Development of Lewis Acid-Assisted Chiral Phosphoric Acid Catalysts for Enantioselective [4 + 2] and [2 + 2] Cycloadditions

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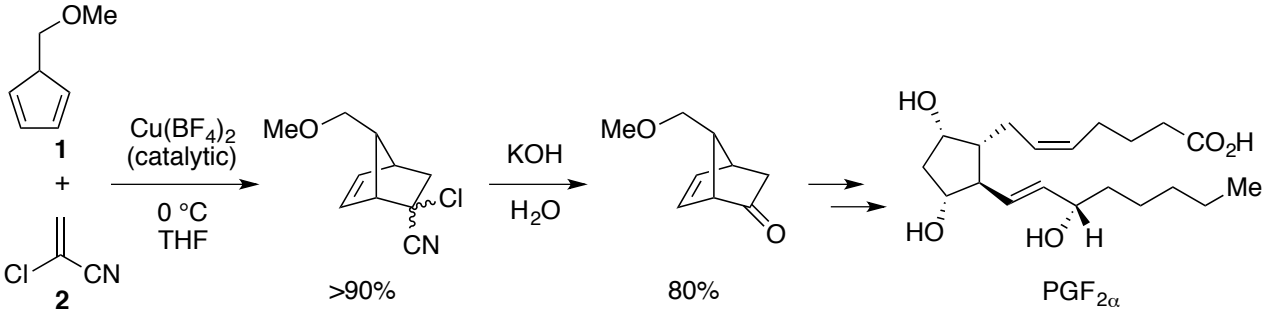
Chapter 1

Introduction and General Summary

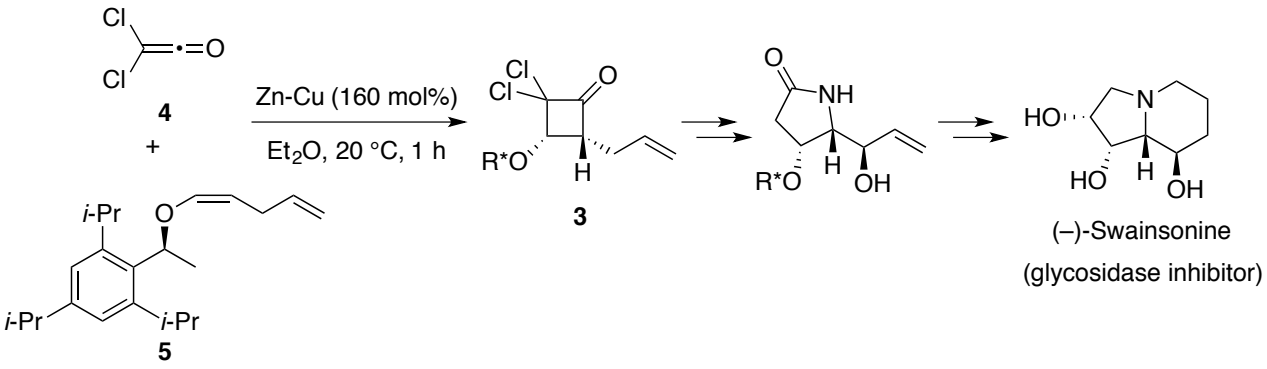
1–1 Introduction

Cycloaddition is a synthetically useful process since it can be used to make two covalent bonds and several chiral centers at the same time. Therefore, cycloaddition has often been used as a key step in total synthesis.[1,2] For example, Corey achieved a total synthesis of prostaglandin ($PGF_{2\alpha}$) by using a Diels–Alder reaction between cyclopentadiene derivative **1** and 2-chloroacrylonitrile **2** catalyzed by Lewis acid (Scheme 1).[3] In addition, Poisson achieved a total synthesis of (–)-swainsonine, which is a glycosidase inhibitor, in which optically pure dichlorocyclobutanone **3** was obtained with high diastereoselectivity through the use of a [2 + 2] cycloaddition reaction of dichloroketene **4** with chiral enol ether **5** (Scheme 2).[4]

Scheme 1. Diels–Alder Reaction in the Total Synthesis of Prostaglandin ($PGF_{2\alpha}$)



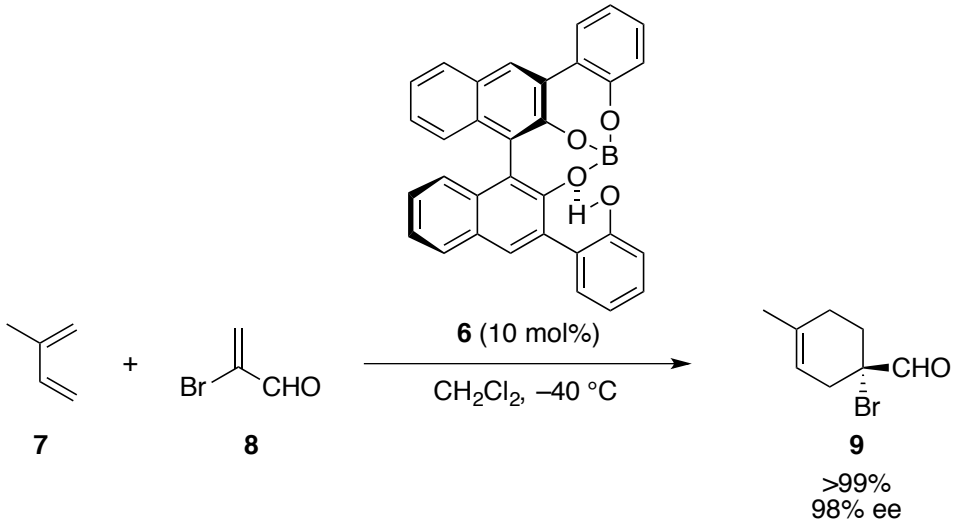
Scheme 2. [2 + 2] Cycloaddition Reaction in the Total Synthesis of (–)-Swainsonine



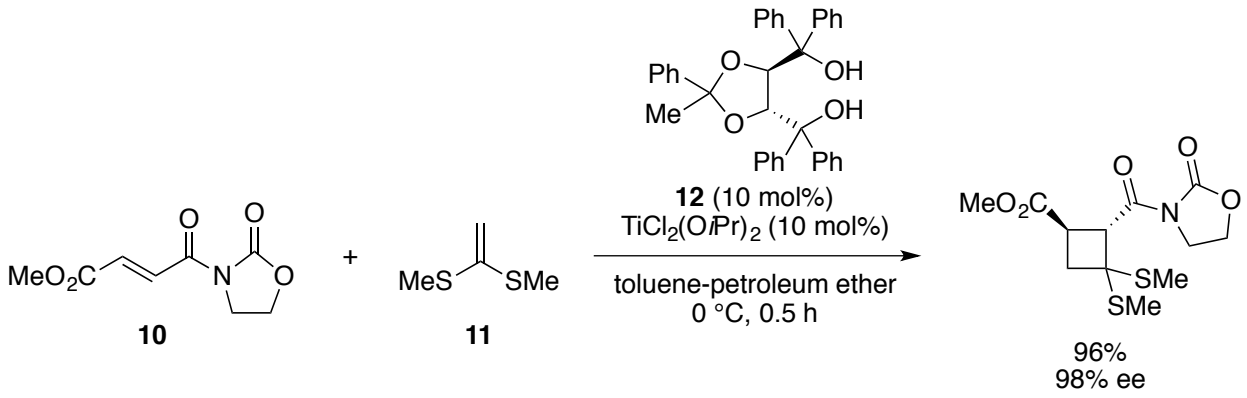
To efficiently obtain optically active cycloaddition adducts, which can then be transformed to valuable compounds such as biologically active natural products and their derivatives, it is important to develop a catalytic enantioselective cycloaddition reaction. In particular, the development of highly active chiral catalysts is essential for industrial-scale process chemistry. Indeed, chiral Lewis acid catalysts have been developed for several asymmetric cycloaddition reactions.[5] For example, Yamamoto and Ishihara developed a Brønsted acid-assisted chiral

Lewis acid (BLA) catalyst **6** for a Diels–Alder reaction between acyclic diene **7** and α-bromoacrolein **8**, and the corresponding product **9** was obtained in high yield with high enantioselectivity (Scheme 3).[6] In addition, Narasaka developed the first catalytic enantioselective [2 + 2] cycloaddition reaction between acrylamide derivative **10** and 1,1-bis(methylthio)ethylene **11** using Ti(IV)-TADDOLate **12** as a chiral Lewis acid catalyst (Scheme 4).[7]

Scheme 3. Brønsted Acid-Assisted Chiral Lewis Acid (BLA) Catalyst **6** for the Diels–Alder Reaction between **7** and **8**



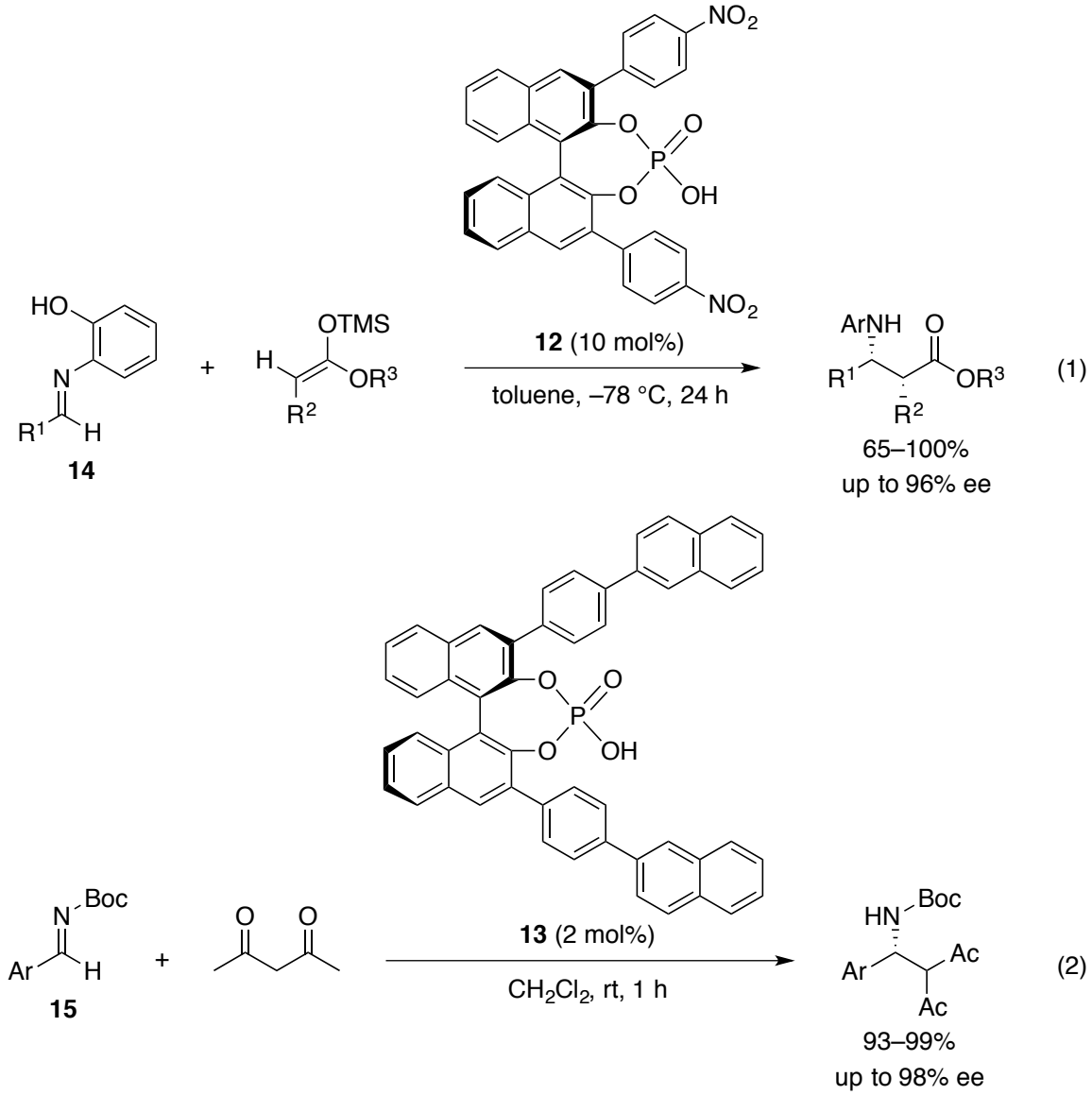
Scheme 4. Chiral Ti(IV)-TADDOLate Catalyst **12** for the [2 + 2] Cycloaddition Reaction between **10** and **11**



To realize a sustainable society, it is important to develop catalytic asymmetric reactions that are environmentally friendly. In particular, highly active chiral catalysts that do not contain

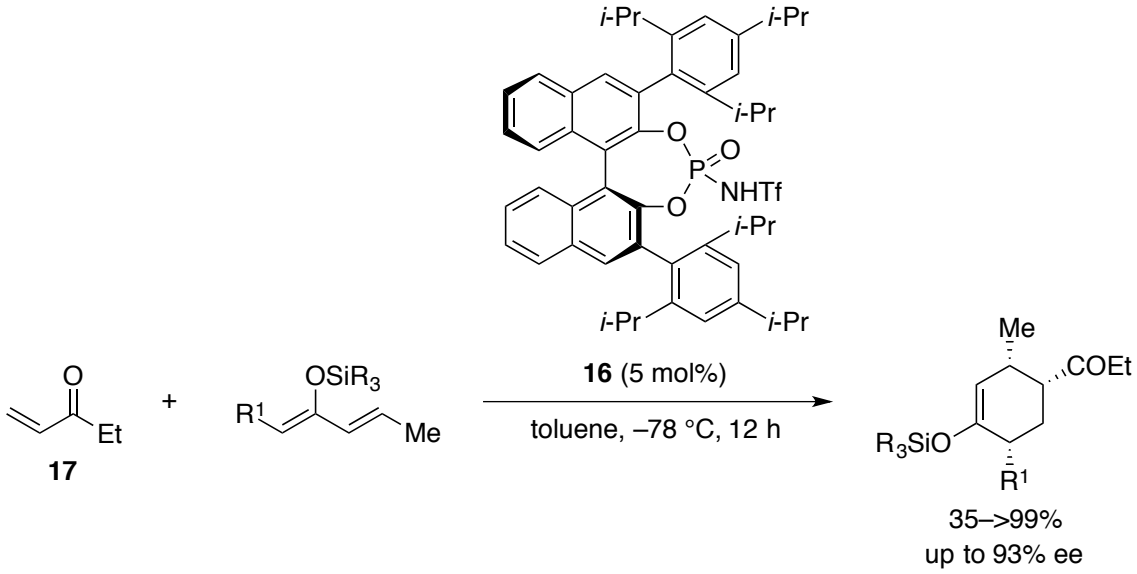
precious metals or toxic elements are needed in industrial large-scale synthesis. In this regard, chiral C_2-symmetric 1,1'-binaphthyl derivatives have been used as chiral organocatalysts since both enantiomers are commercially available and easy to modify.[8] In particular, chiral BINOL-derived phosphoric acids are highly useful acid–base cooperative organocatalysts that can be used in a variety of asymmetric reactions.[9] For example, Akiyama and Terada independently developed chiral phosphoric acid catalysts **12** and **13**, which are respectively effective for activating aldimines **14** and **15** (Scheme 5).[8b,8c]

Scheme 5. Chiral Phosphoric Acid Catalysts for Mannich-type Reactions of Aldimines **14** and **15**



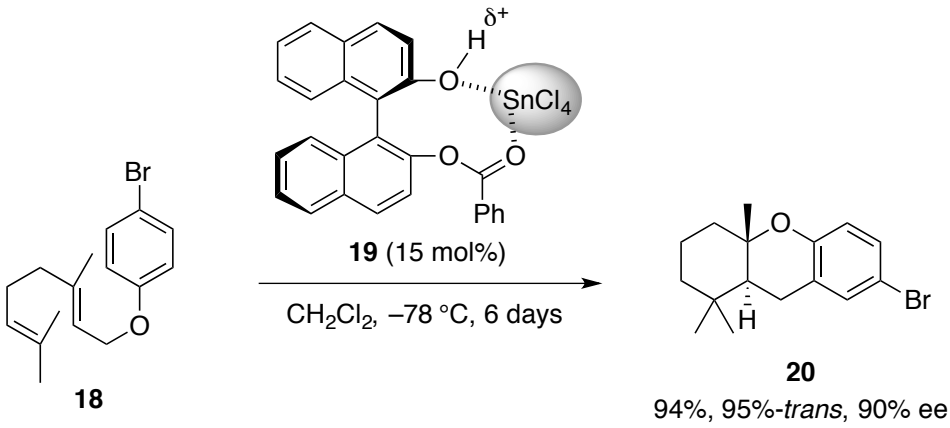
However, the Brønsted acidity of conventional chiral phosphoric acids is generally not strong enough to activate less-basic carbonyl compounds, such as aldehydes and ketones, in contrast to more-basic aldimines. To overcome this serious issue, stronger chiral Brønsted acid catalysts have been developed.[10] For example, Yamamoto developed chiral phosphoramide catalyst **16** with stronger Brønsted acidity, so that it could be applied to carbonyl compounds such as ketone **17** for the first time (Scheme 6).[11] This is an example of how simple chemical modifications can further enhance the Brønsted acidity of previously developed catalysts.

Scheme 6. Chiral Phosphoramide Catalyst **16** for Reactions of **17**



On the other hand, a chiral Brønsted acid can also be activated with an achiral Lewis acid.[12] This method is known as an LBA (Lewis acid-assisted Brønsted acid) system, which was developed by Yamamoto and Ishihara for the asymmetric polyene cyclization of **18** (Scheme 7).[13] LBA catalyst **19** gives the product **20** in high yield with high diastereoselectivity and enantioselectivity. Since Brønsted acidity can be increased by the simple addition of an achiral Lewis acid to a chiral BINOL derivative, it is possible to reduce both the cost and time required for catalyst-synthesis compared to the standard synthetic method by chemical modifications. Moreover, the coordination of Lewis acids to Brønsted acids restricts the orientation of protons.[14]

Scheme 7. Enantioselective Polyene Cyclization Catalyzed by Chiral LBA Catalyst **19**



Therefore, the author envisioned that the design of Lewis acid-assisted chiral phosphoric acid catalysts using the LBA system would enable the activation of carbonyl compounds, which are difficult to activate by a phosphoric acid catalyst alone (Figure 1). There are two approaches to catalyst design: the remote activation method (Figure 1a) and the direct activation method (Figure 1b).

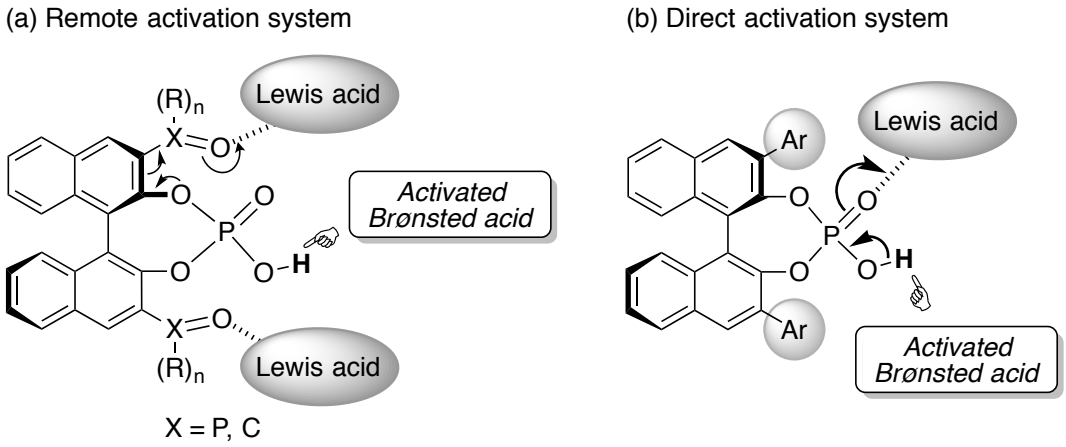


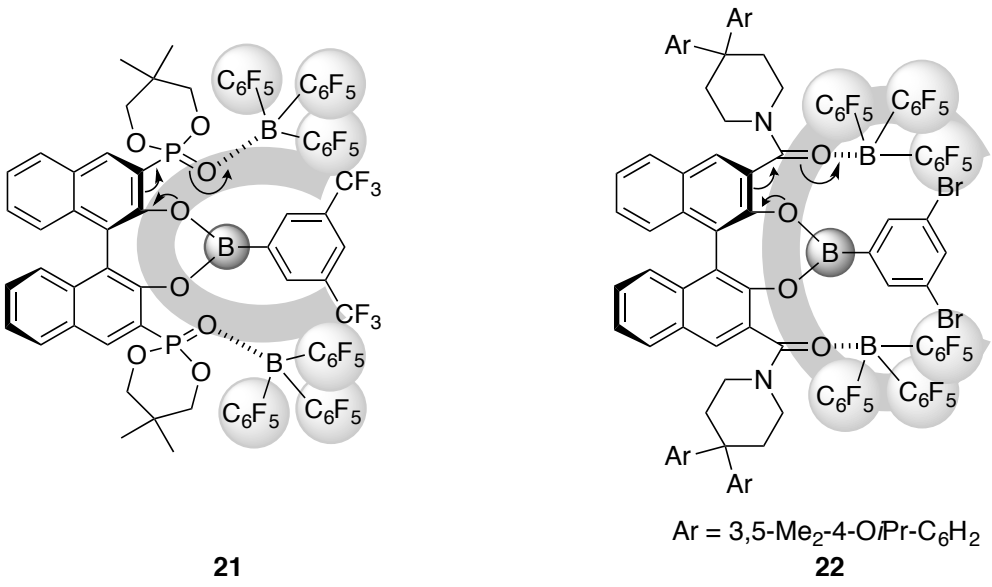
Figure 1. Design of Chiral Stronger Brønsted Acids Based on Lewis Acid-Assisted Chiral Phosphoric Acid Catalysts

In both systems, when an achiral Lewis acid coordinates to Lewis basic moieties, such as a phosphoryl group or carbonyl group, the acidity of the phosphoric acid would increase through the conjugated bonds. Moreover, the asymmetric cavity can be precisely designed by the

substituents at the 3,3'-positions and the Lewis acid itself. In addition, restricting the orientation of protons might provide asymmetric inductions. Based on this working hypothesis for Lewis acid-assisted chiral phosphoric acid catalysts, the author developed an enantioselective Diels–Alder reaction of α,β-unsaturated aldehydes, which is difficult to activate with conventional chiral phosphoric acid catalysts.[15]

1–2 Remote Tris(pentafluorophenyl)borane-Assisted Chiral Phosphoric Acid Catalysts for Enantioselective Diels–Alder Reaction

The design of simple artificial enzymes is an ongoing challenge in modern organic chemistry. In particular, tailor-made chiral supramolecular catalysts might be attractive for use as artificial enzymes, since every part of a supramolecular catalyst can be fine-tuned for each substrate to establish higher-ordered substrate-selectivity and/or stereoselectivity.[16,17] In this regard, our laboratory previously developed enantioselective Diels–Alder reactions with anomalous *endo*/*exo*-selectivities through the use of conformationally flexible chiral supramolecular Lewis acid catalysts **21**and **22** (Figure 2).[18]



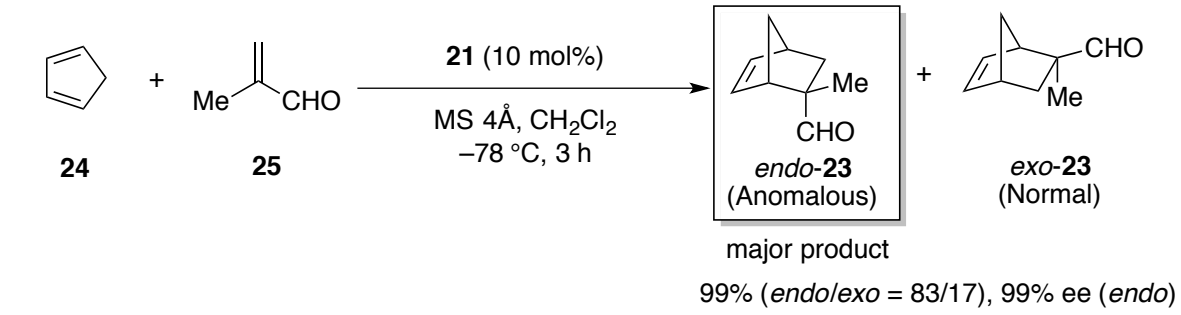
21 **22**

Figure 2. Conformationally Flexible Chiral Supramolecular Lewis Acid Catalysts **21** and **22**

In general, *endo*/*exo*-selectivity in the Diels–Alder reaction depends on the substrates.[19] However, when **21** was used as a catalyst, anomalous *endo*-product **23** was successfully obtained in high yield with high enantioselectivity (Scheme 8), since the chiral deep and narrow cavity

could control the transition states in the reaction of cyclopentadiene **24** with methacrolein **25** (Figure 3).

Scheme 8. Anomalous *endo*-Selective Diels–Alder Reaction between **24** and **25**



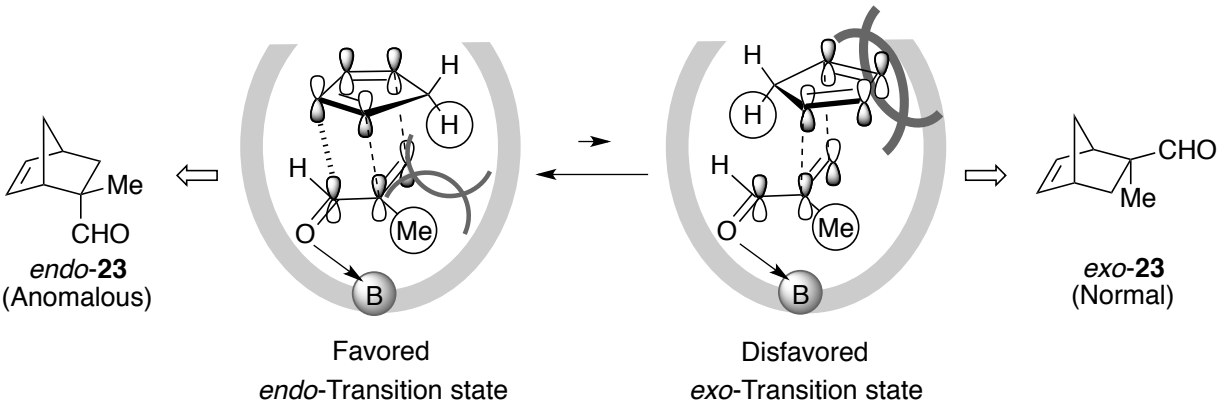
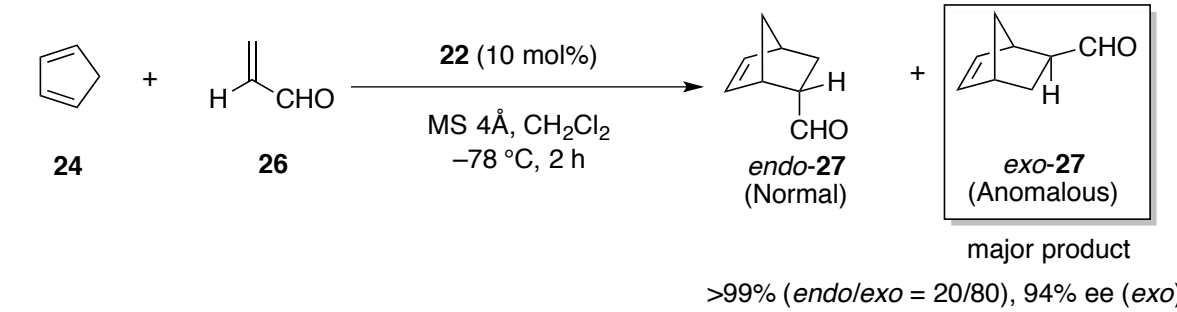


Figure 3. *endo*-Transition State Stabilized in the Cavity of the Catalyst.

Moreover, when **22** is used as a catalyst, another specific cavity can be constructed (Figure 4). In the reaction between cyclopentadiene **24** and acrolein **26** catalyzed by **22**, anomalous *exo*-product **27** could be obtained in high yield with high enantioselectivity, since this cavity might be suitable for these substrates to form an *exo*-transition state (Scheme 9).

Scheme 9. Anomalous *exo*-Selective Diels–Alder Reaction between **24** and **26**



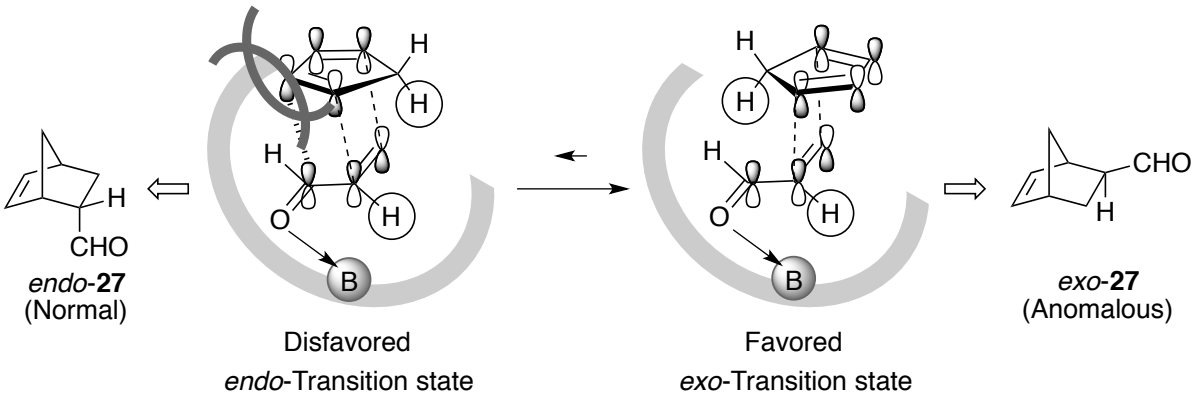
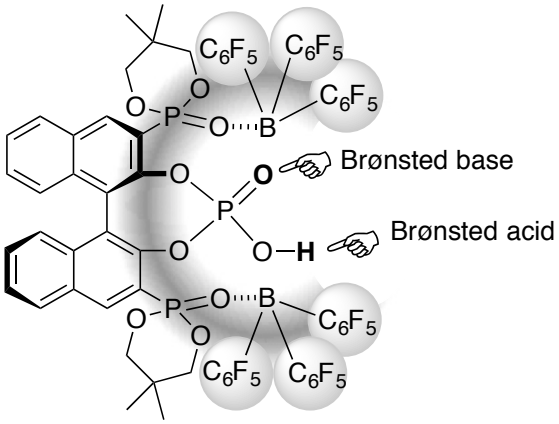


Figure 4. *exo*-Transition State Stabilized in the Cavity of the Catalyst.

Two coordinated tris(pentafluorophenyl)boranes in catalysts **21** and **22** should help to increase the Lewis acidity of the active center and create effective bulkiness for the chiral cavity. To further develop such a supramolecular methodology, the author envisioned that conformationally flexible chiral supramolecular complex **28** might also be effective as a chiral Brønsted acid catalyst (Figure 5).



28

Figure 5. Design of Supramolecular Brønsted Acid Catalyst **28**.

By taking advantage of the conjugated Brønsted acid–Brønsted base bifunctionality of chiral phosphoric acids **28**, aldehydes (i.e., acroleins) should be able to doubly coordinate with the active centers (Figure 6a). Moreover, the addition of an achiral Lewis acid source (ML_n) should

provide bifunctional Lewis acid–Brønsted base catalysts (Figure 6b). Overall, introduction of the phosphoric acid to the center of supramolecular catalysts might provide additional opportunities for versatile molecular recognition according to the size and/or substitution pattern of acroleins.

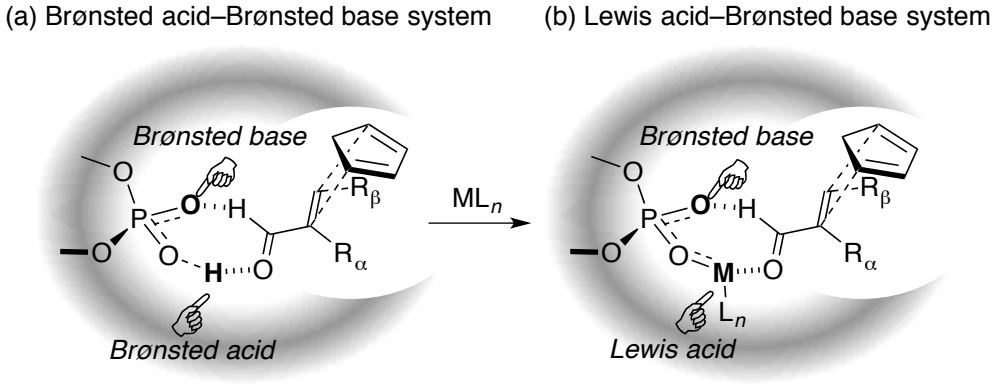
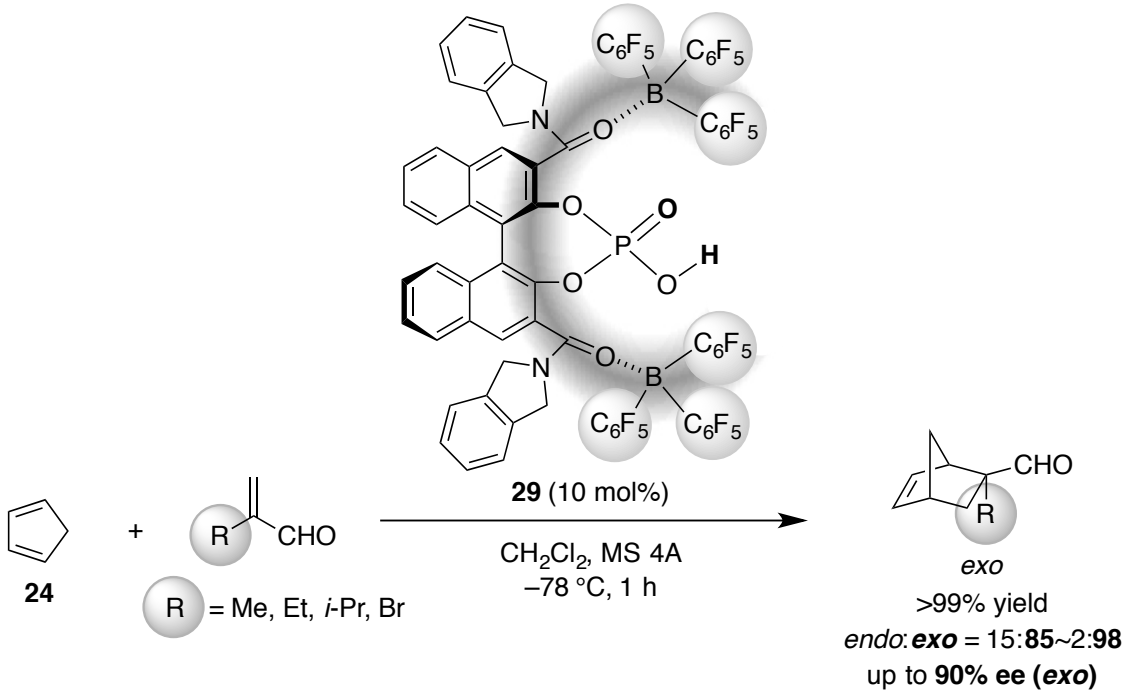


Figure 6. Double Coordination Between the Catalysts and α, β-Unsaturated Aldehydes.

Chapter 2 describes the development of remote tris(pentafluorophenyl)borane-assisted chiral phosphoric acid catalysts for the enantioselective Diels–Alder reaction of α-substituted acroleins with cyclopentadiene **24** as a probe reaction (Scheme 10).[15a] With the use of **29** as a catalyst, the highest enantioselectivity (90% ee) was observed in the Diels–Alder reaction between cyclopentadiene **24** and methacrolein **25**. Moreover, the corresponding supramolecular catalysts would act not only as highly activated conjugated Brønsted acid–Brønsted base catalysts but also as bifunctional Lewis acid–Brønsted base catalysts with the addition of a central achiral Lewis acid source such as catecholborane.

Scheme 10. Remote Tris(pentafluorophenyl)borane-Assisted Chiral Phosphoric Acid Catalyst **29** for the Enantioselective Diels–Alder Reaction



1–3 Boron Tribromide-Assisted Chiral Phosphoric Acid Catalysts for Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines

Isoquinuclidines are useful synthetic intermediates since the isoquinuclidine structure is found in natural products which have biological activities, such as alkaloids (Figure 7).[20] Therefore, the development of an efficient method for the synthesis of optically active isoquinuclidines is strongly desired. Since a catalytic enantioselective Diels–Alder reaction of 1,2-dihydropyridineis one of the most effective methods for obtaining optically active isoquinuclidines, there have been some reports about the development of these reactions (Scheme 11).[21] Rawal developed an asymmetric Diels–Alder reaction of 1,2-dihydropyridines **30** for the first time using chiral chromium(III) catalyst **31**, and the product **32** was obtained with 67% ee

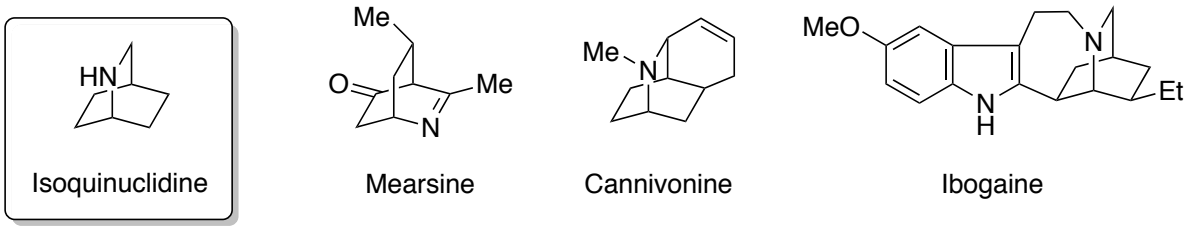
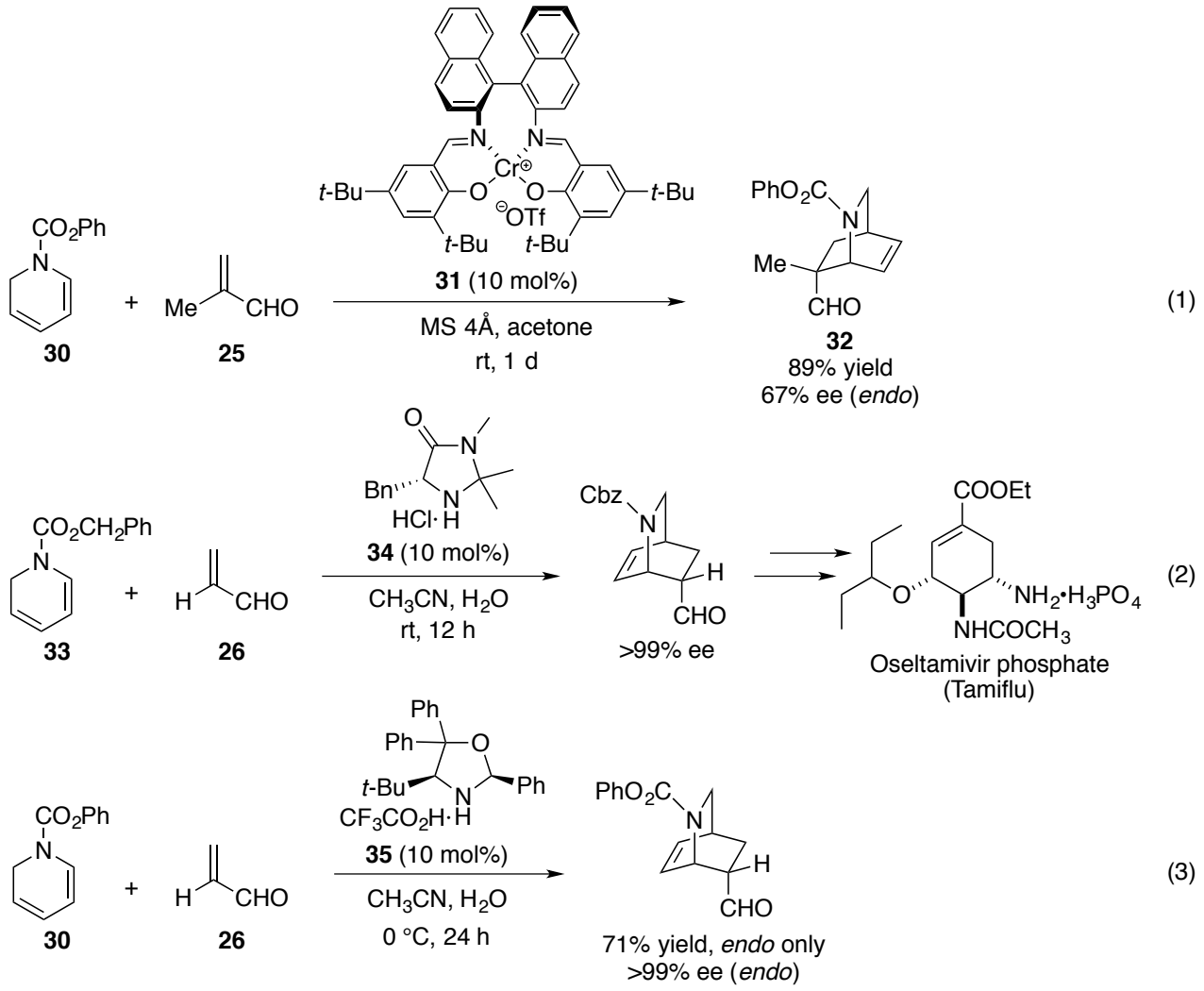


Figure 7. Isoquinuclidine and Natural Products with an Isoquinuclidine Structure.

(Eq. 1).[21a] Fukuyama developed a highly enantioselective Diels–Alder reaction between acrolein **26** and 1,2-dihydropyridine **33** using MacMillan catalyst **34**, and achieved the total synthesis of oseltamivir phosphate (Eq. 2).[22] Nakano developed an enantioselective Diels–Alder reaction between acrolein **26** and 1,2-dihydropyridine **30** using chiral oxazolidine catalyst **35** (Eq. 3).[21c]

Scheme 11. Enantioselective Diels–Alder Reactions of 1,2-Dihydropyridines



However, these chiral secondary amine catalysts cannot be used for α-substituted acroleins such as methacrolein **25**, since the corresponding iminium intermediates would not be generated due to steric hindrance (Figure 8). Therefore, with the use of these secondary amine catalysts, it would not be possible to obtain optically active isoquinuclidine with a chiral quaternary carbon center.

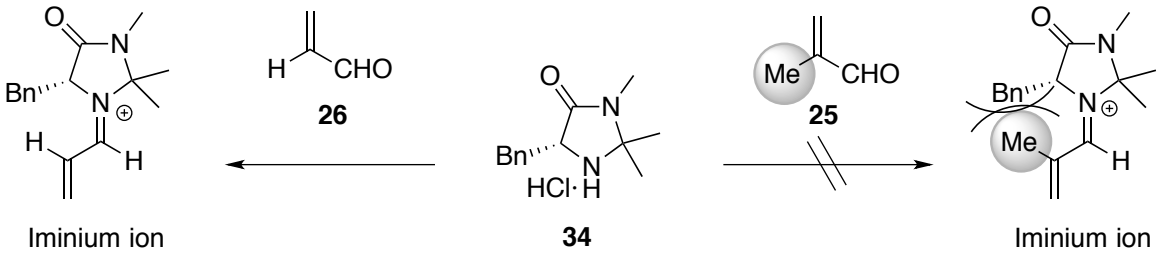
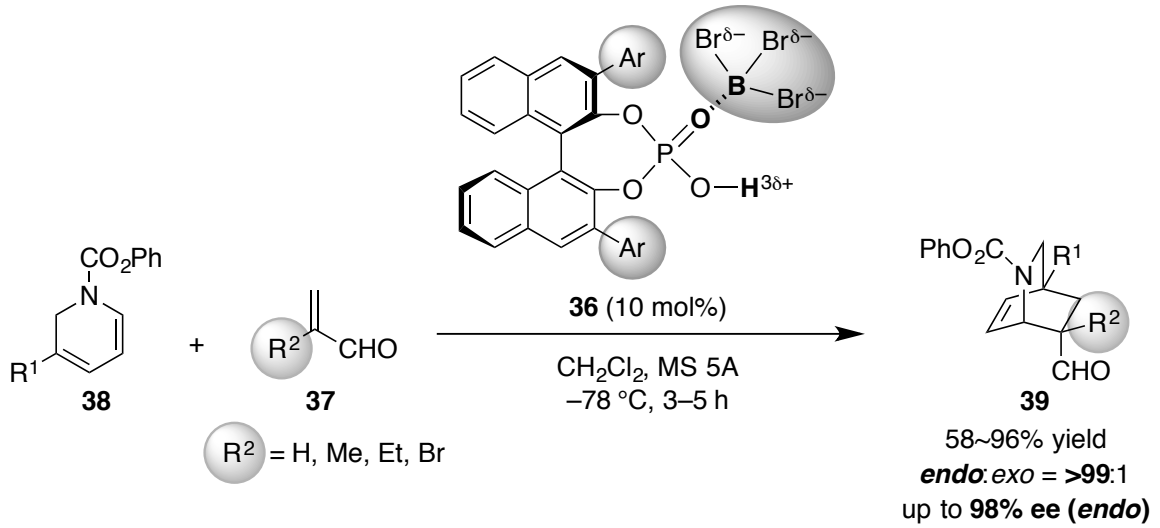


Figure 8. Generation of Iminium Cation Intermediates.

Chapter 3 describes how, to overcome these problems in the catalytic enantioselective Diels–Alder reactions of 1,2-dihydropyridines, the author developed boron tribromide-assisted chiral phosphoric acid catalysts (Scheme 12).[15b] After optimization of the reaction conditions, boron tribromide-chiral phosphoric acid complexes **36** were found to be highly effective and practical Lewis acid-assisted Brønsted acid (LBA) catalysts for promoting the enantioselective Diels–Alder reaction of α-substituted acroleins **37**. In particular, the Diels–Alder reaction of α-substituted acroleins **37** with 1,2-dihydropyridines **38** gave the corresponding optically active isoquinuclidines **39** with high enantioselectivities. Moreover, transformations to the key intermediates of indole alkaloids, catharanthine and allocatharanthine, were demonstrated.

Scheme 12. Enantioselective Diels–Alder Reactions of 1,2-Dihydropyridines **38**

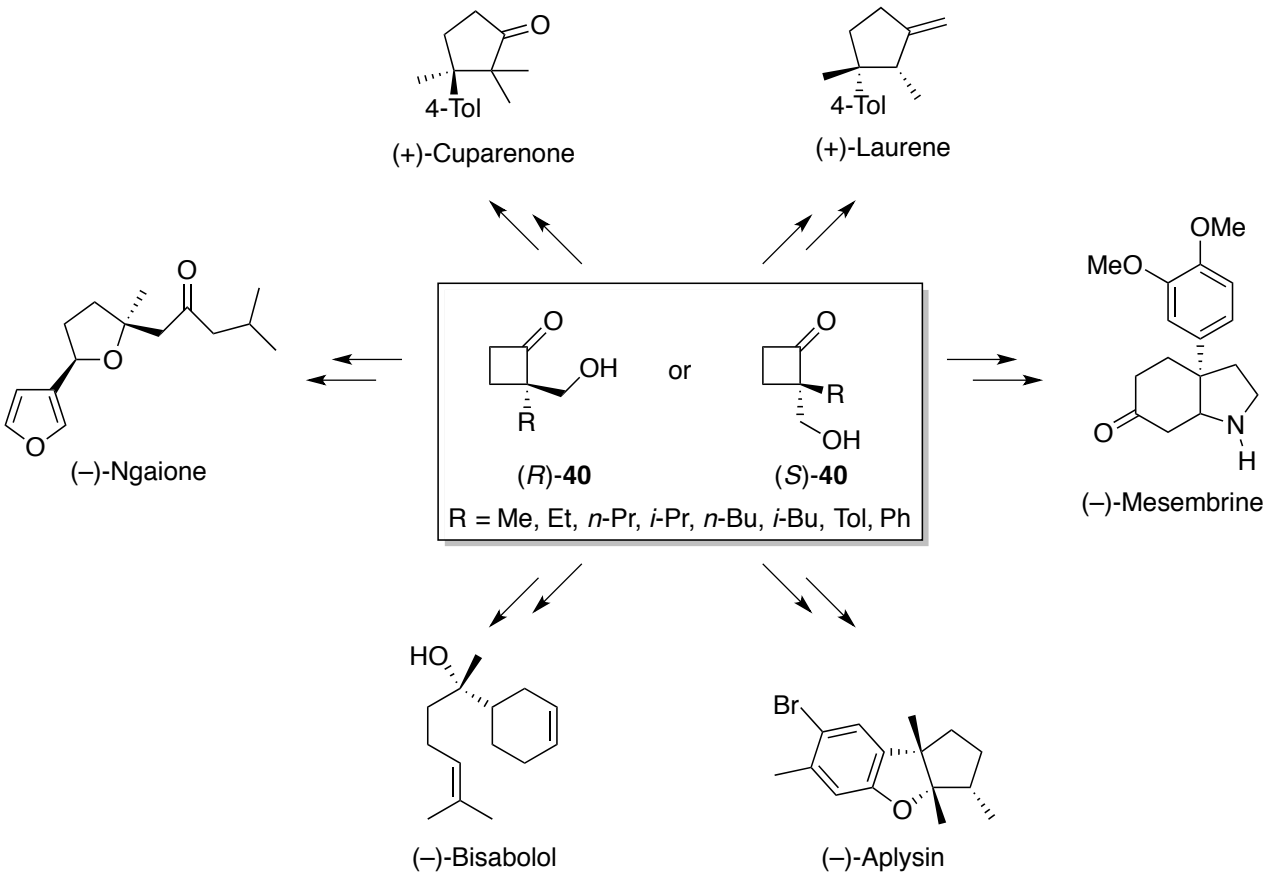


1–4 Boron Tribromide-Assisted Chiral Phosphoric Acid Catalysts for Enantioselective [2 + 2] Cycloaddition

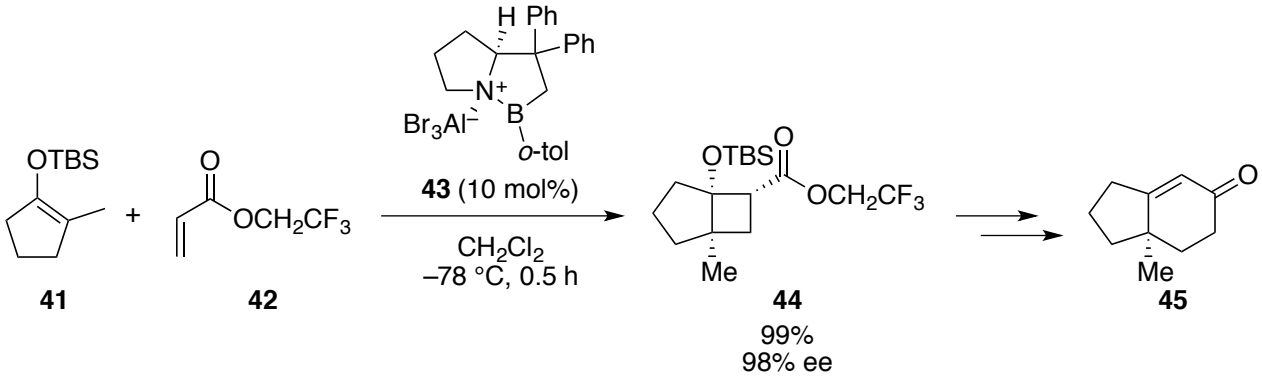
Cyclobutanes are valuable structures since they can be transformed to other useful compounds due to ring strain with high reactivity.[23] For example, chiral alcohols **40**, which have

cyclobutane structures, can be transformed into many natural products (Figure 9).[24] A few catalytic enantioselective [2 + 2] cycloadditions have been developed to obtain enantio-enriched cyclobutanes efficiently.[25] For examples, Corey developed a highly enantio- and diastereoselective [2 + 2] cycloaddition of silyl enol ether **41** derived from 2-methylcyclopentanone and trifluoroethyl acrylate **42** using chiral oxazaborolidine **43** as a catalyst (Scheme 13).[26] This report also described the transformation of the [2 + 2] cycloadduct **44** into the synthetically valuable ketone **45**. As another example, Ishihara developed an enantioselective [2 + 2] cycloaddition of unactivated alkenes **46** with α-acyloxyacroleins **47** for the first time by using chiral ammonium salt **48** (Scheme 14).[27] This reaction proceeds through initial condensation of chiral amine component of **48** with aldehyde **47**. The resulting activated iminium salt can react with **46** to provide optically active cyclobutanes **49** with high enantioselectivities.

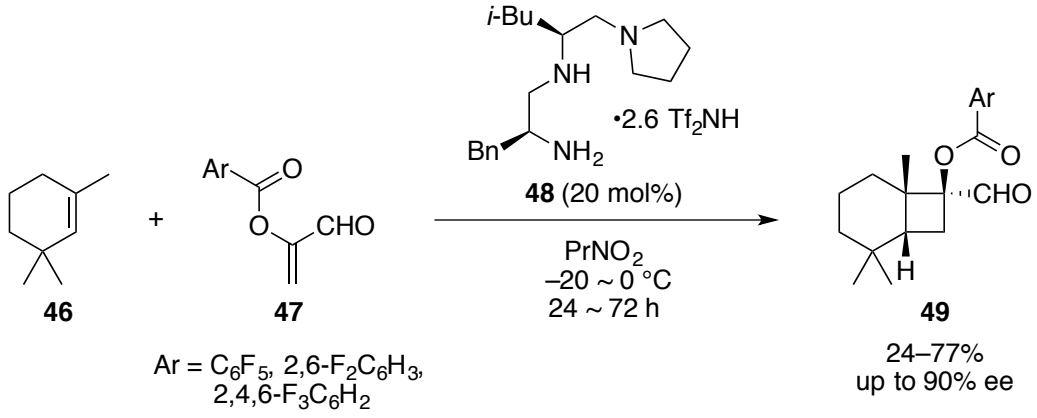
Figure 9. Transformations of Chiral Cyclobutanes **40** into Natural Products.



Scheme 13. Enantioselective [2 + 2] Cycloaddition of **42** with **41** Catalyzed by Chiral Oxazaborolidine **43**

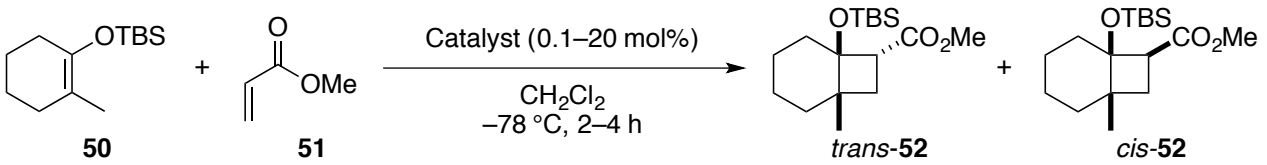


Scheme 14. Enantioselective [2 + 2] Cycloadditions of Unactivated Alkene **46** with **47**



However, there have been no reports of enantioselective [2 + 2] cycloadditions directly activating carbonyl groups with chiral Brønsted acid catalysts. With regard to achiral Brønsted acids, Ihara and Takasu provided the only report on the trifluoromethanesulfonimide-catalyzed [2 + 2] cycloadditions of 2-methylcyclohexanone-derived silyl enol ethers **50** with acrylates **51** (Scheme 15).[28] According to this report, the use of Brønsted acids (Tf_2NH) as catalysts improved the diastereoselectivity of the [2 + 2] cycloadduct **52** and reduced the amounts of catalysts needed compared to the use of Lewis acids ($EtAlCl_2$). Moreover, multigram syntheses of cyclobutanes were achieved.

Scheme 15. [2 + 2] Cycloaddition of **51** with **50** Catalyzed by Trifluoromethanesulfonimide

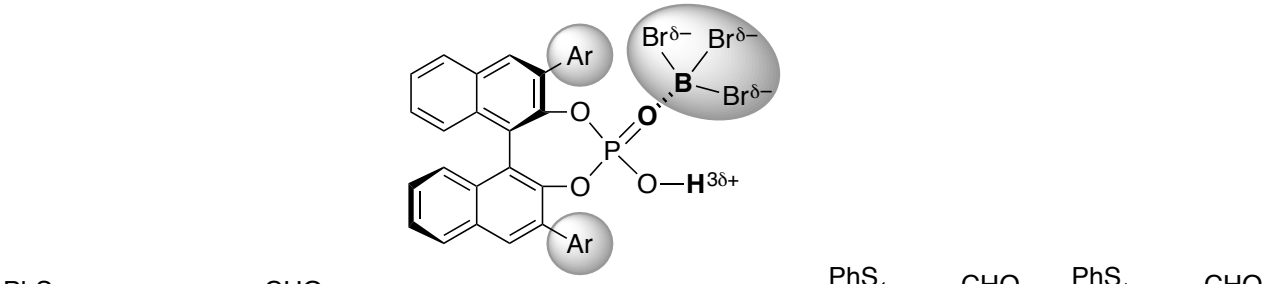


50 **51** *trans*-**52** *cis*-**52**

Tf_2NH (0.1 mol%): 98% (*trans*:*cis* = ~100:trace)
$EtAlCl_2$ (20 mol%): 79% (*trans*:*cis* = 95:5)
up to 7.5 g scale synthesis

Chapter 4 shows how chiral Brønsted acid-catalyzed [2 + 2] cycloaddition might be a powerful method for obtaining enantioenriched cyclobutanes efficiently. Therefore, the author developed an enantioselective [2 + 2] cycloaddition of α-substituted acroleins catalyzed by Lewis acid-assisted chiral phosphoric acid catalysts,[15b] which were effective for the enantioselective [4 + 2] cycloaddition of α-substituted acroleins. After optimization of the reaction conditions, boron tribromide-assisted chiral phosphoric acid catalysts **53** were shown to be effective for the [2 + 2] cycloaddition of methacrolein **25** with phenyl vinyl sulfide **54** (Scheme 16). The optically active cyclobutane **55**, which has both sulfide and aldehyde moieties, was obtained in high yield with high diastereo- and enantioselectivity. Moreover, this optically active cyclobutane **55** could be transformed into a key synthetic intermediate of natural products.

Scheme 16. Enantioselective [2 + 2] Cycloaddition of **25** with **54** Catalyzed by BBr_3-Assisted Chiral Phosphoric Acid **53**



54 **25** **53** (10 mol%) CH_2Cl_2, MS 4A –78 °C, 1 h

trans-**55** 90% yield ***trans***:*cis* = **>99**:1 **89% ee (*trans*)** *cis*-**55**

1–5 Conclusion

In summary, the author has developed enantioselective [4 + 2] and [2 + 2] cycloadditions of acroleins catalyzed by Lewis acid-assisted chiral phosphoric acids. These catalysts are easy to prepare *in situ* from chiral BINOL-derived phosphoric acids and achiral Lewis acids, and provide higher reactivities and selectivities than conventional chiral phosphoric acids. These reactions are powerful methods for asymmetric syntheses of norbornenes, isoquinuclidines, and cyclobutanes that are applicative organic compounds. Further investigations with these Lewis acid-assisted chiral phosphoric acid catalysts, which might contribute to a development of challenging asymmetric reactions, are currently underway.

References and Notes

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Chapter 2

Remote Tris(pentafluorophenyl)borane-Assisted Chiral Phosphoric Acid Catalysts for Enantioselective Diels–Alder Reaction

Abstract: Tris(pentafluorophenyl)borane-assisted chiral supramolecular phosphoric acid catalysts were developed for the model Diels–Alder reaction of α-substituted acroleins with cyclopentadiene. Two remotely coordinated tris(pentafluorophenyl)boranes should help to increase the Brønsted acidity of the active center in the supramolecular catalyst and create effective bulkiness for the chiral cavity. The prepared supramolecular catalysts acted as not only conjugated Brønsted acid–Brønsted base catalysts but also bifunctional Lewis acid–Brønsted base catalysts with the addition of a central achiral Lewis acid source such as catecholborane.

2-1 Introduction

The design of simple artificial enzymes is an ongoing challenge in modern organic chemistry. In particular, tailor-made chiral supramolecular catalysts might be attractive for use as artificial enzymes, since every part of a supramolecular catalyst can be fine-tuned for each substrate to establish higher-ordered substrate-selectivity and/or stereoselectivity.[1,2] In this regard, we previously developed enantioselective Diels–Alder reactions with anomalous *endo*/*exo*-selectivities through the use of conformationally flexible chiral supramolecular Lewis acid catalyst 1 (Figure 1a).[3,4] Based on the chiral deep and narrow cavity control of the transition states in the reaction of α-substituted acroleins and cyclopentadiene, anomalous *endo*-products were successfully obtained in a highly enantio-enriched fashion for the first time.[5]

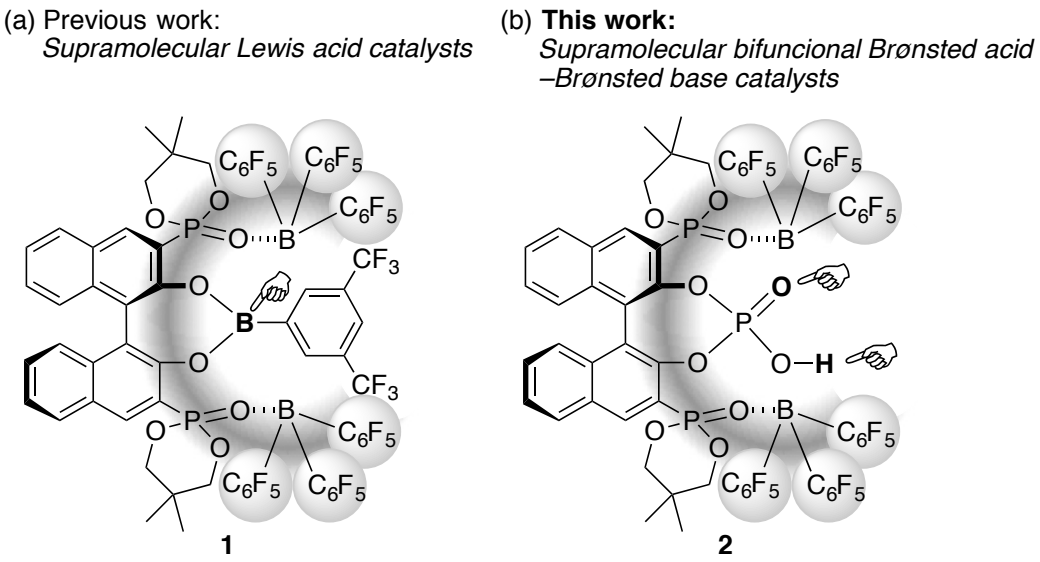


Figure 1. Design of Conformationally Flexible Chiral Supramolecular Catalysts

Two coordinated tris(pentafluorophenyl)boranes in catalyst **1** should help to increase the Lewis acidity of the active center and create effective bulkiness for the chiral cavity. To further develop such a supramolecular methodology, we envisioned that we might be able to use conformationally flexible chiral supramolecular Brønsted acid catalyst **2** (Figure 1b). By taking advantage of the conjugated Brønsted acid–Brønsted base bifunction of chiral phosphoric acids **2**,[6,7] aldehydes (i.e., acroleins) should be able to doubly coordinate with the active centers (Figure 2a). Moreover, the addition of an achiral Lewis acid source (ML_n) should provide bifunctional Lewis acid–Brønsted base catalysts (Figure 2b). Overall, introduction of the phosphoric acid to the center of supramolecular catalysts might provide additional opportunities for versatile molecular recognition according to the size and/or substitution pattern of acroleins. In this

context, we have developed remote tris(pentafluorophenyl)borane- assisted chiral phosphoric acid catalysts for the enantioselective Diels–Alder reaction of α-substituted acroleins with cyclopentadiene as a probe reaction.

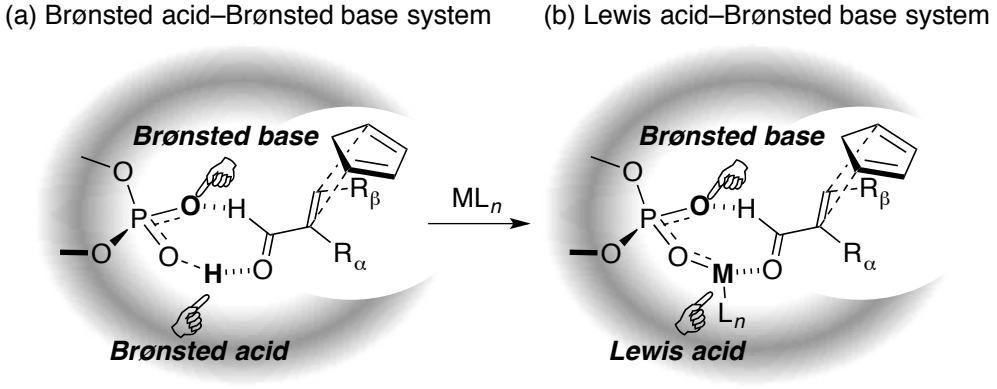


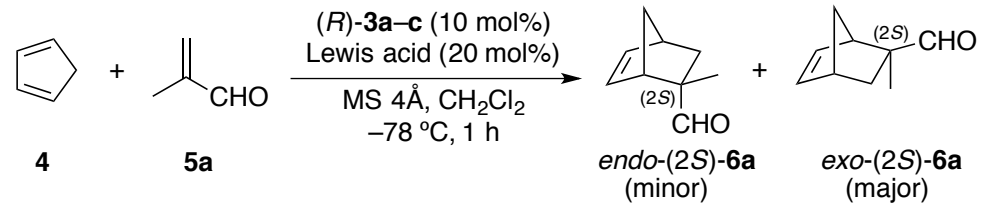
Figure 2. Chiral Supramolecular Phosphoric Acid Catalysts as (a) a Brønsted Acid-Brønsted Base System, and (b) a Lewis Acid-Brønsted Base System

2-2 Results and Discussion

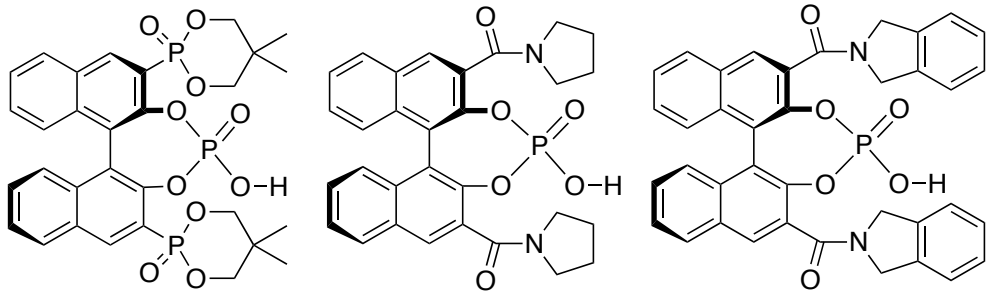
First, we examined the Diels–Alder reaction of methacrolein **5a** with cyclopentadiene **4** in dichloromethane at –78 °C in the presence of chiral supramolecular catalysts (10 mol%), which were prepared *in situ* from chiral phosphoric acid (*R*)-**3a** and achiral boron Lewis acids, such as $BF_3{\cdot}Et_2O$, BBr_3, and $B(C_6F_5)_3$ (Table 1). The reaction did not proceed with the use of (*R*)-**3a** alone (entry 1). In contrast, the combined use of (*R*)-**3a** and Lewis acids showed strong catalytic activities (entries 2–4). In particular, as expected, bulky $B(C_6F_5)_3$ was more effective than $BF_3{\cdot}Et_2O$ and BBr_3, and higher enantioselectivity (53% ee) was observed (entry 4). Fortunately, the enantioselectivity was significantly improved when amide-type (*R*)-**3b** and (*R*)-**3c** were used in place of phosphoryl-type (*R*)-**3a**, and *exo*-**6a** was obtained with 90% ee (entries 10 and 16). For (*R*)-**3b** and (*R*)-**3c** as well as (*R*)-**3a**, $BF_3{\cdot}Et_2O$ and BBr_3 were not effective (entries 8, 9, 14, and 15).

In this reaction, preparation of the catalyst *at room temperature* in advance was critical, and compounds **4** and **5a** were added *within 5 min* just after the mixture of catalysts was cooled to *–78 °C*. In this regard, the enantioselectivity significantly decreased when compounds **4** and **5a** were added to the mixture of $2B(C_6F_5)_3$–(*R*)-**3a** or $2B(C_6F_5)_3$–(*R*)-**3b** after cooling *at –78 °C for 30 min* (Table 1, entries 5 and 11). Once $B(C_6F_5)_3$ is adventitiously released from the

Table 1. Screening of Chiral Supramolecular Catalysts[a]



4 **5a** *endo*-(2*S*)-**6a** (minor) *exo*-(2*S*)-**6a** (major)



(*R*)-**3a** (*R*)-**3b** (*R*)-**3c**

Entry	(*R*)-**3**	Lewis acid	Yield (%)	*Endo*-**6a**:*Exo*-**6a**	Ee (%) of *exo*-**6a**
1	(*R*)-**3a**	–	0	–	–
2	(*R*)-**3a**	$BF_3 \cdot Et_2O$	>99	7:93	2
3	(*R*)-**3a**	BBr_3	98	8:92	14
4	(*R*)-**3a**	$B(C_6F_5)_3$	98	8:92	–53[b]
5[c]	(*R*)-**3a**	$B(C_6F_5)_3$	>99	8:92	–31[b]
6[d]	(*R*)-**3a**	$B(C_6F_5)_3$	20	19:81	–1[b]
7	(*R*)-**3b**	–	0	–	–
8	(*R*)-**3b**	$BF_3 \cdot Et_2O$	>99	7:93	0
9	(*R*)-**3b**	BBr_3	>99	5:95	0
10	(*R*)-**3b**	$B(C_6F_5)_3$	>99	5:95	90
11[c]	(*R*)-**3b**	$B(C_6F_5)_3$	62	11:89	8
12[d]	(*R*)-**3b**	$B(C_6F_5)_3$	0	–	–
13	(*R*)-**3c**	–	0	–	–
14	(*R*)-**3c**	$BF_3 \cdot Et_2O$	98	6:94	0
15	(*R*)-**3c**	BBr_3	96	10:90	0
16	(*R*)-**3c**	$B(C_6F_5)_3$	>99	8:92	90
17[c]	(*R*)-**3c**	$B(C_6F_5)_3$	>99	9:91	85
18[d]	(*R*)-**3c**	$B(C_6F_5)_3$	0	–	–

[a] Unless otherwise noted, the reaction of **5a** (0.5 mmol) with **4** (2.5 mmol) was carried out with the use of (*R*)-**3** (10 mol%), Lewis acid (20 mol%), and MS 4Å in dichloromethane at –78 °C for 1 h. Compounds **4** and **5a** were added to the mixture of catalysts within 5 min just after cooling to –78 °C. [b] Enantioselectivity of *exo*-(2*R*)-**6a**. [c] Compounds **4** and **5a** were added to the mixture of catalysts after it was cooled to –78 °C for 30 min. [d] The reaction was carried out with the use of (*R*)-**3** (10 mol%), $B(C_6F_5)_3$ (10 mol%), and MS 4Å under standard conditions.

supramolecular catalysts 2B(C_6F_5)$_3$–(*R*)-**3a** and 2B(C_6F_5)$_3$–(*R*)-**3b**, the highly basic phosphoryl moiety and pyrrolidine-derived amido moiety would tightly coordinate with the proton of the phosphoric acid *at –78 °C*. The corresponding species B(C_6F_5)$_3$–(*R*)-**3a** and B(C_6F_5)$_3$–(*R*)-**3b**, which might be inactive (Table 1, entries 6 and 12), would then be formed (Figure 3). Simultaneously, achiral B(C_6F_5)$_3$, which might induce a racemic reaction pathway (Table 1, entries 5 and 11), would be released. In sharp contrast, 2B(C_6F_5)$_3$–(*R*)-**3c**, which has a much less basic isoindoline-derived amido moiety, was tolerated under the reaction conditions at –78 °C for 30 min before the addition of substrates **4** and **5a**, and *exo*-**6a** was obtained with 85% ee (Table 1, entry 17). The inter-/intramolecular coordination-exchange between the proton center and B(C_6F_5)$_3$ might still occur due to the weak basicity of the isoindoline-derived amido moiety even at –78 °C. As a result, active 2B(C_6F_5)$_3$–(*R*)-**3c** would be regenerated from less active B(C_6F_5)$_3$–(*R*)-**3c**. These considerations might be supported by finding that the catalytic activity of 2B(C_6F_5)$_3$–(*R*)-**3c** (entry 16) was much higher than those of competitive B(C_6F_5)$_3$–(*R*)-**3c** (entry 18) and free B(C_6F_5)$_3$.[8]

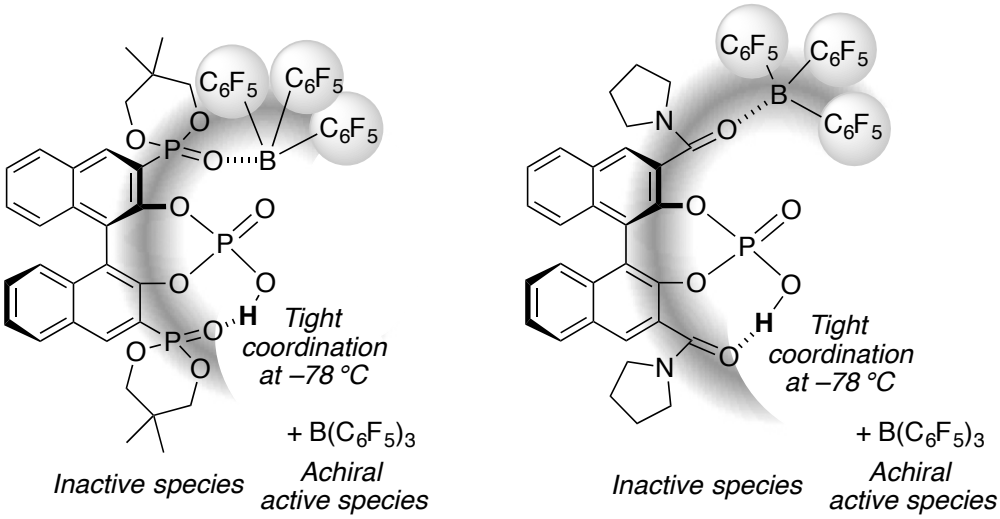


Figure 3. Possible Formations of B(C_6F_5)$_3$–(*R*)-**3a** and B(C_6F_5)$_3$–(*R*)-**3b** with Intramolecular Hydrogen Bonding and the Release of Achiral B(C_6F_5)$_3$

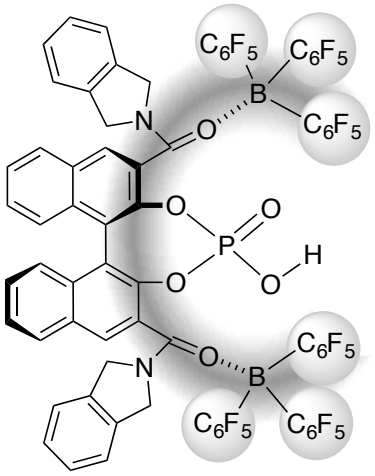
To confirm the complexation of the optimized supramolecular catalyst 2B(C_6F_5)$_3$–(*R*)-**3c**, spectroscopic analyses were performed at room temperature (Scheme 1). We found a peak at 1697.146 in ESI-MS analysis (negative mode), which might be unambiguously attributed to {[2B(C_6F_5)$_3$–(*R*)-**3c**]+2H_2O–H}$^-$ (See the ES). Moreover, peaks at –137.0, –159.5, and –166.3 ppm in ^{19}F NMR (CD_2Cl_2) were slightly shifted from the original peaks of B(C_6F_5)$_3$ at –130.2, –147.1, and –161.4 ppm. However, a peak at 4.6 ppm in ^{31}P NMR (CD_2Cl_2) was scarcely shifted

from the original peak at 4.0 ppm. These observations suggest that coordination to $B(C_6F_5)_3$ at the carbonyl groups of the 3,3'-substituents would precede coordination at the central P=O moiety, probably due to steric constraints at the narrow inner space.[9] Unfortunately, the hydrogen-bonding structures of $B(C_6F_5)_3$–(*R*)-**3a** and $B(C_6F_5)_3$–(*R*)-**3b**, as shown in Figure 3 have not yet been confirmed directly. However, in ^{31}P NMR (CD_2Cl_2) analysis *at –78 °C*, a peak at –4.1 ppm of $2B(C_6F_5)_3$–(*R*)-**3b** gradually decreased, and many other peaks between –5 and –25 ppm were predominantly observed within 30 min.[10] In sharp contrast, the decomposition of $2B(C_6F_5)_3$–(*R*)-**3c** to other species *at –78 °C* was much slower than that of $2B(C_6F_5)_3$–(*R*)-**3b**, and ca. 70% of $2B(C_6F_5)_3$–(*R*)-**3b** was still observed at –0.7 ppm for at least 30 min.[10]

Scheme 1. Spectroscopic Analyses of $2B(C_6F_5)_3$–(*R*)-**3c** at Room Temperature

(*R*)-**3c** (1 equiv)
^{31}P NMR (CD_2Cl_2): 4.0 ppm
+
$B(C_6F_5)_3$ (2 equiv)
^{19}F NMR (CD_2Cl_2): –130.2 (6F) ppm,
–147.1 (3F) ppm,
–161.4 (6F) ppm.

CD_2Cl_2
rt, 30 min

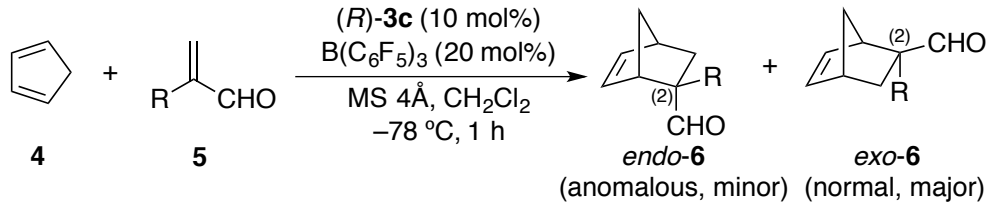


^{31}P NMR (CD_2Cl_2): 4.6 ppm
^{19}F NMR (CD_2Cl_2): –137.0 (6F) ppm,
–159.5 (3F) ppm,
–166.3 (6F) ppm.
ESI-MS (neg): calc. for $C_{74}H_{30}B_2F_{30}N_2O_8P^-$
$[M+2H_2O–H]^-$ 1697.1463, found 1697.1459

Next, we examined the substrate specificity for α-substituted acroleins. In place of methacrolein **5a**, α-ethylacrolein **5b** could be used in the presence of $2B(C_6F_5)_3$–(*R*)-**3c**, and the corresponding normal *exo*-**6b** was obtained with 84% ee (Table 2, entry 3). Partially due to steric mismatch with the chiral cavity, α-isopropylacrolein **5c** and α-bromoacrolein **5d**, which are bulkier than **5a** and **5b**, might be unsuitable for the chiral cavity of $2B(C_6F_5)_3$–(*R*)-**3c**, and low enantioselectivities were observed (entries 5 and 7). Moreover, a racemic pathway also might be promoted in the case of highly reactive **5d** (entry 7). As compared with thermal conditions

(entries 2, 4, 6, and 8), a supramolecular catalyst induced a slight *exo*-preference for **6a** and **6b** (entries 1 and 3).

Table 2. Substrate Specificity with the Use of $2B(C_6F_5)_3$–(*R*)-**3c**[a]

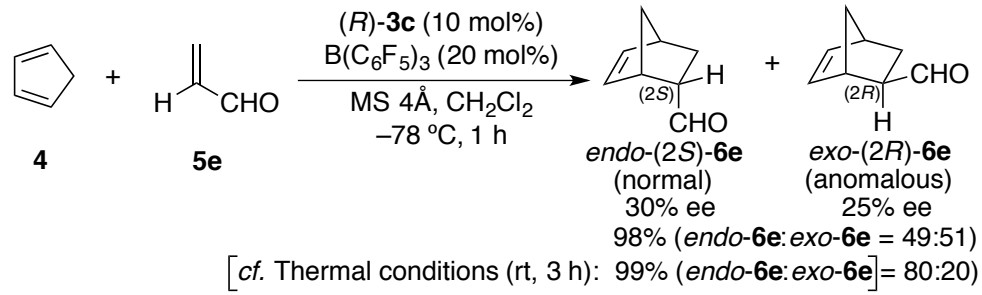


Entry	**5** (R)	Product	Yield (%)	*Endo*-**6**:*Exo*-**6**	Ee (%) of *exo*-**6**
1	**5a** (Me)	**6a**	>99	8:92	90 (2*S*)
2[b]	**5a** (Me)	**6a**	94 (40 °C, 3 h)	16:84	–
3	**5b** (Et)	**6b**	>99	2:98	84 (2*S*)
4[b]	**5b** (Et)	**6b**	73 (110 °C, 24 h)	24:76	–
5	**5c** (*i*-Pr)	**6c**	72	15:85	23 (2*R*)
6[b]	**5c** (*i*-Pr)	**6c**	<5 (110 °C, 3 h)	–	–
7	**5d** (Br)	**6d**	>99	15:85	18 (2*R*)
8[b]	**5d** (Br)	**6d**	>99 (rt, 3 h)	15:85	–

[a] The reaction of **5** (0.5 mmol) with **4** (2.5 mmol) was carried out with the use of (*R*)-**3c** (10 mol%), $B(C_6F_5)_3$ (20 mol%), and MS 4Å in dichloromethane at –78 °C for 1 h. [b] The reactions were carried out under thermal conditions without any catalysts in dichloromethane at room temperature to 40 °C or in toluene at 110 °C.

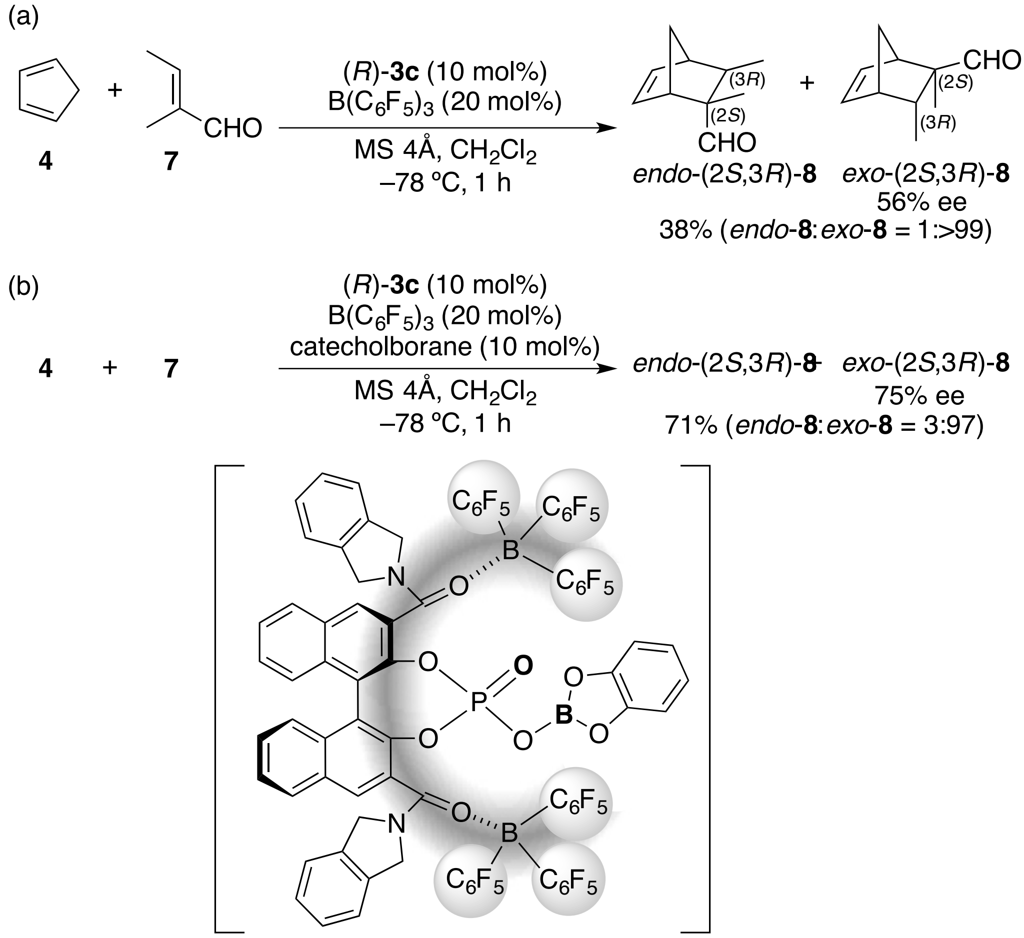
Moreover, with the use of a-nonsubstituted acrolein **5e**, moderate anomalous *exo*-selectivity was observed (*endo*:*exo* = 49:51) (Scheme 2).[11] Although the enantioselectivities of *endo*-**6e** and *exo*-**6e** were low (30% ee and 25% ee, respectively), an unusual disagreement in stereoselectivity (*R*/*S*) was observed between normal *endo*-(2*S*)-**6e** and anomalous *exo*-(2*R*)-**6e**. These results suggest that $2B(C_6F_5)_3$–(*R*)-**3c** might have an *exo*-induced chiral cavity as a supramolecular catalyst.

Scheme 2. Anomalous *Exo*-induced Diels–Alder Reaction of Acrolein **5e** with Cyclopentadiene **4** Catalyzed by $2B(C_6F_5)_3$–(*R*)-**3c**



Finally, we used tiglic aldehyde **7** as a much less reactive α,β-disubstituted acrolein, which did not give product **8** under thermal conditions in toluene at 110 °C. Supramolecular catalyst $2B(C_6F_5)_3$–(*R*)-**3c** showed low reactivity, and *exo*-**8** was obtained in 38% yield with 56% ee (Scheme 3a). To improve both the yield and enantioselectivity, we changed the Brønsted acid–Bønsted base catalyst system (Figure 2a) to a Lewis acid–Bønsted base catalyst system (Figure 2b), by using an additional achiral Lewis acid partner. After screening the acid sources,[12] we found that catecholborane was highly effective as a boron Lewis acid center for $2B(C_6F_5)_3$–(*R*)-**3c**, and *exo*-**8** was obtained in 71% yield with 75% ee (Scheme 3b).[13] Although the enantioselectivity has still been moderate, these results represent at least a partial demonstration of our conceptual catalytic system in Figure 2.

Scheme 3. Effect of the Addition of Catecholborane to $2B(C_6F_5)_3$–(*R*)-**3c** in the Diels–Alder Reaction of **7** with **4**



In this preliminary stage, further information based on experimental and theoretical studies will be necessary to discuss possible structures of the supramolecular catalysts *in situ*. In this regard, the previous supramolecular catalyst **1** has been calculated to be the C_1-symmetric *syn*-conformation due to the sp^3-boron Lewis acid center.[3] In contrast, we can speculate that supramolecular catalyst $2B(C_6F_5)_3$–(*R*)-**3c** would have an *anti*-conformation as shown in Figure 4b, unlike a sterically hindered *syn*-conformation as shown in Figure 4a, due to the essentially C_2-symmetric conjugated phosphoric acid moiety. Catecholborane-introduced supramolecular catalyst might have similar structures although the field would then be C_1-symmetric, as shown in Figure 4c. In *anti*-conformations, as shown in Figures 4b and 4c, a shallow and wide chiral cavity would be formed around the active center which would induce substrate specificity with an *exo*-preference.[3b]

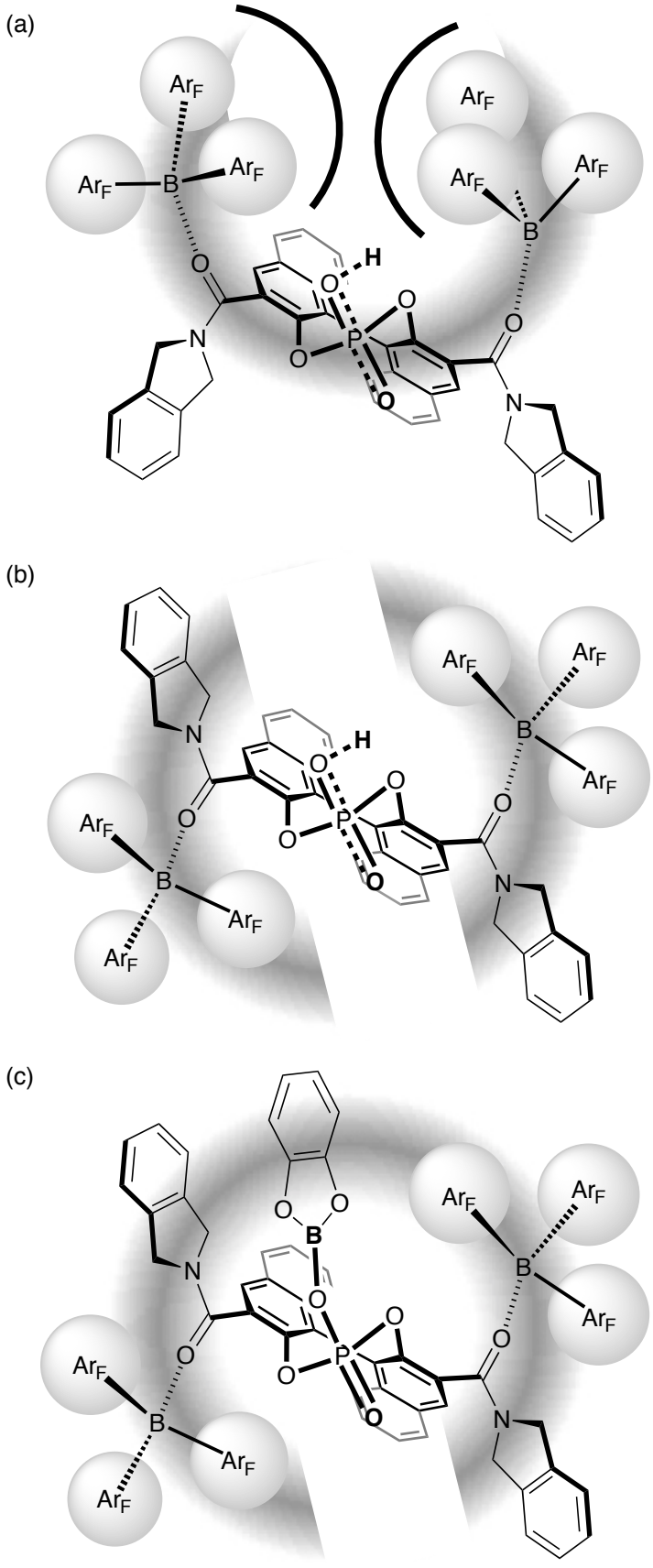


Figure 4. Possible structures and chiral cavities of supramolecular catalysts ($Ar_F = C_6F_5$)

2-3 Conclusion

In summary, we have developed bulky and strong Lewis acid $B(C_6F_5)_3$-assisted chiral phosphoric acids, which were designed for the model Diels–Alder reaction of α-substituted acroleins with cyclopentadiene.[14,15] The corresponding supramolecular catalysts acted not only as highly activated conjugated Brønsted acid–Brønsted base catalysts but also as bifunctional Lewis acid–Brønsted base catalysts with the addition of a central achiral Lewis acid source such as catecholborane. Further investigations with these asymmetric supramolecular methodologies with the use of chiral phosphoric acids, which might contribute to the construction of a conformationally flexible, bulky, and chiral cavity for higher-ordered catalysis, are currently underway.

References and Notes

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8. Compound **5a** is too reactive to evaluate meaningful differences in the catalytic activity between $2B(C_6F_5)_3$–(*R*)-**3c** and free $B(C_6F_5)_3$. However, the catalytic activity of $2B(C_6F_5)_3$–(*R*)-**3c** was much higher than that of free $B(C_6F_5)_3$. See Scheme 3 and the ES.
9. To confirm whether or not the coordination of the P=O moiety to $B(C_6F_5)_3$ would occur, we

used (*R*)-3,3'-Ph_2-BINOL-derived phosphoric acid, which may avoid competitive coordinations. In ^{31}P NMR (CD_2Cl_2) analysis at room temperature, a singlet peak at 1.7 ppm changed to –1.0 ppm with a small up-field shift, which suggests the coordination of the P=O moiety to $B(C_6F_5)_3$. Next, as with $2B(C_6F_5)_3$–(*R*)-**3c**, almost the same shifted peaks at –137.0, –158.8, and –165.8 ppm were observed in ^{19}F NMR (CD_2Cl_2) at room temperature.

10. ^{31}P NMR (CD_2Cl_2) analysis of (*R*)-**3b** and (*R*)-**3c** *at –78 °C* showed a peak at 6.1 ppm and 5.0 ppm, respectively. See the ES.
11. Anomalous *exo*-selective Diels–Alder reactions of α-nonsubstituted acroleins: (a) Maruoka, K.; Imoto, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 12115. (b) Kündig, E. P.; Saudan, C. M.; Alezra, V.; Viton, F.; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4481. (c) Kano, T.; Tanaka Y.; Maruoka, K. *Org. Lett.* **2006**, *8*, 2687. (d) Hayashi, Y.; Samanta, S.; Gotoh H.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6634. Also see ref 3.
12. We examined Me_3Al, Et_3Al, *i*-Bu_2AlH (DIBAL), Me_2AlNTf_2, allyltrimethylsilane, pinacolborane, 9-borabicyclo[3.3.1]nonane (9-BBN), etc. However, the combined use of these achiral Lewis acid sources to $2B(C_6F_5)_3$–(*R*)-**3c** showed low reactivities (0–15% yields), and the sole exception was catecholborane. In this regard, the combined use of a stoichiometric amount of catecholborane with chiral phosphoric acid catalyst in the enantioselective reduction of ketones was reported by Antilla. Zhang, Z.; Jain, P.; Antilla, J. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 10961.
13. We examined the reactions of acroleins **5a**–**e** with cyclopentadiene **4** with the use of a supramolecular catalyst, which was prepared from (*R*)-**3c**, $B(C_6F_5)_3$, and catecholborane, However, better enantioselectivities were not observed compared with $2B(C_6F_5)_3$–(*R*)-**3c** as shown in Table 2 and Scheme 2. The results are summarized in the ES.
14. Hatano, M.; Ishihara, H.; Goto, Y.; Ishihara, K. *Synlett* **2016**, *27*, 564.
15. **Typical Procedure for the Diels–Alder Reaction**

    To a mixture of (*R*)-**3c** (31.9 mg, 0.050 mmol) and powdered MS 4Å (200 mg) in a Schlenk tube under a nitrogen atmosphere, tris(pentafluorophenyl)borane (51.2 mg, 0.10 mmol) and freshly-distilled dichloromethane (2 mL) were added *via* a cannula, and this suspension was stirred at room temperature for 1 h. Next, the mixture was cooled to –78 °C, and as soon as possible (within 5 min) after cooling to –78 °C, methacrolein **5a** (95% purity, 43.4 μL, 0.50 mmol) and freshly-distilled cyclopentadiene **4** (203 μL, 2.5 mmol) were added at –78 °C. After that, the resultant mixture was stirred at –78 °C for 1 h. To quench the reaction, triethylamine (0.2 mL) was poured into the reaction mixture at –78 °C. The product

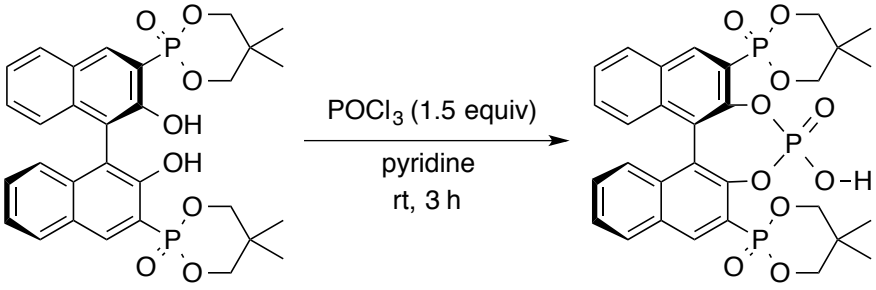
mixture was warmed to room temperature and directly purified by silica gel column chromatography (eluent: pentane:diethyl ether = 9:1). Solvents were removed under 200 Torr at 20 °C by a rotary evaporator, and the product **6a** was obtained (68.2 mg, >99% yield).

Experimental Section for Chapter 2

1. General methods.

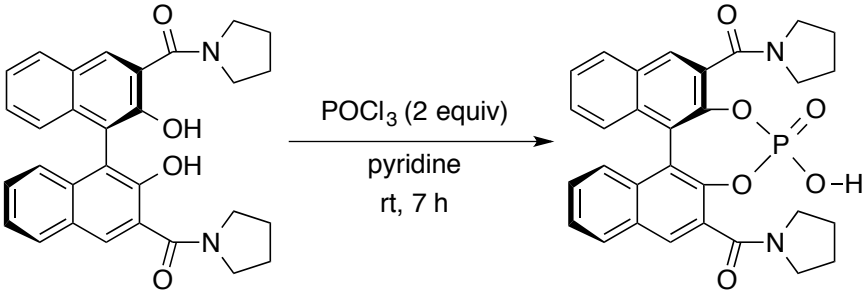
^{1}H NMR spectra were measured on a JEOL ECS400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS400 (100 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.10 ppm). ^{19}F NMR spectra were measured on a JEOL ECS-400 (376 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard ($CFCl_3$ at 0 ppm). ^{31}P NMR spectra were measured on a JEOL ECS-400 (161 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard (H_3PO_4 at 0 ppm). Gas-liquid-phase chromatography (GC) was performed with Shimadzu GC-2010 instrument with a flame-ionization detector and a capillary column of ULBON HR-20M (PEG-20M) (i.d., 0.25 mm × 25 m; GL Science Inc.), or CHIRALDEX B-DM (i.d., 0.25 mm × 20 m; Tokyo Kasei Kogyo Co., LTD). Optical rotations were measured on Rudolph Autopol IV digital polarimeter. The products were purified by column chromatography on silica gel (Kanto Chemical Co., Inc. 37560; Merck silica gel 60, Prod. No. 1.09385.9929). Mass spectral analyses were performed at Chemical Instrument Center, Nagoya University (JEOL JMS-700 (FAB), JEOL JMS-T100GCV (EI), Bruker Daltonics micrOTOF-QII (ESI)). Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60GF254 0.25 mm) were used. Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. Dichloromethane (with P_4O_{10}) was freshly distilled in prior to use. Cyclopentadiene (**4**) was freshly distilled from dicyclopentadiene in prior to use. Methacrolein (**5a**), α-ethylacrolein (**5b**), acrolein (**5e**), and tiglic aldehyde (**7**) are commercially available, and were used without any purification. α-Isopropylacrolein (**5c**)[1] and α-bromoacrolein (**5d**)[2] were synthesized as reported procedures.

2. Preparation of phosphoric acids.



S1 **3a**, 86%

(*R*)-3a: (*R*)-**S1**[2] (1.37 g, 2.36 mmol) was dissolved in pyridine (11.8 mL) and cooled to 0 ºC. Phosphorus oxychloride (330 μL, 3.54 mmol) was added, and the mixture was stirred at room temperature for 3 h. Aqueous 3 *M* HCl solution (12 mL) was then added to pH 1 at 0 ºC, and the mixture was extracted with chloroform (10 mL × 3). Combined organic layer was washed with aqueous 1 *M* HCl, and concentrated under reduce pressure to give the crude product. The crude was purified by precipitation from chloroform/hexane to give the titled compound as a pure white solid (1.31 g, 86% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (s, 6H), 1.31 (s, 6H), 3.86-4.00 (m, 2H), 4.10-4.27 (m, 4H), 4.40-4.50 (m, 2H), 4.50-6.00 (br, 1H), 7.02 (d, J = 8.2 Hz, 2H), 7.44 (t, J = 7.3 Hz, 2H), 7.59 (t, J = 7.3 Hz, 2H), 8.29 (d, J = 8.2 Hz, 2H), 8.58 (d, J_{H-P} = 16.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3 (2C), 21.9 (2C), 32.3 (d, J_{C-P} = 7.6 Hz, 2C), 77.4 (d, J_{C-P} = 7.6 Hz, 2C), 78.5 (d, J_{C-P} = 7.6 Hz, 2C), 120.2 (d, J_{C-P} = 178 Hz, 2C), 122.2 (d, J = 8.5 Hz, 2C), 126.3 (2C), 126.9 (2C), 129.8 (2C), 130.2 (2C), 130.4 (2C), 134.1 (2C), 137.5 (d, J_{C-P} = 6.8 Hz, 2C), 147.3 (d, J_{C-P} = 7.6 Hz, 2C). ^{31}P NMR (161 MHz, DMSO-d_6) δ 5.19 (s, 2P), 0.43 (s, 1P). IR (KBr) 3423, 2968, 1619, 1585, 1471, 1272, 1238, 1065, 1006 cm^{-1}. M.p. 233-258 °C (decomposition). $[\alpha]_D^{25}$ = −334.6 (*c* 1.00, CH_2Cl_2). HRMS (FAB+) calcd for $C_{30}H_{32}O_{10}P_3$ $[M+H]^+$ 645.1203, found 645.1212.

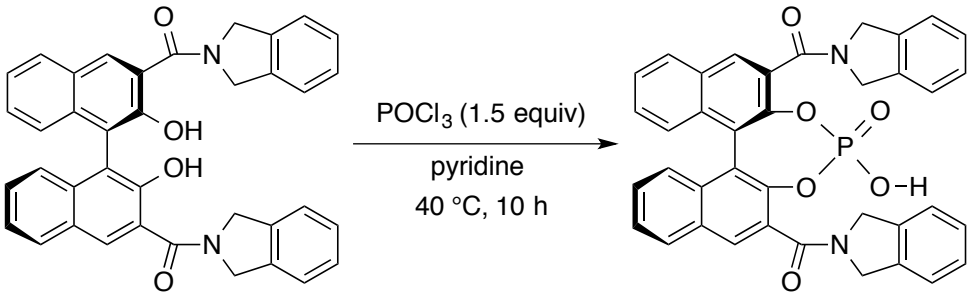


S2 **3b**, 87%

(*R*)-S2: (*R*)-**S2** was prepared based on the literature procedure.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90-2.12 (br, 8H), 3.65-4.04 (br, 8H), 7.14-7.19 (m, 2H), 7.25-7.36 (m, 4H), 7.80-7.76 (m, 2H), 8.12 (s, 2H), 10.56 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3 (2C), 26.8 (2C), 47.4 (2C), 51.0 (2C), 117.1 (2C), 120.4 (2C), 123.8 (2C), 124.9 (2C), 126.9 (2C), 128.3 (2C), 129.0 (2C), 129.6

(2C), 135.3 (2C), 153.0 (2C), 169.9 (2C). IR (KBr) 3421, 2970, 1635, 1567, 1455, 1333, 1191 cm^{-1}. $[\alpha]_D^{28}$ = +46.7 (*c* 1.0, $CHCl_3$). M.p. 153-216 °C (decomposition). HRMS (FAB+) calcd for $C_{30}H_{29}N_2O_4$ $[M+H]^+$ 481.2122, found 481.2134.

(*R*)-3b: ^1H NMR (400 MHz, DMSO-d_6) δ 1.70-2.00 (m, 8H), 3.28-3.37 (m, 2H), 3.43-3.62 (m, 6H), 4.20 (br, 1H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.39 (t, *J* = 8.2 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 2H), 8.10 (d, *J* = 7.8 Hz, 2H), 8.16 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.2 (2C), 25.5 (2C), 45.5 (2C), 48.2 (2C), 121.8 (2C), 125.9 (2C), 126.1 (2C), 127.6 (2C), 128.7 (2C), 128.9 (2C), 130.3 (2C), 130.6 (2C), 131.5 (2C), 143.6 (d, J_{C-P} = 9.5 Hz, 2C), 164.5 (2C). ^{31}P NMR (161 MHz, DMSO-d_6) δ 2.66 (s, 1P). IR (KBr) 3387, 2974, 1604, 1475, 1455, 1239, 1085 cm^{-1}. M.p. 240-322 °C (decomposition). $[\alpha]_D^{29}$ = −76.5 (*c* 0.50, $CHCl_3$). HRMS (FAB+) calcd for $C_{30}H_{28}N_2O_6P$ $[M+H]^+$ 543.1679, found 543.1694.



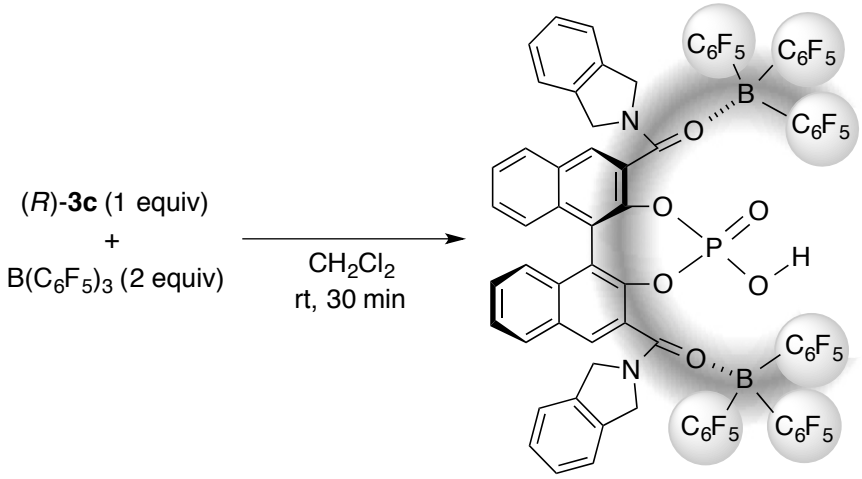
S3 **3c**, 89%

(*R*)-S3: (*R*)-**S3** was prepared based on the literature procedure.[2] ^1H NMR (400 MHz, DMSO-d_6) δ 4.84 (s, 4H), 4.89 (s, 4H), 6.98 (d, *J* = 7.8 Hz, 2H), 7.20-7.36 (m, 10H), 7.38 (d, *J* = 7.3 Hz, 2H), 7.95 (d, *J* = 7.8 Hz, 2H), 8.12 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 52.4 (2C), 54.1 (2C), 116.1 (2C), 123.2 (2C), 123.6 (2C), 123.9 (2C), 124.6 (2C), 127.2 (2C), 127.8 (2C), 127.97 (2C), 128.02 (2C), 128.3 (2C), 128.6 (2C), 129.2 (2C), 134.8 (2C), 136.5 (2C), 137.4 (2C), 150.7 (2C), 168.4 (2C). IR (KBr) 3336, 3044, 2865, 1632, 1573, 1454, 1336, 1196 cm^{-1}. $[\alpha]_D^{25}$ = +52.0 (*c* 1.0, $CHCl_3$). M.p. 200-221 °C. HRMS (ESI+) calcd for $C_{38}H_{28}N_2NaO_4$ $[M+Na]^+$ 599.1941, found 599.1946.

(*R*)-3c: (*R*)-**S3** (1.30 g, 2.25 mmol) was dissolved in pyridine (5 mL) and cooled to 0 ºC. Phosphorus oxychloride (520 μL, 5.6 mmol) was added, and the mixture was stirred at 40 ºC for 10 h. To hydrolyze the corresponding acid chloride, water (2 mL) and chloroform (10 mL) were added to the mixture, and the mixture was heated at 65 ºC for 2 h. Aqueous 1 *M* HCl solution (60 mL) was then added to pH 1 at 0 ºC, and the mixture was extracted with chloroform (10 mL × 7). Combined organic layer was washed with aqueous 1 *M* HCl, and concentrated under reduce pressure to give the crude product. The crude was purified by precipitation from chloroform/hexane to give the titled compound as a pure white solid (1.28 g, 89% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 4.78-5.50 (m, 8H), 5.00-6.20 (br, 1H), 7.19-7.30 (m, 6H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 2H), 8.12 (d,

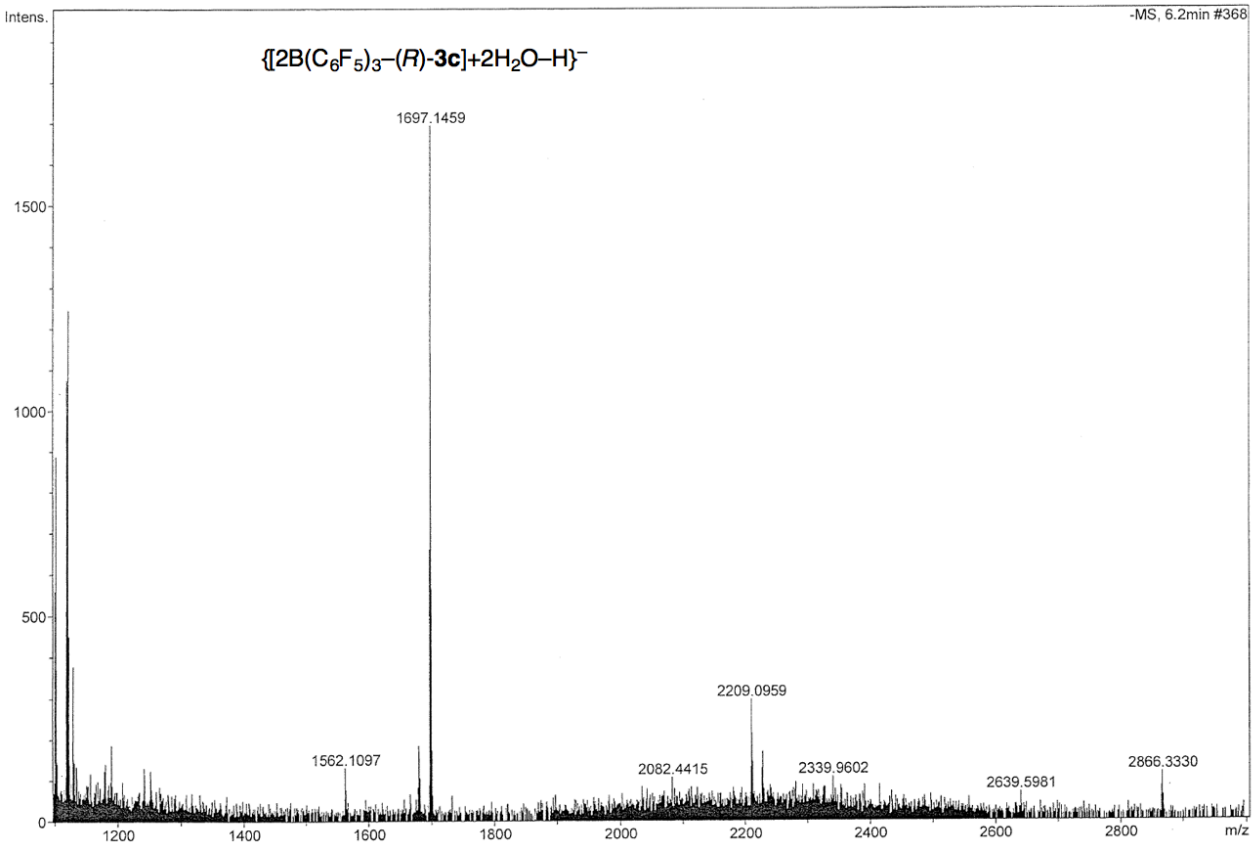
J = 8.2 Hz, 2H), 8.34 (s, 2H). ^{31}P NMR (161 MHz, DMSO-d_6) δ 2.93 (s, 1P). IR (KBr) 3430, 2868, 1627, 1458, 1399, 1286, 1241, 1094 cm^{-1}. M.p. was not measurable; decomposition at >350 °C. $[\alpha]_D^{25}$ = −170.9 (*c* 0.40, DMSO). HRMS (FAB+) calcd for $C_{38}H_{28}N_2O_6P$ $[M+H]^+$ 639.1679, found 639.1690. [^{13}C NMR analysis was performed with the use of (*R*)-**3c**•$(Et_3N)_n$ salt because of low solubility of (*R*)-**3c** only. ^{13}C NMR (100 MHz, DMSO-d_6) of (*R*)-**3c**•$(Et_3N)_n$ salt: δ 52.4 (2C), 54.0 (2C), 122.6 (2C), 122.8 (2C), 123.0 (2C), 125.3 (2C), 125.9 (2C), 127.1 (2C), 127.3 (2C), 128.0 (2C), 128.9 (2C), 129.9 (2C), 131.0 (2C), 132.0 (2C), 135.9 (2C), 137.4 (2C), 145.8 (2C), 145.9 (2C), 166.2 (2C).]

3. ESI-MS analysis of 2B(C_6F_5)$_3$–(*R*)-3c complex (Scheme 1).



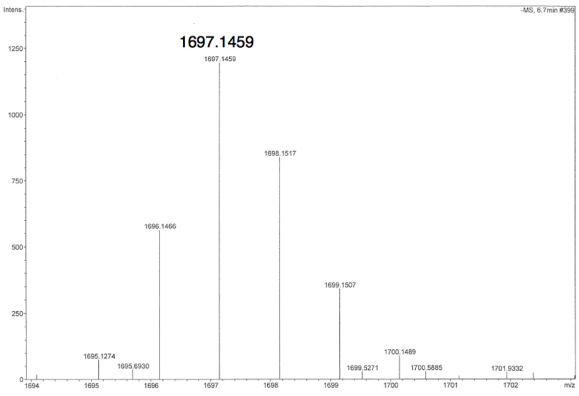
ESI-MS (neg): calc. for $C_{74}H_{30}B_2F_{30}N_2O_8P^-$ $[M+2H_2O–H]^-$ 1697.1463, found 1697.1459

To a solution of (*R*)-**3c** (31.9 mg, 0.050 mmol) in freshly-distilled dichloromethane (1 mL) was added tris(pentafluorophenyl)borane (51.2 mg, 0.10 mmol) in a well-dried Schlenk tube at room temperature (concentration: 50 m*M*). Then, 100 μL of the solution passed through a membrane filter (200 mm mesh) and was diluted with freshly-distilled dichloromethane (10 mL) in a well-dried test tube (final concentration: 0.5 m*M*), and injection to ESI-MS (negative mode). The spectrum with ion distribution for the peak (*m/z* = 1697.1459) is shown in Figure S1. $C_{74}H_{30}B_2F_{30}N_2O_8P^-$ is identified to {[2B(C_6F_5)$_3$–(*R*)-**3c**]+2H_2O–H}$^-$.

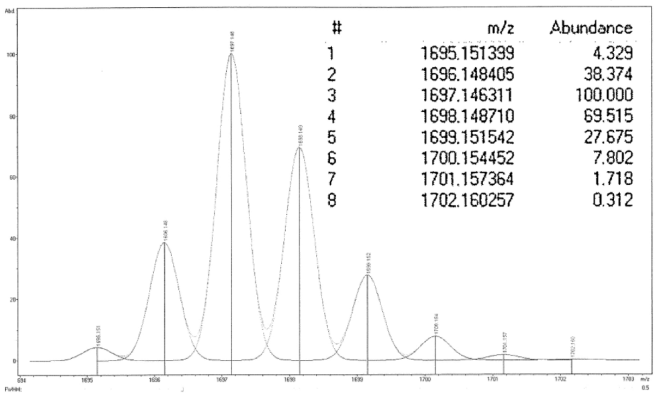


Chemical Formula: $C_{74}H_{30}B_2F_{30}N_2O_8P^-$, Exact mass (calc.): 1697.1463 (100.0%)

Observed



Theoretical



#	m/z	Abundance
1	1695.151399	4.329
2	1696.148405	38.374
3	1697.146311	100.000
4	1698.148710	69.515
5	1699.151542	27.675
6	1700.154452	7.802
7	1701.157364	1.718
8	1702.160257	0.312

Figure S1. ESI-MS spectrum of $2B(C_6F_5)_3$–(*R*)-**3c** complex with a theoretical ion distribution.

4. ^{31}P NMR analysis of 2B(C_6F_5)$_3$–(*R*)-3b and 2B(C_6F_5)$_3$–(*R*)-3c at –78 ºC.

We performed ^{31}P NMR (CD_2Cl_2) analysis of 2B(C_6F_5)$_3$–(*R*)-**3b** and 2B(C_6F_5)$_3$–(*R*)-**3c** at –78 ºC (Figure S2). In advance, complexes 2B(C_6F_5)$_3$–(*R*)-**3b** and 2B(C_6F_5)$_3$–(*R*)-**3c** were prepared in CD_2Cl_2 at room temperature for 30 min in the presence of powdered of MS 4Å, and then cooled to –78 ºC for the analysis. Complex 2B(C_6F_5)$_3$–(*R*)-**3b** (4.1 ppm) gradually decomposed, and many peaks (▼) were observed between –5 to –25 ppm within 15 min (Figures S2a and S2b). In contrast, decomposition of complex 2B(C_6F_5)$_3$–(*R*)-**3c** (–0.7 ppm) to other species (▼) at –78 °C was much slower than 2B(C_6F_5)$_3$–(*R*)-**3b**, and ca. 70% of 2B(C_6F_5)$_3$–(*R*)-**3c** was still observed for at least 15–30 min (Figures S2c and S2d).

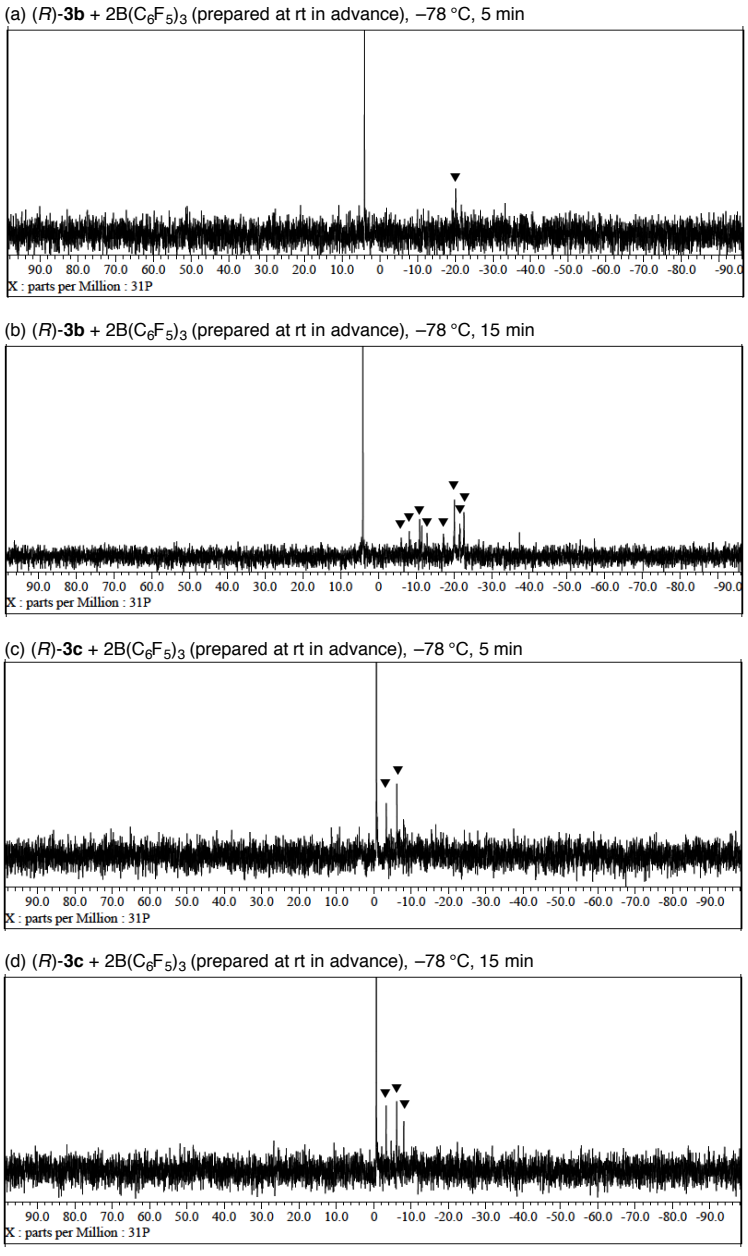
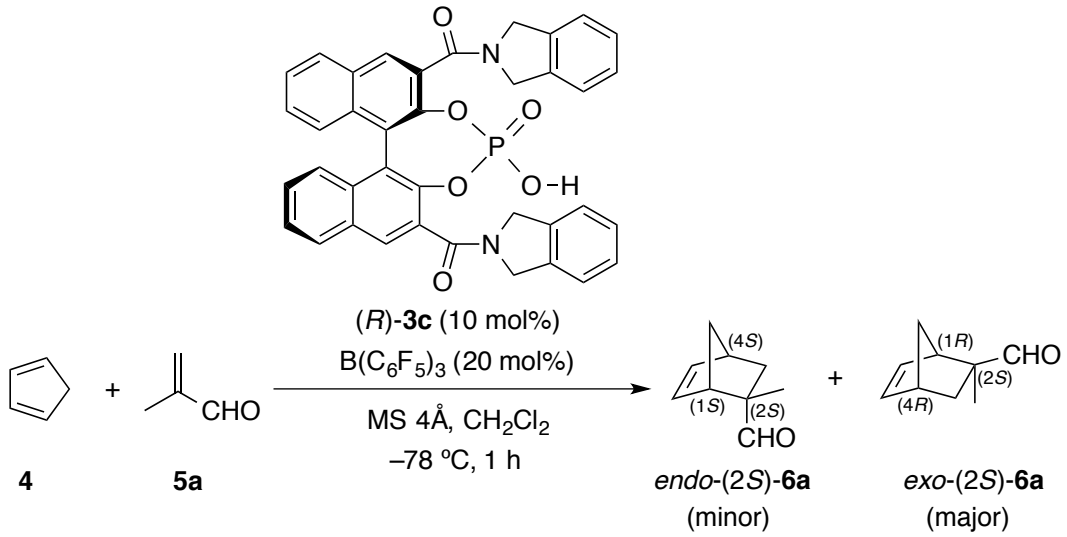
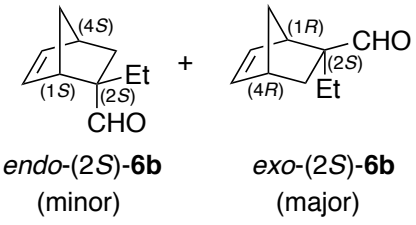


Figure S2. ^{31}P NMR analysis of 2B(C_6F_5)$_3$–(*R*)-**3b** (a and b), and 2B(C_6F_5)$_3$–(*R*)-**3c** (c and d).

5. Diels–Alder reaction of acroleins 5a–e with cyclopentadiene 4 with the use of (*R*)-3c and $B(C_6F_5)_3$ (Tables 1 and 2 and Scheme 2).



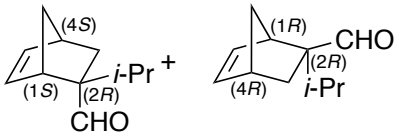
To a mixture of (*R*)-**3c** (31.9 mg, 0.050 mmol) and powdered MS 4Å (200 mg) in a Schlenk tube under a nitrogen atmosphere, tris(pentafluorophenyl)borane (51.2 mg, 0.10 mmol) and freshly-distilled dichloromethane (2 mL) were added *via* a cannula, and this suspension was stirred at room temperature for 1 h. Then, the mixture was cooled to –78 °C, and as soon as possible (within 5 min) after cooling to –78 °C methacrolein **5a** (95% purity, 43.4 μL, 0.50 mmol) and freshly-distilled cyclopentadiene **4** (203 μL, 2.5 mmol) were added at –78 °C. After that, the resultant mixture was stirred at –78 °C for 1 h. To quench the reaction, triethylamine (0.2 mL) was poured into the reaction mixture at –78 °C. The product mixture was directly purified by silica gel column chromatography (Kanto Chemical Co., Inc. 37560; eluent: pentane:diethyl ether = 9:1). Solvents were removed under 200 Torr at 20 °C by a rotary evaporator, and the product was obtained (68.2 mg, >99% yield). ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were consistent with previously reported values.[2] The *endo/exo* ratio of **6a** was determined by ^{1}H NMR ($CDCl_3$) analysis; δ 9.40 (s, 1H, CHO (*endo*-**6a**)), 9.69 (s, 1H, CHO (*exo*-**6a**)). The enantioselectivity and absolute stereochemistry of **6a** was determined by GC analysis according to the literature.[2]



^{1}H NMR data was consistent with previously reported values.[3] The *endo/exo* ratio of **6b** was determined by ^{1}H NMR ($CDCl_3$) analysis; δ 9.42 (s, 1H, CHO (*endo*-**6b**)), 9.69 (s, 1H, CHO

(*exo*-**6b**)). The enantioselectivity and absolute stereochemistry of **6b** was determined by GC analysis (CHIRALDEX B-DM, 90 °C), t_R = 21.9 min. (*exo*-(1*R*,2*S*,4*R*)-isomer), 23.9 min. (*exo*-(1*S*,2*R*,4*S*)-isomer).

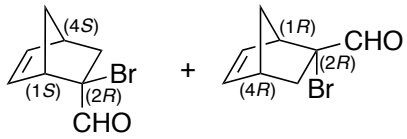
(1*R*,2*S*,4*R*)-2-Ethylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (*exo*-(2*S*)-6b):[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (t, *J* = 7.8 Hz, 3H), 1.20-1.65 (m, 5H), 2.14 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.86 (brs, 1H), 2.94 (brs, 1H), 6.08 (dd, *J* = 5.7, 2.7 Hz, 1H), 6.27 (dd, *J* = 5.7, 2.7 Hz, 1H), 9.69 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 27.8, 32.7, 42.5, 46.6, 47.3, 59.4, 133.1, 139.5, 206.3. HRMS (EI) (*endo*/*exo* = 2/98) calcd for $C_{10}H_{14}O$ $[M]^+$ 150.1045, found 150.1038.



endo-(2*R*)-**6c** (minor) *exo*-(2*R*)-**6c** (major)

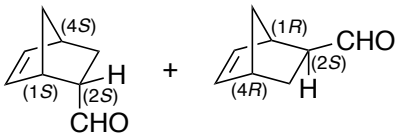
The *endo/exo* ratio of **6c** was determined by ^{1}H NMR ($CDCl_3$) analysis; δ 9.58 (s, 1H, CHO (*endo*-**6c**)), 9.89 (s, 1H, CHO (*exo*-**6c**)). The enantioselectivity and absolute stereochemistry of **6c** was determined by GC analysis (CHIRALDEX B-DM, 80 °C), t_R = 13.1 min. (*exo*-(1*R*,2*R*,4*R*)-isomer), and 13.8 min. (*exo*-(1*S*,2*S*,4*S*)-isomer).

(1*R*,2*R*,4*R*)-2-Isopropylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (*exo*-(2*R*)-6c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (dd, *J* = 11.9, 2.7 Hz, 1H), 0.88 (d, *J* = 7.2 Hz, 3H), 1.09 (d, *J* = 7.2 Hz, 3H), 1.37 (m, 1H), 1.45 (m, 1H), 1.90 (septet, *J* = 7.2 Hz, 1H), 2.28 (dd, *J* = 11.9, 4.1 Hz, 1H), 2.83 (brs, 1H), 3.14 (brs, 1H), 6.10 (dd, *J* = 6.0, 3.0 Hz, 1H), 6.25 (dd, *J* = 6.0, 3.0 Hz, 1H), 9.89 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 19.0, 33.3, 35.8, 42.4, 46.4, 47.4, 62.5, 132.3, 139.8, 207.2. HRMS (EI) (*endo*/*exo* = 15/85) calcd for $C_{11}H_{16}O$ $[M]^+$ 164.1201, found 164.1194.



endo-(2*R*)-**6d** (minor) *exo*-(2*R*)-**6d** (major)

^{1}H NMR, ^{13}C NMR, IR, and HRMS data were consistent with previously reported values.[2] The *endo/exo* ratio of **6d** was determined by ^{1}H NMR ($CDCl_3$) analysis; δ 9.32 (s, 1H, CHO (*endo*-**6d**)), 9.54 (s, 1H, CHO (*exo*-**6d**)). The enantioselectivity and absolute stereochemistry of **6d** was determined by GC analysis according to the literature.[2]

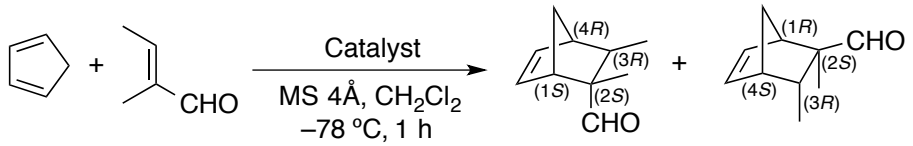


endo-(2*S*)-**6e** *exo*-(2*S*)-**6e**

^{1}H NMR, ^{13}C NMR, IR, and HRMS data were consistent with previously reported values.[2] The *endo/exo* ratio was determined by ^{1}H NMR ($CDCl_3$) analysis; δ 9.42 (d, *J* = 2.7 Hz, 1H, CHO (*endo*-**6e**)), 9.79 (d, *J* = 2.7 Hz, 1H, CHO (*exo*-**6e**)). The enantioselectivity and absolute stereochemistry of **6e** was determined by GC analysis according to the literature.[2]

6. Evaluation of catalytic activity.

We could not evaluate the catalytic activity of $2B(C_6F_5)_3$–(*R*)-**3c** and free $B(C_6F_5)_3$ in the reaction between cyclopentadiene **4** and methacrolein **5a**, since **5a** is highly reactive in Table 1 (See the main text). Therefore, in place of **5a**, we used tiglic aldehyde **7** as shown below (Eq. S1, also see Scheme 3 in the main text). As a result, $2B(C_6F_5)_3$–(*R*)-**3c** (38% yield) was more active than $B(C_6F_5)_3$–(*R*)-**3c** (0% yield) and free $B(C_6F_5)_3$ (3–25% yield). Based on these results, it might be reasonable that *exo*-**6a** was obtained with high enantioselectivity (85% ee) when the catalyst was prepared under the conditions at –78 °C for 30 min before the addition of substrates **4** and **5a** (Table 1, entry 17).

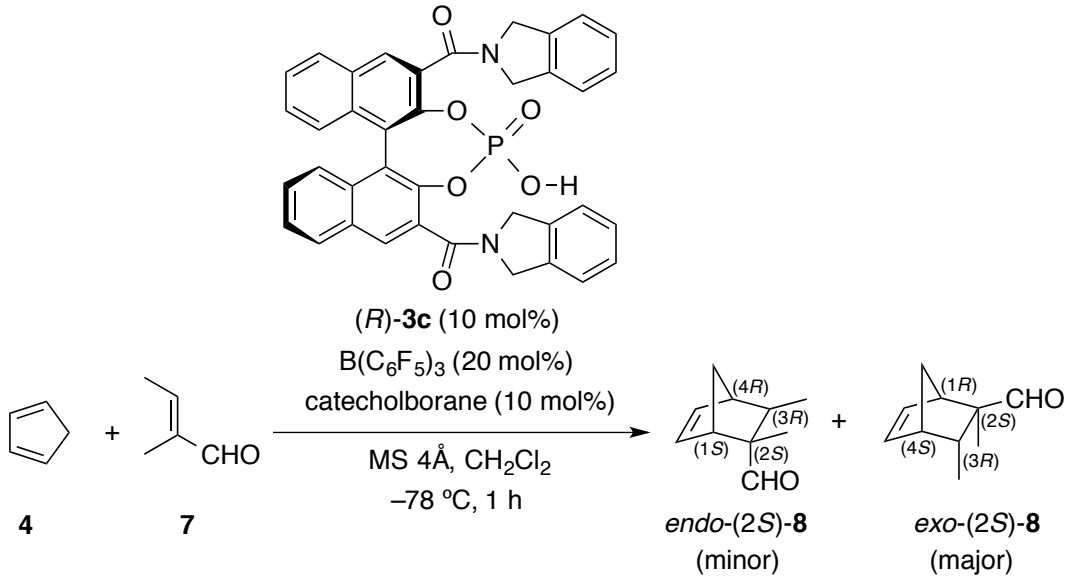


(S1)

4 **7** *endo*-(2*S*)-**8** (minor) *exo*-(2*S*)-**8** (major)

Catalyst	Yield and enantioselectivity
(*R*)-**3c** (10 mol%), $B(C_6F_5)_3$ (20 mol%), and catecholborane (10 mol%)	71% (*endo*:*exo* = 3:97), 75% ee (*exo*)
(*R*)-**3c** (10 mol%) and $B(C_6F_5)_3$ (20 mol%)	38% (*endo*:*exo* = 1:>99), 56% ee (*exo*)
(*R*)-**3c** (10 mol%) and $B(C_6F_5)_3$ (10 mol%)	0%
$B(C_6F_5)_3$ (10 mol%)	3% (*endo*:*exo* = 1:>99)
$B(C_6F_5)_3$ (20 mol%)	25% (*endo*:*exo* = 1:>99)
None (toluene, 110 ºC, 3 h)	0%

7. Diels–Alder reaction of tiglic aldehyde 7 with cyclopentadiene 4 with the use of (*R*)-3c, $B(C_6F_5)_3$, and catecholborane (Scheme 3).

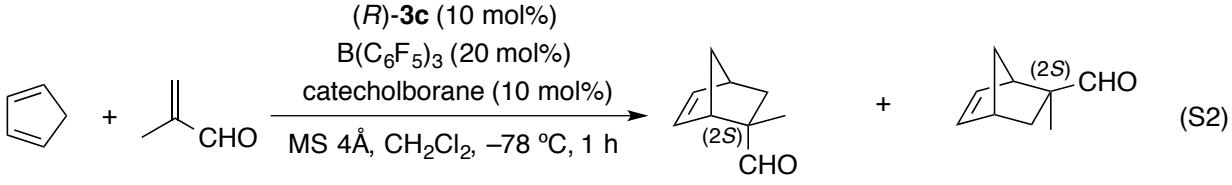


To a mixture of (*R*)-**3c** (31.9 mg, 0.050 mmol) and powdered MS 4Å (200 mg) in a Schlenk tube under a nitrogen atmosphere, tris(pentafluorophenyl)borane (51.2 mg, 0.10 mmol) and freshly-distilled dichloromethane (2 mL) were added *via* a cannula, and this suspension was stirred at room temperature for 1 h. 0.5 *M* Catecholborane dichloromethane solution (100 μL, 0.050 mmol) was added, and the mixture was stirred at room temperature until the finish of H_2 gas generation (ca. 5 min). Then, the mixture was cooled to –78 °C, and tiglic aldehyde **7** (95% purity, 50.4 μL, 0.50 mmol) and freshly-distilled cyclopentadiene **4** (203 μL, 2.5 mmol) were added. After that, the resultant mixture was stirred at –78 °C for 1 h. To quench the reaction, triethylamine (0.2 mL) was poured into the reaction mixture at –78 °C. The product mixture was directly purified by silica gel column chromatography (Kanto Chemical Co., Inc. 37560; eluent: pentane:diethyl ether = 9:1 to 5:1). Solvents were removed under 200 Torr at 20 °C by a rotary evaporator, and the product was obtained (53.3 mg, 71% yield). ^{1}H NMR data was consistent with previously reported values.[4] The *endo/exo* ratio of **8** was determined by ^{1}H NMR ($CDCl_3$) analysis; 9.34 (s, 1H, CHO (*endo*-**8**)) and 9.62 (s, 1H, CHO (*exo*-**8**)). The enantioselectivity and absolute stereochemistry of **6** was determined by GC analysis (CHIRALDEX B-DM, 100 °C),[5] t_R = 3.9 min. (*exo*-(1*S*,2*R*,3*S*,4*R*)-isomer), and 4.1 min. (*exo*-(1*R*,2*S*,3*R*,4*S*)-isomer).

(1*R*,2*S*,3*R*,4*S*)-2,3-Dimethylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (*exo*-(2*S*)-8):[4,5] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.75 (d, *J* = 7.3 Hz, 3H), 0.86 (s, 3H), 1.20-1.50 (m, 2H), 2.54 (dq, *J* = 7.3, 3.2 Hz, 1H), 2.76 (brs, 1H), 2.81 (brs, 1H), 6.20 (dd, *J* = 5.5, 3.2 Hz, 1H), 6.29 (dd, *J* = 5.5, 3.2 Hz, 1H), 9.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 15.4, 37.3, 46.5, 49.2, 50.3, 56.0, 135.2, 138.0, 206.0. HRMS (EI) (*endo*/*exo* = 3/97) calcd for $C_{10}H_{14}O$ $[M]^+$ 150.1045, found 150.1041.

8. Diels–Alder reaction of acroleins 5a–e with cyclopentadiene 4 with the use of (*R*)-3c, $B(C_6F_5)_3$, and catecholborane.

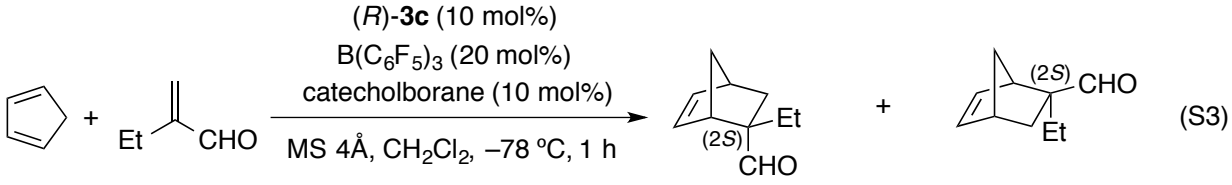
To evaluate the supramolecular catalyst prepared from (*R*)-**3c**, $B(C_6F_5)_3$, and catecholborane, we examined the reactions of acroleins **5a**–**e** with cyclopentadiene **4** (Eqs. S2–S6). However, better enantioselectivities were not observed compared with $2B(C_6F_5)_3$–(*R*)-**3c**, as shown in Table 2 and Scheme 2.



(S2)

4 **5a** *endo*-(2*S*)-**6a**, 59% ee *exo*-(2*S*)-**6a**, 69% ee

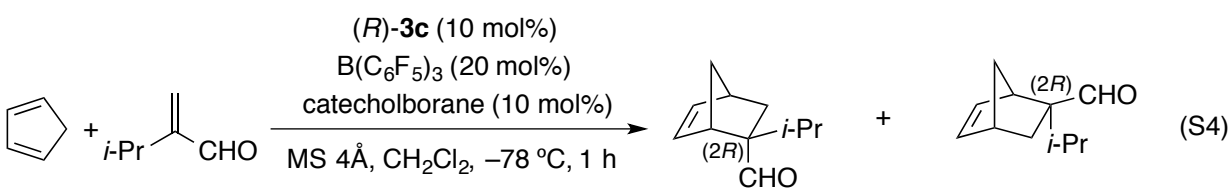
98% (*endo*-**6a**:*exo*-**6a** = 8:92)



(S3)

4 **5b** *endo*-(2*S*)-**6b**, 0% ee *exo*-(2*S*)-**6b**, 17% ee

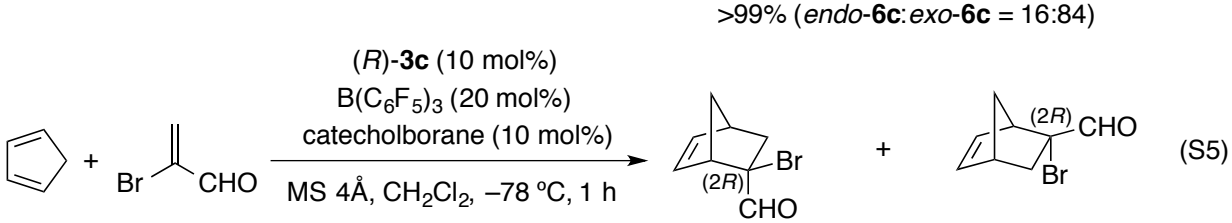
>99% (*endo*-**6b**:*exo*-**6b** = 12:88)



(S4)

4 **5c** *endo*-(2*R*)-**6c**, 0% ee *exo*-(2*R*)-**6c**, 0% ee

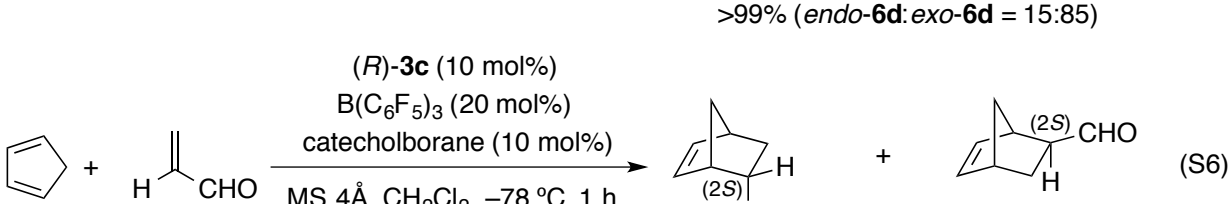
>99% (*endo*-**6c**:*exo*-**6c** = 16:84)



(S5)

4 **5d** *endo*-(2*R*)-**6d**, 0% ee *exo*-(2*R*)-**6d**, 0% ee

>99% (*endo*-**6d**:*exo*-**6d** = 15:85)



(S6)

4 **5e** *endo*-(2*S*)-**6e**, 12% ee *exo*-(2*S*)-**6e**, 0% ee

94% (*endo*-**6e**:*exo*-**6e** = 68:32)

9. References.

1. Erkkilä, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538.
2. Hatano, M.; Mizuno, T.; Izumiseki, A.; Usami, R.; Asai, T.; Akakura, M.; Ishihara, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 12189.
3. Sprott, K. T.; Corey, E. J. *Org. Lett.* **2003**, *5*, 2465.
4. Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920.
5. Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *Chem. Commun.* **2009**, *45*, 1956.

Chapter 3

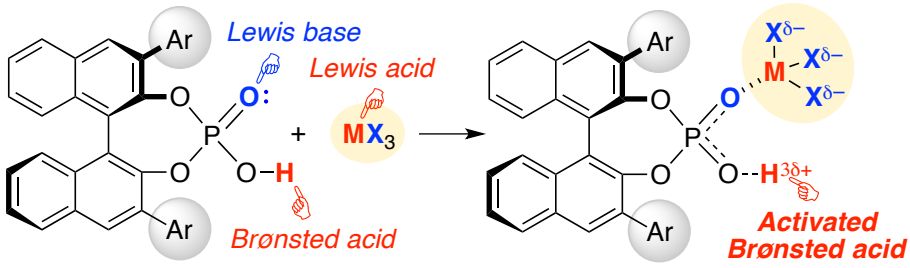
Boron Tribromide-Assisted Chiral Phosphoric Acid Catalysts for Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines

Abstract: BBr_3–chiral phosphoric acid complexes were 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.

3-1 Introduction

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 BINOL (1,1'-bi-2-naphthol)-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).

Scheme 1. Achiral Lewis Acid-assisted Chiral Phosphoric Acid Catalysts as Chiral Acid–base Cooperative Catalysts.



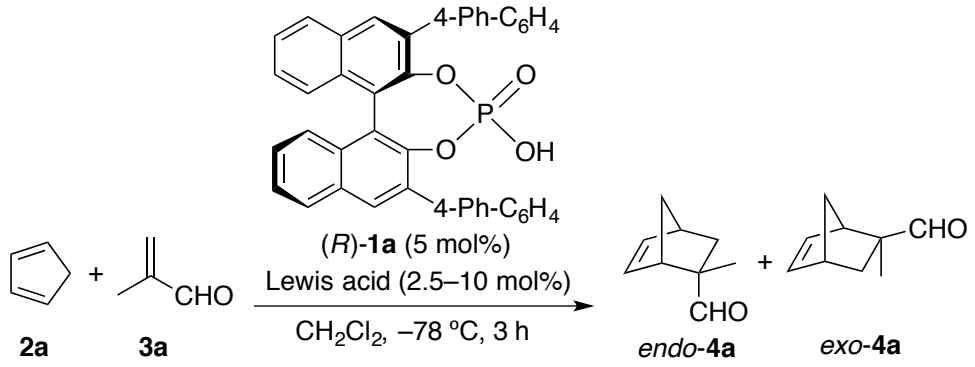
As a great advantage of this LBA system, we can simply use highly practical chiral phosphoric acids without serious synthetic difficulties. In particular, we developed here a BBr_3-assisted chiral phosphoric acid *in situ*, which was highly effective for the enantioselective Diels–Alder reaction of α-substituted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

3-2 Results and Discussion

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 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 (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.

Table 1. Optimization of the Reaction Conditions[a]

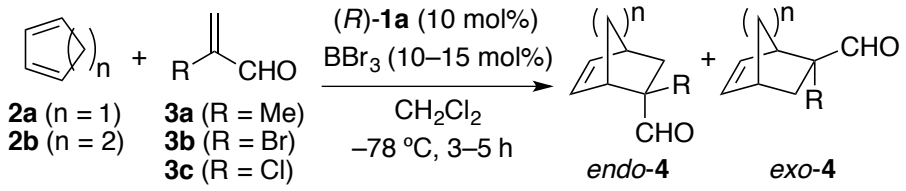


entry	Lewis acid (mol%)	yield (%)	*endo*:*exo*	ee (%) of *exo*-**4a**
1	–	0	–	–
2[b]	–	51	13:87	–7
3	$B(C_6F_5)_3$ (5)	64	10:90	5
4[c]	$BF_3{\cdot}Et_2O$ (5)	87	3:97	52
5	BCl_3 (5)	88	4:96	62
6	BBr_3 (2.5)	92	3:97	61
7	**BBr_3 (5)**	**99**	**2:98**	**89**
8	BBr_3 (7.5)	78	2:98	85
9	BBr_3 (10)	64	8:92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

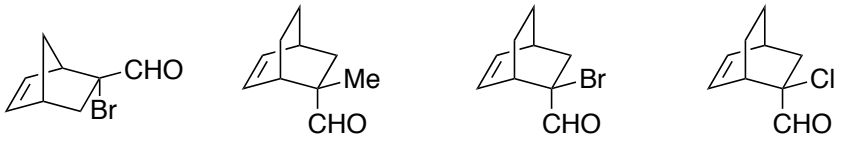
[a] The reaction was carried out with (*R*)-**1a** (5 mol%), Lewis acid (2.5–10 mol%), **2a** (5 equiv), and **3a** (1 equiv) in dichloromethane at –78 °C for 3 h. [b] The reaction was conducted at room temperature for 3 h. [c] Et_2O was removed *in vacuo* during catalyst preparation. [d] The reaction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

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** 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 slightly 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]

Scheme 2. Reactions of α-Substituted Acroleins.



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

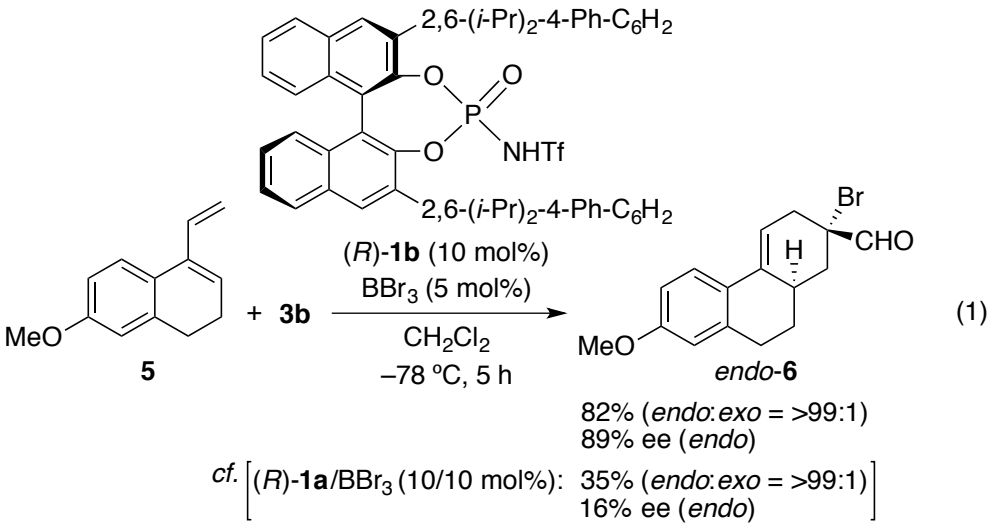


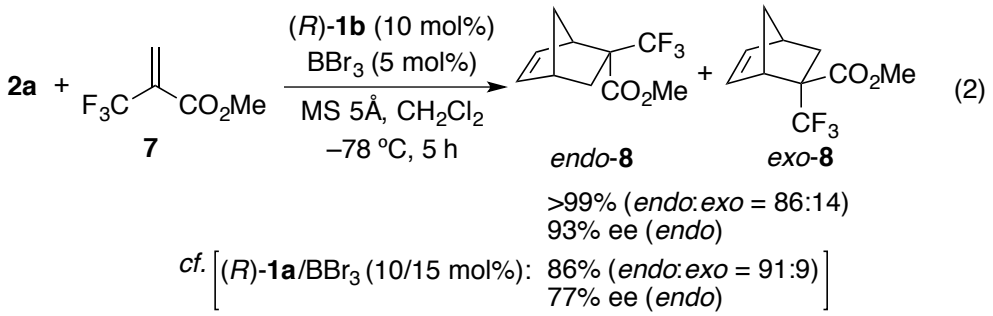
exo-**4b**	*endo*-**4c**	*endo*-**4d**	*endo*-**4e**
3 h, >99% yield[a]	4 h, 88% yield[b]	3 h, >99% yield[a]	5 h, 88% yield[a]
endo:*exo* = 5:95	*endo*:*exo* = 97:3	*endo*:*exo* = 94:6	*endo*:*exo* = 94:6
86% ee (*exo*)	87% ee (*endo*)	91% ee (*endo*)	94% ee (*endo*)

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

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 Diels–Alder 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]

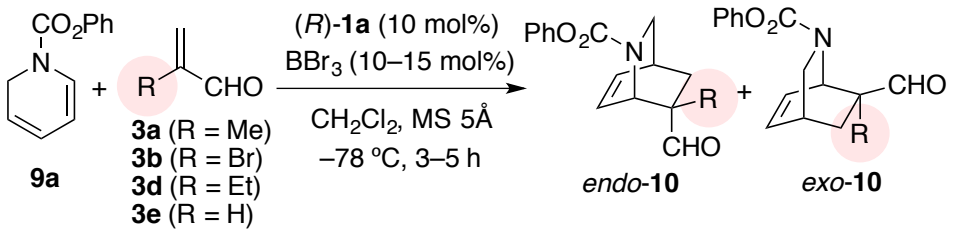




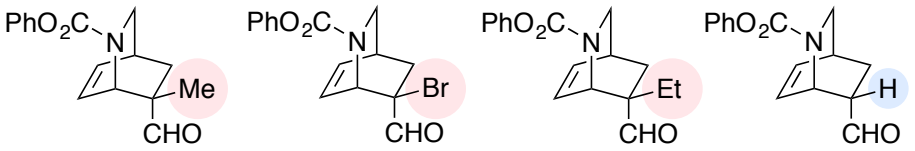
We next performed the reaction with 1,2-dihydropyridine **9a**, which can provide synthetically useful optically active isoquinuclidines.[8] The reactions of **9a** and acrolein **3e** proceeded smoothly with the use of BBr_3–(*R*)-**1a** catalyst, and the key compound **10d** for the important anti-influenza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

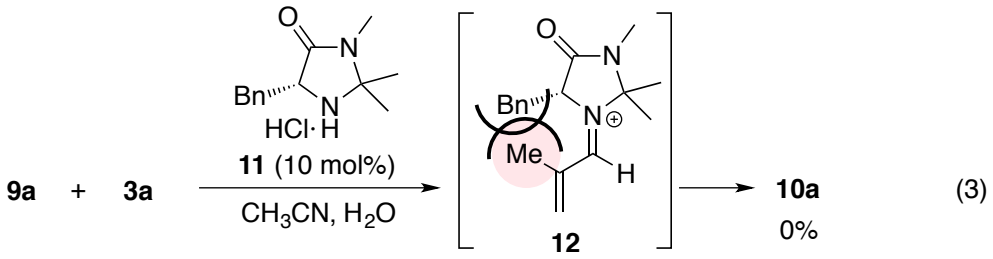
Scheme 3. Reactions of 1,2-Dihydropyridines.

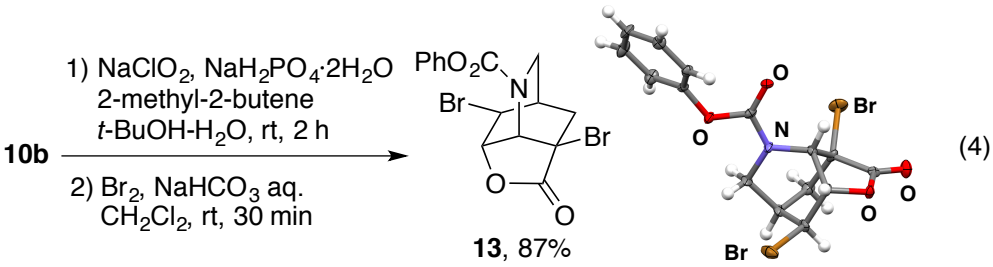


Products **10**, reaction time, yield, and enantioselectivity.



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

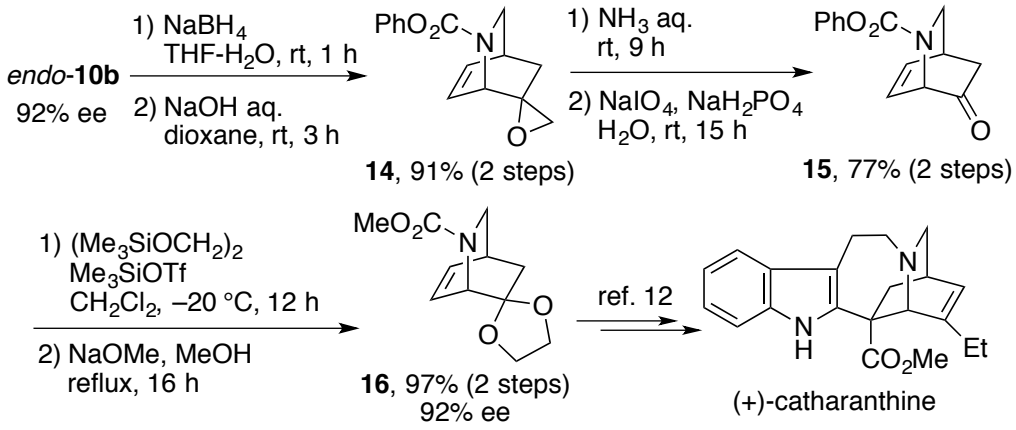




To demonstrate the synthetic utility of our catalytic system, we performed a formal total synthesis of (+)-catharanthine, which is an important indole alkaloid that forms vinblastine, which

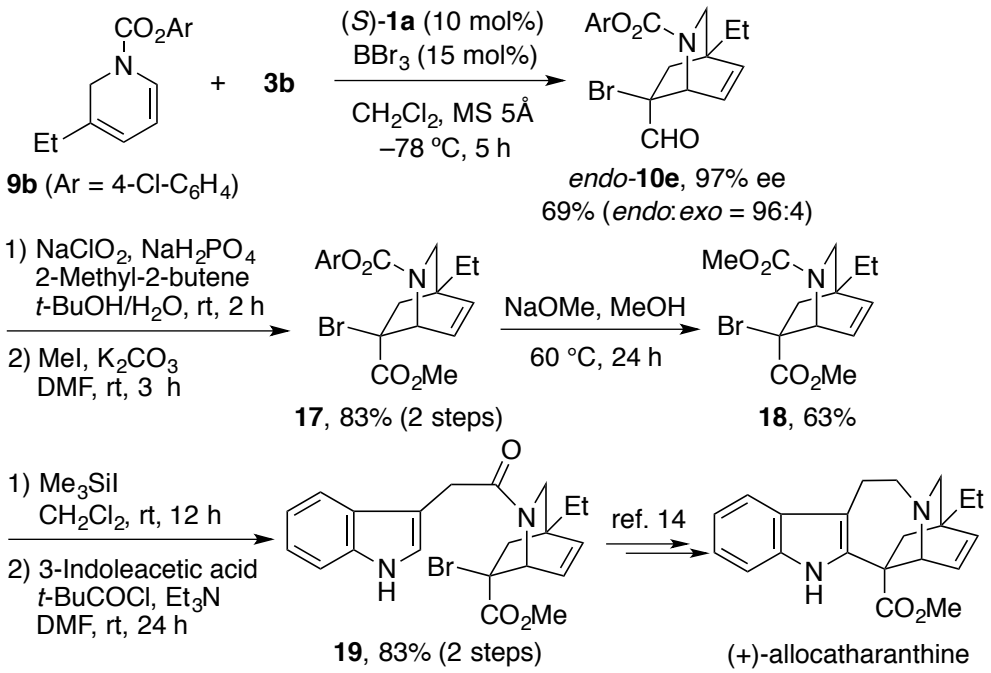
has high antitumor activities (Scheme 4).[11] After Diels–Alder product **10b** was reduced to the alcohol with $NaBH_4$, epoxidation under basic conditions gave **14**. Treatment of **14** with aqueous ammonia and subsequent oxidation with sodium periodate gave the ketone **15**. Acetalization of **15** 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.

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



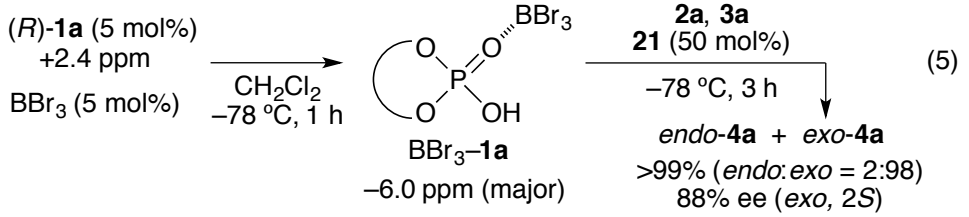
Moreover, we performed a transformation to the key intermediate of (+)-allocatharanthine, which is another component of vinblastine (Scheme 5).[13] Actually, the enantioselective Diels–Alder reactions of alkyl-substituted 1,2-dihydropyridines are still limited with the use of **3e**.[8f] As a great advantage of our catalytic system, the Diels–Alder 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].

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

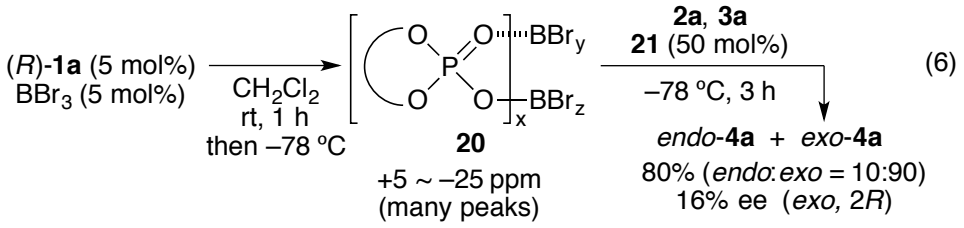


Finally, we turn our attention to mechanistic aspects. To identify a possible P=O···BBr_3 structure without the generation of HBr[15], we performed a ^{31}P NMR analysis of a 1:1 molar ratio of (*R*)-**1a** and BBr_3 in dichloromethane (eq 5). As a result, a new signal, indicating BBr_3–(*R*)-**1a**, 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 ES 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 ES 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 ES). 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 v.s. 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 ES for ^1H NMR for PO_2H).

^{31}P NMR analysis and catalysis:

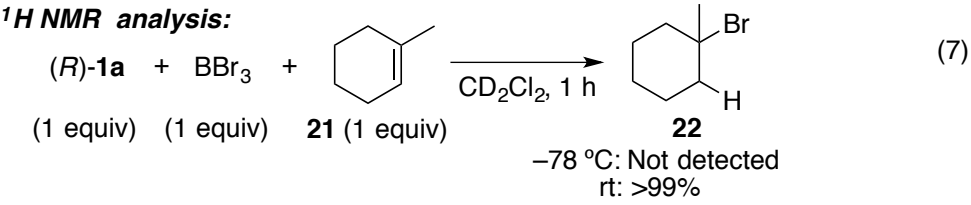


(5)



(6)

^{1}H NMR analysis:



(7)

A possible structure of the BBr_3–**1a**–**3b** complex was considered based on theoretical calculations (See the ES in detail). 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 ES). 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.

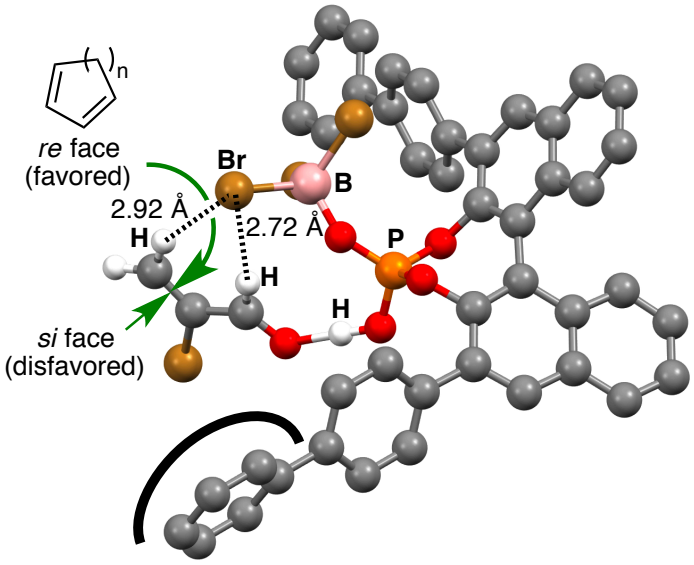


Figure 6. B3LYP/6-31G*-Optimized Geometry of BBr_3–(*R*)-1a–3b Complex

3-3 Conclusion

In summary, we have developed BBr_3-assisted chiral phosphoric acids as highly effective LBA catalysts.[18] In particular, the enantioselective Diels–Alder reactions of α-substituted acroleins with 1,2-dihydropyridines proceeded, and synthetically useful optically active intermediates for bioactive indole alkaloids were obtained.

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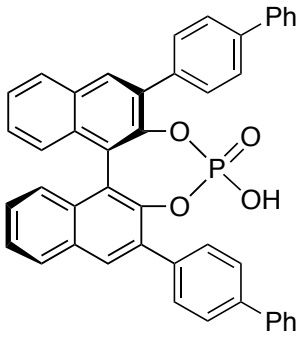
Experimental Section for Chapter 3

1. General methods.

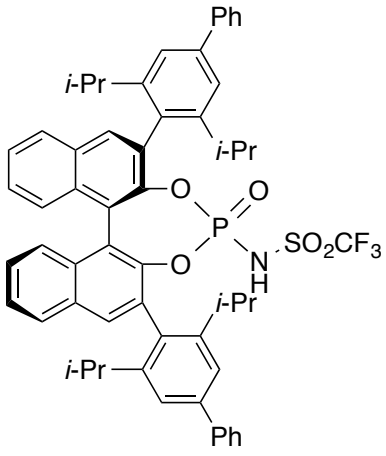
^{1}H NMR spectra were measured on a JEOL ECS400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, sept = septet, m = multiplet, br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS400 (100 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.10 ppm). ^{31}P NMR spectra were measured on a JEOL ECS-400 (161 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard (H_3PO_4 at 0 ppm). ^{19}F NMR spectra were measured on a JEOL ECS-400 (376 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard ($CFCl_3$ at 0 ppm). ^{11}B NMR spectra were measured on a JEOL ECS-400 (128 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard ($BF_3 \cdot Et_2O$ at 0 ppm). Gas-liquid-phase chromatography (GC) was performed with Shimadzu GC-2010 instrument with a flame-ionization detector and a capillary column of ULBON HR-20M (PEG-20M) (i.d., 0.25 mm × 25 m; GL Science Inc.), CP-Cyclodextrin-β-2,3,6-M-19 (i.d. 0.25 mm × 25 m; CHROMPACK; GL Science Inc.), or CHIRALDEX B-CP, B-DM, G-TA (i.d., 0.25 mm × 20 m; Tokyo Kasei Kogyo Co., LTD). High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-20 AD coupled diode array-detector SPD-M20A and chiral column of Daicel CHIRALCEL, CHIRALPAK; AD-H, AD-3, AS-3, OD-H, OJ-H, IA-3, IC-3. Optical rotations were measured on Rudolph Autopol IV digital polarimeter. The products were purified by column chromatography on silica gel (Kanto Chemical Co., Inc. 37560; Merck silica gel 60, Prod. No. 1.09385.9929). Mass spectral analyses were performed at Chemical Instrument Center, Nagoya University (JEOL JMS-700 (FAB), JEOL JMS-T100GCV (EI), Bruker Daltonics micrOTOF-QII (ESI)). X-ray analyses were performed by Rigaku PILATUS-200K. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60GF254 0.25 mm) were used. Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and

phosphomolybdic acid. Dichloromethane (with P_4O_{10}) was freshly distilled in prior to use. Cyclohexadiene (**2b**), methacrolein (**3a**), α-ethylacrolein (**3d**), and acrolein (**3e**) are commercially available and were used without any purification. α-Bromoacrolein (**3b**) and α-chloroacrolein (**3c**) were synthesized as reported procedures.[1] Cyclopentadiene (**2a**) was freshly distilled in prior to use.

2. Preparation of phosphoric acids.

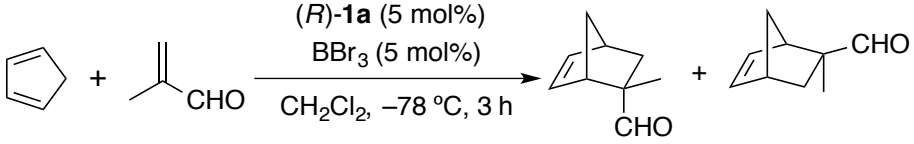


(*R*)-3,3'-Bis(biphenyl-4-yl)-1,1'-binaphthalene-2,2'-diyl hydrogen phosphate (1a): The titled compound was prepared according to the literature procedure.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (br, 1H), 7.13-7.45 (m, 18H), 7.51 (m, 2H), 7.61 (d, J = 8.2 Hz, 4H), 7.96 (d, J = 8.2 Hz, 2H), 8.02 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.5 (2C), 126.0 (2C), 126.6 (2C), 127.0 (4C), 127.1 (2C), 127.2 (4C), 128.5 (4C), 130.1 (4C), 131.3 (2C), 131.6 (2C), 132.0 (2C), 133.6 (2C), 133.7 (2C), 135.6 (2C), 140.5 (2C), 140.8 (2C), 144.5 (2C), 144.6 (2C). ^{31}P NMR (161 MHz, $CDCl_3$) δ 2.8. IR (KBr) 3433, 3051, 1488, 1419, 1244, 1181, 1023 cm^{-1}. M.p. 215–223 °C (decomposition). $[\alpha]_D^{26}$ = –352.0 (*c* 0.40, $CHCl_3$). HRMS (ESI–) calcd for $C_{44}H_{28}O_4P$ $[M–H]^-$ 651.1731, found 651.1740.



(*R*)-3,3'-Bis(2,6-diisopropyl-biphenyl-4-yl)-1,1'-binaphthalene-2,2'-diyl *N*-triflyl phosphoramide (1b): The titled compound was prepared according to the literature procedure.[3–5] ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.90 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H), 1.15 (d, J = 6.4 Hz, 6H), 1.25 (d, J = 6.9 Hz, 6H), 1.30 (d, J = 6.4 Hz, 3H), 1.32 (d, J = 6.4 Hz, 3H), 2.60 (sept, J = 6.8 Hz, 1H), 2.65 (sept, J = 6.8 Hz, 1H), 2.93 (sept, J = 6.4 Hz, 1H), 3.03 (sept, J = 6.4 Hz, 1H), 6.73 (br, 1H), 6.98 (d, J = 6.9 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 7.30-7.54 (m, 14H), 7.69 (d, J = 7.8 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H), 7.98 (s, 1H), 8.00 (s, 1H), 8.08 (d, J = 6.4 Hz, 1H), 8.09 (d, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 22.4, 23.1 (2C), 23.5, 24.6, 24.8, 26.2, 26.5, 30.3, 30.4, 30.7, 30.9, 120.1, 121.9 (q, J_{C-F} = 323 Hz), 120.6, 121.1, 121.4, 121.6, 121.9, 125.3, 125.6, 125.9, 126.5 (2C), 126.7 (2C), 126.9 (2C), 127.1, 127.2, 128.4, 128.5, 128.9 (2C), 130.0, 130.4, 131.2 (2C), 131.5, 131.8, 131.9, 132.1, 132.3, 133.8, 134.3, 139.7, 140.0, 141.1, 141.4, 146.2, 146.3, 147.1, 147.2 (2C), 147.4, 148.0, 148.1. ^{19}F (376 MHz, d_6-DMSO) δ –79.0. ^{31}P NMR (161 MHz, d_6-DMSO) δ –0.70. IR (KBr) 3448, 2962, 1301, 1200, 1149 cm^{-1}. M.p. 204–255 °C (decomposition). $[\alpha]_D^{23}$ = –45.1 (c 1.00, $CHCl_3$). HRMS (FAB+) calcd for $C_{57}H_{53}F_3NO_5PS$ $[M]^+$ 951.3333, found 951.3333.

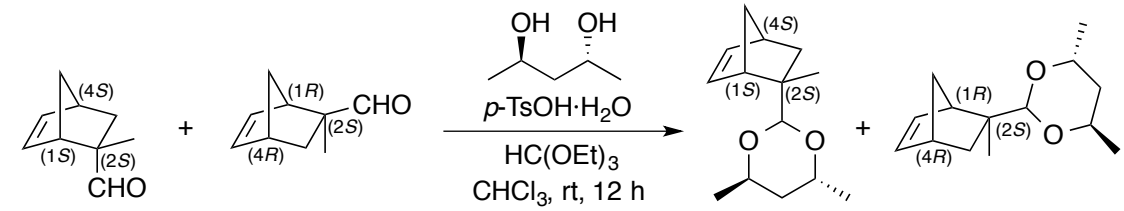
3. Enantioselective Diels–Alder reaction of acroleins 3 with simple cyclic dienes 2 (Table 1 and Scheme 2).



2a **3a** *endo*-**4a** *exo*-**4a**

A solution of (*R*)-**1a** (16.3 mg, 0.025 mmol) in freshly distilled dichloromethane (2 mL) was stirred at room temperature in Schlenk tube under a nitrogen atmosphere. To the mixture was added boron tribromide (1 *M* in dichloromethne, 25 μL, 0.025 mmol) at –78 ºC, and this solution was stirred at that temperature for 20 min. Methacrolein **3a** (95% purity, 43.4 μL, 0.50 mmol) and freshly distilled cyclopentadiene **2a** (203 μL, 2.5 mmol) were then added dropwise at –78 ºC. After 3 h, the reaction was quenched with triethylamine (200 μL) at –78 ºC. The product mixture was directly purified by neutral silica gel column chromatography (eluent: pentane:diethyl ether = 100:1 to 9:1). Solvents were removed under 200 Torr at 15 °C by rotary evaporator, and the product (*endo*/*exo*) mixture was obtained in 99% yield (68.1 mg).

4a: Reaction conditions; (*R*)-**1a**/BBr_3 = 5/5 mol%, –78 ºC, 3 h, 0.25 *M* of **3a**. The *endo*/*exo* ratio was determined by ^{1}H NMR analysis; δ 9.40 (s, 1H, CHO (*endo*-**4a**)), 9.69 (s, 1H, CHO (*exo*-**4a**)), *endo*:*exo* = 2:98. The enantioselectivity was determined by GC analysis after conversion to chiral acetals by (–)-(2*R*,4*R*)-2,4-pentanediol [General procedure for acetalization: A mixture of the Diels–Alder adduct, (–)-(2*R*,4*R*)-2,4-pentanediol (2 equiv), triethyl orthoformate (2 equiv), and *p*-toluenesulfonic acid monohydrate (0.4 equiv) in chloroform was stirred at room temperature for 12 h. After the full conversion (TLC check), neutral silica gel column chromatography (eluent: pentane:diethyl ether = 100:1 to 8:1) afforded the purified chiral acetals.]; GC analysis (ULBON HR-20M (PEG-20M), 80 °C), t_R = 19.5 min. (*endo*-(1*S*,2*S*,4*S*)-isomer), 25.2 min. (*endo*-(1*R*,2*R*,4*R*)-isomer), 27.3 min. (*exo*-(1*S*,2*R*,4*S*)-isomer), and 28.7 min (*exo*-(1*R*,2*S*,4*R*)-isomer).



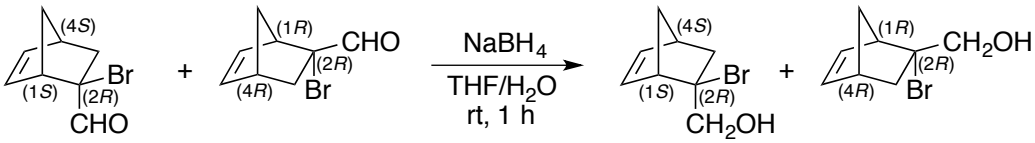
endo-(2*S*)-**4a** (minor) | *exo*-(2*S*)-**4a** (major) | *endo*-(2*S*)-**4a'** (minor) | *exo*-(2*S*)-**4a'** (major)

(1*R*,2*S*,4*R*)-2-Methylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (*exo*-(2*S*)-4a):[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, *J* = 12.0 Hz, 1H), 1.01 (s, 3H), 1.39 (m, 2H), 2.25 (dd, *J* = 12.0, 3.9 Hz, 1H), 2.82 (brs, 1H), 2.90 (brs, 1H), 6.11 (dd, *J* = 6.0, 3.0 Hz, 1H), 6.30 (dd, *J* = 6.0, 3.0 Hz, 1H), 9.69 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 34.6, 43.2, 47.6, 48.5, 53.9, 133.1, 139.6, 205.9. HRMS (EI) calcd for $C_9H_{12}O$ $[M]^+$ 136.0888, found 136.0893.

(4*R*,6*R*)-4,6-Dimethyl-2-((1*R*,2*S*,4*R*)-2-methylbicyclo[2.2.1]hept-5-en-2-yl)-1,3-dioxane (*exo*-(2*S*)-4a'):[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (dd, *J* = 12.0, 2.7 Hz, 1H), 0.87 (s, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.35 (d, *J* = 6.9 Hz, 3H), 1.25-1.84 (m, 5H), 2.74 (brs, 2H), 3.94 (m, 1H), 4.32 (m, 1H), 4.70 (s, 1H), 6.10 (dd, *J* = 5.4, 2.7 Hz, 1H), 6.14 (dd, *J* = 5.4, 2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 18.6, 22.0, 36.9, 37.4, 43.3, 45.5, 47.6, 48.0, 67.5, 68.0, 99.5, 135.8, 137.2. IR (neat) 2970, 2876, 1450, 1375, 1334, 1240, 1158, 1137, 1057, 1023 cm^{-1}. HRMS (EI) calcd for $C_{14}H_{22}O_2$ $[M]^+$ 222.1620, found 222.1623.

4b: Reaction conditions; (*R*)-**1a**/BBr_3 = 10/15 mol%, –78 ºC, 3 h, 0.25 *M* of **3b**. The *endo*/*exo* ratio was determined by ^{1}H NMR analysis; δ 9.32 (s, 1H, CHO (*endo*-**4b**)), 9.54 (s, 1H, CHO (*exo*-**4b**)), *endo*:*exo* = 5:95. The enantioselectivity was determined by GC analysis after

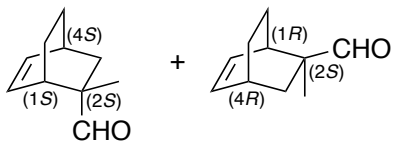
conversion to the corresponding alcohol by $NaBH_4$ in THF and water; GC (CHIRALDEX B-DM, 90 °C) t_R = 36.7 min. (*endo*-(1*R*,2*S*,4*R*)-isomer), 37.5 min. (*endo*-(1*S*,2*R*,4*S*)-isomer), 45.9 min. (*exo*-(1*S*,2*S*,4*S*)-isomer), and 48.9 min. (*exo*-(1*R*,2*R*,4*R*)-isomer).



endo-(2*R*)-**4b** (minor) *exo*-(2*R*)-**4b** (major) *endo*-(2*R*)-**4b'** (minor) *exo*-(2*R*)-**4b'** (major)

(1*R*,2*R*,4*R*)-2-Bromobicyclo[2.2.1]hept-5-ene-2-carbaldehyde (*exo*-(2*R*)-4b):[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, *J* = 9.3 Hz, 1H), 1.49 (dd, *J* = 13.8, 3.6 Hz, 1H), 1.56 (m 1H), 2.65 (dd, *J* = 13.8, 3.6 Hz, 1H), 2.98 (brs, 1H), 3.26 (brs, 1H), 6.15 (dd, *J* = 5.7, 3.3 Hz, 1H), 6.45 (dd, *J* = 5.7, 3.3 Hz, 1H), 9.54 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 42.3, 46.7, 49.6, 72.6, 133.8, 140.1, 192.0. HRMS (EI) calcd for C_8H_9BrO $[M]^+$ 199.9837, found 199.9843.
((1*R*,2*R*,4*R*)-2-Bromobicyclo[2.2.1]hept-5-en-2-yl)methanol (*exo*-(2*R*)-4b'):[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, *J* = 9.3 Hz, 1H), 1.55 (m, 1H), 1.72 (dd, *J* = 13.2, 3.3 Hz, 1H), 1.92 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.30 (br, 1H), 2.92 (brs, 1H), 3.24 (brs, 1H), 3.73 (d, *J* = 12.3 Hz, 1H), 3.85 (d, *J* = 12.3 Hz, 1H), 6.15 (dd, *J* = 5.7, 2.7 Hz, 1H), 6.32 (dd, *J* = 5.7, 2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.4, 42.2, 46.5, 50.6, 72.4, 79.2, 136.8, 137.4. HRMS (EI) calcd for $C_8H_{11}BrO$ $[M]^+$ 201.9993, found 201.9995.

4c: Reaction conditions; (*R*)-**1a**/BBr_3 = 10/10 mol%, –78 ºC, 4 h, 0.25 *M* of **3a**. The *endo/exo* ratio was determined by ^{1}H NMR analysis; δ 9.32 (s, 1H, CHO (*endo*-**4c**)), 9.55 (s, 1H, CHO (*exo*-**4c**)), *endo*:*exo* = 97:3. The enantioselectivity was determined by GC analysis; GC (CHIRALDEX B-DM, 65 °C), t_R = 67.7 min. (*exo*-isomers), 88.6 min. (*endo*-(1*S*,2*S*,4*S*)-isomer, major), and 92.7 min. (*endo*-(1*R*,2*R*,4*R*)-isomer, minor).

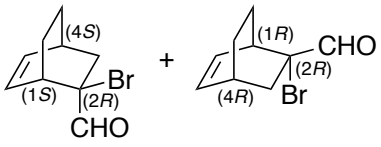


endo-(2*S*)-**4c** (major) *exo*-(2*S*)-**4c** (minor)

(1*S*,2*S*,4*S*)-2-Methylbicyclo[2.2.2]oct-5-ene-2-carbaldehyde (*endo*-(2*S*)-4c):[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13-1.32 (m, 3H), 1.15 (s, 3H), 1.54 (m, 1H), 1.91 (ddt, *J* = 12.4, 9.6, 3.2 Hz, 1H), 2.01 (dt, *J* = 12.8, 3.2 Hz, 1H), 2.48 (m, 1H), 2.61 (m, 1H), 6.21-6.29 (m, 2H), 9.32 (s, 1H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ 20.0, 21.2, 25.1, 30.4, 35.4, 36.1, 50.0, 133.5, 135.1, 205.7. IR (neat) 3046, 2947, 2866, 2691, 1723, 1449 cm^{-1}. HRMS (EI) calcd for $C_{10}H_{14}O$ $[M]^+$ 150.1045, found 150.1044.

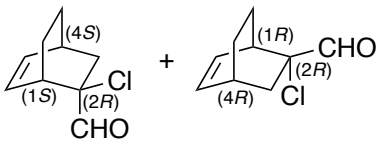
4d: Reaction conditions; (*R*)-**1a**/BBr_3 = 10/15 mol%, –78 ºC, 3 h, 0.25 *M* of **3b**. The *endo/exo* ratio was determined by ^1H NMR analysis; δ 9.14 (s, 1H, CHO (*endo*-**4d**)), 9.40 (s, 1H, CHO (*exo*-**4d**)), *endo*:*exo* = 94:6. The enantioselectivity was determined by GC analysis; GC (CHIRALDEX B-CP, 90 °C), t_R = 81.4 min. (*exo*-isomer, minor), 83.1 min. (*exo*-isomer, major), 94.6 min. (*endo*-(1*R*,2*S*,4*R*)-isomer, minor), and 95.9 min. (*endo*-(1*S*,2*R*,4*S*)-isomer, major).



endo-(2*R*)-**4d** (major) *exo*-(2*R*)-**4d** (minor)

(1*S*,2*R*,4*S*)-2-Bromobicyclo[2.2.2]oct-5-ene-2-carbaldehydee (*endo*-(2*R*)-4d):[6] ^1H NMR (400 MHz, $CDCl_3$) δ 1.30-1.50 (m, 2H), 1.78 (m, 1H), 1.91 (dd, *J* = 14.5, 2.2 Hz, 1H), 2.34 (m, 1H), 2.59 (dt, *J* = 14.5, 3.3 Hz, 1H), 2.68 (m, 1H), 2.97 (m, 1H), 6.07 (t, *J* = 7.3 Hz, 1H), 6.31 (t, *J* = 7.3 Hz, 1H), 9.14 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 25.5, 30.6, 36.6, 38.0, 72.4, 130.3, 137.5, 190.1. IR (neat) 2945, 2868, 1729, 1447 cm^{-1}. HRMS (EI) calcd for $C_9H_{11}BrO$ $[M]^+$ 213.9993, found 213.9995.

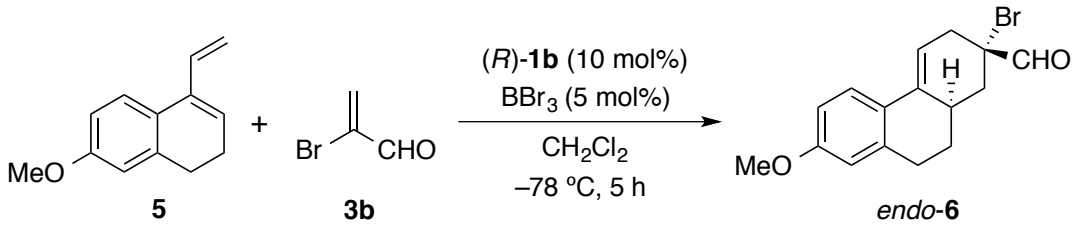
4e: Reaction conditions; (*R*)-**1a**/BBr_3 = 10/15 mol%, –78 ºC, 5 h, 0.25 *M* of **3c**. The *endo/exo* ratio was determined by ^1H NMR analysis; δ 9.16 (s, 1H, CHO (*endo*-**4e**)), 9.41 (s, 1H, CHO (*exo*-**4e**)), *endo*:*exo* = 94:6. The enantioselectivity was determined by GC analysis; GC (CHIRALDEX B-CP, 80 °C), t_R = 80.7 min. (*exo*-isomers), 91.9 min. (*endo*-(1*R*,2*S*,4*R*)-isomer, minor), and 93.4 min. (*endo*-(1*S*,2*R*,4*S*)-isomer, major).



endo-(2*R*)-**4e** (major) *exo*-(2*R*)-**4e** (minor)

(1*S*,2*R*,4*S*)-2-Chlorobicyclo[2.2.2]oct-5-ene-2-carbaldehyde (*endo*-(2*R*)-4e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29-1.42 (m, 2H), 1.69-1.80 (m, 2H), 2.31 (m, 1H), 2.49 (dt, *J* = 14.5, 3.0 Hz, 1H), 2.71 (m, 1H), 2.88 (m, 1H), 6.07 (t, *J* = 7.5 Hz, 1H), 6.33 (t, *J* = 7.5 Hz, 1H), 9.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 25.0, 30.4, 36.1, 37.6, 75.1, 130.1, 137.4, 191.6. IR (neat) 2946, 2867, 2824, 1735 cm^{-1}. HRMS (EI) calcd for $C_9H_{11}ClO$ $[M]^+$ 170.0498, found 170.0497.

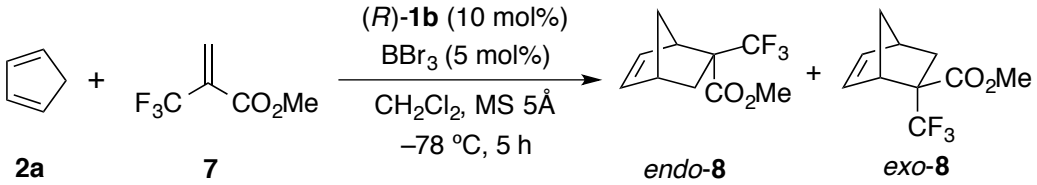
4. Enantioselective Diels–Alder reaction of acyclic diene 5 (eq 1).



A solution of (*R*)-**1b** (23.8 mg, 0.025 mmol) in freshly distilled dichloromethane (1 mL) was stirred at room temperature in Schlenk tube under a nitrogen atmosphere. To the mixture was added boron tribromide (1 *M* in dichloromethne, 12.5 μL, 0.0125 mmol) at –78 ºC, and this solution was stirred at that temperature for 20 min. Freshly-distilled α-bromoacrolein (**3b**, 22.5 μL, 0.25 mmol) was then added at –78 ºC, and a dichloromethane solution (1 mL) of diene **5** (93.1 mg, 0.50 mmol) was added dropwise over 1 h. After 5 h, the reaction was quenched with triethylamine (200 μL) at –78 ºC. The product mixture was directly purified by neutral silica gel column chromatography (eluent: hexane:AcOEt = 20:1 to 9:1). Solvents were removed under reduced pressure by rotary evaporator, and the product (*endo*:*exo* = >99:1) was obtained in 82% yield (65.9 mg).

(2*S*,10a*R*)-2-Bromo-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-2-carbaldehyde (*endo*-6):[7] ^{1}H NMR (400 MHz, d_8-toluene) δ 1.03 (dd, *J* = 13.7, 10.5 Hz, 1H), 1.23 (td, *J* = 12.8, 5.0 Hz, 1H), 1.51 (m, 1H), 1.88 (ddd, *J* = 13.7, 5.0, 2.3 Hz, 1H), 2.43-2.54 (m, 2H), 2.54-2.64 (m, 2H), 2.69 (m, 1H), 3.37 (s, 3H), 5.72 (m, 1H), 6.48 (d, *J* = 2.7 Hz, 1H), 6.66 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 9.16 (s, 1H). ^{13}C NMR (100 MHz, d_8-toluene): δ 30.2 (2C), 34.1, 34.8, 37.2, 54.6, 68.7, 112.0, 113.1, 113.5, 125.5, 126.6, 135.5, 137.9, 159.4, 191.6. IR (KBr) 2927, 1719, 1604, 1497, 1301, 1234 cm^{-1}. M.p. 72–84 °C. HRMS (ESI+) calcd for $C_{16}H_{18}BrO_2$ $[M+H]^+$ 321.0485, found 321.0485. $[\alpha]_D^{23}$ = +10.2 (*c* 1.0, toluene, 89% ee). HPLC analysis; AD-H, hexane:*i*-PrOH = 99:1, 1.0 mL/min, t_R = 17.9 min (major), 21.8 min (minor).

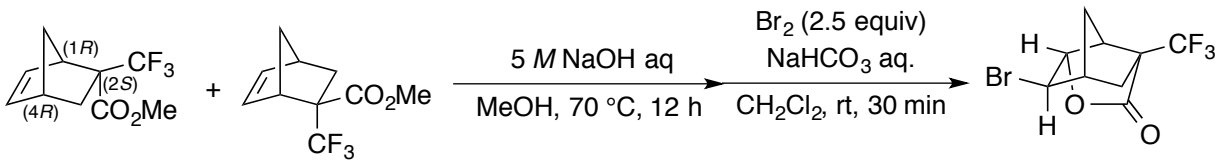
5. Enantioselective Diels–Alder reaction of acrylate 7 (eq 2).



2a **7** *endo*-**8** *exo*-**8**

A suspension of (*R*)-**1b** (23.8 mg, 0.025 mmol) and activated MS 5Å (100 mg) in freshly distilled dichloromethane (1 mL) was stirred at room temperature in Schlenk tube under a nitrogen atmosphere. To the mixture was added boron tribromide (1 *M* in dichloromethne, 12.5 μL, 0.0125 mmol) at –78 ºC, and this suspension was stirred at that temperature for 20 min. Methyl 2-(trifluoromethyl)acrylate **7** (commercially available, 31.3 μL, 0.25 mmol) was then added at –78 ºC, and freshly distilled cyclopentadiene **2a** (103 μL, 1.25 mmol) was added dropwise over 5 min. After 5 h, the reaction was quenched with triethylamine (200 μL) at –78 ºC. The product mixture was directly purified by neutral silica gel column chromatography (eluent: pentane:diethyl ether = 1000:1 to 9:1). Solvents were removed under 200 Torr at 15 °C by rotary evaporator, and the product (*endo*:*exo* = 86:14) mixture was obtained in >99% yield (55.2 mg). The *endo*/*exo* ratio was determined by ^{1}H NMR analysis; δ 3.71 (s, 3H, CO_2Me (*endo*-**8**)), 3.81 (s, 3H, CO_2Me (*exo*-**8**)).

Methyl (1*R*,2*S*,4*R*)-2-(trifluoromethyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*endo*-8):[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, *J* = 8.7 Hz, 1H), 1.76 (d, *J* = 9.0 Hz, 1H), 2.00-2.13 (m, 2H), 2.97 (brs, 1H), 3.37 (brs, 1H), 3.71 (s, 3H), 6.00 (m, 1H), 6.29 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.3, 41.8, 47.6 (2C), 52.7, 60.1 (q, *J* = 24.8 Hz), 126.4 (q, *J* = 281.2 Hz), 134.6, 140.3, 169.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.64. IR (neat) 2959, 1746, 1436, 1266, 1161, 1122, 1049 cm^{-1}. HRMS (EI) calcd for $C_{10}H_{11}F_3O_2$ $[M]^+$ 220.0711, found 220.0714. $[\alpha]_D^{23}$ = 71.5 (*c* 0.82, $CHCl_3$, 93% ee of *endo* [*endo*:*exo* = 86:14]). GC (CHIRALDEX G-TA, 65 °C), t_R = 21.2 min. (*endo*-(1*R*,2*S*,4*R*)-isomer, major), 27.1 min. (*exo*-isomer, major), 29.0 min. (*exo*-isomer, minor), and 29.8 min. (*endo*-(1*S*,2*R*,4*S*)-isomer, minor). The absolute stereochemistry of *endo*-**8** was determined by the X-ray analysis of the corresponding γ-lactone **S1** as shown below.



endo-**8** (85:15) *exo*-**8**
93% ee

S1, 71%
93% ee

The titled compound was synthesized on the basis of a literature procedure.[1] To a solution of **8** (*endo*:*exo* = 85:15, 40.1 mg, 0.18 mmol) in methanol (2 mL) at room temperature was slowly added aqueous NaOH (400 mg, 10 mmol) solution (2 mL). The resulting mixture was heated to 70 °C, and stirred at that temperature for 12 h. After cooling to room temperature, the volatiles were removed under reduced pressure. This crude product was used to the subsequent bromo lactonization without further purification. To a solution of the obtained carboxylic acids in dichloromethane (4 mL) were added saturated $NaHCO_3$ aqueous solution (4 mL) and bromine (22.0 μL, 0.43 mmol). The mixture was stirred at room temperature for 30 min. The aqueous layer was then extracted with dichloromethane (10 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 4:1 to 2:1) to give **S1** as a white solid in 71% yield (36.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (d, J = 11.9 Hz, 1H), 2.03 (dd, J = 14.2, 2.2 Hz, 1H), 2.29 (dd, J = 14.2, 4.3 Hz, 1H), 2.41 (d, J = 11.9 Hz, 1H), 2.79 (brs, 1H), 3.43 (dd, J = 5.0, 1.1 Hz, 1H), 3.85 (d, J = 2.2 Hz, 1H), 4.98 (d, J = 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1, 35.5, 45.2, 48.2, 50.9 (q, $J_{C–F}$ = 30.5 Hz), 51.8, 85.5, 124.6 (q, $J_{C–F}$ = 276.5 Hz), 171.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.14. IR (neat) 2925, 1795, 1451, 1361, 1168, 1057, 1012 cm^{-1}. HRMS (EI) calcd for $C_9H_8BrF_3O_2$ $[M]^+$ 283.9660, found 283.9661. $[\alpha]_D^{28}$ = –44.6 (*c* 0.72, $CHCl_3$, 93% ee). HPLC analysis; IA-3, hexane:*i*-PrOH = 9:1, 1.0 mL/min, t_R = 7.6 min ((3*S*,3a*S*,5*R*,6*R*,6a*R*)-isomer, major), 8.0 min ((3*R*,3a*R*,5*S*,6*S*,6a*S*)-isomer, minor).

Crystal data of S1 ((3*S*,3a*S*,5*R*,6*R*,6a*R*)-6-Bromo-3-(trifluoromethyl)hexahydro-2*H*-3,5-methanocyclopenta[b]furan-2-one): Formula $C_9H_8BrF_3O_2$, colorless, crystal dimensions 0.20 × 0.10 × 0.10 mm^3, orthorhombic, space group $P2_12_12_1$ (#19), a = 6.365(2) Å, b = 12.061(4) Å, c = 12.520(4) Å, α = 90.00 °, β = 90.00 °, γ = 90.00 °, V = 961.1(5) Å^3, Z = 4, ρ_{calc} = 1.970 g cm^{-3}, F(000) = 560, μ(MoKα) = 4.298 mm^{-1}, T = 93 K. 8227 reflections collected, 2163 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 27.48 °), and 168 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0173 and wR_2 = 0.0360. GOF = 0.862. Flack x = 0.005(5). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1416504. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

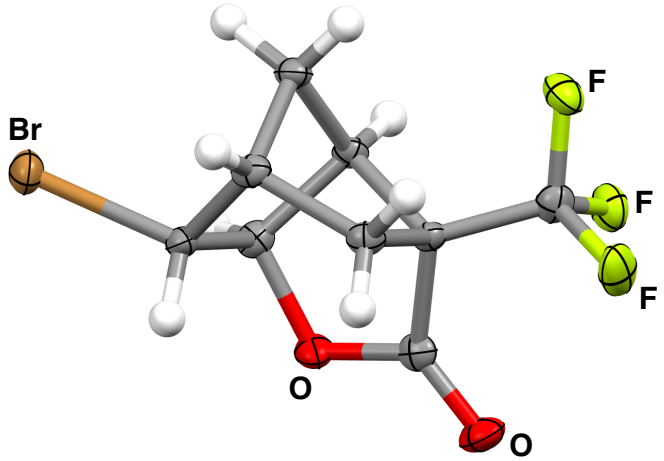
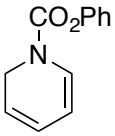
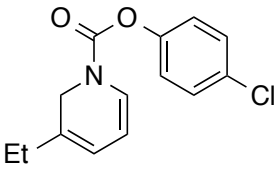


Figure S1. OPTEP drawing of **S1**.

6. Synthesis of 1,2-dihydropyridines.

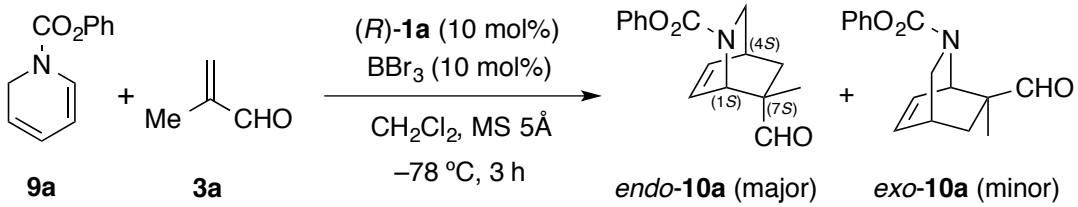


Phenyl pyridine-1(2*H*)-carboxylate (9a):[9] A mixture of pyridine (8.06 mL, 100 mmol) and $NaBH_4$ (4.53 g, 120 mmol) in methanol (150 mL) were stirred at –78 °C. Phenyl chloroformate (15.0 mL, 120 mmol) was then added slowly to the solution by a dropping funnel for 15 minutes at –78 °C. The mixture was stirred at –78 to –55 °C for 3 h and then at room temperature for 1 h. The solution was poured into ice-water, and the mixture was stirred until the H_2 bubble stopped. The mixture was extracted with diethyl ether (200 mL × 2). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: hexane:Et_2O = 20:1 to 9:1), to give the desired product (**9a**) in 88% yield (17.7 g). ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 4.45+4.60 (m, 2H), 5.26 (m, 1H), 5.61 (m, 1H), 5.90 (m, 1H), 6.80+6.88 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 7.6 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 7.38 (t, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 43.8+44.3, 105.8+106.0, 118.9+119.5, 121.5 (2C), 121.8+122.2, 125.3+125.7+125.8+126.0 (2C), 129.4 (2C), 150.8+150.9+151.5+152.5 (2C). IR (KBr) 3411, 3055, 2854, 1709, 1589, 1363, 1204, 1076 cm^{-1}. M.p. 68–69 °C. HRMS (FAB+) calcd for $C_{12}H_{11}NO_2$ $[M]^+$ 201.0790, found 201.0785.



4-Chlorophenyl 3-ethylpyridine-1(2*H*)-carboxylate (9b): The titled compound was prepared on the basis of the above procedure. ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 1.06+1.07 (t, J = 7.2 Hz, 3H), 2.03 (q, J = 7.2 Hz, 2H), 4.28+4.40 (s, 2H), 5.26 (m, 1H), 5.62 (m, 1H), 6.68+6.73 (d, J = 7.8 Hz, 1H), 7.40-7.20 (m, 2H), 7.27-7.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 11.1, 27.3, 46.8+47.3, 106.5, 114.5+114.8, 122.3+123.0, 122.9 (2C), 129.2 (2C), 130.8+130.9, 133.7+134.5, 149.2+149.4, 151.1+152.0. IR (neat) 3430, 2966, 1725, 1605, 1488, 1359, 1208, 1087 cm^{-1}. HRMS (FAB+) calcd for $C_{14}H_{14}ClNO_2$ $[M]^+$ 263.0713, found 263.0716.

7. Enantioselective Diels–Alder reaction of 1,2-dihydropyridines (Scheme 3).



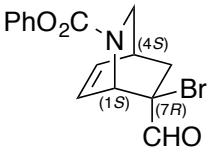
9a **3a** *endo*-**10a** (major) *exo*-**10a** (minor)

A suspension of (*R*)-**1a** (32.6 mg, 0.05 mmol) and MS 5Å (200 mg) in freshly distilled dichloromethane (2 mL) was stirred at room temperature in Schlenk tube under a nitrogen atmosphere. To the mixture was added boron tribromide (1 *M* in dichloromethne, 50 μL, 0.05 mmol) at –78 ºC, and this suspension was stirred at that temperature for 20 minutes. Methacrolein **3a** (95% purity, 174 μL, 2.0 mmol) was added dropwise. A solution of phenyl pyridine-1(2*H*)-carboxylate **9a** (101 mg, 0.50 mmol) in dichloromethane (1 mL) was then added dropwise over 1 h. The reaction mixture was stirred additional 2 h. The reaction was then quenched with triethylamine (200 μL) at –78 ºC. The product mixture was directly purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 4:1 to 2:1). Solvents were removed under reduced pressure by rotary evaporator, and the product (*endo*/*exo*) mixture was obtained in 82% yield (117 mg). The *endo/exo* ratio was determined by ^{1}H NMR analysis; δ 9.39 (s, 1H, CHO (*endo*-**10a**)), 9.68+9.70 (s, 1H, CHO (*exo*-**10a**)), *endo*:*exo* = >99:1.

(1*S*,4*S*,7*S*)-Phenyl 7-formyl-7-methyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (*endo*-10a):[10] ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 1.30+1.35 (s, 3H), 1.30-1.40 (m, 1H), 2.18+2.22 (dm, J = 13.2 Hz, 1H), 2.91 (bs, 1H), 3.10+3.22 (dm, J = 10.5 Hz, 1H), 3.40+3.54 (dm, J = 10.5 Hz, 1H),

4.86 (m, 1H), 6.40-6.53 (m, 2H), 7.08-7.16 (m, 2H), 7.22 (m, 1H), 7.30-7.41 (m, 2H), 9.39 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 21.0+21.1 30.8+31.2, 31.8+31.9, 47.8, 50.7+51.6, 53.4+53.5, 121.5 (2C), 125.2+125.3, 129.2+129.3 (2C), 131.4+131.7, 135.3+135.2, 151.1+151.2, 153.5+154.3, 202.2+202.6. IR (neat) 2963, 2873, 1716, 1404, 1336, 1296, 1209 cm^{-1}. HRMS (ESI+) calcd for $C_{16}H_{18}NO_3$ $[M+H]^+$ 272.1287, found 272.1285. $[\alpha]_D^{22}$ = +113.3 (*c* 0.54, $CHCl_3$, 95% ee). HPLC analysis; AD-H, hexane:*i*-PrOH = 9:1, 1.0 mL/min, t_R = 14.7 min ((1*S*,4*S*,7*S*)-isomer, major), 16.4 min ((1*R*,4*R*,7*R*)-isomer, minor).

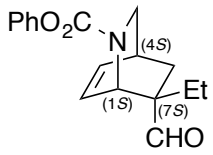
10b: Reaction conditions: (*R*)-**1a**/BBr_3 = 10/15 mol%, **9a** (0.5 mmol)/**3b** (0.25 mmol), 0.08 *M* of **9a, 9a** was added dropwise over 1 h, total reaction time was 5 h. The *endo/exo* ratio was determined by ^{1}H NMR analysis; δ 9.25+9.26 (s, 1H, CHO (*endo*-**10b**)), 9.46+9.54 (s, 1H, CHO (*exo*-**10b**)), *endo*:*exo* = >99:1.



endo-**10b**

(1*S*,4*S*,7*R*)-Phenyl 7-bromo-7-formyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (*endo*-10b): ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 2.11+2.15 (dd, *J* = 14.7, 2.7 Hz, 1H), 2.69+2.73 (dt, *J* = 14.7, 2.7 Hz, 1H), 3.01 (bs, 1H), 3.18+3.31 (dt, *J* = 10.5, 2.3 Hz, 1H), 3.64+3.78 (dd, *J* = 10.5, 2.3 Hz, 1H), 5.24+5.29 (d, *J* = 6.4 Hz, 1H), 6.38 (m, 1H), 6.56 (m, 1H), 7.13-7.23 (m, 3H), 7.34-7.39 (m, 2H), 9.25+9.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 31.0+31.4, 34.1+34.3, 47.1+47.2, 51.7+52.5, 68.9+69.2, 121.6+121.7 (2C), 125.4+125.5, 129.3 (2C), 129.7+129.9, 137.0+137.1, 151.1+151.2, 153.2+154.0, 188.7+188.8. IR ($CHCl_3$) 2922, 2852, 1716, 1406, 1204 cm^{-1}. HRMS (FAB+) calcd for $C_{15}H_{15}BrNO_3$ $[M+H]^+$ 336.0235, found 336.0232. $[\alpha]_D^{22}$ = +36.7 (*c* 1.01, $CHCl_3$, 98% ee). HPLC analysis; IC-3, hexane:*i*-PrOH = 4:1, 1.0 mL/min, t_R = 21.0 min ((1*S*,4*S*,7*R*)-isomer, major), 31.1 min ((1*R*,4*R*,7*S*)-isomer, minor).

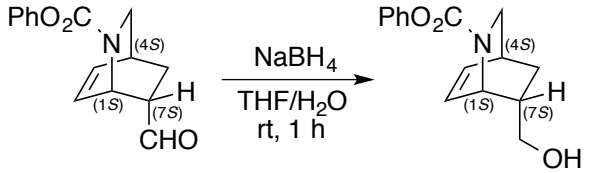
10c: Reaction conditions: (*R*)-**1a**/BBr_3 = 10/10 mol%, **9a** (1 mmol)/**3d** (0.5 mmol), 0.17 *M* of **9a**, **9a** was added dropwise over 3 h, total reaction time was 5 h. The *endo/exo* ratio was determined by ^{1}H NMR analysis; δ 9.35+9.36 (s, 1H, CHO (*endo*-**10c**)), 9.60+9.68 (s, 1H, CHO (*exo*-**10c**)), *endo*:*exo* = >99:1.



endo-**10c**

(1*S*,4*S*,7*S*)-Phenyl 7-ethyl-7-formyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (*endo*-10c): ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 0.89+0.93 (t, *J* = 7.5 Hz, 3H), 1.35+1.38 (dd, *J* = 12.8, 2.3 Hz, 1H), 1.60-1.98 (m, 2H), 2.12+2.16 (dt, *J* = 13.7, 2.7 Hz, 1H), 2.88 (br, 1H), 3.08+3.19 (dt, *J* = 10.5, 2.7 Hz, 1H), 3.35+3.49 (dd, *J* = 10.5, 2.3 Hz, 1H), 4.94-5.05 (m, 1H), 6.40-6.46 (m, 2H), 7.09-7.14 (m, 2H), 7.16-7.23 (m, 1H), 7.31-7.38 (m, 2H), 9.35+9.36 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 8.9, 28.5+28.6, 30.6+30.8, 31.1+31.3, 48.0+48.1, 49.4+49.9, 58.0+58.1, 121.6 (2C), 125.2+125.3, 129.2+129.3 (2C), 131.8+131.9, 135.4, 151.2+151.3, 153.6+154.3, 202.8+203.1. IR (neat) 2965, 2879, 1714, 1402, 1336, 1295, 1208, 1059 cm^{-1}. HRMS (ESI+) $C_{17}H_{20}NO_3$ $[M+H]^+$ 286.1438, found 286.1444. $[\alpha]_D^{28}$ = +97.5 (*c* 1.09, $CHCl_3$, 92% ee). HPLC analysis; AD-H, hexane:*i*-PrOH = 9:1, 1.0 mL/min, t_R = 12.1 min ((1*S*,4*S*,7*S*)-isomer, major), 13.3 min ((1*R*,4*R*,7*R*)-isomer, minor).

10d: Reaction conditions; (*R*)-**1a**/BBr_3 = 10/10 mol%, **9a** (0.5 mmol)/**3e** (2 mmol), 0.25 *M* of **9a,** **9a** was added dropwise over 1 h, total reaction time was 3 h. The *endo/exo* ratio was determined by ^{1}H NMR analysis; δ 9.49+9.52 (s, 1H, CHO (*endo*-**10d**)), 9.82+9.86 (s, 1H, CHO (*exo*-**10d**)), *endo*:*exo* = 99:1. The enantioselectivity of **10d** was determined after conversion to the corresponding alcohol **10d'** by $NaBH_4$ in THF/water.

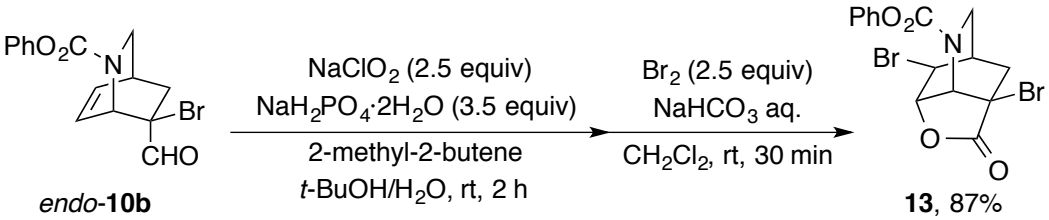


endo-**10d** *endo*-**10d'**

(1*S*,4*S*,7*S*)-Phenyl 7-(hydroxymethyl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (*endo*-10d'):[11] ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 0.87 (m, 1H), 1.83 (m, 1H), 1.96 (br, 1H), 2.44 (m, 1H), 2.80 (m, 1H), 3.07+3.18 (dt, *J* = 11.0, 2.2 Hz, 1H), 3.14-3.35 (m, 2H), 3.32+3.47 (dd, *J* = 10.5, 1.8 Hz, 1H), 4.91+4.99 (m, 1H), 6.38 (m, 1H), 6.46 (m, 1H), 7.08-7.15 (m, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.30-7.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 26.0+26.1, 30.6+30.9, 41.5+41.6, 47.1+47.4+47.5+47.9 (2C), 65.5+65.6, 121.8+121.9 (2C), 125.1, 129.2 (2C), 129.9+130.5, 134.8+135.2, 151.4, 153.2+153.7. IR (neat) 3429, 2932, 2873, 1716, 1409, 1206,

1042 cm^{-1}. HRMS (FAB+) calcd for $C_{15}H_{18}NO_3$ $[M+H]^+$ 260.1287, found 260.1290. $[\alpha]_D^{26}$ = +65.4 (*c* 0.80, $CHCl_3$, 94% ee of *endo* [*endo*:*exo* = 99:1]). HPLC analysis; AD-3+AS-3, hexane:*i*-PrOH = 9:1, 0.75 mL/min, t_R = 71.0 min ((1*R*,4*R*,7*R*)-isomer, minor), 78.9 min ((1*S*,4*S*,7*S*)-isomer, major).

8. Transformation to γ-lactone 13 (eq 4).



The titled compound was synthesized on the basis of a literature procedure.[12] To a solution of *endo*-**10b** (146 mg, 0.435 mmol) and 2-methyl-2-butene (1 mL) in *t*-BuOH/H_2O (4 mL, 3:1 v/v) were added sodium phosphate monobasic dihydrate (238 mg, 1.52 mmol) and sodium chlorite (80 wt%, 123 mg, 1.1 mmol). The mixture was stirred at room temperature for 2 h. To the mixture, ethyl acetate (20 mL) and brine (40 mL) were added, and the aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure to give the corresponding carboxylic acid as colorless oil, which was used without further purification in a next step. To a solution of the corresponding carboxylic acid in dichloromethane (12 mL) were added saturated $NaHCO_3$ aqueous solution (6 mL) and bromine (55.7 μL, 1.08 mmol). The mixture was stirred at room temperature for 30 min. The aqueous layer was then extracted with dichloromethane (10 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 4:1 to 2:1) to give (3*R*,3a*S*,6*R*,7*S*,7a*S*)-phenyl 3,7-dibromo-2-oxohexahydro-3,6-methanofuro[3,2-*b*]pyridine-4(2*H*)-carboxylate (**13**) as a white solid in 87% yield (163 mg). ^1H NMR (400 MHz, $CDCl_3$) rotamers: δ 2.50-2.65 (m, 2H), 2.72 (dt, *J* = 15.6, 2.7 Hz, 1H), 3.58+3.69 (d, *J* = 11.4 Hz, 1H), 4.27 (s, 1H), 4.11+4.31 (dt, *J* = 11.4, 2.7 Hz, 1H), 5.02+5.07 (d, *J* = 5.5 Hz, 1H), 5.14+5.17 (d, *J* = 5.5 Hz, 1H), 7.15-7.23 (m, 2H), 7.23-7.29 (m, 1H), 7.37-7.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 33.8+34.0, 39.7+39.9, 44.6+45.1, 46.2+46.4, 51.0+51.6, 56.9+57.9, 80.9+81.2, 121.5 (2C), 126.0, 129.5 (2C), 150.6+150.8, 153.3+154.2, 170.5+170.7. IR (neat) 2959, 1810, 1725, 1414, 1356, 1308, 1202 cm^{-1}. HRMS (FAB+) calcd for $C_{15}H_{13}Br_2NNaO_4$ $[M+Na]^+$ 451.9109,

found 451.9112. $[\alpha]_D^{28}$ = –39.5 (*c* 0.88, $CHCl_3$, 98% ee). HPLC analysis; AD-H, hexane:*i*-PrOH = 9:1, 1.0 mL/min, t_R = 37.9 min (minor), 40.7 min (major).

Crystal data of 13: Formula $C_{15}H_{13}Br_2NO_4$, colorless, crystal dimensions 0.40 × 0.40 × 0.30 mm^3, orthorhombic, space group $P2_12_12$ (#18), a = 8.8931(17) Å, b = 22.261(4) Å, c = 7.8277(14) Å, α = 90.00 °, β = 90.00 °, γ = 90.00 °, V = 1549.6(5) $Å^3$, Z = 4, ρ_{calc} = 1.848 g cm^{-3}, F(000) = 848, μ(MoKα) = 5.248 mm^{-1}, T = 123 K. 13053 reflections collected, 3535 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 27.47 °), and 200 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0285 and wR_2 = 0.0506. GOF = 0.910. Flack x = 0.007(8). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-937719. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

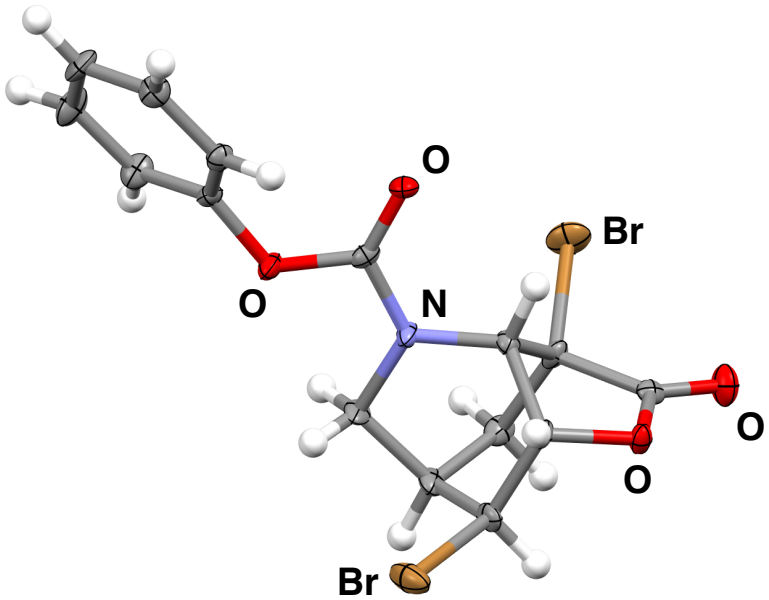
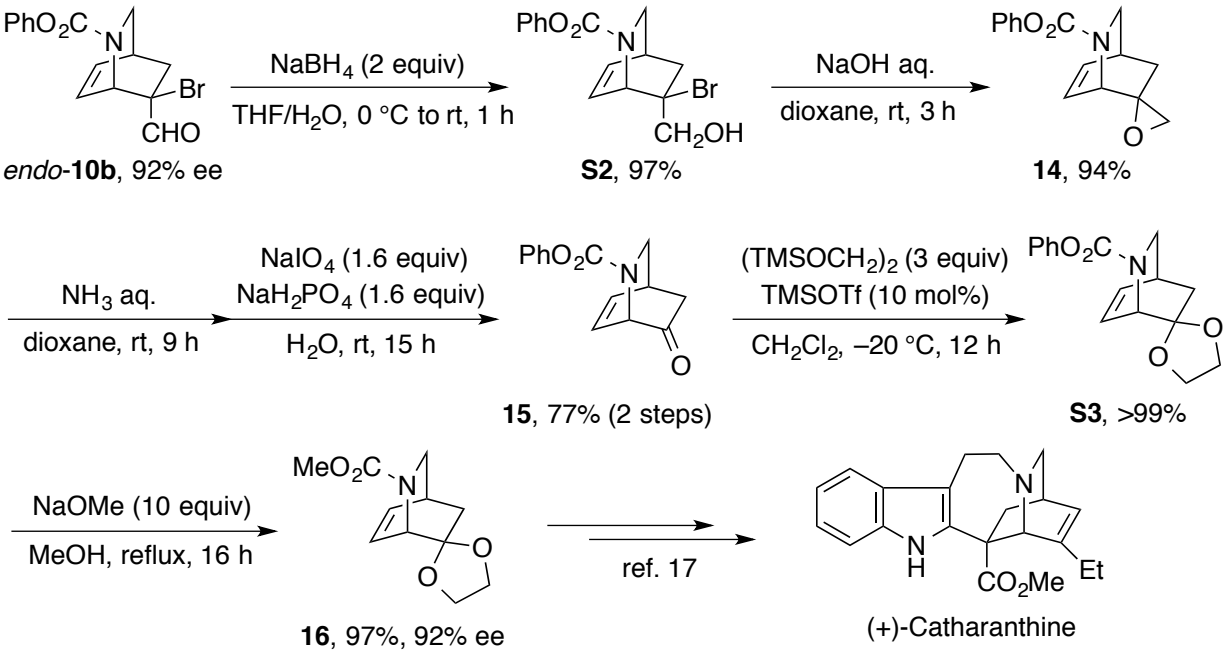
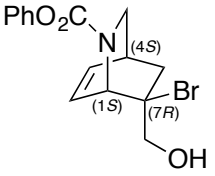


Figure S2. OPTEP drawing of **13**.

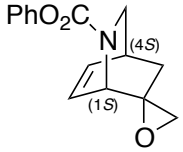
9. Formal total synthesis of (+)-catharanthine (Scheme 4).



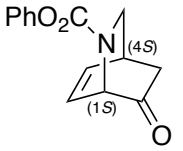


(1*S*,4*S*,7*R*)-Phenyl 7-bromo-7-(hydroxymethyl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (S2): The titled compound was synthesized on the basis of a literature procedure.[13] To a solution of *endo*-**10b** (815 mg, 2.4 mmol, 92% ee) in THF (9 mL) and water (1 mL) was added sodium borohydride (183 mg, 4.8 mmol) at room temperature. After stirring for 1 h, water (10 mL) was added to the reaction mixture. The mixture was extracted with ethyl acetate (10 mL × 3), and the combined organic layer was dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 2:1 to 1:1), to give the desired product (**S2**) in 97% yield (797 mg). ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 1.75+1.77 (dt, *J* = 14.6, 2.8 Hz, 1H), 2.24 (br, 1H), 2.37 (d, *J* = 14.6 Hz, 1H), 2.87 (bs, 1H), 3.17+3.30 (dt, *J* = 10.5, 2.7 Hz, 1H), 3.39+3.40 (d, *J* = 12.8 Hz, 1H), 3.58+3.62 (d, *J* = 13.0 Hz, 1H), 3.57+3.71 (dd, *J* = 10.5, 1.8 Hz, 1H), 5.10-5.22 (m, 1H), 6.45-6.54 (m, 2H), 7.09-7.22 (m, 3H), 7.30-7.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 31.7+31.5, 37.8+38.0, 46.3+46.4, 53.3+54.1, 70.5+70.6, 73.3+76.5, 121.7+121.9 (2C), 125.2+125.3, 129.2 (2C), 130.5+131.1, 134.4+134.8, 151.3, 153.1+153.8. IR (neat) 3444, 3043,

2929, 1715, 1416, 1203 cm^{-1}. HRMS (FAB+) calcd for $C_{15}H_{17}BrNO_3$ $[M+H]^+$ 338.0392, found 338.0395. $[\alpha]_D^{26}$ = +58.7 (*c* 1.10, $CHCl_3$, 92% ee).

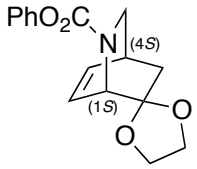


(1*S*,2'*S*,4*S*)-Phenyl 2-azaspiro[bicyclo[2.2.2]oct[5]ene-7,2'-oxirane]-2-carboxylate (14): The titled compound was synthesized on the basis of a literature procedure.[14] To a solution of **S2** (470 mg, 1.39 mmol, 92% ee) in dioxane (12 mL) was added 2.5 *M* NaOH aqueous solution (10 mL) was added at room temperature. After stirring for 3 h, water (10 mL) added to the mixture. The mixture was extracted with ethyl acetate (20 mL × 3), and the combined organic layer was dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 4:1 to 2:1) to give **14** in 94% yield (336 mg). ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 1.69 (d, *J* = 14.2 Hz, 1H), 2.11 (d, *J* = 14.2 Hz, 1H), 2.90+2.94 (d, *J* = 4.6 Hz, 1H), 3.02 (d, *J* = 4.6 Hz, 1H), 3.02 (bs, 1H), 3.09+3.22 (dt, *J* = 10.1, 2.3 Hz, 1H), 3.42+3.54 (dd, *J* = 10.1, 2.3 Hz, 1H), 4.35+4.37 (d, *J* = 6.0 Hz, 1H), 6.56 (m, 1H), 6.65 (m, 1H), 7.11 (t, *J* = 7.8 Hz, 2H), 7.17-7.23 (m, 1H), 7.33-7.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 31.3+31.6, 32.4+32.5, 46.8+46.9, 51.3+52.3+52.7+52.8 (2C), 60.0+60.2, 121.6+121.7 (2C), 125.3+125.4, 129.2+129.3 (2C), 130.3+131.0, 135.7+136.3, 151.1+151.2, 153.1+153.9. IR (neat) 2925, 1716, 1395, 1334, 1284, 1208, 1055 cm^{-1}. HRMS (FAB+) calcd for $C_{15}H_{15}NNaO_3$ $[M+Na]^+$ 280.0950, found 280.0943. $[\alpha]_D^{20}$ = +41.9 (*c* 1.00, $CHCl_3$, 92% ee).

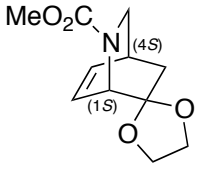


(1*S*,4*S*)-Phenyl 7-oxo-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (15): The titled compound was synthesized on the basis of a literature procedure to prepare 2,2-dimethyl-1,3-dioxane-5-one.[15] To a solution of **14** (156 mg, 0.61 mmol, 92% ee) in dioxane (4 mL) was added 25% ammonia aqueous solution (2 mL) at room temperature. After stirring for 9 h, nitrogen was then bubbled in the solution to remove excess ammonia. The volatiles were removed under reduced pressure, and the resultant residue, which contained the corresponding amino alcohol, was used in a next step without further purification. To a solution of the amino alcohol in water (10 mL), were added sodium phosphate monobasic dihydrate (156 mg, 1 mmol) and sodium periodate (213 mg, 1 mmol) at room temperature. After stirring for 15 h, the mixture was extracted with ethyl acetate (10 mL

× 3), and the combined organic layer was dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 4:1 to 1:1) to give **15** in 77% yield (114 mg). ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 2.23-2.34 (m, 2H), 3.23 (m, 1H), 3.28+3.41 (d, *J* = 10.0 Hz, 1H), 3.57+3.69 (dd, *J* = 10.0, 2.2 Hz, 1H), 5.06+5.08 (d, *J* = 6.4 Hz, 1H), 6.48+6.50 (dd, *J* = 6.4, 1.8 Hz, 1H), 6.72 (m, 1H), 7.11 (d, *J* = 8.0 Hz , 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 32.0+32.3, 36.5+36.6, 46.6+46.7, 57.5+58.4, 121.6 (2C), 125.5, 127.7+128.4, 129.3 (2C), 139.3+139.9, 150.8+151.0 , 153.0+153.4, 202.6. IR (neat) 2961, 1718, 1492, 1391, 1332, 1281, 1209, 1065 cm^{-1}. HRMS (FAB+) calcd for $C_{14}H_{13}NNaO_3$ $[M+Na]^+$ 266.0793, found 266.0788. $[\alpha]_D^{22}$ = –132.8 (*c* 0.99, $CHCl_3$, 92% ee).

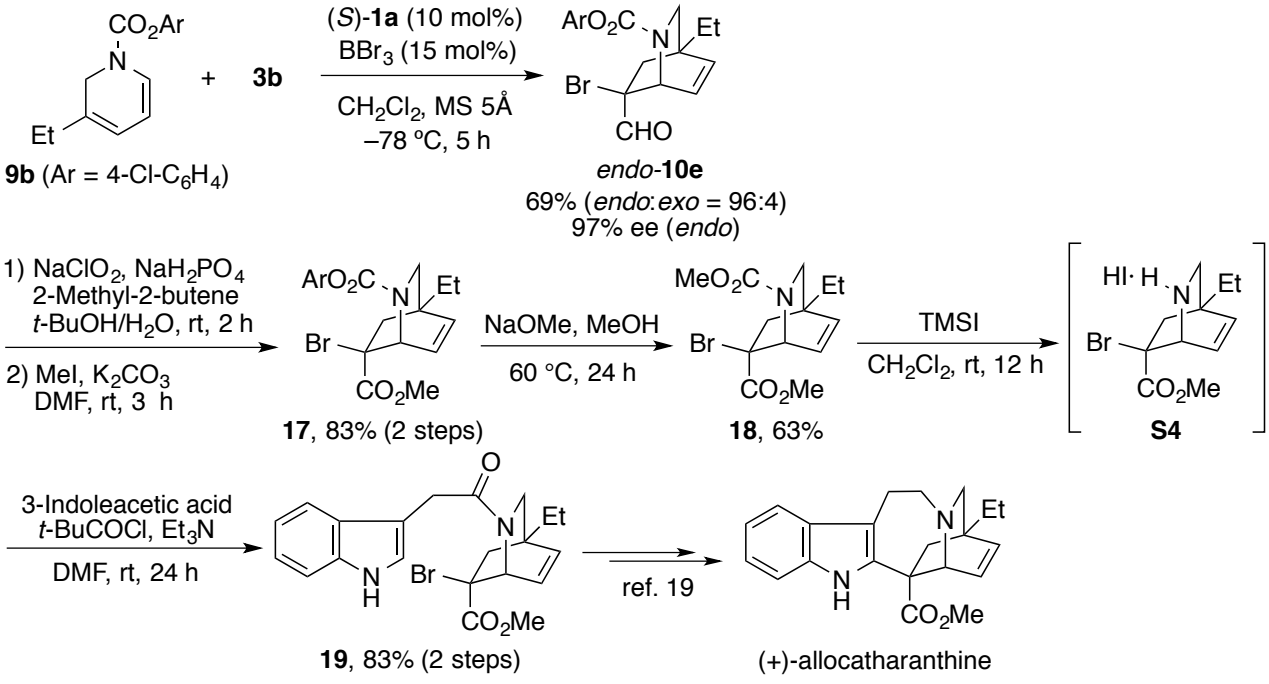


(1*S*,4*S*)-Phenyl 2-azaspiro[bicyclo[2.2.2]oct[5]ene-7,2'-[1,3]dioxolane]-2-carboxylate (S3): The titled compound was synthesized on the basis of a literature procedure.[16] To a solution of 1,2-bis(trimethylsilyloxy)ethane (294 μL, 1.2 mmol) and **15** (97.7 mg, 0.40 mmol) in dichloromethane (2 mL) was trimethylsilyl trifluoromethanesulfonate (7.2 μL, 0.04 mmol) added at –20 °C. The mixture was stirred at –20 °C for 12 h, and quenched by addition of triethylamine (0.2 mL) at the same temperature. The product mixture was directly purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 6:1 to 2:1), to give **S3** in >99% yield (116 mg). ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 1.87 (d, *J* = 13.8, 1H), 1.96 (dt, *J* = 13.8, 2.3 Hz, 1H), 2.89 (s, 1H), 3.07+3.21 (dt, *J* = 10.1, 2.3 Hz, 1H), 3.48+3.58 (dd, *J* = 10.1, 1.8 Hz, 1H), 3.91-4.11 (m, 4H), 4.73 (d, *J* = 6.4 Hz, 1H), 6.44+6.45 (d, *J* = 6.4 Hz, 1H), 6.55 (m, 1H), 7.09-7.24 (m, 3H), 7.30-7.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 31.1+31.4, 37.8, 46.4+46.6, 49.9+51.1, 64.2+64.3, 64.9+65.0, 110.9+111.0, 121.7 (2C), 125.1+125.2, 129.1+129.3 (2C), 129.9+130.6, 135.6+136.2, 151.3+151.4, 153.7+154.3. IR (neat) 2886, 1715, 1401, 1335, 1289, 1205, 1150 cm^{-1}. HRMS (FAB+) calcd for $C_{16}H_{17}NNaO_4$ $[M+Na]^+$ 310.1055, found 310.1051. $[\alpha]_D^{21}$ = +80.2 (*c* 1.08, $CHCl_3$, 92% ee).

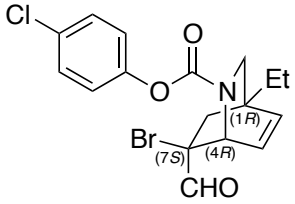


(1*S*,4*S*)-Methyl 2-azaspiro[bicyclo[2.2.2]oct[5]ene-7,2'-[1,3]dioxolane]-2-carboxylate (16):[17] To a solution of **S3** (88.3 mg, 0.31 mmol) in methanol (3 mL), sodium methoxide (162 mg, 3 mmol) was added. The reaction mixture was heated to 90 °C, and stirred for 16 h at that temperature, and then cooled to room temperature. The volatiles were removed under reduced pressure. The resultant residue was purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 6:1 to 2:1), to give **16** in 97% yield (66.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 1.75-1.92 (m, 2H), 2.83 (bs, 1H), 2.98+3.01 (dt, *J* = 10.0, 2.3 Hz, 1H), 3.34+3.37 (dd, *J* = 10.0, 2.3 Hz, 1H), 3.70+3.71 (s, 3H), 3.91-4.10 (m, 4H), 4.49+4.68 (d, *J* = 6.4 Hz, 1H), 6.38 (m, 1H), 6.48 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 31.1+31.4, 37.9, 45.9+46.4, 49.9+50.6, 52.5, 64.2+64.3, 64.8, 111.1, 130.2+130.8, 135.4+135.8, 155.9+156.5. IR (neat) 2956, 1697, 1450, 1394, 1336, 1290, 1097 cm^{-1}. HRMS (FAB+) calcd for $C_{11}H_{15}NNaO_4$ $[M+Na]^+$ 248.0899, found 248.0904. $[\alpha]_D^{21}$ = +64.9 (*c* 0.44, methanol, 92% ee). [lit.[17] $[\alpha]_D^{20}$ = +70 (*c* 0.4, methanol, >99% ee, 1*S*,4*S*)]. HPLC analysis; OD-H, hexane:*i*-PrOH = 9:1, 1.0 mL/min, t_R = 15.2 min ((1*S*,4*S*)-isomer, major), 17.7 min ((1*R*,4*R*)-isomer, minor).

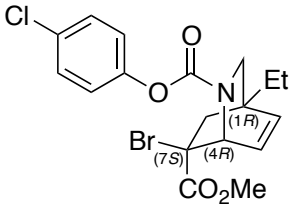
10. Formal total synthesis of (+)-allocatharanthine (Scheme 5).



10e: Reaction conditions; (*S*)-**1a**/BBr_3 = 10/15 mol%, **9b** (0.6 mmol)/**3b** (0.5 mmol), 0.17 *M* of **9b, 9b** was added dropwise over 5 min, total reaction time was 5 h. The *endo/exo* ratio was determined by ^{1}H NMR analysis; δ 9.24+9.25 (s, 1H, CHO (*endo*-**10e**)), 9.45+9.47 (s, 1H, CHO (*exo*-**10e**)), *endo*:*exo* = 96:4.

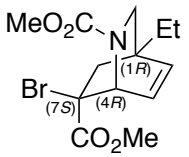


(1*R*,4*R*,7*S*)-4-Chlorophenyl 7-bromo-4-ethyl-7-formyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (*endo*-10e): ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 1.02+1.03 (t, *J* = 7.8 Hz, 3H), 1.67 (q, *J* = 7.8 Hz, 2H), 1.91+1.95 (d, *J* = 14.2 Hz, 1H), 2.55+2.59 (dd, *J* = 14.2, 2.7 Hz, 1H), 3.02+3.13 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.42+3.54 (d, *J* = 10.5 Hz, 1H), 5.20+5.23 (m, 1H), 6.31-6.40 (m, 2H), 7.10+7.11 (d, *J* = 9.2 Hz, 2H), 7.32+7.33 (d, *J* = 9.2 Hz, 2H), 9.24+9.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 8.4+8.5, 27.8, 39.0+39.3, 40.1+40.5, 51.4, 52.3+52.9, 68.8+69.2, 123.0+123.1 (2C), 128.9+129.1, 129.3 (2C), 130.7+130.8, 140.4+140.5, 149.6, 152.7+153.5, 188.6+188.7. IR (neat) 2966, 2880, 1719, 1404, 1213, 1055 cm^{-1}. HRMS (FAB+) calcd for $C_{17}H_{18}BrClNO_3$ $[M+H]^+$ 398.0159, found 398.0151. $[\alpha]_D^{26}$ = –37.1 (*c* 0.63, $CHCl_3$, 97% ee). HPLC analysis; IA-3, hexane:*i*-PrOH = 9:1, 1.0 mL/min, t_R = 20.0 min ((1*S*,4*S*,7*R*)-isomer, minor), 21.3 min ((1*R*,4*R*,7*S*)-isomer, major).

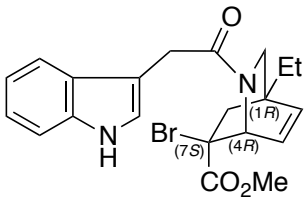


(1*R*,4*R*,7*S*)-2-(4-Chlorophenyl) 7-methyl 7-bromo-4-ethyl-2-azabicyclo[2.2.2]oct-5-ene-2,7-dicarboxylate (17): The titled compound was synthesized on the basis of a literature procedure.[18] To a solution of **10e** (87.7 mg, 0.22 mmol) and 2-methyl-2-butene (0.1 mL) in *t*-BuOH/H_2O (2.4 mL, 5:1 v/v) were added sodium phosphate monobasic dihydrate (101 mg, 0.65 mmol) and sodium chlorite (80 wt%, 74 mg, 0.65 mmol) at room temperature. The mixture was stirred at room temperature for 2 h. To the mixture, ethyl acetate (10 mL) and brine (20 mL) were added, and the aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure to give the

corresponding carboxylic acid as colorless oil, which was used without further purification in a next step. To a solution of the corresponding carboxylic acid in DMF (2 mL) were added K_2CO_3 (46 mg, 0.33 mmol) and iodomethane (21 μL, 0.33 mmol). The mixture was stirred at room temperature for 3 h. The aqueous layer was then extracted with diethyl ether (10 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 6:1 to 2:1) to give **17** in 83% yield (78.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 1.00+1.02 (t, *J* = 7.8 Hz, 3H), 1.64 (q, *J* = 7.8 Hz, 2H), 2.06+2.08 (d, *J* = 14.6 Hz, 1H), 2.68+2.70 (d, *J* = 14.6 Hz, 1H), 2.97+3.08 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.35+3.46 (d, *J* = 10.5 Hz, 1H), 3.76+3.79 (s, 3H), 5.34+5.36 (d, *J* = 6.4 Hz, 1H), 6.30+6.32 (d, *J* = 8.7 Hz, 1H), 6.39+6.40 (d, *J* = 6.6 Hz, 1H), 7.08+7.11 (d, *J* =8.7 Hz, 2H), 7.31+7.12 (d, *J* =8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 8.4+8.5, 27.7, 39.9+40.2, 43.3+43.4, 51.3, 53.4+53.5+53.7+54.4 (2C), 59.6+60.1, 123.0+123.2 (2C), 129.0+129.6, 129.2 (2C), 130.6+130.7, 139.6+140.1, 149.8, 153.0+153.6, 170.1+170.2. IR (neat) 2965, 1725, 1488, 1402, 1267, 1213 cm^{-1}. HRMS (FAB+) calcd for $C_{18}H_{20}BrClNO_4$ $[M+H]^+$ 428.0264, found 428.0264. $[\alpha]_D^{25}$ = –78.0 (*c* 0.40, $CHCl_3$, 97% ee).



(1*R*,4*R*,7*S*)-Dimethyl 7-bromo-4-ethyl-2-azabicyclo[2.2.2]oct-5-ene-2,7-dicarboxylate (18): To a solution of **17** (40.0 mg, 0.093 mmol) in methanol (3 mL), sodium methoxide (20 mg, 0.37 mmol) was added. The reaction mixture was heated to 60 °C, and stirred for 24 h at that temperature, and then cooled to room temperature. The volatiles were removed under reduced pressure. The resultant residue was purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 6:1 to 2:1), to give **18** in 63% yield (19.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 0.98 (t, *J* = 7.8 Hz, 3H), 1.58+1.60 (q, *J* = 7.8 Hz, 2H), 1.98+1.99 (d, *J* = 14.2 Hz, 1H), 2.63+2.65 (dd, *J* = 14.2, 3.2 Hz, 1H), 2.86+2.90 (dd, *J* = 10.8, 3.2 Hz. 1H), 3.24+3.26 (d, *J* = 9.2 Hz, 1H), 3.74+3.76+3.77+3.78 (6H), 5.14+5.31 (d, *J* = 6.0 Hz, 1H), 6.23+6.25 (d, *J* = 8.2 Hz, 1H), 6.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 8.4, 27.8, 39.9+40.2, 43.3, 51.0+51.2, 52.7+52.8, 53.3+53.4, 53.5+53.9, 59.8+60.0, 129.3+129.7, 139.3+139.7, 155.8+156.3, 170.3+170.4. IR (neat) 2956, 2879, 1740, 1707, 1450, 1393, 1267 cm^{-1}. HRMS (FAB+) calcd for $C_{13}H_{19}BrNO_4$ $[M+H]^+$ 332.0497, found 332.0501. $[\alpha]_D^{25}$ = –35.3 (*c* 0.78, $CHCl_3$, 97% ee).

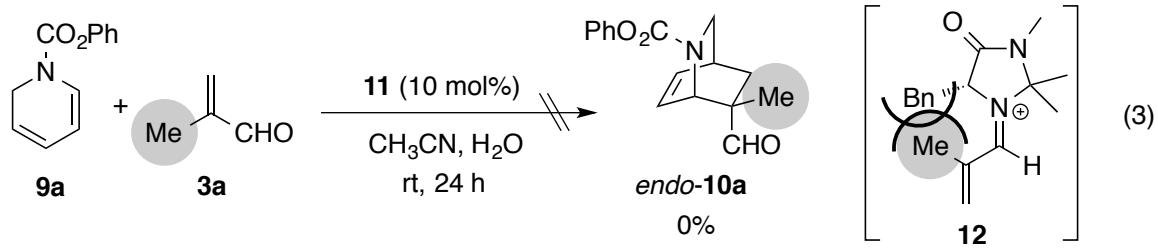


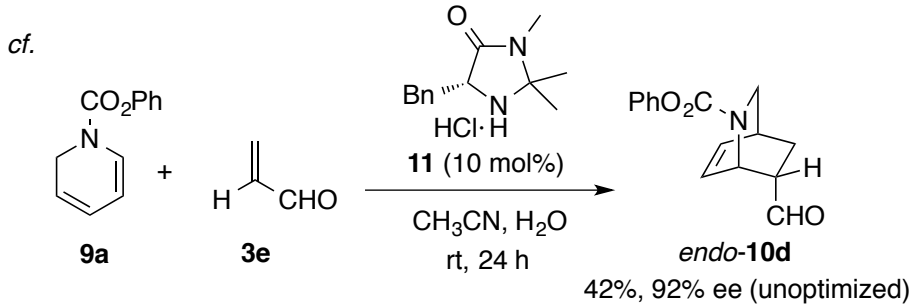
(1*R*,4*R*,7*S*)-Methyl 2-(2-(1*H*-indol-3-yl)acetyl)-7-bromo-4-ethyl-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate (19):[19] The titled compound was synthesized on the basis of a literature procedure,[19,20] and a next photoreaction to form the iboga structure could proceed in 22% yield (literature:[19] 28.5% yield). A mixture of iodine (14.0 mg, 0.054 mmol) and hexamethyldisilane (22 μL, 0.11 mmol) was heated at 120 °C with stirring until a colorless solution resulted (ca. 15 min). The mixture was cooled to room temperature, and a solution of **18** (6.1 mg, 0.018 mmol) in dichloromethane (1 mL) was added. The reaction mixture was stirred at room temperature for 12 h and quenched with methanol (10 mL). The volatiles were removed under reduced pressure, and a mixture of hydrogen iodide salts (**S4**) was obtained as an orange foam, which was used without further purification in a next step [**S4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, *J* = 7.3 Hz, 3H), 1.69 (q, *J* = 7.3 Hz, 2H), 2.15 (d, *J* = 15.2 Hz, 1H), 2.68 (dd, *J* = 15.1, 3.2 Hz, 1H), 2.99 (m, 1H), 3.43 (m, 1H), 3.81 (s, 3H), 4.90 (d, *J* = 6.0 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 6.42 (dd, *J* = 8.2, 5.9 Hz, 1H), 8.40, 9.57. ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.3, 26.9, 38.0, 42.8, 46.3, 54.1, 54.3, 54.4 126.4, 142.3, 168.3.]. To a stirred solution of **S4** (4.2 mg, 0.024 mmol) and triethylamine (3.6 μL, 0.026 mmol) in DMF (1 mL), pivaloyl chloride (3.2 μL, 0.026 mmol) was added dropwise at –10 °C. After 20 min stirring at room temperature, a thick suspension was obtained. A solution of hydrogen iodide salt in DMF (1 mL) was added dropwise at –10 °C, and then riethylamine (3.6 μL, 0.026 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The precipitated triethylamine hydrogen iodide and hydrogen chloride salts were filtered and washed with ethyl acetate. The filtrate was evaporated under reduced pressure. The residual oil was dissolved in ethyl acetate (10 mL) and water (10 mL), and extracted with ethyl acetate (10 mL × 3) and dried over Na_2SO_4. The combined organic layers were concentrated under reduced pressure. The resultant residue was purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 1:1 to 1:4) to give **19** in 83% yield (6.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 0.93+0.96 (t, *J* = 7.3 Hz, 3H), 1.55+1.59 (q, *J* = 7.3 Hz, 2H), 1.94+2.01 (d, *J* = 14.7 Hz, 1H), 2.64+2.67 (dd, *J* = 14.7, 2.7 Hz, 1H), 3.00+3.03 (dd, *J* = 9.6, 2.7 Hz, 1H), 3.35+3.38 (d, *J* = 9.6 Hz, 1H), 3.71-3.80 (m, 1H), 3.74+3.76 (s, 3H), 3.94+4.14 (d, *J* = 15.6 Hz, 1H), 5.08+5.89 (d, *J* = 6.0 Hz, 1H), 5.95+6.33 (dd, *J* = 7.8, 6.0 Hz, 1H), 6.19+6.23 (d, *J* = 7.8 Hz, 1H), 7.05-7.24 (m, 3H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.59+7.67 (d, *J* = 7.8 Hz, 1H), 8.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) rotamers: δ 8.4, 27.7+27.8, 31.3+31.6, 39.7+40.6, 43.3+43.4,

50.9+51.3+52.0+53.4+53.5+55.9 (3C), 59.2+60.5, 108.3+109.1, 111.2+111.3, 118.6+118.9, 119.5+119.6, 122.1+122.2, 122.8+123.0, 128.6, 129.9, 136.1+136.2, 139.4+140.2, 170.1+170.3, 170.9. IR (neat) 3284, 2918, 1738, 1634, 1431, 1266 cm^{-1}. HRMS (ESI+) calcd for $C_{21}H_{24}BrN_2O_3$ $[M+H]^+$ 431.0970, found 431.0973. $[\alpha]_D^{23}$ = –67.4 (*c* 0.30, $CHCl_3$, 97% ee). HPLC analysis; OJ-H, hexane:*i*-PrOH = 4:1, 1.0 mL/min, t_R = 48.8 min (minor), 114.4 min (major).

11. Diels–Alder reaction of acroleins 3 with the use of MacMillan catalyst 11 (eq 3).

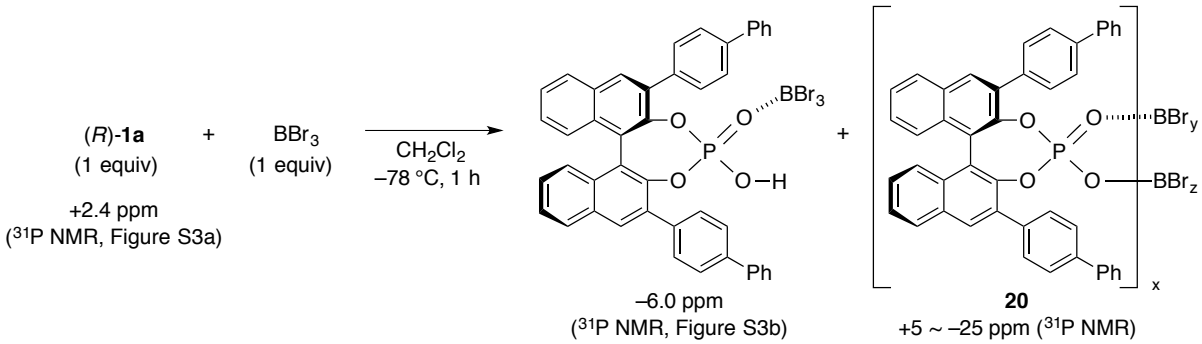
According to Fukuyama's report,[12] we confirmed that the MacMillan catalyst **11** could be used for the reaction of **9a** with **3e**, and the corresponding product *endo*-**10d** was obtained in 42% yield with 92% ee, although the conditions were not strictly optimized. In sharp contrast, under the same conditions, catalyst **11** did not promote the reaction of **9a** with **3a,** probably due to steric constraints in the iminium intermediate **12** (eq 3).





12. ^{31}P NMR analysis of BBr_3–(*R*)-1a complex (eqs 5 and 6).

To analyze the catalysts *in situ*, we examined ^{31}P NMR experiments. All samples below were measured in dichloromethane at –78 °C. (*R*)-**1a** shows a singlet peak at +2.4 ppm (Figure S3a). First, we prepared a sample from (*R*)-**1a** (1 equiv) and BBr_3 (1 equiv) in dichloromethane **at –78 °C** for 1 h. The corresponding complexes were then analyzed at –78 °C, and a major peak was observed at –6.0 ppm (Figure S3b, also see eq 5 in the main text). Some minor peaks were also observed at –3~–25 ppm probably due to some technical reasons in NMR experiments unlike under the standard reaction conditions, and adventitious water might be involved in the NMR tube



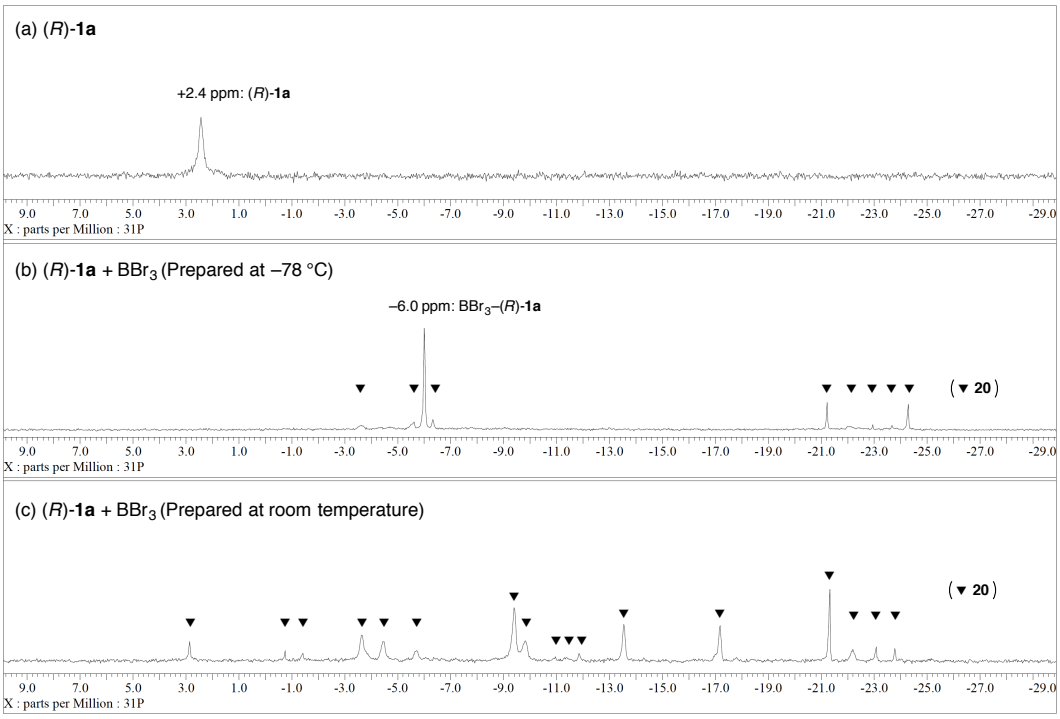


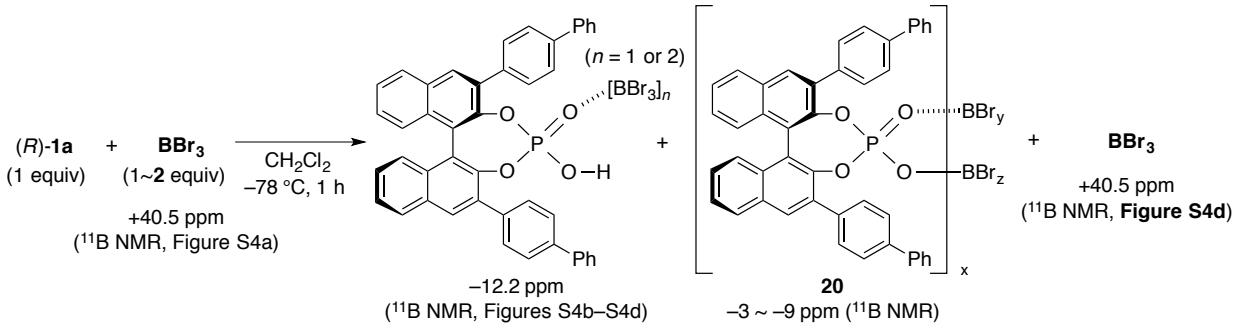
Figure S3. ^{31}P NMR analysis of BBr_3–(*R*)-**1a** complex. All samples were measured in dichloromethane at –78 °C. (a) (*R*)-**1a** in dichloromethane. (b) (*R*)-**1a** (1 equiv) + BBr_3 (1 equiv) in dichloromethane, which were prepared at –78 °C. (c) (*R*)-**1a** (1 equiv) + BBr_3 (1 equiv) in dichloromethane, which were prepared at room temperature.

and trigger the partial decomposition of BBr_3 and/or the resulting complexes (i.e., **20**). Next, we prepared another sample from (*R*)-**1a** (1 equiv) and BBr_3 (1 equiv) in dichloromethane **at room temperature** for 1 h, and the corresponding complexes were then analyzed at –78 °C. As a result, many new peaks were observed at +5 to –25 ppm (Figure S3c, also see eq 6 in the main text). The result in Figure S3c suggests that preparation of the catalyst at room temperature might cause the partial decomposition of BBr_3 along with the generation of some aggregated complexes (i.e., **20**) and HBr. Therefore, preparation of the catalyst preparation at –78 °C should be important for generating the possible active catalyst BBr_3–(*R*)-**1a**.

13. ^{11}B NMR analysis of BBr_3–(*R*)-1a complex.

Next, we examined ^{11}B NMR experiments to investigate a correlation with the former ^{31}P NMR experiments. All samples below were measured in dichloromethane at –78 °C. BBr_3 shows a broad singlet peak at +40.5 ppm (Figure S4a). First, we prepared a sample from (*R*)-**1a** (1 equiv) and BBr_3 (1 equiv) in dichloromethane **at –78 °C** for 1 h. The corresponding complexes were then analyzed at –78 °C, and one broad peak was observed at –12.2 ppm and small multiplet peaks were observed at –3~–9 ppm, although free BBr_3 was not observed (Figure S4b). In this regard, due to some technical reasons in NMR experiments unlike under the standard reaction conditions, adventitious water might be involved in the NMR tube and trigger the partial decomposition of the BBr_3 and the corresponding complexes, which were also observed in ^{31}P NMR (Figure S3b). In fact, the shape and size of the multiplet peaks at –3~–9 ppm subtly changed in every experiment. To support this results, we next prepared another sample from (*R*)-**1a** (1 equiv) and BBr_3 (1 equiv) in dichloromethane **at room temperature** for 1 h, and the corresponding complexes were then analyzed at –78 °C. As a result, the multiplet peaks at –3~–9 ppm were observed as major peaks, while the peak at –12.2 ppm decreased (Figure S4e). These results suggests that the multiplet peaks at –3~–9 ppm might be identified to the decomposed and aggregated complexes (i.e., **20**), which were also observed in ^{31}P NMR (Figure S3c), and the broad peak at –12.2 ppm might be identified to BBr_3-(*R*)-**1a**.

Interestingly, free BBr_3 signal was observed when we used more than 2 equiv of BBr_3 (Figure S4d), while free BBr_3 signal was not observed when we used less than 1.5 equiv of BBr_3 (Figures S4b and S4c). These NMR results suggest that the coordination of BBr_3 to (*R*)-**1a** might be tight and BBr_3 might not be released from the complex. Moreover, these NMR results also suggest that a slightly excess amount of BBr_3 (i.e., 1–1.5 equiv) might act as the dimer $(BBr_3)_2$ in partial.



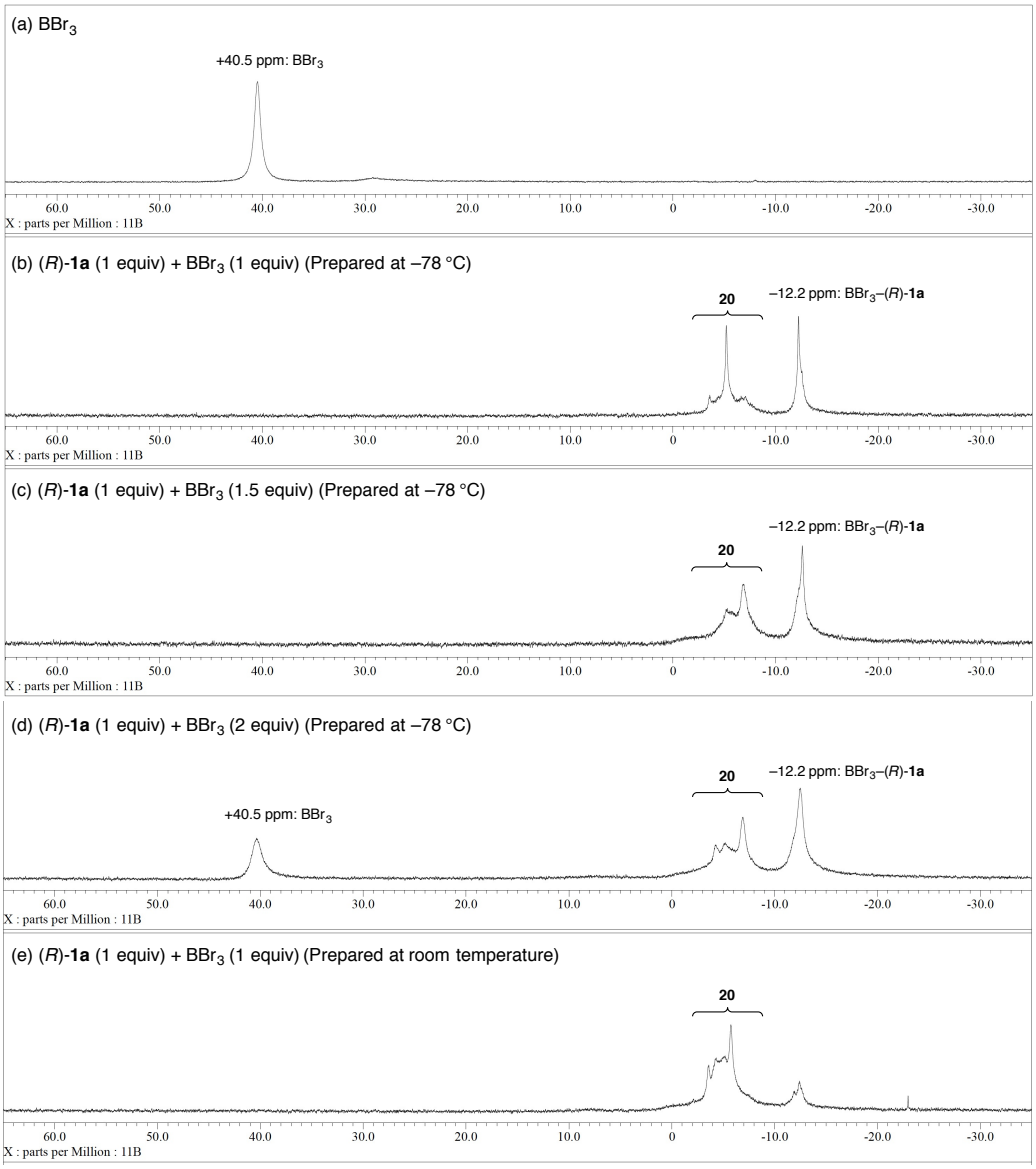
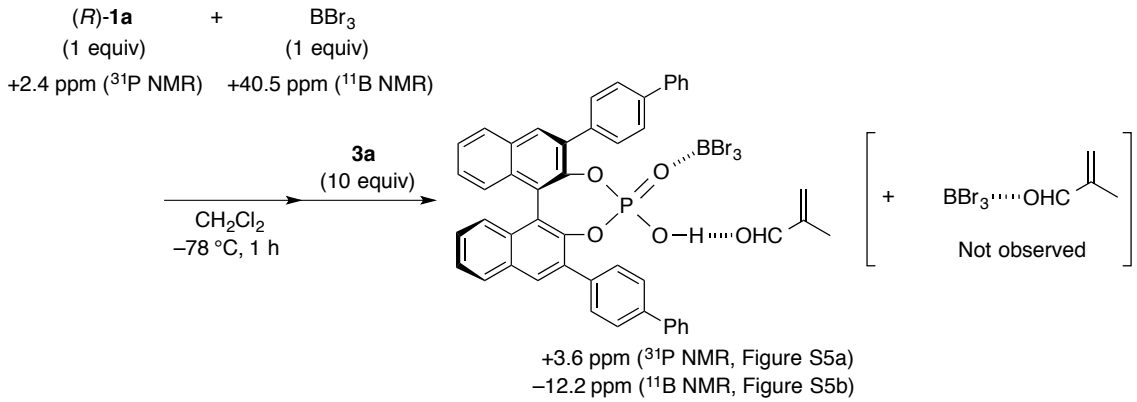


Figure S4. ^{11}B NMR analysis of BBr_3–(*R*)-**1a** complex. All samples were measured in dichloromethane at –78 °C. (a) BBr_3 in dichloromethane. (b) (*R*)-**1a** (1 equiv) + BBr_3 (1 equiv) in dichloromethane, which were prepared at –78 °C. (c) (*R*)-**1a** (1 equiv) + BBr_3 (1.5 equiv) in dichloromethane, which were prepared at –78 °C. (d) (*R*)-**1a** (1 equiv) + BBr_3 (2 equiv) in dichloromethane, which were prepared at –78 °C. (e) (*R*)-**1a** (1 equiv) + BBr_3 (1 equiv) in dichloromethane, which were prepared at room temperature.

14. ^{31}P and ^{11}B NMR analysis of BBr_3–(*R*)-1a–3a complex.

We examined ^{31}P and ^{11}B NMR experiments to investigate the complexation of BBr_3 (1 equiv), (*R*)-**1a** (1 equiv), and **3a** (10 equiv). First, we prepared a sample from (*R*)-**1a** (1 equiv) and BBr_3 (1 equiv) in dichloromethane **at –78 °C** for 1 h. Then **3a** (10 equiv) was added **at –78 °C**, and the mixture was soon analyzed in ^{31}P and ^{11}B NMR at –78 °C. As a result, significant change was observed in ^{31}P NMR, and a new peak appeared at +3.6 ppm (Figure S5a). This peak (+3.6 ppm) is not the same peak of free (*R*)-**1a** (+2.4 ppm, see Figure S3a), and thus at this preliminary stage



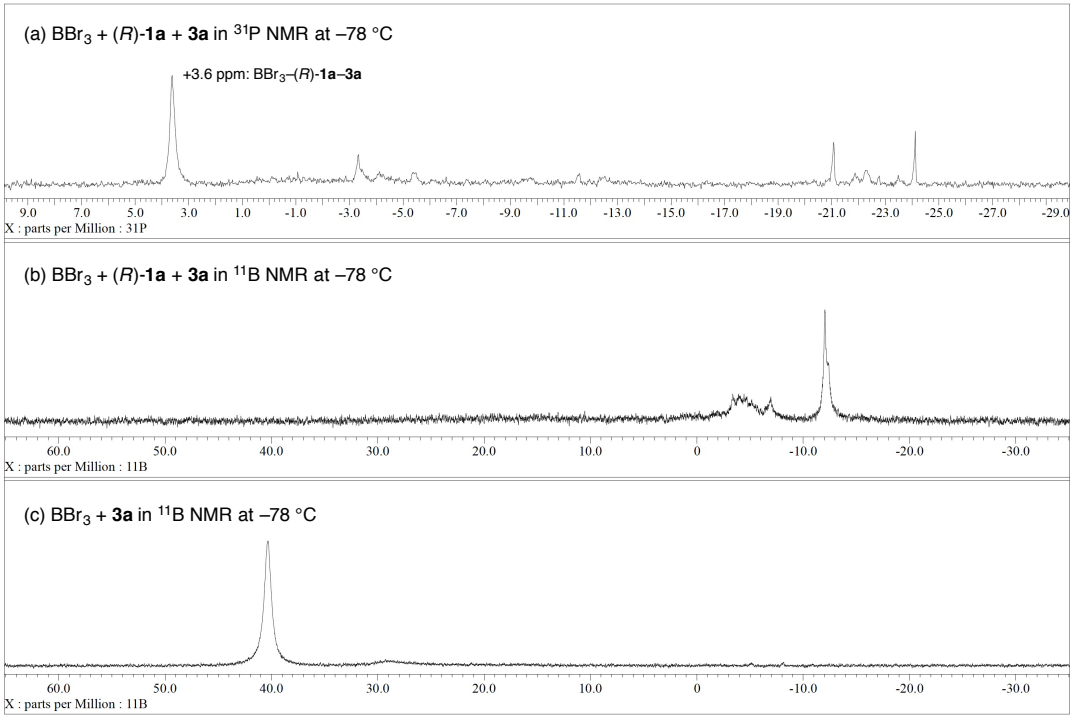
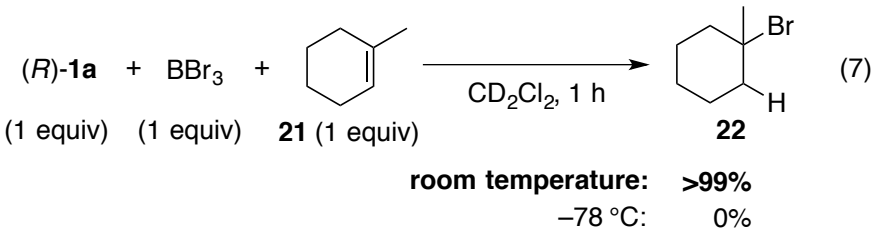


Figure S5. ^{31}P and ^{11}B NMR analysis of BBr_3–(*R*)-**1a**–**3a** complex. (a) ^{31}P NMR of (*R*)-**1a** (1 equiv) + BBr_3 (1 equiv) + **3a** (10 equiv) in dichloromethane at –78 °C. (b) ^{11}B NMR of (*R*)-**1a** (1 equiv) + BBr_3 (1 equiv) + **3a** (10 equiv) in dichloromethane at –78 °C. (c) ^{11}B NMR of BBr_3 (1 equiv) + **3a** (10 equiv) in dichloromethane at –78 °C.

we speculate that it might be BBr_3–(*R*)-**1a**–**3a** complex *in situ*, although further investigations will be needed. In contrast, no significant change was observed in ^{11}B NMR, although a singlet peak at –5.2 ppm disappeared (Figure S5b v.s. Figure S4b). Moreover, free BBr_3 (ca. +40 ppm) was not observed in Figure S5b, in spite of that the excess amount (10 equiv) of small molecule **3a** might kick out and/or coordinate BBr_3. In this regard, a control experiment with BBr_3 (1 equiv) and **3a** (10 equiv) was also conducted. As a result, a clear coordination between BBr_3 and **3a** in ^{11}B NMR was not observed (Figure S5c). Possibly, the release of BBr_3 from the BBr_3–(*R*)-**1a** complexes in the presence of **3a** might not occur. In anyway at this time, we could not completely conclude whether an equilibrium would exist or not among BBr_3, **3a**, BBr_3–**3a**, BBr_3–(*R*)-**1a**, and BBr_3–(*R*)-**1a**–**3a**.

15. Effect of HBr scavenger 21 (eqs 5–7).

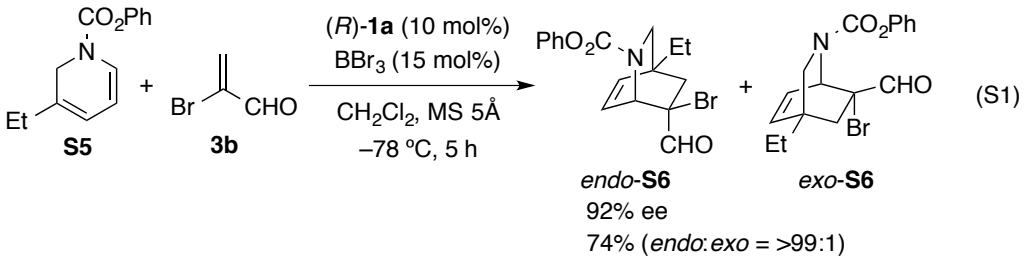
As shown in eq 7 in the main text, the release of HBr **at room temperature** was confirmed by the generation of **22** from 1-methyl-1-cyclohexene **21** as a HBr-scavenger. According to the literature,[21] the generation of **22** from **21** and HBr would proceed more smoothly **at –78 °C** than at room temperature. Therefore, the result in eq 7 suggests that HBr might not be generated during catalyst preparation **at –78 °C**.

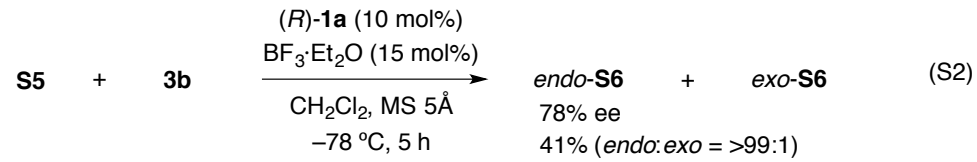


1-Bromo-1-methylcyclohexane (22):[21,22] ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (m, 1H), 1.40-1.52 (m, 2H), 1.54-1.80 (m, 5H), 1.82 (s, 3H), 2.06-2.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5 (2C), 25.2, 35.3, 43.0 (2C), 71.7. ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (m, 1H), 1.40-1.52 (m, 2H), 1.54-1.80 (m, 5H), 1.82 (s, 3H), 2.06-2.10 (m, 2H).

16. Spectroscopic analyses of BF_3–(*R*)-1a and BF_3–(*R*)-1b complexes.

Unfortunately, we could not observe the desired peak for unstable BBr_3–(*R*)-**1a** in the ESI-MS analysis. Instead, we performed an ESI-MS analysis of more stable BF_3–(*R*)-**1a**, since BF_3–(*R*)-**1a** also showed good catalytic activity in some reactions, such as Eqs S1 and S2. These results suggest that BF_3–(*R*)-**1a** would have a similar structure and function as BBr_3–(*R*)-**1a**. As a result, we could observe the desired peak for BF_3–(*R*)-**1a** in ESI-MS analysis, as shown in Figure S6.





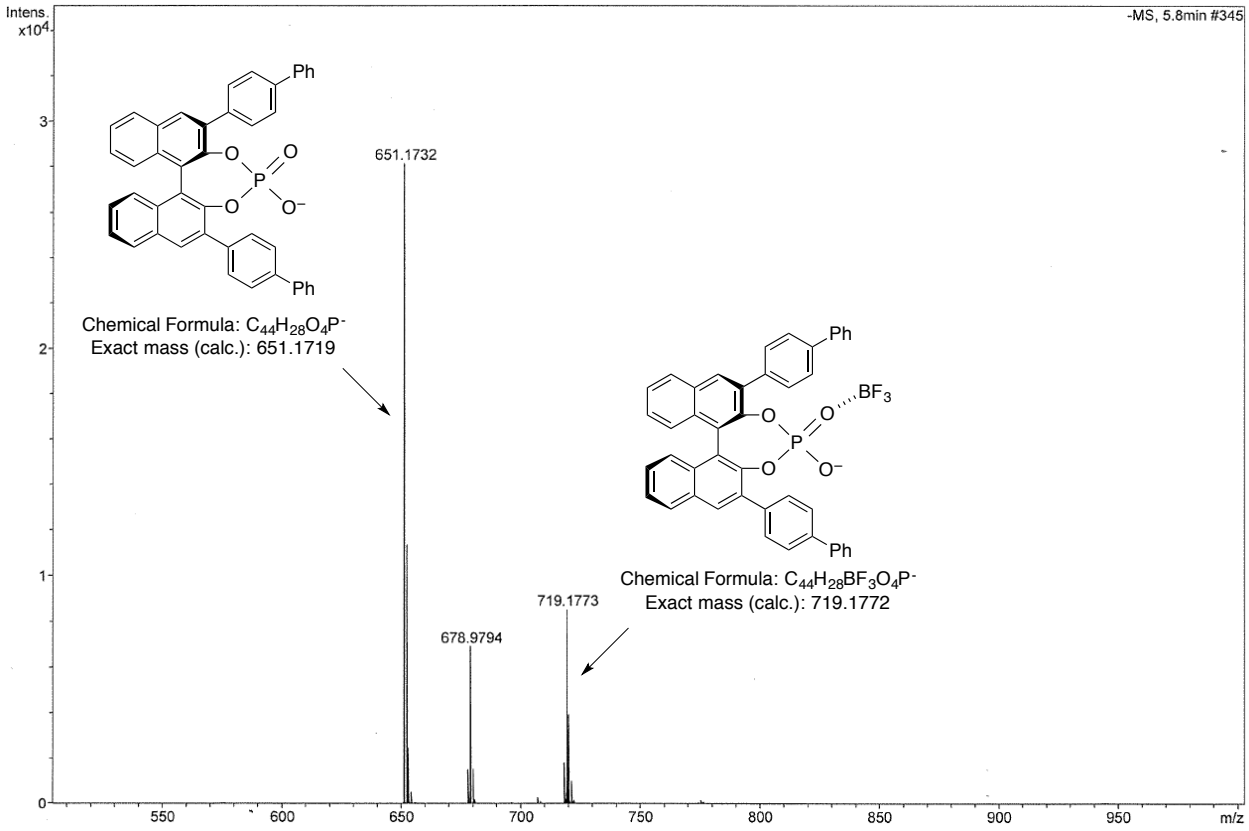


Figure S6. ESI-MS spectrum of (*R*)-**1a**/BF_3 = 1/1 solution.

To a solution of (*R*)-**1a** (16.3 mg, 0.025 mmol) in dichloromethane (1 mL) was added boron trifluoride diethyl etherate (0.25 *M* in dichloromethane, 100 μL, 0.025 mmol) in well-dried Schlenk tube at room temperature. After 20 min, the volatiles were removed under <5 Torr for 1 h. Dichloromethane (4 mL) was added to the residue at room temperature (concentration: 5 m*M*), and the solution was cooled to –78 °C. Then, 75 μL of the solution was diluted with dichloromethane (5 mL) in a well-dried test tube (final concentration: 0.075 m*M*), and passed through a membrane filter (200 mm mesh) just before injection to ESI-MS (negative mode). The spectrum is shown in Figure S6. Moreover, correlation of theoretical and observed ion distribution for the peaks (*m/z* = 651.1732, 719.1773) is shown in Figure S7. For *m/z* = 651.1732, $C_{44}H_{28}O_4P^-$ is identified to [(*R*)-**1a**–H]$^-$. For *m/z* = 719.1773, $C_{44}H_{28}BF_3O_4P^-$ is identified to [(*R*)-**1a**+BF_3–H]$^-$.

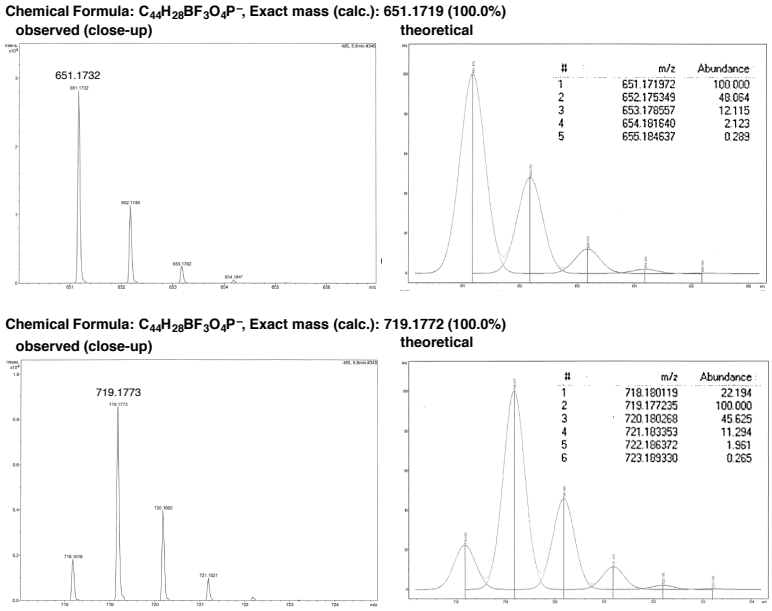


Figure S7. Theoretical and observed ion distribution for the major peaks.

Moreover, a reasonably shifted new peak of BF_3–(*R*)-**1a** was observed at –143.3 ppm in ^{19}F NMR (CD_2Cl_2) at room temperature (Figure S8a). Similarly, a reasonably shifted new peak of BF_3–(*R*)-**1b** was also observed at –151.04 ppm in ^{19}F NMR at room temperature (Figure S8b).

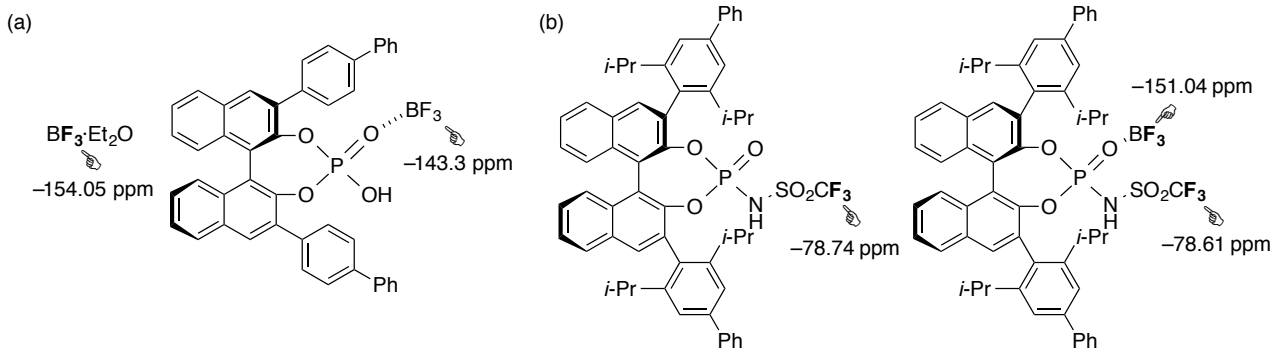
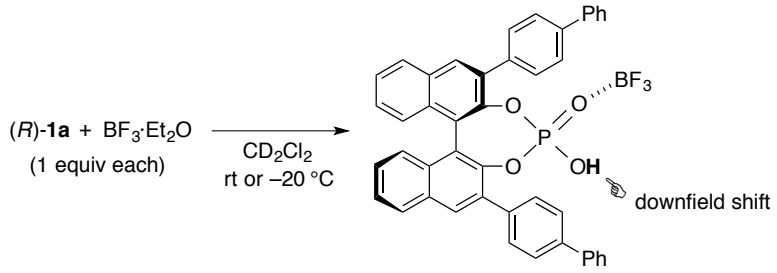


Figure S8. ^{19}F NMR (CD_2Cl_2) of BF_3–(*R*)-**1a** and BF_3–(*R*)-**1b**.

Finally, we tried to examine ^{1}H NMR experiment to see a shift in PO_2**H** of (*R*)-**1a** consistent with increased acidity with the use of BBr_3. Unfortunately, however, the peak of PO_2**H** of (*R*)-**1a** cannot be observed in CD_2Cl_2 at lower temperature than –20 °C. Therefore, we cannot use BBr_3, since it would decompose at that temperature. We thus used stable $BF_3 \cdot Et_2O$ in place of unstable BBr_3 even at higher temperature than –20 °C. As a result, a somewhat broad peak was clearly observed with downfield shift from (*R*)-**1a** both at room temperature (Figures S9a and S9b) and at –20 °C (Figures S9c and S9d). These results strongly suggest that the acidity of PO_2**H** of (*R*)-**1a** would increase with the combined use of achiral Lewis acids.



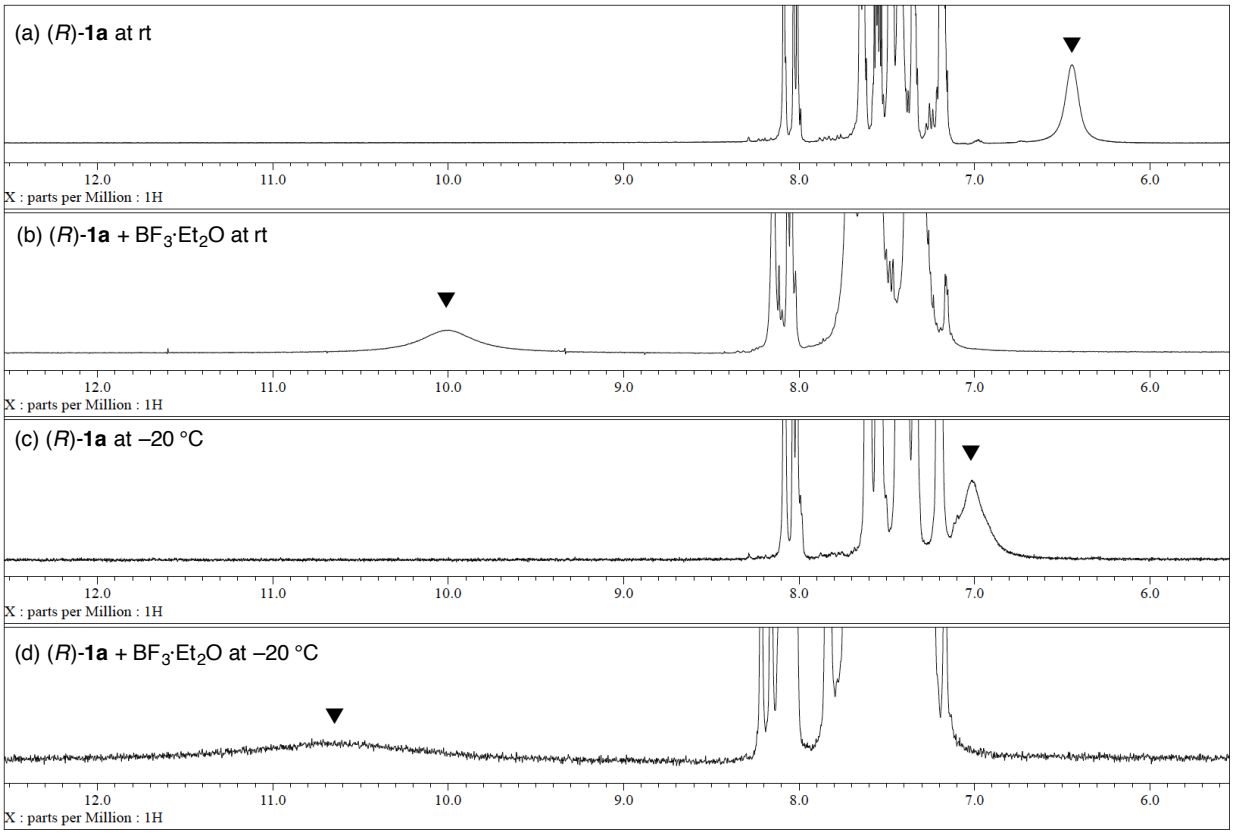


Figure S9. ^{1}H NMR analysis of (*R*)-**1a** and BF_3–(*R*)-**1a**. All samples were measured in CD_2Cl_2. (a) (*R*)-**1a** at room temperature. (b) (*R*)-**1a** (1 equiv) + $BF_3 \cdot Et_2O$ (1 equiv) at room temperature. (c) (*R*)-**1a** at –20 °C. (d) (*R*)-**1a** (1 equiv) + $BF_3 \cdot Et_2O$ (1 equiv) at –20 °C.

17. Theoretical calculations for BBr_3–(*R*)-1a–3b complex.

Molecular geometries of the stable structures of the complexes were optimized using Density Functional Theory with Becke's three-parameter hybrid functional[23] and Lee, Yang, and Parr's (LYP)[24] correlation functional. The 6-31G(d) basis sets were used in this study. All geometries were optimized without any symmetry restrictions and characterized as stable points (no imaginary frequency) by calculations of harmonic vibrational frequencies. Natural bond orbital (NBO)[25] analysis were performed and bond orders are represented by the Wiberg index.[26] All calculations have been carried out using the Gaussian 03 program package.[27] The most stable conformer is shown in Figure S10.

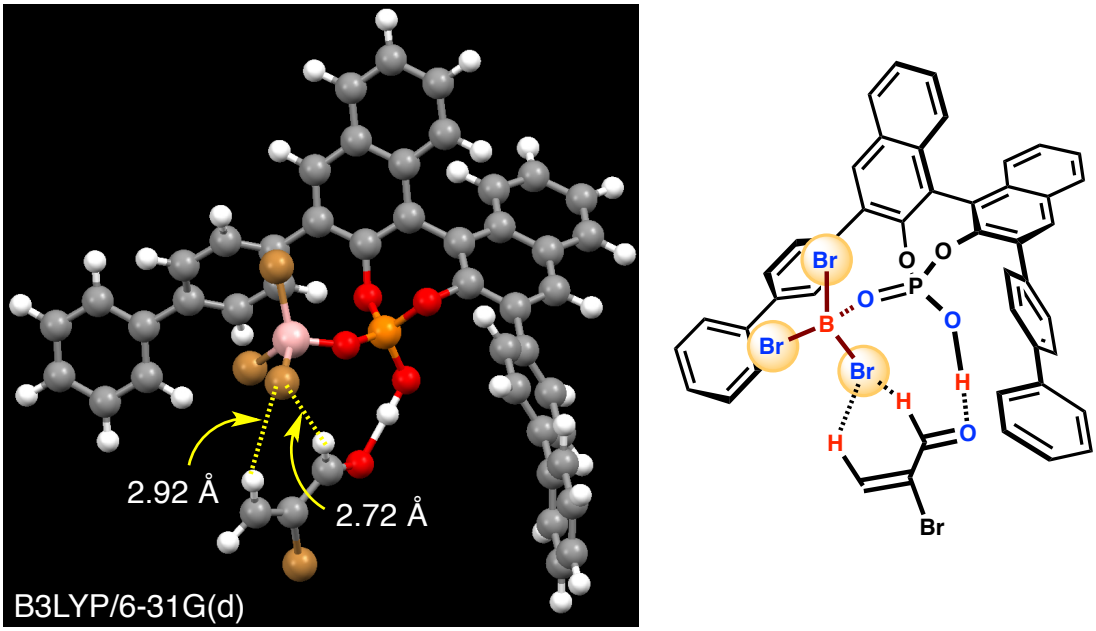
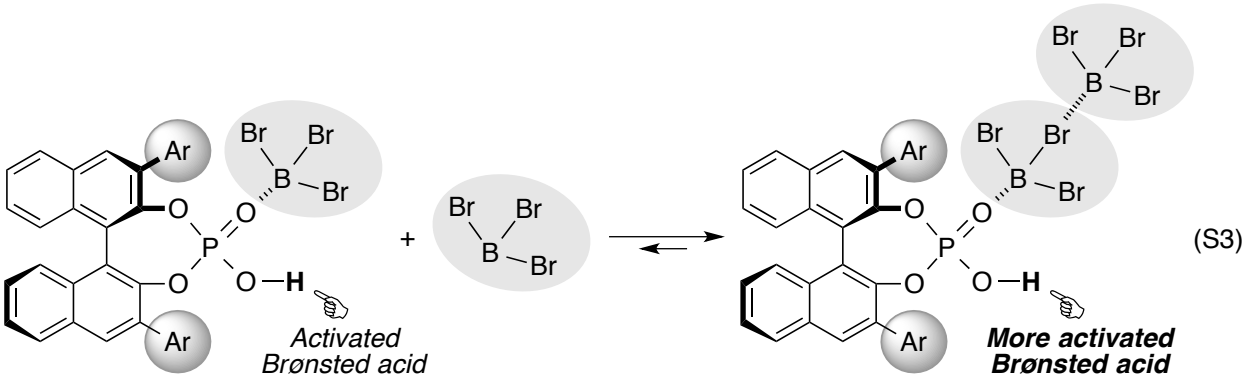


Figure S10. Theoretical calculation of BBr_3–(*R*)-**1a**–**3b** complex.

In some cases, a small excess amount of BBr_3 (15 mol%) relative to phosphoric acid (*R*)-**1a** (10 mol%) was needed in order to achieve high yields and high enantioselectivities. In those cases, the similar transition states might be possible, since excess BBr_3 might act as the dimer $(BBr_3)_2$[28] which has stronger Lewis acidity and bulkier structure than monomeric BBr_3 (Eq S3).



(S3)

Theoretical calculation of BBr_3-(*R*)-**1a**-**3b** complex (Figure S10)
Method: B3LYP/6-31G(d)
SCF Done: E(RB+HF-LYP) = -12839.6766161 A.U. after 8 cycles
Imaginary frequencies: 0
Zero-point correction= 0.668218 (Hartree/Particle)
Thermal correction to Energy= 0.719072
Thermal correction to Enthalpy= 0.720016
Thermal correction to Gibbs Free Energy= 0.574343
Sum of electronic and zero-point Energies= -12839.008398
Sum of electronic and thermal Energies= -12838.957544
Sum of electronic and thermal Enthalpies= -12838.956600
Sum of electronic and thermal Free Energies= -12839.102273

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.410909	2.301633	-1.014293
2	6	0	2.096725	2.444990	-0.489800
3	6	0	3.827470	3.280706	-1.896331
4	8	0	1.630582	1.431427	0.376710
5	6	0	1.246316	3.498642	-0.762548
6	8	0	0.210958	-0.486832	0.980644
7	6	0	1.670944	4.464762	-1.742353
8	6	0	-0.087950	3.601604	-0.095841
9	6	0	0.831179	5.507140	-2.221212
10	6	0	2.987053	4.347793	-2.297623
11	6	0	3.425888	5.299716	-3.257868
12	6	0	-1.022609	2.584387	-0.194318
13	6	0	-0.450411	4.770807	0.661003
14	6	0	-2.382448	2.701209	0.208113
15	8	0	-0.640498	1.356788	-0.785462
16	6	0	-1.790859	4.886995	1.151183
17	6	0	0.474847	5.800973	0.982742
18	6	0	-2.161242	6.036128	1.901142
19	6	0	-2.728337	3.865323	0.867032
20	6	0	-1.244251	7.020937	2.184292
21	6	0	1.280591	6.401548	-3.167671
22	6	0	0.088468	6.893478	1.727575
23	6	0	2.594129	6.308245	-3.684089
24	15	0	0.520941	0.440427	-0.193554

25	8	0	1.048714	-0.342942	-1.420274
26	5	0	-0.904013	-0.982353	1.850792
27	35	0	-0.074025	-2.445167	2.990363
28	35	0	-1.573374	0.531672	2.976717
29	35	0	-2.322653	-1.761589	0.638747
30	6	0	-0.560490	-5.446218	0.504043
31	6	0	-0.142557	-4.879775	-0.636036
32	35	0	-0.192527	-5.771098	-2.315313
33	6	0	0.340835	-3.497759	-0.618797
34	8	0	0.643477	-2.856378	-1.624259
35	6	0	-3.415813	1.683225	-0.109836
36	6	0	-3.529355	1.130858	-1.394941
37	6	0	-4.359126	1.307124	0.858449
38	6	0	-4.550653	0.237327	-1.698493
39	6	0	-5.497141	-0.142237	-0.732438
40	6	0	-6.582328	-1.100752	-1.057881
41	6	0	-5.377918	0.411914	0.552163
42	6	0	-6.345823	-2.200035	-1.900904
43	6	0	-7.874690	-0.935138	-0.531454
44	6	0	-7.365617	-3.099263	-2.208450
45	6	0	-8.894692	-1.834454	-0.838026
46	6	0	-8.644984	-2.920632	-1.678849
47	6	0	4.303468	1.170220	-0.653626
48	6	0	5.039988	0.513317	-1.652561
49	6	0	4.479205	0.752174	0.676118
50	6	0	5.920934	-0.516093	-1.335961
51	6	0	6.102218	-0.934563	-0.007507
52	6	0	7.040842	-2.033529	0.331161
53	6	0	5.360924	-0.277295	0.989290
54	6	0	7.183555	-3.147756	-0.513483
55	6	0	7.811917	-1.988579	1.505285
56	6	0	8.065820	-4.179214	-0.196133
57	6	0	8.694054	-3.019965	1.823168
58	6	0	8.825370	-4.120059	0.973665
59	1	0	4.834047	3.230654	-2.302076
60	1	0	-0.180828	5.589777	-1.843696
61	1	0	4.431726	5.204646	-3.659266
62	1	0	1.502895	5.714597	0.650610
63	1	0	-3.185225	6.113865	2.257750
64	1	0	-3.760602	4.005200	1.174900
65	1	0	-1.536297	7.890511	2.766244
66	1	0	0.616771	7.184226	-3.524040
67	1	0	0.816825	7.661810	1.971493
68	1	0	2.937280	7.025608	-4.424180
69	1	0	0.912574	-1.369141	-1.459656
70	1	0	-0.530833	-4.868730	1.426396
71	1	0	0.431365	-3.069493	0.388802
72	1	0	-0.950628	-6.457366	0.540702
73	1	0	-2.826717	1.417162	-2.171174
74	1	0	-4.258079	1.677584	1.873029
75	1	0	-4.633553	-0.150238	-2.709918
76	1	0	-6.068139	0.106165	1.333071
77	1	0	-5.346402	-2.365024	-2.293604
78	1	0	-8.085410	-0.079400	0.104129
79	1	0	-7.157222	-3.947372	-2.855596
80	1	0	-9.888539	-1.681681	-0.425179
81	1	0	-9.439665	-3.622190	-1.918128

82	1	0	4.909883	0.805159	-2.690963
83	1	0	3.924887	1.236436	1.473078
84	1	0	6.489719	-0.991275	-2.130073
85	1	0	5.458876	-0.591983	2.024204
86	1	0	6.576983	-3.218662	-1.412072
87	1	0	7.737146	-1.125342	2.160682
88	1	0	8.152955	-5.035326	-0.860010
89	1	0	9.285732	-2.959768	2.732838
90	1	0	9.512679	-4.924309	1.221612

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Chapter 4

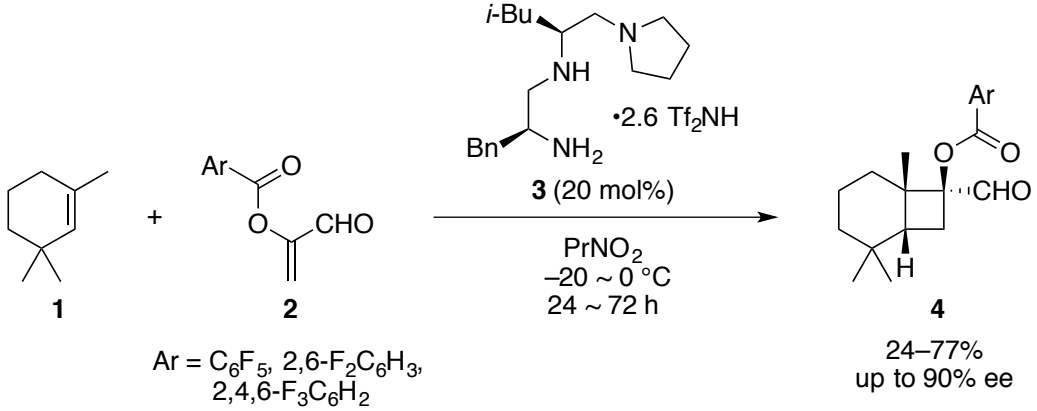
Boron Tribromide-Assisted Chiral Phosphoric Acid Catalysts for Enantioselective [2 + 2] Cycloaddition

Abstract: Lewis acid-assisted chiral phosphoric acid catalysts were effective for promoting an enantioselective [2 + 2] cycloaddition between methacrolein and electron-rich olefins. In particular, the [2 + 2] cycloaddition of methacrolein with phenyl vinyl sulfide gave the corresponding optically active cyclobutane in high yield with high diastereo- and enantioselectivity. Moreover, a preliminary transformation into the synthetic intermediate of natural products, (+)-frontalin, is demonstrated.

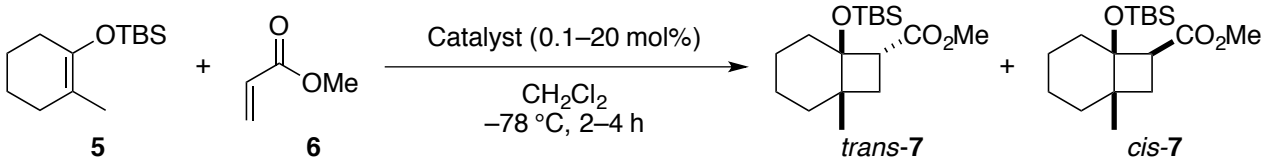
4-1 Introduction

Cyclobutanes are versatile synthetic intermediates since they can be transformed into other useful compounds due to their ring strain with high reactivity.[1] Therefore, chiral cyclobutanes have been used in the key transformation in the synthesis of many natural products.[2] Moreover, recently, a few catalytic methodologies in the enantioselective [2 + 2] cycloadditions with use of chiral acids have been reported to obtain enantio-enriched cyclobutanes toward natural product synthesis.[3] In particular, chiral Lewis acids have been mostly used in the catalytic enantioselective [2 + 2] cycloadditions.[4] As for chiral organocatalysts, Ishihara developed an enantioselective [2 + 2] cycloaddition of unactivated alkenes **1** with α-acyloxyacroleins **2** for the first time by using chiral ammonium salt **3** (Scheme 1).[5] This reaction proceeds through initial condensation of chiral amine component of **3** with aldehyde **2**. The resulting activated iminium salt can react with **1** to provide optically active cyclobutanes **4** with high enantioselectivities. However, there have been no reports of enantioselective [2 + 2] cycloadditions directly activating carbonyl groups of substrates with chiral Brønsted acid catalysts. With regard to achiral Brønsted acids, Ihara and Takasu provided the only report on the trifluoromethanesulfonimide-catalyzed [2 + 2] cycloadditions of 2-methylcyclohexanone-derived silyl enol ethers **5** with acrylates **6** (Scheme 2).[6] According to their report, Brønsted acid catalysts (eg., Tf_2NH) improved the diastereoselectivity of the [2 +2] cycloadduct **7** with the much reduced amounts of catalysts (0.1 mol%) unlike Lewis acid catalysts (eg., $EtAlCl_2$, 20 mol%). Moreover, multigram syntheses of the cyclobutanes were achieved.

Scheme 1. Enantioselective [2 + 2] Cycloadditions of Unactivated Alkene **1** with **2**



Scheme 2. [2 + 2] Cycloaddition of **5** with **6** Catalyzed by Trifluoromethanesulfonimide

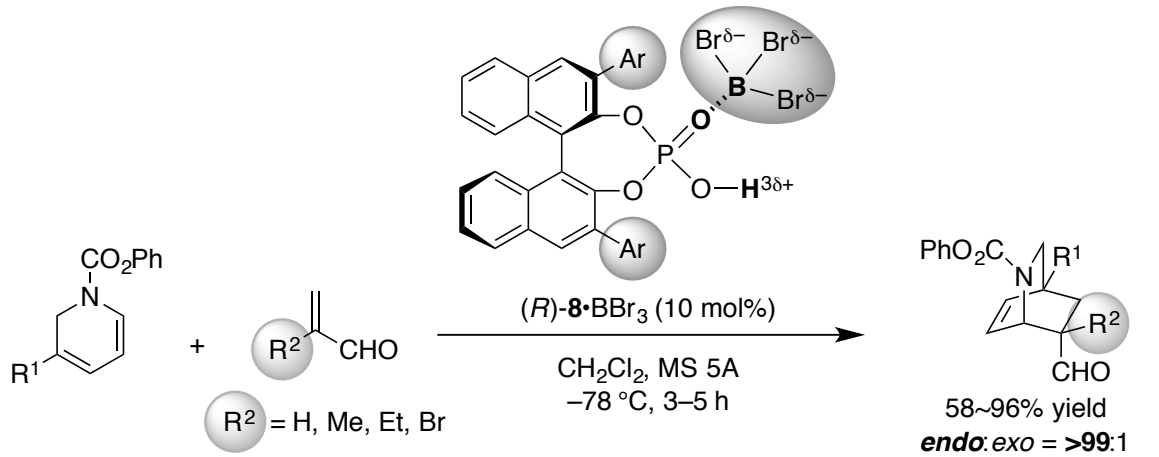


5 **6** *trans*-**7** *cis*-**7**

Tf_2NH (0.1 mol%): 98% (*trans*:*cis* = ~100:trace)
$EtAlCl_2$ (20 mol%): 79% (*trans*:*cis* = 95:5)
up to 7.5 g scale synthesis

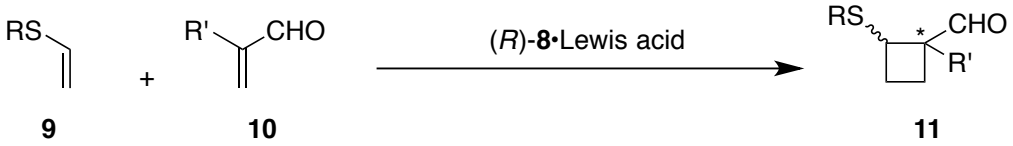
Recently, the author developed Lewis acid-assisted chiral phosphoric acid catalysts, which were prepared *in situ* from chiral BINOL-derived phosphoric acids **8** and achiral Lewis acids for an enantioselective Diels–Alder reaction of α,β-unsaturated aldehydes (Scheme 3).[7] Therefore, the author envisioned that Lewis acid-assisted chiral phosphoric acid catalysts might be applied to a [2 + 2] cycloaddition between vinyl sulfides **9** as electron-rich olefins and α-substituted acroleins **10** (Scheme 4). This chapter will show a powerful method for the chiral Brønsted acid-catalyzed [2 + 2] cycloaddition for the first time.

Scheme 3. Lewis Acid-assisted Chiral Phosphoric Acid Catalysts for Enantioselective Diels–Alder Reaction of α,β-Unsaturated Aldehydes



58~96% yield
endo:*exo* = **>99**:1
up to **98% ee (*endo*)**

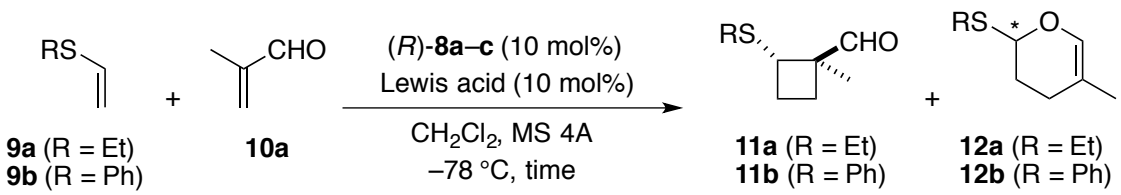
Scheme 4. Enantioselective [2 + 2] Cycloaddition between **9** and **10** Catalyzed by Lewis Acid-Assisted Chiral Phosphoric Acids

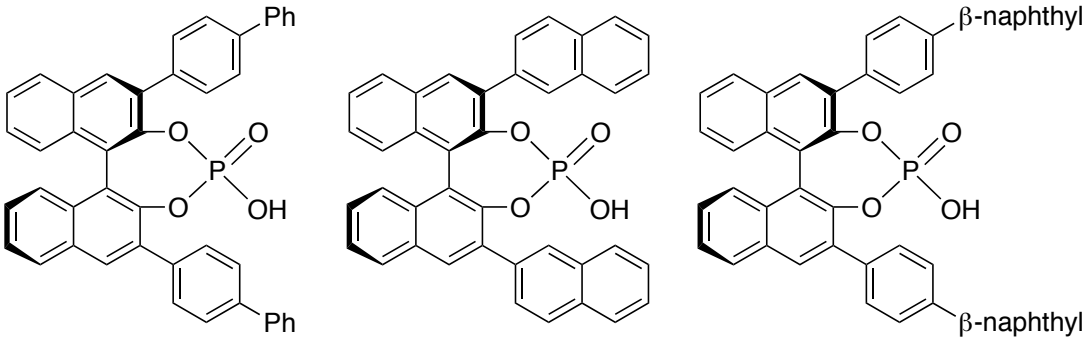


4-2 Results and Discussion

First, the author examined a [2 + 2] cycloaddition of methacrolein **10a** with ethyl vinyl sulfide **9a** or phenyl vinyl sulfide **9b**[8] in dichloromethane at –78 °C for 1–24 h in the presence of Lewis acid-assisted chiral phosphoric acid catalysts (10 mol%), which were prepared *in situ* from chiral phosphoric acids (*R*)-**8** and $B(C_6F_5)_3$ or BBr_3 (Table 1). When **9a** was used as a substrate, the reaction with the use of (*R*)-**8a**•$B(C_6F_5)_3$ afforded *trans* [2 + 2] cycloadduct **11a** as a single diastereomer in 51% yield with 50% ee within 24 h (entry 1). In this time, the Diels–Alder adduct **12a**, which was generated via intermediate **13a** (Scheme 5, Eq. 1), was obtained in 18% yield. In contrast, when **9b** was used as a substrate, generation of the side product **12b** was almost completely prevented since decomposition of **11b** might be slow (Scheme 5, Eq. 2), and the desired product **11b** as a single diastereomer was obtained in 81% yield but with 3% ee (entry 3). Fortunately, the enantioselectivity of **11b** was significantly improved when (*R*)-**8a**•BBr_3, which was the most effective for the enantioselective Diels–Alder reaction of methacrolein **10a**,[7b] was used in place of (*R*)-**8a**•$B(C_6F_5)_3$, and **11b** was obtained in 87% yield with 83% ee (entry 4). As a result of the screening of 3,3'-positions of chiral phosphoric acids, (*R*)-**8b**•BBr_3 did not improve the enantioselectivity of **11b** significantly (entry 5), whereas (*R*)-**8c**•BBr_3 improved the enantioselectivity up to 89% ee (entry 6). Unfortunately, even the optimized catalysts, (*R*)-**8a**•BBr_3, was not effective for the reaction between **9a** and **10a**, and **11a** was obtained in 16% yield with 11% ee (entry 2). The continuous investigations of substrate scopes are currently underway.

Table 1. Optimization of the Reaction Conditions[a]



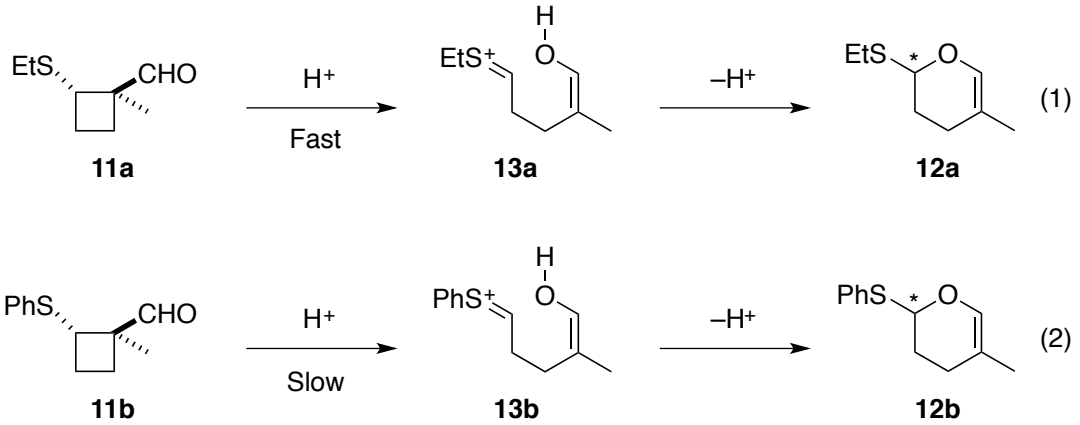


(*R*)-**8a** (*R*)-**8b** (*R*)-**8c**

entry	**9**	(*R*)-**8**	Lewis acid	time (h)	yield (%) of **11**	ee (%) of **11**	yield (%) of **12**
1	**9a**	(*R*)-**8a**	$B(C_6F_5)_3$	24	51	50	18
2[b]	**9a**	(*R*)-**8a**	BBr_3	24	16	11	22
3	**9b**	(*R*)-**8a**	$B(C_6F_5)_3$	12	81	3	4
4	**9b**	(*R*)-**8a**	BBr_3	1	87	83	3
5	**9b**	(*R*)-**8b**	BBr_3	1	76	84	6
6	**9b**	(*R*)-**8c**	BBr_3	1	90	89	4

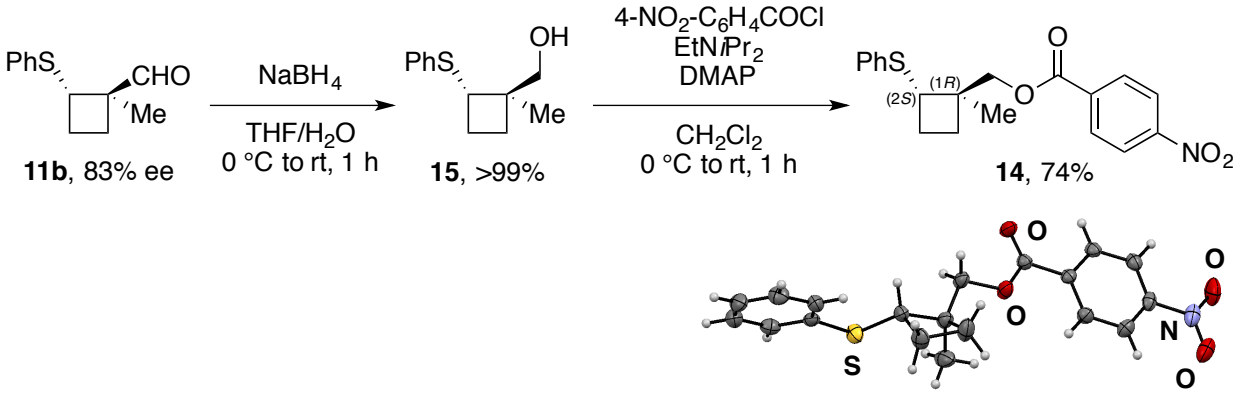
[a] The reaction was carried out with (*R*)-**8** (10 mol%), Lewis acid (10 mol%), **9** (1.2 equiv), **10a** (1 equiv), and MS 4A in dichloromethane at –78 °C for 1–24 h. [b] The reaction was carried out with (*R*)-**8a** (5 mol%), and BBr_3 (5 mol%) at –60 °C.

Scheme 5. Decompositions of **11** in Acidic Conditions



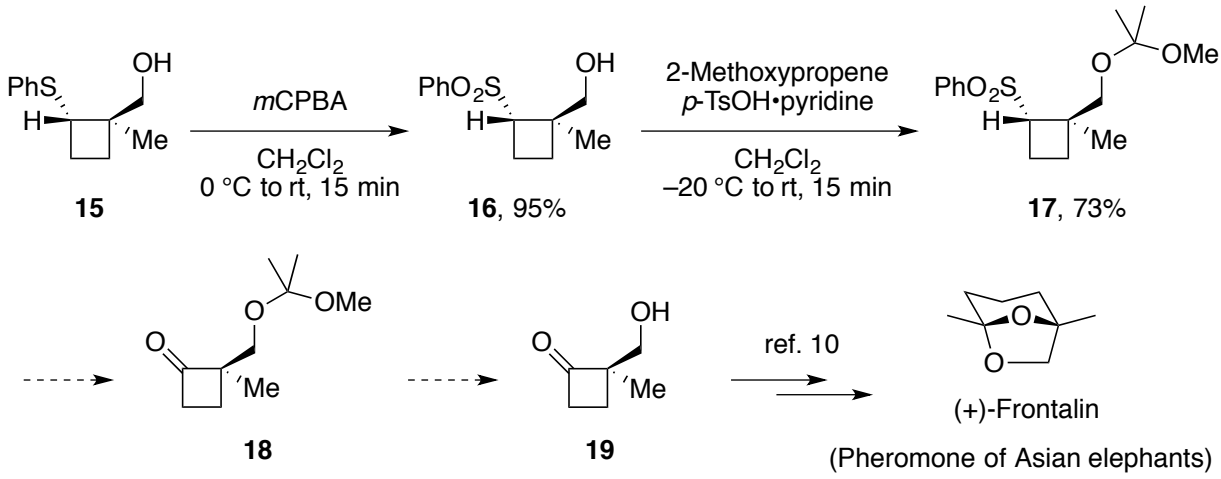
To determine the absolute configuration of enantio-enriched **11b** in X-ray analysis, a transformation of **11b** into **14** was performed (Scheme 6). Treatment of **11b** with $NaBH_4$ gave the corresponding alcohol **15** in quantitative yield. Acylation of **15** with 4-nitrobenzoyl chloride under basic conditions provided the desired product **14** in 74% yield without a loss of optical purity. Finally, X-ray structural analysis of **14** determined the absolute configuration of **14** as shown in Scheme 6.

Scheme 6. Transformation of **11b** into **14**

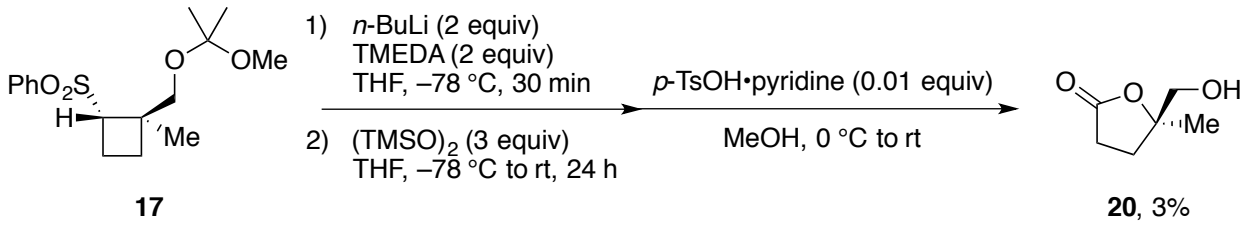


Next, to demonstrate a synthetic utility of the present catalysis, a transformation to the key intermediate of (+)-frontalin,[9] which is pheromone of Asian elephants, was conducted (Scheme 7). Sulfide **15** was transformed to sulfone **16** in 95% yield by oxidation of *m*-chloroperoxybenzoic acid (*m*CPBA). Protection of hydroxy group of **16** with 2-methoxypropene under acidic conditions provided acetal **17** in 73% yield. Since a formal total synthesis of (+)-frontalin[10] might be achieved when a transformation of sulfone **17** into ketone **18**, a subsequent deprotection of **18** would be conducted. Indeed, the author examined the transformations of **17** according to some literature procedures.[11] For example, after deprotonation of sulfone **17** was conducted with *n*-BuLi, addition of $(TMSO)_2$ and subsequent deprotection under acidic conditions gave γ-butyrolactone **20** in 3% yield instead of desired product **19** (Scheme 8). γ-Butyrolactone **20** might be generated by Baeyer–Villiger oxidation of ketone **18** with $(TMSO)_2$ and subsequent deprotection.[12]

Scheme 7. Formal Total Synthesis of (+)-Frontalin

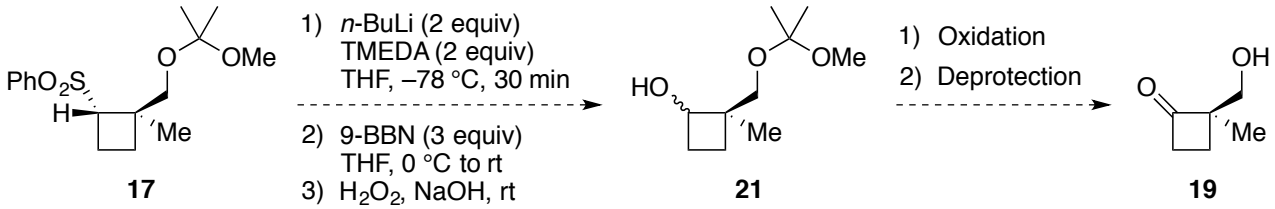


Scheme 8. Transformation of **17** into **20**



To obtain ketone **19** efficiently, the utility of other reagents are currently underway. For example, a transformation of sulfone **17** into alcohol **21** with the use of 9-BBN and H_2O_2 may be one of other possible routes to ketone **19** (Scheme 9).[13]

Scheme 9. Strategy of Transformation of **17** into **19**



4-3 Conclusion

In summary, the author has developed the enantioselective [2 + 2] cycloadditions between methacrolein and electron-rich olefins catalyzed by Lewis acid-assisted chiral phosphoric acids. In particular, boron tribromide-assisted chiral phosphoric acid catalysts were effective for the

enantioselective [2 + 2] cycloaddition of methacrolein with phenyl vinyl sulfide, and the corresponding optically active cyclobutane was obtained in high yield with high diastereo- and enantioselectivity. Moreover, preliminary investigations of transformations into the synthetic intermediate of (+)-frontalin are demonstrated.

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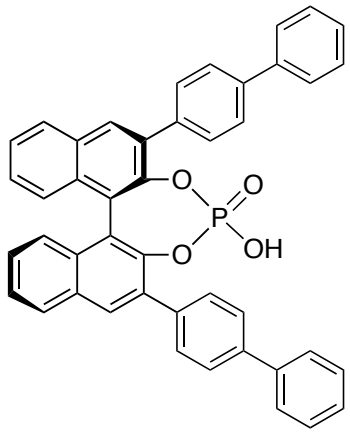
Experimental Section for Chapter 4

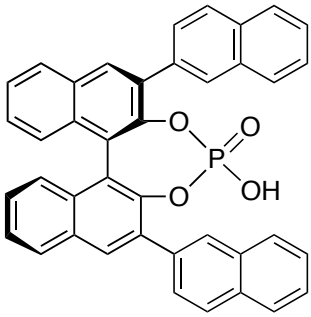
1. General methods.

^{1}H NMR spectra were measured on a JEOL ECS400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, sept = septet, m = multiplet, br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS400 (100 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.10 ppm). ^{31}P NMR spectra were measured on a JEOL ECS-400 (161 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard (H_3PO_4 at 0 ppm). Gas-liquid-phase chromatography (GC) was performed with Shimadzu GC-2010 instrument with a flame-ionization detector and a capillary column of CHIRALDEX G-TA (i.d., 0.25 mm × 20 m; Tokyo Kasei Kogyo Co., LTD). High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-20 AD coupled diode array-detector SPD-M20A and chiral column of Daicel CHIRALCEL, CHIRALPAK; OD-3, AD-3, IC-3. Optical rotations were measured on Rudolph Autopol IV digital polarimeter. The products were purified by column chromatography on silica gel (Kanto Chemical Co., Inc. 37560; Merck silica gel 60, Prod. No. 1.09385.9929). Mass spectral analyses were performed at Chemical Instrument Center, Nagoya University (JEOL JMS-700 (FAB), JEOL JMS-T100GCV (EI), Bruker Daltonics micrOTOF-QII (ESI)). X-ray analyses were performed by Rigaku PILATUS-200K. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60GF254 0.25 mm) were used. Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. Dichloromethane (with P_4O_{10}) was freshly distilled in prior to use. Ethyl vinyl sulfide (**9a**), phenyl vinyl sulfide (**9b**), methacrolein (**10a**) are commercially available and were used without any purification.

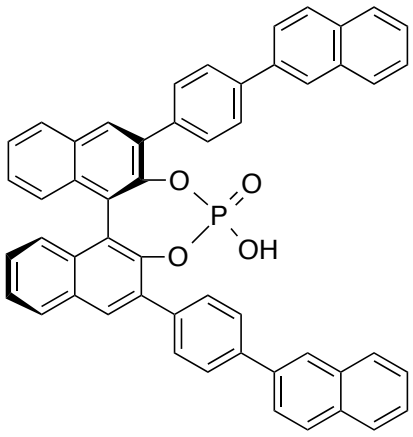
2. Preparation of phosphoric acids.



(*R*)-3,3'-Bis(biphenyl-4-yl)-1,1'-binaphthalene-2,2'-diyl hydrogen phosphate (8a): The titled compound was prepared according to the literature procedure.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (br, 1H), 7.13-7.45 (m, 18H), 7.51 (m, 2H), 7.61 (d, *J* = 8.2 Hz, 4H), 7.96 (d, *J* = 8.2 Hz, 2H), 8.02 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.5 (2C), 126.0 (2C), 126.6 (2C), 127.0 (4C), 127.1 (2C), 127.2 (4C), 128.5 (4C), 130.1 (4C), 131.3 (2C), 131.6 (2C), 132.0 (2C), 133.6 (2C), 133.7 (2C), 135.6 (2C), 140.5 (2C), 140.8 (2C), 144.5 (2C), 144.6 (2C). ^{31}P NMR (161 MHz, $CDCl_3$) δ 2.8. IR (KBr) 3433, 3051, 1488, 1419, 1244, 1181, 1023 cm^{-1}. M.p. 215–223 °C (decomposition). $[\alpha]_D^{26}$ = –352.0 (*c* 0.40, $CHCl_3$). HRMS (ESI–) calcd for $C_{44}H_{28}O_4P$ $[M–H]^-$ 651.1731, found 651.1740.

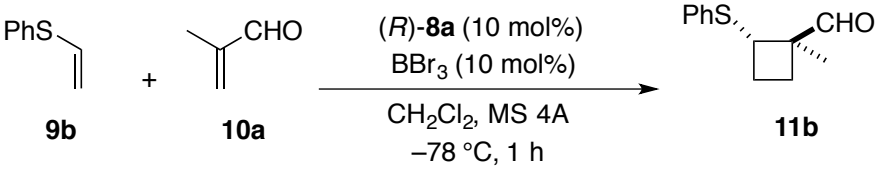


(*R*)-3,3'-Bis(naphthalen-2-yl)-1,1'-binaphthalene-2,2'-diyl hydrogen phosphate (8b): The titled compound was prepared according to the literature procedure.[2] The ^{1}H NMR spectrum and the ^{13}C NMR spectrum were consistent with the spectrum reported in the literature.[3]



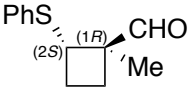
(*R*)-3,3'-Bis(4-(naphthalen-2-yl)phenyl)-1,1'-binaphthalene-2,2'-diyl hydrogen phosphate (8c): The titled compound was prepared according to the literature procedure.[2] The ^{1}H NMR spectrum and the ^{13}C NMR spectrum were consistent with the spectrum reported in the literature.[4] IR (KBr) 3051, 1501, 1419, 1180, 1020 cm^{-1}. M.p. 210–224 °C (decomposition). $[\alpha]_D^{25}$ = –368.8 (*c* 1.03, $CHCl_3$). HRMS (ESI–) calcd for $C_{52}H_{32}O_4P$ $[M–H]^-$ 751.2044, found 751.2036.

3. Enantioselective [2 + 2] cycloaddition of methacrolein 10a with phenyl vinyl sulfide 9b (Table 1).



9b **10a** **11b**

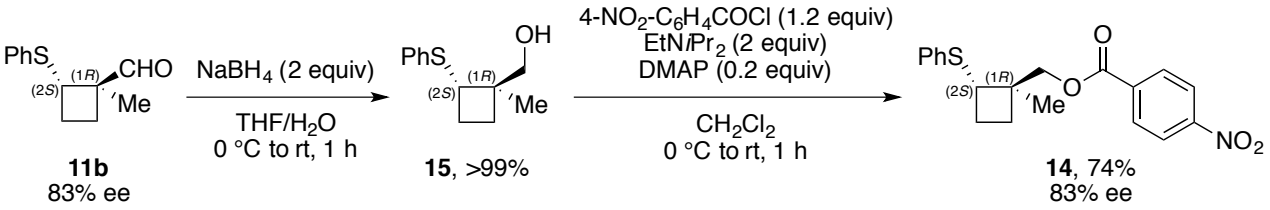
A suspension of (*R*)-**8a** (16.3 mg, 0.025 mmol) and activated MS 4Å (100 mg) in freshly distilled dichloromethane (1 mL) was stirred at room temperature in Schlenk tube under a nitrogen atmosphere. To the mixture was added boron tribromide (1 *M* in dichloromethne, 2.5 μL, 0.025 mmol) at –78 ºC, and this suspension was stirred at that temperature for 20 min. Methacrolein **10a** (95% purity, 21.7 μL, 0.25 mmol) and phenyl vinyl sulfide **9b** (39.3 μL, 0.3 mmol) were then added dropwise at –78 °C. After 1 h, the reaction was quenched with triethylamine (100 μL) at –78 °C. The product mixture was directly purified by neutral silica gel column chromatography (eluent: pentane/diethyl ether = 100/1 to 9/1) to give **11b** (42.8 mg, 87%, 83% ee) as a colourless oil.

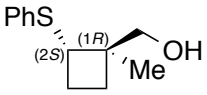


(1*R*,2*S*)-1-Methyl-2-(phenylthio)cyclobutane-1-carbaldehyde (11b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.64-1.79 (m, 1H), 2.03-2.19 (m, 1H), 2.27-2.45 (m, 2H), 4.22 (t, *J* = 9.1 Hz, 1H), 7.14-7.26 (m, 5H), 9.50 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 24.6, 26.3, 44.5, 53.3, 126.4, 129.0 (2C), 129.5 (2C), 136.0, 202.9. IR (neat) 3058, 2969, 2863, 2804, 2710 1716,

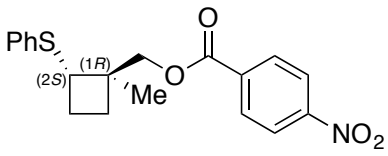
1583, 1480, 1438 cm^{-1}. HRMS (EI) calcd for $C_{12}H_{14}OS$ $[M]^+$ 206.0765, found 206.0762. GC (CHIRALDEX G-TA, 115 °C), t_R = 22.8 min (major), 25.3 min (minor).

4. Transformation to 14 (Scheme 6).





((1*R*,2*S*)-1-methyl-2-(phenylthio)cyclobutyl)methanol (15): The titled compound was synthesized on the basis of a literature procedure.[1] To a solution of **11b** (25.2 mg, 0.122 mmol, 83% ee) in tetrahydrofuran (2 mL) and water (0.2 mL) was added sodium borohydride (9.24 mg, 0.244 mmol) at room temperature. After stirring for 1 h, water (10 mL) was added to the reaction mixture. The mixture was extracted with diethyl ether (10 mL × 3) and the combined organic layer was dried over sodium sulfate. The organic phase was concentrated under reduced pressure, and purified by neutral silica gel column chromatography (eluent: pentane/Et_2O = 1/1), to give the desired product **15** in >99% yield (28.6 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.54 (s, 1H), 1.57-1.66 (m, 1H), 1.88-2.13 (m, 2H), 2.30-2.43 (m, 1H), 3.38 (s, 2H), 3.90 (t, *J* = 8.5 Hz, 1H), 7.15 (tt, *J* = 8.3, 1.3 Hz, 1H), 7.20-7.27 (m, 2H), 7.31 (dd, *J* = 8.3, 1.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 25.4, 27.0, 45.2, 46.0, 69.7, 125.8, 128.9 (2C), 129.3 (2C), 137.2. IR (neat) 3388, 3057, 2931, 1583, 1479, 1437, 1025 cm^{-1}. HRMS (EI) calcd for $C_{12}H_{16}OS$ $[M]^+$ 208.0922, found 208.0923. HPLC analysis; OD-3, hexane:*i*-PrOH = 9:1, 1.0 mL/min, t_R = 5.8 min (major), 9.1 min (minor).



((1*R*,2*S*)-1-Methyl-2-(phenylthio)cyclobutyl)methyl 4-nitrobenzoate (14): The titled compound was synthesized on the basis of a literature procedure.[5] A mixture of **15** (27.5 mg, 0.132 mmol) and *N*,*N*-diisopropylethylamine (44.6 μL, 0.244 mmol) was cooled to 0 °C, then 4-nitrobenzoyl chloride (27.2 mg, 0.145 mmol) and *N*,*N*-dimethyl-4-aminopyridine (2.98 mg, 0.0244 mmol) were added. The cooling bath was removed, and the mixture was stirred at room temperature for 1 h. The product mixture was directly purified by flash chromatography (eluent: hexane/ethyl

acetate = 9/1) to give **14** (35.1 mg, 74%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.76-1.82 (m, 1H), 1.98-2.16 (m, 2H), 2.41-2.49 (m, 1H), 3.95 (d, J = 8.4 Hz, 1H), 4.17 (d, J = 11.4 Hz, 1H), 4.25 (d, J = 11.4 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 7.19 (t, J = 8.7 Hz, 2H), 7.30 (d, J = 7.3 Hz, 2H), 8.10 (d, J = 9.1 Hz, 2H), 8.25 (d, J = 9.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 25.5, 28.0, 43.9, 46.6, 72.3, 123.5 (2C), 126.1, 128.9 (2C), 129.5 (2C), 130.7 (2C), 135.4, 136.5, 150.5, 164.6. IR (KBr) 3112, 2965, 2863, 1716, 1521, 1276 cm^{-1}. M.p. 73–76 °C. HRMS (EI) calcd for $C_{19}H_{19}NO_4S$ $[M]^+$ 357.1035, found 357.1041. $[\alpha]_D^{26}$ = –20.8 (*c* 0.90, $CHCl_3$, 83% ee). HPLC analysis; IC-3, hexane:*i*-PrOH = 49:1, 1.0 mL/min, t_R = 22.4 min (major), 25.2 min (minor).

Crystal data of 14: Formula $C_{19}H_{19}NO_4S$, light yellow, crystal dimensions 0.20 × 0.20 × 0.20 mm^3, triclinic, space group P_1 (#1), a = 9.6247(9) Å, b = 10.1973(10) Å, c = 10.9089(6) Å, α = 62.223(7) °, β = 69.588(9) °, γ = 84.072(11) °, V = 885.54(15) $Å^3$, Z = 2, ρ_{calc} = 1.340 g cm^{-3}, F(000) = 376, μ(MoKα) = 0.206 mm^{-1}, T = 123 K. 7536 reflections collected, 5331 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 27.51 °), and 453 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0530 and wR_2 = 0.1361. GOF = 1.028. Flack x = –0.03(3).

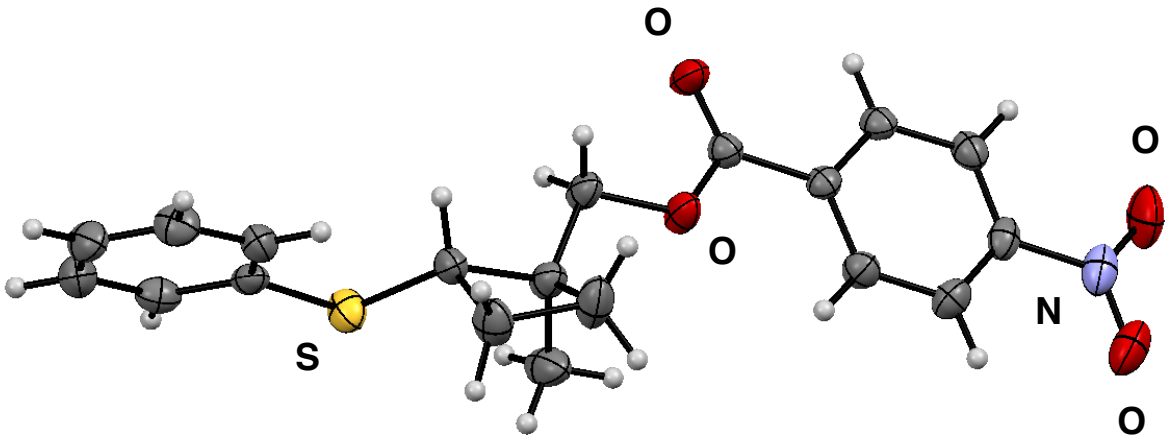
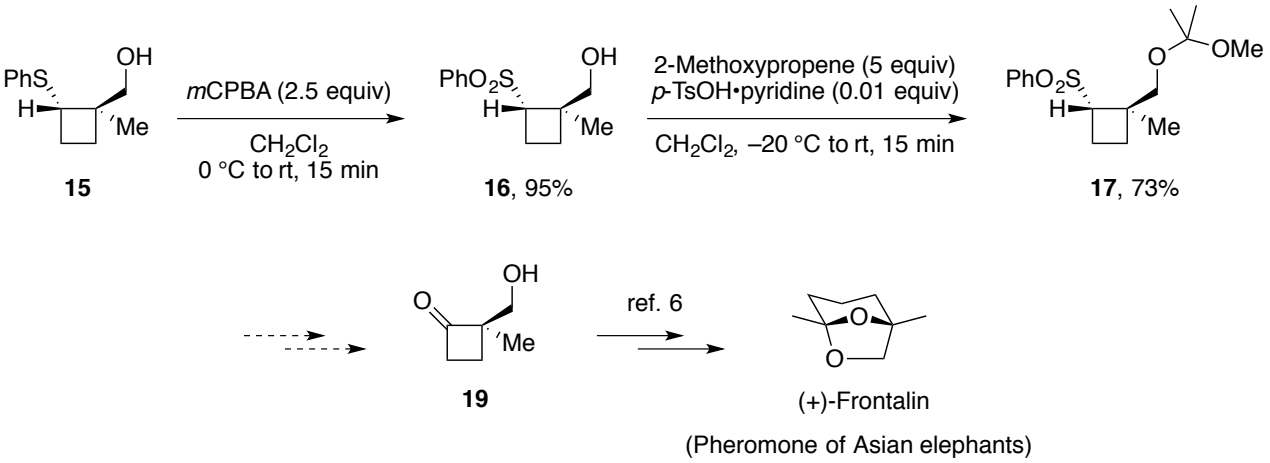
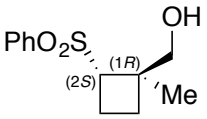


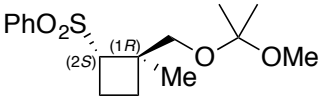
Figure S1. OPTEP drawing of **14**.

5. Formal total synthesis of (+)-frontalin (Scheme 7).[6]





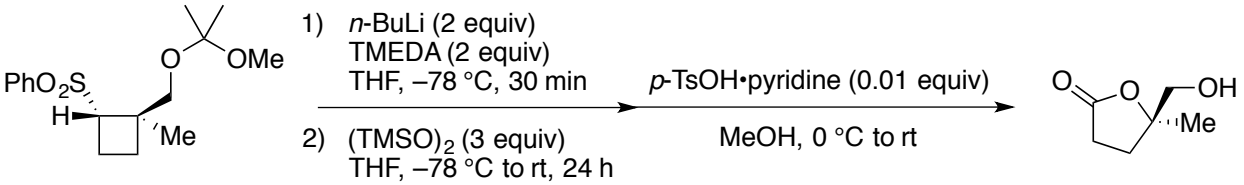
((1*R*,2*S*)-1-Methyl-2-(phenylsulfonyl)cyclobutyl)methanol (16): The titled compound was synthesized on the basis of a literature procedure.[7] To a solution of **15** (128 mg, 0.61 mmol) in dichloromethane (6 mL) were added *m*-chloroperoxybenzoic acid (344 mg, 1.53 mmol) at 0 °C. The mixture was stirred at room temperature for 15 min. To the mixture, sodium hydrogen carbonate aqueous solution (10 mL) was added, and the aqueous layer was extracted with dichloromethane (10 mL × 3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure to give the corresponding sulfone as colorless oil. The resultant residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 2/1 to 1/1) to give pure **16** in 95% yield (140 mg, 0.58 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 3H), 1.67 (t, *J* = 9.1 Hz, 1H), 1.88-2.07 (m, 3H), 2.48-2.61 (m, 1H), 3.38-3.52 (m, 2H), 3.73 (dd, *J* = 10.2, 7.8 Hz, 1H), 7.49-7.60 (m, 2H), 7.58-7.69 (m, 1H), 7.81-7.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 19.2, 26.2, 46.5, 60.3, 70.1, 127.8 (2C), 129.3 (2C), 133.5, 140.0. IR (neat) 3513, 2939, 1584, 1446, 1285, 1144 cm^{-1}. HRMS (FAB+) calcd for $C_{12}H_{16}O_3SNa$ $[M+Na]^+$ 263.0718, found 263.0728. HPLC analysis; AD-3, hexane:*i*-PrOH = 4:1, 1.0 mL/min, t_R = 7.4 min, 9.7 min.



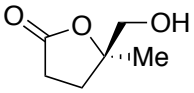
(((1*S*,2*R*)-2-(((2-Methoxypropan-2-yl)oxy)methyl)-2-methylcyclobutyl)sulfonyl)benzene (17): The titled compound was synthesized on the basis of a literature procedure.[8] A solution of **16** (140 mg, 0.58 mmol) in dichloromethane (2 mL) was cooled to –20 °C, then 2-methoxypropene (0.29 mL, 2.9 mmol) and pyridinium *p*-toluenesulfonate (1.5 mg, 0.006 mmol) were added. The

cooling bath was removed, and the mixture was stirred at room temperature for 15 min. The product mixture was directly purified by flash chromatography (eluent: hexane/ethyl acetate = 4/1) to give **17** (133 mg, 73%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.30 (s, 3H), 1.47 (s, 3H), 1.57-1.64 (m, 1H), 1.91-2.04 (m, 1H), 2.10 (m, 1H), 2.44-2.63 (m, 1H), 3.04 (d, *J* = 10.4 Hz, 1H), 3.15 (d, *J* = 10.4 Hz, 1H), 3.15 (s, 3H), 3.87 (t, *J* = 8.9 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 18.9, 24.4 (2C), 26.4, 44.6, 48.6, 58.8, 66.4, 99.9, 127.8 (2C), 129.1 (2C), 133.3, 140.6. IR (neat) 2990, 2942, 2868, 1446, 1378, 1305, 1213, 1147, 1051 cm^{-1}. HRMS (FAB+) calcd for $C_{16}H_{24}O_4SNa$ $[M+Na]^+$ 335.1293, found 335.1286. HPLC analysis; IC-3, hexane:*i*-PrOH = 9:1, 1.0 mL/min, t_R = 25.9 min (major), 44.5 min (minor).

6. Transformation to 20 (Scheme 8).



17 **20**, 3%



(*R*)-5-(Hydroxymethyl)-5-methyldihydrofuran-2(3*H*)-one (20): The titled compound was synthesized on the basis of a literature procedure.[9,10] To a stirred solution of **17** (180 mg, 0.58 mmol) in tetrahydrofuran (5 mL) at –78 °C were added tetramethylethylenediamine (0.17 mL, 1.15 mmol) and *n*-BuLi (0.7 mL, 1.15 mmol, 1.64 *M* in hexane). The reaction was stirred for other 30 min before $(TMSO)_2$ (1.24 mL, 1.73 mmol, 1.39 *M* in hexane) was added to the reaction mixture. After 15 min, the reaction was warmed to room temperature and stirred for 24 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and diluted with diethyl ether (5 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL) and the dried ($MgSO_4$) extract was concentrated in vacuo. The residue was purified by flash chromatography over silica gel (eluent: hexane/ethyl acetate = 9/1 to 1/1) to sequentially give carbonyl compound (11 mg, 10%) as colorless oil followed by recovered **17** (59 mg, 33%). A solution of carbonyl compound (11 mg, 0.06 mmol) and pyridinium *p*-toluenesulfonate (1.5 mg, 0.006 mmol) in methanol (2 mL) was stirred at 0 °C to room temperature for 30 min. The reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel (eluent: hexane/ethyl acetate = 1/1 to 1/2) to give **20** (1.8 mg, 27%) as a colorless oil. The ^{1}H NMR spectrum and the ^{13}C NMR spectrum were consistent with the spectrum reported in the literature.[11]

7. References.

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Research Achievement

Publications

Chapter 3

1. "Boron Tribromide-Assisted Chiral Phosphoric Acid Catalyst for a Highly Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines"
   Manabu Hatano, Yuta Goto, Atsuto Izumiseki, Matsujiro Akakura and Kazuaki Ishihara
   J. Am. Chem. Soc. **2015**, *137*, 13472–13475.
   Most read articles ranking-in, October, 2015.

Chapter 2

2. "Remote Tris(pentafluorophenyl)borane-Assisted Chiral Phosphoric Acid Catalysts for the Enantioselective Diels–Alder Reaction"
   Manabu Hatano, Hideyuki Ishihara, Yuta Goto and Kazuaki Ishihara
   Synlett, **2016**, *27*, 564-570.

Chapter 4

3. "Boron Tribromide-Assisted Chiral Phosphoric Acid Catalysts Enantioselective [2 + 2] Cycloaddition"
   Manabu Hatano, Yuta Goto, and Kazuaki Ishihara
   In preparation.

International conferences

Oral Presentations

1. "Chiral Supramolecular Phosphoric Acid Catalysts for Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines toward Alkaloid Synthesis"
   ◯Yuta Goto, Matsujiro Akakura, Manabu Hatano, Kazuaki Ishihara
   The 4th Junior International Conference on Cutting-Edge Organic Chemistry in Asia (JICCEOCA-4), Bangkok, Thailand, O-02, November 2014.

2. **"**Boron tribromide-assisted chiral phosphoric acid catalysts for highly enantioselective Diels–Alder reaction of 1,2-dihydropyridines**"**
   ◯Manabu Hatano, Yuta Goto, Kazuaki Ishihara
   Pacifichem 2015, Hawaii, USA, Recent Trends in Organocatalysis (#122), December 2015.

Poster Presentations

3. **"**Boron Tribromide-Assisted Chiral Phosphoric Acid Catalysts for Highly Enantioselective Diels– Alder Reaction of 1,2-Dihydropyridines**"**

◯Manabu Hatano, Yuta Goto, Kazuaki Ishihara
The 39th Naito Conference, The chemistry of organocatalysts, Sappro, PS-24, July 2015.

Domestic conferences

Oral Presentations

1. 「ルイス酸複合型キラルリン酸触媒を用いるエナンチオ選択的 Diels–Alder 反応」
◯後藤 優太, 泉関 督人, 波多野 学, 石原 一彰
日本化学会第 92 春季年会, 1K7-35, 神奈川, 2012 年 3 月

2. 「ルイス酸複合型キラルリン酸触媒を用いるエナンチオ選択的 Diels–Alder 反応」
◯後藤 優太, 泉関 督人, 波多野 学, 石原 一彰
名古屋大学–理化学研究所有機化学系研究交流会, 15, 埼玉, 2012 年 3 月

3. 「光学活性アルカロイド合成を指向したルイス酸複合型キラルリン酸触媒を用いる高エナンチオ選択的 Diels–Alder 反応」
◯後藤 優太, 赤倉 松次郎, 波多野 学, 石原 一彰
日本化学会第 93 春季年会, 1E4-40, 滋賀, 2013 年 3 月

4. 「ルイス酸複合型キラルリン酸触媒を用いるα-ハロアクロレインと 1,2-ジヒドロピリジンのエナンチオ選択的 Diels–Alder 反応とその合成的応用」
◯後藤 優太, 波多野 学, 石原 一彰
日本化学会第 94 春季年会, 2B7-33, 愛知, 2014 年 3 月

5. 「テーラーメイド型キラル超分子ルイス酸触媒によるアセチレン類を親ジエンとする高次立体選択的 Diels–Alder 反応」
◯阪本 竜浩, 後藤 優太, 波多野 学, 石原 一彰
日本化学会第 94 春季年会, 2B7-32, 愛知, 2014 年 3 月

6. 「三臭化ホウ素で活性化されたキラルリン酸触媒を用いる 1,2-ジヒドロピリジンのエナンチオ選択的 Diels–Alder 反応」
◯後藤 優太, 波多野 学, 石原 一彰
日本化学会第 95 春季年会, 3E3-04, 千葉, 2015 年 3 月

7. 「ホウ素 Lewis 酸-キラルリン酸複合触媒を用いるエナンチオ選択的 Diels–Alder 反応」
◯石原 英幸, 後藤 優太, 波多野 学, 石原 一彰
日本化学会第 95 春季年会, 3E3-05, 千葉, 2015 年 3 月

8. 「三臭化ホウ素-キラルリン酸複合触媒を用いる光学活性アルカロイド合成を指向し

たエナンチオ選択的 Diels–Alder 反応」
○後藤 優太, 波多野 学, 石原 一彰
日本化学会第 96 春季年会, 2H2-28, 京都, 2016 年 3 月

9. “Boron Tribromide-Assisted Chiral Phosphoric Acid Catalysts for Enantioselective [4 + 2] and [2 + 2] Cycloaddition Reactions”
○後藤 優太, 波多野 学, 石原 一彰
日本化学会第 97 春季年会, 2E5-08, 神奈川, 2017 年 3 月（発表予定）

Poster Presentations

10. 「Lewis 酸複合型キラルリン酸触媒を用いるエナンチオ選択的 Diels–Alder 反応」
○後藤 優太, 泉関 督人, 波多野 学, 石原 一彰
第 45 回有機金属若手の会 夏の学校 2012, 山梨, 2012 年 7 月

11. “Lewis Acid-Assisted Chiral Phosphoric Acid Catalysts for Highly Enantioselective Diels–Alder Reaction toward Synthesis of Optically Active Alkaloids”
○Yuta Goto, Matsujiro Akakura, Manabu Hatano, Kazuaki Ishihara
IGER Annual meeting 2012, G-17, Aichi, January 2013.

12. 「光学活性アルカロイド合成を指向したルイス酸複合型キラルリン酸触媒を用いる高エナンチオ選択的 Diels–Alder 反応」
○後藤 優太, 赤倉 松次郎, 波多野 学, 石原 一彰
第 2 回 JACI/GSC シンポジウム, A-34, 大阪, 2013 年 6 月

13. 「光学活性アルカロイド合成を指向したルイス酸複合型キラルリン酸触媒を用いる高エナンチオ選択的 Diels–Alder 反応」
○後藤 優太, 赤倉 松次郎, 波多野 学, 石原 一彰
第 48 回有機反応若手の会, 茨城, 2013 年 7 月

14. 「光学活性アルカロイド合成を指向した高エナンチオ選択的 Diels–Alder 反応に有効なルイス酸複合型キラルリン酸触媒の開発」
○後藤 優太, 赤倉 松次郎, 波多野 学, 石原 一彰
第 44 回中部化学関係学協会支部連合秋季大会, 2P-05, 静岡, 2013 年 11 月
優秀賞受賞

15. “Enantioselective Diels–Alder Reaction of α-Haloacroleins with 1,2-Dihydropyridines Catalyzed by Lewis Acid-Assisted Chiral Phosphoric Acid and the Synthetic Application”
○Yuta Goto, Matsujiro Akakura, Manabu Hatano, Kazuaki Ishihara

IGER Annual meeting 2013, G-4, Aichi, January 2014.

16. 「高活性 Lewis 酸複合型キラルリン酸触媒を用いるエナンチオ選択的 Diels–Alder 反応とアルカロイド合成への応用」
○後藤 優太, 赤倉 松次郎, 波多野 学, 石原 一彰
第 49 回天然物化学談話会, 67, 岡山, 2014 年 7 月

17. 「高活性 Lewis 酸複合型キラルリン酸触媒を用いるエナンチオ選択的 Diels–Alder 反応とアルカロイド合成への応用」
○後藤 優太, 赤倉 松次郎, 波多野 学, 石原 一彰
第 4 回「企業と博士人材の交流会」, B-1, 愛知, 2014 年 8 月

18. "BBr_3-Assisted Chiral Phosphoric Acid Catalysts for Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines"
○Yuta Goto, Manabu Hatano, Kazuaki Ishihara
IGER Annual meeting 2014, G-1, Aichi, December 2014.

19. 「高エナンチオ選択的 Diels–Alder 反応に有効な三臭化ホウ素で活性化されたキラルリン酸触媒の開発」
○後藤 優太, 波多野 学, 石原 一彰
第 5 回「企業と博士人材の交流会」, P-13, 愛知, 2015 年 9 月

20. 「1,2-ジヒドロピリジンの高エナンチオ選択的 Diels–Alder 反応に有効な三臭化ホウ素で活性化されたキラルリン酸触媒の開発」
○後藤 優太, 波多野 学, 石原 一彰
第 5 回 CSJ 化学フェスタ 2015, P3-030, 東京, 2015 年 10 月
優秀ポスター発表賞受賞

21. 「1,2-ジヒドロピリジンのエナンチオ選択的 Diels–Alder 反応に有効な三臭化ホウ素で活性化されたキラルリン酸触媒の開発」
○後藤 優太, 波多野 学, 石原 一彰
分子科学研究所リトリート研修, P02, 愛知, 2015 年 11 月

22. "Boron Tribromide-assisted Chiral Phosphoric Acid Catalysts for Enantioselective Diels–Alder Reaction toward Alkaloid Synthesis"
○Yuta Goto, Manabu Hatano, Kazuaki Ishihara
IGER Annual meeting 2015, G18, Aichi, January 2016.

23. “Boron Tribromide-Assisted Chiral Phosphoric Acid Catalysts for Enantioselective [4 + 2] and [2 + 2] Cycloaddition Reactions”
    ◯Yuta Goto, Manabu Hatano, Kazuaki Ishihara
    IGER Annual meeting 2016, G18, Aichi, January 2017.
    Poster Award 受賞

Awards

1. 優秀賞、第 44 回中部化学関係学協会支部連合秋季大会 (Poster Award at 44th Annual Meeting of Union of Chemistry-Related Societies in Chubu Area, Japan, 2013.)
2. 優秀ポスター発表賞、5th CSJ 化学フェスタ 2015 (Poster Award at 5th CSJ Chemistry Festa, Japan, 2015.)
3. Poster Award（IGER Annual Meeting 2016）

Visiting Scholar

“2-Iminopyridine Ligands for Fe, Ni Catalyzed Enantioselective Hydroboration of Olefins”
Professor Paul J. Chirik, Department of Chemistry, Princeton University.
9/1/2016–11/29/2016

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