Brønsted Acid Assisted Chiral Lewis Acid (BLA) Catalyst for Asymmetric Diels–Alder Reaction

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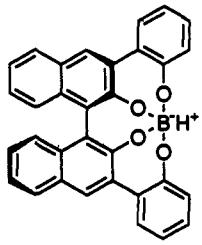
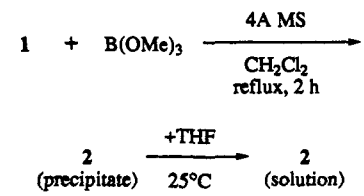
The power of organic synthesis has been expanded in recent years by advances in catalytic asymmetric reactions mediated by chiral Lewis acids.[1] The utility of the chiral boron complexes[2–5] as Lewis acids in enantioselective synthesis has encouraged us to seek new members of this class which achieve selectivity through a double effect of *intramolecular hydrogen binding interaction* and attractive π–π donor–acceptor interaction[2f,3d,e,5d] in the transition state by a hydroxy aromatic group. This paper describes a successful and practical methodology based on this approach, which we believe has wide implications in catalyst design and which deals specifically with catalysis of the Diels–Alder reaction.[6,7]



BLA ((*R*)-2)



Reaction of (*R*)-3,3′-bis(2-hydroxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (**1**)[8] with $B(OMe)_3$ in dichloromethane at reflux with removal of methanol (4-Å molecular sieves in a Soxhlet thimble) gave after 2–3 h a white precipitate, (*R*)-**2**. To the suspension of (*R*)-**2** in dichloromethane was added THF (1 mL/(mmol of **2**)) at 25 °C, and after 2 h the mixture turned to a colorless solution. The ^{11}B NMR spectrum of a solution of **2** in CD_2Cl_2 showed a single broad peak at 10 ppm (downfield from external $BF_3{\cdot}Et_2O$).[9] The ^1H NMR spectrum of **2** after addition of D_2O showed no peak of methanol.

In the presence of 5 mol % of (*R*)-**2**, α-bromoacrolein (1 equiv) and cyclopentadiene (ca. 4 equiv) underwent smooth Diels–Alder addition (–78 °C, 4 h) to give (1*S*,2*S*,4*S*)-2-bromobicyclo[2.2.1]-hept-5-ene-2-carboxaldehyde (**3**) in >99% yield, >99% ee (*S* only), and >99% de (exo only); chiral ligand **1** was efficiently recovered.[11]

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*)-**2**. These results are summarized in Table 1. Enantioselectivities were in the range >99–92% ee, and the major enantiomer in several cases was found to have the predictable absolute configuration. Corey's group[3dg,12] 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, the important intermediate for prostaglandin synthesis, **4**, was synthesized with remarkable ease.[3d]

The absolute stereopreference in the Diels–Alder reaction can be easily understood in terms of the most favorable transition-state assembly **A**, in which an attractive donor–acceptor interaction favors coordination of the dienophile at the face of boron which is cis to the 2-hydroxyphenyl substituent. At this time there is a high s-trans preference for the conformation of α,β-enal.[13,14] 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 binding interaction *via* a Brønsted acid would cause the Lewis acidity of boron and the π-basicity of the phenoxyl moiety to increase, and the transition-state assembly **A** would be

(1) For recent reviews of chiral ligands in asymmetric synthesis, see: (a) Tomioka, K. *Synthesis* **1990**, 541. (b) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

(2) For references on chiral (acyloxy)borane (CAB) complexes using tartaric acid for catalytic asymmetric Diels–Alder reactions, see: (a) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254. (b) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481. (c) Furuta, K.; Kanematsu, A.; Yamamoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231. (d) Gao, Q.; Yamamoto, H. *Org. Synth.*, in press. (e) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917. (f) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412.

(3) For references on CAB complexes using amino acids for catalytic asymmetric Diels–Alder reactions, see: (a) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194. (b) Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197. (c) Sartor, D.; Saffrich, J.; Helmchen, G.; Richards, C. J.; Lambert, H. *Tetrahedron: Asymmetry* **1991**, *2*, 639. (d) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (e) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (f) Seerden, J.-P. G.; Scheeren, H. W. *Tetrahedron Lett.* **1993**, *34*, 2669. (g) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979.

(4) For references on chiral borate complexes using binaphthol for catalytic asymmetric Diels–Alder reactions, see: (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.

(5) For references on asymmetric Diels–Alder catalysts using boron trihalide, see: (a) Bir, G.; Kaufmann, D. *Tetrahedron Lett.* **1987**, *28*, 777. (b) Bir, G.; Kaufmann, D. *J. Organomet. Chem.* **1990**, *390*, 1. (c) Kobayashi, S.; Murakami, M.; Harada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, 1341. (d) Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794.

(6) For our report on helical titanium complexes using (*R*)-3,3′-bis(2-hydroxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl derivatives as chiral ligands for catalytic asymmetric Diels–Alder reactions, see: K. Maruoka, Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938.

(7) As an interesting report on asymmetric Diels–Alder catalysts using vaulted biaryls as chiral ligands, see: Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814.

(8) Preparation of (*R*)-**1**. The 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*-tolyl)phosphine (10 mol %), and barium hydroxide (2.5 equiv) at 80 °C for 2 h resulted in the formation of (*R*)-3,3′-bis(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*)-**1** (98%): mp 145 °C; $[\alpha]^{23}_D$ = –104.4° (*c* 1.00, $CHCl_3$); HPLC analysis (Daicel OD, 1:1 hexane–*i*-PrOH, flow rate = 0.3 mL/min) for tetraacetate of (*R*)-**1**, t_R = 26.6 min (t_R = 23.3 min for tetraacetate of (*S*)-**1**). For the synthesis of sterically hindered biaryls *via* the palladium-catalyzed cross-coupling reaction, see: Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.

(9) The ^{11}B NMR data are consistent with structure **2** as the major species. It is known that conversion of the trigonal ($B(OR)_3$, ^{11}B NMR 18 ± 2 ppm) to the tetrahedral molecule ($B(OR)_4^-$) by nucleophilic addition of the fourth ligand increases the boron shielding by 16 ppm.[10a] In the cases of $B(OPh)_3$, $B(OPh)_3$ including excess PhOH, and $LiB(OPh)_4$, the ^{11}B NMR peaks appear at 16.5,[10b] 14.5,[10c] and 3.0 ppm,[10c] respectively. The fact that boron shieldings increase in the order $B(OPh)_3$ + PhOH) < **2** < $LiB(OPh)_4$ suggests that **2** is a tetrahedral structure close to an ionic ate complex.

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

(11) Representative procedure for asymmetric Diels–Alder reaction catalyzed by (*R*)-**2**. A dry, 25-mL round-bottom flask fitted with a stir bar 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*)-**1** (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 μL) at 25 °C, and after 2 h the precipitate was completely dissolved. After a colorless solution of the catalyst (*R*)-**2** 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*-bromo aldehyde **3** as a white solid (1.0 mmol, >99% yield, exo:endo = >99:1, >99% ee) and quantitative recovery of pure (*R*)-**1**.

(12) Corey, E. J.; Cywin, C. L. *J. Org. Chem.* **1992**, *57*, 7372.

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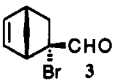
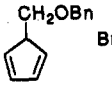
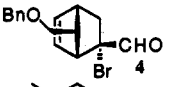
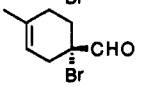
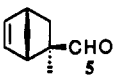
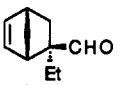
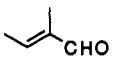
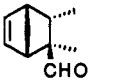
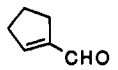
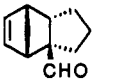
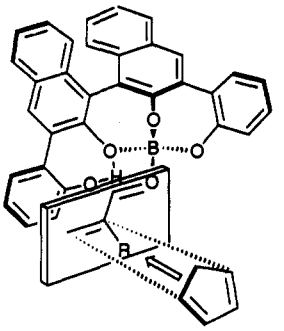
Table 1. Asymmetric Diels–Alder Reaction Catalyzed by (*R*)-**2**[a]

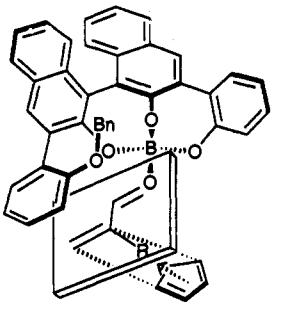
dienophile	diene	product[b]	yield[c] (%)	%ee (confign)	exo/ endo[d]
		 **3**	>99 >99[g]	99[e] (*S*)[f] >99[e,h] (*S*)[f]	>99/1 >99/1
		 **4**	>99	94[i] (*S*)[f]	>99/1
			>99[j]	98[k] (*S*)[f]	
		 **5**	>99 88[g]	99[l] (*R*)[m] 98[l] (*R*)[m]	>99/1 >99/1
			>99	92[i]	97/3
			>99	98[l]	>99/1
			>99	93[i]	98/2

[a] Unless otherwise noted, the reaction was carried out in freshly distilled dichloromethane using 10 mol % of catalyst (*R*)-**2** and 4 equiv of the diene per aldehyde at −78 °C. [b] The structure depicted for the product shows the major diastereomer. [c] Isolated yield by column chromatography for the exo/endo mixture. [d] Diastereoselectivity was determined by ^{1}H NMR analysis or GC analysis of Diels–Alder adducts. [e] Enantioselectivity was determined by reduction with $NaBH_4$, conversion to the Mosher ester, and HPLC analysis (Daicel AD). [f] Reference 3d. [g] Five mole percent of catalyst (*R*)-**2** was used. [h] (*R*)-**3** was not formed in a detectable amount. [i] Enantioselectivity was determined by reduction with $NaBH_4$, conversion to the Mosher MTPA ester, and ^{1}H NMR measurement. [j] The reaction temperature was −40 °C. [k] Enantioselectivity was determined by reduction with $NaBH_4$, conversion to the benzoyl ester, and HPLC analysis (Daicel AD). [l] Enantioselectivity was determined by acetalization with (−)-(2*R*,4*R*)-2,4-pentanediol and GC analysis or ^{1}H NMR analysis. [m] Reference 2b.

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 *si* face of the dienophile (R = Br), leaving the *re* face open to approach by diene. This surmise has been confirmed by experiment.[11] 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 prepared from (*R*)-3-(2-(benzyloxy)phenyl)-2,2′-dihydroxy-3′-(2-hydroxyphenyl)-1,1′-binaphthyl (**6**) and BH_3·THF[15] gave the (2*S*) enantiomer of **5** as major product with 65% enantioexcess (exo:endo = 97:3). With the boron catalysts prepared from BH_3·THF[15] and the monoisopropyl ether and the mono-*tert*-butyldimethylsilyl ether of **1**, the reactions with methacrolein exhibited low enantioselectivities (17% and 29% ee, respectively), but the opposite face selectivity ((2*S*)-**5** as major enantiomer) predominated. The dramatically opposite results using the tetrol **1** and the triols provide strong evidence for transition-state assemblies **A** and **B**, respectively: the former has a fixed nonhelical structure *via* an intramolecular hydrogen binding interaction *via* Brønsted acid, while the latter has a helical structure.[6,16]



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



Helical Transition-State (**B**)

In conclusion, a new concept for the design of an enantioselective Lewis acid has been supported by experiments which demonstrate that it is a very practical and promising methodology for enantioselective synthesis.[17]

(13) Methacrolein and trimethylsilyl enol ether derived from acetophenone underwent aldol reaction under catalysis by 10 mol % of (*R*)-**2** at −78 °C for 15.5 h to form (*R*)-aldol adduct as the major isomer (13%) with 78:22 enantioselectivity. The reaction was stoichiometric since boron–oxygen bonds of (*R*)-**2** 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 if the aldol result is relevant to the Diels–Alder transition state.[2f]

(14) Interestingly, the (*S*)-tryptophan-derived chiral Lewis acid catalyst system developed by Corey et al.[3d,e] 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 (acyloxy)borane catalyst system[2f] as well as in the present system.

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

(16) 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**.

(17) This research was assisted financially by grants from the Sumitomo Foundation (92-103-325).