, K.; Yamamoto, H. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: London, 1995; Vol. 1, p 29. (b) Ishihara, K.; Yamamoto, H. *CatTech* **1997**, 51. (c) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289.

(2) For the enantioselective Diels−Alder reaction catalyzed by chiral metal aryloxide, see $B(OAr)_3$: (a) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510. (b) Kaufmann, D.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545. $MeAl(OAr)_2$: (c) Maruoka, K.; Conception, A. B.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3501. $ClAl(OAr)_2$: (d) Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814. (e) Heller, D. P.; Goldberg, D. R.; Wulff, W. D. *J. Am. Chem. Soc.* **1997**, *119*, 10551. $Ti(OAr)_4$: (f) Maruoka, K.; Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938. $Cl_2Ti(OAr)_2$: (g) Reetz, M. T.; Kyung, S. H.; Bolm, C.; Zierke, T. *Chem. Ind. (London)* **1986**, 2409. (h) Mikami, K.; Motoyama, Y.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, *2*, 643. (i) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812. (j) Motoyama, Y.; Terada, M.; Mikami, K. *Synlett* **1995**, 967. (k) Harada, T.; Takeuchi, M.; Hatsuda, M.; Ueda, S.; Oku, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2479. (l) Matsukawa, S.; Mikami, K. *Tetrahedron: Asymmetry* **1997**, *8*, 815.

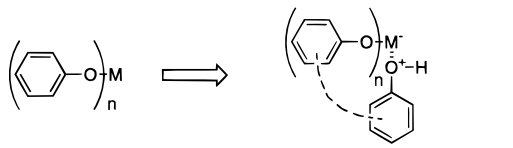
(3) (a) Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794. Hawkins, J. M.; Loren, S.; Nambu, M. *J. Am. Chem. Soc.* **1994**, *116*, 1657. (b) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (c) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412.

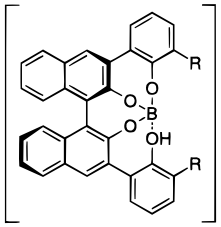
(4) Part of this work has been published as preliminary communications: (a) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561. (b) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049.

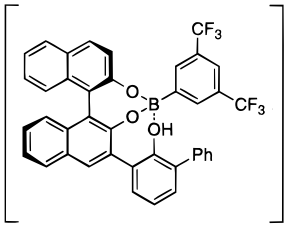
(5) For examples of BLA catalysts, see: (a) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520. (b) Koboyashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758. (c) Aggarwal, V. K.; Anderson, E.; Giles, R.; Zaparucha, A. *Tetrahedron: Asymmetry* **1995**, *6*, 1301. (d) Ishihara, K.; Kondo, S.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1997**, *62*, 3026.

(6) For synthesis of sterically hindered biaryls via the palladium-catalyzed cross-coupling reaction, see: Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.

S0002-7863(98)01028-2 CCC: $15.00
Published on Web 06/29/1998




BLAs **1a** (R=H), **1b** (R=Ph)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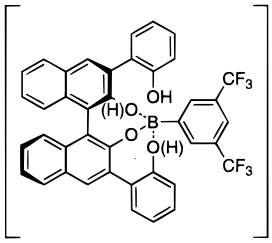
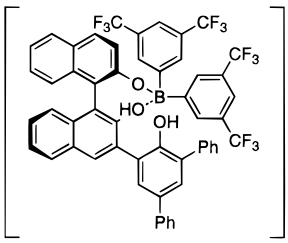
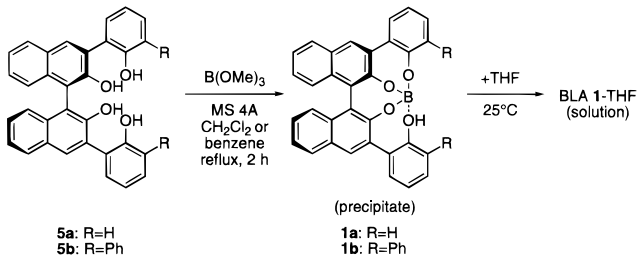

BLA **3**


BLA **4a**

consistent with structure **1a** as the major species. Conversion of the trigonal ($B(OR)_3$, ^{11}B NMR 18 ± 2 ppm) to the tetrahedral molecule ($B(OR)_4^-$) by nucleophilic addition of a fourth ligand increases the shielding of boron by 16 ppm.[7a] With $B(OPh)_3$, $B(OPh)_3$ including excess PhOH, and $LiB(OPh)_4$, the ^{11}B NMR peaks appear at 16.5 ppm,[7b] 14.5 ppm,[7c] and 3.0 ppm,[7c] respectively. The fact that boron shielding increases in the order $[B(OPh)_3 + PhOH] <$ **1a** $< LiB(OPh)_4$ suggests that **1a** is a tetrahedral structure close to an ionic ate complex.



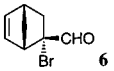
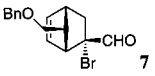
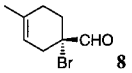
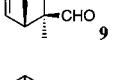
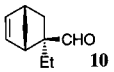
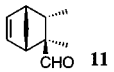
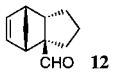
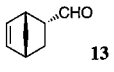
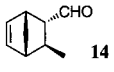
In the presence of 5 mol % of (*R*)-**1a**, α-bromoacrolein (1 equiv) and cyclopentadiene (ca. 4 equiv) underwent smooth Diels−Alder addition (−78 °C, 4 h) to give the (1*S*,2*S*,4*S*)-2-bromobicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (**6**) in >99% yield, >99% ee (*S* only), and >99% de (exo only); chiral ligand **5a** was efficiently recovered.

Extremely high enantioselectivity and exo selectivity were obtained for Diels−Alder additions of α-substituted α,*β*-enals with dienes in the presence of the catalyst (*R*)-**1a**. These results are summarized in Table 1. Enantioselectivities were in the range >99 to 92% ee, and the major enantiomer in several cases was found to have the predicted absolute configuration. Corey's group[3b,8] has demonstrated that α-bromoacrolein is an outstanding dienophile in a catalytic Diels−Alder process because of the exceptional synthetic versatility of the resulting adducts. For instance, an important intermediate for prostaglandin synthesis, **7**, was synthesized with remarkable ease.[3b]

With BLA **1** as well as most chiral Lewis acids,[1] however, the corresponding reactions of α-unsubstituted α,*β*-enals such as acrolein and crotonaldehyde exhibit low enantioselectivity and/or reactivity. Lack of an α-substituent on the dienophile decreases the enantioselectivity, and an existence of α, *β*-substituent strikingly decreases the selectivity and reactivity. To raise the enantioselectivity for α-unsubstituted α,*β*-enals, the substituent effect of chiral tetraol **1** was examined in the Diels−Alder reaction of cyclopentadiene and acrolein.[2f] The enantioselectivity was raised to 92% ee by using (*R*)-**1b** in place of (*R*)-**1a** (see Table 1).

To determine the activated face of the carbonyl group in the coordination complex of methacrolein and (*R*)-**1a**, the aldol reaction of methacrolein with trimethylsilyl enol ether derived from acetophenone was carried out in the presence of 10 mol

Table 1. Enantioselective Diels−Alder Reaction Catalyzed by (*R*)-BLA **1**[a]

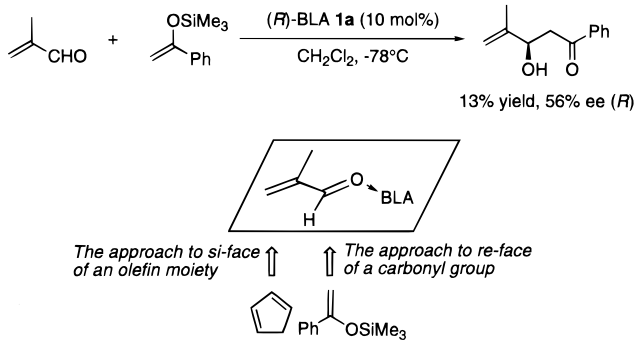
entry	dienophile	diene	product[b]	yield (%)[c] [exo:endo][d]	ee (%)[e] [config]
1			 **6**	>99 [>99:1]	99 [*S*]
2				>99[f] [>99:1]	>99[g] [*S*]
3			 **7**	>99 [>99:1]	94 [*S*]
4			 **8**	>99[h]	94 [*S*]
5			 **9**	>99[f] [>99:1]	99 [*R*]
6				88 [>99:1]	98 [*R*]
7			 **10**	>99 [97:3]	92
8			 **11**	>99 [>99:1]	98
9			 **12**	>99 [98:2]	93
10			 **13**	91 [9:91]	40 [*R*]
11				85 [14:86]	92[i] [*R*]
12			 **14**	12 [11:89]	36 [*R*]

[a] Unless otherwise noted, the reaction was carried out in freshly distilled dichloromethane using 10 mol % of catalyst (*R*)-**1a** and 4 equiv of the diene per aldehyde at −78 °C. [b] The figure given for product shows the major diastereomer. [c] Isolated yield by column chromatography for the exo/endo mixture. [d] Diastereoselectivity was determined by ^1H NMR analysis or GC analysis of Diels−Alder adducts. [e] The ee of major isomer and the absolute configuration of its carbonyl α-carbon are indicated. The absolute configuration indicated in entry 4 was assigned by analogy with cyclopentadiene,[3b] and the others were assigned by comparison with data in the literatures. For determination methods, see Experimental Section. [f] 5 mol % of catalyst (*R*)-**1a** was used. [g] (*R*)-**6** was not formed in a detectable amount. [h] The reaction temperature was −40 °C. [i] (*R*)-**1b** was used in place of (*R*)-**1a**. For preparation of **1b**, see Experimental Section.

(7) (a) Kidd, R. G. In *NMR of Newly Accessible Nuclei*; Laszlo, P., Ed.; Academic Press: New York, 1983; Vol. 2, pp 49−77. (b) Olah, G. A.; Wu, A. *Synthesis* **1991**, 204 and references therein. (c) Our experimental results.

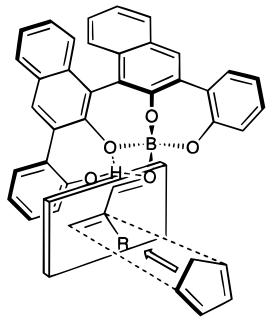
(8) (a) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979. (b) Corey, E. J.; Cywin, C. L. *J. Org. Chem.* **1992**, *57*, 7372.

Scheme 1. The Absolute Stereopreference on Mukaiyama Aldol Reaction Promoted by (*R*)-**1**

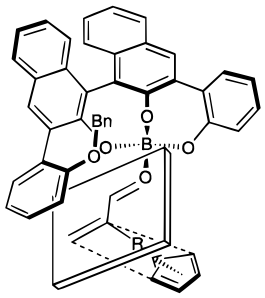


% of (*R*)-**1a** at −78 °C for 15.5 h to form (*R*)-aldol adduct as a major isomer (13%) with 78:22 enantioselectivity (Scheme 1). The reaction was stoichiometric since the boron−oxygen bonds of (*R*)-**1a** were easily cleaved by trimethylsilyl enol ethers. The observed stereoselectivity in this catalytic Diels−Alder process is probably a consequence of the shielded *si*-face of a carbonyl group and a high *s*-trans preference of α,*β*-enal[9] if the aldol result is relevant to the Diels−Alder transition state.[3c,5d]

The absolute stereopreference in the Diels−Alder reaction can be easily understood in terms of the most favorable transition-state assembly **A** which is proposed on the basis of the above assumption. An attractive donor−acceptor interaction favors coordination of the dienophile at the face of boron which is cis to the 2-hydroxyphenyl substituent in **A**. We believe that the coordination of a proton of the 2-hydroxyphenyl group with an oxygen of the adjacent B−O bond in complex **A** plays an important role in asymmetric induction; this hydrogen bonding via the Brønsted acid would cause the Lewis acidity of boron and *π*-basicity of phenoxyl moiety to increase, and the transition-state assembly **A** would be stabilized. Subsequently, the *π*-basic phenoxyl moiety and the *π*-acidic dienophile can assume a parallel orientation at the ideal separation (3 Å) for donor−acceptor interaction. In this conformation, the hydroxyphenyl group blocks the *re*-face of olefin in the dienophile (R = Br), leaving the *si*-face open to approach by diene. This assumption has been confirmed by experiment. Of great mechanistic significance is the fact that the Diels−Alder reaction of cyclopentadiene and methacrolein at −78 °C for 14 h under catalysis by 10 mol % of the boron complex **15** prepared from (*R*)-3-(2-benzyloxyphenyl)-2,2′-dihydroxy-3′-(2-hydroxyphenyl)-1,1′-binaphthyl (**16**) and BH_3−THF[10] gave the (2*S*)-enantiomer of **9** as a major product with 65% ee (exo:endo = 97:3). With the boron catalysts prepared from BH_3−THF[10] and monoisopropyl ether and mono-*tert*-butyldimethylsilyl ether of **5a**, the reactions with methacrolein exhibited low enantioselectivities (17% ee and 29% ee, respectively), but the opposite face selectivity ((2*S*)-**9** as a major enantiomer) predominated. The dramatically opposite results using the tetraol **5a** and the triols provide strong evidence for transition-state assemblies **A** and **B**, respectively; the former has a fixed nonhelical structure via intramolecular hydrogen bonding via the Brønsted acid, while the latter has a helical structure.[2f,11]



Non-Helical Transition-State (**A**)



Helical Transition-State (**B**)

Design of BLA Using 3,5-Bis(trifluoromethyl)phenylboronic Acid. BLA **1a** is one of the best catalysts for the enantio- and exo-selective cycloaddition of α-substituted α,*β*-enals with highly reactive dienes such as cyclopentadiene.[4a] However, the corresponding reactions of α-unsubstituted α,*β*-enals such as acrolein and crotonaldehyde exhibit low enantioselectivity and/or reactivity. The scope of dienophiles which are applicable for less reactive dienes is quite limited. We previously reported the development of helical titanium catalysts which were effective for the enantioselective cycloaddition of both α-substituted and α-unsubstituted dienophiles.[2f] Unfortunately, their catalytic activities are moderate even for methacrolein because of an excess of steric hindrance due to the bulky substituents of the ligands. Thus, we subsequently studied the design and synthesis of a more practical BLA which has greater catalytic activity in the enantioselective cycloaddition of both α-substituted and α-unsubstituted α,*β*-enals with various dienes.

3,5-Bis(trifluoromethyl)phenylboronic acid (**17**) was chosen as the Lewis acidic metal component of the new BLA. We have found that this air-stable boronic acid has enough Lewis acidity to promote some reactions by itself.[12] Chiral ligands for **17** require the inclusion of a biphenol moiety to form a bidentate complex with the boron atom and a phenol moiety which functions as a Brønsted acid. Thus, several chiral triol ligands **18a**−**d** were designed based on the terphenol structure and synthesized from (*R*)-binaphthol using the Pd(0)-catalyzed-coupling reaction as a key step.[2f,6]

BLA **2a**−**d** were prepared in situ as follows. **Method A**. A mixture of chiral triol **18a** (1.2 equiv) and a solution of monomeric boronic acid **17** (1 equiv) in dichloromethane−THF[13] was stirred at ambient temperature for 2 h. The resulting colorless solution was transferred to a Schlenk tube containing dichloromethane and powdered MS 4A (250 mg per 0.05 mmol of **17**, activated[14]), and the mixture was stirred at ambient temperature for another 12 h. The solvents were then evaporated and the resulting solid was heated to 100 °C (oil bath) for 2 h under vacuum to dry the catalyst. After cooling to ambient

(9) Interestingly, the (*S*)-tryptophan-derived chiral Lewis acid catalyst system developed by Corey *et al.*[3b] appears to function via an *s*-cis-α-substituted-α,*β*-enal complex, in contrast to our results that α,*β*-enal prefers the *s*-trans conformation in the tartaric acid-derived chiral acyloxyborane catalyst system[3c] as well as in the present system.

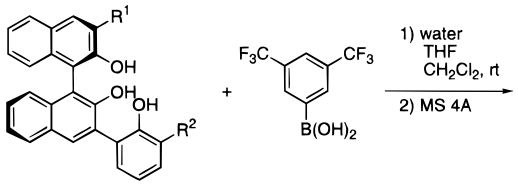
(10) Monoethers of **5a** coexistent with $B(OMe)_3$ in dichloromethane were partially decomposed under a reflux condition. The reaction of methacrolein with cyclopentadiene under catalysis by 10 mol % of the boron complex **1a** prepared from BH_3−THF and **5a** gave (2*R*)-**7** as major product with 86% ee (exo: endo = 99: 1).

(11) If it is assumed that the Diels−Alder reaction occurs only through that conformation that has the dienophile and the phenyl group the closest together in space (via the attractive interaction), the absolute stereocourse can be understood in terms of the two possible transition-state assemblies **A** and **B**.

(12) For references on chiral Lewis acid using **17**, see: (a) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483. (b) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490.

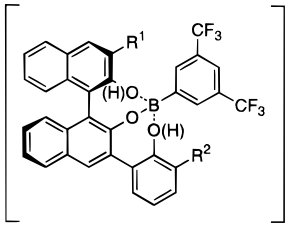
(13) Boronic acid **17**, which is commercially available from Lancaster Synthesis, Ltd., contains varying amounts of cyclic trimeric anhydrides (boroxines). A 0.043 M solution of monomeric **17** was prepared by addition of water (54 mL, 3 mmol), dry THF (3 mL), and dichloromethane (20 mL) to a commercial **17** (1 mmol, >90% trimer).

(14) MS 4A was activated by heating at 200 °C under vacuum for 12 h.



18a: R^1=H, R^2=Ph
18b: R^1=H, R^2=Me
18c: R^1, R^2=H
18d: R^1=Ph, R^2=H

17



BLA **2a-d**

temperature, the Schlenk tube was charged with dichloromethane to give an active catalyst solution including MS 4A. **Method B** (a simplification of method A). A mixture of chiral triols **18a−d** (1.2 equiv), commercial boronic acid **17** (1 equiv),[13] THF (150 mL per 0.05 mmol of **17**, without drying),[15] powdered MS 4A (250 mg per 0.05 mmol of **17**, nonactivated), and dichloromethane was stirred at ambient temperature for 12 h. The active catalyst solution was then prepared as in method A.

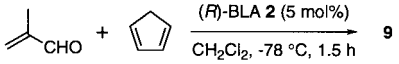
For studies of catalytic, enantioselective cycloaddition using **2a-d**, methacrolein and cyclopentadiene were selected as representative substrates. The results are summarized in Table 2. In the presence of 5 mol % of **2a-d** prepared by method A or B, the reaction proceeded smoothly and was controlled sterically to form (*S*)-exo-adduct enantioselectively. In contrast, the reactions using chiral Lewis acids prepared from (*R*)-diols which did not contain a Brønsted acid component were relatively slow under the same conditions, and low conversion and a reduced level of absolute induction were observed (entries 7 and 8). *The presence of a Brønsted acid in BLA catalysts clearly accelerates the cycloaddition.*

The substituents R^1 and R^2 of triol ligands **18** appear to be significant in determining which hydroxy group in **18** best serves as a Brønsted acid. The best enantioselectivity and highest reactivity were obtained in the reaction using **2a** (entries 1 and 2), while a dramatic decrease in rate and selectivity was observed with **2b-d** (entries 4−6). Although the formation of two bidentate complexes between **18** and **17** is possible, R^2 sterically prevents the formation of a complex between the hydroxy group adjacent to R^2 and the boron atom.

The most striking feature in the present process is the role of water, THF, and MS 4A in the preparation of the catalyst. The enantioselectivity was reduced to less than 80% ee in the reaction using **2a** prepared in situ in the presence of activated MS 4A under anhydrous conditions. Preparation of a sufficient amount of **2a** is assumed to be difficult under these conditions since the trimer of **17** is easily generated by dehydration and is not readily dissociated by the addition of **18a**. In fact, **17** usually exists as a mixture of monomer, trimer, and oligomer.[13] To prevent trimerization of **17** in preparing the catalyst, **18a** and **17** were mixed under aqueous conditions and then dried (methods A and B) since the presence of water or THF deactivates **2a**; in this manner, 99% ee was obtained (entry 1). Significantly, use of the solution obtained by filtering the MS

(15) THF (none stabilizer) was purchased from Wako Pure Chemical Industries, Ltd.

Table 2. Modification and Preparation of Diels−Alder Catalysts[a]



entry	chiral ligand	method[b]	yield[c] (%)	ee (%)[d] [config]
1	(*R*)-**18a**	A	96	99 [*S*]
2		B	94	98 [*S*]
3		A[e]	95	48 [*S*]
4	(*R*)-**18b**	B	89	50 [*S*]
5	(*R*)-**18c**	B	97	77 [*S*]
6	(*R*)-**18d**	B	63	60 [*S*]
7	(*R*)-**18a** (MeO)[f]	B	9	45 [*S*]
8	(*R*)-Binaphthol	B	22	46 [*S*]

[a] The reactions were conducted in dichloromethane using aldehyde (1 equiv, 0.25 M) and diene (4 equiv) in the presence of 5 mol % of **2** at −78 °C for 1.5 h. [b] See text. [c] Isolated yield. [d] The ee of major isomer and the absolute configuration of its carbonyl α-carbon are indicated. The absolute configuration was assigned by comparison with data in the literature. For the determination method, see Experimental Section. [e] No THF was added. [f] (*R*)-3-(2-Methoxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl was used.

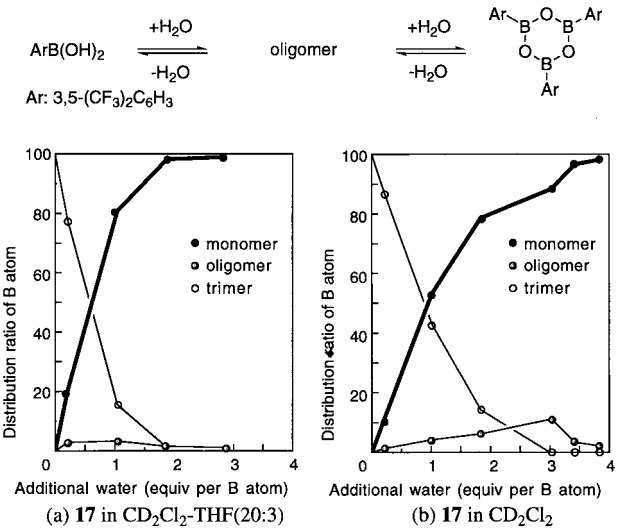


Figure 1. Plot of the distribution ratio of boron atom in a solution of **17** versus additional water.

4A off of **2a** after preparation by method B provided the same high level of enantioselectivity. Although molecular sieves are essential for dehydration, they may facilitate the aryloxy-ligand exchange reaction in the in situ preparation of **2a**. However, using **2a** prepared without the addition of THF gave a low enantiomeric excess (48%, entry 3); this may be due to the stability of monomeric **17** by coordination of THF. Actually, more than 98% of **17** existed as a monomer in dichloromethane−THF (20:3) with the addition of 2 equiv of water, while ca. 20% of **17** is a mixture of trimer and oligomer in dichloromethane alone (Figure 1).

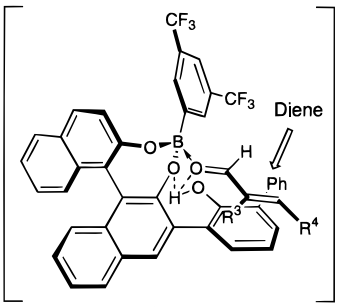
The present results indicate that BLA **2a** was the optimum catalyst, and representative results in the cycloadditions between various α,*β*-enals and dienes are given in Table 3. In each case the adducts were formed in high yield with excellent enantioselectivity. As expected, the additions of the less-reactive *β*-substituted α,*β*-enals with cyclopentadiene gave very good results. In addition, **2a** was an excellent catalyst for not only less-reactive dienophiles but also less-reactive dienes such as acyclic dienes and cyclohexadiene. However, moderate enantioselectivity was observed in the reaction of phenyl acrylate and cyclopentadiene. Chiral ligand **18a** could be recovered readily, and could be reused efficiently. The reaction mixture

Table 3. Enantioselective Diels−Alder Reaction Catalyzed by (*R*)-BLA **2a**[a]

entry	dienophile	diene[b]	**2a** (mol%) [method][c]	yield (%)[d] [exo:endo][e]	ee (%)[e] [config][e]
1	CH_2═CBrCHO	CP	5 [B][f]	>99 [90:10]	>99 [*R*]
2		CP	1 [B][f]	97 [88:12]	97 [*R*]
3		BMCP	10 [A]	>99 [89:11]	>99 [*R*]
4		CH	10 [B][g]	65 [10:90]	95
5		DMB	10 [B][h]	95	91
6		IP	10 [B]	95	>99 [*R*]
7	CH_2═CMeCHO	CH	20 [B]	87 [11:89]	95
8		DMB	10 [B]	81	>99
9		IP	10 [B]	73	>99
10	(*E*)-MeCH═CMeCHO	CP	20 [A][i]	90 [98:2]	96
11	CH_2═CHCHO	CP	5 [A]	84 [3:97]	95 [*S*]
12		CH	10 [B]	>99 [0:100]	96 [*S*]
13		DMB	10 [B]	97	>99
14		IP	10 [A]	95	99
15	(*E*)-MeCH═CHCHO	CP	20 [A]	94 [10:90]	95 [*S*]
16	(*E*)-EtCH═CHCHO	CP	20 [A][j]	73 [9:91]	98
17		CP	20 [B][k]	57 [18:82]	75
18	(*E*)-PhCH═CHCHO	CP	20 [A][l]	94 [26:74]	80
19	(*E*)-EtO_2CCH═CHCHO	CP	5 [A]	91 [2:98]	95 [*R*]
20	CH_2═$CHCO_2$Ph	CP	20 [B][m]	57 [25:75]	56 [*S*]
21	CH_2═$CHCO_2C_6H_4$-*p*-F	CP	20 [B][n]	90 [28:72]	67 [*S*]

[a] Unless otherwise noted, reactions were conducted in dichloromethane using aldehyde (1 equiv, 0.25 M) and diene (4 equiv) in the presence of **2a** at −78 °C for 1−24 h. [b] CP, cyclopentadiene; BMCP-, 1-benzyloxymethylcyclopentadiene; CH, 1,3-cyclohexadiene; DMB, 2,3-dimethylbutadiene; IP, isoprene. [c] See text. [d] Isolated yield for the exo/endo mixture. [e] The ee of major isomer and the absolute configuration of its carbonyl α-carbon are indicated. The absolute configuration indicated in entry 6 was assigned by analogy with cyclopentadiene,[3b] and the others were assigned by comparison with data in the literatures. For determination methods, see Experimental Section. [f] Aldehyde (0.5 M) in dichloromethane. [g] 50 mg of MS 4A per 0.05 mmol of **17** was used. [h] MS 4A was removed after preparation of **2a**. [i] −78 °C, 50 h. [j] −78 °C, 72 h. [k] −40 °C, 38 h. [l] −40 °C, 60 h. [m] −20 °C, 4 days. [n] −20 °C, 39 h.

was treated with aqueous 2 N NaOH, and the products were extracted with pentane. Acidification of the aqueous layer and extraction with dichloromethane afforded **18a** (>90%). On the whole, method A was superior to method B with regard to both catalytic activity and enantioselectivity for the cycloaddition (e.g., (*E*)-2-pentenal in Table 3).



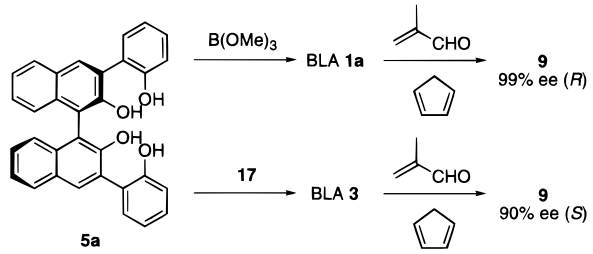
Proposed Transition State Model **C**

The high enantioselectivity and stereochemical results attained in these reactions can be understood in terms of transition-state model **C**. This model is consistent with the observed absolute stereochemical selectivity and is analogous to that proposed for BLA **1a**.[4a,5]

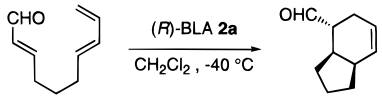
The absolute stereopreference in the Diels−Alder reaction catalyzed by (*R*)-**2a** is opposite that catalyzed by (*R*)-**1a**. This means that the presence of the 3,5-bis(trifluoromethyl)phenyl group greatly affects the asymmetric induction of BLAs prepared from chiral ligands **5a** and **18a** with the same absolute configuration. In fact, the use of BLAs **1a** and **3** prepared from the common chiral tetraol **5a** in the Diels−Alder reaction, respectively, gave an opposite enantiomer with high selectivity, as shown in Scheme 2.

We extended this approach to the intramolecular cycloaddition of an α-unsubstituted trienal. The reaction of (*E*,*E*)-2,7,9-decatrienal in the presence of **2a** (30 mol %, method A) provided

Scheme 2. Both Enantiomers Available from the Same Chiral Tetraol **5a**



only the endo adduct in 95% yield with 80% ee (*R*). This result was much better than that (74% yield, 46% ee, exo:endo = 1:99) previously given by a CAB-catalyzed reaction.[16]

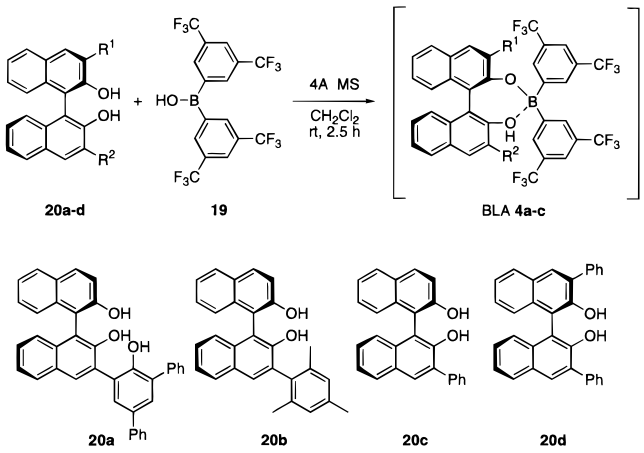


Design of BLA Using Bis[3,5-bis(trifluoromethyl)phenyl]-borinic Acid. The use of arylboronic acid with electron-withdrawing substituents such as **17** in the preparation of BLA greatly enhanced its catalytic activity and asymmetry-inducing ability.[4b] Next, we examined bis[3,5-bis(trifluoromethyl)phenyl]-borinic acid (**19**) as a component of BLA to obtain an even better asymmetric Diels−Alder catalyst. A diarylborinic acid is a stronger Lewis acid than the corresponding boronic acid,[17] and we recently reported its unique characteristics as a Lewis acid catalyst.[18] A new BLA **4** was prepared by stirring **19** and a chiral ligand in dichloromethane in the presence of MS 4A

(16) Furuta, K.; Kanematsu, A.; Yamamoto, H. *Tetrahedron Lett.* **1989**, *30*, 7231.

(17) *Stereodirected Synthesis with Organoboranes*; Matteson, D. S., Ed.; Springer: Berlin, Heidelberg, New York, 1995; see also references therein cited.

(18) (a) Ishihara, K.; Kurihara, H.; Yamamoto, H. *Synlett* **1997**, 597. (b) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1997**, *62*, 5664.



(activated powder)[14] at room temperature. MS 4A was indispensable in preparing **4** as well as **2**, while THF and water were not essential. It has been ascertained by ^{1}H NMR analysis that **19** exists as a single species of monomer.[18]

Table 4 summarizes the results of the cycloaddition of methacrolein and cyclopentadiene catalyzed by BLA prepared from **19** and various (*R*)-binaphthol derivatives. A bulky substituent at the 3-position of (*R*)-binaphthol enhanced enantioselectivity (entries 1−5), while the use of chiral C_2 symmetrical diols was less effective (entries 6 and 7). In particular, good enantioselectivity was attained with **18a**, the chiral ligand of BLA **2a** (entry 2). Finally, enantioselectivity was raised to 86% ee using the more bulky triol **20a** (entry 1). Although bis(pentafluorophenyl)borinic acid,[18] which is a stronger Lewis acid than **19**, was also examined, lower enantioselectivity was observed (entry 4 versus 5). It seems that the steric bulkiness of the aryl groups in diarylborinic acid is important for a high level of asymmetric induction because BLA formed from diarylborinic acids and chiral ligands has a conformationally flexible structure.

Based on the above experimental results, BLA **4a** was examined in the reaction of cyclopentadiene and other representative dienophiles, i.e., acrolein and crotonaldehyde (Table 5). The reactions proceeded smoothly, and in both cases good enantioselectivity was observed for the exo adduct. The exo adduct was obtained as a major diastereomer in the reaction of crotonaldehyde and cyclopentadiene, compared with the high endo-selectivity that is generally observed in Lewis acid-promoted reactions.

Conclusions

The combined use of a Brønsted acid is a new concept in the design of chiral Lewis acid catalysts. This paper describes a rational basis for the design of BLA complexes which possess sufficient Lewis acidity to catalyze a wide range of synthetically useful enantioselective Diels−Alder reactions. Intramolecular Brønsted acids in BLA play an important role in the rate acceleration and the high level of enantioselectivity which were observed in the enantioselective Diels−Alder reaction. Various boron compounds such as trialkylborate, arylboronic acid, and diarylborinic acid can be used in the design of BLA. An arylboronic acid with electron-withdrawing substituents has the advantage of having strong Lewis acidity and constructing a bidentate complex with a chiral ligand. In contrast, although diarylborinic acid is a stronger Lewis acid, it is difficult to use to construct a rigid monodentate complex.

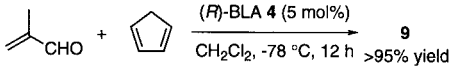
Experimental Section

General. Infrared (IR) spectra were recorded on a Shimazu FT-IR 8100 spectrometer. ^{1}H NMR spectra were measured on Varian Gemini-200 (200 MHz), 300 (300 MHz), and VXR 500 (500 MHz) spectrometers. High-performance liquid chromatography (HPLC) was done with Shimazu Model 6A or 9A instruments using 4.6 mm × 25 cm Daicel CHIRALCEL OD, OD-H, OJ, AD, and AS. Gas−liquid-phase chromatography (GC) was done with Shimadzu Model 8A instrument with a flame-ionization detector and a capillary column of PEG-HT Bonded (25 m × 0.25 mm) using nitrogen as carrier gas. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. Melting points were determined using a Yanaco MP-J3. All experiments were carried out under an atmosphere of dry argon. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF^{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel (E. Merck 9385). Microanalyses were accomplished at the School of Agriculture, Nagoya University. The high-resolution mass spectra (HRMS) were conducted at Daikin Industries, Ltd., Japan.

In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Aldrich Chemical Co. as "anhydrous" and stored over 4 Å molecular sieves (MS 4A). Benzene, hexane, and toluene were dried over sodium metal. Methylene chloride was freshly distilled from calcium hydride. α,β-Enals were freshly distilled from MS 4A. Trimethyl borate was distilled from sodium metal under argon. Other simple chemicals were purchased and used as such.

Preparation of Chiral Ligands. (*R*)-3,3′-Di(2-hydroxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (5a). To a mixture of (*R*)-3,3′-dibromo-2,2′-di(methoxymethoxy)-1,1′-binaphthyl (1.06 g, 2 mmol), 2-methoxyphenylboronic acid (966 mg, 6 mmol), and barium hydroxide octahydrate (1.89 g, 6 mmol) in DME−H_2O (6:1, 21 mL) under argon was added $Pd(PPh_3)_4$ (231 mg, 0.2 mmol), and then the mixture was degassed three times, and charged with argon.[6] The mixture was warmed to 80 °C and stirred for 12 h. The resulting mixture was cooled

Table 4. Modification and Preparation of Diels−Alder Catalysts[a]



entry	chiral ligand	exo:endob	ee (%)[c] [config]
1	(*R*)-**20a**	94:6	86 [*R*]
2	(*R*)-**18a**	95:5	80 [*R*]
3	(*R*)-**20b**	95:5	55 [*R*]
4	(*R*)-**20c**	92:8	49 [*R*]
5[d]	(*R*)-**20c**	91:9	28 [*R*]
6	(*R*)-binaphthol	89:11	15 [*R*]
7	(*R*)-**20d**	90:10	1 [*R*]

[a] The reactions were conducted in dichloromethane using methacrolein (1 equiv, 0.25 M) and cyclopentadiene (4 equiv) in the presence of 5 mol % of **4** at −78 °C for 12 h. [b] Diastereoselectivity was determined by ^{1}H NMR analysis or GC analysis of Diels−Alder reaction. [c] The ee of major isomer and the absolute configuration of its carbonyl α-carbon are indicated. The absolute configuration was assigned by comparison with data in the literature. For the determination method, see Experimental Section. [d] $(C_6F_5)_2BOH$ was used in place of **19**.

Table 5. Enantioselective Diels−Alder Reaction Catalyzed by (*R*)-BLA **4a**[a]

dienophile	diene[b]	yield (%)[c] [exo:endo][d]	ee (%)[e] [config][e] exo	ee (%)[e] [config][e] endo
CH_2═CHCHO	CP	87 [23:77]	87	73 [*R*]
(*E*)-MeCH═CHCHO	CP	83 [58:42]	83	47 [*R*]

[a] The reactions were conducted in dichloromethane using aldehyde (1 equiv, 0.25 M) and cyclopentadiene (4 equiv) in the presence of **4a** at −78 °C for 14 h. [b] CP, cyclopentadiene. [c] Isolated yield for the exo/endo mixture. [d] Diastereoselectivity was determined by ^{1}H NMR analysis or GC analysis of Diels−Alder reaction. [e] The absolute configuration of the carbonyl α-carbon in Diels−Alder adducts is indicated. The absolute configurations were assigned by comparison with data in the literatures. For determination methods, see Experimental Section.

to ambient temperature, and filtered through a Celite pad; the filtrate was diluted with saturated NH_4Cl (aq) and extracted twice with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel using hexanes−ethyl acetate (10:1 to 5:1) as eluent to give 1.16 g (99%) of (*R*)-3,3′-di(2-methoxyphenyl)-2,2′-di(methoxymethoxy)-1,1′-binaphthyl as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.39 (s, 6H), 3.80 (s, 6H), 4.41 (d, J = 5.6 Hz, 2H), 4.46 (d, J = 5.6 Hz, 2H), 6.99 (dd, J = 0.8, 8.6 Hz, 2H), 7.07 (dd, J = 1.0, 7.4 Hz, 2H), 7.28−7.44 (m, 8H), 7.47 (dd, J = 1.8, 7.4 Hz, 2H), 7.82−7.88 (m, 2H), 7.88 (s, 2H).

To a solution of (*R*)-3,3′-di(2-methoxyphenyl)-2,2′-di(methoxymethoxy)-1,1′-binaphthyl (1.16 g, 1.98 mmol) in THF (20 mL) was added 3 N HCl (20 mL) at room temperature. After being stirred for 13 h at 50 °C, the mixture was cooled to room temperature, extracted with ether twice, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel using hexanes−ethyl acetate (4:1 to 2:1) as eluent to give 987 mg (>99%) of (*R*)-3,3′-di(2-methoxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.82 (s, 6H), 5.76 (s, 2H), 7.03 (d, J = 8.4 Hz, 2H), 7.12 (dt, J = 1.0, 7.4 Hz, 2H), 7.24−7.46 (m, 8H), 7.52 (dd, J = 1.8, 7.6 Hz, 2H), 7.85−7.92 (m, 2H), 7.93 (s, 2H).

To a solution of (*R*)-3,3′-di(2-methoxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (987 mg, 1.98 mmol) in dichloromethane (10 mL) was added dropwise boron tribromide (759 μL, 8 mmol) at −78 °C. The reaction mixture was allowed to warm to 0 °C. After being stirred for 30 min, the solution was quenched with ice−water, extracted with ether twice, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel using hexanes−ethyl acetate (3:1 to 2:1) as eluent to give 922 mg (99%) of (*R*)-**5a** as a white solid: mp 145 °C; $[\alpha]^{23}_D$ = −104.4 (*c* 1.00, $CHCl_3$); HPLC analysis (Daicel OD, hexane−*i*-PrOH = 1:1, flow rate = 0.3 mL/min) for tetraacetate of (*R*)-**5a**, t_R = 26.6 min [t_R = 23.3 min for tetraacetate of (*S*)-**5a**]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.05 (br, 2H), 6.09 (br, 2H), 6.82 (t, J = 7.6 Hz, 2H), 6.92 (dt, J = 1.2, 7.2 Hz, 2H), 7.14−7.60 (m, 10H), 7.64−7.69 (m, 2H), 7.78 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 114.34, 116.98, 121.37, 124.52, 124.70, 125.39, 127.42, 127.90, 128.60, 129.81, 129.88, 131.76, 132.52, 133.69, 150.07, 153.21; HRMS (FAB) *m*/*z* calcd for [$C_{32}H_{22}O_4$] 470.5234, found 470.5248.

Alternative Method. Coupling reaction of (*R*)-3,3′-dibromo-2,2′-dimethoxy-1,1′-binaphthyl (1 equiv) and 2-methoxyphenylboronic acid (2.5 equiv) in 6:1 DME−H_2O solution in the presence of palladium(II) acetate (5 mol %), tris-*o*-tolylphosphine (10 mol %), and barium hydroxide (2.5 equiv) at 80 °C for 2 h resulted in formation of (*R*)-3,3′-di(2-methoxyphenyl)-2,2′-dimethoxy-1,1′-binaphthyl (97%), which was treated with 4 equiv of boron tribromide in dichloromethane at −78 °C for 0.5 h and purified by column chromatography on silica gel to give (*R*)-**5a** (98%).

(*R*)-3,3′-Di(2-hydroxy-3-phenylphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (5b). Tetraol **5b** was synthesized from (*R*)-3,3′-dibromo-2,2′-di(methoxymethoxy)-1,1′-binaphthyl and 2-methoxy-3-phenylphenylboronic acid in 94% over yield by essentially the same procedure as above: $[\alpha]^{30.0}_D$ = +4.4 (*c* = 0.8, $CHCl_3$); mp 113−115 °C; TLC (hexanes−EtOAc, 4:1), R_f = 0.26; IR (KBr) 3445, 1622, 1601, 1498, 1427, 1321, 1225, 1134, 760, 748, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.70−6.30 (br, 4H), 7.12−7.55 (m, 22H), 7.92 (d, J = 7.8 Hz, 2H), 8.06 (s, 2H); ^{13}C NMR (75 Mz, $CDCl_3$) δ 113.80, 121.30, 124.42, 124.46, 125.46, 127.40, 127.60, 128.42, 128.73, 129.34, 129.73, 130.72, 131.24, 132.43, 133.26, 137.42, 149.67, 150.01; HRMS (EI) *m*/*z* calcd for [$C_{44}H_{30}O_4$] 622.7186, found 622.7181.

(*R*)-3-(2-Benzyloxyphenyl)-3′-(2-hydroxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (16): $[\alpha]^{27.7}_D$ = +37.6 (*c* = 0.5, $CHCl_3$); mp 115−117 °C; TLC (hexanes−EtOAc, 2:1), R_f = 0.33; IR (KBr) 3517, 3431, 1622, 1489, 1452, 1423, 1383, 1360, 1261, 1149, 1130, 897, 852, 748, 696 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.07 (d, J = 11.6 Hz, 1H), 5.08 (d, J = 11.6 Hz, 1H), 5.60 (s, 1H), 6.03 (s, 1H), 6.29 (s, 1H), 7.06−7.54 (m, 18H), 7.55 (dd, J = 1.6, 7.4 Hz, 1H), 7.92 (d, J = 8.2 Hz, 2H), 8.01 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 71.25, 112.95, 113.34, 115.23, 117.82, 121.36, 122.38, 124.43, 124.51, 124.66, 124.95, 126.13, 126.97, 127.26, 127.34, 127.41, 127.54, 128.28, 128.57, 128.81, 129.17, 129.61, 129.74, 129.82, 130.14, 131.85, 132.35, 132.41, 132.70, 133.43, 133.67, 136.18, 148.84, 151.14, 154.20, 155.95; HRMS (EI) *m*/*z* calcd for [$C_{39}H_{28}O_4$] 560.6478, found 560.6486.

(*R*)-3-(2-Hydroxy-3-phenylphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (18a). To a mixture of (*R*)-3-bromo-2,2′-di(methoxymethoxy)-1,1-binaphthyl (2.90 g, 6.4 mmol), 2-methoxy-3-phenylphenylboronic acid (2.92 g, 12.8 mmol), and barium hydroxide octahydrate (4.04 g, 12.8 mmol) in DME−H_2O (6:1, 56 mL) under argon was added $Pd(PPh_3)_4$ (148 mg, 0.13 mmol), and then the mixture was degassed three times and charged with argon.[6] The mixture was warmed to 80 °C and stirred for 12 h. The resulting mixture was cooled to ambient temperature, filtered through a Celite pad, and the filtrate was diluted with saturated NH_4Cl (aq), extracted with ether twice, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel using hexanes−ethyl acetate−dichloromethane (10:1:1) as eluent to give 3.49 g (98%) of (*R*)-3-(2-methoxy-3-phenylphenyl)-2,2′-di(methoxymethoxy)-1,1-binaphthyl as a white solid: $[\alpha]^{25}_D$ = +115.5 (*c* = 1.0, $CHCl_3$); TLC (hexanes−EtOAc, 4:1), R_f = 0.37; IR ($CHCl_3$) 3011, 1593, 1472, 1460, 1240, 1200, 1150, 1073, 1036, 972, 924, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.22 (s, 3H), 3.31 (s, 3H), 4.38 (d, J = 5.9 Hz, 1H), 4.49 (d, J = 5.9 Hz, 1H), 5.06 (d, J = 6.9 Hz, 1H), 5.18 (d, J = 6.9 Hz, 1H), 7.22−7.65 (m, 15H,), 7.86 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 9.3 Hz, 1H), 8.01 (s, 1H). Anal. Calcd for $C_{37}H_{32}O_5$: C, 79.84; H, 5.79. Found: C, 79.80; H, 5.88.

A solution of (*R*)-3-(2-methoxy-3-phenylphenyl)-2,2′-di(methoxymethoxy)-1,1-binaphthyl (3.28 g, 5.9 mmol) in 4 *M* HCl−THF (1:1, 40 mL) was refluxed for 5 h, and cooled to ambient temperature. After being diluted with H_2O, the mixture was extracted with ether twice. The combined extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel using hexanes−ethyl acetate−dichloromethane (10:1:1∼7:1:1) as eluent to give 2.63 g (95%) of (*R*)-3-(2-methoxy-3-phenylphenyl)-2,2′-dihydroxy-1,1-binaphthyl as a white solid: $[\alpha]^{25}_D$ = +132.4 (*c* = 0.82, $CHCl_3$); TLC (hexanes−EtOAc, 4:1) R_f = 0.25; IR ($CHCl_3$) 3260, 1622, 1597, 1460, 1412, 1177, 1146, 1132, 1003 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.31 (s, 3H), 7.18−7.60 (m, 15H), 7.89 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 9.1 Hz, 1H), 8.09 (s, 1H). Anal. Calcd for $C_{13}H_{14}O_3$: C, 84.59; H, 5.16. Found: C, 84.62; H, 5.34.

To a solution of (*R*)-3-(2-methoxy-3-phenylphenyl)-2,2′-dihydroxy-1,1-binaphthyl (2.57 g, 5.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C under argon was added BBr_3 (1.56 mL, 16.5 mmol) slowly; the mixture was stirred at same temperature for 1 h. After ice-cold H_2O was added to the reaction mixture to quench an excess of BBr_3, the mixture was extracted with CH_2Cl_2 twice. The combined extracts were washed with saturated $NaHCO_3$ (aq), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel using hexanes−ethyl acetate−dichloromethane (7:1:1) as eluent to give 2.30 g (93%) of (*R*)-**18a** as a white solid: $[\alpha]^{23.5}_D$ = +121.6 (*c* = 1.25, $CHCl_3$); mp 96−97 °C; TLC (hexanes−EtOAc, 4:1), R_f = 0.29; IR ($CHCl_3$) 3400, 1622, 1599, 1501, 1431, 1383, 1202, 1181, 1144 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15−7.24 (m, 3H), 7.27−7.57 (m, 12 H), 7.89 (d, J = 7.5 Hz, 1H), 7.93−7.96 (m, 1H), 7.98 (d, J = 8.8 Hz, 1H), 8.09 (s, 1H); HRMS (EI) *m*/*z* calcd for [$C_{32}H_{22}O_3$] 454.1569, found 454.1561.

The other ligands synthesized by essentially the same procedure were the following.

(*R*)-3-(2-Hydroxy-3-methylphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (18b). $[\alpha]^{28.0}_D$ = +110 (*c* = 0.6, $CHCl_3$); mp 110−112 °C; TLC (hexanes−EtOAc, 4:1), R_f = 0.30; IR (KBr) 3410, 1620, 1597, 1446, 1431, 1265, 1201, 1142, 960, 746 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 5.12 (br, 1H), 5.57 (br, 1H), 6.00 (br, 1H), 7.01 (t, J = 7.4 Hz, 1H), 7.18−7.27 (m, 3H), 7.30−7.47 (m, 7H), 7.92 (t, J = 8.0 Hz, 2H), 8.00 (d, J = 9.1 Hz, 1H), 8.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.40, 110.91, 112.54, 117.84, 120.97, 124.05, 124.30, 124.75, 126.45, 127.08, 127.58, 127.68, 128.47, 129.11, 129.39, 129.62, 131.20, 131.50, 132.92, 133.26, 149.39, 151.74, 152.64; HRMS (EI) *m*/*z* calcd for [$C_{27}H_{20}O_3$] 392.1413, found 392.1415.

(*R*)-3-(2-Hydroxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (18c). $[\alpha]^{30.0}_D = +92.0$ ($c = 0.6$, $CHCl_3$); mp 97−100 °C; TLC (hexanes−EtOAc, 2:1), $R_f = 0.21$; IR (KBr) 3389, 1620, 1597, 1500, 1431, 1383, 1350, 1265, 1209, 1142, 848, 817, 749, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15−7.24 (m, 3H), 7.27−7.57 (m, 12 H), 7.89 (d, $J = 7.5$ Hz, 1H), 7.93−7.96 (m, 1H), 7.98 (d, $J = 8.8$ Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.06, 112.75, 117.52, 117.99, 121.43, 124.03, 124.09, 124.31, 124.69, 125.35, 127.03, 127.51, 127.61, 128.40, 128.47, 129.38, 129.64, 129.80, 131.44, 131.56, 132.82, 133.04, 133.32, 149.32, 152.64, 153.38; HRMS (EI) *m*/*z* calcd for $[C_{26}H_{18}O_3]$ 378.1256, found 378.1259.

(*R*)-3-(2-Hydroxyphenyl)-3′-phenyl-2,2′-dihydroxy-1,1′-binaphthyl (18d). $[\alpha]^{30.2}_D = +62.7$ ($c = 0.6$, $CHCl_3$); mp 125−128 °C; TLC (hexanes−EtOAc, 4:1), $R_f = 0.18$; IR (KBr) 3410, 1628, 1602, 1508, 1489, 1425, 1360, 1239, 1200, 1128, 897, 748, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15−7.24 (m, 3H), 7.27−7.57 (m, 12 H), 7.89 (d, $J = 7.5$ Hz, 1H), 7.93−7.96 (m, 1H), 7.98 (d, $J = 8.8$ Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 112.22, 113.49, 117.26, 121.27, 124.13, 124.29, 124.39, 124.49, 125.20, 127.02, 127.33, 127.40, 127.82, 128.39, 128.56, 129. 31, 129.52, 129.68, 130.72, 131.35, 131.49, 132.56, 132.94, 133.10, 137.20, 149.29, 150.06, 153.25; HRMS (EI) *m*/*z* calcd for $[C_{32}H_{22}O_3]$ 454.1570, found 474.1567.

(*R*)-3-(2-Hydroxy-3,5-diphenylphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (20a). $[\alpha]^{30.0}_D = +93.6$ ($c = 0.6$, $CHCl_3$); mp 153−155 °C; TLC (hexanes−EtOAc, 4:1), $R_f = 0.18$; IR (KBr) 3410, 1697, 1618, 1597, 1499, 1464, 1435, 1381, 1146, 889, 818, 750, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.14 (s, 1H), 5.69 (s, 1H), 6.02 (s, 1H), 7.19−7.52 (m, 13H), 7.58−7.69 (m, 5H), 7.75 (d, $J = 2.4$ Hz, 1H), 7.88−8.01 (m, 3H), 8.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.43, 112.74, 117.79, 123.94, 124.18, 124.37, 124.67, 125.98, 126.88, 126.99, 127.38, 127.45, 127.65, 127.75, 128.39, 128.48, 128.80, 129.42, 129.55, 129.90, 130.24, 131.29, 132.81, 133.21, 133.35, 134.44, 137.50, 140.37, 149.71, 149.89, 152.53; HRMS (EI) *m*/*z* calcd for $[C_{38}H_{30}O_3]$ 534.2196, found 534.2194.

(*R*)-3-Mesityl-2,2′-dihydroxy-1,1′-binaphthyl (20b). $[\alpha]^{30.0}_D = +109.0$ ($c = 0.5$, $CHCl_3$); mp 110 °C; TLC (hexanes−EtOAc, 4:1), $R_f = 0.30$; IR (KBr) 3496, 1620, 1597, 1518, 1487, 1383, 1259, 1181, 821, 750, 684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.15 (s, 3H), 2.37 (s, 3H), 5.00 (s, 1H), 5.08 (s, 1H), 7.80 (s, 2H), 7.19−7.45 (m, 7H), 7.80 (s, 1H), 7.90 (d, $J = 8.0$ Hz, 2H), 7.98 (d, $J = 8.9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.48, 20.59, 21.14, 111.39, 112.44, 117.60, 123.72, 124.11, 124.22, 124.34, 127.11, 127.16, 128.26, 128.37, 128.53, 129.36, 129.46, 129.55, 130.86, 131.24, 132.53, 133.22, 133.39, 136.97, 137.14, 137.88, 150.51, 152.10; HRMS (EI) *m*/*z* calcd for $[C_{29}H_{24}O_2]$ 404.1777, found 404.1782.

(*R*)-3-Phenyl-2,2′-dihydroxy-1,1′-binaphthyl (20c). $[\alpha]^{30.5}_D = +132.0$ ($c = 1.18$, $CHCl_3$); mp 152−155 °C; TLC (hexanes−EtOAc, 4:1), $R_f = 0.22$; IR (KBr) 3474, 1620, 1597, 1504, 1429, 1339, 1271, 1242, 1184, 1130, 964, 814, 752, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.11 (s, 1H), 5.28 (s, 1H), 7.15 (d, $J = 8.4$ Hz, 1 H), 7.23 (d, $J = 8.5$ Hz, 1H), 7.28−7.58 (m, 8H, ArH), 7.70−7.76 (m, 2H), 7.91 (t, $J = 7.5$ Hz, 2 H), 7.99 (d, $J = 8.8$ Hz, 1H), 8.03 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.41, 111.71, 117.72, 123.97, 124.16, 124.27, 124.37, 127.40, 127.78, 128.39, 128.47, 129.43, 129.58, 130.66, 131.33, 131.47, 132.91, 133.38, 137.37, 150.23, 152.62; HRMS (EI) *m*/*z* calcd for $[C_{26}H_{18}O_2]$ 362.1307, found 362.1311.

(*R*)-3,3′-Diphenyl-2,2′-dihydroxy-1,1′-binaphthyl (20d). Physical properties were identical with those reported.[30]

Preparation of (*R*)-BLA 1a and the Representative Procedure for Enantioselective Diels−Alder Reaction. A dry 25-mL round-bottom flask fitted with a stirbar and a 10-mL pressure-equalized addition funnel (containing a cotton plug and ca. 4 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with (*R*)-**5a** (23.5 mg, 0.05 mmol), trimethyl borate (0.5 mL, 0.1 *M* solution in dichloromethane, 0.05 mmol), and dichloromethane (3 mL). An argon atmosphere was secured and the solution was brought to reflux (bath temperature 50∼60 °C). After 2 h the reaction mixture was cooled to 25 °C and the addition funnel and condenser were quickly removed and replaced with a septum. To the white precipitate in dichloromethane was added dry THF (50 mL) at 25 °C and after 2 h the precipitate was completely dissolved. After a colorless solution of the catalyst (*R*)-**1a** was cooled to −78 °C, α-bromoacrolein (80.8 μL, 1.0 mmol) and cyclopentadiene (332 μL, 4.0 mmol) were added dropwise. After 4 h, 50 μL of H_2O was added and the mixture was warmed to 25 °C, dried over $MgSO_4$, filtrated, and purified by eluting with hexane/ethyl acetate (10:1) to afford 201 mg of Diels−Alder adduct (1*S*,2*S*,4*S*)-bromoaldehyde **6** as a white solid (1.0 mmol, >99% yield, exo:endo = >99:1, >99% ee), and quantitative recovery of pure (*R*)-**5a**.

Preparation of (*R*)-BLA 1b. A dry 25-mL round-bottom flask fitted with a stirbar and a 10-mL pressure-equalized addition funnel (containing a cotton plug and ca. 4 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with (*R*)-**5b** (62.3 mg, 0.1 mmol), trimethyl borate (1.0 mL, 0.1 *M* solution in dichloromethane, 0.10 mmol), THF (70 μL), and benzene (3 mL). An argon atmosphere was secured and the solution was stirred at 45 °C for 1 h and then brought to reflux (bath temperature 100 °C). After 3 h the reaction mixture was cooled to 25 °C and the addition funnel and condenser were quickly removed and replaced with a septum. The solvents were pumped off, and then dichloromethane (5 mL) was added to dissolve (*R*)-**1b**. A colorless solution of (*R*)-**1b** was immediately used for the Diels−Alder reaction.

Preparation of (*R*)-BLA 2a and the Representative Procedure of Diels−Alder Reaction. Method A. A mixture of the chiral ligand **18a** (27.3 mg, 0.06 mmol) and a solution of monomeric 3,5-bis(trifluoromethyl)benzeneboronic acid **17** (1.16 mL, 0.05 mmol, 0.043 *M*) in CH_2Cl_2−THF−H_2O (20:3:0.054) was stirred at ambient temperature for 2 h. The resulting colorless solution was transferred into a Schlenk tube containing anhydrous dichloromethane and powdered MS 4A [250 mg, activated by heating at 200 °C under vacuum (ca. 3 Torr) for 12 h], and the mixture was stirred at ambient temperature for another 12 h. Then the solvents were evaporated and the resulting solid was heated to 100 °C (oil bath) for 2 h under vacuum (ca. 3 Torr) to dry catalyst. After cooling to ambient temperature, the flask was purged with argon and then charged with dichloromethane (2 mL, distilled from CaH_2). The mixture was cooled to −78 °C, dienophile (1 mmol) was added dropwise, and 1 min later freshly distilled diene (4 mmol) was slowly added along the wall of the flask. After the reaction mixture was stirred under the conditions indicated in Table 2, the reaction was quenched with pyridine (20 mL, 0.25 mmol), warmed to ambient temperature, and filtered to remove molecular sieves. The filtrate was washed with ether, dried ($MgSO_4$), and concentrated to afford the crude products. Purification by silica gel chromatography eluting with pentane−ether provided the pure Diels−Alder adduct.

Method B (a simplification of method A). A mixture of chiral triols **18a**−**d** (1.2 equiv), commercial boronic acid **17** (1 equiv),[13] THF (150 mL per 0.05 mmol of **17**, without drying),[15] powdered MS 4A (250 mg per 0.05 mmol of **17**, nonactivated), and dichloromethane was stirred at ambient temperature for 12 h. The active catalyst solution was then prepared by treatment similar to method A.

Preparation of (*R*)-BLA 4a and the Representative Procedure of Diels−Alder Reaction. A solution of the chiral ligand **20a** (15.9 mg, 0.03 mmol) and bis[(3,5-bis(trifluoromethyl)phenyl)]borinic acid **19** (11.4 mg, 0.025 mmol) in CH_2Cl_2 (2 mL) was transferred into a Schlenk tube containing anhydrous dichloromethane and powdered MS 4A [250 mg, activated by heating at 200 °C under vacuum (ca. 3 Torr) for 12 h], and the mixture was stirred at ambient temperature for another 3 h. The mixture was cooled to −78 °C, dienophile (0.5 mmol) was added dropwise, and 1 min later freshly distilled diene (2 mmol) was slowly added along the wall of the flask. After the reaction mixture was stirred under the conditions indicated in Tables 4 and 5, the reaction was quenched with methanol, warmed to ambient temperature, and filtered to remove molecular sieves. The filtrate was washed with ether, dried ($MgSO_4$), and concentrated to afford the crude products. Purification by silica gel chromatography eluting with pentane−ether provided the pure Diels−Alder adduct.

The exo/endo ratios, % ee's, and absolute configurations of the Diels−Alder adducts were determined as follows.

***exo*-2-Bromobicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (6) (Entries 1 and 2 in Table 1 and Entries 1 and 2 in Table 3).**[19] The

(19) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917.

exo/endo ratio was determined by ^{1}H NMR and GC analyses.[19] The ee was determined by reduction with $NaBH_4$, conversion to the Mosher ester, and ^{1}H NMR and HPLC analyses (Daicel AD).[19] The absolute configuration was determined by conversion to the known norbornen-2-one by a literature procedure.[3b]

***exo*-7-Benzyloxymethyl-2-bromobicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (7) (Entry 3 in Table 1 and Entry 3 in Table 3).**[3b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, J = 13.7 Hz, 1H), 2.07 (t, J = 7.0 Hz, 1H), 2.74 (dd, J = 3.8, 13.7 Hz, 1H), 2.91 (br, 1H), 3.22 (br, 1H), 3.36 (dd, J = 1.8, 7.0 Hz, 2H), 4.40 (s, 2H), 6.02 (dd, J = 2.9, 5.6 Hz, 1H), 6.32 (dd, J = 2.9, 5.5 Hz, 1 H), 7.24−7.40 (m, 5H), 9.51 (s, 1H). The exo/endo ratio was determined by ^{1}H NMR analysis of Diels−Alder adducts: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (s, 1H, CHO (endo), 9.51 (s, 1H, CHO (exo)). The ee was determined by reduction with $NaBH_4$, conversion to the ester with (+)-Mosher chloride, and ^{1}H NMR analysis:[3b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (d, J = 12.0 Hz, 1H, C*H* = CH (1*R*,2*S*,4*R*,7*R*)-isomer), 4.66 (d, J = 12.0 Hz, 1H, C*H* = CH (1*S*,2*R*,4*S*,7*S*)-isomer), 4.70 (d, J = 12.0 Hz, 1H, CH=C*H* (1*S*,2*R*,4*S*,7*S*)-isomer), 4.76 (d, J = 12.0 Hz, 1H, CH=C*H* (1*R*,2*S*,4*R*,7*R*)-isomer). The absolute configuration was determined by conversion to the known norbornen-2-one by a literature procedure.[3b]

1-Bromo-4-methyl-3-cyclohexene-1-carboxaldehyde (8) (Entry 4 in Table 1 and Entry 6 in Table 3).[19] The ee was determined by reduction with $NaBH_4$, conversion to benzoyl ester, and HPLC analysis (Daicel AD). Absolute stereochemistry was assigned by analogy with cyclopentadiene.[3b]

***exo*-2-Methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (9) (Entries 5 and 6 in Table 1, Table 2, and Table 4).**[20] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (d, J = 12.0 Hz, 1H), 1.01 (s, 3H), 1.38−1.40 (m, 2H), 2.25 (dd, J = 3.8, 12.0 Hz, 1H), 2.82 (br, 1H), 2.90 (br, 1H), 6.11 (dd, J = 3.0, 5.7 Hz, 1H), 6.30 (dd, J = 3.0, 5.7 Hz, 1H), 9.69 (s, 1H). The exo/endo ratio was determined by ^{1}H NMR analysis of Diels−Alder adducts and GC analysis after conversion to chiral acetals by (−)-(2*R*,4*R*)-2,4-pentanediol:[20] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H, CHO (endo)), 9.69 (s, 1H, CHO (exo)). The ee was determined by GC analysis after conversion to chiral acetals by (−)-(2*R*,4*R*)-2,4-pentanediol:[20] GC (80 °C) t_R = 37.7 and 47.6 min (endo-isomers), 51.5 min ((1*S*,2*R*,4*S*)-isomer), 54.7 min ((1*R*,2*S*,4*R*)-isomer). The absolute configuration was established by comparison of optical rotation values with data in the literature.[21]

***exo*-2-Ethylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (10) (Entry 7 in Table 1).**[26] ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.78 (t, J = 7.4 Hz, 3H), 1.25−1.65 (m, 5H), 2.15 (dd, J = 3.8, 12.0 Hz, 1H), 2.87 (br, 1H), 2.95 (br, 1H), 6.08 (dd, J = 3.2, 5.6 Hz, 1H), 6.27 (dd, J = 3.2, 5.8 Hz, 1H), 9.70 (s, 1H, CHO). The exo/endo ratio was determined by ^{1}H NMR analysis of Diels−Alder adducts: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.42 (s, 1H, CHO (endo)), 9.70 (s, 1H, CHO (exo)). The ee was determined by ^{1}H NMR analysis after conversion to chiral acetals by (2*R*,4*R*)-2,4-pentanediol:[20b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (s, 1H, CHO_2 (minor exo-isomer), 4.85 (s, 1H, CHO_2 (major exo-isomer). The absolute configuration was not established.

***exo*-2,3-Dimethylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (11) (Entry 8 in Table 1 and Entry 10 in Table 3).**[20] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.76 (d, J = 7.4 Hz, 3H), 0.87 (s, 3H), 1.20−1.50 (m, 2H), 2.55 (dq, J = 3.6, 7.4 Hz, 1H), 2.77 (br, 1H), 2.82 (br, 1H), 6.21 (dd, J = 3.2, 5.8 Hz, 1H), 6.31 (dd, J = 3.0, 5.8 Hz, 1H), 9.66 (s, 1H). The exo/endo ratio was determined by ^{1}H NMR analysis: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.66 (s, 1H, CHO (exo)). The ee was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and GC analysis:[20b] GC (90 °C) t_R = 54.4 min (major exo-isomer), 55.9 min (minor exo-isomer). The absolute configuration was not established.

***exo*-Tricyclo[5.2.1.0^{2,6}]dec-8-ene-2-carboxaldehyde (12) (Entry 9 in Table 1).** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00−1.40 (m, 3H), 1.40−1.90 (m, 7H), 2.83−2.94 (m, 1H), 2.86 (s, 1H), 2.97 (s, 1H), 6.22 (dd, J = 3.2, 5.7 Hz, 1H), 6.32 (dd, J = 2.6, 5.7 Hz, 1H), 9.46(s, 0.02H, endo), 9.75 (s, 0.98H, exo). Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.48; H, 8.69. The exo/endo ratio was determined by ^{1}H NMR analysis of Diels−Alder adducts: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.47 (s, 1H, CHO (endo)), 9.75 (s, 1H, CHO (exo)). The ee was determined by GC analysis after conversion to chiral acetals by (−)-(2*R*,4*R*)-2,4-pentanediol:[20b] GC (120 °C) t_R = 27.3 and 34.9 min (endo-isomers), 42.1 min (major exo-isomer), 44.6 min (minor exo-isomer). The absolute configuration was not established.

***endo*-Bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (13) (Entries 10 and 11 in Table 1, Entry 11 in Table 3, and Table 5).**[20] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, J = 8.2 Hz, 1H), 1.40−1.52 (m, 2H), 1.91 (ddd, J = 3.6, 9.1, 12.0 Hz, 1H), 2.90 (m, 1H), 2.99 (br, 1H), 3.25 (br, 1H), 6.00 (dd, J = 2.8, 5.9 Hz, 1H), 6.22 (dd, J = 3.2, 5.9 Hz, 1H), 9.42 (d, J = 3.0 Hz, 1H). The exo/endo ratio was determined by ^{1}H NMR analysis of Diels−Alder adducts and GC analysis after conversion to chiral acetals by (2*R*,4*R*)-2,4-pentanediol:[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (d, J = 3.0 Hz, 1H, CHO (endo)), 9.79 (d, J = 3.0 Hz, 1H, CHO (exo)). The ee was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and GC analysis:[20] GC (90 °C) t_R = 35.4 min ((1*S*,2*S*,4*S*)-isomer), 41.1 min ((1*R*,2*R*,4*R*)-isomer), 42.6 and 44.6 min (exo-isomers). The absolute configuration was established by comparison of optical rotation values with data in the literature.[21]

***endo*-3-Methylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde (14) (Entry 12 in Table 1, Entry 15 in Table 3, and Table 5).**[20] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J = 6.9 Hz, 3H), 1.44−1.51 (m, 1H), 1.55−1.60 (m, 1H), 1.77−1.87 (m, 1H), 2.34 (dd, J = 3.2, 4.3 Hz, 1H), 2.56 (br, 1H), 3.13 (br, 1H), 6.05 (dd, J = 2.8, 5.6 Hz, 1H), 6.29 (dd, J = 3.0, 5.8 Hz, 1H), 9.37 (d, J = 3.2 Hz, 1H). The exo/endo ratio was determined by ^{1}H NMR analysis of Diels−Alder adducts and GC analysis after conversion to chiral acetals by (−)-(2*R*,4*R*)-2,4-pentanediol:[20] ^{1}H NMR ($CDCl_3$) δ 9.37 (d, J = 3.2 Hz, 1H, CHO (endo)), 9.78 (d, J = 3.2 Hz, 1H, CHO (exo)). The ee was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and GC analysis:[20] GC (90 °C) t_R = 22.9 min ((1*S*,2*S*,3*S*,4*R*)-isomer), 25.5 min ((1*R*,2*R*,3*R*,4*S*)-isomer), 27.1 and 28.7 min (exo-isomers). The absolute configuration was established by comparison with authentic material prepared independently.[22]

***endo*-2-Bromobicyclo[2.2.2]oct-5-ene-2-carboxaldehyde (Entry 4 in Table 3).**[23] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30−1.52 (m, 2H), 1.74−1.83 (m, 1H), 1.91 (dd, J = 2.2, 14.5 Hz, 1H), 2.30−2.40 (m, 1H), 2.59 (dt, J = 3.0, 14.5 Hz, 1H), 2.65−2.73 (m, 1H), 2.96−3.02 (m, 1H), 6.07−6.11 (m, 1H), 6.29−6.33 (m, 1H), 8.91 (s, 1H). The exo/endo ratio was determined by ^{1}H NMR analysis:[23] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (s, 1H, CHO (endo), 9.40 (s, 1H, CHO (exo)). The ee was determined from ^{1}H NMR spectrum of Diels−Alder adducts (5 mg) in the presence of the chiral shift reagent Eu(hfc)$_3$ (ca. 30 mg):[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H, CHO (minor endo-isomer)), 9.73 (s, 1H, CHO (major endo-isomer)), 9.84 (s, 1H, CHO (one exo-isomer)), 9.88 (s, 1H, CHO (another exo-isomer)). The absolute configuration was not determined.

1-Bromo-3,4-dimethyl-3-cyclohexene-1-carboxaldehyde (Entry 5 in Table 3).[19] The ee was determined by reduction with $NaBH_4$, conversion to the benzoyl ester, and HPLC analysis (Daicel OD-H, hexane−*i*-PrOH = 1000:1, flow rate = 0.5 mL/min): t_R = 20.3 min (major isomer) and 22.7 min (minor isomer). The absolute configuration was not determined.

***endo*-2-Methylbicyclo[2.2.2]oct-5-ene-2-carboxaldehyde (Entry 7 in Table 3).**[31] The exo/endo ratio was determined by ^{1}H NMR analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H, CHO (endo), 9.56 (s, 1H, CHO (exo)). The ee was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and GC analysis:[20b] GC (80 °C) t_R = 61.6 min (major endo-isomer), 64.4 min (major exo-isomer), 70.4 min (minor endo-isomer), 76.8 min (minor exo-isomer). The absolute configuration was not determined.

1,3,4-Trimethyl-3-cyclohexene-1-carboxaldehyde (Entry 8 in Table 3).[32] The ee was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and ^{1}H NMR analysis:[20b] ^{1}H NMR (300 MHz, $CDCl_3$)

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δ 4.45 (s, 1H, CHO (minor isomer)), 4.47 (s, 1H, CHO (major isomer). The absolute configuration was not determined.

1,4-Dimethyl-3-cyclohexene-1-carboxaldehyde (Entry 9 in Table 3).[32] The ee was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and GC analysis:[20b] GC (80 °C) t_R = 33.8 min (minor isomer), 36.7 min (major isomer). The absolute configuration was not determined.

(1*S*,2*S*,4*S*)-Bicyclo[2.2.2]oct-5-ene-2-carboxaldehyde (Entry 12 in Table 3).[20] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19−1.41 (m, 2H), 1.50−1.78 (m, 4H), 2.56 (m, 2H), 2.65 (m, 1H), 2.96 (m, 1H), 6.12 (t, J = 6.9 Hz, 1H), 6.34 (t, J = 6.9 Hz, 1H), 9.46 (d, J = 1.4 Hz, 1H). The exo/endo ratio was determined by ^{1}H NMR analysis of Diels−Alder adducts:[20] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (d, J = 1.4 Hz, 1H, CHO). The ee was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and GC analysis:[1,20b] GC (80 °C) t_R = 72.9 ((1*S*,2*S*,4*S*)-isomer) min, 75.5 ((1*R*,2*R*,4*R*)-isomer) min. The absolute configuration was established by comparison with authentic material prepared independently.[24]

3,4-Dimethyl-3-cyclohexene-1-carboxaldehyde (Entry 13 in Table 3).[20] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.65 (s, 3H), 1.90−2.06 (m, 4H), 2.09−2.19 (m, 2H), 2.42−2.58 (m, 1H), 9.69 (s, 1H). The ee was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and ^{1}H NMR analysis:[1,20b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (d, J = 6.0 Hz, 1 H, CHO_2 (major isomer)), 4.61 (d, J = 6.0 Hz, CHO_2 (minor isomer)). The absolute configuration was not determined.

4-Methyl-3-cyclohexene-1-carboxaldehyde (Entry 14 in Table 3).[25] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 3H), 1.67−1.78 (m, 1H), 1.93−2.05 (m, 4H), 2.17−2.24 (m, 2H), 2.40−2.50 (m, 1H), 5.40 (br, 1H), 9.70 (s, 1H). The ee was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and ^{1}H NMR and GC analyses:[20b] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.59 (d, J = 6.0 Hz, CHO_2 (minor isomer)), 4.62 (d, J = 6.0 Hz, CHO_2 (major isomer)); GC (80 °C) t_R = 91.9 min (minor isomer), 93.9 min (major isomer). The absolute configuration was not established.

***endo*-3-Ethylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde (Entries 16 and 17 in Table 3).**[26] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3H), 1.41−1.63 (m, 5H), 2.67−2.71 (br, 1H), 3.10−3.14 (br, 1H), 6.28 (dd, J = 3.1, 5.7 Hz, 1H), 9.38 (d, J = 3.3 Hz, 1H). The exo/endo ratio was determined by ^{1}H NMR analysis (500 MHz): δ 9.38 (d, J = 3.3 Hz, 1H, CHO (endo)), 9.79 (d, J = 2.9 Hz, 1H, CHO (exo)). The ee was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and GC analysis (90 °C):[20b] t_R = 29.0 min (major endo-isomer), 36.0 min (minor endo-isomer), 37.8 min (minor exo-isomer), 38.5 min (major exo-isomer). The absolute configuration was not established.

***endo*-3-Phenylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde (Entry 18 in Table 3).**[27] $[\alpha]^{23}_D$ = −107.6 (c = 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59−1.65 (m, 1H), 1.79−1.84 (m, 1H), 2.98 (ddd, J = 2.3, 3.5, 4.9 Hz, 1H), 3.09 (dd, J = 1.6, 4.9 Hz, 1H), 3.14 (br, 1H), 6.17 (dd, J = 2.8, 5.8 Hz, 1H), 3.34 (br, 1H), 6.17 (dd, J = 2.8, 5.8 Hz, 1H), 6.42 (dd, J = 3.3, 5.8 Hz, 1H), 7.13−7.34 (m, 5H), 9.60 (d, J = 2.3 Hz, 1H). The exo/endo ratio was determined by ^{1}H NMR analysis (500 MHz): δ 9.60 (d, J = 2.3 Hz, 1H, CHO (endo)), 9.93 (d, J = 2.3 Hz, 1H, CHO (exo)). The ee was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and GC analysis (180 °C):[20b] t_R = 13.2 min (major endo isomer), 13.9 min (exo isomers), 14.4 min (minor endo isomer). The absolute configuration was not established.

Ethyl (1*R*,2*R*,3*R*,4*S*)-3-Formylbicyclo[2.2.1]hept-5-ene-2-carboxylate (Entry 19 in Table 3). $[\alpha]^{23}_D$ = −77.6 (c = 1.2, $CHCl_3$); TLC (hexanes−EtOAc, 4:1), R_f = 0.33; IR (film) 2982, 1717, 1453, 1393, 1352, 1333, 1262, 1036, 729 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 1.49−1.54 (m, 1H), 1.65−1.70 (m, 1H), 2.70 (dd, J = 1.4, 3.9 Hz, 1H), 3.19 (brs, 1H), 3.33−3.39 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 6.09 (dd, J = 2.5, 5.6 Hz, 1H), 6.27 (dd, J = 3.2, 5.6 Hz, 1H), 9.55 (d, J = 1.1 Hz, 1H, CHO). Anal. Calcd for $C_{13}H_{14}O_3$: C, 68.02; H, 7.26. Found. C, 68.08; H, 7.30. The exo/endo ratio was determined by ^{1}H NMR analysis (300 MHz): δ 9.55 (d, J = 1.1 Hz, 1H, CHO (endo)), 9.85 (s, 1H, CHO (exo)). The absolute configuration of the adduct was determined by conversion of the known diol[28] by reduction with $LiAlH_4$. The ee was determined by analytical GC of the chiral acetal derived from the Diels−Alder adduct and (−)-(2*R*,4*R*)-2,4-pentanediol:[20b] t_R = 15.2 min (endo (3*R*)-isomer), 17.0 min (endo (3*S*)-isomer), 18.6 min (exo isomers).

Phenyl (1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-ene-2-carboxylate (Entry 20 in Table 3). $[\alpha]^{23.0}_D$ = -39.8 (c = 0.97, $CHCl_3$); TLC (hexanes−EtOAc, 4:1), R_f = 0.59; IR (film) 2976, 1759, 1593, 1495, 1335, 1198, 1146, 1107, 1064, 980, 922, 837, 739, 711, 691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J = 8.2 Hz, 1H), 1.40−1.64 (m, 2H), 1.97−2.06 (m, 1H), 2.98 (br, 1H), 3.22 (dt, J = 8.6, 9.2 Hz, 1H), 3.39 (br, 1H), 6.08 (dd, J = 2.9, 5.8 Hz, 1H), 6.27 (dd, J = 3.0, 5.8 Hz, 1H), 7.01−7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.21, 42.55, 43.49, 45.81, 121.41, 125.41, 129.18, 132.03, 138.03, 150.79, 173.04. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found. C, 78.49; H, 6.52. The exo/endo ratio and the ee were determined by reduction with $LiAlH_4$, conversion to the ester with (+)-Mosher chloride, and ^{1}H NMR analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (t, J = 10.1 Hz, 1H, C*H*HO (endo (2*S*)-isomer)), 3.94 (t, J = 10.1 Hz, 1H, C*H*HO (endo (2*R*)-isomer), 4.06 (dd, J = 6.7, 10.7 Hz, 1H, CH*H*O (endo (2*R*)-isomer)), 4.11 (dd, J = 6.7, 10.7 Hz, CH*H*O (endo (2*S*)-isomer), 4.18 (dd, J = 7.0, 11.0 Hz, 1H, C*H*HO (one exo isomer)), 4.23 (dd, J = 9.0, 11.0 Hz, 1H, C*H*HO (another exo isomer)), 4.42 (dd, J = 6.9, 11.0 Hz, 1H, CH*H*O (another exo isomer)), 4.38 (dd, J = 7.0, 11.0 Hz, 1H, CH*H*O (one exo isomer)), 5.87 (dd, J = 2.9, 5.7 Hz, 1H, C(5)H (endo (2*R*)-isomer)), 5.93 (dd, J = 2.8, 5.6 Hz, 1H, C(5)H (endo (2*S*)-isomer)). The absolute configuration was established by comparison with authentic Mosher esters prepared from the corresponding aldehydes independently.

***p*-Fluorophenyl (1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-ene-2-carboxylate (Entry 21 in Table 3).** TLC (hexanes−EtOAc, 4:1), R_f = 0.54; IR (film) 2979, 1758, 1500, 1337, 1271, 1190, 1144, 1107, 1015, 980, 866, 837, 746, 711 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J = 8.5 Hz, 1 H), 1.43−1.62 (m, 2H), 2.01 (ddd, J = 3.6, 9.4, 11.9 Hz, 1H), 2.99 (br, 1H), 3.21 (dt, J = 3.8, 9.4 Hz, 1H), 3.38 (br, 1H), 6.06 (dd, J = 2.7, 5.7 Hz, 1H), 6.26 (dd, J = 3.0, 5,7 Hz, 1H), 6.96−7.09 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.31, 42.63, 43.51, 45.89, 49.72, 115.90 (d, J_{C-F} = 23.4 Hz), 122.86 (d, J_{C-F} = 8.7 Hz), 132.01, 138.25, 146.67, 160.05 (d, J_{C-F} = 246.7 Hz), 173.27. Anal. Calcd for $C_{14}H_{13}O_2F$: C, 72.40; H, 5.64. Found. C, 72.40; H, 5.65. The exo/endo ratio and the ee were determined in the similar manner as above.

(1*R*,2*R*,6*R*)-Bicyclo[4.3.0]non-4-ene-2-carboxaldehyde.[16] $[\alpha]^{25.2}_D$ = −92.3 (c = 1.05, $CHCl_3$); TLC (hexanes−EtOAc, 4:1), R_f = 0.46; IR (film) 2957, 2870, 1725, 1455, 1435, 1111, 1067, 681 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10−1.51 (m, 3H), 1.71−2.02 (m, 5H), 2.19−2.40 (m, 2H), 2.45−2.56 (m, 1H), 5.63 (dq, J = 3.6, 9.9 Hz, 1H), 5.88 (m, 1H), 9.69 (d, J = 3.0 Hz, 1H). The exo/endo ratio was determined by ^{1}H NMR analysis of Diels−Alder adducts and GC analysis after conversion to chiral acetals by (−)-(2*R*,4*R*)-2,4-pentanediol:[16,20b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (d, J = 2.4 Hz, 1H, CHO (exo)), 9.69 (d, J = 3.0 Hz, 1H, CHO (endo)). The ee was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and GC analysis:[16,20b] GC (110 °C) t_R = 44.4 min (1*R*,2*R*,6*R*)-isomer), 45.4 min (one exo isomer), 46.4 min (another exo isomer), 49.9 min ((1*S*,2*S*,4*S*)-isomer). The absolute configuration was determined by conversion to the known alcohol by a literature procedure.[2929−32]

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Acknowledgment. Part of this work was financially supported by a Grant-in-Aid for Scientific Study from the Ministry of Education, Science and Culture of the Japanese Government and grants from the Sumitomo Fundation (92-103-325). H.K. also acknowldeges a JSPS Fellowship for Japanese Junior Scientists.

JA9810282