Enantio- and Diastereoselective Carbonyl-Ene Cyclization–Acetalization Tandem Reaction Catalyzed by Tris(pentafluorophenyl)borane-Assisted Chiral Phosphoric Acids

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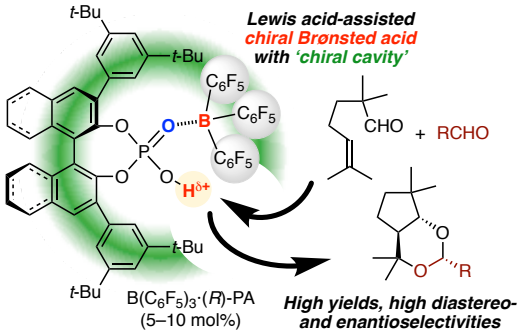
Supporting Information Placeholder

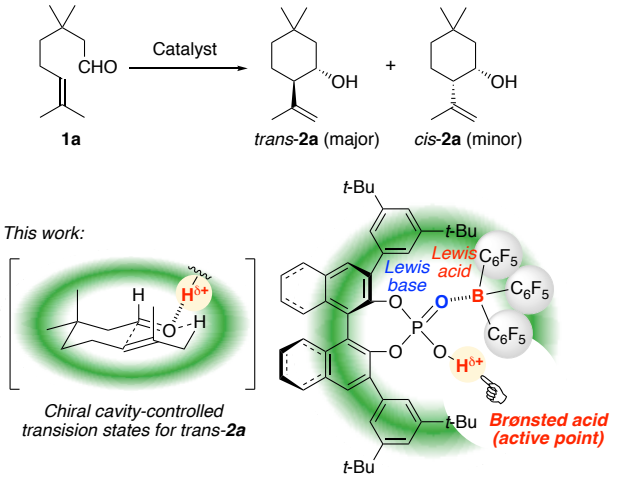


ABSTRACT: Highly enantio- and diastereoselective carbonyl-ene cyclization was developed with the use of chiral LBA catalysts, which were prepared *in situ* from both sterically demanding tris(pentafluorophenyl)borane and chiral phosphoric acids. Along with the performance of standard carbonyl-ene cyclizations, carbonyl-ene cyclization–acetalization tandem reactions with the use of additional aldehydes were demonstrated with high enantio- and diastereoselectivities. Based on mechanistic examinations, a stepwise reaction pathway *via* tertiary carbocation intermediates involving possible transition states is proposed.

Key words: acetal, boron, Brønsted acid, carbonyl-ene cyclization, chiral phosphoric acid, Lewis acid, organocatalyst, tandem reaction

Carbonyl-ene cyclization is one of the most useful and simplest methods for synthesizing cyclic homoallylic alcohols.[1] In particular, two adjacent carbon atoms can be stereocontrolled by chiral catalysts in the carbon–carbon bond-forming reaction (Scheme 1). Since Yamamoto developed the catalytic enantioselective carbonyl-ene cyclization of 3-methylcitronellal **1a** with the use of a *stoichiometric amount* of a chiral 1,1'-bi-2-naphthol (BINOL)-Zn(II) catalyst for the first time in 1985,[2,3] a few research groups have reported the still-challenging reaction with the use of a *catalytic amount* of chiral catalysts.[4–6] In particular, chiral Lewis acid catalysts, such as BINOL-Ti(IV) catalysts by Mikami/Nakai,[4] Schiff base-Cr(III) catalysts by Jacobsen,[5b,d] bis(oxazolinyl)pyridine (PyBOX)-Sc(III) catalysts by Loh,[5c] and BINOL-Al(III) by Mino,[5g,h] have been regarded. In contrast, List recently developed the first organocatalytic enantioselective carbonyl-ene cyclization with the use of confined chiral Brønsted acid catalysts based on a BINOL-derived imidodiphosphate.[7,8] List's report greatly encouraged us to use our Lewis acid-assisted chiral Brønsted acid (LBA)[9] catalysts based on chiral BINOL-derived phosphoric acids, which were previously designed and used for the enantioselective Diels–Alder, [2+2] cycloaddition, and hetero-Diels–Alder reactions.[10] In particular, the coordination of a phosphoryl moiety of chiral phosphoric acid to a bulky boron Lewis acid would increase the Brønsted acidity of phosphoric acid through the conjugated bonds and create an effective chiral cavity for controlling the reaction with higher-ordered stereoselectivity. We thus envisioned that the sterically demanding and conformationally flexible chiral cavity of our catalysts might also be suitable for such carbonyl-ene cyclization which should involve folding transition states (Scheme 1).

We initially examined the reaction of **1a** with the combination of tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) (10 mol%) and (*R*)-3,3'-Ar_2-BINOL-derived phosphoric acid **3** (10 mol%) in dichloromethane with MS 4A at –78 °C for 3 h (Table 1). MS 4A was used as a drying agent. Through the screening of 3,3'-

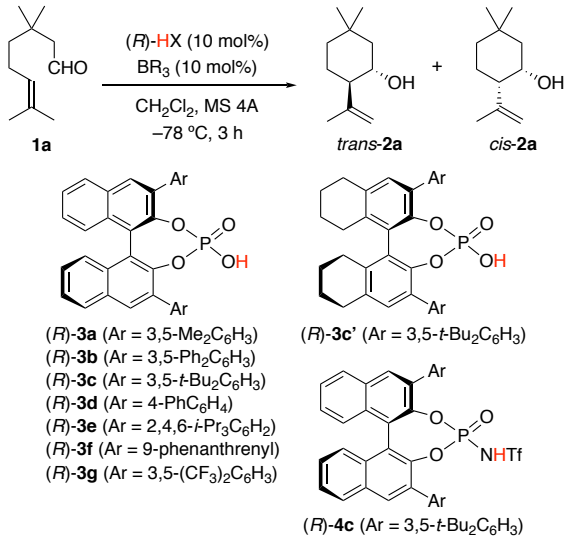


Scheme 1. Sterically demanding chiral tris(pentafluorophenyl)borane-assisted chiral phosphoric acid catalysts for the enantio- and diastereoselective carbonyl-ene cyclization.

substituents of (*R*)-**3** (entries 1–7), (*R*)-**3c** (Ar = 3,5-*t*-$Bu_2C_6H_3$), was much better than others, and *trans*-**2a** with a six-membered ring was exclusively obtained in >99% yield with 94% ee (entry 3). Less sterically demanding (*R*)-**3a** (Ar = 3,5-$Me_2C_6H_3$, entry 1), (*R*)-**3b** (Ar = 3,5-$Ph_2C_6H_3$, entry 2), (*R*)-**3d** (Ar = 4-PhC_6H_4, entry 4), more sterically demanding (*R*)-**3e** (Ar = 2,4,6-*i*-$Pr_3C_6H_2$, entry 5), and (*R*)-**3f** (Ar = 9-phenanthrenyl, entry 6) were less effective. Acidic (*R*)-**3g** (Ar = 3,5-$(CF_3)_2C_6H_3$, entry 7) was not effective in this reaction, and low enantioselectivity (15% ee) was induced. In contrast, (*R*)-**3c'** (Ar = 3,5-*t*-$Bu_2C_6H_3$) with the H_8-BINOL-skeleton was also effective, and *trans*-**2a** was exclusively obtained in >99% yield with 90% ee (entry 8). However, as expected, highly acidic chiral phosphoramide (*R*)-**4c** (Ar = 3,5-*t*-$Bu_2C_6H_3$) was not effective, and *trans*-**2a** was obtained with 63% ee (entry 9). The combined use of $B(C_6F_5)_3$ was critical, since BBr_3, BPh_3, and $BF_3{\cdot}Et_2O$ were much less effective with regard to the yield and diastereo- (i.e., *trans/cis*), and/or enantioselectivity (entries 10–12). Moreover, in the absence of $B(C_6F_5)_3$ (i.e., (*R*)-**3c** alone), the reaction did not proceed (entry 13). Since the reaction proceeded with the use of $B(C_6F_5)_3$ alone (entry 14), the LBA catalyst $B(C_6F_5)_3{\cdot}$(*R*)-**3c** *in situ* (entry 3) might show much higher catalytic activity than either starting component, $B(C_6F_5)_3$ or (*R*)-**3c**. Moreover, 5 mol% of $B(C_6F_5)_3{\cdot}$(*R*)-**3c** was also effective, and *trans*-**2a** was obtained in >99% yield with 93% ee (entry 15).

With the optimized reaction conditions in hand, we examined a few typical substrates (Scheme 2). With the use of 10 mol% of $B(C_6F_5)_3{\cdot}$(*R*)-**3c** (Conditions A), dimethyl-substituted azacyclized product **2b** was successfully obtained in 88% yield (*trans:cis* = 82:18) with 96% ee (*trans*-**2b**). With the use of 10 mol% of $B(C_6F_5)_3{\cdot}$(*R*)-**3c'** (Conditions B), better enantioselectivity (>99% ee) was observed. Traditionally, dialkyl-substituted alkenyl aldehydes have often been used in the carbonyl-ene cyclization by taking advantage of the Thorpe–Ingold effect.[11] In contrast, due to the difficulty to use non-substituted alkenyl aldehydes in this reaction, remarkable results with good yields and good stereoselectivities have been very limited.[5b,7] In this context, we examined non-substituted simple alkenyl

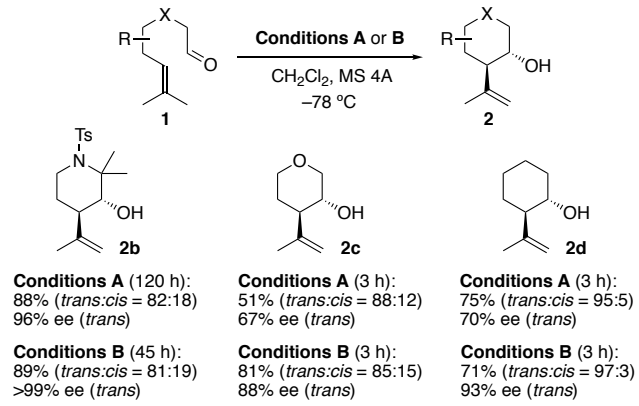
Table 1. Optimization of the Catalysts.[a]



entry	(*R*)-HX	BR_3	yield (%) of **2a**	*trans:cis* of **2a**	ee (%) of *trans*-**2a**
1	(*R*)-**3a**	$B(C_6F_5)_3$	95	>99:<1	38
2	(*R*)-**3b**	$B(C_6F_5)_3$	>99	>99:<1	46
3	(*R*)-**3c**	$B(C_6F_5)_3$	>99	>99:<1	94
4	(*R*)-**3d**	$B(C_6F_5)_3$	>99	>99:<1	8
5	(*R*)-**3e**	$B(C_6F_5)_3$	94	>99:<1	38
6	(*R*)-**3f**	$B(C_6F_5)_3$	>99	>99:<1	7
7	(*R*)-**3g**	$B(C_6F_5)_3$	>99	>99:<1	15
8	(*R*)-**3c'**	$B(C_6F_5)_3$	>99	>99:<1	90
9	(*R*)-**4c**	$B(C_6F_5)_3$	>99	98:2	63
10	(*R*)-**3c**	BBr_3	90	83:17	0
11	(*R*)-**3c**	BPh_3	8	91:9	32
12	(*R*)-**3c**	$BF_3{\cdot}Et_2O$	0	–	–
13	(*R*)-**3c**	–	0	–	–
14	–	$B(C_6F_5)_3$	>99	>99:<1	0
15[b]	(*R*)-**3c**	$B(C_6F_5)_3$	>99	>99:<1	93

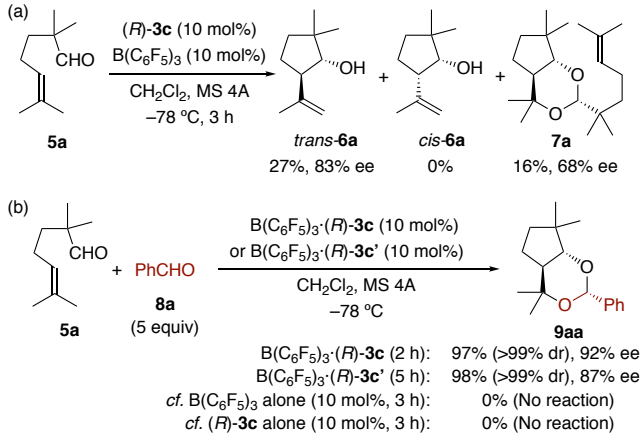
[a] The reaction was carried out with (*R*)-HX (10 mol%), BR_3 (10 mol%), **1a** (0.50 mmol), and MS 4A in dichloromethane at –78 °C for 5 h. [b] The reaction was carried out with 5 mol% each of $B(C_6F_5)_3$ and (*R*)-**3c**.

aldehydes, such as **1c**[4a,b,5b] and **1d**[4a,b], in the presence of $B(C_6F_5)_3{\cdot}$(*R*)-**3c**. As a result, the corresponding tetrahydropyran **2c** and cyclohexane **2d** were obtained with a high *trans/cis* ratio, but the enantioselectivities were moderate (67% ee and 70% ee, respectively). In contrast, when the reactions were conducted in the presence of $B(C_6F_5)_3{\cdot}$(*R*)-**3c'**, both the yield and enantioselectivity were greatly improved (88% ee and 93% ee, respectively). This result indicated that tight complexation of $B(C_6F_5)_3{\cdot}$(*R*)-**3c'** with the more basic P=O moiety might partially suppress the dissociation of $B(C_6F_5)_3$ from (*R*)-**3c'**. Probably, prevention of the undesired reaction by released $B(C_6F_5)_3$ alone,[12] might be important for the less-favored cyclizations of these non-substituted substrates.



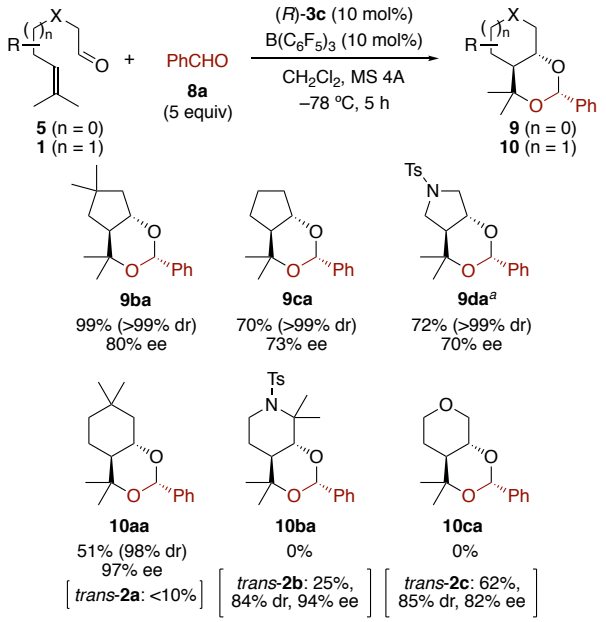
Scheme 2. Carbonyl-ene cyclization. **Conditions A**: (*R*)-**3c** (10 mol%), $B(C_6F_5)_3$ (10 mol%), **1b**–**d** (0.25 mmol), and MS 4A in dichloromethane at –78 °C. **Conditions B**: Same as Conditions A, except that (*R*)-**3c'** (10 mol%) was used instead of (*R*)-**3c**.

Unexpectedly, when we used substrate **5a** in the presence of $B(C_6F_5)_3$·(*R*)-**3c**, along with the five-membered ring *trans*-**6a** (27% yield, 83% ee), ene cyclization–acetalization tandem reaction product **7a** was obtained in 16% yield with 68% ee (Scheme 3a), although Andersen previously reported the ene cyclization of **5a** to **6a** with the use of a stoichiometric amount of Me_2AlCl.[6a] Inspired by this interesting new tandem acetalization, we envisioned that the additional use of a reactive aldehyde should be effective (For other additives for the tandem reactions, see Scheme S3 in the Supporting Information). The reaction of **5a** (1 equiv) with benzaldehyde **8a** (5 equiv)[13] was carried out in the presence of $B(C_6F_5)_3$·(*R*)-**3c** (Scheme 3b). As a result, a successive carbonyl-ene cyclization–acetalization proceeded, and the corresponding acetal **9aa** was obtained as a sole product without decomposition in 97% yield with 92% ee. $B(C_6F_5)_3$·(*R*)-**3c'** was less effective than $B(C_6F_5)_3$·(*R*)-**3c**, and **9aa** was obtained with 87% ee. Since neither $B(C_6F_5)_3$ or (*R*)-**3c** alone promoted any reactions under the same reaction conditions, the use of $B(C_6F_5)_3$·(*R*)-**3c**, as a sterically demanding and activated Brønsted acid catalyst, should be essential for the present reaction. Moreover, the structure of **5a** should be important for this reaction, since other alkenyl aldehydes **5b**–**5d**



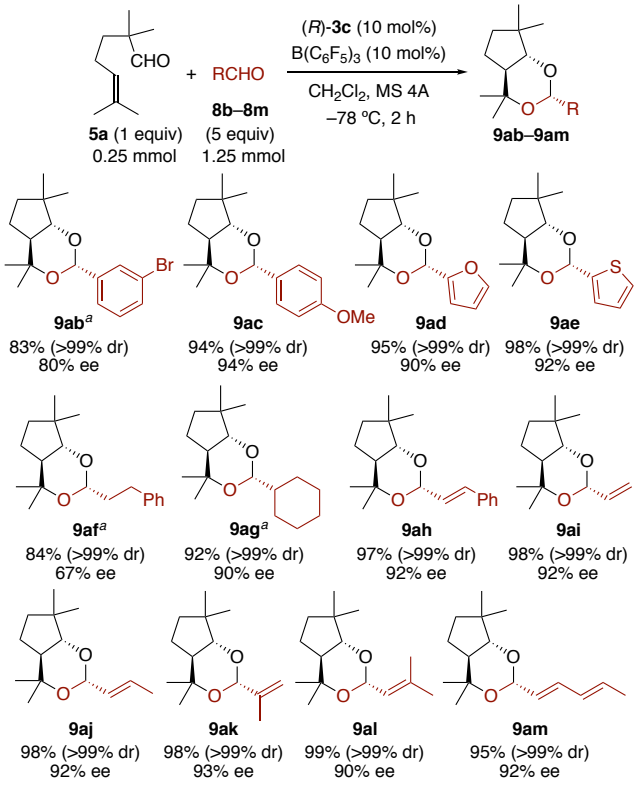
Scheme 3. Unexpected carbonyl-ene cyclization–acetalization tandem reactions.

and **1a**–**1c** were less effective than **5a** as shown in Scheme 4. For example, even very similar five/six-membered-fused ring **9ba** was obtained from **5b** with 80% ee, whereas dimethyl-non-substituted **9ca** was obtained from **5c** with lower yield and enantioselectivity. For a useful glycosidase inhibitor analogue,[14] azacyclic compound **9da** was obtained from **5d** in 72% yield by using $B(C_6F_5)_3$·(*R*)-**3c'**, although the enantioselectivity was still 70% ee. Moreover, six/six-membered-fused heterocycles **10ba** (from **1b**) and **10ca** (from **1c**) were not obtained, and standard carbonyl-ene cyclized products were obtained (see Scheme S1 in the Supporting Information for details). In contrast, **10aa** was obtained from **1a** in 51% yield with 97% ee. Overall, the present novel carbonyl-ene cyclization–acetalization tandem reactions might strongly depend on the structure of alkenyl aldehydes at this stage, partially due to the confined structure of our LBA catalysts $B(C_6F_5)_3$·(*R*)-**3c** and $B(C_6F_5)_3$·(*R*)-**3c'**.



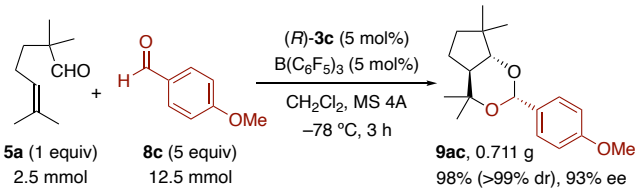
Scheme 4. Synthesis of other acetals. Conditions: (*R*)-**3c** (10 mol%), $B(C_6F_5)_3$ (10 mol%), alkenyl aldehyde **5** or **1** (0.25 mmol), **8a** (1.25 mmol), and MS 4A in dichloromethane at –78 °C unless otherwise noted. Also see the Supporting Information for details. [a] (*R*)-**3c'** was used instead of (*R*)-**3c**.

Next, we examined the substrate scope of additional aldehydes for the carbonyl-ene cyclization–acetalization tandem reactions (Scheme 5). Not only aromatic aldehydes with electron-withdrawing and -donating groups (**8b** and **8c**) but also heteroaromatic aldehydes (**8d** and **8e**) could be used, and the corresponding acetals (**9ab**–**9ae**) were obtained in high yield with high diastereo- (>99% dr) and enantioselectivities (80–94% ee).[15] For aliphatic aldehydes, hydrocinnamaldehyde **8f** with a linear alkyl moiety was not effective, and **9af** was obtained with 67% ee. However, cyclohexanecarboxaldehyde **8g** with a branched alkyl moiety gave **9ag** with >99% dr and 90% ee. Generally, it is difficult to perform the selective acetalization of relatively unstable α,β-unsaturated aldehydes because it competes with the Michael addition of alcohols.[16–18] Nevertheless, it is noteworthy that a series of α,β-unsaturated aldehydes (**8h**–**8l**) could be used in this reaction, and the corresponding acetals were obtained in 97–99% yields with >99% dr and 90–93% ee

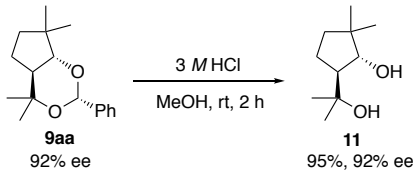


Scheme 5. Tandem carbonyl-ene cyclization–acetalization. [a]After the reaction, the resultant mixture was stirred at 0 °C for an additional 1 h.

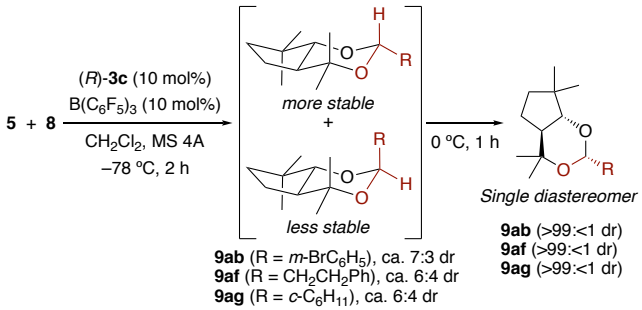
(see **9ah**–**9al**). α,β,γ,δ-Unsaturated aldehyde **8m** could also be used, and **9am** was obtained in 92% yield with >99% dr and 92% ee. Moreover, to demonstrate the synthetic utility of this reaction, 10-fold scale-up (2.5 mmol) synthesis of **9ac** was successfully performed with a reduced amount of catalyst (5 mol%), and 0.711 g of **9ac** was obtained with >99% dr and 93% ee (Scheme 6). Furthermore, the obtained acetals, such as **9aa**, could be readily hydrolyzed to synthetically useful 1,3-diol **11** without compromising the optical purity (Scheme 7). It is notable that, during the examination of scope in the acetal synthesis in Schemes 5 and 6, we found that **9ab**, **9af**, and **9ag** required further stirring of the reaction mixture at 0 °C for 1 h, whereas other products **9** did not. In fact, just after the reaction at –78 °C for 2 h, two diastereomers for the acetal center were observed for **9ab** (ca. 7:3), **9af** (ca. 6:4), and **9ag** (ca. 6:4) (Scheme 8). However, by stirring the reaction mixture at 0 °C for 1 h, one isomer could completely convert to the thermodynamically more stable other isomer, as shown.



Scheme 6. Ten-fold scale-up synthesis of **9ac**.



Scheme 7. Transformation of **9aa** to optically active 1,3-diol **11**.



Scheme 8. Epimerization to thermodynamically stable single acetals.

Finally, we turn our attention to mechanistic aspects. We found a linear relationship between the ee values of (*R*)-**3c** and *trans*-**2a** with constant yields (>99%) in the probe reaction of **1a** (see Scheme S4 in the Supporting Information). This result supports the notion that the active species might be a *monomeric* LBA-structure as shown in Scheme 1. Moreover, ESI-MS analysis of $B(C_6F_5)_3$·(*R*)-**3c'**[19] also supported the monomeric structures, which showed a peak of 1243.41 for $[B(C_6F_5)_3$·(*R*)-**3c'**–H$]^-$ (see Figure S4 in the Supporting Information). Based on the working hypothesis derived from the above experiments, possible transition states TS-**12** and TS-**13** for the probe carbonyl-ene cyclization of **1a** are shown in Figure 1. Coordination of the P=O moiety of (*R*)-**3c** to bulky $B(C_6F_5)_3$ would increase the Brønsted acidity of phosphoric acid through the conjugated bonds (Also see Figure S2 in the Supporting Information for ^{1}H NMR analysis of BF_3·(*R*)-**3c** complex, where a downfield shift from (*R*)-**3c** was observed.).[10] Throughout the reaction, the C=O moiety of **1a** would coordinate to the active proton of (*R*)-**3c** with the pseudo-equatorial conformation *via* carbocation intermediates. In TS-**13**, considerable steric constraints between the closing ring part (in particular, the β-dimethyl moieties) and bulky $B(C_6F_5)_3$ would be observed. In contrast, TS-**12** can avoid such notable steric constraints from $B(C_6F_5)_3$·(*R*)-**3c**. Therefore, TS-**12** would be more favored than TS-**13**, and the observed stereoselectivity (94% ee, see Table 1) might be reasonably explained. In the same way, possible transition states TS-**14**–TS-**19** for the probe carbonyl-ene cyclization–acetalization tandem reactions of **5a**–**5c** with **8a** could be considered in Figure 2. In particular, the α-dimethyl moieties of **5a** should be critical for these possible transition states, and considerable steric constraints would be observed in TS-**15** (see Figure 2b), whereas TS-**14** can avoid the notable steric constraints (see Figure 2a). The α-dimethyl template in **5a** might be effective for increasing the enantioselectivity, whereas **5b** with β-dimethyl substituents (see TS-**16** in Figure 2c and TS-**17** in Figure 2d) and **5c** with non-substituents (see TS-**18** in

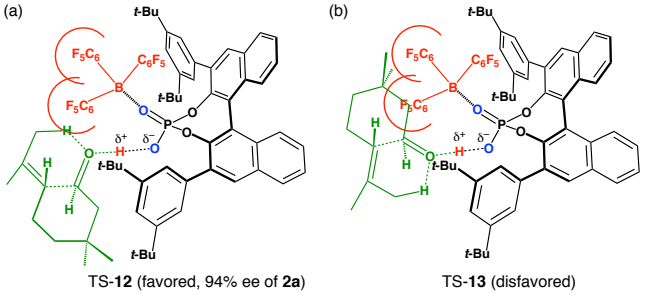


Figure 1. Possible transition states for the carbonyl-ene reaction. (a) TS-**12** (favored). (b) TS-**13** (disfavored).

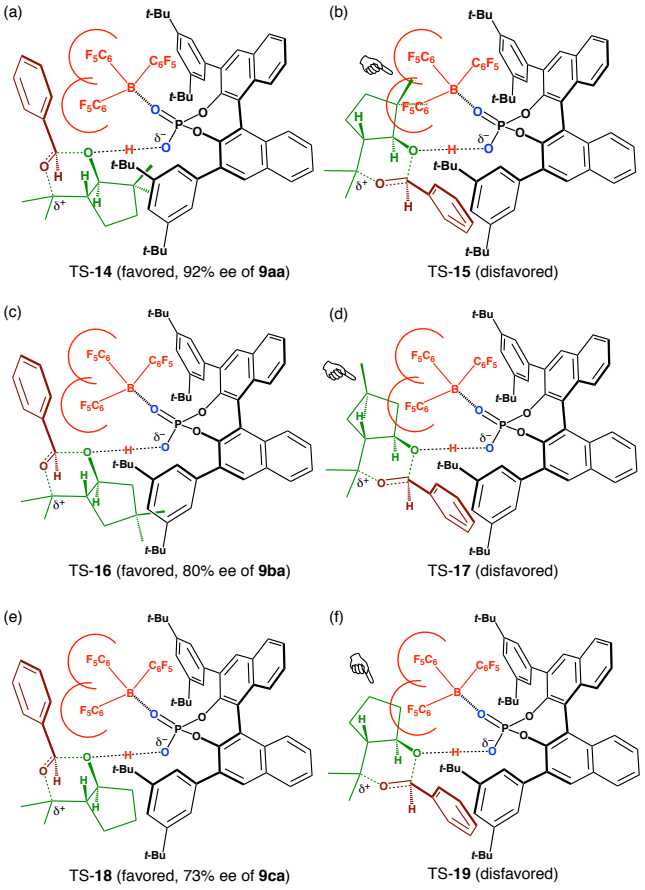


Figure 2. Possible transition states for the acetalization. (a) TS-**14** (favored). (b) TS-**15** (disfavored). (c) TS-**16** (favored). (d) TS-**17** (disfavored). (e) TS-**18** (favored). (f) TS-**19** (disfavored).

Figure 2e and TS-**19** in Figure 2f) would partially avoid such steric constraints from $B(C_6F_5)_3$·(*R*)-**3c**, and thus induce lower enantioselectivities (80% ee and 73% ee, respectively) than **5a** (92% ee). Overall, the reactions would proceed in such matched pairs with the catalyst, which can control the reactions with higher-ordered stereoselectivity during the present cyclizations by taking advantage of the effective chiral cavity of $B(C_6F_5)_3$·(*R*)-**3c**.

In summary, we have developed a highly enantio- and diastereoselective carbonyl-ene cyclization of alkenyl aldehydes with the use of sterically demanding tris(pentafluorophenyl)borane-assisted chiral phosphoric acid catalysts, which were prepared *in situ*. The catalysts could promote the reaction even with low-reactive non-substituted substrates, which were hardly used by conventional catalysts. Moreover, with the use of additional aldehydes, carbonyl-ene cyclization–acetalization tandem reactions were demonstrated with high enantio- and diastereoselectivities for the first time. The outstanding performance of the present catalysts might be attributed to the confined chiral cavity of the conformationally flexible catalysts, and this result will inspire the further development of reactions that have so far been eluded by conventional catalysts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0cXXXXX.

Experimental procedures, characterization data, additional control experiments, copies of NMR spectra for all products, GC and HPLC profiles (PDF), and cif files for X-ray analysis.

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Notes

The authors declare no competing financial interest.

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