Brønsted Acid/Lewis Base Hybrid Complexes

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Abstract Recent progress on our Brønsted acid/Lewis base hybrid complexes in some asymmetric catalyses is reviewed. Based on the rational design of conjugated acid–base catalysts, tailor-made supramolecular catalysts can show remarkable catalytic activity and higher-ordered selectivities that cannot be realized by ready-made single molecule catalysts. The chiral supramolecular magnesium(II) binaphtholate complexes trigger the highly enantioselective 1,4-hydrophosphinylation and 1,2-hydrophosphonylation of α,β-unsaturated carbonyl compounds, direct Mannich-type reaction, and hetero-Diels–Alder reaction. Moreover, the advanced supramolecular catalysts are prepared *in situ* from chiral 3,3'-disubstituted binaphthols and biphenols, arylboronic acid, and $B(C_6F_5)_3$, for promoting the anomalous *endo*/*exo*-selective Diels–Alder reaction. The specific mechanism and deep in-

sights into the possible key intermediates are discussed on the basis of rational design of chiral supramolecular Brønsted acid/Lewis base hybrid catalysts as artificial enzymes.

Keywords acid–base catalyst • BINOL • boron • magnesium • supramolecular catalyst

Abbreviations

acac	acetylacetonate
BINOL	1,1'-bi-2-naphthol
Boc	*tert*-butoxycarbonyl
cod	cyclooctadiene
DABCO	1,4-diazabicyclo[2.2.2]octane
DMF	*N*,*N*-dimethylformamide
MS	molecular sieves
TBHP	*tert*-butyl hydroperoxide
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
Ts	toluenesulfonyl

1. Introduction

A natural enzyme with an induced-fit function is a wonderful tailor-made biocatalyst, which can control both activity and multi-stereoselectivities of a specific substrate for a specific organic reaction. The huge enzymes have 'key holes', which can lead only suitable substrates ('keys') into the deep active sites. On the other hand, small molecule catalysts in common organic reactions are much smaller than enzymes. Therefore, their key holes are too small and provide poor conformational flexibility. That is why we cannot expect the induced-fit function in those reactions with the use of conventional ready-made small molecule catalysts. However, these ready-made catalysts can often exhibit some excellent points depending on the kind of the desired organic reactions and substrates; they are easy to design and handle, practical, and versatile. For some previous periods, our study has focused on the rational design of conjugated acid–base catalysts (i.e., ready-made single molecule catalysts). Recently, however, our interest turned to the rational design of tailor-made supramolecular catalysts based on conjugated acid–base units. *'Supramolecule'* is simply defined by Lehn for the first time as *'Beyond molecular chemistry based on the covalent bond lies supramolecular chemistry based on molecular interactions–the associations of two or more chemical entities and the intermolecular bond'* [1]. Therefore, we envisioned that supramolecular catalysts, which are prepared *in situ* from already fine-tuned chiral conjugated acid–base units and achiral acid or base units at an appropriate molar ratio, can show unusual catalytic activity and higher-ordered selectivity that cannot be realized by single-molecule catalysts. Here we review our successive chal-

lenges of some asymmetric supramolecular catalyses by virtue of Brønsted acid/Lewis base hybrid complexes.

2. Chiral Supramolecular Magnesium(II) Binaphtholate Catalysts

2.1 General Properties of Magnesium(II) Binaphtholate Catalysts

Chiral BINOLs (1,1'-bi-2-naphthols) are some of the most versatile C_2-symmetric chiral ligands of metal complexes for both stoichiometric and catalytic asymmetric reactions [2]. In particular, parent (*R*)- and (*S*)-BINOL and (*R*)- and (*S*)-H_8-BINOL are commercially available as both enantiomers and are inexpensive in bulk quantities (Fig 1). For effective designs of monomeric metal species, *3,3'-disubstituted* binaphthyl skeletons in BINOL and H_8-BINOL are the most commonly accepted. In sharp contrast, chiral lithium(I) and magnesium(II) binaphtholates [3,4], which are usually prepared *in situ* from BuLi or Bu_2Mg and chiral *3,3'-non-substituted* BINOL or H_8-BINOL, are practical acid–base combination catalysts [5,6], since the ligands are the simplest and the metals are abundant, inexpensive, harmless, and environmentally benign. However, unsurprisingly, enantioselective induction with high catalytic activity is sometimes problematic, due to their oligomeric or polymeric nature. To avoid the aggregation of these complexes, not only the molar ratio of the metal ion and the BINOL ligand, but also the use of highly coordinative simple additives such as water and alcohols as cocatalysts is effective. Overall, suitable disaggregated active species would be provided *in situ* as monomers and/or combinations of monomers (i.e., supramolecules) *via* self-assembly.

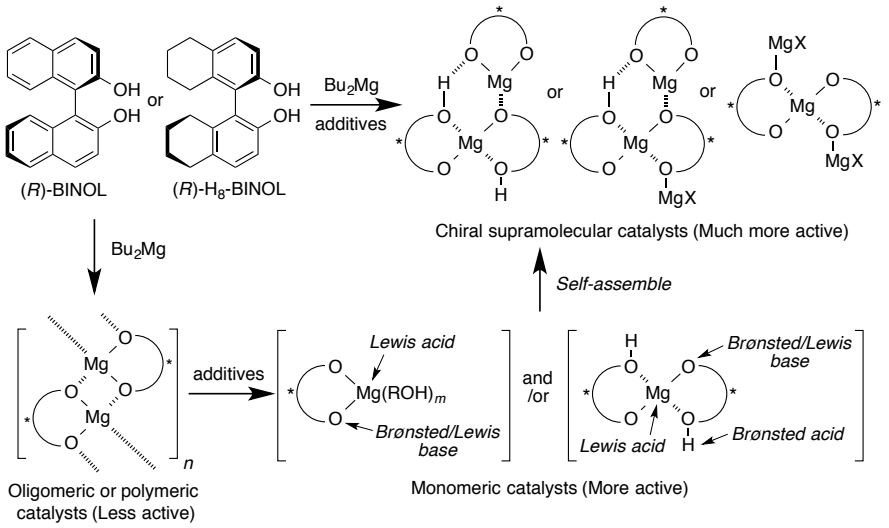


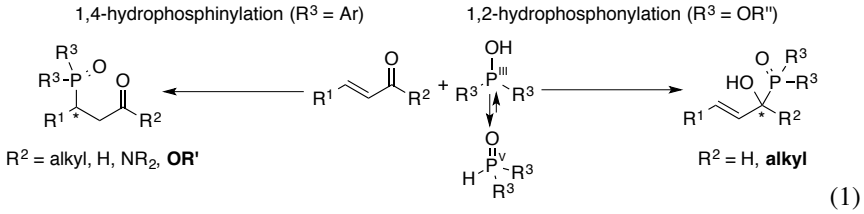
Fig. 1 *In situ* preparation of chiral magnesium(II) binaphtholates as cooperative Brønsted/Lewis acid–base catalysts

In this review, we focused on recent chiral supramolecular magnesium(II) binaphtholate complexes. In such catalysts, naphthoxide moieties would exhibit strong Brønsted/Lewis basicity, while Mg(II) centers would show inherent strong Lewis acidity. Also, the Lewis basic hydroxy group of BINOLs can increase the Brønsted acidity, since the Mg(II) center would be coordinated and effectively activate the hydroxy group. Due to such a diversity of the supramolecular structures of cooperative Brønsted/Lewis acid–base catalysts, conventional substituents at the 3,3'-positions in BINOL-skeleton would not be necessary.

2.2 Catalytic Enantioselective Addition of Phosphorus Nucleophiles to α,β-Unsaturated Esters and Ketones

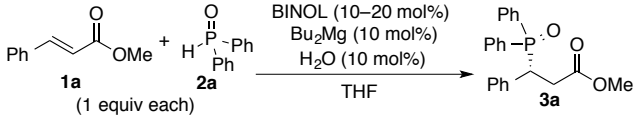
Chiral organophosphorus compounds show various biological activities due to their chemical properties, and thus are used in many pharmaceuticals as biophosphate mimics, antibiotics, antivirals, and antitumor agents [7]. Moreover, the corresponding chiral phosphine ligands for transition metal catalysts are also important [8]. In particular, the catalytic enantioselective addition of phosphorus nucleophiles is one of the most powerful synthetic methodologies for constructing functionalized organophosphorus compounds *via* phosphorus–carbon (P–C) bond-formation [9] (Eq. 1). In general, reactivity and regioselectivity of hydrophosphonylation and hydrophosphinylation strongly depend on substrates, solvents, temperature, etc. However, catalytic enantioselective 1,4-addition to α,β-unsaturated esters has not been reported, despite their importance in synthesis. Moreover, catalytic enantioselective 1,2-addition to ketones has been limited in a few examples

[10], unlike aldehydes and aldimines [11]. To overcome the difficulties in these undeveloped catalytic systems, catalysts must exhibit not only suitable Brønsted basicity to activate non-nucleophilic $R_2P(=O)H$ (major, valence +V) into nucleophilic R_2POH (minor, valence +III) [12], but also strong Brønsted or Lewis acidity to activate less-reactive substrates such as esters and ketones.



(1)

In this situation, Ishihara developed the enantioselective 1,4-hydrophosphinylation and 1,2-hydrophosphonylation of α,β-unsaturated carbonyl compounds with phosphorus nucleophiles by the use of chiral magnesium(II) binaphtholate complexes as cooperative Brønsted/Lewis acid–base catalysts [13]. At the beginning of the study, Ishihara investigated the enantioselective 1,4-hydrophosphinylation of methyl cinnamate (**1a**) with diphenylphosphine oxide (**2a**) in the presence of Bu_2Mg (10 mol%), (*R*)-BINOL (10–20 mol%), and H_2O (10 mol%) in THF at 0 °C (Scheme 1). As a result, the use of 15 mol% of (*R*)-BINOL gave **3a** with better enantioselectivity than the others. This result suggests that a 2:3 ratio of Mg(II)/(*R*)-BINOL might be more effective than a 1:1 or 1:2 molar ratio (i.e., Mg(II)((*R*)-BINOLate) and Mg(II)((*R*)-BINOLate)$_2$ respectively, in Fig. 1). (*R*)-H_8-BINOL in place of (*R*)-BINOL increased the catalytic activity, and the reaction proceeded smoothly even at –40 °C with high enantioselectivity (95% ee). Water is essential to induce the catalytic activity [3c,3d,4e], since water would promote the dissociation of oligomeric magnesium(II) species into monomeric ones.

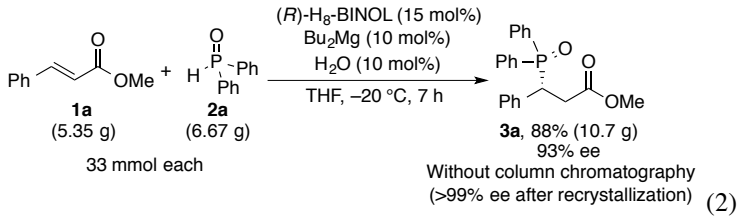


BINOL (mol%)	temperature (°C)	time (h)	yield (%)	ee (%)
(*R*)-BINOL (10)	0	22	81	80
(*R*)-BINOL (15)	0	22	76	85
(*R*)-BINOL (20)	0	22	52	82
(*R*)-H_8-BINOL (15)	–40	16	91	95
(*R*)-BINOL (15)	0	22	38	60

Scheme 1 Optimization of catalysts in 1,4-hydrophosphinylation

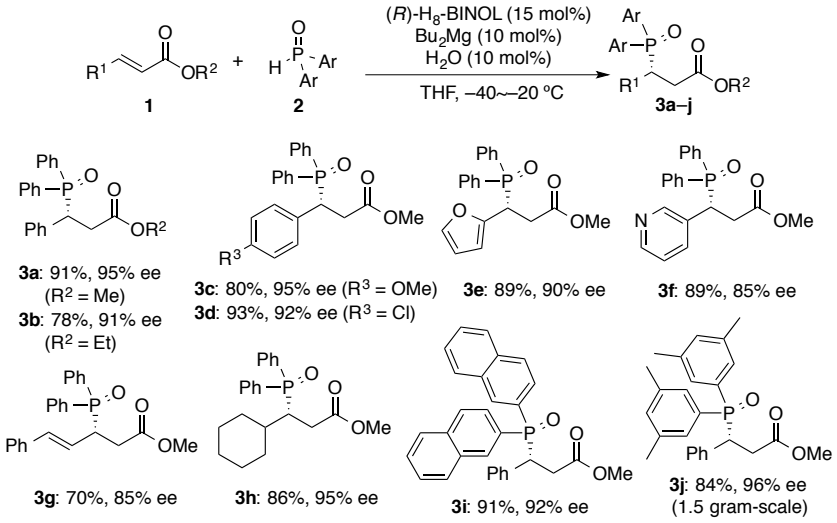
To show the synthetic potential of the present approach, >10 gram-scale synthesis of **3a** was performed (Eq. 2). Since **3a** was highly crystalline, **3a** was crystal-

ized in crude mixture by ether in 88% yield (10.7 g) with 93% ee without silica gel column chromatography. Furthermore, recrystallization of the powdered **3a** from chloroform gave the single crystal (>99% ee).



(2)

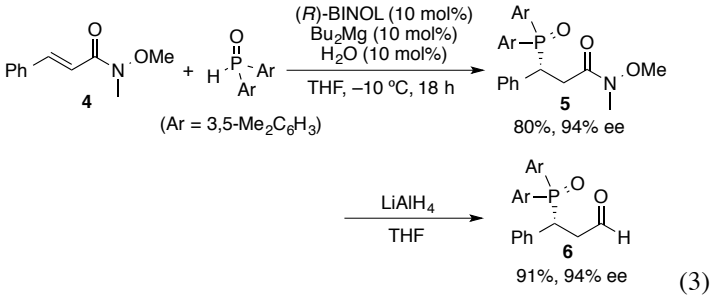
With the optimized reaction conditions in hand, the unprecedented 1,4-hydrophosphinylation of methyl and ethyl cinnamates with diarylphosphine oxides was examined [13] (Scheme 2). For a variety of α,β-unsaturated esters with an aryl moiety (**3a**–**d**), a heteroaryl moiety (**3e** and **3f**), a conjugated olefin (**3g**), and an alicyclic moiety (**3h**), the corresponding 1,4-adducts were exclusively obtained with 85–95% ee. Moreover, sterically demanding diarylphosphine oxides could be used, and the corresponding 1,4-adducts (**3i** and **3j**) were obtained with 92% ee and 96% ee, respectively, even in gram-scale synthesis.



Scheme 2 1,4-Hydrophosphinylation of methyl cinnamates with diarylphosphine oxides

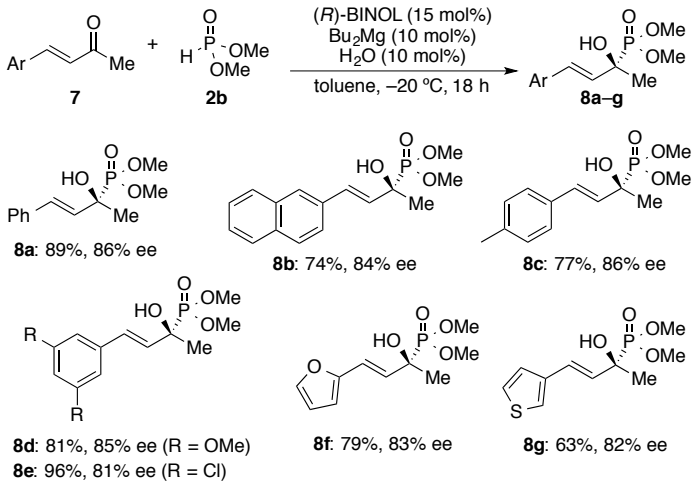
Synthetically useful Weinreb amide **4** was also applicable, and the corresponding 1,4-adduct **5** was obtained in 80% yield with 94% ee [13] (Eq. 3). Since compounds **4** and **5** are highly chelatable to Mg(II), the use of 10 mol% each of (*R*)-BINOL and Bu_2Mg exhibited good reactivity. A transformation of **5** to aldehyde

6, which is usually difficult to synthesize directly by hydrophosphinylation, was readily achieved with the treatment of $LiAlH_4$ without epimerization.



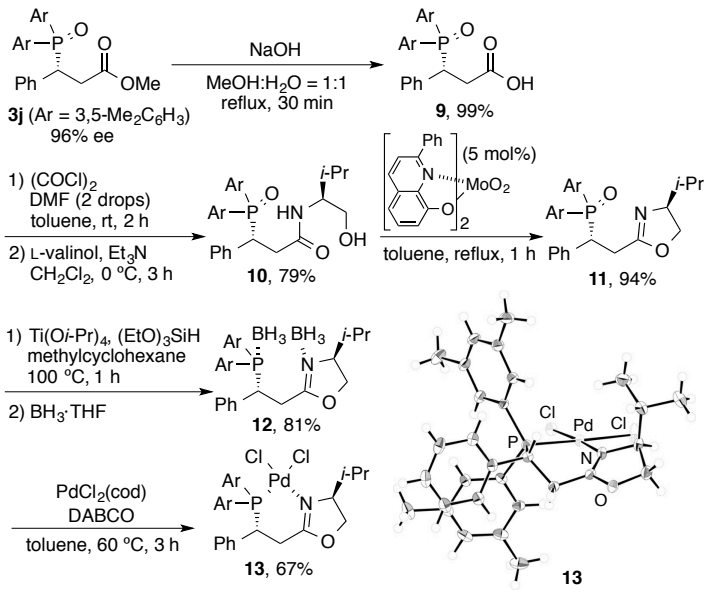
(3)

Despite the strong dependence for regioselectivity (1,2- vs. 1,4-) on substrates, solvents, and catalysts, Ishihara developed a 1,2-hydrophosphonylation of unreactive α,β-unsaturated ketones in the presence of almost the same catalyst [13] (Scheme 3). While the 1,4-hydrophosphinylation with (*R*)-H_8-BINOL/Bu_2Mg/H_2O = 3:2:2 (10 mol%/Mg(II)) in THF at –40 °C, the use of (*R*)-BINOL/Bu_2Mg/H_2O = 3:2:2 (10 mol%/Mg(II)) in toluene at –20 °C was effective in 1,2-hydrophosphonylation of benzalacetones (**7**) and dimethyl phosphite (**2b**). Both aromatic and heteroaromatic benzalacetones **7** were acceptable, and the corresponding novel optically active tertiary allylic alcohols (**8a–g**) were obtained with good to high enantioselectivities without the possible phospha-Brook rearrangement and/or retro-reaction [14]. The products were highly crystalline, and recrystallization from ethanol increased the optical purity (91~>99 % ee) without any serious loss of yield.



Scheme 3 1,2-Hydrophosphonylation of benzalacetones with dialkyl phosphites

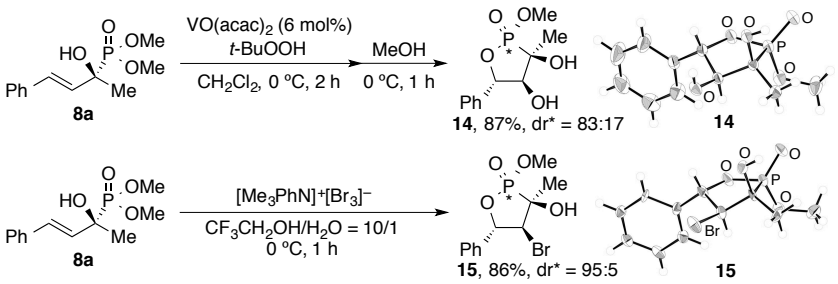
By taking advantage of the synthetic utility of esters [15], a chiral palladium(II) complex was synthesized from optically active 1,4-adduct **3j**, since chiral PN-ligand is one of the most important applications of organophosphorous compounds [13] (Scheme 4). After hydrolysis and amidation with L-valinol, the oxazoline moiety was synthesized in 94% yield without epimerization when bulky bis(7-phenylquinolinolate)dioxomolybdenum(IV) complex was used as a dehydrative cyclization catalyst [16]. This method is important, since $MoO_2(acac)_2$ induced epimerization (74% de) with low reactivity (38% yield), and basic conditions using $MsCl/Et_3N$ were much less effective (<5% yield). Eventually, the reduction of phosphine oxide, followed by treatment with BH_3·THF, resulted in diborane complex **12** in 81% yield as a stable ligand precursor. Finally, decomplexation of the BH_3-complex by DABCO and recomplexation *in situ* with $PdCl_2(cod)$ gave the desired chiral PN-ligand-Pd(II)Cl_2 complex **13** in 67% yield, which could be analyzed by X-ray diffraction. The bulkiness in the PN-ligand with three sterically-demanding aryl backbones could be rewarding for asymmetric transition metal catalyses.



Scheme 4 Synthesis of a chiral palladium(II) complex with a PN ligand

Since the obtained 1,2-adducts are functionalized tertiary allylic alcohols, an oxidative transformation of **8a** was conducted *via* diastereoselective epoxidation with TBHP and $VO(acac)_2$ [13] (Scheme 5). Moreover, bromocyclization of **8a** with $[PhMe_3N]^+[Br_3]^-$ gave the desired cyclized compound **15** in 86% yield with 95:5 diastereoselectivity. These novel five-membered oxaphospholanols **14** and

15 are analogues of bioactive materials with anticholinesterase properties [17], and the relative configurations of the four successive stereogenic centers (C-C-C-P) were determined by X-ray diffraction analysis.



Scheme 5 Synthesis of optically active cyclic oxaphospholanols

According to the established mechanistic study by Shibasaki [18], Ishihara investigated the positive non-linear effect in 1,4-addition between **1a** and **2a** and the initial rate kinetic study, so that three (*R*)-H_8-BINOLs and two Mg(II) centers would be involved in the transition states. Moreover, ESI-MS analysis of the mixture of Bu_2Mg, (*R*)-H_8-BINOL, and H_2O (2:3:2 molar ratio) in THF showed 1:1 and 1:2 complexes of Mg(II)/(*R*)-H_8-BINOLate (Fig. 2). Overall, a correlation of cooperative 2:3 complex of Mg(II)/(*R*)-H_8-BINOLate might be strongly suggested [19], since the 2:3 complex might be supramolecularly constructed from the directly observed 1:2 and 1:1 complexes *in situ*. In a possible transition state, nucleophile **2** would be activated by the highly Brønsted basic naphthoxide moiety, and then electrophile **1** or **7** would be activated by the associated Brønsted acid moiety of the naphthol. In this transition state, the absolute stereochemistry of **3** or **8** with high enantioselectivity can be rationalized due to the significant steric hindrance of the congested naphthyl moieties even if 3,3'-nonsubstituted BINOLs are used.

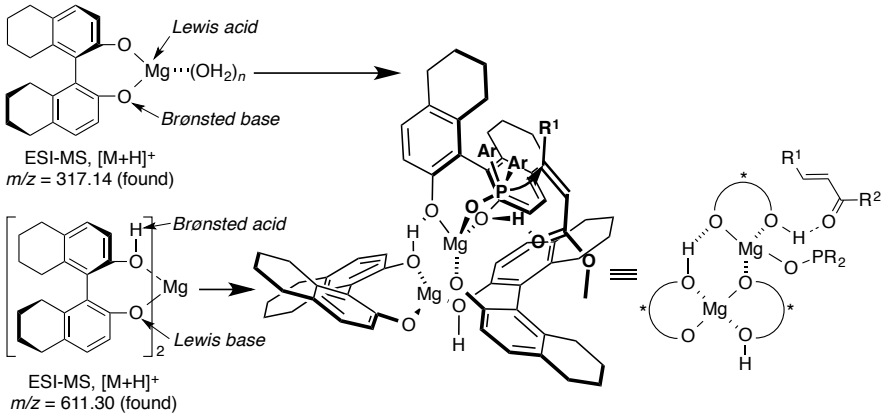
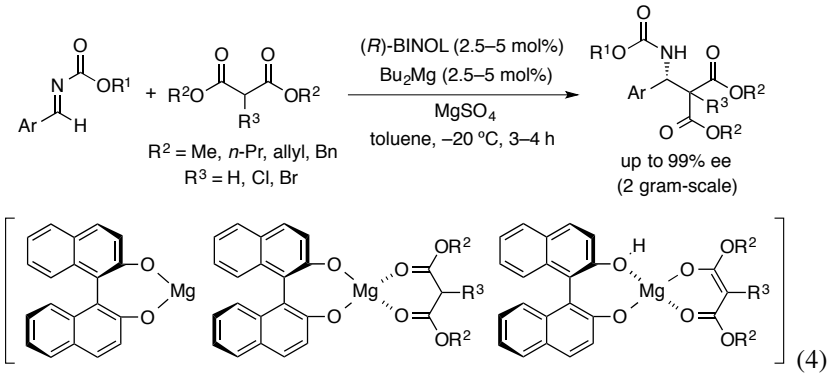


Fig. 2 ESI-MS analysis and possible transition state

2.3 Catalytic Enantioselective Direct Mannich-Type Reaction

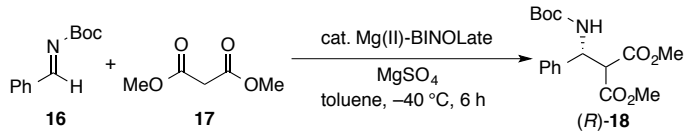
Ishihara has already developed the direct Mannich-type reaction between aldimines and dialkyl malonates [4d,4e] (Eq. 4). In that report, they assumed the presence of some disaggregated mononuclear 1:1 complexes of Mg(II)/(*R*)-BINOLate, since the catalyst was prepared *in situ* from 1:1 molar ratio of Bu_2Mg and (*R*)-BINOL. However, a 1:1 complex of Mg(II)/BINOLate is too simple to explain the possible asymmetric field to induce high enantioselectivities of over 90% ee. Therefore, the presence of other higher ordered magnesium(II) complexes (e.g., di- or trinuclear magnesium(II) complexes) would not be completely ruled out.



(4)

Actually, the further careful investigation of the reactions, they found that a negative non-linear relationship was observed between (*R*)-BINOL and the products [20]. Moreover, after the further optimization of the catalysts, a 2:3 ratio of Mg(II)/(*R*)-BINOL gave better results than a 1:1 ratio of Mg(II)/(*R*)-BINOL as the

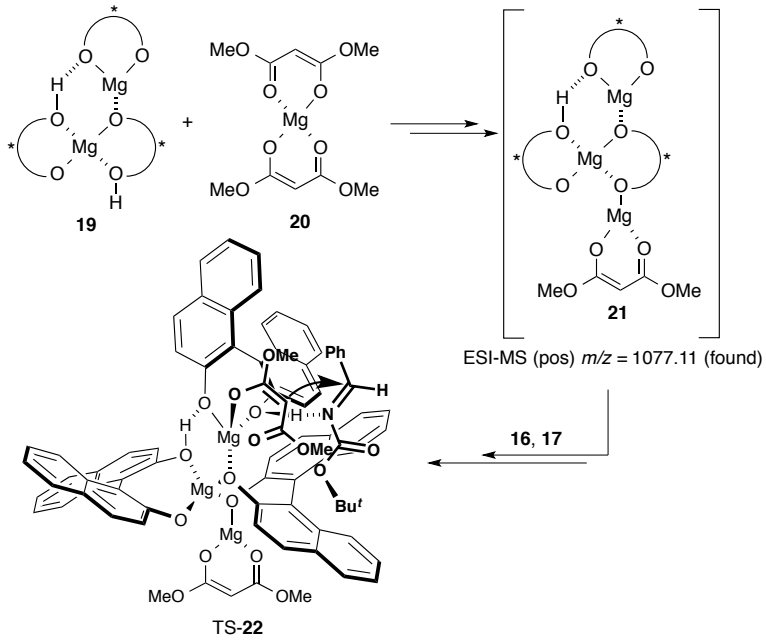
original optimal catalyst (Eq. 5). Therefore, it is possible that the expected chiral supramolecular 2:3 complexes of Mg(II)/(*R*)-BINOLate (**19**) or similar supramolecular complexes might be involved in this reaction.



16 **17** (*R*)-**18**

Bu_2Mg (5 mol%)/(*R*)-BINOL (5 mol%): 98%, 92% ee
Bu_2Mg (5 mol%)/(*R*)-BINOL (7.5 mol%): 99%, 95% ee (5)

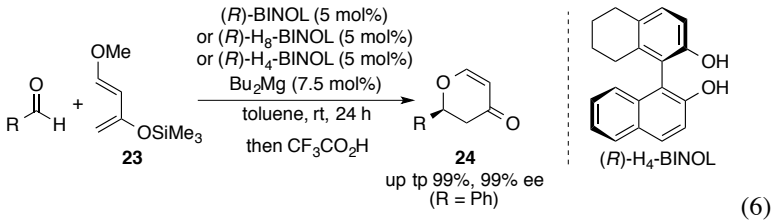
To support the assumption regarding possible supramolecules, ESI-MS analysis of a mixture of (*R*)-BINOL, Bu_2Mg, and **17** (1:1:20 molar ratio) showed a peak at *m*/*z* = 1077.11 as the 3:3:1 complex of Mg(II)/(*R*)-BINOLate/malonate (**21**) [20] (Scheme 6). This 3:3:1 complex **21** would be based on a 2:3 complex of Mg(II)/(R)-BINOLate (**19**) and magnesium(II) dimethyl malonate (**20**). The corresponding transition state TS-**22** might explain the (*R*)-absolute stereochemistry of **18**. Nucleophile **17** would be activated by the Brønsted basic naphthoxide moiety, and then electrophile **16** would be activated by the associated Brønsted acid moiety of the naphthol. Overall, in the case of the direct Mannich-type reaction, the chiral supramolecular 3:3:1 complex of Mg(II)/(*R*)-BINOLate/malonate (**21**) would be likely rather than the originally-expected 1:1 complexes of Mg(II)/(*R*)-BINOLate in Eq. 4.



Scheme 6 Possible chiral supramolecular catalyst in direct Mannich-type reaction

2.4 Catalytic Enantioselective Hetero-Diels–Alder Reaction

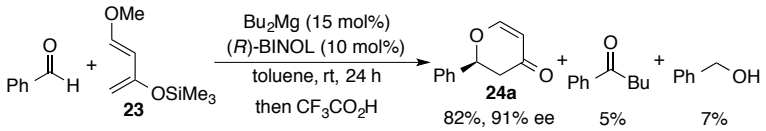
As another example of magnesium(II) binaphtholate-catalysis, Ding has already reported the hetero-Diels–Alder reaction of aldehydes with Danishefsky's diene (**23**) [4c] (Eq. 6). Aggregation behavior of the catalysts was observed by ^{1}H NMR study and a positive non-linear effect of the reaction. Totally, they concluded that the active site of the catalysts would be the chain ends of the zigzag-aggregated chiral magnesium(II) binaphtholates.



(6)

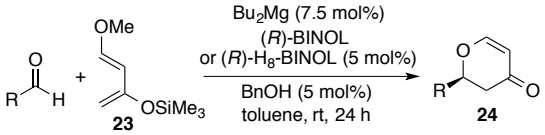
With the interest of a supramolecular approach, Ishihara examined the same reaction of benzaldehyde and **23**. However, the yield and enantioselectivity were not reproducible at the beginning. After the careful investigation, Ishihara found that valerophenone (5% yield) and benzyl alcohol (7% yield) were obtained in addition to **24a** (82% yield and 91% ee) [20] (Eq. 7). Valerophenone and benzyl alcohol

might be generated by the Oppenauer-type oxidation of 1-phenyl-1-pentanol and benzaldehyde.



(7)

Therefore, Ishihara used benzyl alcohol in advance as an additive (10 mol%) in the reaction. As a result, the reaction proceeded smoothly, and **24a** was obtained in 90% yield with 93% ee, even when 5 mol% of catalysts were used [20] (Eq. 8).

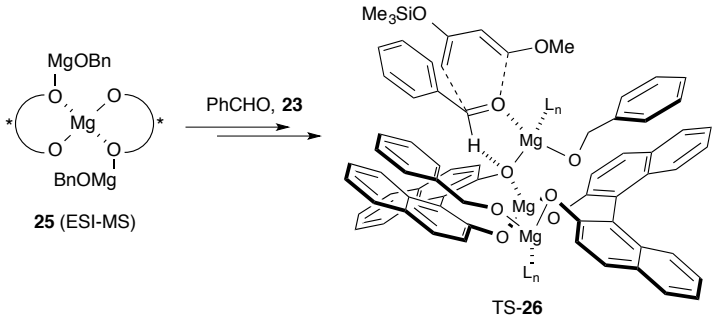


90%, 93% ee (R = Ph, with (*R*)-BINOL)
93%, 96% ee (R = $PhCH_2CH_2$, with (*R*)-H_8-BINOL)
72%, 96% ee (R = *n*-C_5H_{11}, with (*R*)-H_8-BINOL)
47%, 97% ee (R = *c*-C_6H_{13}, with (*R*)-H_8-BINOL)

(8)

This supramolecular approach (*vide infra*) was effective for not only benzaldehyde but also aliphatic aldehydes, which have not yet been well developed in the asymmetric hetero-Diels–Alder reaction among many research groups [21] (Eq. 8). For dihydrocinnamaldehyde, which is the sole aliphatic aldehyde in Ding's report (up to 80% ee) [4c], the corresponding product was obtained in 93% yield with greatly improved enantioselectivity (96% ee) in the presence of benzyl alcohol. Moreover, hexanal and cyclohexanecarboxaldehyde gave the corresponding products in 16% and 17% yields, respectively, in the absence of benzyl alcohol. In sharp contrast, the corresponding products were obtained in remarkably improved yields (72% and 47%, respectively) with high enantioselectivity (96% ee and 97% ee, respectively).

The ESI-MS analysis showed a peak at m/z = 945.32, which should be identified as trinuclear supramolecular magnesium(II) complex **25** (*vide supra*) [20] (Scheme 7). Complex **25** might be based on the rigid ((*R*)-BINOLate)$_2$Mg core structure, which can ionically bind two MgOBn moieties. Although other candidates still can be considered to be active species under our reaction conditions, a plausible transition state (TS-**26**) can promote the *si*-face attack of benzaldehyde to lead to the (*S*)-product (**24a**). Probably, benzyl alcohol and/or benzyloxy moieties might keep on coordinating to the Mg(II) centers and help preventing the supramolecular catalysts from being further assembled.



Scheme 7 Possible chiral supramolecular catalyst in hetero-Diels–Alder reaction

3. Chiral Supramolecular Boron(III) Binaphtholate Catalysts

3.1 General Properties of Diels–Alder Reaction

The Diels–Alder reaction is one of the most fundamental higher-ordered stereoselective reactions that involve the formation of two carbon–carbon bonds [22]. Via [4 + 2] cycloadditions, the efficient formation of a cyclohexane skeleton with four successive chiral carbon centers offers synthetic versatility particularly in the total synthesis of many complex natural products [22]. In fact, in several studies to date, enantioselectivity in the Diels–Alder reaction has been successfully controlled by a variety of chiral catalysts or chiral auxiliaries in substrates. On the other hand, *endo*/*exo*-selectivity in the Diels–Alder reaction strongly depends on the substrates, based on the Woodward–Hoffmann rule and Fukui's conservation rule of orbital symmetry interactions and steric interactions between dienes and dienophiles via the formation of [4 + 2] pericyclic transition states under thermodynamic or photoreaction conditions [23] (Fig. 3).

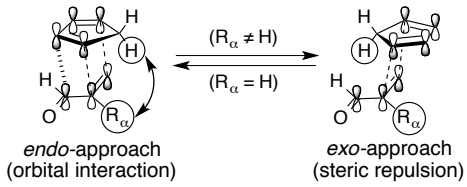


Fig. 3 Substrate-controlled *endo*/*exo*-selectivity

Therefore, it is quite difficult to control not only enantioselectivity but also substrate-independent anomalous *endo*/*exo*-selectivity, since most conventional chiral catalysts can discriminate the enantiofaces of dienophiles, but not the approach of

dienes [22] (Fig. 4). In fact, many combinations of dienes with dienophiles, particularly α,β-unsaturated carbonyl compounds, allow a well-known *endo*-rule that is based on second-order orbital interactions (Fig. 4a). However, when steric interactions between dienes and dienophiles overcome the second-order orbital interactions in *endo*-transition states, less-familiar *exo*-adducts are often predominantly obtained against the *endo*-rule (Fig. 4b).

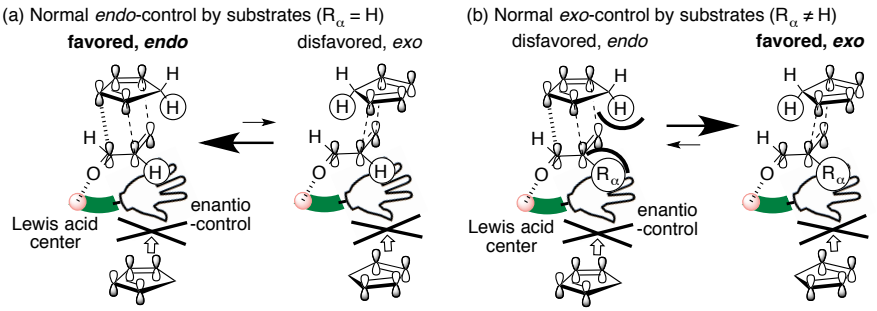
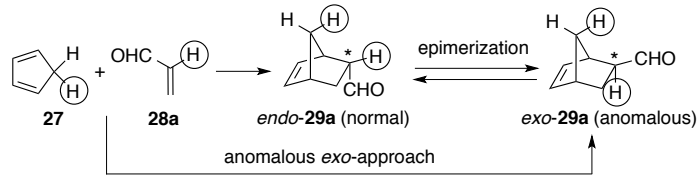


Fig. 4 Normal *endo*/*exo*-selectivity with conventional chiral catalysts

For example, in the reaction between cyclopentadiene (**27**) and acrolein (**28a**), an *endo*-preference is observed with regard to second-order orbital interactions without significant steric interactions (Eq. 9). In sharp contrast, in the reaction between **27** and methacrolein (**28b**), an *exo*-preference is observed with regard to steric interaction between the methylene moiety of **27** and the methyl moiety of **28b** (Eq. 10).



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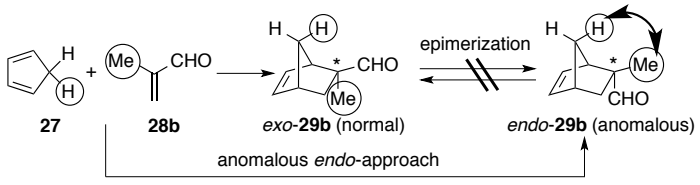


(10)

Of course, thermodynamically more stable optically active *exo*-**29a**, which has a chiral tertiary carbon center at the 2-position, can also be generated by the epimerization of *endo*-**29a** (Eq. 9), since optically active *endo*-**29a** has been synthesized using many conventional chiral catalysts. In contrast, optically active *endo*-**29b**, which has a chiral quaternary carbon center at the 2-position, cannot be generated by the epimerization of easily available *exo*-**29b** (Eq. 10).

To address the major unexplored subject in anomalous *endo*/*exo* control in the Diels–Alder reaction, catalysts must be able to accurately discriminate chiral transition state structures, by recognizing not only the *re*/*si*-face of dienophiles but also the *endo*/*exo*-approach of dienes (Fig. 5). First, catalysts must be able to discriminate the enantiofaces of dienophiles. Second, catalysts must be able to discriminate the *endo*/*exo*-approach of dienes. Overall, the catalysts must discriminate both the diene and dienophile at the same time in transition states. For anomalous *exo*-control, the catalysts should have a shallow and wide cavity (Fig. 5a). On the other hand, for anomalous *endo*-control, the catalysts should have a deep and narrow cavity (Fig. 5b).

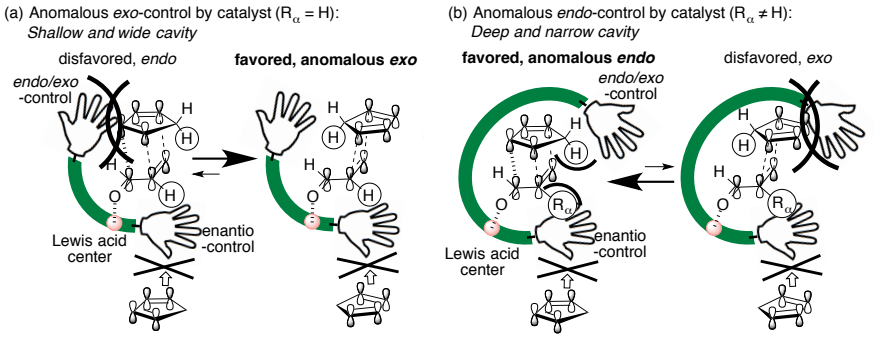
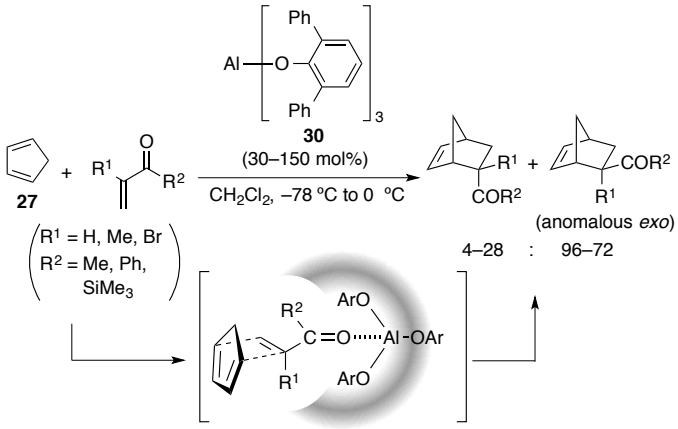


Fig. 5 Anomalous *endo*/*exo*-selectivity with specially designed chiral catalysts

3.2 Anomalous *Exo*-Selective Diels–Alder Reaction with Single-Molecule Catalysts

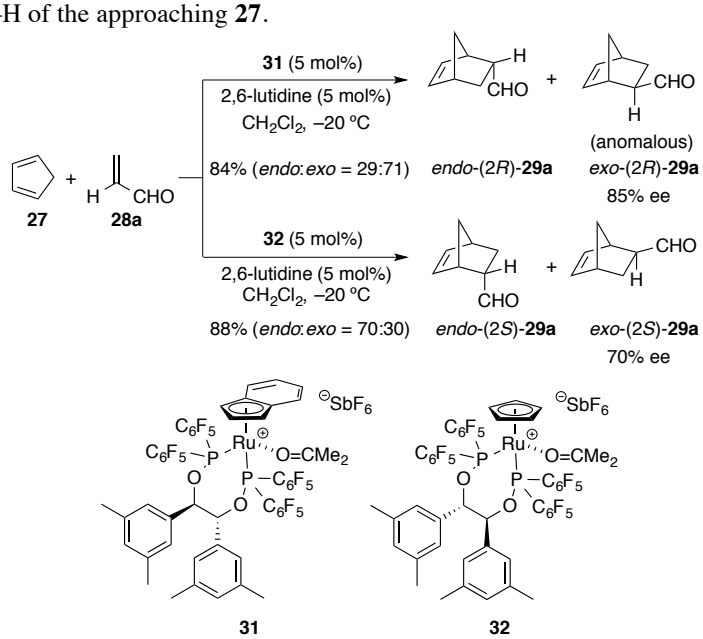
It should be less heavy task to design promising catalysts for anomalous *exo*-control than for anomalous *endo*-control, since the external *exo*-approach can be realized when the internal *endo*-approach would be effectively prevented even with single-molecule catalysts with a relatively small structure (Fig. 5a). Thus, a deep and narrow cavity for both a diene and a dienophile is not necessary for anomalous *exo*-control.

In fact, relatively small single-molecule catalyst-induced anomalous *exo*-selective Diels–Alder reactions against the original *endo*-rule have been investigated by a few research groups. For example, Yamamoto reported a molecular recognition approach by using a bulky aluminum(III) Lewis acid catalyst, ATPH (**30**), which provides an effective small carbonyl pocket, in a non-asymmetric manner for the first time (Eq. 11) [24]. Dienophiles are effectively shielded by complexation with the bulky achiral aluminium(III) catalyst, and the external *exo*-approach can be preferred (*endo*:*exo* = up to 4:96) while secondary interactions are significantly diminished.



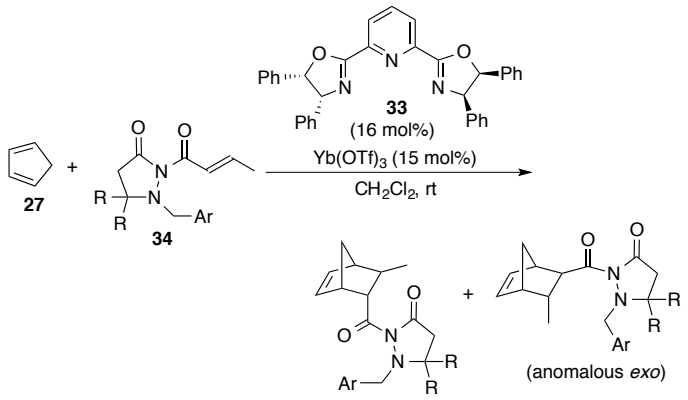
(11)

Later, Kündig developed the first anomalous *exo*-selective, catalytic enantioselective Diels–Alder reaction between **27** and **28a** that usually favors the *endo* cycloadduct (Eq. 12) [25]. With cationic chiral indenyl ruthenium(II) catalyst (**31**), the reaction afforded anomalous *exo*-**29a** with 85% ee as major product with an *endo*:*exo* ratio of 29:71. Interestingly, complete inversion of *endo*/*exo*-selectivity compared to that obtained with the cyclopentadienyl catalyst (**32**) was observed, which gave normal *endo*-**29a** as major product with an *endo*:*exo* ratio of 70:30. They concluded that the bulky indenyl arene ring would interfere with C(2)–H and C(3)–H of the approaching **27**.



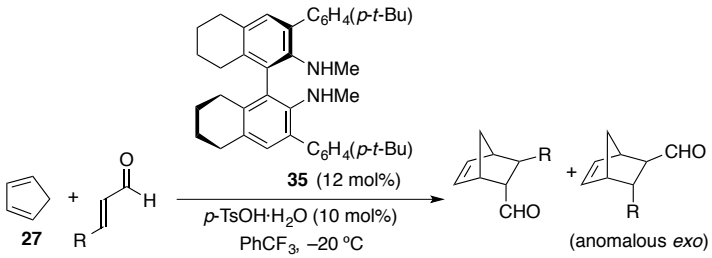
(12)

Sibi developed the chiral Pybox (**33**)–ytterbium(III)-catalyzed anomalous *exo*-selective Diels–Alder reaction with a bulky achiral pyrazolidinone auxiliary in dienophiles (**34**) (Eq. 13) [26]. In this case, sterically hindered N-1 mesitylmethyl and C-5 ethyl substitutions in pyrazolidinone **34** were essential for realizing improved anomalous *exo*-selectivity (*endo*:*exo* = 16:84). For instance, less-hindered N-1 benzyl- and C-5 methyl-substituted substrate led to a lower *endo*:*exo* ratio of 56:44.



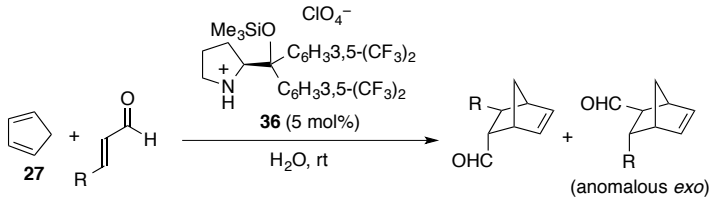
R = Et, Ar = 2,4,6-$Me_3C_6H_2$: 62% [*endo*:*exo* = 16:84 (93% ee)]
R = Me, Ar = Ph: 93% [*endo*:*exo* = 56:44 (84% ee)] (13)

Maruoka reported the chiral diamine salt-catalyzed anomalous *exo*-selective enantioselective Diels–Alder reaction (Eq. 14) [27]. The reaction of cinnamaldehyde in the presence of 12 mol% of chiral 3,3'-disubstituted *N*,*N*'-dimethyl H_8-binaphthyldiamine (**35**) and 10 mol% of *p*-TsOH· H_2O in α,α,α-trifluorotoluene at –20 °C gave the corresponding anomalous *exo*-adduct with 92% ee (80% yield, *endo*:*exo* = 7:93). Moreover, the reaction of acrolein (**28a**) in the presence of the same catalyst gave the anamalous *exo*-**29a** with moderate *endo*/*exo*-selectivity (93% yield, *endo*:*exo* = 34:66, 86% ee for *exo*-**29a**). This is the first example of an organocatalytic anomalous *exo*-selective Diels–Alder reaction, although a prolonged reaction time was needed (40–160 h).



R = Ph: 160 h, 80% (*endo*:*exo* = 7:93) 91% ee 92% ee
R = H: 45 h, 93% (*endo*:*exo* = 34:66) 68% ee 86% ee (14)

Hayashi reported that a chiral salt of diarylprolinol silyl ether (**36**) induced anomalous *exo*-selectivity in the enantioselective Diels–Alder reaction between **27** and α,β-unsaturated aldehydes (Eq. 15) [28]. In particular, the reaction of cinnamaldehyde in the presence of 5 mol% of catalyst **36** in water at room temperature gave the corresponding anomalous *exo*-adduct with 97% ee (93% yield, *endo*:*exo* = 20:80). Moreover, the reaction of acrolein (**28a**) gave the anomalous *exo*-**29a** with moderate *endo*/*exo*-selectivity (*endo*:*exo* = 38:62, 98% ee for *exo*-**29a**).



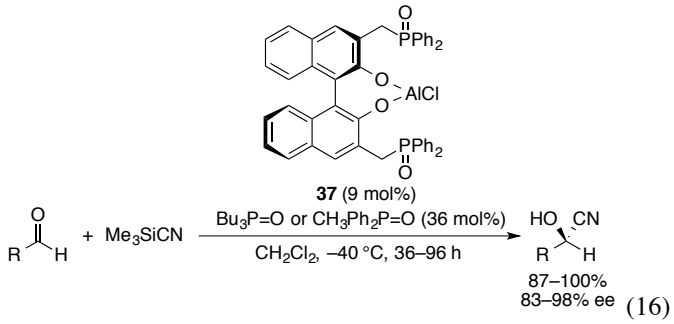
R = Ph: 7 h, 93% (*endo*:*exo* = 20:80) 92% ee 97% ee
R = H: 24 h, 85% (*endo*:*exo* = 38:62) 94% ee 98% ee (15)

3.3 Anomalous *Endo*-Selective Diels–Alder Reaction with Chiral Supramolecular Catalysts

In sharp contrast to previous anomalous *exo*-induced Diels–Alder reactions with α-non-substituted acroleins, there have been no reports on anomalous *endo*-induced catalytic enantioselective Diels–Alder reactions with α-substituted acroleins against the original *exo*-rule. In principle, for anomalous *endo*-control, a reaction intermediate should have a folding structure regardless of considerable steric repulsion between the reactants as seen in Fig. 5b. Therefore, a deep and narrow cavity in the catalyst is necessary to hold both a diene and a dienophile together throughout the transition states.

To realize this strategy, a rational design of conformationally flexible chiral supramolecular catalysts, similar to natural enzymes, might be possible. Moreover, according to the Lehn's original definition of 'supramolecule' [1], which include more than two molecules with non-covalent intermolecular bonds, supramolecular catalysts might be simple extension from single-molecular catalysts.

In regard to the construction of supramolecular catalysts, non-covalent acid–base attractive interaction might be useful. In particular, Shibasaki has pioneeringly developed the acid–base combination chemistry [5], in which they often use phosphine oxides as functionalized Lewis bases [29]. In their early studies, for example, they developed the catalytic enantioselective cyanosilylation of aldehydes, ketones, and aldimines with the use of acid–base bifunctional catalysts **37** and **38** [29a–e] (Eqs. 16, 17). In these reactions, phosphine oxides plays an important role to activate trimethylsilylcyanide or coordinate to the Lewis acid center in supramolecular fashions (Fig. 6).



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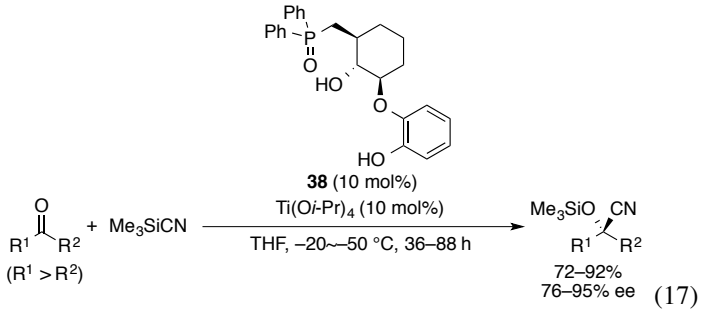

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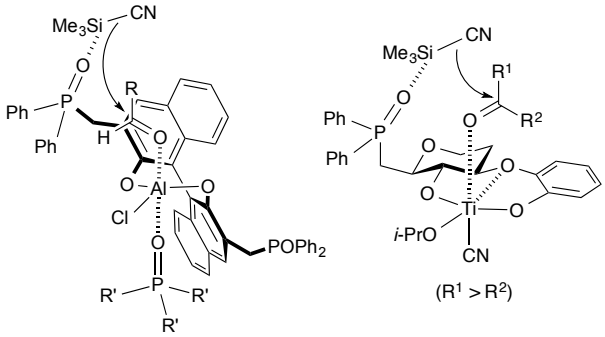
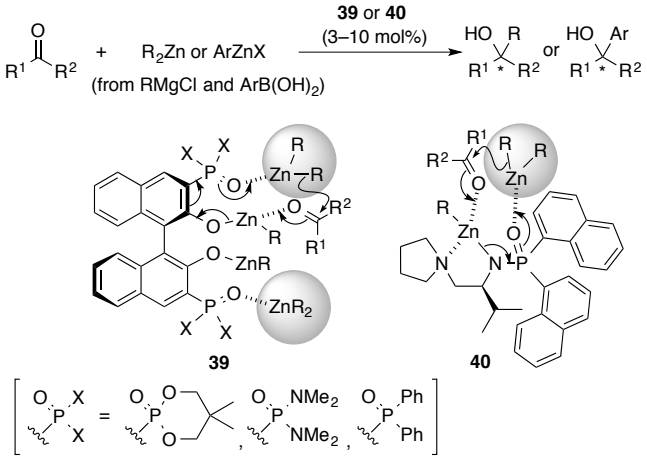


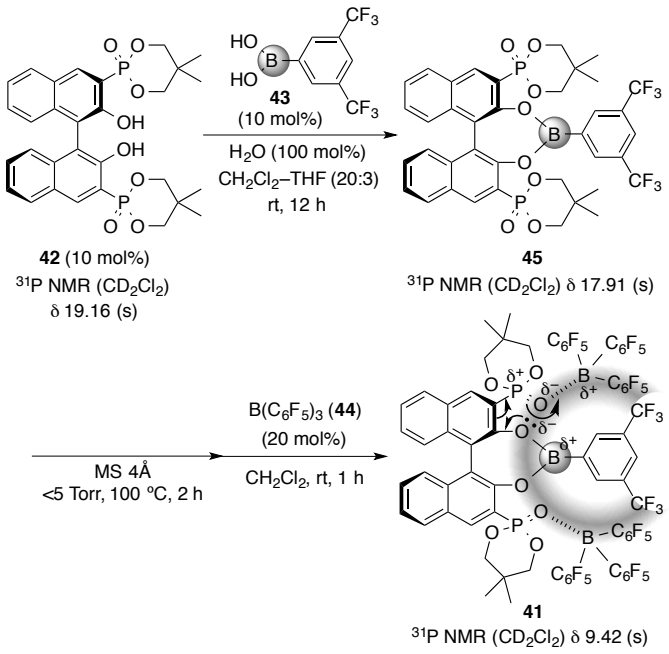
Fig. 6 Strategic phosphoryl groups as Lewis bases in asymmetric catalysis

Ishihara has developed the catalytic enantioselective organozinc addition to aldehydes and ketones using acid–base conjugate Zn(II) catalysts (**39** and **40**) [30] (Eq. 18). In these catalysts, acid–base remote activation of both the carbonyl compound and the organozinc reagent is important. In particular, the phosphoryl moieties would have good Lewis basicity to activate the electron-deficient organozinc center. They expected that this acid–base activation system, in particular with possible bulkiness based on the C_2-symmetric chiral BINOL moiety, might be applicable to the design of novel conformationally flexible chiral supramolecular catalysts.

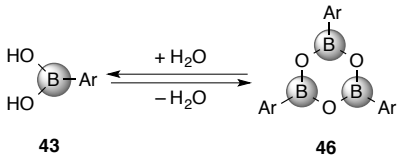


(18)

In such a situation, Ishihara developed a new type of conformationally flexible, highly active, chiral supramolecular catalyst based on well-designed single-molecule components [31]. A chiral supramolecular catalyst (**41**) was readily prepared *in situ* from three components, including 10 mol% of chiral (*R*)-3,3'-bis(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphorinan-2-yl)-BINOL (**42**), 10 mol% of 3,5-bis(trifluoromethyl)phenylboronic acid (**43**), and 20 mol% of tris(pentafluorophenyl)borane (**44**) [31] (Scheme 8). Since the arylboronic acid **43** is usually allowed at hydrolysis equilibrium with the triarylboroxin **46** (Eq. 19), the addition of a small amount of water is necessary to provide the boron BINO-Late intermediate **45** [32]. On the other hand, highly coordinative water molecules must be removed by MS 5Å before the subsequent supramolecular formation of non-covalent bonds between **44** and **45**. Preliminary investigations by ^{31}P NMR analysis in CD_2Cl_2 showed a corresponding peak shift of two C_2-symmetric phosphoryl moieties; 19.16 ppm for **42**, 17.91 ppm for **45**, and 9.42 ppm for **41**.



Scheme 8 Preparation of a chiral supramolecular catalyst

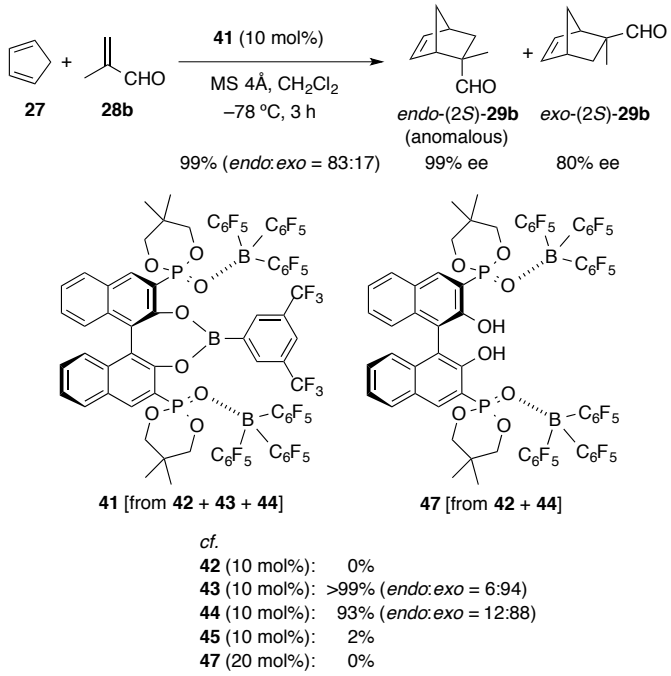


(19)

For the design of conformationally flexible supramolecule **41**, intermolecular acid–base coordination bonds in the two P=O···B(C_6F_5)$_3$ are critical [33]. Compound **44** would act as a bulky functional group to make a chiral, narrow and deep cavity around the Lewis acidic boron center. Moreover, the strong electron-recipient ability of Lewis acid **44** would increase the Lewis acidity of the central boron through conjugate bonds (Scheme 8), which would take advantage of Lewis acid-assisted chiral Lewis acid (LLA) catalysts [34].

In the presence of chiral supramolecular catalyst **41** (10 mol%), the Diels–Alder reaction between **27** and **28b** was conducted in dichloromethane at –78 °C for 3 h [31] (Scheme 9). As a result, anomalous *endo*-(2*S*)-**29b** was obtained as a major product (99% yield, *endo*:*exo* = 83:17) with excellent enantioselectivity (99% ee). In sharp contrast, **42** and incomplete complexes **45** (i.e., [**42** + **43**]) and **47** (i.e., [**42** + **44**]) showed almost no catalytic activity (0–2% yield). Moreover, **43** and **44** gave the normal *exo*-**29b** as a major product (*endo*:*exo* = 6–12:94–88). For catalyst **27**, the phosphoryl moieties of **42** would coordinate to **44**, and thus **44** as a

Lewis acid would be deactivated. For catalyst **45**, the corresponding boron(III) BINOLate would not be reactive, since it lacks conjugated activation by Lewis acid **44**. Therefore, the catalytic activity of **41** decreased even in the absence of either **43** or **44**.



Scheme 9 Anomalous *endo*-selective enantioselective Diels–Alder reaction between **27** and **28b**

To date, there has been no solid evidence for the possible geometry of the supramolecular catalyst. However, as a working model to explain the anomalous stereoselectivity, a chiral, narrow, and deep cavity is assumed due to the six bulky C_6F_5 moieties. In this regard, theoretical calculations for a **28b**–**41** complex with the B3LYP/6-31G* method supported that the two non-covalent P=O···B$(C_6F_5)_3$ moieties have a *syn*-conformation (**48**) on one hand and an *anti*-conformation (**49**) on the other hand [31] (Fig. 7). Remarkably, *syn*-**48** is more stable than *anti*-**49** by 3.86 kcal/mol. In *anti*-**49**, significant steric repulsion would be observed among the C_6F_5 moieties and the central 3,5-$(CF_3)_2C_6H_3B$ moiety. Therefore, *syn*-**48** is more favored.

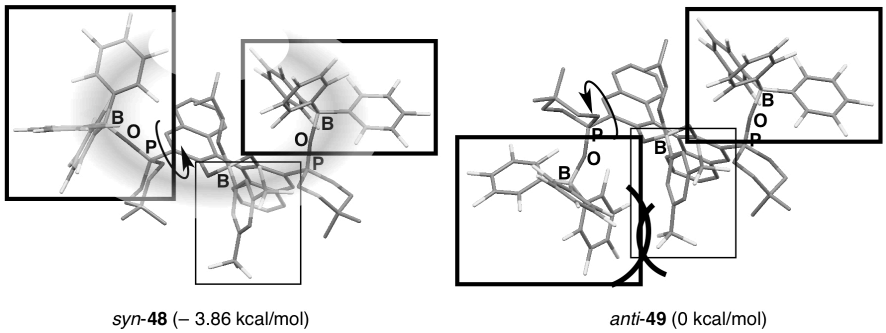


Fig. 7 Theoretical calculations using Gaussian03 (B3LYP/6-31G*)

In *syn*-**48**, the formyl moiety of **28b** with a favored *s*-trans geometry was doubly coordinated with the B-O(Naph) moiety at the C(=O)H and C(=O)H parts (Fig. 7). Among the possible transition states, a *si*-face attack would be disfavored due to enantio-face control by a C_6F_5 group. In a possible transition state (TS)-**50**, an *endo*-approach inside the cavity via a *re*-face attack would be relevant, while an *exo*-approach via a *re*-face attack (TS-**51**) would be unlikely because of the bulkiness of another C_6F_5 group [31] (Fig. 8).

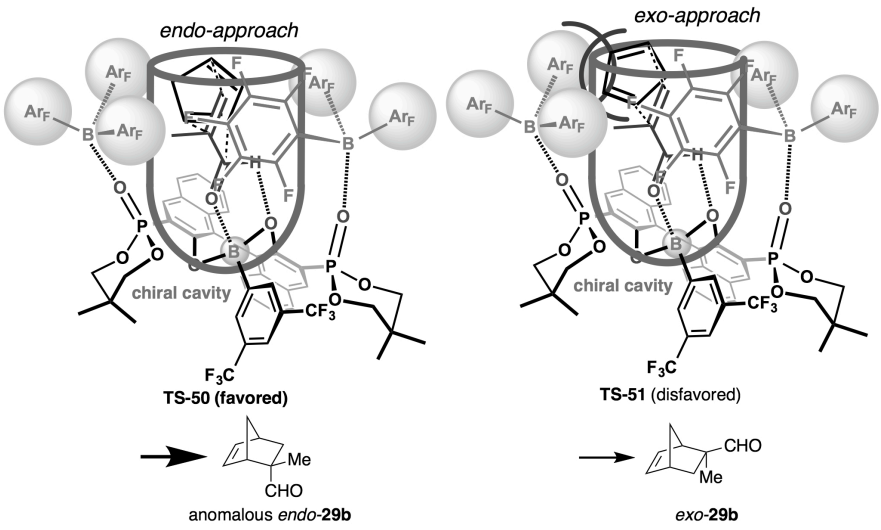
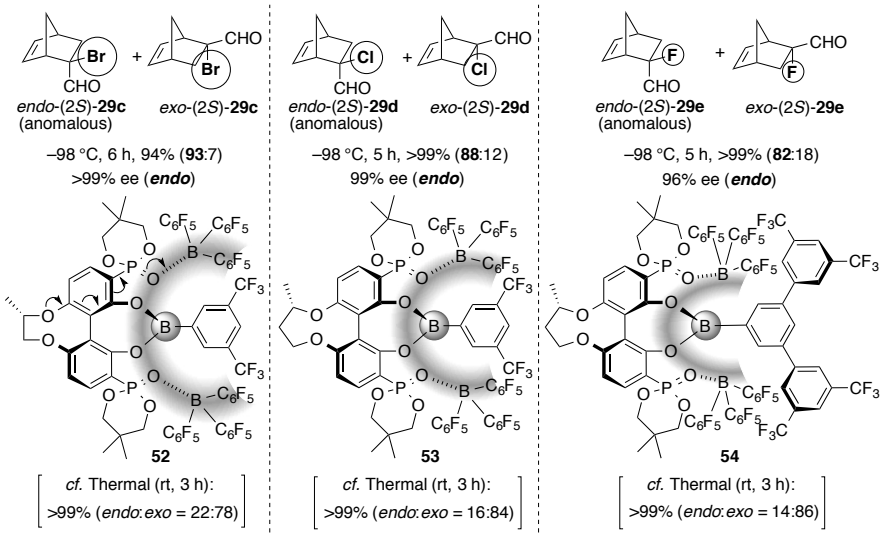


Fig. 8 Possible transition states for anomalous *endo*-selectivity

To demonstrate other anomalous *endo*-selective Diels–Alder reactions, the reactions between **27** and α-haloacroleins, which usually provided *exo*-adducts as major products (Scheme 10), were examined [31]. Electron-deficient α-haloacroleins

are extremely reactive, and thus their enantioselective Diels–Alder reactions have been especially limited. Moreover, the reports were on substrate-dependent *exo*-selective reactions. Corey reported pioneering *exo*-selective examples with both α-bromoacrolein (**28c**) [35] and α-chloroacrolein (**28d**) [36], and other research groups later came to report *exo*-selective and enantioselective catalysis with **28c**. However, there have been no catalytic asymmetric examples of the Diels–Alder reactions of α-fluoroacrolein (**28e**).



Scheme 10 Anomalous *endo*-selective enantioselective Diels–Alder reaction of α-haloacroleins

In the reaction between **27** and **28c** in dichloromethane at –98 °C for 6 h, supramolecular catalyst **41** was ineffective, and *exo*-**29c** was obtained as a major product with low enantioselectivity (>99% yield, *endo*:*exo* = 16:84, 10–11% ee). However, after optimization of the chiral biaryl skeleton, another supramolecular catalyst **52** with chiral biphenol in place of chiral binaphthol **42** was extremely effective, and the anomalous *endo*-selectivity was dramatically improved (94% yield, *endo*:*exo* = 93:7) with excellent enantioselectivity for *endo*-(2*R*)-**29c** (>99% ee). Furthermore, in the reaction between **27** and **28d** in dichloromethane at –98 °C for 5 h in the presence of hydroquinone (10 mol%) as a polymerization inhibitor, after another fine-tuning for the chiral biaryl skeleton, supramolecular catalyst **53** provided anomalous *endo*-selectivity, and *endo*-(2*R*)-**29d** was obtained as a major product (>99% yield, *endo*:*exo* = 88:12) with excellent enantioselectivity (>99% ee). Finally, unprecedented α-fluoroacrolein (**28e**) was examined. Under thermodynamic conditions without catalysts, *exo*-product **29e** was obtained predominantly (>99% yield, *endo*:*exo* = 14:86). On the other hand, anomalous *endo*-(2*R*)-**28e** was obtained as a major product (>99% yield, *endo*:*exo* = 82:18) with

high enantioselectivity (96% ee) when bulky **54**, which was derived from 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenylboronic acid, was used.

Overall, as with an enzymatic methodology, fine-tuning of the conformationally flexible supramolecular catalysts for each α-haloacrolein was essential for establishing anomalous *endo*-selectivity as well as excellent enantioselectivity. As the halogen in α-haloacrolein become smaller, larger components at the central aryl boran moiety and the biphenyl moiety were effective. The more bulkiness may directly or indirectly create a smaller cavity that could suitably recognize a smaller substrate (Fig. 9).

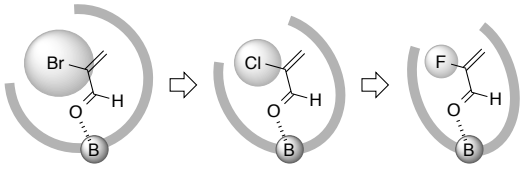
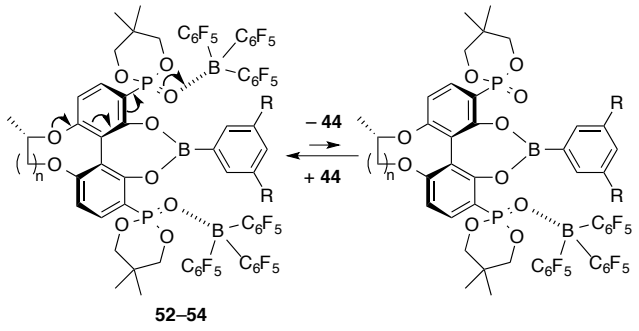


Fig. 9 Tuning the size of a suitable cavity for each substrate

The reason why the anomalous *endo*-selectivity of **29c** was significantly improved when biphenyl catalyst **52** was used in place of binaphthyl catalyst **41** is not yet completely solved. As a possible explanation, there might be a slight difference in the dihedral angle of the binaphthyl or biphenyl skeleton. As another possible explanation, the electron-donating ability of the 6,6'-ether moieties in **52**–**54** (i.e., -$OCH(CH_3)CH_2O$- or -$OCH(CH_3)CH_2CH_2O$-), through a resonance effect in the conjugate system, might induce a stronger intermolecular acid–base coordination of non-covalent P=O···$B(C_6F_5)_3$ (Scheme 11). This stabilization of the supramolecular catalysts might reduce the adventitious dissociation of achiral **44**. Consequently, normal Diels–Alder reactions with extremely low enantioselectivity by incomplete supramolecular catalysts and/or **44** would be prevented when reactive **28c**–**e** were used in place of much less reactive **28b**.

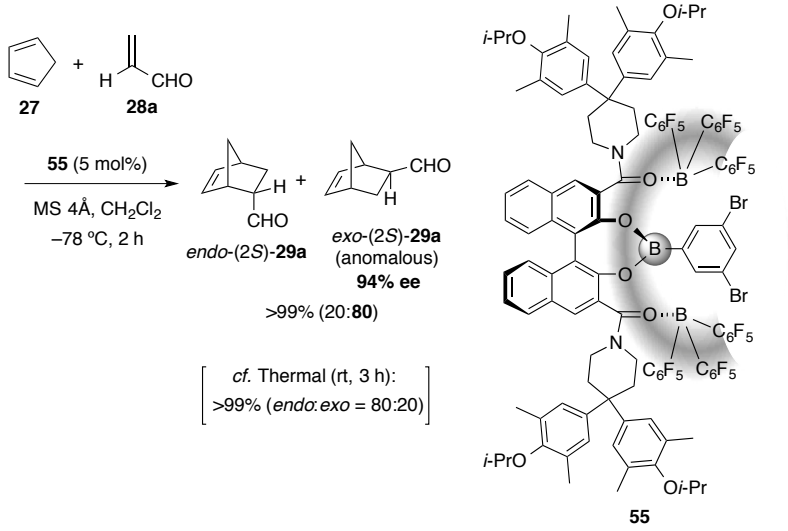


52–54

Scheme 11 A resonance effect in chiral biphenol catalysts

3.4 Anomalous Exo-Selective Diels–Alder Reaction with a Chiral Supramolecular Catalyst

The reaction with acrolein (**28a**) in place of α-haloacroleins was examined [31] (Scheme 12). Generally, the reaction of **27** with **28a** was *endo*-selective under substrate-control (e.g., *endo*:*exo* = 80:20 under thermal conditions). For anomalous *exo*-control, another supramolecular catalyst with amido moieties in place of phosphoryl moieties was developed. Supramolecular catalyst **55** (5 mol%) was thus prepared *in situ* from chiral 3,3'-(dicarbamoyl)binaphthol, (3,5-dibromophenyl)boronic acid, and **44**. As a result, **55** was highly effective for the anomalous *exo*-selective Diels–Alder reaction of **28a** with high enantioselectivities (94% ee for *exo*-(2*S*)-**29a**, *endo*:*exo* = 20:80).



Scheme 12 Anomalous *exo*-selective enantioselective Diels–Alder reaction between **27** and **28a**

Similar to the case of supramolecule **41** with phosphoryl moieties, a possible transition state (TS-**56**) for supramolecular **55** with amide moieties is shown in Fig. 10 [31]. Unlike the pseudo-tetrahedral phosphorous structure, the amide has a less-hindered planar structure, and the non-covalent amide–$B(C_6F_5)_3$ moiety may turn outside the **27**–**28a**–**55** complex in the transition states. Therefore, a shallow and wide cavity would be provided, and this would promote the anomalous *exo*-approach without significant steric repulsion via TS-**56**.

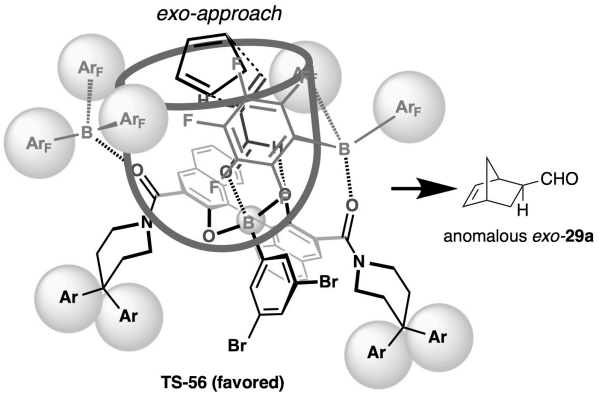
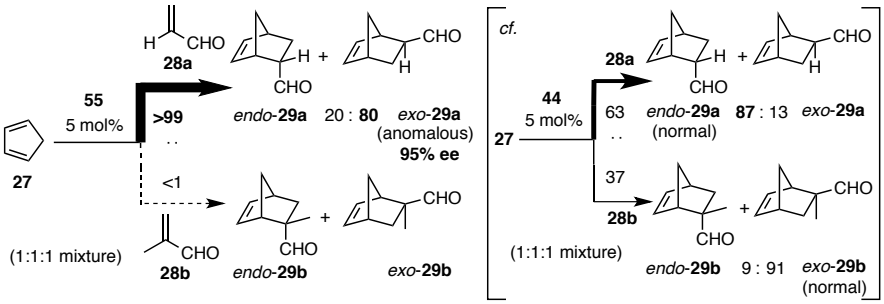


Fig. 10 Possible transition states for anomalous *exo*-selectivity

3.5 Molecular Recognition by the Chiral Supramolecular Catalyst

To further investigate the function of conformationally flexible supramolecular catalysts, a molecular recognition under substrate-competitive Diels–Alder reaction conditions was performed. For a 1:1:1 equimolar mixture of **27**, **28a**, and **28b**, *exo*-inducing supramolecular catalyst **55** (5 mol%) promoted the reaction of **28a** exclusively (**28a**:**28b** = >99:<1), and anomalous *exo*-(2*S*)-**29a** was obtained as a major product (*endo*:*exo*-**29a** = 20:80, 95% ee for *exo*-(2*S*)-**29a**) [31] (Scheme 13). In sharp contrast, achiral Lewis acid catalyst **44** (10 mol%) gave a mixture of *endo*-**29a** and *exo*-**29b** as major products with low substrate-selectivity (**28a**:**28b** = 63:37) and normal *endo*/*exo*-selectivity (*endo*:*exo*-**29a** = 87:13, *endo*:*exo*-**29b** = 9:91). This result suggests that the supramolecular catalyst may have some induced-fit functions to adapt to a specific substrate.



Scheme 13 Molecular recognition under substrate-competitive reaction conditions

4. Conclusion

Here we discussed key issues based on our supramolecular Brønsted acid/Lewis base hybrid catalysts. In one section, we reviewed the highly enantioselective 1,4-hydrophosphinylation and 1,2-hydrophosphonylation of α,β-unsaturated carbonyl compounds, which were catalyzed by simple chiral aggregated magnesium(II) binaphtholate aqua complexes as cooperative Brønsted acid/Lewis base hybrid catalysts *in situ*. Insights into the mechanistic details showed that 2:3 supramolecular complexes of Mg(II)/(*R*)-BINOLate were involved as the active species. This finding encouraged us to investigate the two precedent reactions, such as the direct Mannich-type reaction and the hetero-Diels–Alder reaction. As a result, the detailed mechanistic studies strongly suggested that chiral di- and trinuclear supramolecular magnesium(II) complexes should play key roles as the active catalytic species in these reactions. Such a practical methodology with a fundamental acid–base aggregation, which is induced by diversity of simple, inexpensive, and harmless magnesium(II) binaphtholate catalysts, can open up further efficient asymmetric catalyses in the future. In the other section, we reviewed more artificial enzymatic supramolecular catalysts, which were readily prepared *in situ* from chiral 3,3'-disubstituted binaphthols and biphenols, arylboronic acid, and $B(C_6F_5)_3$. The evolution from 'ready-made' single-molecule catalysts to 'tailor-made' supramolecular catalysts based on conjugated acid–base units could offer not only high enantioselectivity but also anomalous *endo*/*exo*-selectivities in the Diels–Alder reaction. Conformationally flexible chiral cavity like 'key holes' in enzymes with an induced-fit function was provided in 'tailor-made' chiral supramolecular catalysts for each substrate. This unique methodology might be hardly achieved by conventional 'ready-made' single-molecule catalysts. Totally, the full properties of chiral supramolecular catalysts to realize substrate-independent regio- and/or stereoselectivity in organic synthesis have just taken off, and these ongoing studies shown here might be the tip of iceberg. Therefore, trial and error approach will be necessary to overcome unprecedented difficulties, and the supramolecular Brønsted/Lewis acid–base hybrid catalysts will contribute the further increasing progress in the near future.

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