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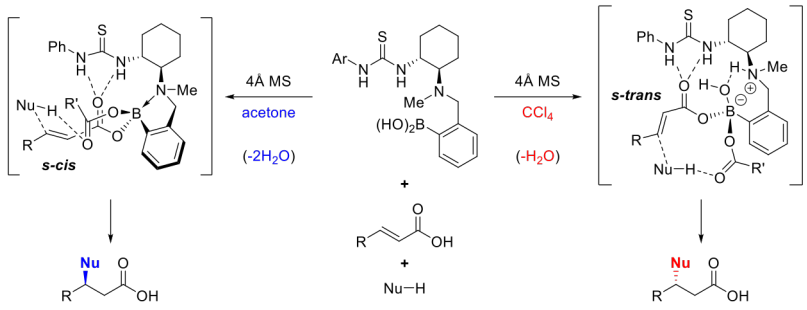

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Asymmetric hetero-Michael addition to α,β-unsaturated carboxylic acids using thiourea–boronic acid hybrid catalysts

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ABSTRACT

The first catalytic asymmetric Michael addition of heteroatomic nucleophiles to α,β-unsaturated carboxylic acids is summarized. Direct Michael addition is one of the most straightforward and atom-economical methods for constructing pharmaceutically beneficial building blocks and intermediates, although unsaturated carboxylic acids are known to be inactive Michael acceptors. We designed hybrid catalysts comprising arylboronic acid, thiourea, and tertiary amine to activate the unsaturated carboxylic acids. This review describes the aza- and thia-Michael additions using chiral multifunctional hybrid catalysts, their synthetic applications to biologically active compounds, and the mechanistic consideration of multicomponent borate complexes.

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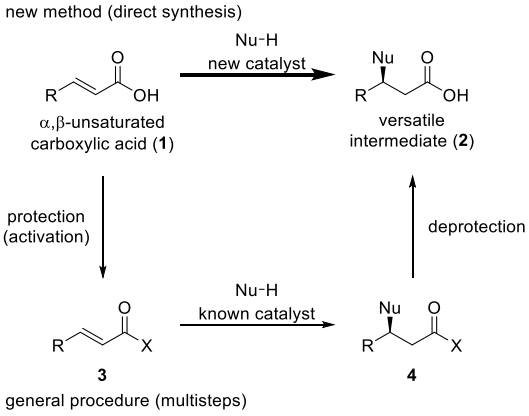
Contents

1. Introduction

Michael addition reactions can efficiently generate asymmetric carbons, which are commonly present in pharmaceutical and natural products. Therefore, such reactions are considered an essential research subject [1]. Since the conjugate adduct **2** of α,β-unsaturated carboxylic acid **1** is a highly practical building block, the Michael receptor **3**, which is conventionally obtained by activating **1**, is generally utilized in catalytic asymmetric Michael additions. However, this robust strategy is accompanied by several challenges, such as atom economy and step efficiency. The additional protecting and deprotecting manipulations inevitably require the same amount of an activating reagent (X) and a multi-step process. Therefore, we planned to develop the first catalytic asymmetric Michael addition using new catalysts that directly convert unprotected **1** into **2** to solve these challenges (Scheme 1).



Scheme 1. Concept of the Direct Michael Addition

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To accomplish the first asymmetric Michael addition to **1**, it was necessary to configure a novel artificial catalyst. Thus, the catalyst was designed according to the reaction mechanism that is mediated by enzymes, such as ammonia lyase and aminomutase (Fig. 1). In the reaction, a carboxylate anion was expected to be stabilized by several hydrogen-bond interactions with arginine 299 and asparagine 340. Thus, we expected appropriate functional groups, such as thiourea, tertiary amine, and boronic acid, to function as hydrogen-bond donors or Lewis acids to stabilize and/or activate the carboxy group, thereby producing the hybrid catalyst **5**, as shown in Fig. 1.

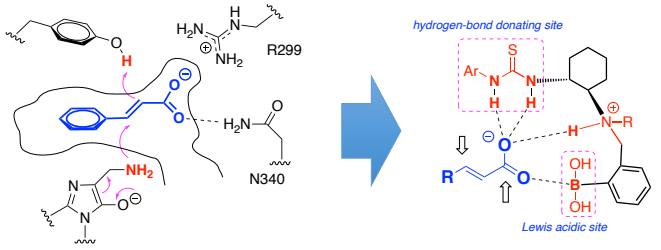
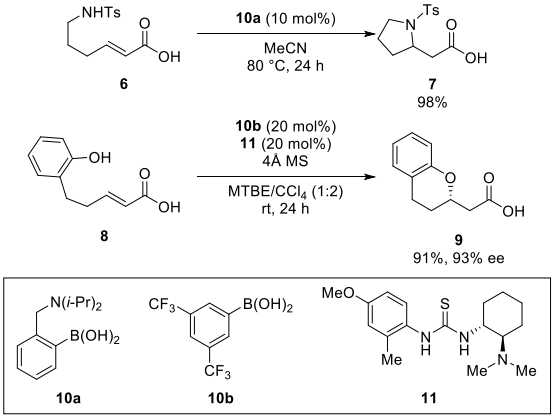


Fig 1. Design of the Artificial Hybrid Catalyst for the Activation of the Carboxylic Acids

In this review, we first introduced the asymmetric aza-Michael addition reaction between **1** and nitrogen nucleophiles using a multifunctional boronic acid **5**. Thereafter, the plausible reaction mechanism via catalytically active borate complexes was clarified by a spectroscopic analysis, density-functional theory (DFT) calculations, and kinetic studies. Applying the optimized conditions, the asymmetric synthesis of an antidiabetic drug, sitagliptin, was achieved with high enantioselectivity. Furthermore, it was demonstrated that catalyst **5** could be effective in the asymmetric thia-Michael addition reaction with appropriate sulfur nucleophiles. The catalytically active coordination mode of the borate complexes could be controlled by the reaction solvent. Thus, the chirality switch was achieved by switching the solvent, affording both enantiomers of the product in good to high yields and with good enantioselectivities.

2. Catalyst design

α,β-Unsaturated carboxylic acids **1** are less electrophilic compared with unsaturated aldehydes and ketones and possess acidic protons that could deactivate nucleophiles and catalysts, thus complicating their application in Michael additions. We first focused on arylboronic acids, which activate carboxylic acids as Lewis acids, and examined the intramolecular hetero-Michael additions of α,β-unsaturated carboxylic acid **6** (Scheme 2) [2]. As a result, only aminoboronic acid **10a** [3] was revealed as an efficient catalyst for both the aza- and oxa-Michael reactions to achieve the desired adducts **7** and **9** in good yields. A further investigation could facilitate the accomplishment of the asymmetric oxa-Michael addition by combining an electron-deficient arylboronic acid **10b** with chiral aminothiourea **11** [4] (Scheme 2) [5].



Scheme 2. Catalytic Asymmetric Intramolecular Michael Addition of α,β-Unsaturated Carboxylic Acids

Based on the foregoing, we explored the intermolecular asymmetric hetero-Michael additions using chiral arylboronic acids. Unlike the intramolecular reactions (Scheme 2), the dual catalysis with **10a-b** and **11** did not efficiently promote the intermolecular reactions, resulting in low yields of racemic products. Therefore, **5** was designed as a new single catalyst that was expected to synergistically activate an unsaturated carboxylic acid and a nucleophile, i.e., the reaction of substrate **1** and catalyst **5** afforded a 1:1 complex **I**, in which a carboxylate ligand was activated by the hydrogen-bond network with thiourea N–H protons and a borate hydroxy proton, as well as the coordination with a Lewis acidic boron atom. Additionally, protic nucleophiles, such as NH_2OR and RSH, can interact with another borate hydroxy group via hydrogen bonding. These multiple synergistic interactions enhance the electrophilicity and nucleophilicity of the carboxylate ligands and internal nucleophiles, respectively (Fig. 2).

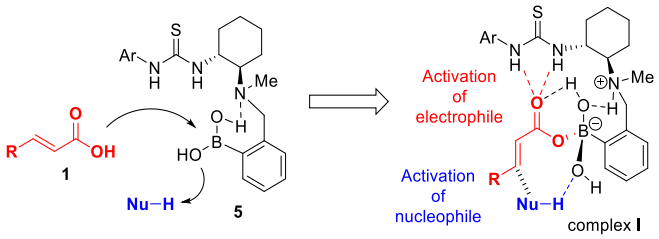
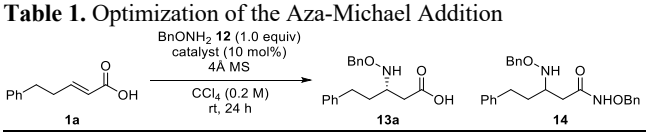


Fig 2. Concept of the Multifunctional Boronic Acid Catalyst

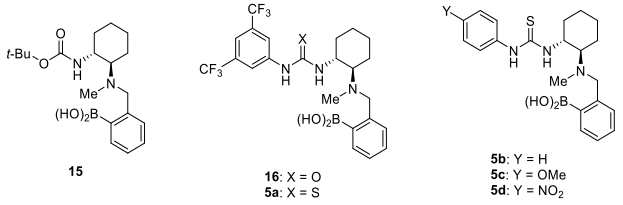
3. Development of asymmetric aza-Michael addition [6]

The aza-Michael addition with nitrogen nucleophiles is an efficient method for synthesizing β-amino acid derivatives, which are valuable raw pharmaceutical materials. Thus, the catalytic asymmetric versions of the α,β-unsaturated carboxylic acid derivatives possessing activating groups, such as imide [7], pyrazole [8], and pyrrole [9], were actively developed. However, the catalytic methods using less active Michael acceptors, such as esters and amides, are still limited [10]; particularly, the aza-Michael addition to unsaturated carboxylic acids has been achieved with perfect selectivity by only enzymes [11], and no artificial catalyst has been successfully applied to the reaction.

Table 1. Optimization of the Aza-Michael Addition

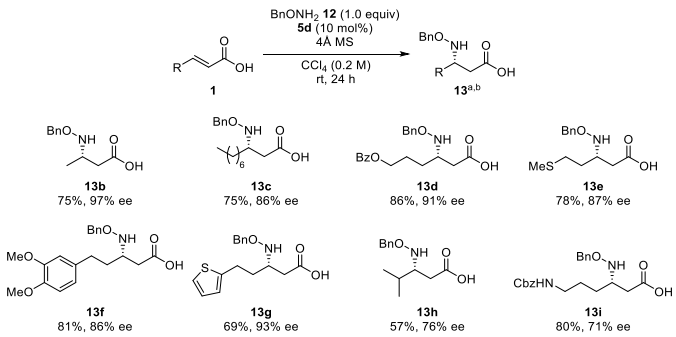


Entry	Catalyst	13a		14
		Yield (%)[a]	Ee (%)[b]	Yield (%)
1	**10a**	15	-	7
2	**10b** + **11**	0	-	41
3	**15**	40	58	0
4	**16**	52	33	0
5	**5a**	81	80	0
6	**5b**	73	87	0
7	**5c**	65	78	0
8	**5d**	83	90	0



[a]Isolated yield after the treatment with $TMSCHN_2$. [b]Estimated by chiral HPLC after the treatment with $TMSCHN_2$.

We first screened several arylboronic acid catalysts for the aza-Michael addition of *O*-benzylhydroxylamine **12** to unsaturated carboxylic acid **1a**. The reaction was carried out in carbon tetrachloride in the presence of a 10 mol% catalyst and molecular sieves (MS) 4Å. Although a low yield was obtained, aminoboronic acid **10a** gave the desired 1,4-adduct **13a** together with the bis-adduct **14**. The results indicate that catalyst **10a** promotes not the 1,4-addition, as well as the undesired 1,2-addition (Table 1, Entry 1). The dual catalysis using boronic acid **10b** and aminothiourea **11**, which was effective in the intramolecular reaction, facilitated the formation of the by-product **14** as the single product (Entry 2). Contrarily, the *N*-Boc catalyst **15** containing a carbamate N–H proton provided the product **13a** in a 40% yield with 58% ee without forming **14** (Entry 3). The appropriate alignments of boronic acid, tertiary amine, and the hydrogen-bond donor are vital to suppress the generation of **14**. To estimate the effect of the hydrogen-bond donors, a range of urea and thiourea catalysts **16** and **5a-d** were subjected to the same reaction conditions. Thus, thiourea apparently exhibits better catalytic performance compared with urea, achieving increased enantioselectivity. Among these catalysts, electron-deficient thiourea **5d** furnished the best results regarding the yield and selectivity, obtaining **13a** in 83% yield with 90% ee as a single adduct (Entries 4-8). Furthermore, **13a** was converted into a known compound, and its absolute configuration was determined to be *S* by comparing the specific rotations of the synthetic and authentic samples [12]. Notably, the addition of the MSs was also essential for the progress of this catalytic reaction.

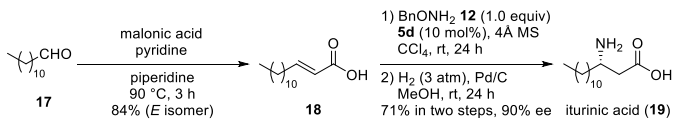


[a]Isolated yield after the treatment with $TMSCHN_2$. [b]Estimated by chiral HPLC after the treatment with $TMSCHN_2$.

Fig. 3. Scope of the Aza-Michael Addition

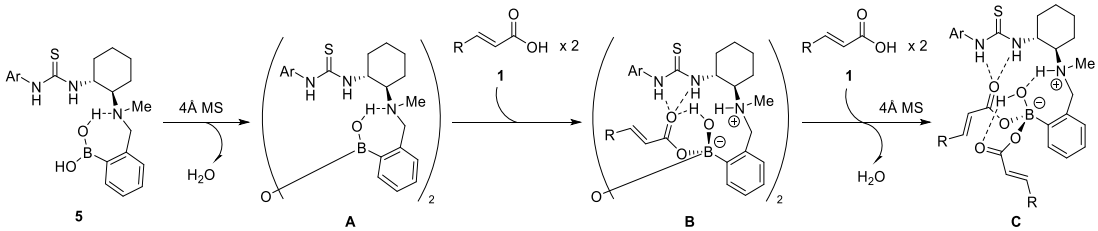
Dissimilar to the enzymes, the multifunctional boronic acid **5d** could be applied to a wide range of α,β-unsaturated carboxylic acids **1b–i** (Fig. 3). For example, adducts **13b–g**, bearing different alkyl chains, could be synthesized with high ee irrespective of the chain length of the substrates. Additionally, various functional groups and aromatic rings, including ethers, esters, and sulfide, were tolerated in the reaction. However, the enantioselectivity of **13h** and **13i** with a sterically hindered or polar substituent remained moderate, and no conjugate addition occurred with cinnamic acid.

The catalytic reaction features the short-step synthesis of unnatural amino acids. For example, beginning from the readily available aldehyde **17**, the optically active iturinic acid (**19**) [14] was synthesized in only three steps. The initial treatment of **17** with malonic acid according to the Doebner method [13] selectively produced (*E*)-unsaturated carboxylic acid **18**, which was converted afterward into the desired product **19** by aza-Michael addition using a nucleophile **12** and a catalyst **5d**, followed by an N–O bond cleavage via hydrogenolysis with Pd/C [14] (Scheme 3).

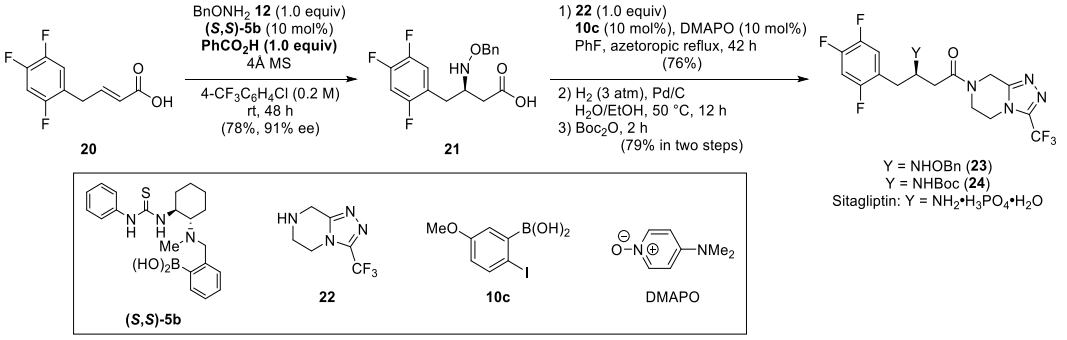


Scheme 3. Synthetic Application to β-Amino Acid

We explored the reaction mechanism of the aza-Michael addition to clarify the structure and function of the catalytically active borate complexes. The boron complex in the reaction system could be changed depending on the ratio of the catalyst and substrate. Thus, titration experiments were conducted as shown in Scheme 4. Even without the substrate **1a**, **5** formed a dimer **A**, which was detected on the electrospray ionization (ESI) mass spectrum, in the presence of MSs [15]. By adding 1 equiv of carboxylic acid **1a**, the carboxylate was coordinated to **A**, thus producing a tetracoordinate borate complex **B**. Further addition of one more equivalent of **1a** resulted in a 1:2 complex **C** of **5** and carboxylic



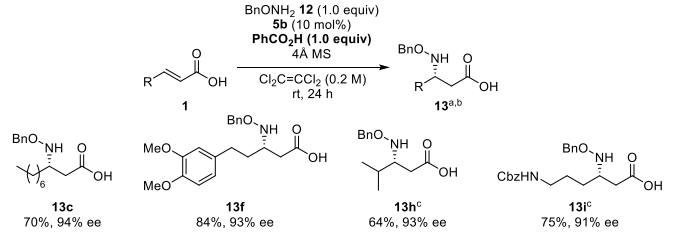
Scheme 4. Plausible Catalyst-Substrate Complexes



Scheme 5. Synthetic Application to Sitagliptin

acid **1a**. The ^{11}B NMR spectra displayed the different signals of these borate complexes **B** and **C** between 0 and 10 ppm, which proved that these complexes were tetracoordinate borate complexes. Contrarily, no significant shift of the signal was observed in the presence of 10 equiv of **1a**.

Assuming the presumed **C** was vital to the stereo-determining step, the addition of a different carboxylic acid, which does not function as a Michael receptor, to the reaction mixture might influence the stereoselectivity of **13**. Thus, we investigated the **5b**-catalyzed aza-Michael addition of **12** in the presence of benzoic acid (Fig. 4). As expected, the addition of 1 equiv of benzoic acid enhanced the stereoselectivity of products **13c** from 86% to 94% ee without a significant decrease in the yield, while tetrachloroethylene was not an optimal solvent (Fig. 4). Although we screened other aliphatic and cinnamic acids as additives, benzoic acid delivered the best result. The equivalence of benzoic acid was also beneficial: the yield and selectivity were reduced with more and fewer equivalents, respectively. Similarly, in the cases examined, the enantioselectivities of products **13f**, **13h**, and **13i** were improved to >90% ee by just adding one equivalent of benzoic acid.



[a]Isolated yield after the treatment with $TMSCHN_2$. [b]Estimated by chiral HPLC after the treatment with $TMSCHN_2$. [c]Reaction time was 48 h.

Fig. 4. Improved Substrate Scope

We next applied the modified catalytic reaction to the asymmetric synthesis of sitagliptin [16], an antidiabetic drug (Scheme 5). The aza-Michael addition between **12** and **20** in the presence of benzoic acid and catalyst **(*S*,*S*)-5b** proceeded enantioselectively in 4-$CF_3C_6H_4Cl$, giving the desired product **21** in good yield. The following condensation of **21** with a secondary amine **22** was efficiently achieved by the catalytic system using boronic acid **10c** and 4-(dimethylamino)pyridine *N*-oxide (DMAPO) [17]. Finally, the obtained amide was subjected to hydrogenolysis and Boc protection, which delivered the target compound without a detrimental decrease in ee. The formal asymmetric synthesis of sitagliptin was accomplished in four steps from α,β-unsaturated carboxylic acid **20** without using any chiral auxiliary and protecting groups. The catalytic reaction was further extended to the asymmetric syntheses of *N*-hydroxy aspartic acid derivatives beginning from fumarate monoesters as the substrates [18]. Since the N–O bond of the product was not only easily cleaved (it was rather effectively extended to peptide ligation with keto-acids), our catalytic method would reveal a new door for the green synthesis of unnatural chiral synthons.

The transition state of the enantio-determining step was elucidated by computational studies (Fig. 5). As described, catalyst **5** and substrate **1** formed the 1:2 borate complex **C**. In a modified method, a similar complex **C** consisting of **1** and benzoic acid would be formed as the catalytically active species. The carboxylate ligand of **1** could be synergistically activated by the thiourea N–H protons and boronic acid to enhance its electrophilicity as a Michael acceptor. Conversely, the benzoate ligand of complex **C** could form a hydrogen bond with the N–H proton of nucleophile **12**. The benzoate ligand is suspected to be key (as a Brønsted base) to bringing the nucleophile closer to the coordinated Michael acceptor in the transition state. Concurrently, the second molecule of benzoic acid is strongly suspected to function as a proton shuttle to accelerate the protonation of the resultant enolate anion, as well as the deprotonation of **12** by the DFT calculations. Altogether, the nucleophile approaches from the *si* face of the Michael receptor in the *s*-trans conformation, thereby supporting the major production of the *S*-isomers.

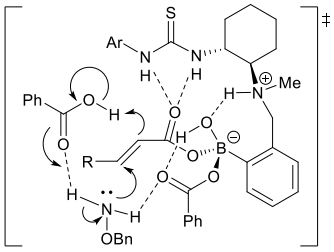


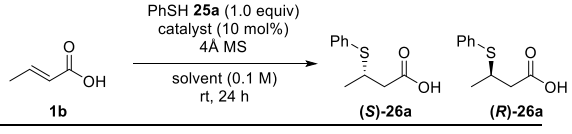
Fig. 5. Plausible Transition States of the Aza-Michael Addition

4. Development of asymmetric thia-Michael addition [19]

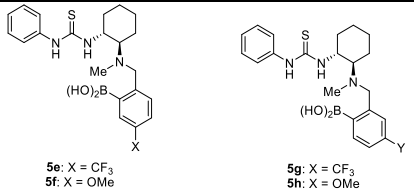
Organosulfur compounds exhibit a wide variety of functions in vivo and have long been validated as synthesis targets for novel bioactive compounds [20]. The thia-Michael addition with sulfur nucleophiles is an efficient method of producing the sulfur-containing compounds [21]. Thus far, many catalytic asymmetric reactions using α,β-unsaturated carboxylic acid derivatives including esters [22], as well as good Michael acceptors, such as imide [23] and pyrazole [24], have been reported. Comparatively, the asymmetric catalytic reactions of carboxylic acids are limited. Particularly, the thia-Michael addition to α,β-unsaturated carboxylic acids have not yet been achieved [25]. To verify the further utility of the multifunctional arylboronic acid catalyst **5**, we attempted to develop a catalytic asymmetric thia-Michael addition for the efficient construction of organosulfur compounds.

We first examined the conjugate additions of crotonic acid **1b** and thiophenol **25a** as model substrates. The reaction was carried out with 10 mol% of a chiral hybrid catalyst **5b** in carbon tetrachloride in the presence of MSs, thus affording the Michael adducts (*S*)-**26a** in a 90% yield with 41% ee (Table 2, Entry 1). Notably, similar to the aza-Michael addition, the *S*-enantiomer was obtained as a major product [22a]. Subsequent investigations also revealed the interesting solvent effects of this catalytic reaction. The Michael adduct with the *S*-configuration could be formed preferentially with **5b** in nonpolar solvents, such as dichloromethane and hexane (Entries 2 and 3). In sharp contrast, the same catalyst **5b** produced the opposite enantiomer (*R*)-**26a**, when the reaction was conducted in acetonitrile and acetone (Entries 4 and 5), although the aza-Michael addition provided no desired products in such polar solvents. Thus, the chirality switch of the products was observed by simply changing the reaction solvent. This phenomenon could be applied to construct a chemical library for drug discovery research requiring both enantiomers [26]. Therefore, further optimization of the reaction conditions in carbon tetrachloride was performed. The enantioselectivity was satisfactorily improved when the reaction took place at a high concentration (2.0 M) (Entry 6). Therefore, **5b** supports the syntheses of both enantiomers with >80% ee by simply changing the reaction solvent (Entries 5 vs. 6). Regarding the optimization of catalysts **5b-h**, **5h** exhibited the highest ee in acetone, while **5b** achieved the best result in carbon tetrachloride. Namely, these results demonstrate the importance of the substituent on the aromatic ring of arylboronic acid. The substituents at the meta position of the boronic acid exerted a minimum effect on the enantioselectivity (Entries 7 and 8), whereas the substituent at the para position significantly affected the stereoselectivity (Entries 9 and 10). In fact, (*R*)-**26a** was obtained with up to 92% ee with catalyst **5h**, in which the methoxy group was substituted at the para position. Moreover, the catalytic activities of **5b** and **5h** in each solvent were significantly reduced without MSs. Conversely, increasing the number of MSs improved the yield of **26a** without decreasing ee (Entry 11).

Table 2. Optimization of the Thia-Michael Addition

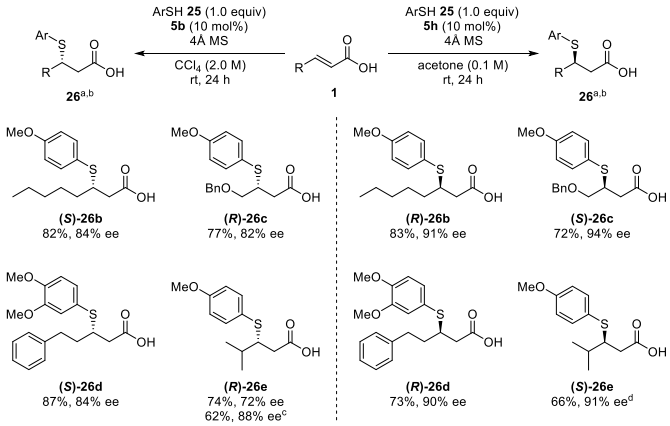


Entry	solvent	catalyst	26a	
			Yield (%)[a]	Ee (%)[b]
1	CCl_4	**5b**	90	41 (*S*)
2	CH_2Cl_2	**5b**	21	22 (*S*)
3	*n*-hexane	**5b**	28	48 (*S*)
4	CH_3CN	**5b**	36	39 (*R*)
5	acetone	**5b**	68	82 (*R*)
6[c]	CCl_4	**5b**	91	81 (*S*)
7	acetone	**5e**	57	81 (*R*)
8	acetone	**5f**	61	68 (*R*)
9	acetone	**5g**	35	45 (*R*)
10	acetone	**5h**	60	92 (*R*)
11[d]	acetone	**5h**	80	92 (*R*)



[a]Isolated yield after the treatment with $TMSCHN_2$. [b]Estimated by chiral HPLC after the treatment with $TMSCHN_2$. The absolute configuration is indicated in parentheses. [c]CCl_4 (2.0 M), 4Å MS (20 mg). [d]4Å MS (100 mg).

Next, the scope of the substrate of the reaction was verified regarding thiol **25** and carboxylic acid **1**. It was clarified that the arylthiols with electron-donating groups, such as a methoxy group, were suitable as sulfur nucleophiles. A variety of unsaturated carboxylic acids **1a-e** bearing different functional groups were tolerated. Irrespective of the alkyl chain length, the two enantiomers were prepared in good yields and high ee's by switching the solvent (Fig. 6). The reaction in carbon tetrachloride follows a similar trend as the aza-Michael addition. In the case of bulky substrates, the addition of benzoic acid efficiently restores the stereoselectivity of product **(*R*)-26e**.



[a]Isolated yield after the treatment with $TMSCHN_2$. [b]Estimated by chiral HPLC after the treatment with $TMSCHN_2$. [c]1.0 equivalent of benzoic acid was added. [d]Reaction time was 48 h.

Fig. 6. Scope of the Thia-Michael Addition

To clarify the interesting phenomenon of the chirality switch, we proceeded to detect any reaction intermediates by spectroscopic analysis (Fig. 7). The same complex **C** consisting of **5b** and two molecules of **1** would be generated in carbon tetrachloride (Scheme 4). Thereafter, the nucleophile, ArSH, would approach from the *si* face of the *s*-trans formed Michael acceptor, thereby favoring the *S*-isomer. Contrarily, a distinct ternary complex was observed when substrate **1b** and catalyst **5b** were mixed in acetone in a 10:1 ratio. The ESI mass spectrometry revealed a new molecular ion peak ($C_{29}H_{35}BN_3O_4S^-$ [M-H]$^-$: 532.2440) but not that of complex **C** ($C_{29}H_{37}BN_3O_5S$ [M-H]$^-$: 550.2552). A new boron complex could be probably formed by releasing one molecule of water. Additionally, the ^{11}B-NMR spectrum showed a peak at 4 ppm for the tetracoordinate boron complex **C** in deuterated chloroform (Fig 8), whereas in deuterated acetone, the peak near 4 ppm decayed with time, and a new peak was observed around 10 ppm (Fig 9). These results strongly suggest that complex **C** loses one molecule of water in a polar solvent to yield complex **D** (without thiol), where the boron and the tertiary amine are connected by a B–N dative bond. In the transition state via **D**, the thiols approached from the *re* face of the Michael acceptor in an *s-cis* form, causing the predominant formation of the *R*-isomers.

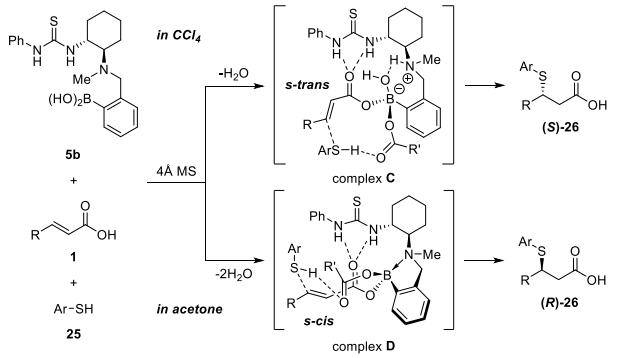
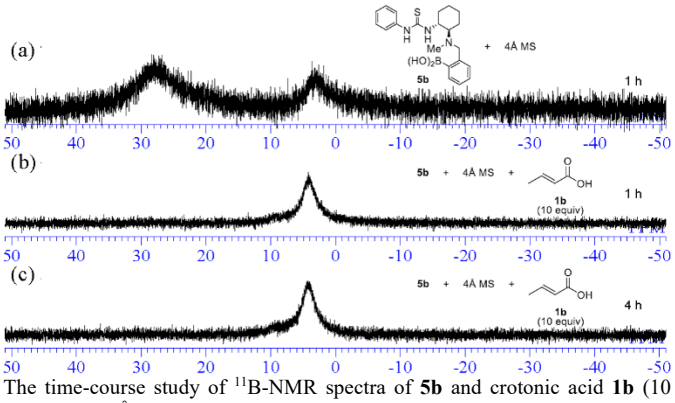
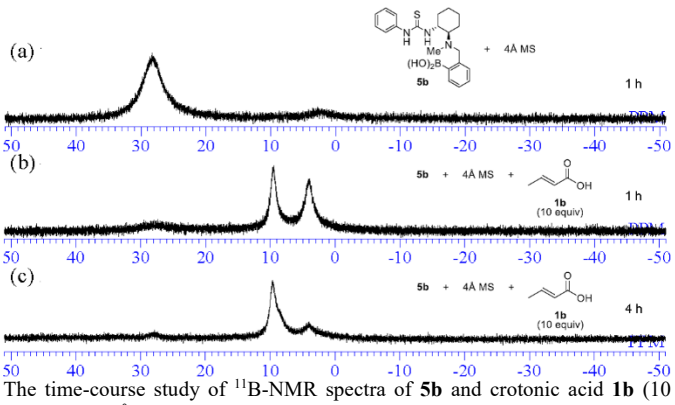


Fig. 7. Plausible Transition States of the Thia-Michael Addition



The time-course study of ^{11}B-NMR spectra of **5b** and crotonic acid **1b** (10 equiv) with 4Å MS. (a) without crotonic acid **1b**; (b) after 1 h; (c) after 4 h.

Fig. 8. ^{11}B-NMR in $CDCl_3$



The time-course study of ^{11}B-NMR spectra of **5b** and crotonic acid **1b** (10 equiv) with 4Å MS. (a) without crotonic acid **1b**; (b) after 1 h; (c) after 4 h.

Fig. 9. ^{11}B-NMR in acetone-d_6

5. Conclusions

A new multifunctional arylboronic acid catalyst possessing both thiourea and tertiary amine in the molecule was developed for detecting α,β-unsaturated carboxylic acids and enhancing the electrophilicity of the unsaturated bonds. This catalyst enables the direct intermolecular asymmetric hetero-Michael addition of nitrogen and sulfur nucleophiles to α,β-unsaturated carboxylic acids, which has not been achieved thus far with artificial catalysts. Moreover, the hybrid catalysts afford an unprecedented synthetic strategy for practical and reliable drug synthesis and discovery research. Recently, the asymmetric Michael additions of carbon nucleophiles were achieved by boronic acid catalysis. Moreover, the catalytic asymmetric reactions using carboxylic acids as substrates can be further improved [27]. We believe that the concept of multifunctional hybrid catalysts described here will expose new areas of catalysis and contribute to the further development of the research field.

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