

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

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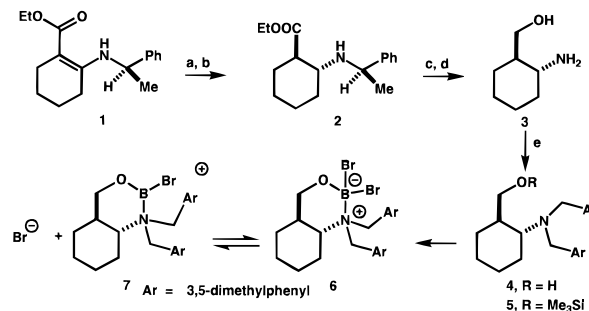
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The exceptional power of the Diels–Alder reaction in the synthesis of complex organic molecules has been greatly enhanced by newly developed enantioselective versions, especially chiral Lewis acid catalyzed Diels–Alder reactions using recoverable chiral ligands.<sup>1</sup> 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.<sup>2,3</sup> 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,<sup>4</sup> 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)<sub>3</sub> in benzene at reflux for 3 h with removal of water, was reduced as previously described<sup>5</sup> to the *cis*- $\beta$ -amino ester which was then isomerized by *tert*-butoxide to the more stable *trans*- $\beta$ -amino ester **2** (oil, obtained in diastereomerically pure form by chromatography on silica). Reduction of the ester function in **2**, hydrogenolysis of the *N*- $\alpha$ -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**.<sup>6</sup> A key element



Reagents and conditions: (a) NaBH(OAc)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, AcOH, 0 °C, 3 h (99%, 81% de); (b) *tert*-BuOH, THF, 23 °C, 3 h; purification by silica gel chromatography (60%); (c) LiBH<sub>4</sub>, THF, reflux, 12 h (91%); (d) Pd(OH)<sub>2</sub>-on-C, H<sub>2</sub> (300 psi), MeOH (99%); (e) 3,5-dimethylbenzyl bromide, Ba(OH)<sub>2</sub>, EtOH, reflux (50% after recrystallization of **4**, mp 128.2–129.5 °C)

of this research was the idea that the cationic oxazaborinane **7** would be a much stronger Lewis acid than any of the previously studied<sup>1,4</sup> 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<sub>2</sub>Cl<sub>2</sub> within 1 h with cleavage of the trimethylsilyl ether and formation of Me<sub>3</sub>SiBr (as monitored by <sup>1</sup>H NMR at –80 °C); (2) the resulting oxazaborinane is a mixture of **6** (mainly) and the cation **7**; (3) a molar ratio of BBr<sub>3</sub> to silyl ether of between 0.9:1 and 1.6:1 can be used to generate the oxazaborinane system **6**  $\rightleftharpoons$  **7**; (4) <sup>11</sup>B NMR spectroscopy revealed increased formation of BBr<sub>4</sub><sup>–</sup> as the amount of BBr<sub>3</sub> reagent was raised from 1 to 1.6 equiv, indicating that BBr<sub>3</sub> probably enhances the conversion of **6** to the cationic form **7** (with BBr<sub>4</sub><sup>–</sup> counterion); (5) the oxazaborinane system **6**  $\rightleftharpoons$  **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<sub>3</sub> with 0.9 equiv of dry Ag<sup>+</sup>[C<sub>6</sub>H<sub>3</sub>–3,5-(CF<sub>3</sub>)<sub>2</sub>]<sub>4</sub><sup>–</sup> (**8**)<sup>7</sup> in CH<sub>2</sub>Cl<sub>2</sub> 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<sub>3</sub>, and the second, designated as catalyst B, is the tetraarylborate salt, **7**<sup>+</sup>[C<sub>6</sub>H<sub>3</sub>–3,5-(CF<sub>3</sub>)<sub>2</sub>]<sub>4</sub><sup>–</sup>.

The application of the oxazaborinane catalytic system **6**  $\rightleftharpoons$  **7** (10 mol %) to Diels–Alder reactions of cyclopentadiene with a variety of  $\alpha,\beta$ -unsaturated aldehydes in CH<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub> 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.<sup>8</sup>

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.

(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<sub>6</sub>H<sub>3</sub>–3,5-(CF<sub>3</sub>)<sub>2</sub>)<sub>4</sub>] (Brookhart, M.; Grant, B.; Volpe, A. F., Jr. *Organometallics* **1992**, *11*, 3920) was shaken with 2 equiv of aqueous AgNO<sub>3</sub> 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<sub>2</sub>Cl<sub>2</sub>, 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<sub>2</sub>Cl<sub>2</sub> solution of Ag<sup>+</sup>[B(C<sub>6</sub>H<sub>3</sub>–3,5-(CF<sub>3</sub>)<sub>2</sub>)<sub>4</sub>]<sup>–</sup> (**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  $\alpha,\beta$ -Unsaturated Aldehydes in  $\text{CH}_2\text{Cl}_2$  at  $-94^\circ\text{C}$  for 2 h Catalyzed by Cationic Lewis Acid **7**

Dienophile	Cat.	<i>exo:endo</i> <sup>a</sup>	Yield <sup>b</sup> (%)	ee (%) <sup>c</sup> (config)	Product
	A	94:6	99	95 (2 <i>R</i> ) <sup>d</sup>	
	B	91:9	99	98 (2 <i>R</i> ) <sup>d</sup>	
	A	88:12	99	90 (2 <i>S</i> ) <sup>e</sup>	
	B	89:11	98	87 (2 <i>S</i> ) <sup>e</sup>	
	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	

<sup>a</sup> *Exo-endo* ratios were determined by  $^1\text{H}$ -NMR analysis. <sup>b</sup> Yields refer to the isolated amount of *exo-endo* mixture (from silica gel chromatography). <sup>c</sup> Enantioselectivities were determined by reduction to the primary alcohol ( $\text{NaBH}_4$ ), conversion to the Mosher ester, and  $^1\text{H}$ -NMR (500 MHz) analysis. <sup>d</sup> Reference 4i. <sup>e</sup> Reference 4c.

**Table 2.** Diels–Alder Reaction of 1,3-Dienes with 2-Bromoacrolein Catalyzed by  $7^+\text{B}[\text{C}_6\text{H}_3-3,5-(\text{CF}_3)_2]_4^-$  (10 mol %) in  $\text{CH}_2\text{Cl}_2$  (Catalyst B)

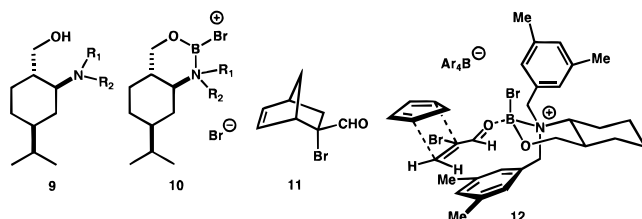
Diene	Product	Cond. ( $^\circ\text{C}$ , h)	Yield <sup>a</sup> (%)	ee (%) (config)
		-94, 1	99	94 <sup>c</sup>
		-94, 1	99	96 <sup>d</sup> (1 <i>R</i> ) <sup>f</sup>
		-94, 2	99 <i>exo:endo</i> = 4:96 <sup>b</sup>	93 <sup>g</sup> (2 <i>R</i> ) <sup>g</sup>
		-94, 0.5	99 <i>exo:endo</i> = 91:9 <sup>b</sup>	98 <sup>g</sup> (2 <i>R</i> ) <sup>f</sup>

<sup>a</sup> Isolated yield by column chromatography for the *endo/exo* mixture. <sup>b</sup> Diastereoselectivity was determined by  $^1\text{H}$ -NMR analysis of Diels–Alder adducts. <sup>c</sup> Enantioselectivity was determined by reduction with  $\text{NaBH}_4$ , conversion to the benzoyl ester, and HPLC analysis (Chiracel AD). <sup>d</sup> Enantioselectivity was determined by reduction with  $\text{NaBH}_4$ , conversion to the benzoyl ester, and HPLC analysis (Chiracel OD). <sup>e</sup> Enantioselectivity was determined by reduction with  $\text{NaBH}_4$ , conversion to Mosher ester, and  $^1\text{H}$ -NMR (500 MHz) analysis. <sup>f</sup> Reference 4i. <sup>g</sup> Configuration was determined by conversion to (–)-(5*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  $-94^\circ\text{C}$  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  $-94^\circ\text{C}$ .<sup>9</sup> This result provides a clear indication of the super-Lewis acidity of the uncoordinated cation **7**.<sup>10</sup> 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.

(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  $\text{CH}_2\text{Cl}_2$  at  $-94^\circ\text{C}$  (hexane–liquid  $\text{N}_2$  bath) under dry argon was treated with a solution of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  (0.115 mmol in 250  $\mu\text{L}$  of  $\text{CH}_2\text{Cl}_2$ ), and after 5 min the temperature was brought to  $-78^\circ\text{C}$  by replacing the cooling bath by dry ice–acetone. After 1 h at  $-78^\circ\text{C}$  the bath temperature was again changed to  $-94^\circ\text{C}$ , and 93  $\mu\text{L}$  (1.15 mmol) of 2-bromoacrolein was added. A cold solution of 355  $\mu\text{L}$  of cyclopentadiene in 0.5 mL of  $\text{CH}_2\text{Cl}_2$  was then added slowly down the wall of the flask, and the reaction mixture was maintained at  $-94^\circ\text{C}$  for 1 h and then quenched with 150  $\mu\text{L}$  (1 mmol) of triethylamine. Removal of solvent *in vacuo* and column chromatography on silica gel afforded 229 mg (99%) of the adduct<sup>4i</sup> shown in Table 1 of 95% enantiomeric purity with respect to the *exo*-formyl diastereomer and 40 mg (85%) of recovered amino alcohol **4**.

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  $-94^\circ\text{C}$  using the type A catalyst (**10**) (without addition of  $\text{Ag}^+$ ), under which conditions the major product was the (2*S*)-adduct **11**:  $\text{R}_1 = \text{R}_2 = 3,5\text{-dimethylbenzyl}$ , 94% ee;  $\text{R}_1 = \text{R}_2 = \text{CH}_2\text{C}_6\text{H}_5$ , 90% ee;  $\text{R}_1 = \text{CH}_3$ ,  $\text{R}_2 = \text{CH}_2\text{C}_6\text{H}_5$ , 45% ee;  $\text{R}_1 = \text{CH}_3$ ,  $\text{R}_2 = \text{C}_2\text{H}_5$ , 53% ee;  $\text{R}_1 = \text{CH}_3$ ,  $\text{R}_2 = \beta\text{-naphthylmethyl}$ , 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  $\text{N}-\text{CH}_2\text{Ar}$  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  $\text{N}-\text{CH}_2\text{Ar}$  moieties.<sup>4i,4j,11</sup> It is interesting in connection with structure **12** that a very similar arrangement of the two  $\text{N}-\text{CH}_2\text{Ar}$  groups and the cyclohexane ring is observed in the X-ray structure of **4**·HCl.<sup>12</sup>

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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(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  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$  was prepared as described in ref 8. A freshly prepared dry solution of  $\text{Ag}^+\text{B}[\text{C}_6\text{H}_3-3,5-(\text{CF}_3)_2]_4^-$  (**8**) (0.086 mmol) in 1 mL of  $\text{CH}_2\text{Cl}_2$  was added, and the reaction mixture was stirred for 20 min at  $-78^\circ\text{C}$  and then cooled to  $-94^\circ\text{C}$ . 2-Bromoacrolein (76  $\mu\text{L}$ , 0.94 mmol) and isoprene (500  $\mu\text{L}$ ) were added successively (each dropwise), and the reaction mixture was stirred for 1 h at  $-94^\circ\text{C}$  and then quenched by addition of 150  $\mu\text{L}$  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,  $[\alpha]_D^{25} + 82.2^\circ$  (c 0.8,  $\text{CH}_2\text{Cl}_2$ ), and also recovered ligand **4** (28.6 mg, 83%).

(10) Other silver salts have also been investigated in place of  $\text{Ag}^+\text{B}[\text{C}_6\text{H}_3-3,5-(\text{CF}_3)_2]_4^-$  (**8**), including  $\text{AgOSO}_2\text{CF}_3$  and  $\text{AgSbF}_6$ , but were less effective.

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(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.