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Boron Tribromide-Assisted Chiral Phosphoric Acid Catalyst for a Highly Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines

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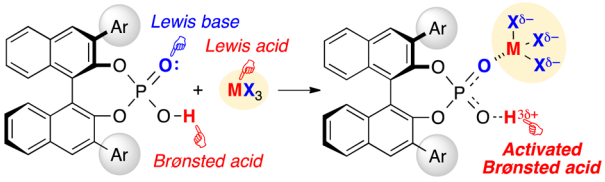
Supporting Information

ABSTRACT: BBr_3–chiral phosphoric acid complexes are highly effective and practical Lewis acid-assisted Brønsted acid (LBA) catalysts for promoting the enantioselective Diels–Alder (DA) reaction of α-substituted acroleins and α-CF_3 acrylate. In particular, the DA reaction of α-substituted acroleins with 1,2-dihydropyridines gave the corresponding optically active isoquinuclidines with high enantioselectivities. Moreover, transformations to the key intermediates of indole alkaloids, catharanthine and allocatharanthine, are demonstrated.

Chiral phosphoric acids are highly useful acid–base cooperative organocatalysts for a variety of asymmetric catalyses.[1] However, their Brønsted acidity is generally not strong enough to activate less-basic aldehydes rather than more-basic aldimines. To overcome this serious issue, stronger Brønsted acid catalysts, such as chiral 1,1′-bi-2-naphthol (BINOL)-derived *N*-sulfonyl phosphoramides,[2a] *N*-phosphinyl phosphoramides,[2b] and disulfonimides,[2c] have been developed. In sharp contrast, we envisioned that the addition of an achiral Lewis acid to the chiral phosphoric acid would be highly promising, since the conjugate acid–base moiety of the phosphoric acid is suitable for the Lewis acid-assisted Brønsted acid (LBA)[3] catalyst system (Scheme 1). As a great advantage

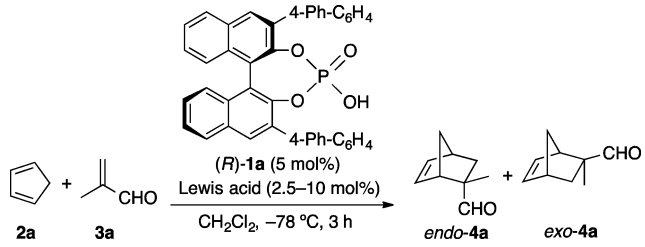
Scheme 1. Achiral Lewis Acid-Assisted Chiral Phosphoric Acid Catalysts as Chiral Acid–Base Cooperative Catalysts



of this LBA system, we can simply use highly practical chiral phosphoric acids without serious synthetic difficulties. In particular, we developed a BBr_3-assisted chiral phosphoric acid *in situ*, which was highly effective for the enantioselective Diels–Alder (DA) reaction of α-substituted acroleins with 1,2-dihydropyridines to afford the synthetically useful optically active isoquinuclidine scaffold.

We initially examined the reaction of methacrolein **3a** with cyclopentadiene **2a** through the use of chiral phosphoric acid (*R*)-**1a** (5 mol%) and an achiral Lewis acid (2.5–10 mol%) in dichloromethane at −78 °C for 3 h (Table 1). The reaction was

Table 1. Optimization of the Reaction Conditions[a]



entry	Lewis acid (mol%)	yield (%)	*endo*:*exo*	ee (%) of *exo*-**4a**
1	–	0	–	–
2[b]	–	51	13:87	−7
3	$B(C_6F_5)_3$ (5)	64	10:90	5
4[c]	$BF_3{\cdot}Et_2O$ (5)	87	3:97	52
5	BCl_3 (5)	88	4:96	62
6	BBr_3 (2.5)	92	3:97	61
7	**BBr_3 (5)**	**99**	**2:98**	**89**
8	BBr_3 (7.5)	78	2:98	85
9	BBr_3 (10)	64	8:92	18
10	BI_3 (5)	98	7:93	37
11[d]	BBr_3 (5)	66	10:90	–

[a]The reaction was carried out with (*R*)-**1a** (5 mol%), Lewis acid (2.5–10 mol%), **2a** (5 equiv), and **3a** (1 equiv) in dichloromethane at −78 °C for 3 h. [b]The reaction was conducted at room temperature for 3 h. [c]Et_2O was removed *in vacuo* during catalyst preparation. [d]The reaction was conducted without (*R*)-**1a**.

slow with the use of (*R*)-**1a** alone at −78 °C or room temperature to afford **4a** with poor enantioselectivity (entries 1 and 2). Through preliminary investigations, we found that boron compounds were highly effective as achiral Lewis acids for (*R*)-**1a** (entries 3–10). In particular, BBr_3 (entry 7) showed higher enantioselectivity than other similar compounds, such as $B(C_6F_5)_3$, $BF_3{\cdot}Et_2O$, BCl_3, and BI_3. The amount of BBr_3 was important, and the use of more or less than 5 mol% of BBr_3 for 5 mol% of (*R*)-**1a** decreased the yield and/or enantioselectivity

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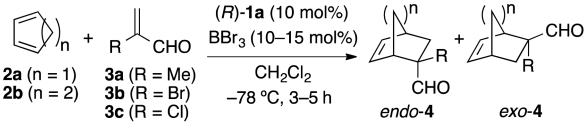
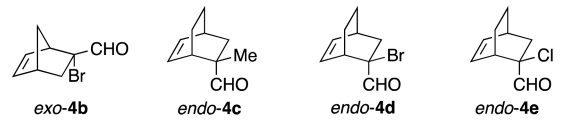
(entries 6–9). The reaction proceeded moderately with the use of 5 mol% of BBr_3 in the absence of (*R*)-**1a** (entry 11). Therefore, this result strongly suggests that the LBA catalyst BBr_3–(*R*)-**1a** *in situ* might show higher catalytic activity than either starting component, (*R*)-**1a** and BBr_3.

With the optimized reaction conditions in hand, we next examined the scope of α-substituted acroleins **3a–c** with **2a** and cyclohexadiene **2b** (Scheme 2). As a result, *exo*-adduct **4b**

Scheme 2. Reactions of α-Substituted Acroleins



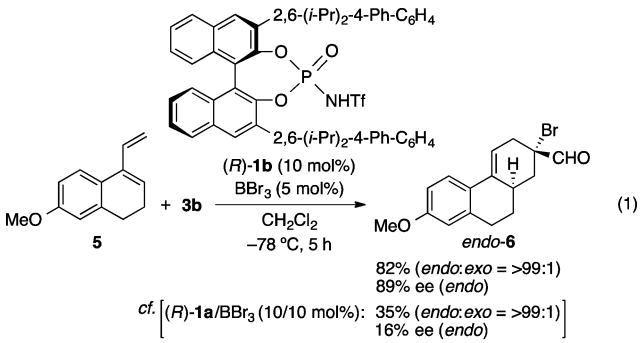
Products **4**, reaction time, yield, and enantioselectivity.

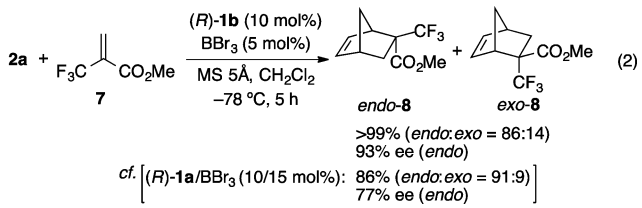


[a]15 mol% of BBr_3 was used. [b]10 mol% of BBr_3 was used.

was obtained with 86% ee as a major product with the use of **2a**, while *endo*-adducts **4c–e** were obtained with 87–94% ee as major products with the use of **2b**, according to the usual substrate-dependent *endo*/*exo* controls.[4] Interestingly, the reactivity of the substrates strongly influences the optimized molar ratio of BBr_3 to (*R*)-**1a**, and a slight excess amount of BBr_3 to (*R*)-**1a** was effective for more-reactive α-haloacroleins **3b** and **3c** in place of less-reactive **3a** to achieve high enantioselectivities for **4b**, **4d**, and **4e**.[5]

In place of **2**, less-reactive acyclic diene **5** was examined (eq 1). Although BBr_3–(*R*)-**1a** showed low catalytic activity (16%

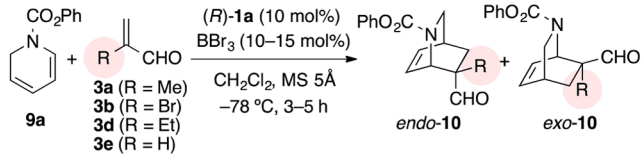




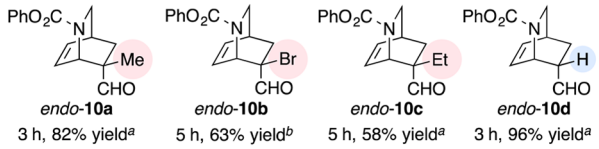
ee) even under the optimized conditions in this case, BBr_3–*N*-sulfonyl phosphoramide (*R*)-**1b** was much more effective than BBr_3–(*R*)-**1a**, and *endo*-**6** was obtained with 89% ee. Moreover, **7** with an electron-withdrawing CF_3 group was examined in place of acroleins (eq 2). BBr_3–(*R*)-**1b** gave better results than BBr_3–(*R*)-**1a**,[6] and the corresponding *endo*-**8** was obtained as a major product with 93% ee. Although only the specialized acrylate **7** was shown at this stage, the enantioselective DA reactions of α-substituted acrylates with chiral Brønsted acid catalysts might be valuable since α-substituted acrylates have not yet been used with any conventional chiral Lewis acid catalysts.[4,7]

We next performed the reaction with 1,2-dihydropyridine **9a**, which can provide synthetically useful optically active isoquinuclidines.[8] The reactions of **9a** and acrolein **3e** proceeded smoothly with the use of BBr_3–(*R*)-**1a** catalyst, and the key compound **10d** for the important anti-influenza drug oseltamivir phosphate (Tamiflu)[9] was obtained in 96% yield with 94% ee (Scheme 3). Rawal previously reported the

Scheme 3. Reactions of 1,2-Dihydropyridines

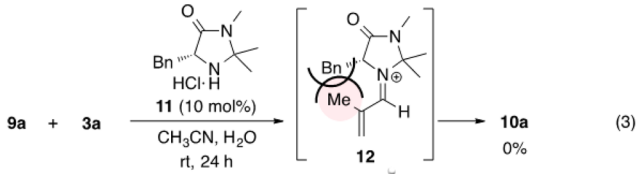


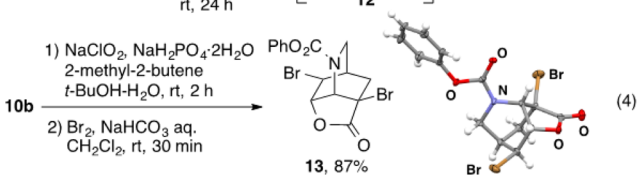
Products **10**, reaction time, yield, and enantioselectivity.



[a]10 mol% of BBr_3 was used. [b]15 mol% of BBr_3 was used.

Lewis acidic chiral salen Cr(III)-catalyzed reaction of **9a** with **3a**, as a sole example using α-substituted acrolein, and **10a** was obtained with 67% ee.[8a] Moreover, the MacMillan catalyst **11**, which was reported to be an excellent chiral secondary amine catalyst for the reaction of **3e** by Fukuyama,[10] could not be used for the reaction of **3a**, probably due to the steric constraints in the iminium intermediate **12** (eq 3). Fortunately,





in our Brønsted acid catalysis, not only **3e** but also α-substituted acroleins **3a**, **3b**, and **3d** could be used successfully, and the corresponding products **10a**, **10b**, and **10c** were obtained with 92–98% ee, respectively (Scheme 3). Moreover, the novel compound **10b** was readily transformed to the γ-lactone **13** in 87% yield, and its stereochemistry was determined by X-ray analysis (eq 4).

To demonstrate the synthetic utility of our catalytic system, we performed a formal total synthesis of (+)-catharanthine,

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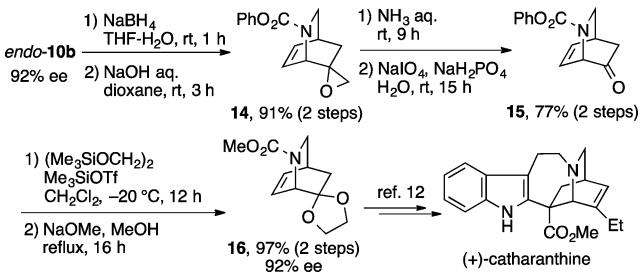
which is an important indole alkaloid that forms vinblastine, which has high antitumor activities (Scheme 4).[11] After DA

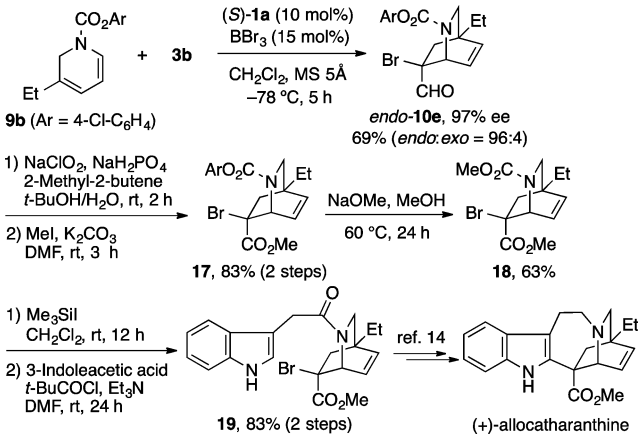
Scheme 4. Formal Total Synthesis of (+)-Catharanthine



product **10b** was reduced to the alcohol with $NaBH_4$, epoxidation under basic conditions gave **14**. Treatment of **14** with aqueous ammonia and subsequent oxidation with sodium periodate gave the ketone **15**. Acetalization of **15** with $(Me_3SiOCH_2)_2/Me_3SiOTf$ and subsequent transesterification provided the desired key compound **16**[12] without a loss of optical purity. These easy high-yield transformations in six steps from **10b** to **16** might be attractive as a concise synthesis of (+)-catharanthine.

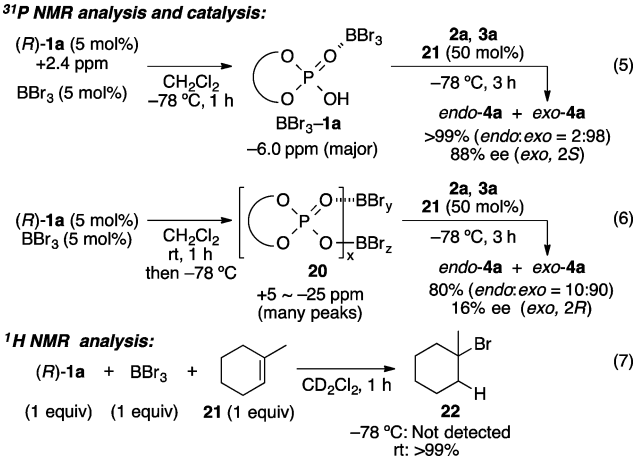
Moreover, we performed a transformation to the key intermediate of (+)-allocatharanthine, which is another component of vinblastine (Scheme 5).[13] Actually, the enantio-

Scheme 5. Formal Total Synthesis of (+)-Allocatharanthine



selective DA reactions of alkyl-substituted 1,2-dihydropyridines are still limited with the use of **3e**.[8f] As a great advantage of our catalytic system, the DA reaction of **9b** with **3b** gave the desired **10e** as a major product with the use of BBr_3–(*S*)-**1a**. Aldehyde **10e** was transformed to ester **17** and subsequent transesterification provided ester **18**. After *N*-decarbomethoxylation of **18**, condensation with 3-indoleacetic acid gave the desired key intermediate **19**.[14]

Finally, we turn our attention to mechanistic aspects. To identify a possible P═O···BBr_3 structure without the generation of HBr,[15] we performed a ^{31}P NMR analysis of a 1:1 molar ratio of (*R*)-**1a** and BBr_3 in dichloromethane (eq 5). As a result, a new signal, indicating BBr_3–(*R*)-**1a**, was observed as a major peak at −6.0 ppm at −78 °C, which was shifted from the original peak of (*R*)-**1a** at 2.4 ppm (eq 5, also see the SI with ^{11}B NMR). In contrast, the catalyst obtained by preparation at room temperature gave many new peaks at +5



to −25 ppm, which might be attributed to boronphosphonate derivatives **20** after the release of HBr (eq 6, also see the SI with ^{11}B NMR). Actually, the release of HBr at room temperature was confirmed by the generation of **22** from 1-methyl-1-cyclohexene **21**[16] as a HBr-scavenger (eq 7, also see the SI). Moreover, the reaction between **2a** and **3a** with the use of **20** and **21** provided **4a** with low enantioselectivity (eq 6). In contrast, upon the addition of **21** to BBr_3–(*R*)-**1a**, which was prepared at −78 °C in advance, the enantioselectivity was essentially the same (eq 5 vs Table 1, entry 7). This result suggests that adventitious HBr, which would induce an uncatalyzed reaction, might not be generated *in situ* at −78 °C. By the LBA strategy for phosphoric acids, which is different from the design of metal phosphates as bifunctional Lewis acid catalysts,[1c,17] powerful Brønsted acid catalysts can be easily obtained *in situ*. (See the SI for ^1H NMR for PO_2H.)

A possible structure of the BBr_3–**1a**–**3b** complex was considered based on theoretical calculations (see the SI for details). In the optimized geometry, the P═O moiety of (*R*)-**1a** coordinates to BBr_3 and the C═O moiety of **3b** coordinates to the proton of phosphoric acid (see the SI). Moreover, two hydrogen bonds for **3b**, such as Br···H–C═O and Br···H–C═C, were observed. These hydrogen bonding interactions show that the base function of the LBA shifts from the original P═O moiety to the terminal Br moiety, and thus the BBr_3–(*R*)-**1a** complex would also act as an acid–base cooperative catalyst.

In summary, we have developed BBr_3-assisted chiral phosphoric acids as highly effective LBA catalysts. In particular, the enantioselective Diels–Alder reactions of α-substituted

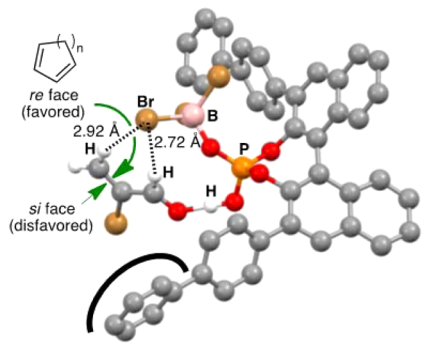


Figure 1. B3LYP/6-31G*-optimized geometry of BBr_3–(*R*)-**1a**–**3b** complex.

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acroleins with 1,2-dihydropyridines proceeded, and synthetically useful optically active intermediates for bioactive indole alkaloids were obtained.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08693.

Experimental procedures and characterization data (PDF)

X-ray crystallographic data for **S1** (CIF)

X-ray crystallographic data for **13** (CIF)

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Notes

The authors declare no competing financial interest.

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