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 complexes²⁻⁵ 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 $\pi - \pi$ 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}



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

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colorless solution. The ¹¹B NMR spectrum of a solution of 2 in CD_2Cl_2 showed a single broad peak at 10 ppm (downfield from external BF₃·Et₂O).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 (15,25,45)-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 case.^{3d}

The absolute stereopreference in the Diels-Alder reaction can be easily understood in terms of the most favorable transitionstate 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 $\alpha_n\beta$ 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

(9) The ¹¹B NMR data are consistent with structure 2 as the major species. It is known that conversion of the trigonal $(B(OR)_3, {}^{11}B NMR 18 \pm 2 ppm)$ to the tetrahedral molecule $(B(OR)_4)$ by nucleophilic addition of the fourth ligand increases the boron shielding by 16 ppm. {}^{log} In the cases of B(OPh)₃, B(OPh)₃ including excess PhOH, and LiB(OPh)₄, the ¹¹B NMR peaks appear at 16.5, {}^{log} 14.5, {}^{log} and 3.0 ppm, {}^{log} 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.

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(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 μ L) 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 μ L, 1.0 mmol) and cyclopentadiene (332 μ L, 4.0 mmol) were added dropwise. After 4 h, 50 μ L of H₂O was added and the mixture was warmed to 25 °C, dried over MgSO₄, filtrated, and purified by eluting with hexane/ethyl acetate (10:1) to afford 201 mg of Diels-Alder adduct 1*S*,*2S*,*4S*-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.

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⁽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. J. Org. Chem. 1989, 54, 1481. (c) Furuta, K.; Kanematsu, A.; Yamamoto, H. J. Org. Chem. 1989, 56, 161, 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.

⁽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-H₂O 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 thromatography on silica gel to give (R)-1 (98%): mp 145 °C; [α]²³_D = -104.4° (c 1.00, CHCl₃); 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.

Table 1. Asymmetric Diels-Alder Reaction Catalyzed by (R)-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. ' 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. * Enantioselectivity was determined by reduction with NaBH4, conversion to the Mosher ester, and HPLC analysis (Daicel AD). f Reference 3d. 8 Five mole percent of catalyst (R)-2 was used. h(R)-3 was not formed in a detectable amount. ¹ Enantioselectivity was determined by reduction with NaBH₄, conversion to the Mosher MTPA ester, and ¹H NMR measurement. ¹ The reaction temperature was -40 °C. k Enantioselectivity was determined by reduction with NaBH₄, conversion to the benzoyl ester, and HPLC analysis (Daicel AD). ¹ Enantioselectivity was determined by acetalization with -)-(2R,4R)-2,4-pentanediol and GC analysis or ¹H 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 (2S) 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 ((2S)-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.²¹

(14) Interestingly, the (S)-tryptophan-derived chiral Lewis acid catalyst system developed by Corey et al.^{3ds} 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 BH₃-THF and 1 gave (2R)-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.

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