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A Dual Arylboronic Acid–Aminothiourea Catalytic System for the Asymmetric Intramolecular Hetero-Michael Reaction of α,β-Unsaturated Carboxylic Acids

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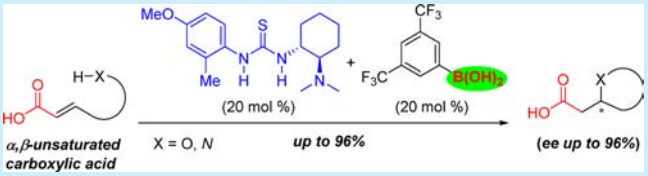
Supporting Information

ABSTRACT: A bifunctional aminoboronic acid has been used to facilitate for the first time the intramolecular aza- and oxa-Michael reactions of α,β-unsaturated carboxylic acids. The combination of an arylboronic acid with a chiral aminothiourea allowed for these reactions to proceed successfully in an enantioselective manner to afford the desired heterocycles in high yields and ee's (up to 96% ee). The overall utility of this dual catalytic system was demonstrated by a one-pot enantioselective synthesis of (+)-erythrococcamide B, which proceeded via sequential Michael and amidation reactions.



N- and O-containing heterocycles bearing a stereogenic carbon center adjacent to a heteroatom are important scaffolds, and heterocycles containing a C2 acetic acid unit can be found in a large number of natural products (Figure 1), most likely because of the way in which they are biosynthesized.[1,2]

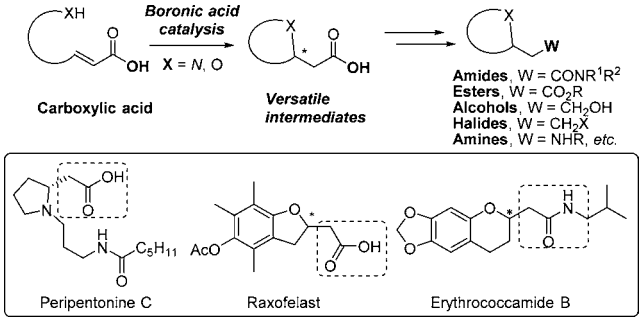


Figure 1. Synthetic strategy for the heterocycles containing C2 acetic acid units through an asymmetric Michael addition of α,β-unsaturated carboxylic acids.

The development of a strategy for the construction of these heterocyclic rings from a simple precursor that would allow for the simultaneous control of the stereogenic centers would represent a straightforward approach for the synthesis of these compounds. With this in mind, it was envisioned that the direct catalytic asymmetric intramolecular hetero-Michael reaction[3−7] of α,β-unsaturated carboxylic acids would provide facile access to heterocyclic compounds bearing a stereogenic carbon center adjacent to the heteroatom (Figure 1). Furthermore, the carboxylic acid moiety could then be used as a versatile synthetic intermediate.[8,9] There are, however, several challenging issues associated with reactions of this type that would need to be addressed, including (1) the reactivity of α,β-unsaturated carboxylic acid derivatives[4,6] as Michael acceptors being much lower than that of the corresponding α,β-unsaturated aldehydes, ketones, and activated ester surrogates;[3,5,7] and (2) the carboxylic acid moiety forming an inert salt with the base,[10] preventing it from behaving as a nucleophile. In fact, to the best of our knowledge, there have been no reports in the literature pertaining to the catalytic asymmetric Michael addition of α,β-unsaturated carboxylic acids either intra- or intermolecularly.[11] To address these challenges, we focused our initial efforts on the boronic acids,[12] because boronic acids have been utilized to activate not only carboxylic acids[10] by Yamamoto and Ishihara but also α,β-unsaturated carboxylic acids[13] by Hall's group[14] through the formation of acyloxyborane species.[15] Herein, we report the direct aza- and oxa-Michael reactions of α,β-unsaturated carboxylic acids using bifunctional aminoboronic acids, together with the asymmetric versions of these reactions using a dual catalytic system composed of a boronic acid and a chiral aminothiourea.[16,17]

We initially investigated the Michael reaction of **1a** using boronic acids **3a−d**, which have been reported to be efficient catalysts for the amidation of carboxylic acids[10] (Table 1, entries 1−4). Disappointingly, only boronic acid **3d** bearing an amine moiety, which was developed by Whiting,[10b,c,18] promoted the reaction to give the pyrrolidine derivative **2a**, albeit in a low yield (Table 1, entry 4). We also screened various solvents for the reaction with **3d** (Table 1, entries 5−8), which revealed that acetonitrile dramatically accelerated the reaction (Table 1, entry

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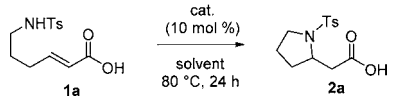
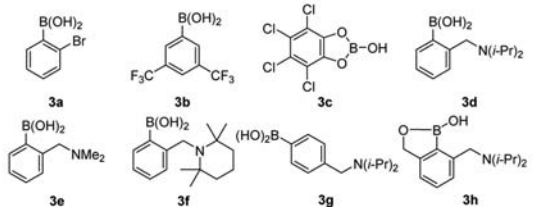
Table 1. Screening of the Reaction Conditions



entry	catalyst	solvent	yield (%)[a]
1	**3a**	toluene	<1
2	**3b**	toluene	<1
3	**3c**	toluene	<1
4	**3d**	toluene	15
5	**3d**	acetone	<1
6	**3d**	DMF	2
7	**3d**	DCE	37
8	**3d**	MeCN	99 (98)[b]
9	**3e**	MeCN	18
10	**3f**	MeCN	7
11	**3g**	MeCN	<1
12	**3h**	MeCN	<1



[a]Determined by ^{1}H NMR spectroscopy. [b]Isolated yield.

8), whereas other polar solvents such as DMF, acetone, and dichloroethane had very little impact on the reaction outcome (Table 1, entries 5−8). The following results show the importance of having a suitable *N*-substituent on the aminoboronic acid (Table 1, entry 8 vs entries 9 and 10): boronic acid **3e** bearing the *N*,*N*-dimethylamino group gave a lower yield compared to **3d**, which was attributed to the reduced Lewis acidity of the catalyst resulting from the coordination of the less hindered amine group to the boron atom (Table 1, entry 9).[18] The use of boronic acid **3f** bearing a bulkier amino group led to a dramatic reduction in the rate of the Michael reaction (Table 1, entry 10), and the *N*,*N*-diisopropyl group was found to give the most suitable results in terms of steric hindrance. In addition to the steric effects, it was also established that the position of the amino group was critical to the reaction outcome. For example, the use of the *para*-substituted catalyst **3g** did not result in the formation of any of the desired product **2a** (Table 1, entry 11). Furthermore, the low activity of benzoxaborole **3h** indicated that the presence of two hydroxyl groups on the boron atom was essential for the reaction to proceed efficiently (Table 1, entry 12).

With the optimized reaction conditions in hand, we proceeded to investigate the application of this protocol to the synthesis of other heterocyclic compounds (Figure 2). We initially examined the effect of the *N*-protecting group (**2b**−**e**). Although the Michael reaction of the substrate bearing an *N*-Cbz group did not proceed even at 110 °C, the *N*-sulfonyl analogues reacted smoothly, with the reaction conditions required (i.e., temperature) appearing to be dependent on the acidity of the NH proton of the substrate (**2c**−**e**). It is noteworthy that the reaction of the *N*-triflate group proceeded at rt to afford the cyclized product **2e** in 89% yield. These results suggested that the rate-determining step in this reaction was the deprotonation or C−N bond forming reaction rather than the formation of an acyloxyborane species.

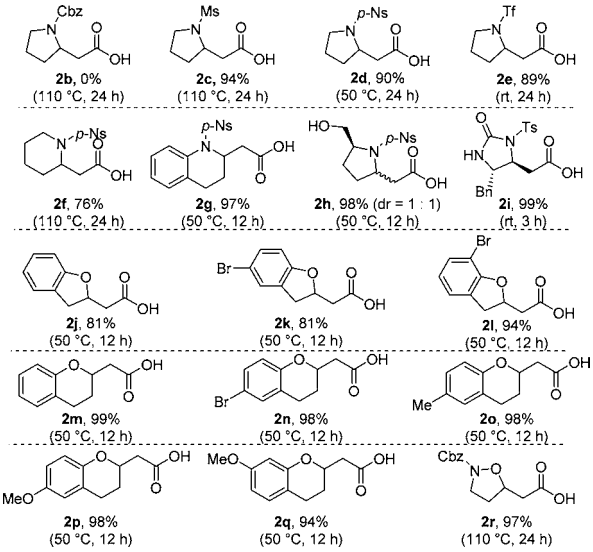


Figure 2. Substrate scope of the Michael addition of α,β-unsaturated carboxylic acids catalyzed by aminoboronic acid **3d** (10 mol %) in MeCN.

The aza-Michael reaction of α,β-unsaturated carboxylic acid derivatives was also applied to the synthesis of the piperidine and tetrahydroquinoline derivatives **2f** and **2g**, which were formed in 76% and 97% yields, respectively. We then moved on to investigate the diastereoselectivity of the reaction with substrates bearing a chiral center derived from an L-amino acid, and the β,γ-diamino acid derivative **2i** was obtained in excellent yield with complete stereoselectivity. We also used the optimized conditions to investigate the intramolecular oxa-Michael reactions of α,β-unsaturated carboxylic acids, which are also challenging transformations because of the poor nucleophilicity of the substrate and the inherent likelihood of a retro-Michael addition. Pleasingly, the oxa-Michael reaction proceeded smoothly under mild conditions to afford the dihydrobenzofuran scaffolds as well as the chroman derivatives in excellent yields (**2j**−**q**). Notably, this strategy also provided access to the isooxazolidine ring **2r** in 97% yield.

A plausible mechanism for this reaction is shown in Figure 3. It was envisioned that the aminoboronic acid **3d** would form a seven-membered H-bonded ring between its boronic acid moiety

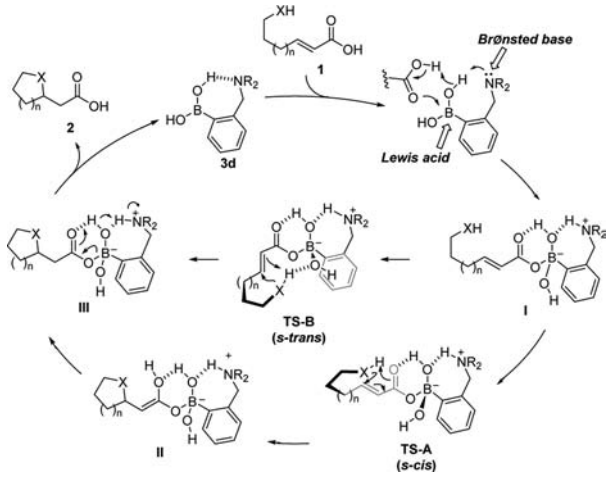


Figure 3. Proposed mechanism.

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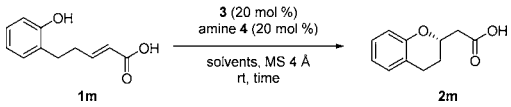
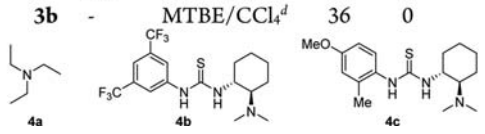
and amino group (B−O−H···N*i*-Pr$_2$) rather than a dative N → B bond, because of the potential for steric hindrance from the *N*,*N*-diisopropylamino group.[8d,18] The trigonal planar boron species would then form an acyloxyborane complex (complex **I**) bearing the carboxylic acid moiety of substrate **1** with the aid of the Lewis acidity of the boron atom and the Brønsted basic moiety of **3d**. The subsequent C−X (X = N, O) bond-forming step would then proceed via **TS-A** or **TS-B**. In the **TS-A** pathway, the consecutive 6- and 7-membered H-bonding interactions would promote the cyclization of the complex with an *s-cis* conformation, which would give intermediate **III** via the tautomerization of cycloadduct **II**. For the alternative mechanism involving **TS-B**, the hydroxyl group on the tetrahedral boronate anion would assist in the formation of the C−X bond via the *s-trans* conformation of the complex. Consideration of the experimental results shown in Table 1 (entry 12), where the benzoxaborole compound **3g** bearing only one hydroxyl group did not facilitate the Michael addition, would support the **TS-B** pathway. Finally, a carboxylic acid exchange reaction would afford the desired product **2**, which would complete the catalytic cycle of **3d**.

As shown in the proposed mechanism, the amino group of the aminoboronic acid would not be directly involved in the activation of the nucleophilic moiety of **1**. It was therefore envisioned that the reaction would be further facilitated by the addition of an external base and that the use of a chiral base catalyst would enable an asymmetric reaction. To evaluate this hypothesis, we investigated the reaction of *α*,*β*-unsaturated carboxylic acid **1m** with boronic acids **3b** and **3d** in the presence of several amines **4** as a dual catalytic system (Table 2).

Table 2. Screening of the Reaction Conditions for the Asymmetric Michael Reaction



entry	3	4	solvent	time (h)	yield (%)[a]	ee (%)[b]
1[c]	**3d**	-	MeCN	8	36	-
2[c]	**3d**	**4a**	MeCN	8	65	-
3	**3d**	**4b**	DCE	36	99	0
4	**3b**	**4b**	DCE	36	67	31
5	**3b**	**4b**	MTBE/CCl_4[d]	36	79	59
6	**3b**	**4c**	MTBE/CCl_4[d]	24	99(91)[e]	93
7	-	**4c**	MTBE/CCl_4[d]	36	0	-
8	**3b**	-	MTBE/CCl_4[d]	36	0	-



[a]Determined by ^{1}H NMR spectroscopy. [b]Estimated by chiral HPLC after treatment with $TMSCHN_2$. [c]The reactions were performed using 10 mol % of **3d** (and **4a**) in the absence of MS 4 Å. [d]The ratio of MTBE/CCl_4 was 1:2 (v/v). [e]Isolated yield.

An acceleration effect was observed when the aminoboronic acid **3d** was used in conjunction with Et_3N (**4a**) in MeCN (entry 1 vs 2). Encouraged by these results, we proceeded to investigate the use of a chiral aminothiourea[16] instead of Et_3N (Table 2, entry 3). Although the reaction itself proceeded efficiently, no enantioinduction was observed during this reaction. It is noteworthy that the replacement of **3d** with the simple boronic acid **3b** effectively suppressed the racemic reaction, and the desired chromane product **2m** was obtained in 31% ee, albeit in a reduced chemical yield (Table 2, entry 4). Following a period of extensive screening,[19] it was established that the yield and enantioselectivity could be improved significantly (79% yield, 59% ee) using a mixed solvent system composed of MTBE and CCl_4 (Table 2, entry 5). Screening of the chiral catalysts[19] revealed that the newly designed aminothiourea **4c** gave a satisfactory result in terms of the yield and enantioselectivity (Table 2, entry 6). Both **3b** and **4c** were essential for the reaction to proceed (Table 2, entries 7 and 8), which strongly suggested that the reaction proceeded via an acyloxyborane species with subsequent activation by an aminothiourea. Although the exact function and role of **4c** remains unclear at this stage, the decreased H-bond-donating ability of the thiourea moiety may have prevented the formation of an inert complex between **4c** and **1** through anion binding,[16,19] and consequently enhanced the formation of an acyloxyborane species.

With the optimized reaction conditions in hand, we proceeded to investigate the scope and limitations of this transformation (Figure 4). These scoping reactions afforded the benzofuran

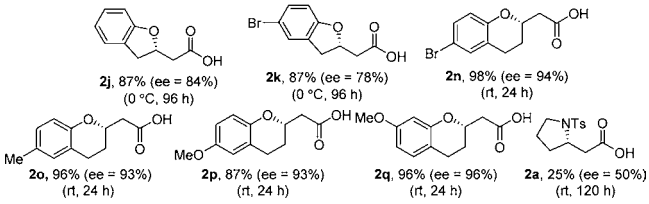
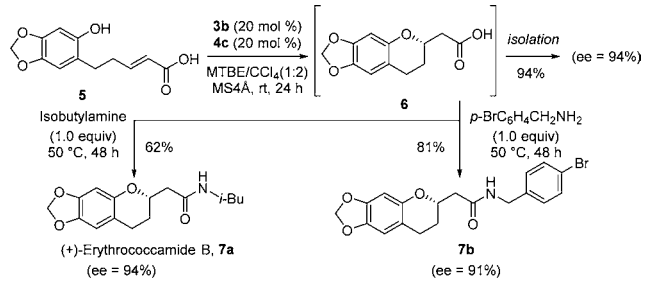


Figure 4. Asymmetric Michael addition catalyzed by boronic acid **3b** (20 mol %) and thiourea **4c** (20 mol %).

derivatives **2j** and **2k** in good yields with moderate to good enantioselectivities.[20] The chromane derivatives were generally obtained in excellent yields and stereoselectivities (93−96% ee's) regardless of the substituent on the aromatic ring (**2n**−**q**). In contrast, the asymmetric aza-Michael reaction proceeded slowly to give the Michael adduct **2a** with only 50% ee.

One of the greatest advantages of this method was demonstrated by our efficient asymmetric synthesis of erythrococcamide B[21] (**7a**) (Scheme 1). The asymmetric oxa-

Scheme 1. Total Synthesis of (+)-Erythrococcamide B via One-Pot Reaction



Michael reaction of the *α*,*β*-unsaturated carboxylic acid **5** proceeded to completion within 24 h under the optimized conditions to give the corresponding carboxylic acid **6** in 94% yield and 94% ee. Pleasingly, the oxa-Michael reaction of **5** followed by the one-pot amidation with isobutylamine proceeded smoothly to give highly enantioenriched (+)-erythrococcamide B (**7a**). It is noteworthy that no racemization was observed during the one-pot reaction process. Subsequent

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derivatization was readily achieved by changing the amine unit, and the amide **7b**, bearing a different *N*-substituent, was also synthesized in an analogous manner.[20]

In conclusion, we have described for the first time the use of aminoboronic acids as efficient catalysts for the direct intramolecular hetero-Michael addition of α,β-unsaturated carboxylic acids. In addition, we have developed an asymmetric version of this protocol using a dual catalytic system composed of an aminothiourea and an arylboronic acid[22] and demonstrated the potential of this system for the facile construction of heterocyclic compounds with a high level of enantioselectivity. Further studies toward elucidating the mechanism of this reaction as well as identifying further uses for this dual catalytic system are currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) The detailed optimization is described in the Supporting Information (SI).

(20) The method for determining the absolute configuration is described in the SI.

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