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Chiral Supramolecular *U-Shaped* Catalysts Induce the Multiselective Diels–Alder Reaction of Propargyl Aldehyde

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ABSTRACT: Diels–Alder reaction, which is a traditional [4 + 2] cycloaddition with two carbon–carbon bond formations, is one of the most powerful tools to synthesize versatile and unique 6-membered rings. We show that chiral supramolecular *U-shaped* boron Lewis acid catalysts promote the unprecedented multiselective Diels–Alder reaction of propargyl aldehyde with cyclic dienes. Independent from the substrate-control, enantio-, *endo/exo*-, π-facial-, regio-, site-, and substrate-selectivities could be controlled by the present *U-shaped* catalysts. The obtained reaction products could access to the concise synthesis of chiral diene ligands and a key intermediate of (+)-sarkomycin. The results presented here might partially contribute the development of artificial enzyme-like supramolecular catalysts for multiselective reactions, which will be able to target organic compounds that have thus far eluded synthesis.

INTRODUCTION

The control of multiple selectivities is one of the most challenging subjects in modern organic chemistry. In this regard, the Diels–Alder (DA) reaction is a significant tool for the total synthesis of complex organic molecules.[1–8] Nevertheless, the DA reaction shows relatively strong substrate-dependence based on the HOMO/LUMO-frontier orbital theory,[9–11] and universal control of multiselectivity is very difficult. When actually used in the DA reaction, conventional chiral catalysts can discriminate the prochiral enantioface (i.e., *re/si*-face) of a dienophile regardless of the diene (two-dimensional discrimination). However, most of them cannot control the diastereo- (i.e., *endo/exo*-), π-facial-, regio-, site-, nor substrate-selectivity, since this would require the three-dimensional discrimination of isomeric transition-state structures. In general, enzymes *in vivo* can realize such multiselectivity among a myriad of other possibilities by using a chiral cavity, which provides a three-dimensional space that includes an active site.[12] The cavities of enzymes are conformationally flexible to catch substrates and release products (induced fit function). To overcome the limited selectivity due to the small cavity and conformational rigidity of conventional chiral Lewis acid catalysts, supramolecular catalysts,[13–16] which are prepared *in situ* from small components by coordinating bonds, have been considered. Indeed, there are a few examples of the use of supramolecular *O-shaped* catalysts that induce unusual reactivity and/or selectivity in DA reactions.[17–23] However, their inherent catalytic activities are sometimes reduced due to their conformationally rigid structures. In contrast, we envisioned that chiral supramolecular *U-shaped* catalysts, which are more conformationally flexible than *O-shaped* catalysts, can induce high catalytic activity with unusual multiselectivity. Here we show, for the first time, that an asymmetric DA reaction of propargyl aldehyde[24] with cyclic dienes, triene, and tetraene can be controlled so as to provide multiselectivity by using chiral supramolecular *U-shaped* catalysts,[25] which should hold great potential for the non-enzymatic construction of fundamental and unusual molecules.

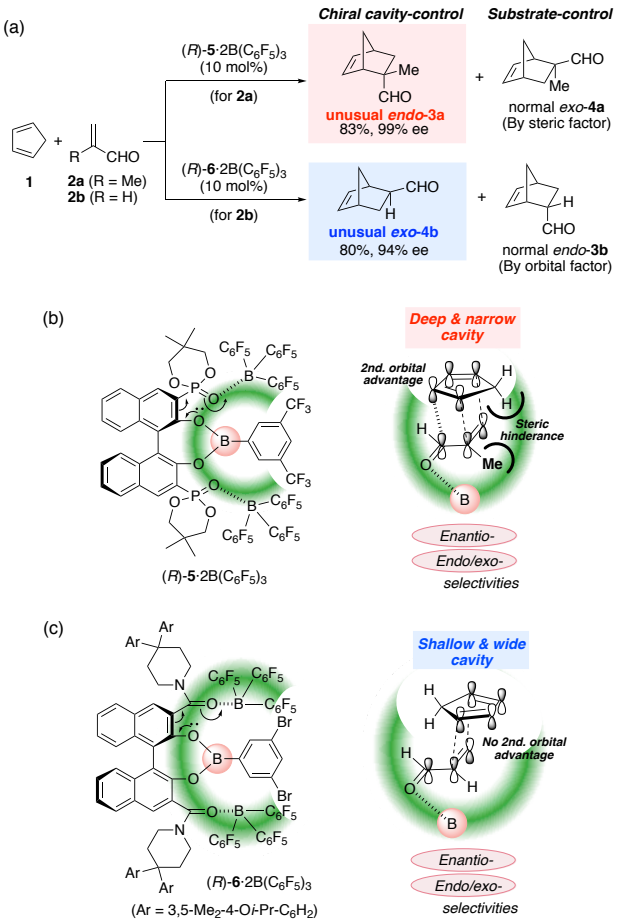


Figure 1. Outline of our previous chiral cavity-controlled Diels–Alder (DA) reaction of acroleins **2** with cyclopentadiene **1**. (a) Previous results for the catalyst-controlled *endo/exo*-selective DA reaction using chiral *U-shaped* catalysts. (b) *Endo*-induced chiral *U-shaped* catalyst (*R*)-**5**•2B(C_6F_5)$_3$. (c) *Exo*-induced chiral *U-shaped* catalyst (*R*)-**6**•2B(C_6F_5)$_3$.

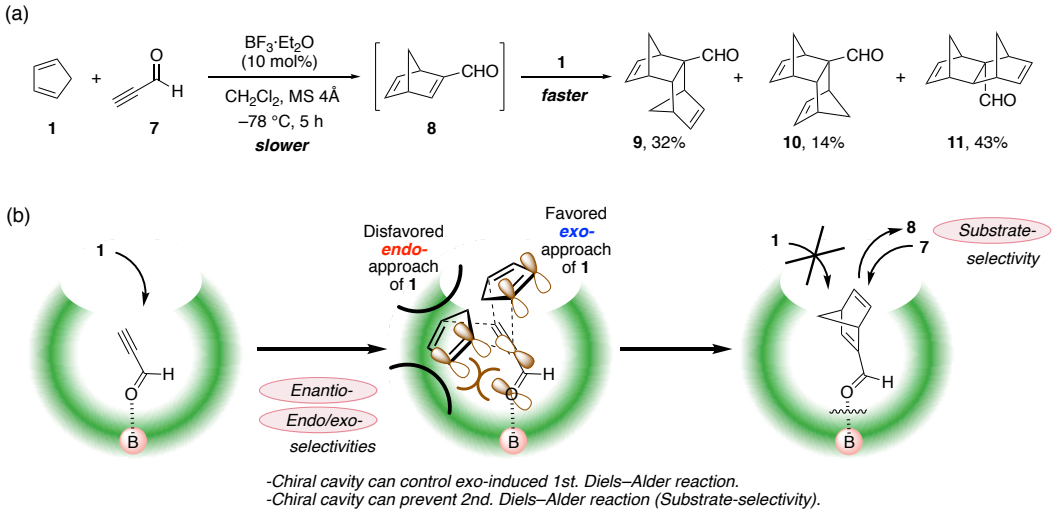


Figure 2. General strategy for the present multiselective DA reaction of propargyl aldehyde **7** with cyclopentadiene **1**. (a) A control experiment using BF_3•Et_2O in the reaction between **1** and **7**. (b) Multiselective induction in the DA reaction of **7** with **1** with the use of chiral supramolecular *U-shaped* catalysts.

In general, *endo/exo*-selectivity in the DA reaction strongly depends on the substrates used (Figure 1a).[26,27] In this regard, we have previously succeeded in the enantio- and *endo/exo*-selective DA reactions of acroleins **2** with cyclopentadiene **1** induced by chiral supramolecular *U-shaped* catalysts, (*R*)-**5**•2B$(C_6F_5)_3$ and (*R*)-**6**•2B$(C_6F_5)_3$ (Figures 1b and 1c).[25] These catalysts are prepared *in situ* from 3,3'-Lewis base-functionalized chiral BINOL, arylboronic acid, and tris(pentafluorophenyl)borane, and the size of the *U-shaped* cavity can be tuned for each substrate: (*R*)-**5**•2B$(C_6F_5)_3$, which has a deep and narrow chiral cavity, gives catalyst-controlled unusual *endo*-product **3a** with 99% ee from methacrolein **2a** overriding of intrinsic *exo*-product **4a**, whereas (*R*)-**6**•2B$(C_6F_5)_3$ which has a shallow and wide chiral cavity, gives catalyst-controlled unusual *exo*-product **4b** with 94% ee from acrolein **2b** overriding of intrinsic *endo*-product **3b**.[25] Notably, the centered Lewis acidity of these catalysts was enhanced based on the concept of a Lewis acid-assisted Lewis acid (LLA).[28]

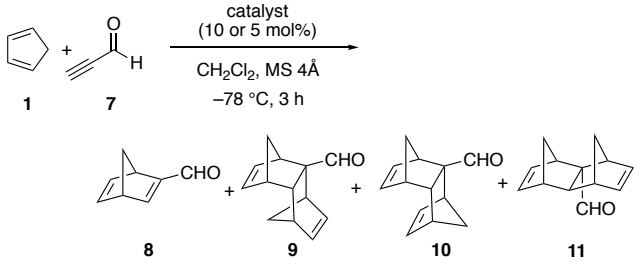
In this context, we are currently interested in whether or not these chiral supramolecular *U-shaped* catalysts can control multiselectivities in DA reactions. Thus, we focused on a reaction of propargyl aldehyde **7** with cyclopentadiene **1**. To the best of our knowledge, there has been only one prior study with a chiral boron Lewis acid catalyst reported by Yamamoto et al.,[24] although there are some examples of the use of alkynes other than **7**.[29,30] According to Yamamoto's report,[24] the desired DA adduct **8** was obtained with 95% ee but in only 28% yield due to the overreaction of **8** with **1**. Indeed, our preliminary investigation of the DA reaction of **7** with **1** in the presence of BF_3•Et_2O (10 mol%) shows that the 2nd DA reaction was much faster than the 1st DA reaction and the 2nd DA adducts (i.e., sesquinorbornadienes[31]) **9**–**11** were exclusively obtained (Figure 2a, also see the Supporting Information (SI), pages S10–S11). To avoid undesired overreactions, a catalyst must control the substrate-selectivities of **7** and **8**. Moreover, as indicated by Yamamoto's report,[24] although the *endo/exo*-selectivity is reflected convergently in the enantioselectivity, the *exo*-transition state might be favored because of the secondary repulsive HOMO–LUMO orbital interaction in the *endo*-transition state (see the SI, pages S11–S13).[32] Overall, we envisioned that our *exo*-induced chiral supramolecular *U-shaped* catalysts would control such the enantio-, *endo/exo*-, and substrate-selectivities through a conformationally flexible chiral cavity with reasonable turnover, as if an artificial enzyme-like cavity with three-dimensional stereocontrols under non-aqueous conditions (Figure 2b).

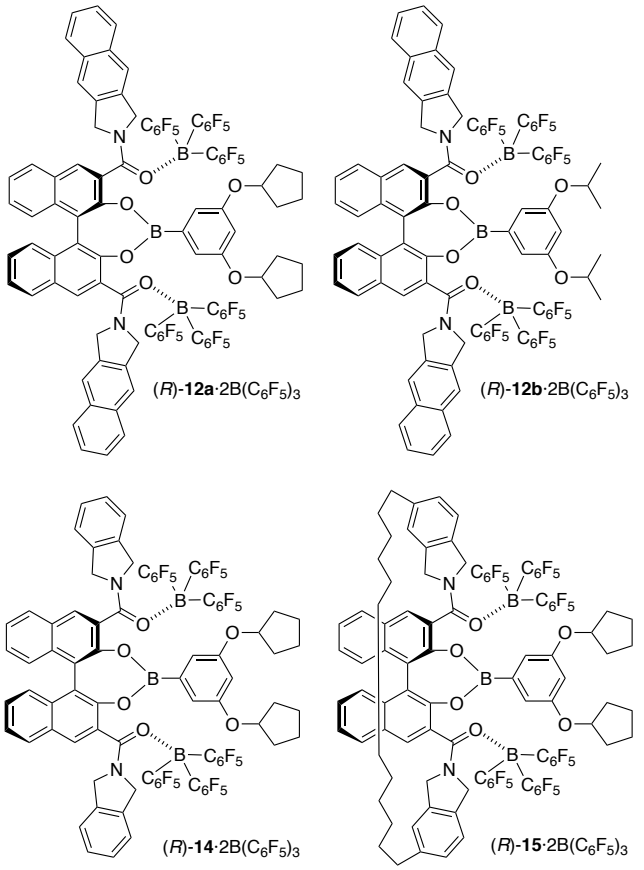
RESULTS AND DISCUSSION

At the beginning of the study, we examined the previous *endo*-induced catalyst (*R*)-**5**•2B$(C_6F_5)_3$[25] and *exo*-induced catalyst (*R*)-**6**•2B$(C_6F_5)_3$[25] in the reaction of **7** with **1** in dichloromethane with molecular sieves (MS) 4Å at –78 °C for 3 h (Table 1, entries 1 and 2). As a result, (*R*)-**5**•2B$(C_6F_5)_3$ showed a poor result (entry 1). In contrast, the desired 1st DA-adduct **8** was actually obtained in 60% yield with 54% ee with the use of (*R*)-**6**•2B$(C_6F_5)_3$, but the undesired 2nd DA-adducts **9**–**11** and further reacted byproducts were also obtained (entry 2). The size of the possible chiral cavity of the *U-shaped* catalysts can be tuned by modification of the amide moieties and arylboronic acid, since the distance between the two coordinated B$(C_6F_5)_3$ in a *syn*-relationship can be controlled by the steric hindrance between two amide moieties and arylboronic acid moieties. After the thorough optimization (see the SI, pages S8–9 and S14–S15), **8** was obtained in 95% yield with 90% ee, particularly when (*R*)-**12a**•2B$(C_6F_5)_3$, which involves flat isoindoline-derived amides, was used (entry 3). Remarkably, >1 gram scale synthesis could be achieved with the reduced catalytic amount (5 mol%) (entry 4). Ultimately, the more reduced catalytic amount (2.5 mol%) was still effective, and **8** was obtained in 90% yield with 90% ee (entry 5). The fine-tuning of the aryl boronic acid part should also be important, and (*R*)-**12b**•2B$(C_6F_5)_3$ was much less effective than (*R*)-**12a**•2B$(C_6F_5)_3$ in terms of the yield (49%), although the ee value was essentially the same (89% ee) (entry 6).

Unfortunately, conformationally flexible (*R*)-**12a**•2B$(C_6F_5)_3$ was not suitable for crystallization for X-ray analysis to give crucial structural evidence, although NMR and ESI-MS analyses could provide some information (see the SI, pages

Table 1. Initial Catalyst Screening and Mechanistic Consideration in the DA Reaction of Propargyl Aldehyde **7** with Cyclopentadiene **1** by Using Chiral Supramolecular *U-Shaped* Catalysts[a]





Entry	Catalyst (mol%)	Yield and ee of **8**	Yield of **9**–**11**
1	(*R*)-**5**•2B(C$_6$F$_5$)$_3$ (10)	24%, –6% ee[b]	32%
2	(*R*)-**6**•2B(C$_6$F$_5$)$_3$ (10)	60%, 54% ee	12%
3	(*R*)-**12a**•2B(C$_6$F$_5$)$_3$ (10)	95%, 90% ee	3%
4[c]	(*R*)-**12a**•2B(C$_6$F$_5$)$_3$ (5)	95%, 90% ee	4%
5[d]	(*R*)-**12a**•2B(C$_6$F$_5$)$_3$ (2.5)	90%, 90% ee	3%
6	(*R*)-**12b**•2B(C$_6$F$_5$)$_3$ (10)	49%, 89% ee	21%
7	(*R*)-**14**•2B(C$_6$F$_5$)$_3$ (10)	80%, 81% ee	9%
8	(*R*)-**15**•2B(C$_6$F$_5$)$_3$ (10)	72%, 80% ee	8%

[a] The reaction was carried out with **1** (2.5 mmol), **7** (0.5 mmol), and catalyst (10 mol%) in dichloromethane with MS 4Å at –78 °C for 3 h unless otherwise noted. [b] *ent*-**8** was obtained with 6% ee. [c] 12 mmol of **7** was used. 1.37 g of **8** was obtained. [d] Reaction time was 5 h.

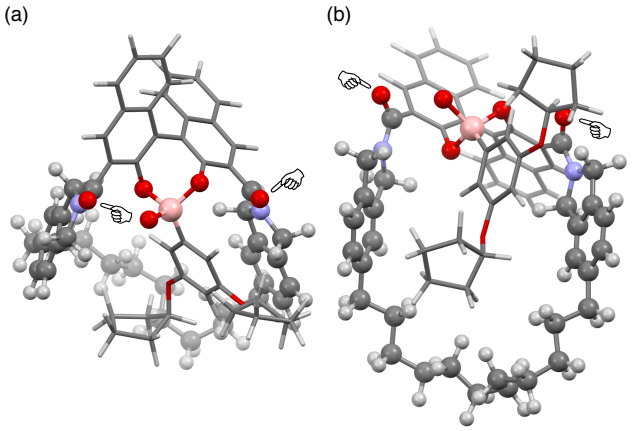


Figure 3. Theoretical study by a molecular mechanics method for model compound (*R*)-**15**•H$_2$O. Two hydrogen atoms of H$_2$O are omitted for clarity. (a) Top view. (b) Side view.

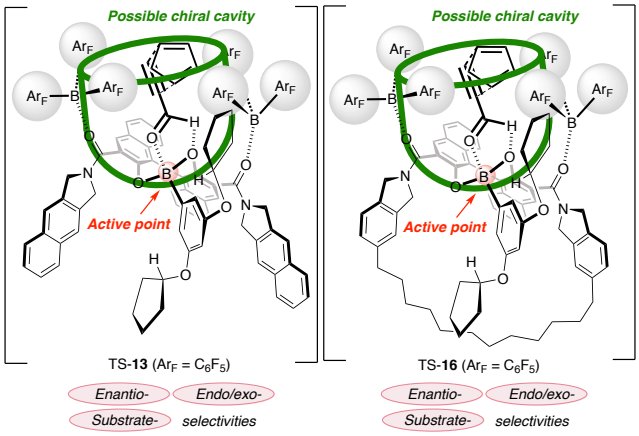


Figure 4. Possible transition states of the chiral supramolecular *U-shaped* catalysts (*R*)-**12a**•2B(C$_6$F$_5$)$_3$ without the macrocyclic structure (TS-**13**) and (*R*)-**15**•2B(C$_6$F$_5$)$_3$ with the macrocyclic structure (TS-**16**).

S22–S27). To confirm the possible *syn*-B(C$_6$F$_5$)$_3$/B(C$_6$F$_5$)$_3$-conformation of (*R*)-**12a**•2B(C$_6$F$_5$)$_3$, we designed alkyl-chain-linked catalyst (*R*)-**15**•2B(C$_6$F$_5$)$_3$, which cannot geometrically give an *anti*-B(C$_6$F$_5$)$_3$/B(C$_6$F$_5$)$_3$-conformation. The possible *syn*-B(C$_6$F$_5$)$_3$/B(C$_6$F$_5$)$_3$-conformation of catalysts (or their transition states) can be strongly assumed based on a preliminary theoretical study by a molecular mechanics method for the boron BINOLate aqua complex (*R*)-**15**•H$_2$O as a model unit (Figure 3, also see the SI, pages S35–S39). Although (*R*)-**15**•H$_2$O does not have two coordinated B(C$_6$F$_5$)$_3$ molecules, (*R*)-**15**•H$_2$O alone clearly showed the *syn*-C=O/C=O-conformation. As expected, the reaction proceeded smoothly even with the use of (*R*)-**15**•2B(C$_6$F$_5$)$_3$, and **8** was obtained in 72% yield with 80% ee (Table 1, entry 8). This result was comparable to the result with the use of non-alkyl-chain-linked (*R*)-**14**•2B(C$_6$F$_5$)$_3$ in a control experiment (80% yield and 81% ee of **8**) (entry 7). Therefore, the postulated TS-**16**, and thus TS-**13**, should be acceptable based on the possible *syn*-B(C$_6$F$_5$)$_3$/B(C$_6$F$_5$)$_3$-conformation (Figure 4).

Next, we transformed **8** into synthetically useful optically active compounds (Figure 5). Pinnick oxidation of **8** and subsequent methylation gave α,β-unsaturated ester **17** in 92% yield in two steps (Figure 5a). Ester **17** was much more stable than aldehyde **8**[33] and would be suitable for 1,2- and 1,4-addition reactions with some nucleophiles. Indeed, 1,2-addition of methyllithium provided compound **18** in 69% yield, which is Corey's chiral diene ligand[34] for asymmetric transition-metal catalysis (Figure 5b). On the other hand, the addition of benzyl alcohol under conventional basic conditions gave 1,4-adduct **19a** in 93% yield with high diastereoselectivity (dr = 98:2).[35] Further transformation of **19a** with $LiAlH_4$ was conducted to afford **20** in 94% yield, which is a key intermediate of (+)-sarkomycin.[36] Other C-, N-, O-, P-, and S-nucleophiles could also be used, and the corresponding novel 1,4-adducts **19b–g** were selectively obtained via *exo*-facial addition (Figure 5c). The transformations to optically active functionalized norbornenes **19a–g** are valuable, since they have not been synthesized directly in DA reactions using less reactive electron-rich β-substituted acroleins or acrylates.[37]

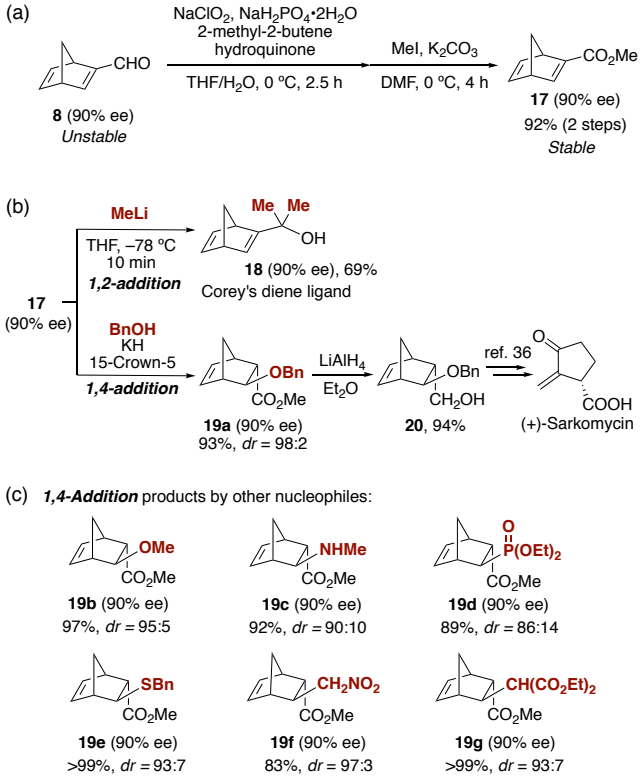


Figure 5. Transformation of DA adduct **8**. (a) Oxidative transformation of unstable **8** to stable ester **17**. (b) Transformation to Corey's diene ligand **18** and key intermediate **20** for (+)-sarkomycin. (c) Diastereoselective 1,4-addition to **17** with various C-, N-, O-, P-, and S-nucleophiles.

Next, we considered the substrate- and regioselective DA reaction of **7** with 2-alkyl-substituted cyclopentadienes **22** (Figure 6a). Although **22** cannot be isolated from a ca. 1:1 mixture of 1-/2-alkyl-substituted cyclopentadienes **21/22** due to isomerization,[38] we envisioned that chiral *U-shaped* catalysts might be effective to discriminate **22** from **21**. In principle, this reaction might give eight-isomeric 1st DA adducts (±)-**23**–

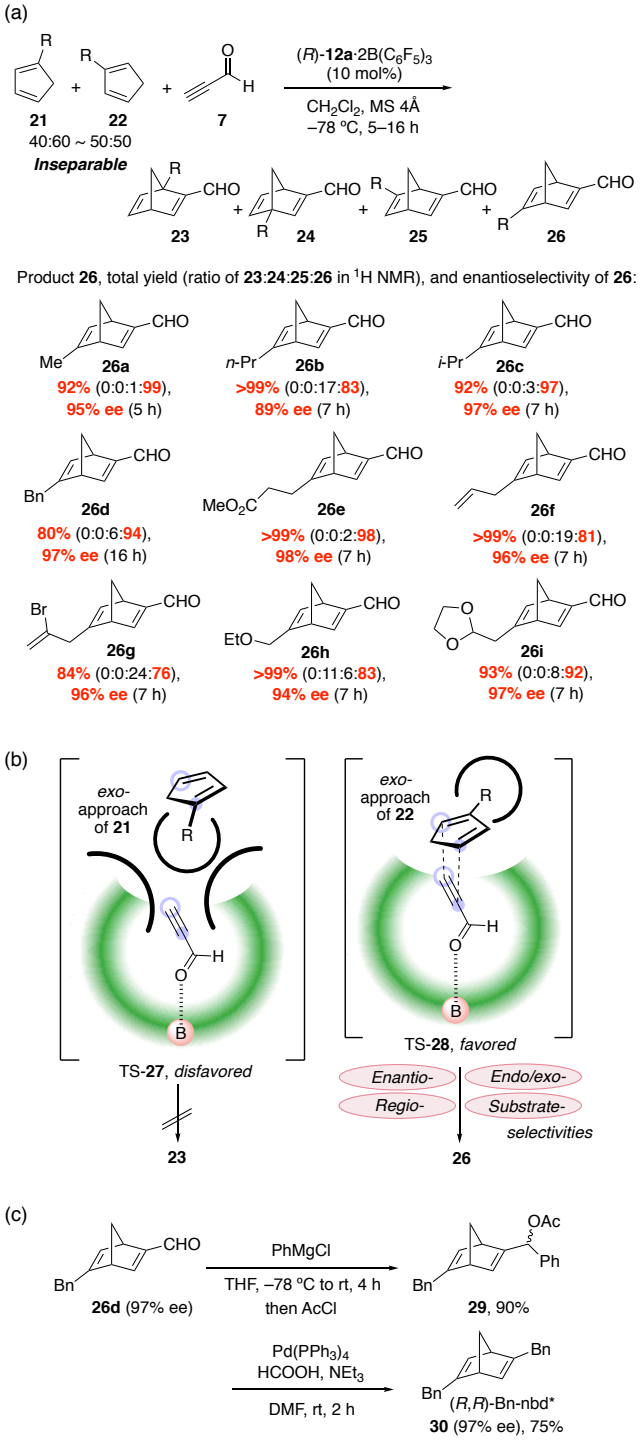


Figure 6. Substrate- and regioselective DA reaction with 1-/2-alkyl-substituted cyclopentadienes **21/22**. (a) The DA reaction of **7** with **21/22** by using (*R*)-**12a**•2B(C_6F_5)$_3$. (b) Possible *exo*-approaches of **21** (disfavored TS-**27**) and **22** (favored TS-**28**) to the activated **7**. A regioselection rule is indicated by the purple circles due to the theoretical orbital coefficients (see Supplementary Information). (c) Concise synthesis of Hayashi's chiral diene ligand **30** ((*R*,*R*)-Bn-nbd*).

26 and numerous (theoretically, up to 64) corresponding 2nd DA adducts. (±)-**23** and (±)-**26** were obtained almost equally under thermal conditions without catalysts consistent with the

orbital symmetry/coefficient theory,[9–11] whereas control experiments with BF_3•Et_2O, $B(C_6F_5)_3$, and $EtAlCl_2$ as typical Lewis acid catalysts provided a complex mixture and (±)-**23**–**26** could not be detected due to the undesired cationic polymerization of dienes (see the SI, pages S52–S58). In sharp contrast, (*R*)-**12a**•2B$(C_6F_5)_3$ gave the desired DA adducts **26** in high yield with high substrate-, enantio-, *endo/exo*-, and regioselectivities (Figure 6a). Both primary and secondary alkyl-substituted **21a**–**d**/**22a**–**d**, as well as **21e**–**i**/**22e**–**i** with a functionalized group, such as ester, allyl, haloallyl, alkoxy, and acetal moieties, could be used. These successful results can be understood in terms of either selective stabilization of the (1*R*,4*R*)-*exo*-transition state TS-**28** or destabilization of other transition states such as TS-**27** in the chiral *U-shaped* cavity of (*R*)-**12a**•2B$(C_6F_5)_3$ (Figure 6b). Since C_2-symmetric norbornadienes are very important chiral ligands for asymmetric Rh(I)- and Ir(I)-catalysis,[39] a concise synthesis of Hayashi's representative diene ligand **30**[40] was demonstrated (Figure 6c). Optically active DA product **26d** (including 6% of **25d**) reacted with PhMgCl and then acetyl chloride to give **29** in 90% yield. Although compound **29** still involved **25d**-derived by products, subsequent deacetoxylation by Pd(0)-catalyzed reduction with formic acid and the purification could gave **30** in 75% yield with 97% ee. Overall, our method also could readily provide **30** from **7** and **21d**/**22d** without the use of corrosive and explosive trichlorosilane, which is part of the original and improved synthesis of **30** in 4–9 steps from norbornadiene (see the SI, pages S67–S69).[40,41]

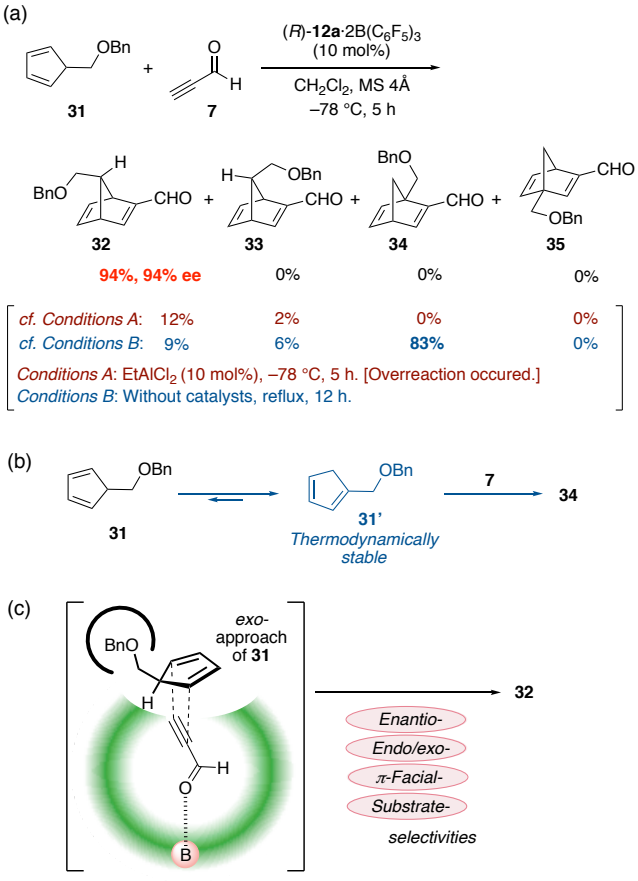


Figure 7. π-Facial selective DA reaction of with 5-alkyl-substituted cyclopentadiene **31**. (a) The DA reaction of **7** with **31** by using (*R*)-**12a**•2B$(C_6F_5)_3$. (b) Isomerization of **31** to **31'** under the thermal conditions. (c) Possible π-facial selective *exo*-approach of **31**.

Moreover, the π-facial selective DA reaction[42] of 5-alkyl-substituted cyclopentadiene **31** was also examined (Figure 7a, also see the SI, pages S71–S72). Unlike previous **21**/**22**, **31** could be available without isomerization at low temperature (less than 0 °C), and we could carefully use pure **31**. From sterically less-hindered **7**, unlike acrolein **2b**, the other π-facial-adduct (±)-**33** was obtained along with the expected (±)-**32** under $EtAlCl_2$ or thermal reaction conditions. At that time, compound (±)-**34** was also obtained due to isomerization to thermodynamically stable **31'** (Figure 7b). In contrast, **32** was exclusively obtained in 94% yield with 94% ee with the use of (*R*)-**12a**•2B$(C_6F_5)_3$. The remarkable π-facial selectivity as well as enantio-, *endo/exo*-, and substrate-selectivities might be reasonably considered by the possible transition state model with the chiral *U-shaped* catalyst as shown in Figure 7c.

We next tried to apply the catalysis to 1- or 2-alkyl-substituted cyclohexadienes **36** and **37** (Figure 8, also see the SI, pages S82–S87). Unlike 1-/2-alkyl-substituted cyclopentadienes **21**/**22**, **36** and **37** can be separated from each other. As control experiments using **7** and 2-alkyl-substituted cyclohexadienes **36**, (±)-**38** with adequate orbital coefficients rather than (±)-**39** with inadequate orbital coefficients were exclusively obtained under thermal conditions without any catalysts (Figure 8a). In contrast, the use of achiral Lewis acid catalysts, such as BF_3•Et_2O, $B(C_6F_5)_3$, and $EtAlCl_2$, could promote the reaction of **7** with **36** but gave a complex mixture. In such a situation, (*R*)-**12a**•2B$(C_6F_5)_3$ was still effective, and **38** were obtained with high enantio-, *endo/exo*-, regio-, and substrate-selectivities. Next, 1-alkyl-substituted cyclohexadienes **37** were also examined. As control experiments, (±)-**40** with adequate orbital coefficients were exclusively obtained under thermal conditions without any catalysts (Figure 8b). As other control experiments, the use of $EtAlCl_2$ gave both 1st DA-adducts (±)-**40** (major) and (±)-**41** (minor), whereas the use of BF_3•Et_2O or $B(C_6F_5)_3$ gave a complex mixture. In sharp contrast, **41** with inadequate orbital coefficients was selectively obtained with enantio-, *endo/exo*-, regio-, and substrate-selectivities, particularly with the use of another finely optimized *U-shaped* catalyst (*R*)-**12b**•2B$(C_6F_5)_3$. In both reactions of **36** and **37**, steric constraints of these substrates in the chiral *U-shaped* cavity might be reasonably considered for the possible transition states as shown in Figures 8c and 8d.

Furthermore, we examined the site- and regioselective DA reaction of triene **42**, which has two DA reaction sites due to the additional 3-vinyl moiety (Figure 9a, also see the SI, pages S97–S101). As control experiments, the reaction of **7** with **42** with the use of promising $EtAlCl_2$ gave a complex mixture, whereas (±)-**43** and (±)-**45** with both adequate orbital coefficients were obtained in respective yields of 50% under thermal conditions without catalysts. In sharp contrast, with the use of (*R*)-**12b**•2B$(C_6F_5)_3$, novel tetrahydronaphthalene **45** was multiselectively obtained in 94% yield with 97% ee without the generation of **43**, **44**, **46**, nor other byproducts. Moreover, we examined tetraene **47** with 2,3-divinyl moieties (Figure 9b, also see the SI, pages S107–S111), which showed similar results under the control reaction conditions. Remarkably, in the presence of (*R*)-**12b**•2B$(C_6F_5)_3$, **49** was obtained in 97%

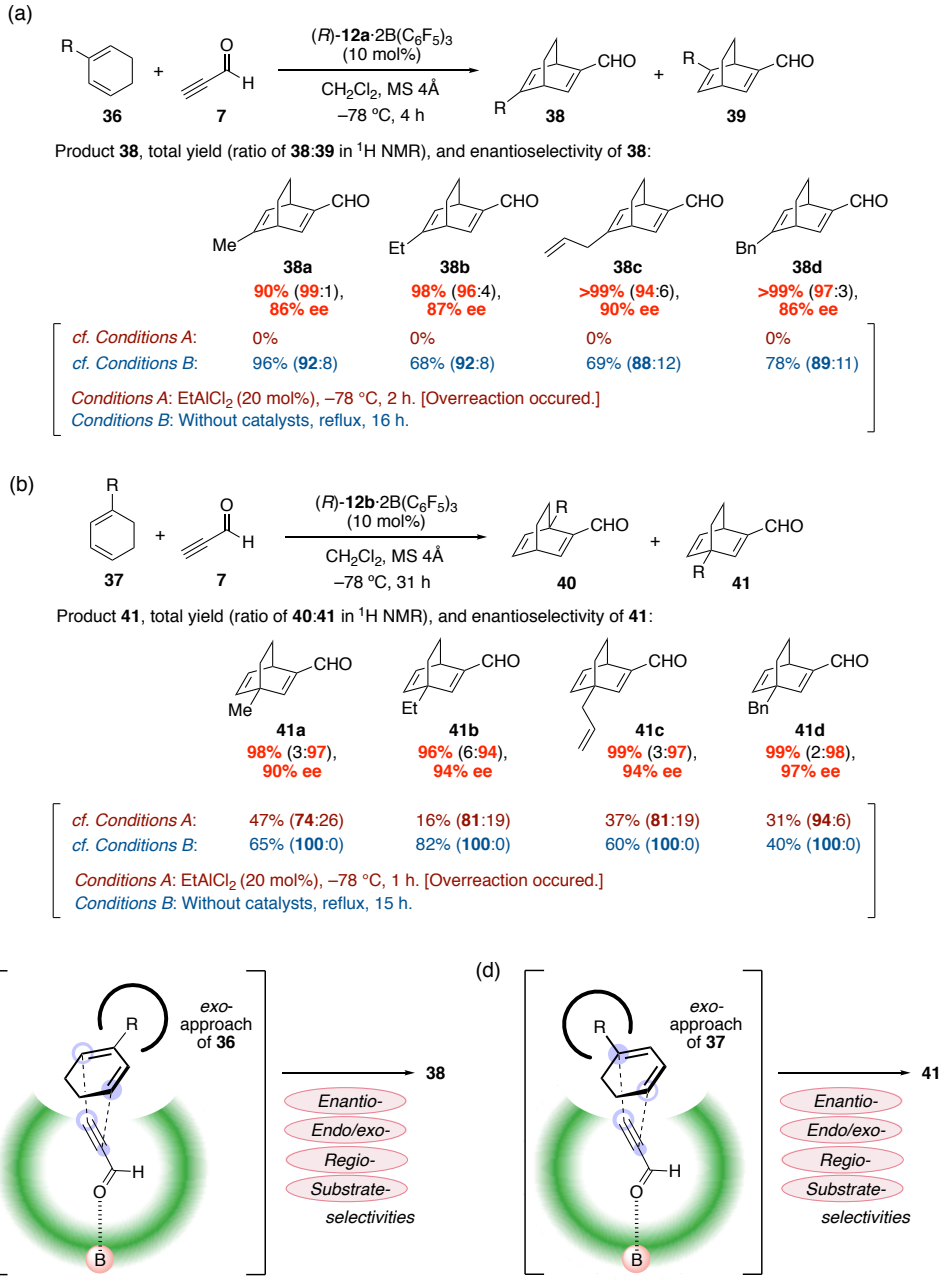


Figure 8. Regioselective DA reaction with 2- or 1-alkyl-substituted cyclohexadienes **36** and **37**. (a) The DA reaction of **7** with 2-alkyl-substituted cyclohexadienes **36** by using (*R*)-**12a**•2B(C_6F_5)$_3$. (b) The DA reaction of **7** with 1-alkyl-substituted cyclohexadienes **37** by using (*R*)-**12b**•2B(C_6F_5)$_3$. (c) Possible *exo*-approach of **36**. (d) Possible *exo*-approach of **37** regardless the less-favored orbital coefficients (see the Supporting Information).

yield with 95% ee. Since the observed preference for **45** or **49** over other compounds cannot be explained by the substrate-dependant orbital theory alone, the possible chiral cavity of the *U-shaped* catalyst might preferentially induce these remarkable enantio-, *endo/exo*-, regio-, site-, and substrate-selectivities (Figure 9c).

Finally, we considered preliminary theoretical calculations involving the possible geometry of the supramolecular catalyst (*R*)-**12a**•2B(C_6F_5)$_3$ as a working model. A chiral *U-shaped* cavity is assumed due to the six bulky and dynamic C_6F_5 moieties, and the two C=O•••B(C_6F_5)$_3$ moieties could have a *syn*-conformation. As expected above, the geometry of *syn*-(*R*)-**12a**•2B(C_6F_5)$_3$•**7** was much more stable than *anti*-(*R*)-**12a**•2B(C_6F_5)$_3$•**7** by using a semi-empirical method AM1 (see the SI, page S117). In these intermediates, the formyl moiety of **7** was doubly coordinated with the B-O(Naph) moiety at the C(=O)*H* and C(=*O*)H parts. Based on these results, we further optimized the intermediates before and after the transition states, such as *syn*-(*R*)-**12a**•2B(C_6F_5)$_3$•**7** and *syn*-(*R*)-**12a**•2B(C_6F_5)$_3$•**8**, with the DFT method (B3LYP/6-31G*), and the results are summarized in Figure 10 (also see the SI, page S117–S119). The average of the five shortest distances between F atoms of the two different B(C_6F_5)$_3$ moieties is 6.498 Å in *syn*-(*R*)-**12a**•2B(C_6F_5)$_3$•**7** and 7.117 Å in *syn*-(*R*)-**12a**•2B(C_6F_5)$_3$•**8**. Accordingly, the virtual bore size of the

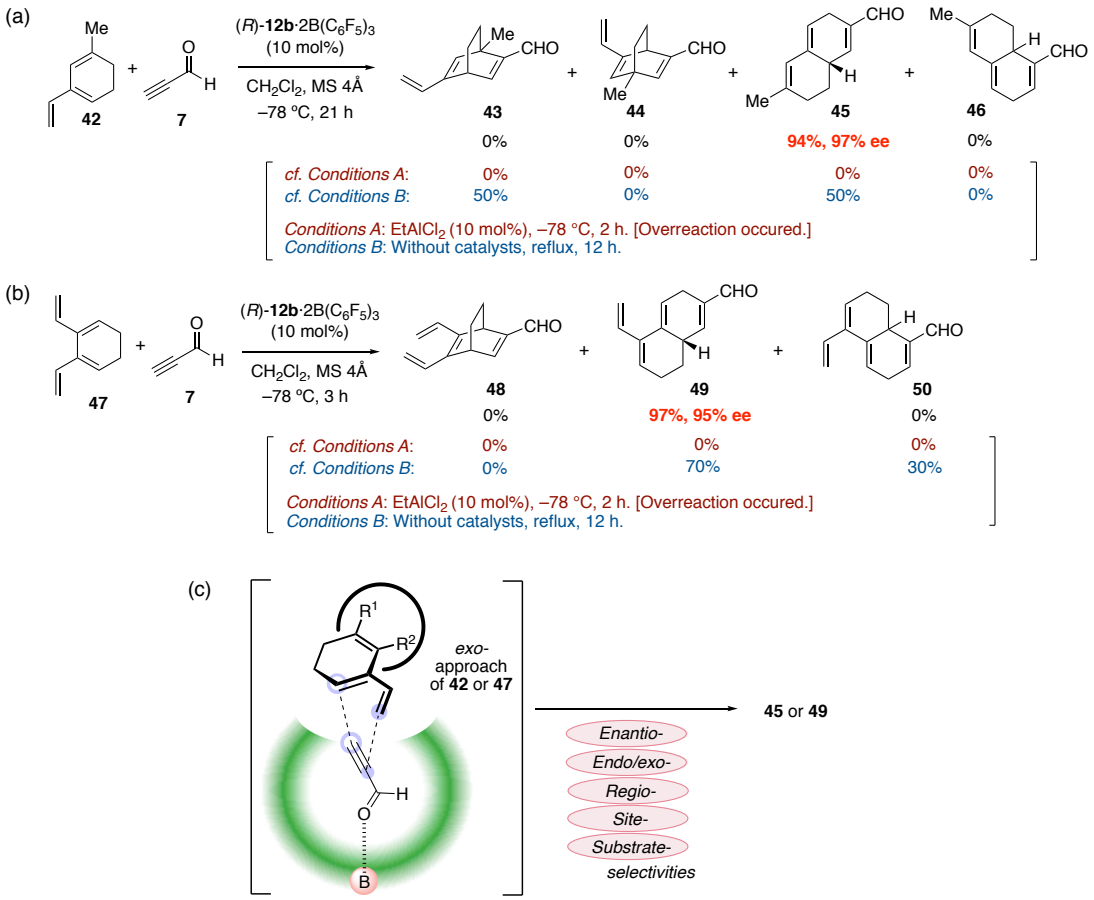


Figure 9. Site- and regioselective DA reaction with cyclohexadiene-derived triene and tetraene. (a) The DA reaction of **7** with triene **42** by using (*R*)-**12b**•2B(C_6F_5)$_3$. (b) The DA reaction of **7** with tetraene **47** by using (*R*)-**12b**•2B(C_6F_5)$_3$. (c) Possible *exo*-approach of **42** or **47** due to the cavity's steric controls.

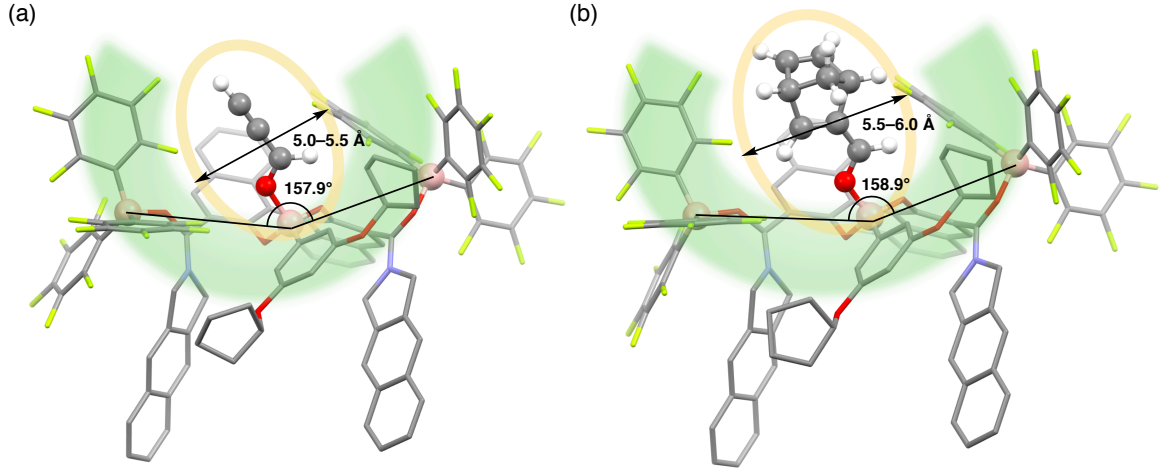


Figure 10. DFT calculations of possible key intermediates. (a) *syn*-(*R*)-**12a**•2B(C_6F_5)$_3$•**7**. (b) *syn*-(*R*)-**12a**•2B(C_6F_5)$_3$•**8**. Hydrogen atoms of the catalyst are omitted for clarity.

cavity of *syn*-(*R*)-**12a**•2B(C_6F_5)$_3$•**8** (ca. 5.5–6.0 Å) is larger than that of *syn*-(*R*)-**12a**•2B(C_6F_5)$_3$•**7** (ca. 5.0–5.5 Å). Moreover, the angle of B–B–B (158.9°) in *syn*-(*R*)-**12a**•2B(C_6F_5)$_3$•**8** is slightly larger than the angle (157.9°) in *syn*-(*R*)-**12a**•2B(C_6F_5)$_3$•**7**. The observed differences of the bore size in these calculated intermediates might possibly include expansion and contraction of the cavity, which might be featured by our conformationally flexible supramolecular *U-shaped* catalysts.[43] As a result, the desired compounds can properly hold in the chiral cavity with the 'induced-fit function'. Actually, as shown above, our con-

formationally flexible chiral *U-shaped* cavity could avoid the undesired overreactions in the DA reactions of propargyl aldehyde **7**. In this regard, for example, the diameters of cylinder including each compound, such as **7** (2.0 Å), **8** (5.1 Å), **9** (6.9 Å), **10** (6.8 Å), and **11** (6.9 Å), might include a correlation to the cavity size of the catalyst (See the SI, page S121). In particular, since the 2nd DA-adducts **9**–**11** would be too large and mismatched to the present cavity, the related transition states toward these compounds would be disfavored. Although these preliminary theoretical study may somewhat help considering the reaction mechanism for extraordinary multiselectivity using the present supramolecular *U-shaped* catalysts,[44] further investigations must be necessary to full understanding particularly the possible transition states. A continuous study for the comprehensive mechanistic investigations is underway.

CONCLUSION

Despite remarkable developments in the field of asymmetric catalysis, there are still many difficulties that are beyond the reach of current synthetic technology in organic chemistry. We have developed here a new synthetic method based on the supramolecular technology with conformationally flexible chiral supramolecular *U-shaped* catalysts particularly for the enantio-, *endo*/*exo*-, π-facial, regio-, site-, and substrate-selective Diels–Alder reactions of propargyl aldehyde with various cyclic dienes, triene, and tetraene. We hope that the results presented here might partially contribute the development of artificial enzyme-like supramolecular catalysts for multiselective reactions, which will be able to target organic compounds that have thus far eluded synthesis.

EXPERIMENTAL SECTION

Representative procedure of the DA reaction (0.50 mmol scale of 7): A pale brown solution of the chiral (*R*)-Ar_2-BINOL ligand (33.8 mg, 0.050 mmol) and 3,5-bis(cyclopentyl)phenylboronic acid (14.5 mg, 0.050 mmol) in dichloromethane (1 mL), THF (0.15 mL), and water (9 μL, 0.50 mmol) was stirred at room temperature for 12 h in a Pyrex Schlenk tube under a nitrogen atmosphere. The volatiles were removed under reduced pressure, and powdered MS 4Å (250 mg, used as received commercially) was added. The drying agent MS 4Å was required to complete dehydrative preparation of (*R*)-**12a** and to prevent the release of $B(C_6F_5)_3$•H_2O due to competitive coordination with water. The resulting pale yellow solid was heated to 100 °C (bath temperature) under <5 Torr for 2 h. After the sample 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. The mixture was then cooled to −78 °C, and **7** (d = 0.915, 89% purity, 33.2 μL, 0.50 mmol) was added. Subsequently, freshly-distilled cyclopentadiene **1** (203 μL, 2.5 mmol) was added at −78 °C over 15 min. The resultant mixture was then stirred at −78 °C for 3 h. Triethylamine (0.5 mL) was poured into the reaction mixture at −78 °C to quench the reaction. The product mixture was purified by silica gel column chromatography (Kanto Chemical Co., Inc. 37560; eluent: pentane:Et_2O = 100:1 to 8:1). Solvents were carefully removed under 200 Torr at 15 °C by a rotary evaporator to give **8** (57.0 mg, 95% yield). The enantioselectivity of **8** was determined by HPLC analysis (90% ee, Daicel CHIRALPAK AS-H, *n*-hexane:*i*-PrOH = 9:1, 1.0 mL/min, t_R = 8.3 min ((1*R*,4*S*)-**8**, major), 12.3 min ((1*S*,4*R*)-**8**, minor). Compounds **9**, **10**, and **11** were also obtained as a mixture by the same silica gel column chromatography. The ratio of **9**:**10**:**11** was determined by ^{1}H NMR analysis [**9**: 9.72 ppm, **10**: 10.02 ppm, **11**: 9.42 ppm].

1 g scale DA reaction of 7 with 1 (Table 1, entry 4): A pale brown solution of the chiral (*R*)-Ar_2-BINOL ligand (405 mg, 0.60 mmol) and (3,5-bis(cyclopentyloxy)phenyl)boronic acid (174 mg, 0.60 mmol) in dichloromethane (12 mL), THF (1.8 mL), and water (108 μL, 6 mmol) was stirred at room temperature for 12 h in a Pyrex Schlenk tube under a nitrogen atmosphere. The volatiles were removed under reduced pressure, and powdered MS 4Å (2.50 g, used as received commercially) was added. The resulting pale yellow solid was heated to 100 °C (bath temperature) under <5 Torr for 2 h. After the sample was cooled to room temperature under a nitrogen atmosphere, tris(pentafluorophenyl)borane (614 mg, 1.2 mmol) and freshly-distilled dichloromethane (48 mL) were added under an argon atmosphere in a glove box. The pale brown mixture was stirred at room temperature for 1 h. The mixture was then cooled to −78 °C, and propargyl aldehyde **7** (d = 0.915, 85% purity) (835 μL, 12.0 mmol) was added. Subsequently, freshly-distilled cyclopentadiene **1** (5.04 mL, 60 mmol) was added at −78 °C over 30 min. The resultant mixture was stirred at −78 °C for 3 h. Triethylamine (2.0 mL) was poured into the reaction mixture at −78 °C to quench the reaction. Solvent (dichloromethane) was removed under 150 Torr at 25 °C by a rotary evaporator. The product mixture was purified by silica gel column chromatography (Kanto Chemical Co., Inc. 37560; eluent: pentane:Et_2O = 100:1 to 8:1). Solvents were removed under 200 Torr at 15 °C by a rotary evaporator to give **8** (1.37 g, 95% yield). The enantioselectivity of **8** was determined by HPLC analysis (90% ee) in the same procedure described above.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedure, characterization data, additional control experiments, copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds, and copies of HPLC/GC analysis to determine the enantio-purity (PDF).

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Notes

The authors declare no competing financial interest.

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(32) *Exo*-approach of dienes to the activated **7** should be required in the multiselective synthesis of **26**, **32**, **38**, **41**, **45**, and **49** as well as **8**, although how repulsive the disfavored HOMO-LUMO interactions has not yet been quantitative in the present study. The ultimate ee values through the enantioselective DA reaction of **7** should be affected by both enantio-facial selectivity of **7** and *endo/exo*-discrimination of dienes, and these involvements cannot be individually considered from the resulting ee value.

(33) Compound **8** is unstable particularly under acidic and/or moisture conditions. Other DA-adducts in the present report, such as **26**, **32**, **38**, **41**, **45**, and **49**, are also not so stable, but more stable than **8** at least.

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(43) Conformational flexibility of our catalyst should be considerably attributed to not only a rotation of 3,3'-substituents on the binaphthyl moiety (i.e., consecutive conformation favored *syn-* to disfavored *anti*-(*R*)-**12a**•2B(C_6F_5)$_3$) but also a rotation of the B(C_6F_5)$_3$ units on the O=C moieties. To evaluate the cavity expansion/contraction by these factors, further mechanistic approach by Monte Carlo simulations and/or calculation of related transition states, should be necessary.

(44) The observed multiselectivity in the present DA reactions to provide **8**, **26**, **32**, **38**, **41**, **45**, and **49** might be partially addressed by the preliminary consideration of the result of the DFT-calculated intermediate *syn*-(*R*)-**12a**•2B(C_6F_5)$_3$•**7**. See the SI on detail (page S120).

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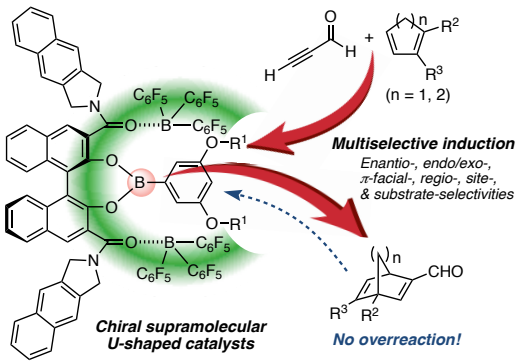

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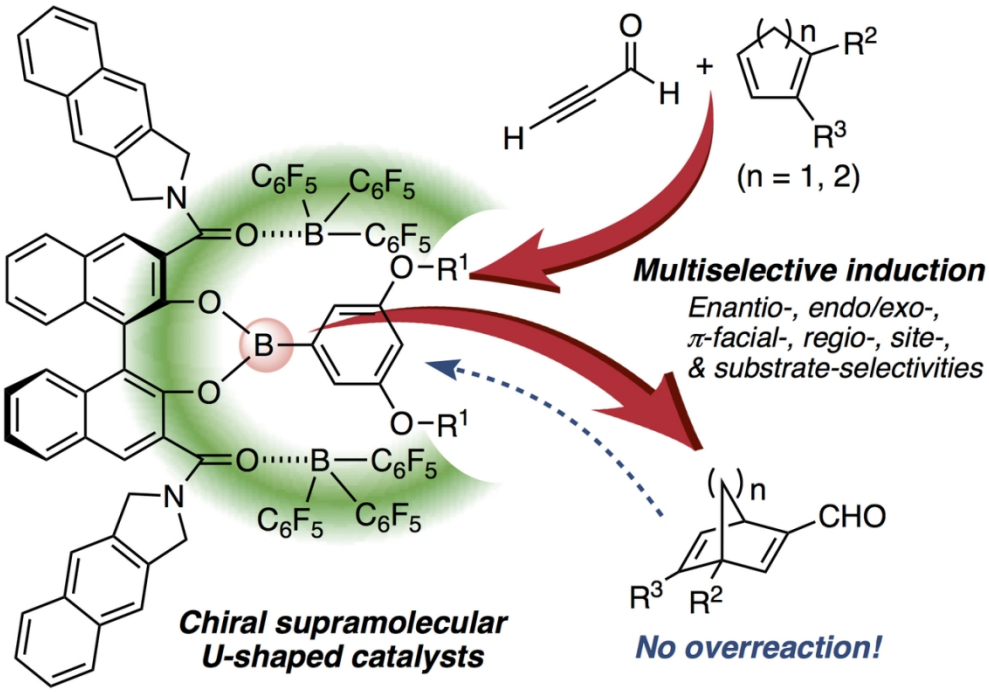

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