Asymmetric Catalysis

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Enantioselective Diels–Alder Reactions with Anomalous *endo*/*exo* Selectivities Using Conformationally Flexible Chiral Supramolecular Catalysts**

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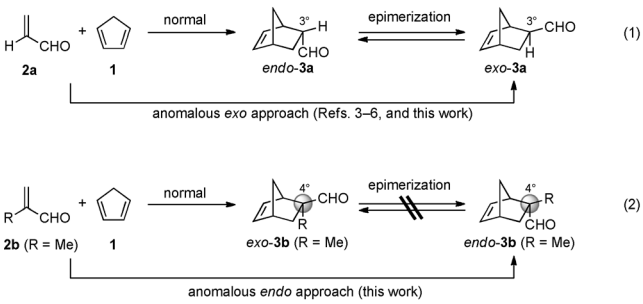
On the basis of Woodward–Hoffmann frontier molecular orbital interactions and steric interactions between dienes and dienophiles during the formation of [2+4] pericyclic transition states, *endo*/*exo* selectivity in the Diels–Alder reaction strongly depends on the substrates.[1] Therefore, it is quite difficult to control both enantioselectivity[2] and anomalous *endo*/*exo* selectivity by conventional chiral catalysts, which can discriminate only the enantiofaces of the dienophiles. For example, in the reaction between cyclopentadiene (**1**) and acrolein (**2a**), an *endo* preference is observed with regard to second-order orbital interactions without significant steric interactions [Eq. (1)]. In sharp contrast, in the reaction between **1** and an α-substituted acrolein (R ≠ H), such as methacrolein (**2b**), an *exo* preference is observed with regard to steric interactions between the methylene moiety of **1** and the substituent R at the α position of the dienophile [Eq. (2)]. Therefore, enantiomerically enriched *endo*-**3a** and *exo*-**3b** have been synthesized by using many conventional chiral catalysts.[2] Moreover, thermodynamically more stable and enantiomerically enriched *exo*-**3a** can be generated by the epimerization of *endo*-**3a** [Eq. (1)]. Alternatively, catalyst-induced anomalous *exo*-selective Diels–Alder reactions that contravene the *endo* rule have been performed by Yamamoto and co-workers[3] in a non-asymmetric manner, and later by Maruoka and co-workers,[4] Sibi et al.,[5] and Hayashi et al.[6] in an asymmetric manner. In contrast, enantiomerically enriched *endo*-**3b** with a quaternary carbon center can not be generated by the epimerization of *exo*-**3b** or by other known synthetic methods [Eq. (2)]. To the best of our knowledge, no examples of catalyst-induced anomalous *endo*-selective enantioselective Diels–Alder reactions with α-substituted acroleins have been reported to date. To address this major yet unexplored subject, catalysts must discriminate chiral transition-state structures by precisely recognizing the *re* or *si* face of dienophiles, and the *endo* or *exo* approach of dienes, thus, the rational design of conformationally flexible chiral supramolecular catalysts, such as enzymes, is necessary.[7] As such, conformationally rigid metal–organic frameworks (MOFs) are not suitable as artificial enzymes because they have few induced-fit properties to adapt dynamics in transition states.[8]



A chiral supramolecular catalyst (**4a**) was readily prepared in situ from three components, which included 10 mol% of chiral (*R*)-3,3′-bis(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphorinan-2-yl)-BINOL (**5a**; BINOL = 1,1′-bi(2-naphthol)),[9] 10 mol% of 3,5-bis(trifluoromethyl)phenylboronic acid (**6a**), and 20 mol% of tris(pentafluorophenyl)borane (**7**), by taking advantage of the typical preparation of boron BINOLates[10] (Scheme 1). Intermolecular acid–base coordinate bonds in the two P=O···B(C_6F_5)$_3$ moieties[11] are critical for the design of conformationally flexible complex **4a**; compound **7** acts as a bulky functional group to form a chiral, narrow, and deep cavity around the Lewis acidic boron center. Moreover, the strong electron-accepting nature of Lewis acid **7** increases the Lewis acidity of the central boron through conjugated bonds, thus taking advantage of Lewis acid assisted chiral Lewis acid (LLA) catalysts.[12] The Diels–Alder reaction between **1** and **2b** was conducted in the presence of the catalyst **4a** (10 mol%) in dichloromethane at −78 °C for 3 h (Scheme 2). As a result, the anomalous product *endo*-(2*S*)-**3b** was obtained as the major product (99% yield, *endo*/*exo* = 83/17) with excellent enantioselectivity (99% *ee*). This result is remarkable because the use of compounds **6a**

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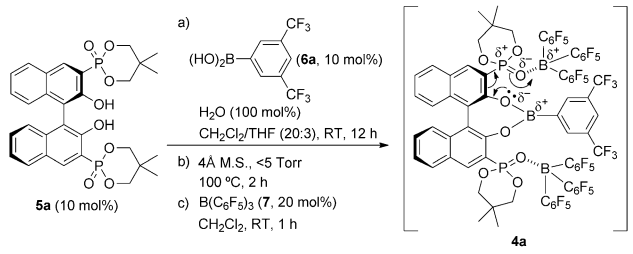
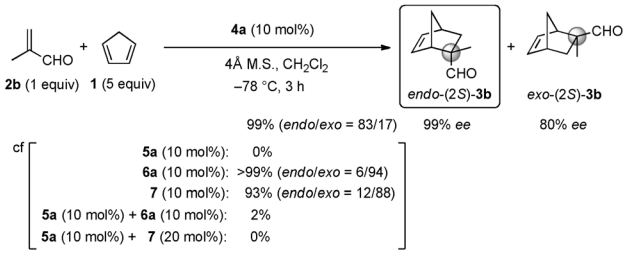
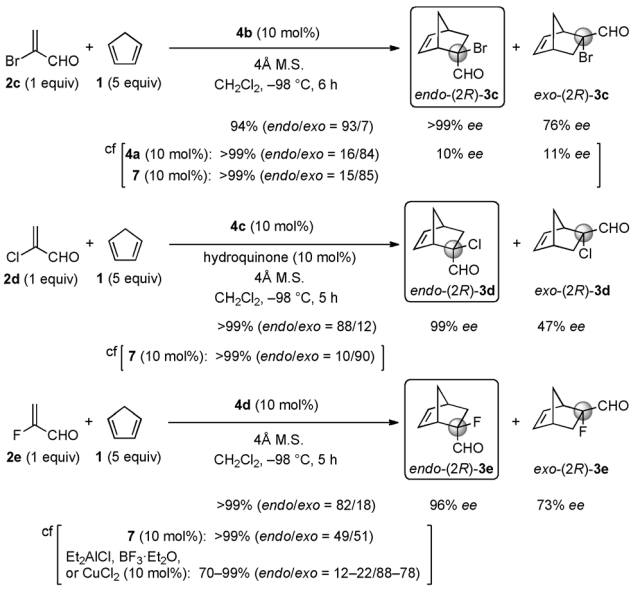


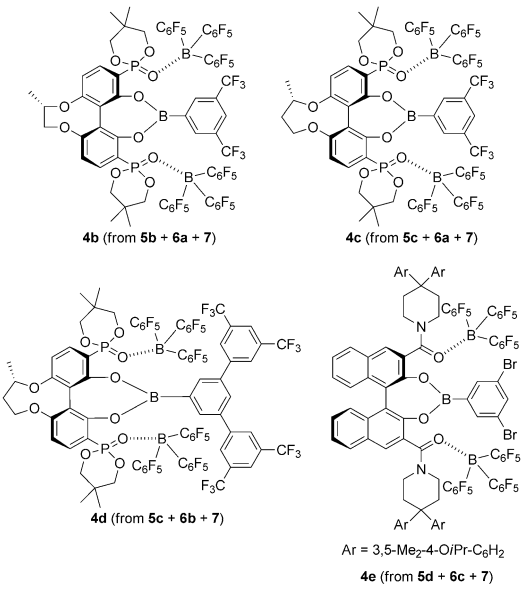
Scheme 1. Preparation of a chiral supramolecular catalyst **4a**. M.S. = molecular sieves.



Scheme 2. Anomalous *endo*-selective asymmetric reaction between **1** and methacrolein (**2b**).



Scheme 3. Anomalous *endo*-selective asymmetric reactions between **1** and α-haloacroleins (**2c**–**e**).



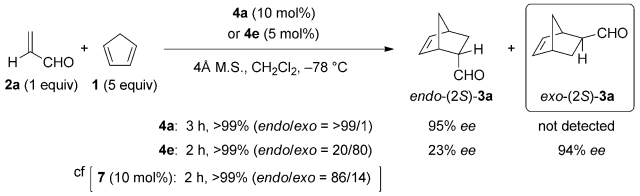
Scheme 4. In situ generated chiral supramolecular catalysts.

and **7** instead of catalyst **4a** gave the expected product *exo*-**3b** as the major product (*endo*/*exo* = 6–12/94–88); compound **5a** and the conjugates derived from **5a** and **6a**, and **5a** and **7**, respectively, showed low catalytic activity (0–2% yield).[13]

In order to explore anomalous *endo*-selective Diels–Alder reactions, we examined the reactions between **1** and α-haloacroleins, which normally provide *exo* adducts as major products (e.g., by catalysis with **7**; see Scheme 3). Electron-deficient α-haloacroleins are extremely reactive, and thus examples of enantioselective Diels–Alder reactions with these substrates have been limited. Moreover, these reports were based on substrate-dependent *exo*-selective Diels–Alder reactions; Corey and co-workers reported pioneering *exo*-selective examples with both α-bromoacrolein (**2c**)[14] and α-chloroacrolein (**2d**),[15] and other research groups later reported *exo*-selective enantioselective examples with **2c**[16] but not **2d**. Catalyst **4a** was not effective in the reaction between **1** and **2c** in dichloromethane at −98 °C for 6 h, and *exo*-**3c** was obtained as a major product with low enantioselectivity (> 99% yield, *endo*/*exo* = 16/84, 10–11% *ee*; Scheme 3). However, after optimization of the chiral biaryl skeleton, we found that chiral biphenol **5b** in place of chiral binaphthol **5a** was extremely effective, and the anomalous *endo* selectivity was dramatically improved (94% yield, *endo*/*exo* = 93/7) with excellent enantioselectivity for *endo*-(2*R*)-**3c** (> 99% *ee*) when catalyst **4b** (Scheme 4) was used. Furthermore, after more fine-tuning of the chiral biaryl skeleton, catalyst **4c** provided anomalous *endo* selectivity in the reaction between **1** and **2d** in the presence of hydroquinone (10 mol%) as a polymerization inhibitor in dichloromethane at −98 °C for 5 h, and *endo*-(2*R*)-**3d** was obtained as the major product (> 99% yield, *endo*/*exo* = 88/12) with 99% *ee*. α-Fluoroacrolein (**2e**) was next examined and preferentially provided the *exo* product when representative Lewis acid catalysts were used. Anomalous product *endo*-(2*R*)-**3e** was obtained as the major product (> 99% yield, *endo*/*exo* = 82/18) with 96% *ee* when **4d**, which was derived from a chiral biphenol **5c**, 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenylboronic acid (**6b**) and **7**, was used as an optimal catalyst. This is the first example of a catalytic asymmetric Diels–Alder reaction with **2e**, and moreover this case was an anomalous *endo*-selective reaction. Overall, as in enzyme catalysis, the fine-tuning of the conformationally flexible supramolecular catalysts for each α-haloacrolein was essential to establish anomalous *endo* selectivity as well as excellent enantioselectivity. In this preliminary stage, it is not entirely clear why the anomalous *endo* diastereoselectivity of **3c**–**e** was significantly

improved when **4b–d** were used instead of **4a**, although there is a slight difference in the dihedral angle between the covalent boron binaphtholate and biphenolate skeletons. However, one possible explanation is that the electron-donating ability of the 6,6′-O(R*)O moieties in **4b–d** might induce a stronger intermolecular acid–base coordination of P=O···$B(C_6F_5)_3$ through a resonance effect in the conjugated system. This coordination might reduce the adventitious dissociation of **7** that promotes an achiral pathway, particularly in the case of highly reactive **2c–e** in comparison with less reactive **2b**.

We next examined the reaction with less-reactive acrolein (**2a**) in place of α-haloacroleins (Scheme 5). The reaction with catalyst **4a** (10 mol%) provided *endo*-(2*S*)-**3a** in more

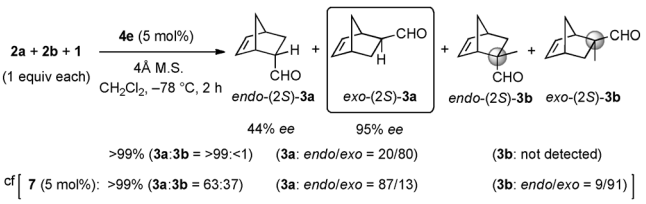


Scheme 5. Highly *endo*-selective and anomalous *exo*-selective reaction of **1** with **2a** by using chiral catalysts **4a** and **4e**, respectively.

than 99% yield and with excellent *endo* selectivity (*endo*/*exo* = > 99/1) and high enantioselectivity (95% *ee*), whereas the extent of *endo* selectivity was normal when the reaction was catalyzed by **7** (*endo*/*exo* = 86/14). In sharp contrast, another catalyst **4e** (5 mol%), which was prepared in situ from chiral 3,3′-(dicarbamoyl)binaphthol (**5d**), (3,5-dibromophenyl)boronic acid (**6c**), and **7**, led to anomalous *exo* selectivity (*endo*/*exo* = 20/80), and *exo*-(2*S*)-**3a** was obtained with high enantioselectivity (94% *ee*). Thus, we developed chiral supramolecular catalysts for not only anomalous *endo*-selective but also anomalous *exo*-selective Diels–Alder reactions based on the same concept.

Although further investigation of the function and the flexible structure of the in situ prepared catalysts is in progress,[17] preliminary examination of molecular recognition by these supramolecular catalysts under the competitive Diels–Alder reaction conditions was examined. For a 1:1:1 molar mixture of **1**, **2a**, and **2b**, catalyst **4e** promoted exclusively the reaction of **1** with **2a** (**3a**:**3b** = > 99: < 1), and anomalous *exo*-(2*S*)-**3a** was obtained as the major product (*endo*/*exo*-**3a** = 20/80) with 95% *ee* (Scheme 6). In contrast, achiral catalyst **7** gave a mixture of *endo*-**3a** and *exo*-**3b** as major products with low substrate selectivity (**3a**:**3b** = 63:37) and normal *endo*/*exo* selectivity (*endo*/*exo*-**3a** = 87/13, *endo*/*exo*-**3b** = 9/91). This result might suggest that the supramolecular catalyst **4e** has some induced-fit functions to adapt to a specific substrate.

In summary, we have developed anomalous *endo*/*exo*-selective enantioselective Diels–Alder reactions between cyclopentadiene and acrolein, methacrolein, α-bromoacrolein, α-chloroacrolein, and α-fluoroacrolein, catalyzed by novel chiral supramolecular complexes. In sharp contrast to rigid MOFs, our chiral supramolecular in situ prepared



Scheme 6. Molecular recognition with chiral catalyst **4e** in the competitive reaction of **2a** and **2b**.

catalysts were conformationally flexible, and are as active as single-molecule catalysts although significant bulkiness was involved to discriminate both the dienophile and diene. In this work, we demonstrated that, like artificial enzymes, chiral "tailor-made" supramolecular catalysts are essential to establish high anomalous *endo*/*exo* selectivity, which is hard to induce by conventional 'ready-made' catalysts.

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[13] Low catalytic activities of **5a**, (**5a**+**6a**), and (**5a**+**7**) are reasonable. The Brønsted acidity of **5a** is not sufficient to catalyze the reaction. For the (**5a**+**7**) catalyst, the phosphoryl moieties of **5a** coordinate to **7**, and thus the Lewis acidity of **7** is decreased. For the (**5a**+**6a**) catalyst, the corresponding boron BINOLate is not reactive because it lacks the conjugated activation by Lewis acid **7**. Therefore, the catalytic activity of the conjugates based on **5a** decreased if either **6a** or **7** were not present.

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[17] We can not fully explain the reason why the anomalous *endo* selectivity was observed for α-substituted acroleins under catalysis with **4a–d** while the anomalous *exo* selectivity was observed for acrolein under catalysis with **4e**. Nevertheless, as a working model, mechanistic aspects that involve the geometry of a possible **2b**–**4a** complex were preliminary examined by using theoretical calculations with the B3LYP/6-31G* method. The two conformationally flexible P=O···B(C_6F_5)$_3$ moieties could have a *syn* conformation since it is more stable than the *anti* conformation by 3.86 kcal mol^{-1}. See the Supporting Information for the detailed results.

