# A Novel Chiral Super-Lewis Acidic Catalyst for Enantioselective Synthesis

Yujiro Hayashi, Jeffrey J. Rohde, and E. J. Corey*

*Department of Chemistry, Harvard University*
*Cambridge, Massachusetts, 02138*

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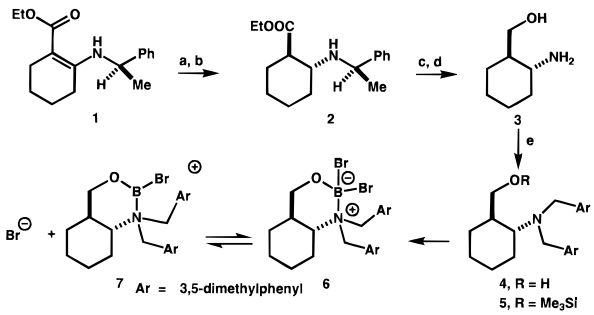
The exceptional power of the Diels−Alder reaction in the synthesis of complex organic molecules has been greatly enhanced by newly developed enantioselective versions, especially chiral Lewis acid catalyzed Diels−Alder reactions using recoverable chiral ligands.[1] Catalytic enantioselective Diels−Alder reactions have amply demonstrated their effectiveness recently in the direct and simplified construction of target molecules such as prostaglandins, gibberellic acid, cassiol, and gracillin B.[2,3] However, there are major limitations of currently available chiral Diels−Alder catalysts with regard to the range of dienes to which they can be applied successfully. In fact, most of the reported catalytic enantioselective Diels−Alder reactions have involved reactive dienes such as cyclopentadiene,[4] and, as far as we are aware, 1,3-butadiene and 1,3-cyclohexadiene have not been successfully used. In order to expand the scope and utility of the catalytic enantioselective Diels−Alder reaction, we set out to develop a new class of *super-reactive* chiral Lewis acid catalysts. This paper reports a very promising discovery which has emerged from these studies.

The most useful chiral ligand developed in this investigation was the chiral amino alcohol **4**, best employed as the corresponding trimethylsilyl ether, **5**. The synthetic route to **4** and **5** followed the path shown herein. The starting material **1**, prepared in 93% yield by heating (*R*)-1-phenylethylamine, 2-carboethoxycyclohexanone, and 1 mol % $Yb(OTf)_3$ in benzene at reflux for 3 h with removal of water, was reduced as previously described[5] to the *cis*-*β*-amino ester which was then isomerized by *tert*-butoxide to the more stable *trans*-*β*-amino ester **2** (oil, obtained in diastereomerically pure form by chromatography on silica). Reduction of the ester function in **2**, hydrogenolysis of the *N*-α-phenylethyl group, and *N*-dialkylation with 3,5-dimethylbenzyl bromide produced the tertiary amino alcohol **4**.

The next objective of our research was the conversion of the trimethylsilyl ether **5** of chiral ligand **4** to the cationic oxazaborinane **7** via the neutral oxazaborinane **6**.[6] A key element of this research was the idea that the cationic oxazaborinane **7** would be a much stronger Lewis acid than any of the previously studied[1,4] neutral chiral Lewis acids. After innumerable experiments on the conversion of **5** to the oxazaborinane system, several key findings emerged: (1) boron tribromide reacts with **5** at −78 °C in dry $CH_2Cl_2$ within 1 h with cleavage of the trimethylsilyl ether and formation of $Me_3SiBr$ (as monitored by $^1H$ NMR at −80 °C); (2) the resulting oxazaborinane is a mixture of **6** (mainly) and the cation **7**; (3) a molar ratio of $BBr_3$ to silyl ether of between 0.9:1 and 1.6:1 can be used to generate the oxazaborinane system **6** ⇄ **7**; (4) $^{11}B$ NMR spectroscopy revealed increased formation of $BBr_4^-$ as the amount of $BBr_3$ reagent was raised from 1 to 1.6 equiv, indicating that $BBr_3$ probably enhances the conversion of **6** to the cationic form **7** (with $BBr_4^-$ counterion); (5) the oxazaborinane system **6** ⇄ **7** is unstable and undergoes gradual decomposition at temperatures above −60 °C with formation of the primary bromide corresponding to amino alcohol **4**; (6) reaction of the oxazaborinane from ligand **5** and 0.9−1.0 equiv of $BBr_3$ with 0.9 equiv of dry $Ag^+B[C_6H_3{-}3,5\text{-}(CF_3)_2]_4^-$ (**8**)[7] in $CH_2Cl_2$ solution affords the most active catalyst system as expected for the conversion of **6** to the tetraarylborate of cation **7** (and AgBr). Two catalyst preparations were used in the experiments described herein; the first, designated as catalyst A, is the mixture of **6** and **7** produced from **5** with 0.9−1 equiv of $BBr_3$, and the second, designated as catalyst B, is the tetraarylborate salt, $7^+B[C_6H_3{-}3,5\text{-}(CF_3)_2]_4^-$.

The application of the oxazaborinane catalytic system **6** ⇄ **7** (10 mol %) to Diels−Alder reactions of cyclopentadiene with a variety of α,*β*-unsaturated aldehydes in $CH_2Cl_2$ has been very successful as shown by the results summarized in Table 1. The effectiveness of the cation **7** as a chiral catalyst is evident from these data; the reactions in $CH_2Cl_2$ are fast even at −94 °C, and the enantioselectivities are very good. In general, with cyclopentadiene, an unusually reactive diene, there is no advantage in using silver tetraarylborate enhancement (catalyst B), and the procedure with catalyst A is simpler.[8]

Less reactive dienes, for example 1,3-cyclohexadiene or isoprene, are unreactive with 2-bromoacrolein using catalyst A at −94 or −78 °C. At higher temperatures the reactions do not proceed well, probably due to decomposition of the catalyst.




Reagents and conditions: (a) $NaBH(OAc)_3$, $CH_3CN$, AcOH, 0 °C, 3 h (99%, 81% de); (b) *tert*-BuONa, *tert*-BuOH, THF, 23 °C, 3 h; purification by silica gel chromatography (60%); (c) $LiBH_4$, THF, reflux, 12 h (91%); (d) $Pd(OH)_2$-on-C, $H_2$ (300 psi), MeOH (99%); (e) 3,5-dimethylbenzyl bromide, $Ba(OH)_2$, EtOH, reflux (50% after recrystallization of **4**, mp128.2-129.5 °C)

(1) For recent reviews, see: (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (b) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497. (c) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (d) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763. (e) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley: New York, 1993.

(2) Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611.

(3) Corey, E. J.; Letavic, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 9616.

(4) For previous studies of catalytic enantioselective Diels−Alder reactions, see: (a) Iwasawa, N.; Sugimori, J.; Kawase, Y.; Narasaka, K. *Chem. Lett.* **1989**, 1947 and references cited therein. (b) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (c) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481. (d) Takemura, H.; Komeshima, N.; Takahashi, I.; Hashimoto, S.-I.; Ikota, N.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 5687. (e) Hashimoto, S.-I.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437. (f) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194. (g) Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197. (h) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. (i) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (j) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (k) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412. (l) Maruoka, K.; Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938. (m) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561. (n) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (o) Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794. (p) Bav, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814. (q) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(5) Cimarelli, C.; Palmieri, G.; Bartoli, G. *Tetrahedron: Asymmetry* **1994**, *5*, 1455.

(6) Parallel experimentation on the synthesis of the oxazaborinanes **6** and **7** directly from the amino alcohol **4** afforded much poorer results than with the trimethylsilyl ether **5**.

(7) The silver salt **8** was prepared by a modification of a previous method (Gorden, J. H.; Mutolo, P. F.; Lobkovsky, E. B.; DiSalvo, F. J. *Inorg. Chem.* **1994**, *33*, 5374) as follows. An ethereal solution of $Na\,B[C_6H_3{-}3,5\text{-}(CF_3)_2]_4$ (Brookhart, M.; Grant, B.; Volpe, A. F., Jr. *Organometallics* **1992**, *11*, 3920) was shaken with 2 equiv of aqueous $AgNO_3$ in a separatory funnel for 5 min, and the layers were separated. Evaporation of the ether layer afforded a quantitative yield of the colorless silver salt which was dissolved in ether to give a clear 0.1 M solution which was stored at −78 °C in a flask wrapped with aluminum foil to exclude light. For the preparation of the catalyst, a measured amount of this ethereal solution was concentrated *in vacuo* to remove ether, dissolved in dry $CH_2Cl_2$, and dried over activated molecular sieves, 4 Å, for 1 h at room temperature (with constant protection from light). The appropriate amount of the dry $CH_2Cl_2$ solution of $Ag^+B[C_6H_3{-}3,5\text{-}(CF_3)_2]_4^-$ (**8**) was then used for reaction with **6** to form catalyst B.

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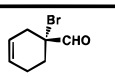
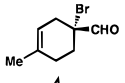
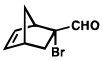
**Table 1.** Enantioselective Diels−Alder Reaction of 1,3-Cyclopentadiene with α,β-Unsaturated Aldehydes in $CH_2Cl_2$ at −94 °C for 2 h Catalyzed by Cationic Lewis Acid **7**

| Dienophile | Cat. | *exo:endo*[a] | Yield[b] (%) | ee (%)[c] (config) | Product |
|---|---|---|---|---|---|
|  | A | 94:6 | 99 | 95 (2*R*)[d] |  |
| | B | 91:9 | 99 | 98 (2*R*)[d] | |
|  | A | 88:12 | 99 | 90 (2*S*)[e] |  |
| | B | 89:11 | 98 | 87 (2*S*)[e] | |
|  | A | >98:2 | 99 | 91 |  |
| | B | >98:2 | 99 | 96 | |
|  | A | >98:2 | 88 | 89 |  |
| | B | >98:2 | 97 | 89 | |
|  | A | >98:2 | 99 | 96 |  |
| | B | >98:2 | 97 | 82 | |

[a] *Exo−endo* ratios were determined by $^1$H-NMR analysis. [b] Yields refer to the isolated amount of *exo−endo* mixture (from silica gel chromatography). [c] Enantioselectivities were determined by reduction to the primary alcohol ($NaBH_4$), conversion to the Mosher ester, and $^1$H-NMR (500 MHz) analysis. [d] Reference 4i. [e] Reference 4c.

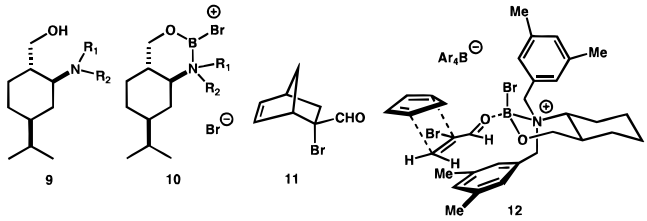
**Table 2.** Diels−Alder Reaction of 1,3-Dienes with 2-Bromoacrolein Catalyzed by $7^+B[C_6H_3-3,5-(CF_3)_2]_4^-$ (10 mol %) in $CH_2Cl_2$ (Catalyst B)

| Diene | Product | Cond. (°C, h) | Yield[a] (%) | ee (%) (config) |
|---|---|---|---|---|
|  |  | -94, 1 | 99 | 94[c] |
|  |  | -94, 1 | 99 | 96[d] (*R*)[f] |
|  |  | -94, 2 | 99 *exo:endo* = 4:96[b] | 93[e] (2*R*)[g] |
|  |  | -94, 0.5 | 99 *exo:endo* = 91:9[b] | 98[e] (2*R*)[f] |

[a] Isolated yield by column chromatography for the *endo*/*exo* mixture. [b] Diastereoselectivity was determined by $^1$H-NMR analysis of Diels−Alder adducts. [c] Enantioselectivity was determined by reduction with $NaBH_4$, conversion to the benzoyl ester, and HPLC analysis (Chiracel AD). [d] Enantioselectivity was determined by reduction with $NaBH_4$, conversion to the benzoyl ester, and HPLC analysis (Chiracel OD). [e] Enantioselectivity was determined by reduction with $NaBH_4$, conversion to Mosher ester, and $^1$H-NMR (500 MHz) analysis. [f] Reference 4i. [g] Configuration was determined by conversion to (−)-(*S*)-bicyclo[2.2.2]oct-5-en-2-one.

However, unreactive dienes do react readily with 2-bromoacrolein using catalyst B, the tetraarylborate of cation **7,** at −94 °C with excellent yields and enantioselectivity as indicated in Table 2. Even 1,3-butadiene, which is considerably less reactive than isoprene and very much less reactive than cyclopentadiene, reacts completely with 2-bromoacrolein within 1 h at −94 °C.[9] This result provides a clear indication of the super-Lewis acidity of the uncoordinated cation **7**.[10] Because of this high reactivity, catalyst **7** and structural variants represent a promising new generation of chiral Lewis acids for enantioselective catalysis. These catalysts could substantially broaden the range of possible enantioselective Diels−Alder additions.

The two 3,5-dimethylbenzyl substituents on the nitrogen of the ligand are important determinants of enantioselectivity. This fact was first discovered using a series of oxazaborinane catalysts based on the related ligand **9**, which was synthesized starting with commercially available perillyl alcohol. The following enantioselectivities were observed in the test reaction of cyclopentadiene and 2-bromoacrolein at −94 °C using the type A catalyst (**10**) (without addition of $Ag^+$), under which conditions the major product was the (2*S*)-adduct **11**: $R_1 = R_2$ = 3,5-dimethylbenzyl, 94% ee; $R_1 = R_2 = CH_2C_6H_5$, 90% ee; $R_1 = CH_3$, $R_2 = CH_2C_6H_5$, 45% ee; $R_1 = CH_3$, $R_2 = C_2H_5$, 53% ee; $R_1 = CH_3$, $R_2 = \beta$-naphthylmethyl, 65% ee.




These results are relevant to the question of the nature of the transition state assembly leading to the predominating Diels−Alder enantiomer. Although it is not possible to decide this issue at present, one possible arrangement which is consistent with presently available information is shown in **12**. In this hypothetical transition state model, one of the N−$CH_2$Ar substituents serves to block attack on the lower face of the *s-trans*-coordinated dienophile while the other screens off another region in space and limits the rotational position of both dienophile and N−$CH_2$Ar moieties.[4i,4j,11] It is interesting in connection with structure **12** that a very similar arrangement of the two N−$CH_2$Ar groups and the cyclohexane ring is observed in the X-ray structure of **4**·HCl.[12]

In conclusion, a new and effective type of very strong chiral Lewis acid has been developed, and its utility has been demonstrated in Diels−Alder reactions with both reactive and unreactive 1,3-dienes. Exploratory studies indicate that this area of research will produce other catalyst structures and other useful enantioselective reactions.

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**Supporting Information Available:** Experimental procedures for the synthesis of **4** along with spectral data on Diels−Alder adducts (21 pages). Ordering information is given on any current masthead page.

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(8) The following procedure for the reaction of cyclopentadiene with 2-bromoacrolein is illustrative. A solution of 56 mg (0.128 mmol) of silyl ether **5** in 1 mL of $CH_2Cl_2$ at −94 °C (hexane−liquid $N_2$ bath) under dry argon was treated with a solution of $BBr_3$ in $CH_2Cl_2$ (0.115 mmol in 250 μL of $CH_2Cl_2$), and after 5 min the temperature was brought to −78 °C by replacing the cooling bath by dry ice−acetone. After 1 h at −78 °C the bath temperature was again changed to −94 °C, and 93 μL (1.15 mmol) of 2-bromoacrolein was added. A cold solution of 355 μL of cyclopentadiene in 0.5 mL of $CH_2Cl_2$ was then added slowly down the wall of the flask, and the reaction mixture was maintained at −94 °C for 1 h and then quenched with 150 μL (1 mmol) of triethylamine. Removal of solvent *in vacuo* and column chromatography on silica gel afforded 229 mg (99%) of the adduct[4i] shown in Table 1 of 95% enantiomeric purity with respect to the *exo*-formyl diastereomer and 40 mg (85%) of recovered amino alcohol **4**.

(9) The following experiment illustrates the procedure using the tetraarylborate of **7** as catalyst (catalyst B). A solution of the oxazaborinane **7** (0.086 mmol) in $CH_2Cl_2$ at −78 °C was prepared as described in ref 8. A freshly prepared dry solution of $Ag^+B[C_6H_3-3,5-(CF_3)_2]_4^-$ (**8**) (0.086 mmol) in 1 mL of $CH_2Cl_2$ was added, and the reaction mixture was stirred for 20 min at −78 °C and then cooled to −94 °C. 2-Bromoacrolein (76 μL, 0.94 mmol) and isoprene (500 μL) were added successively (each dropwise), and the reaction mixture was stirred for 1 h at −94 °C and then quenched by addition of 150 μL of triethylamine. After the mixture warmed to room temperature and the inorganic salts were removed by filtration, the solvent was removed *in vacuo*, and the residue was chromatographed on a column of silica gel to give 191 mg (99%) of the isoprene Diels−Alder adduct shown in Table 2, $[\alpha]^{23}_D$ + 82.2° (*c* 0.8, $CH_2Cl_2$), and also recovered ligand **4** (28.6 mg, 83%).

(10) Other silver salts have also been investigated in place of $Ag^+B[C_6H_3-3,5-(CF_3)_2]_4^-$ (**8**), including $AgOSO_2CF_3$ and $AgSbF_6$, but were less effective.

(11) (a) Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938. (b) Corey, E. J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12089. (c) Corey, E. J. Proceedings 33rd National Organic Chemistry Symposium of the American Chemical Society, 1993; p 30. (d) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. (e) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807.

(12) The ammonium and hydroxyl groups in the hydrochloride of **4** are hydrogen bonded. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.