Tris(pentafluorophenyl)borane-Assisted Chiral Phosphoric Acid Catalysts for Enantioselective Inverse-Electron-Demand Hetero-Diels–Alder Reaction of α,β-Substituted Acroleins

Manabu Hatano, Tatsuhiro Sakamoto, Takuya Mochizuki, and Kazuaki Ishihara*

[*] Dr. M. Hatano, T. Sakamoto, T. Mochizuki, and Prof. Dr. K. Ishihara
Graduate School of Engineering
Nagoya University
Furo-cho, Chikusa, Nagoya 464-8603 (Japan)
E-mail: ishihara@cc.nagoya-u.ac.jp

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/

Abstract: In the enantioselective inverse-electron-demand hetero-Diels–Alder reaction, simple α,β-unsaturated aldehydes (i.e., acroleins) are still challenging substrates, unlike α,β-unsaturated carbonyl compounds containing electron-withdrawing groups. In the present study, the reaction of α-aryl-β-alkyl-substituted acroleins with ethyl vinyl sulfide was developed with the use of bulky chiral supramolecular Brønsted acid catalysts, such as tris(pentafluorophenyl)borane-assisted chiral phosphoric acid catalysts. As a result, *cis*-cycloadducts as optically active 3,4-dihydro-2*H*-pyrans were exclusively obtained in high yields with high enantioselectivities *via* the favored *endo* orbital approach. An obtained optically active *cis*-isomer could be transformed into the corresponding *trans*-isomer without a loss of enantiopurity by *O,S*-acetal epimerization. Moreover, transformations to synthetically useful optically active epoxide and δ-valerolactone are also demonstrated.

The catalytic enantioselective inverse-electron-demand hetero-Diels–Alder reaction of α,β-unsaturated carbonyl compounds with electron-rich alkenes provides optically active 3,4-dihydro-2*H*-pyrans,[1] which are useful heterocyclic compounds for synthesizing natural products and pharmaceuticals.[2] The reaction is controlled by the HOMO–LUMO interactions of the respective alkenes and α,β-unsaturated carbonyl compounds. Therefore, electron-withdrawing functional groups, such as sulfone,[3] phosphonate,[4] and ester,[5] are usually introduced to α,β-unsaturated carbonyl compounds to enhance the reactivity (Figure 1a).[6,7] These substrates are suitable for chelating the active center of the catalysts, and thus the enantio-face would be preferably discriminated. Moreover, the *s-cis* conformation would be promoted by the steric effect from such introduced groups. In sharp contrast, simple α,β-unsaturated aldehydes (i.e., acroleins) are challenging substrates, since they cannot chelate the active center of the catalysts, although the formyl proton[8] might sometimes be coordinated by the Brønsted basic site of the catalysts (Figure 1b). In this regard, Corey[9a,b] and Ishihara/Yamamoto[9c] independently reported the chiral B(III)-Lewis acid catalysts, which can control both enantio-face and *s-cis/s-trans* of simple acroleins in the enantioselective Diels–Alder reactions. Much later, Jacobsen developed chiral Cr(III)-Lewis acid catalyst **1** (Figure 2a),[10] which is the only reported example

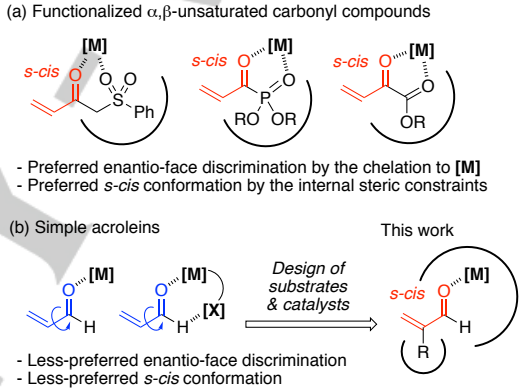


Figure 1. Activation of α,β-unsaturated carbonyl compounds. [M] = Chiral Brønsted or Lewis acid center. [X] = Chiral Brønsted base center.

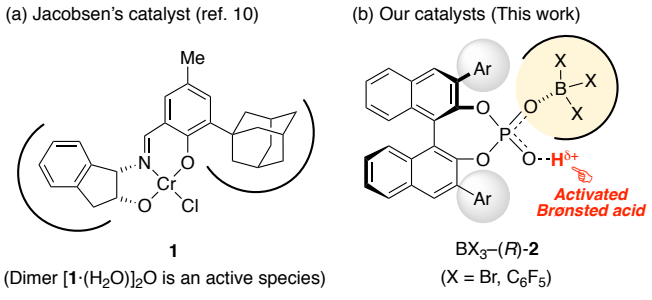
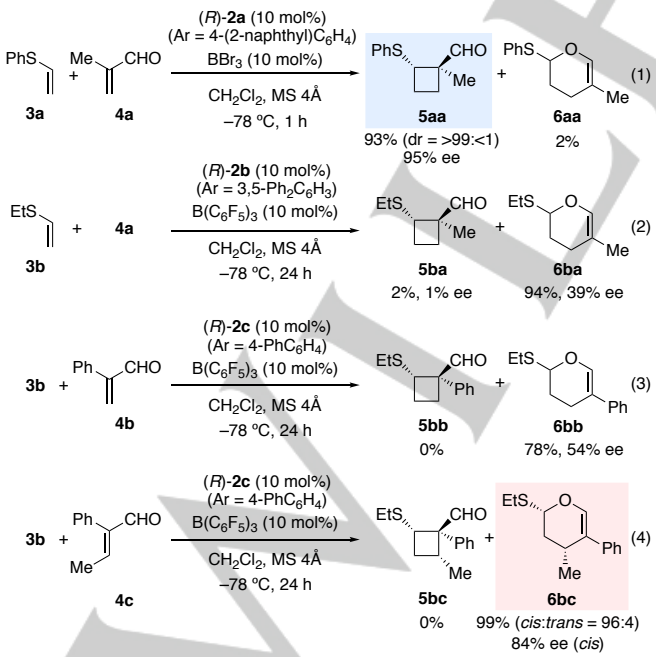


Figure 2. Design of catalysts for α,β-unsaturated aldehydes (i.e., acroleins). (a) Jacobsen's catalyst **1** (ref. 10). (b) The present BX_3-assisted chiral phosphoric acid catalysts BX_3-(*R*)-**2** (X = Br, C_6F_5).

in the enantioselective inverse-electron-demand hetero-Diels–Alder reaction of simple acroleins,[11] despite reports of numerous catalysts for more reactive and *s-cis*-preferred functionalized α,β-unsaturated carbonyl compounds.[1] In particular, the sterically hindered design of the chiral B(III)-Lewis acid catalysts by Ishihara/Yamamoto[9c] and the Cr(III)-Lewis acid catalyst **1** by Jacobsen[10] was one of the good solutions for controlling *s-cis/s-*

trans geometry of simple acroleins. In this context, here we developed bulky tris(pentafluorophenyl)borane-assisted chiral phosphoric acid catalysts $B(C_6F_5)_3$-(*R*)-**2** for the enantioselective inverse-electron-demand hetero-Diels–Alder reaction of acroleins with ethyl vinyl sulfide (Figure 2b), by taking advantage of our previous boron tribromide-assisted chiral phosphoric acid catalysts BBr_3-(*R*)-**2** for the enantioselective Diels–Alder reaction of acroleins with 1,2-dihydropyridines and [2+2] cycloaddition of acroleins with phenyl vinyl sulfide.[12,13]

In our previous report,[12b] we achieved a highly enantioselective [2+2] cycloaddition of methacrolein **4a** with phenyl vinyl sulfide **3a** in the presence of BBr_3-(*R*)-**2a** (Ar = 4-(2-naphthyl)C_6H_4), as an *in situ*-prepared chiral supramolecular Brønsted acid catalyst, in dichloromethane at –78 °C, and **5aa** was obtained in 93% yield with 95% ee (Scheme 1, eq. 1). The reaction selectivity between [2+2] cycloaddition and the inverse-electron-demand hetero-Diels–Alder reaction (i.e., [4+2] cycloaddition) strongly depended on the substrates and catalysts, and the use of ethyl vinyl sulfide **3b** instead of **3a** in the presence of sterically hindered $B(C_6F_5)_3$-(*R*)-**2b** (Ar = 3,5-$Ph_2C_6H_3$) selectively provided the inverse-electron-demand hetero-Diels–Alder reaction product **6ba** in 94% yield with 39% ee (eq. 2). However, at that time, **6ba** was generated not only directly but also *via* the enantiomerically-uncontrolled isomerization from [2+2] cycloadduct **5ba**.[12b] Therefore, to achieve both high reaction selectivity and high asymmetric induction of the inverse-electron-demand hetero-Diels–Alder reaction, a more careful combination of substrates and the corresponding catalysts might be necessary. In this regard, when we here used α-phenylacrolein **4b** instead of **4a** in the presence of $B(C_6F_5)_3$-(*R*)-**2c** (Ar = 4-PhC_6H_4), **6bb** was exclusively obtained in 78% yield with 54% ee (eq. 3). Moreover, when we used α-Ph-β-Me-substituted acrolein **4c** instead of **4b**, desired **6bc** was exclusively



Scheme 1. Initial screening of substrates and catalysts. The reaction was carried out with **3** (0.30 mmol), **4** (0.25 mmol), (*R*)-**2** (10 mol%), and BBr_3 or $B(C_6F_5)_3$ (10 mol%) in dichloromethane with MS 4Å at –78 °C.

obtained with high diastereoselectivity (*cis:trans* = 96:4) with 84% ee for *cis*-**6bc** (eq. 4).[14] Throughout the reactions in eqs. 3 and 4, the generation of [2+2] cycloadduct **5bb** or **5bc** was not observed. Therefore, an α-Ph substituent in acroleins **4** might be important for the desired reaction selectivity toward the inverse-electron-demand hetero-Diels–Alder reaction. Notably, (*R*)-**2c** alone could not promote the reaction at –78 °C, and the catalytic activity of $B(C_6F_5)_3$-(*R*)-**2c** is much higher than that of (*R*)-**2c** alone.[15] Overall, we could control the reaction selectivity, [2+2] cycloaddition vs. inverse-electron-demand hetero-Diels–Alder reaction, by optimizing the substrates **4**, reagents **3**, and the corresponding chiral supramolecular Brønsted acid catalysts, such as BBr_3-(*R*)-**2a** and $B(C_6F_5)_3$-(*R*)-**2c**.[16]

The observed reaction selectivity among **4a**–**c** might be due to the stability of the *s-cis* geometry of **4a**–**c** (Figure 3), which should be the preferred conformation for the inverse-electron-demand hetero-Diels–Alder reaction.[17] It has been reported that the α-substituents in acroleins would significantly affect the *s-cis/s-trans* geometry, and Corey[9a,b] and Ishihara/Yamamoto[9c] independently investigated a few substrates in the catalytic enantioselective Diels–Alder reaction with cyclopentadiene. In the present study, introduction of the α-Ph moiety (i.e., **4b**) instead of the α-Me moiety (i.e., **4a**) would be effective for inducing an *s-cis* geometry. Moreover, the closely-positioned β-Me moiety relative to the α-Ph moiety as in **4c** would further promote steric repulsions between the α-Ph and the C=O moiety. Therefore, **4c** would be more suitable than **4a** and **4b** in the inverse-electron-demand hetero-Diels–Alder reaction. In this regard, computational calculations for the thermodynamic stability (MMFF94) of *s-cis/s-trans*-**4a**–**c** were preformed, and preferences for *s-trans*-**4a** (–3.15 kcal/mol based on *s-cis*-**4a**), *s-cis*-**4b** (–0.93 kcal/mol based on *s-trans*-**4b**), and *s-cis*-**4c** (–1.64 kcal/mol based on *s-trans*-**4c**) were observed (see the Supporting Information (SI) for details). This result supports the notion that the reaction of *s-trans*-**4a** was favored in the previous asymmetric [2+2] cycloaddition.

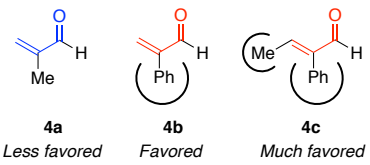
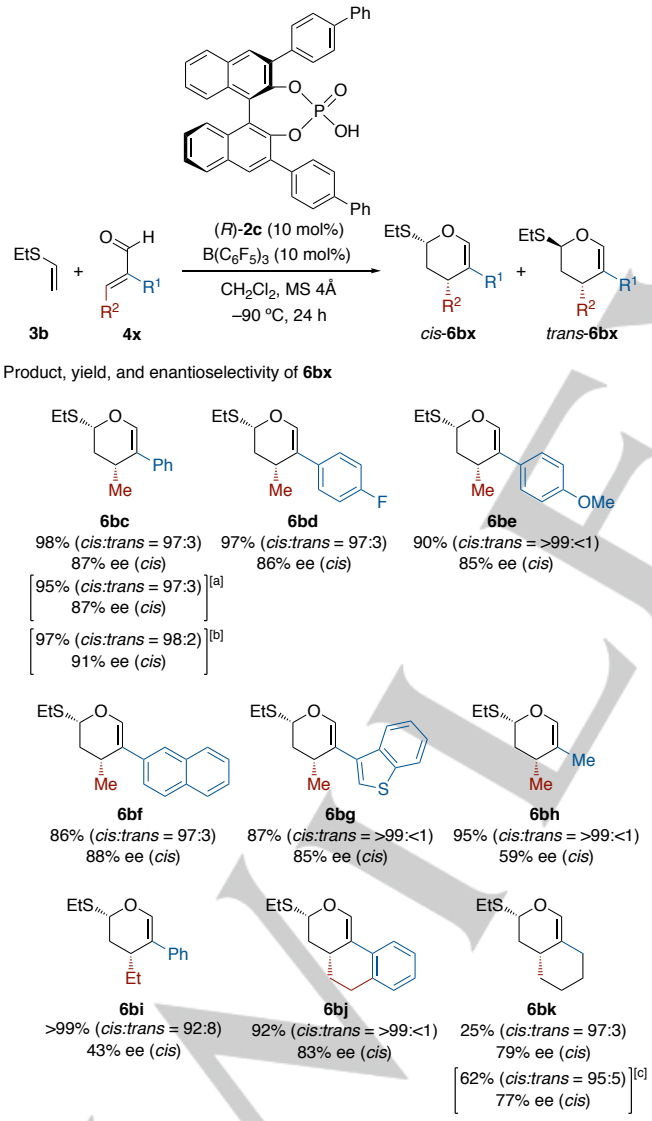


Figure 3. The *s-cis* geometry of **4a**–**c**.

Next, we examined the substrate scope of acroleins (0.25 mmol scale) with the use of $B(C_6F_5)_3$-(*R*)-**2c** (10 mol%) (Scheme 2). Fortunately, the enantioselectivity of **6bc** was slightly improved when the reaction was conducted at –90 °C. With the optimized reaction conditions in hand (see the SI for details), we found that the reactions of α-(4-F-C_6H_4)-β-Me-substituted acrolein **4d**, α-(4-MeO-C_6H_4)-β-Me-substituted acrolein **4e**, and α-2-naphthyl-β-Me-substituted acrolein **4f** also proceeded smoothly, and the corresponding *cis*-**6bd**, *cis*-**6be**, and *cis*-**6bf** could be obtained as major products in high yields with high enantioselectivities (85–88% ee). Moreover, α-heteroaryl-substituted acrolein **4g** could be used, and the corresponding *cis*-**6bg** was obtained in 85% ee. To investigate the importance of the α-aryl and/or β-Me moieties in acroleins **4**, we examined a few more reactions. When α,β-Me_2-substituted acrolein (i.e., tiglic aldehyde) **4h** was used, *cis*-

6bh was obtained in 95% yield, but the enantioselectivity was moderate (59% ee). Moreover, in place of a β-Me substituent as in **4c**, a β-Et substituent as in **4i** was examined. As a result, *cis*-**6bi** was obtained in high yield, but the enantioselectivity was 43% ee. These results suggest that both the α-aryl moiety and the β-Me moiety are basically required for the present asymmetric reaction. However, exceptionally, structurally-rigid cyclic acroleins **4j** and **4k** provided the desired *cis*-**6bj** with 83% ee and *cis*-**6bk** with 79% ee, respectively, although the yield of **6bk** was low (25%). The yield of **6bk** was improved to 62% yield when 20 mol% of $B(C_6F_5)_3$-(*R*)-**2c** was used, and *cis*-**6bk** was obtained with 77% ee. In contrast, the catalyst loadings of $B(C_6F_5)_3$-(*R*)-**2c** could be reduced to 5 mol% in the reaction of **4c** (1 mmol scale) and **3b**, and **6bc** was obtained in 95% yield with high *cis*-selectivity (*cis:trans* = 97:3) and 87% ee. Moreover, lower temperature (–100 °C) in CH_2Cl_2/*n*-hexane provided **6bc** in 97% yield (*cis:trans* = 98:2) with 91% ee (*cis*-**6bc**).



Scheme 2. Substrate scope of acroleins. The reaction was carried out with **3b** (0.30 mmol), **4x** (0.25 mmol), (*R*)-**2c** (10 mol%), and $B(C_6F_5)_3$ (10 mol%) in dichloromethane with MS 4Å at –90 °C for 24 h. [a] The reaction was performed with 1 mmol scale of **4b** in the presence of 5 mol% of $B(C_6F_5)_3$-(*R*)-**2c**. [b] The reaction was performed in CH_2Cl_2/*n*-hexane (1/1) at –100 °C for 24 h. [c] 20 mol% of $B(C_6F_5)_3$-(*R*)-**2c** was used.

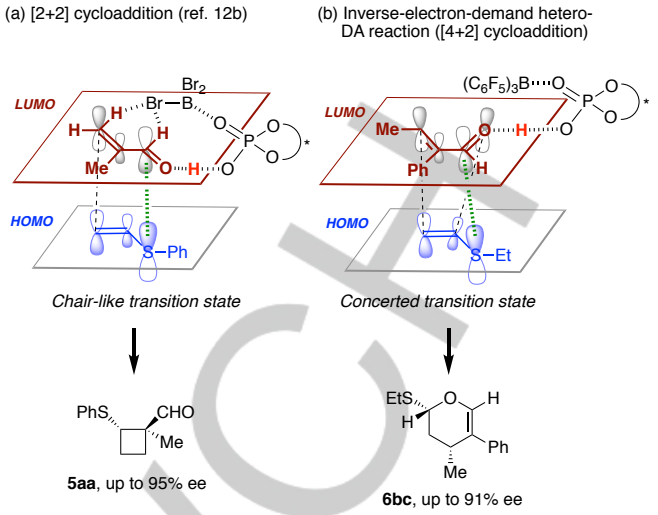


Figure 4. Possible reaction mechanisms for the previous reaction system with BBr_3-(*R*)-**2a** and the present reaction system with $B(C_6F_5)_3$-(*R*)-**2c**.

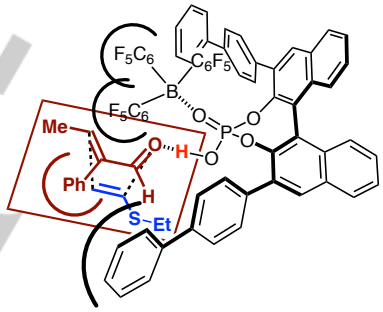


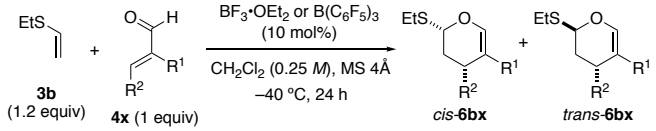
Figure 5. A possible transition state.

Next, we turned our attention to mechanistic aspects. First, we examined a non-linear effect in a probe reaction of **4c** with **3b** in the presence of $B(C_6F_5)_3$ and 0–100% ee of (*R*)-**2c**. As a result, we found a linear relationship between the ee values of (*R*)-**2c** and **6bc** (see the SI for details), which strongly supports the notion that the active species of our bulky chiral supramolecular catalyst might be a monomeric structure as shown in Figure 2b. Based on the results, possible mechanistic considerations are shown in Figure 4. In the previous [2+2] cycloaddition system with BBr_3-(*R*)-**2a**, *s-trans*-**4a** would be activated by not only the $H^{\delta+}$ moiety of (*R*)-**2a** but also the $Br^{\delta-}$ moiety of BBr_3 (Figure 4a).[12b] In sharp contrast, in the present reaction system with $B(C_6F_5)_3$-(*R*)-**2c**, *s-cis*-**4c** would be activated through one-point binding activation by the $H^{\delta+}$ moiety of (*R*)-**2c** (Figure 4b). Although the previous and present reaction systems have different sulfide nucleophiles (**3a** and **3b**), the approaching enantio-face to acroleins would be the same because of steric repulsions between one of the 3,3'-substituents on the binaphthyl skeleton of (*R*)-**2a** or (*R*)-**2c**. Moreover, in suitable HOMO–LUMO interactions at a ground state in Figure 4b, second orbital interactions due to a large lobe of the sulfur[18] might help to promote the reaction and discriminate the enantio-face selectivity of *s-cis*-**4c**. Finally, a possible transition state as a working model is shown in Figure 5 based on the above considerations. In this transition state, the sterically hindered C_6F_5 moieties of $B(C_6F_5)_3$ would also induce favored *s-*

cis-**4c** because of steric repulsions between the C_6F_5 moieties and the α-Ph moiety of *s-trans*-**4c**. For *s-cis*-**4i** in place of *s-cis*-**4c**, the β-Et moiety might have steric repulsion toward the C_6F_5 moieties, and the present possible transition state might partially explain the substrate limitation of **4i** in Scheme 2.

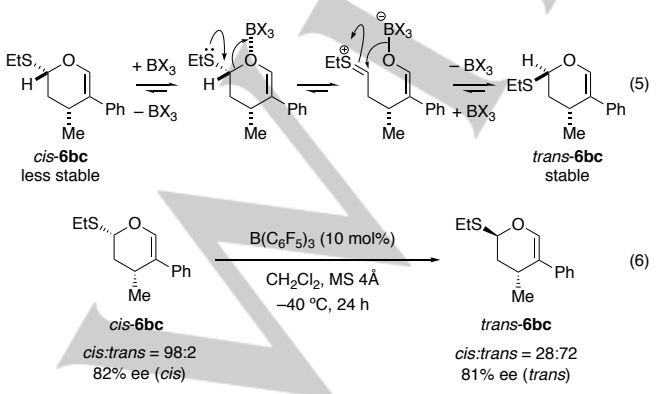
During our investigation of the reactions with achiral boron Lewis acids, such as BF_3•Et_2O and $B(C_6F_5)_3$, we found a changeover in the *cis/trans*-selectivity of the products **6bx** (Table 1). The reactions with the use of BF_3•Et_2O (10 mol%) at –40 °C[19] provided *cis*-**6bx** as major isomers (entries 1–7). In sharp contrast, when $B(C_6F_5)_3$ was used, *trans*-**6bx** was selectively obtained (entries 8–14), although the *trans*-selectivity of bicyclic

Table 1. BF_3•Et_2O or $B(C_6F_5)_3$-Catalyzed reaction of **4x** with **3b**.[a]



Entry	Catalyst	6bx	Yield [%]	*cis*-6bx:*trans*-6bx
1	BF_3•Et_2O	**6bc**	89	**84**:16
2	BF_3•Et_2O	**6bd**	90	**75**:25
3	BF_3•Et_2O	**6be**	72	**84**:16
4	BF_3•Et_2O	**6bf**	76	**80**:20
5	BF_3•Et_2O	**6bg**	81	**95**:5
6	BF_3•Et_2O	**6bi**	99	**71**:29
7	BF_3•Et_2O	**6bk**	71	**97**:3
8	$B(C_6F_5)_3$	**6bc**	92	3:**97**
9	$B(C_6F_5)_3$	**6bd**	95	3:**97**
10	$B(C_6F_5)_3$	**6be**	84	6:**94**
11	$B(C_6F_5)_3$	**6bf**	80	<1:**>99**
12	$B(C_6F_5)_3$	**6bg**	66	5:**95**
13	$B(C_6F_5)_3$	**6bi**	98	<1:**>99**
14	$B(C_6F_5)_3$	**6bk**	50	38:**62**

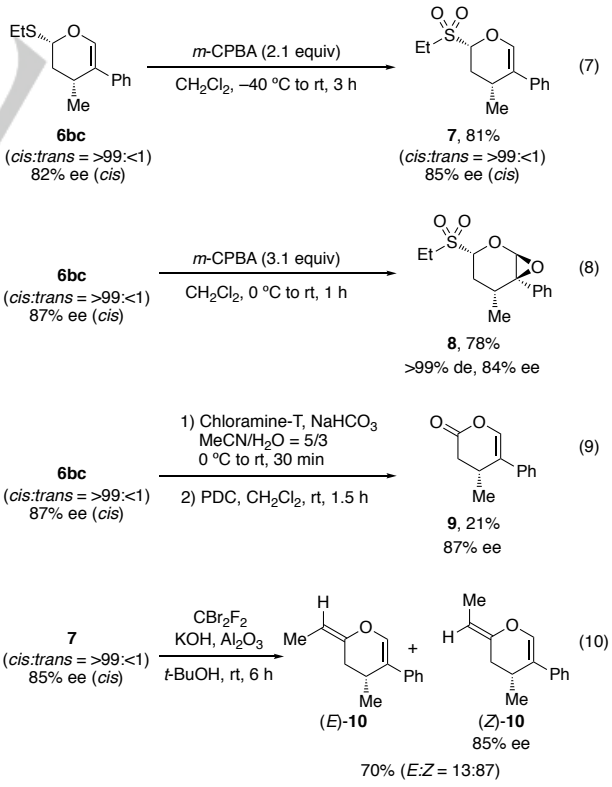
[a] The reaction was carried out with **3b** (0.30 mmol), **4x** (0.25 mmol), and BF_3•Et_2O or $B(C_6F_5)_3$ (10 mol%) in dichloromethane with MS 4Å at –40 °C for 24 h.



Scheme 3. Epimerization of *cis*-**6bc** to *trans*-**6bc**.

6bk was exceptionally moderate (entry 14). In the $B(C_6F_5)_3$-catalysis, *trans*-**6bx** might be directly generated *via* an *exo* orbital approach without the secondary orbital interactions of sulfur, since the bulky Lewis acid $B(C_6F_5)_3$ might disturb such secondary orbital preferences. However, a Lewis acid-catalyzed *O*,*S*-acetal-epimerization pathway from *cis*-**6bx** to *trans*-**6bx** cannot be completely excluded (Scheme 3, eq. 5). Therefore, we conducted the reaction of *cis*-**6bc** (*cis:trans* = 98:2) with 82% ee by using $B(C_6F_5)_3$ (10 mol%) in dichloromethane at –40 °C. As a result, *trans*-**6bc** (*cis:trans* = 28:72) was obtained with 81% ee (Scheme 3, eq. 6). This result might support the epimerization pathway. However, since the observed *cis/trans*-ratio of **6bc** (*cis:trans* = 3:97) was not the same as that in the $B(C_6F_5)_3$-catalysis of **3b** and **4c**, the direct *exo*-pathway cannot be excluded at this time. For the unclear pathways at the present stage, further investigations are still needed. Totally, we might selectively synthesize both optically active isomers, *cis*-**6bx** and *trans*-**6bx**, in the present study.

Finally, to demonstrate the synthetic utility of the present catalysis, a few transformations were performed (Scheme 4). Cycloadduct **6bc** was selectively oxidized to sulfone **7** with the use of 2.1 equiv of *m*-CPBA (*m*-chloroperoxybenzoic acid) (eq. 7).[20] Interestingly, with the use of 3.1 equiv of *m*-CPBA, further-oxidized epoxide **8** was isolated as a single diastereomer in 78% yield,[21] although the other diastereomer might be involved in the resulting complex mixture (eq. 8). Unfortunately, compared to the desulfurization of aryl sulfides, aryl sulfoxides, and aryl sulfones, the desulfurization of alkyl sulfides, alkyl sulfoxides, and alkyl sulfones from the cyclized products, particularly 2-ethylthio-3,4-dihydro-2*H*-pyrans in the present case, has not been well established.[22] In this regard, according to a reported procedure



Scheme 4. Transformations to synthetically useful compounds.

by Denmark,[23] **6bc** was treated with chloramine-T (sodium *N*-chloro-*p*-toluenesulfonamide), and the obtained hemiacetal was sequentially oxidized by PDC (pyridinium dichromate) to afford δ-valerolactone **9** in 21% yield (eq. 9). The present result was not adequately optimized, and further optimization might improve the generation and transformation of the unstable hemiacetal intermediate. Instead, fortunately, sulfone **7** was transformed to desulfurized **10** in 70% yield by the Ramberg–Bäcklund rearrangement[24] (eq. 10).

In summary, we have developed bulky $B(C_6F_5)_3$-assisted chiral phosphoric acid catalysts for the enantioselective inverse-electron-demand hetero-Diels–Alder reaction of acroleins. The reaction of α-aryl-β-alkyl-substituted acroleins with ethyl vinyl sulfide proceeded smoothly in the presence of the *in situ*-prepared chiral supramolecular Brønsted acid catalysts, and the corresponding cycloadducts, which are synthetically useful optically active 3,4-dihydro-2*H*-pyrans, were obtained with high *cis*- and enantioselectivity *via* the *endo* orbital reaction pathway. One of the obtained *cis*-cycloadducts was transformed to a *trans*-isomer without a loss of enantiopurity by *O,S*-acetal epimerization. Moreover, transformations to synthetically useful optically active epoxide and δ-valerolactone were also demonstrated.

Experimental Section

General procedure for the catalytic enantioselective inverse-electron-demand hetero-Diels–Alder reaction of acroleins **4x** with ethyl vinyl sulfide **3b**: A suspension of (*R*)-**2c** (16.3 mg, 0.025 mmol) and activated MS 4Å (100 mg) in freshly distilled dichloromethane (0.5 mL) was stirred at room temperature in a Schlenk tube under a nitrogen atmosphere. To the mixture was added tris(pentafluorophenyl)borane (12.8 mg, 0.025 mmol) in dichloromethane (0.5 mL) at –90 °C, and this suspension was stirred at that temperature for 20 min. Acrolein **4x** (0.25 mmol) was added under flowing nitrogen, and then ethyl vinyl sulfide **3b** (30.0 μL, 0.30 mmol) was added dropwise. After 24 h, the reaction was quenched with triethylamine (100 μL) at –90 °C. The resultant mixture was directly purified by neutral silica gel column chromatography (eluent: *n*-pentane:Et_2O = 100:1 to 9:1) to give a mixture of *cis*-**6bx** and *trans*-**6bx**. The diastereomeric ratio (*cis:trans*) was determined by ^{1}H NMR ($CDCl_3$) analysis. The enantiomeric purity was determined by chiral GC or HPLC analysis.

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Keywords: [4+2] cycloaddition • boron Lewis acid • chiral Brønsted acid catalyst • inverse-electron-demand hetero-Diels–Alder reaction • phosphoric acid

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[14] The *endo* orbital approach of **4c** to **3b** would provide *cis*-**6bc**, whereas the *exo* orbital approach of **4c** to **3b** would provide *trans*-**6bc**. The *endo* orbital approach is usually advantageous due to secondary orbital interactions on sulfur of **3b**. The advantages of vinyl sulfides rather than vinyl ethers are shown in the Supporting Information.

[15] The reactions proceeded slowly at –78 °C in the presence of $B(C_6F_5)_3$ alone. For example, **6bc** was obtained in 45% yield (*cis:trans* = 3:97) within 24 h. The changeover of the *cis/trans*-ratio is discussed below.

[16] Interestingly, BBr_3-(*R*)-**2a** did not effectively promote the reaction of **4c** with **3b**, and **6bc** was obtained in 10% yield (*cis:trans* = 79:21) with –10% ee (i.e., the opposite enantiomer) for *cis*-**6bc**.

[17] In general, the correlation of *s-cis/s-trans* geometry in the catalyst-complexed and/or uncomplexed substrates should be carefully imported into their transition state rationalization according to the Curtin–Hammet principle. J. I. Seeman, *Chem. Rev.* **1983**, *83*, 83–134.

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[19] The reactions proceeded slowly at –78 °C in the presence of BF_3•Et_2O alone. For example, **6bc** was obtained in 89% yield (*cis:trans* = 82:18) within 51 h.

[20] Since enantio-pure **7** was highly crystalline, the absolute configuration of **7** was determined by X-ray analysis. See the SI for details.

[21] The relative configuration of **8** was determined by X-ray analysis of racemate **8**. See the SI for details.

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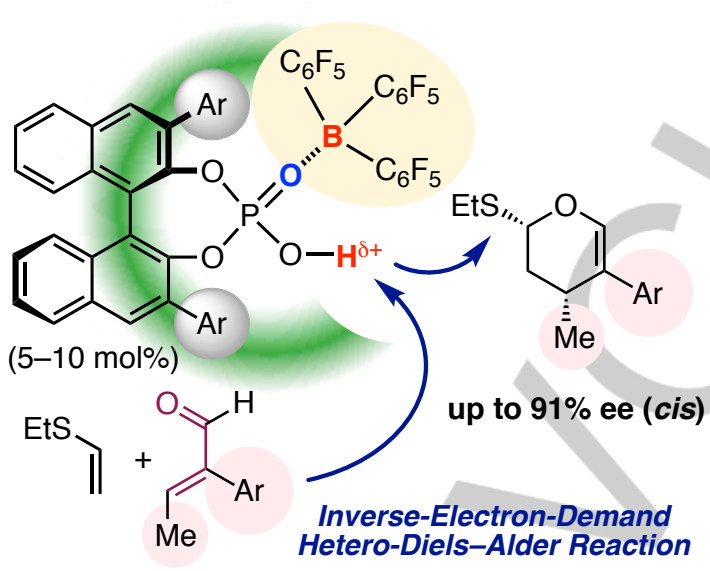

H⁺ in the chiral cavity: The enantioselective inverse-electron-demand hetero-Diels–Alder reaction of acroleins with ethyl vinyl sulfide was developed with the use of bulky tris(pentafluorophenyl)borane-assisted chiral phosphoric acid catalysts. The chiral cavity of the supramolecular Brønsted acid catalysts controlled the multiselectivity of the present reaction, and the optically active 3,4-dihydro-2*H*-pyrans were obtained in high yields.

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