Enantioselective Diels–Alder Reaction Induced by Chiral Supramolecular Lewis Acid Catalysts Based on CN···B and PO···B Coordination Bonds

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Abstract
Chiral supramolecular boron Lewis acid catalysts were developed with the use of chiral 3-phosphoryl-BINOLs, 2-cyanophenylboronic acids, and tris(pentafluorophenyl)boranes based on CN···B and PO···B coordination bonds. In particular, coordinated tris(pentafluorophenyl)boranes can increase the Lewis acidity of the active center based on the Lewis acid-assisted Lewis acid catalyst system. A possible cavity in these catalysts was highly suitable for some probe Diels–Alder reactions of acroleins with cyclic and acyclic dienes, and the corresponding adducts were obtained in good to high yields with high enantioselectivities.

Key words: supramolecular catalyst, chiral cavity, Diels–Alder reaction, Lewis acid, phosphoryl moiety, cyano moiety

Making the most of coordinative interactions is the principal approach used to construct conformationally flexible complexes based on supramolecular chemistry, as reflected by early work by Lehn.1,2 If some small molecules are added based on acid–base chemistry,3 tailor-made chiral supramolecular catalysts can be fine-tuned in situ without producing any corresponding waste. In this regard, we previously developed chiral supramolecular Lewis acid catalysts such as 1 (Figure 1a), which was highly effective for enantioselective Diels–Alder reactions with anomalous endo/exo-selectivities.4,5,6 In catalyst 1, two bulky tris(pentafluorophenyl)boranes [B(C6F5)3] are coordinated to phosphoryl (PO) groups,7,8 and provide a deep chiral cavity. Moreover, the coordinated tris(pentafluorophenyl)boranes can increase the Lewis acidity of the active boron center based on a Lewis acid-assisted Lewis acid (LLA)9 catalyst system. In this context, we envisioned that we might be able to use CN···B(C6F5)310 as another useful coordination bond to generate a new type of chiral supramolecular catalyst. In particular, the CN moiety is an attractive option at the ortho-position of arylboronic acids, which would exert both steric and electron-withdrawing effects on the active boron center (Figure 1b). We report here chiral Lewis acid catalysts 2 based on CN···B and PO···B coordination bonds for the enantioselective Diels–Alder reaction of various acroleins with cyclic and acyclic dienes.

Figure 1 Design of chiral supramolecular catalysts with coordination bonds between PO···B(C6F5)3 and CN···B(C6F5)3

First, we examined the Diels–Alder reaction of methacrolein 4a with cyclopentadiene 3 in dichloromethane11 at −78 °C in the presence of chiral supramolecular catalyst 6 (10 mol%). Catalyst 6 was a simple extension of catalyst 1, and was prepared in situ from (R)-3,3′-bis(phosphoryl)-BINOL (BINOL = 1,1′-bi-2-naphthol). 2-cyano-5-fluorophenylboronic acid, and B(C6F5)3 (Scheme 1). Unfortunately, however, the enantioselectivity of the corresponding product exo-(2S)-5a was low (6% ee).

To avoid the excessive conflict of three bulky tris(pentafluorophenyl)boranes, we next used (R)-3-phosphoryl-BINOL in place of (R)-3,3′-bis(phosphoryl)-BINOL (Figure 2). As a result, the enantioselectivity of 5a was dramatically improved: 5a was obtained in 93% yield with 89% ee when we used catalyst 2a. Replacement of the binaphthyl skeleton (2a) with an H2-binaphthyl skeleton (2b) slightly improved the enantioselectivity (91% ee) of 5a. Moreover, replacement of the 5-F moiety in the arylboronic acid part (2b) with a 5-CF3 moiety (2c) improved the enantioselectivity (98% ee).
In a control experiment, the use of catalyst 2d with a 4-CF₃ moiety was slightly less effective than 2c in terms of the enantioselectivity. Moreover, both catalyst 2e with no substituents and catalyst 2f with a 5-CH₃ moiety were much less effective than 2c.

We next examined the effect of a bulky 3-substituent in the binaphthyl skeleton of the catalysts. In place of PO=-(C₆F₅), in catalyst 2c, we used a bulky electron-withdrawing aryl moiety, 3,5-(CF₃)₂C₆H₃, in catalyst 7a (Figure 3). As a result, catalyst 7a was also effective in the reaction of 4a with 3, and 5a was obtained in 96% yield with 84% ee. In sharp contrast, catalyst 7b with a less bulky 3-(CF₃)₂C₆H₃ moiety was less effective at inducing enantioselectivity, and 5a was obtained with 50% ee. Overall, when we compared 2c and 7a, the enantioselectivity of 5a with the use of 2c (98% ee) was higher than that with 7a (84% ee). Moreover, the catalytic activity of 2c might be higher than that of 7a, since the enantioselectivity with the use of 2c in the presence of an additional 5 mol% of B(C₆F₅)₃ was still high (90% ee), unlike with the use of 7a with an additional 5 mol% of B(C₆F₅)₃ (66% ee) (see the brackets a in Figures 2 and 3).

We next investigated the scope of substrates with the use of catalysts 2c and 7a (Scheme 2). α-Substituted acroleins, such as α-ethylacrolein 4b, α-bromoacrolein 4c, and tiglic aldehyde 4d, were examined. As a result, catalyst 7a was as effective as catalyst 2c for the reaction of 4b with 3 (Scheme 2a). However, for the reactions of 4c and 4d with 3, catalyst 7a was less effective than catalyst 2c (Schemes 2b and 2c). Compound 4c was extremely reactive, and enantioselectivity was low (44% ee) at −78 °C. However, the use of catalyst 2c at −98 °C improved the enantioselectivity up to 52% ee. Catalyst 2c was also more effective than catalyst 7a in the reactions of α-non-substituted acroleins, such as acrolein 4e and ethyl trans-4-oxo-2-butenoate 4f (Schemes 2d and 2e). Moreover, acyclic diene 8 was used in place of cyclopentadiene 3 (Scheme 3). As a result, endo-9 was obtained as a sole product in 97% yield with 85% ee when we used catalyst 2c, whereas catalyst 7a gave endo-9 in 95% yield with 80% ee. Overall, in these Diels-Alder reactions of 4a-f with the use of catalyst 2c, anomalous endo/exo-selectivities were not observed, unlike with the use of our previous catalyst 1.⁴ Although catalyst 2c might have the chiral cavity (see Figure 6), the structure might be too flexible to control anomalous endo/exo-selectivities. Therefore, moderately rigid conformationally flexible supramolecular catalyst such as 1 might be essential to induce anomalous endo/exo-selectivities. Instead, more flexible catalyst 2c showed a relatively wide generality for the substrates to induce...
the high enantioselectivities, whereas more rigid catalyst 1 showed the substrate specificity to induce the high enantioselectivities with anomalous endo/exo-selectivities.

![Scheme 2](image)

Scheme 2 Generality of acroleins 4 with the use of chiral supramolecular catalysts 2c and 7a 

![Scheme 3](image)

Scheme 3 Diels–Alder reaction of methacrolein 4a with acyclic diene 8 with the use of chiral supramolecular catalysts 2c and 7a

To confirm the roles of the main parts in the optimized supramolecular catalysts 2c and 7a, we performed control experiments with the use of simplified model compounds. First, we investigated the effect of the CN–B(C6F5)3 moiety in 2c and 7a, and the reaction of 4a with 3 was conducted with the use of catalysts 10 and 11 (Figure 4). As a result, low and no catalytic reactivities were observed, respectively. Moreover, 5a was produced as a racemate with the use of catalyst 10. Therefore, the CN–B(C6F5)3 moiety in 2c and 7a should be essential for providing the products in high yields with high enantioselectivities in the Diels–Alder reactions.

![Figure 4](image)

Figure 4 Control experiments to examine the effect of CN–B(C6F5)3 on the yield and enantioselectivity in the reaction of 3 with 4a. The reaction was carried out with the use of 10 or 11 (10 mol%) in dichloromethane with MS 4Å at −78 °C for 3 h.

The next fundamental control experiments were performed with the use of achiral supramolecular catalysts 14a–d with 4- or 5-substituted arylboronic acids in the reaction of 4a with poorly reactive cyclohexadiene 12 at room temperature for 30 min (Scheme 4). As a result, electron-withdrawing 5-CF3- and 4-CF3-substituted catalysts 14c and 14d showed high yields, whereas non-substituted catalyst 14a and electron-donating 5-Me-substituted catalyst 14b showed much lower yields. Therefore, an electron-withdrawing group such as CF3 might be effective for producing high yields in the Diels–Alder reactions. Moreover, the further control experiments at −40 °C for 48 h demonstrated that catalyst 14c showed higher activity than catalyst 14d (see the brackets a in Scheme 4).

![Scheme 4](image)

Scheme 4 Diels–Alder reaction of methacrolein 4a with cyclohexadiene 12 catalyzed by achiral supramolecular catalysts 14

Additional control experiments involved 1H and 13C NMR and analyses (CDCl3 at −40 °C) with the use of achiral supramolecular catalysts 14a–d and methacrolein 4a (Figure 5). We did not observe any shifts (Δ) of the formyl proton (9.50 ppm) or the formyl carbon (195.3 ppm) of 4a when we used 2-boryl-benzonitrile in the absence of B(C6F5)3 (Figure 5b). In contrast, when we used complexes 14a and 14b, a slight upfield shift was observed of the formyl proton (Δ −0.02 ppm).
to –0.04 ppm) and a slight downfield shift was observed of the formyl carbon (Δ +0.3 to +0.5 ppm) (Figures 5c and 5d). Moreover, when we used complex 14c, which has an electron-withdrawing 5-CF₃ moiety, a large upfield shift was observed of the formyl proton (Δ –0.14 ppm) and a large downfield shift was observed of the formyl carbon (Δ +1.6 ppm) (Figure 5e). Similar shifts (1H: Δ –0.14 ppm; 13C: Δ +0.8 ppm) were observed for 14d, which has an electron-withdrawing 4-CF₃ moiety (Figure 5f). These results might indicate that methacrolein 4a coordinates to complex 14c better than complexes 14a, 14b, and 14d. Overall, 4a would be more activated with 14c than with 14a, 14b, and 14d, and this observation agrees well with the reaction yields as shown in Scheme 4. Moreover, the enantioselectivities in the reaction of 4a with 3 in the presence of catalysts 2c-f in Figure 2 might be rationalized in part, since stronger Lewis acids would activate the substrate in shorter distance with low electronic energies and would help enantiomeric discrimination of the substrate better than weaker Lewis acids.¹⁸

Figure 5 ¹H and ¹³C NMR analysis of achiral complexes 14 with methacrolein 4a in CD₂Cl₂ at −40 °C.

Finally, we considered possible transition-state (TS) structures of the Diels–Alder reaction of 4a with 3 by the use of supramolecular catalysts 2c and 7a (Figure 6). Based on C₁-symmetric (R)-3-R-BINOLs, two major intermediates with 4a are shown in Figures 6a and 6b. The substituent R of (R)-3-R-BINOL is located far from the Ar moiety of aryloboronic acid in Figure 6a, while the substituent R is located close to the Ar moiety in Figure 6b. Due to steric reasons, the intermediate shown in Figure 6a might be more favored than that in Figure 6b. Based on this hypothesis, TS-15 in Figure 6c might be a favored TS for catalyst 2c. TS-15 has a syn-conformation for two bulky tris(pentfluorophenyl)boranes,¹⁹ which would provide a chiral cavity around the active boron Lewis acid center. On the other hand, much less bulky catalyst 7a might be much more conformationally flexible than catalyst 2c, and similar TS-16 in Figure 6d might be a favored TS. Consequently, a possible chiral cavity in TS-16 with 7a might be less effective than TS-15 with 2c, which could explain why catalyst 2c induced generally higher enantioselectivity than catalyst 7a. Via a re-face attack to 4a, which is activated due to non-covalent interactions,exo-(2S)-5a might be reasonably provided from TS-15 and TS-16. More information based on experimental and theoretical studies will be needed to discuss further possible structures.²⁰

Figure 6 Possible structures and chiral cavities of supramolecular catalysts in transition states (Ar₅ = C₅F₅) (a) Favored intermediate with R far from the Ar moiety. (b) Disfavored intermediate with R close to the Ar moiety. (c) Possible TS-15 with catalyst 2c. (d) Possible TS-16 with catalyst 7a.

In summary, we have developed conformationally flexible chiral supramolecular Lewis acid catalysts from chiral 3-substituted-BINOLs, 2-cyano phenylboronic acids, and tris(pentfluorophenyl)borane based on a coordination bond between the cyano moiety and tris(pentfluorophenyl)borane. Moreover, a second coordination bond between the phosphonyl moiety at the 3-position of the BINOL and tris(pentfluorophenyl)borane could increase both the catalytic reactivity and enantioselectivity in some Diels–Alder reactions.²¹
by providing a chiral cavity. In particular, chiral supramolecular catalyst 2c was effective for inducing high enantioselectivity for a variety of acroleins and cyclic and acyclic dienes. Further investigations of mechanistic aspects and application to other substrates and/or other catalytic asymmetric reactions are currently underway.

Acknowledgment

Financial support was provided in part by KPS. KAKENHI (15H05755, 26288046, and 26105723), Program for Leading Graduate Schools “IGER program in Green Natural Sciences”, MEXT, Japan.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.10155/s-0035-XXXXX.

References and Notes

(11) Dichloromethane was essential to induce good reactivity and enantioselectivity in this catalytic system. Toluene as another non-polar solvent was also effective to promote the reaction, although the enantioselectivity decreased significantly (ca. 60% ee). In contrast, the use of coordinative polar solvent such as EtO and THF showed almost no catalytic activity.
(12) In the ESi-MS (positive mode) analysis of catalyst 2c, a peak for [2H+H0+H+] was observed. See the SI.
(13) Consequently, when we compared the catalytic reactivity of 10 with a phosphoryl moiety to that of 11 with a 3,5-(3,5-(CF3)2C6H4)2CH2 moiety, 10 showed higher yield. This tendency would be correlated to the reaction with the use of 2c or 7a in the presence of competitive 5 mol% of B(C6F5)3 (See the brackets in Figures 2 and 3).
(14) Position of CN group influenced on enantioselectivity. The use of 3-cyanophenylboronic acid and 4-cyanophenylboronic acid in place of 2-cyanophenylboronic acid for catalyst 10 gave exo(2S)-5a in ca. 80% yield with 9% ee and 11% ee, respectively.
(15) Since cyclopentadiene is too reactive for evaluating meaningful differences in catalytic activity among 14a-d, we used cyclohexadiene 12.
(16) 1H and 13C NMR (CD2Cl2) analyses of 14 and 4a at room temperature did not show clear interactions, since a somewhat broad chart was observed.
(19) The previous supramolecular catalyst 1 was calculated to be a similar C3-symmetric syn-conformation for two bulky tris(pentafluorophenyl)boranes. See ref. 4.
(20) Other possible TS are discussed in the SI, which also gives the results with other supramolecular catalysts.
(21) Typical Procedure for the Diels–Alder Reaction

A solution of (R)-(3-(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphorin-2-yl)-5,5,6,7,7,8,8,8’-H8-BINOL (221 mg, 0.050 mmol) and 2-cyano-5-(trifluoromethyl)phenylboronic acid (10.7 mg, 0.050 mmol) in dichloromethane (1 mL), THF (0.3 mL),
and water (9 μL, 0.5 mmol) was stirred at room temperature for 12 h in a Pyrex Schlenk tube under a nitrogen atmosphere. Volatile compounds were removed under reduced pressure, and powdered MS 4Å (250 mg, used as received from a commercial source) was added. The resulting white solid was heated to 100 °C (bath temperature) under <5 Torr for 2 h. After the resulting substance was cooled to room temperature under a nitrogen atmosphere, tris(pentafluorophenyl)borane (51.2 mg, 0.10 mmol) and freshly-distilled dichloromethane (2 mL) were added under an argon atmosphere in a glove box. The pale brown mixture was stirred at room temperature for 1 h and then cooled to –78 °C, and methacrolein 4a (95% purity, 43.4 μL, 0.50 mmol) was added. Subsequently, freshly-distilled cyclopentadiene 3 (210 μL, 2.5 mmol) was added at –78 °C over 15 min. The resultant mixture was then stirred at –78 °C for 3 h. To quench the reaction, triethylamine (0.5 mL) was poured into the reaction mixture at –78 °C. The product mixture was directly purified by silica gel column chromatography (eluent: n-pentane:diethyl ether = 100:1–8:1). Solvents were removed under 200 Torr at 15 °C by a rotary evaporator, and the product 5a was obtained. "H NMR (400 MHz, CDCl₃) 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). "C NMR (100 MHz, CDCl₃) δ 20.1, 34.6, 43.2, 47.6, 48.5, 53.9, 133.1, 139.6, 205.9. HRMS (EI) calcd for C₉H₁₂O [M]+ 136.0888, found 136.0893. The endo/exo ratio of 5a was determined by "H NMR (CDCl₃) analysis; δ 9.40 (s, 1H, CHO (endo-5a)), 9.69 (s, 1H, CHO (exo-5a)). The enantioselectivity and absolute stereochemistry of 5a were determined by GC analysis according to the literature."