Asymmetric Catalysis

DOI: 10.1002/anie.201106497

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

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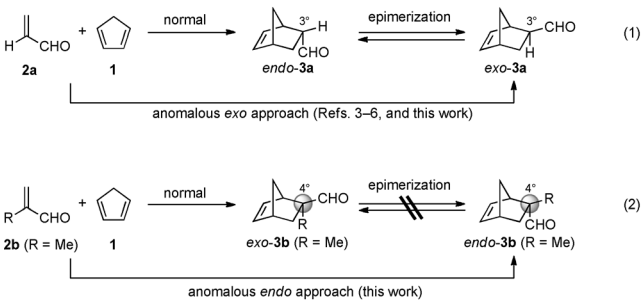
On the basis of Woodward–Hoffmann frontier molecular orbital interactions and steric interactions between dienes and dienophiles during the formation of [2+4] pericyclic transition states, *endo*/*exo* selectivity in the Diels–Alder reaction strongly depends on the substrates.[1] Therefore, it is quite 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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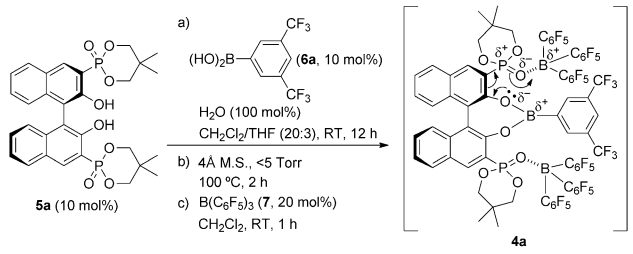
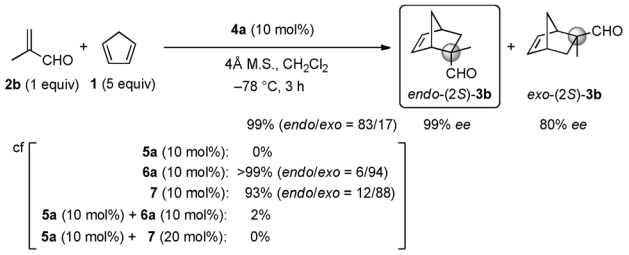
[**] Financial support for this project was partially provided by MEXT, KAKENHI (21750094, 21200033), the Global COE Program of MEXT, and Yazaki Memorial Foundation for Science and Technology. We are grateful to the Tosoh Finechem Corporation and Central Glass Co., Ltd. for providing organometallic reagents.

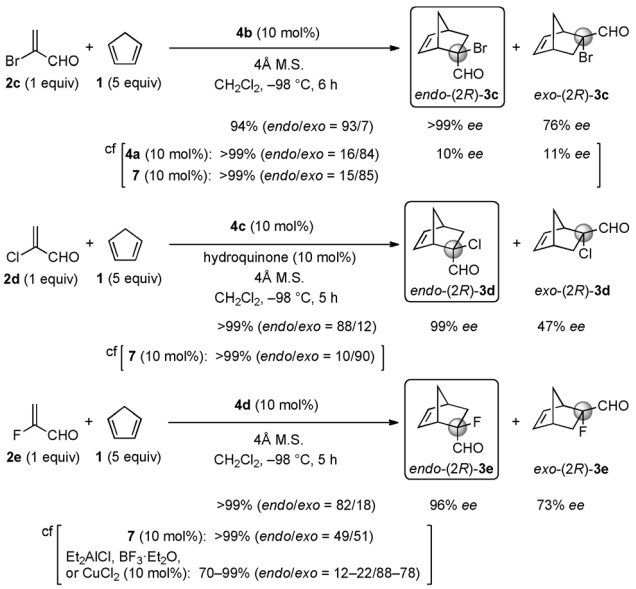
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201106497.



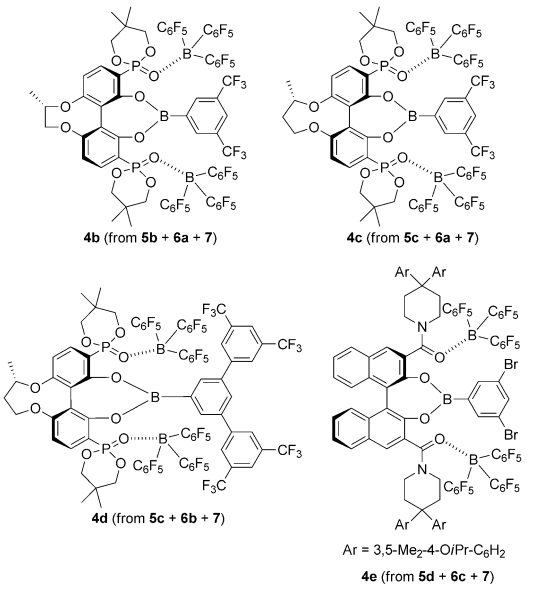
Scheme 1. Preparation of a chiral supramolecular catalyst **4a**. M.S. = molecular sieves.



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**).



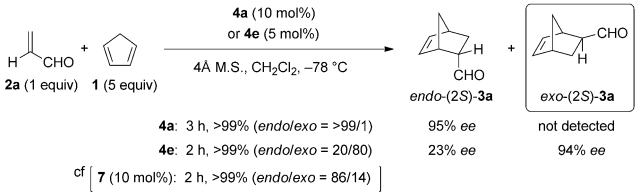
Scheme 4. In situ generated chiral supramolecular catalysts.

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

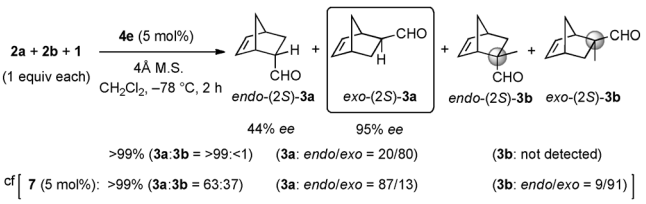


Scheme 5. Highly *endo*-selective and anomalous *exo*-selective reaction of **1** with **2a** by using chiral catalysts **4a** and **4e**, respectively.

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.

Received: September 14, 2011
Published online: October 25, 2011

Keywords: acroleins · asymmetric catalysis · cycloaddition · cyclopentadiene · supramolecular catalysis

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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.

