Novel Aza-Michael Addition–Asymmetric Protonation to α,β-Unsaturated Carboxylic Acids with Chiral Thiourea–Boronic Acid Hybrid Catalysts

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Abstract: In this study, an efficient method has been developed for controlling carbonyl α-chirality with functionalizing β-position by the conjugate addition–asymmetric protonation (CAAP) of α,β-unsaturated carboxylic acids using chiral thiourea–amino boronic acid hybrid catalysts. In addition, the method is applied to the asymmetric synthesis of biologically active compounds.

Carbonyl compounds that are adjacent to a chiral tertiary carbon center are common structures in pharmaceuticals and natural products. Due to their ubiquity, numerous studies have analyzed the asymmetric synthesis of this important substructure. Asymmetric protonation of enolates is one of the most versatile methods for fabricating chiral carbonyl α-carbon centers. Thus, the enantioselective protonation of preformed enolates, such as metal enolate or silyl enol ether, has been investigated using stoichiometric amounts of chiral proton sources or chiral catalysts (Scheme1-1).[1],[2] Furthermore, another attractive approach with β-functionalization is the combination of the Michael addition and the enantioselective α–protonation of the resulting enolates (Scheme1-2). To date, such transformation using unsaturated aldehyde, ketone, ester, amide, and others as Michael acceptors has been successfully studied.[3],[4] However, to the best of our knowledge, the CAAP reaction of α,β-unsaturated carboxylic acids has not yet been reported, despite their chemical stability and availability as starting materials.
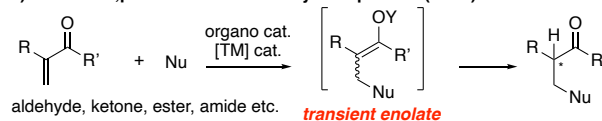
Due to their improved stability to enzymatic hydrolysis, peptides containing β-amino acids are commonly found in pharmaceuticals and biopolymers.[5] β-Amino acids are mainly classified as five categories: β^2, $\beta^{2,2}$ $\beta^{2,3}$, β^3, and $\beta^{3,3}$-amino acids. Although catalytic asymmetric synthesis of β-amino acid derivatives has been well developed, the direct transformation of α,β-unsaturated carboxylic acids into chiral β^2-amino acids is still rare, despite the unnecessary use of carboxy protecting groups.[6],[7]

In recent decades, catalytic asymmetric reactions using carboxylic acids have emerged, and their versatile potential as substrates in synthetic chemistry has been demonstrated. In 1988, Yamamoto described the first catalytic asymmetric Diels–Alder reaction of α,β-unsaturated carboxylic acids using a chiral borane catalyst.[8] Recently, the Ishihara group developed an enantioselective Michael addition of ketones to α,β-unsaturated carboxylic acids using an arylboronic acid and a chiral secondary amine.[9] Furthermore, several asymmetric reactions with aliphatic carboxylic acids using chiral organoboron and organosilane complexes have been reported.[10] Moreover, we have been involved in the asymmetric hetero-Michael additions to α,β-unsaturated carboxylic acids and have developed
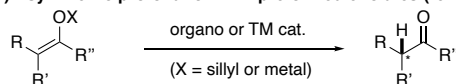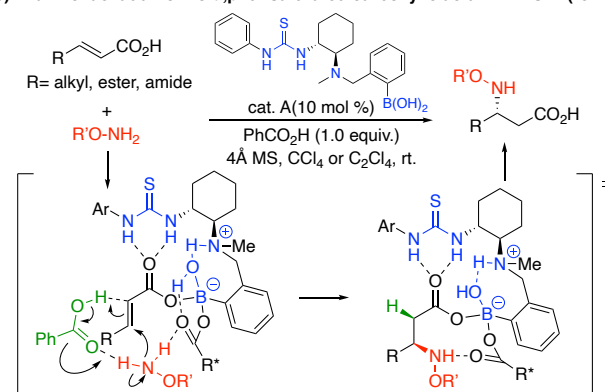
Scheme 1. Strategy for aza-Michael addition-asymmetric protonation to unsaturated carboxylic acids.

chiral thiourea–amino boronic acid hybrid catalysts and a dual catalytic system comprising an arylboronic acid and a chiral aminothiourea[11a-c] (Scheme 1-3). In the course of these projects, mechanistic studies (kinetics, NMR titration experiments, and computational studies) revealed that high enantioselectivity was attributed to asynchronous concerted face-selective nucleophilic addition at the β-position and carboxylic acid-mediate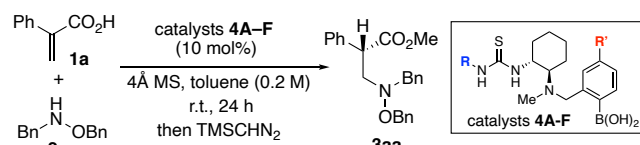d protonation at the α-position.[11d] In particular, the third molecule of the carboxylic acid plays a crucial role as a proton shuttle in the deprotonation of nucleophiles and the protonation of transient enolate anions. With these in mind, we envision that the same catalyst would control the carbonyl α-carbon centers of α-substituted α,β-unsaturated carboxylic acids through a similar stereoselective protonation via a proton shuttle during the CAAP reaction (Scheme1-4). However, some problems remain to be considered in CAAP reaction with carboxylic acids: (1) the reactivity of α-substituted carboxylic acids and (2) conformational control of α-substituted unsaturated carboxylic acid (s-cis vs s-trans). Thus, we aimed to develop the CAAP reaction of α-substituted acrylic acid derivatives through aza-Michael addition and the subsequent face-selective protonation to provide a straightforward

route to chiral β^2-amino acids without the protection of carboxylic acid. Moreover, the direct synthetic method could offer efficient access to a variety of natural products and drugs, such as (–)-nakinadine B[12] and Ipatasertib[13] (Scheme1-5).

Table 1. Optimization of reaction conditions

entry	catalyst R	R'	additive		yield (%)	ee (%)[a]
1	**4A** (phenyl)	H	-		47	1
2	**4B** (MeO-phenyl)	H	-		38	2
3	**4C** (3,5-(CF₃)₂-phenyl)	H	-		51	16
4	**4D**	H	-		51	23
5	**4E** (NC, CF₃)	OMe	-		40	21
6	**4F**	CF₃	-		64	24
7	**4F**			(1.0 eq.)	65	51
8	**4F**		Ph⌒CO₂H	(2.0 eq.)	72	60
9[b]	**4F**			(2.0 eq.)	63	77
10[b]	**4F**		PhCO₂H	(2.0 eq.)	46	51

[a] Determined by chiral HPLC analysis.
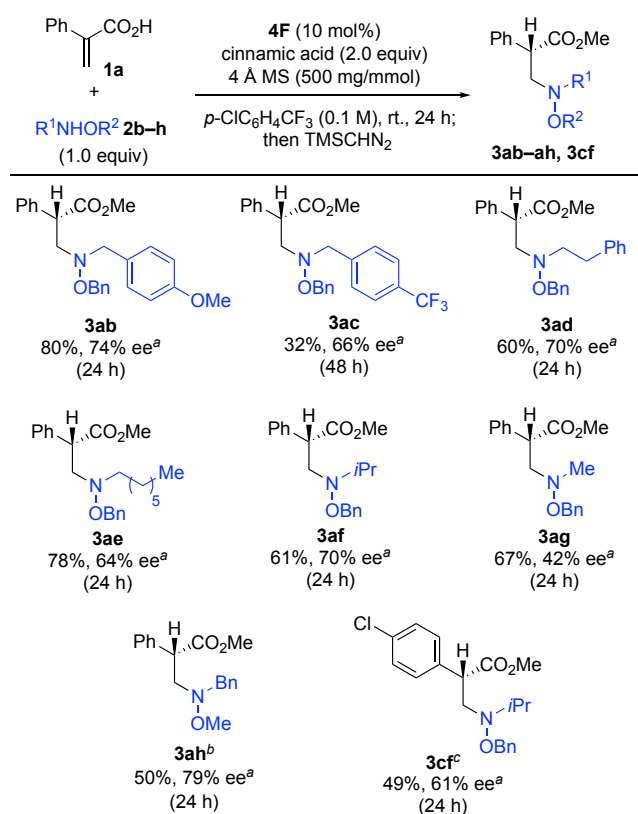[b] p-ClC$_6$H$_4$CF$_3$ (0.1 M) was used as solvent.

First, we attempted tandem aza-Michael addition and asymmetric α-protonation using atropic acid (**1a**) and BnONH$_2$ as model substrates. However, the double Michael addition predominantly occurred, affording a mixture of *N*-alkyl and *N,N*-dialkyl-*O*-benzylhydroxylamine. Based on the results, to obtain the desired product (**3aa**), we investigated the asymmetric protonation of **1a** with BnONHBn (**2a**) in the presence of various catalysts **4A–F** (Table 1). The reaction was performed in toluene (0.2M) with 10 mol% of catalyst and 4Å MS (500 mg/mmol) at room temperature. When Ph-substituted thiourea **4A** was used, the monoalkylated adduct **3aa** was afforded in moderate yield and with poor selectivity (47%, 1% ee). The same reaction with catalysts **4B–D** bearing different aryl groups clearly demonstrated that the installation of additional electron-withdrawing substituents to the aryl group significantly improved enantioselectivity (entries 1–4). Comparison of catalysts **4E** and **4F** showed that the introduction of the CF$_3$ group in the arylboronic acid moiety increased the yield of **3aa** with similar selectivity (entries 5 and 6). Overall, catalyst **4F** exhibited the best catalytic performance. Since we previously found that the addition of 2 equiv. of benzoic acid to the reaction mixture enhanced both yield and selectivity, a series of carboxylic acids were tested as proton shuttles (see Table S1 in supporting information). As expected, among the examined carboxylic acids, cinnamic acid greatly increased both yield and ee (entries 7 and 8). Furthermore, switching the solvent from toluene to p-ClC$_6$H$_4$CF$_3$ (p-CBTF) further increased selectivity, subsequently affording the best results (entry 9, 63% yield, 77% ee). In contrast to the previous cases, the use of benzoic acid as a proton shuttle only

provided unsatisfactory selectivity (entry 10)[11d]. These results indicate that each reaction has a different matched combination of substrate and additive, which depends on the catalysts used and their transition state.
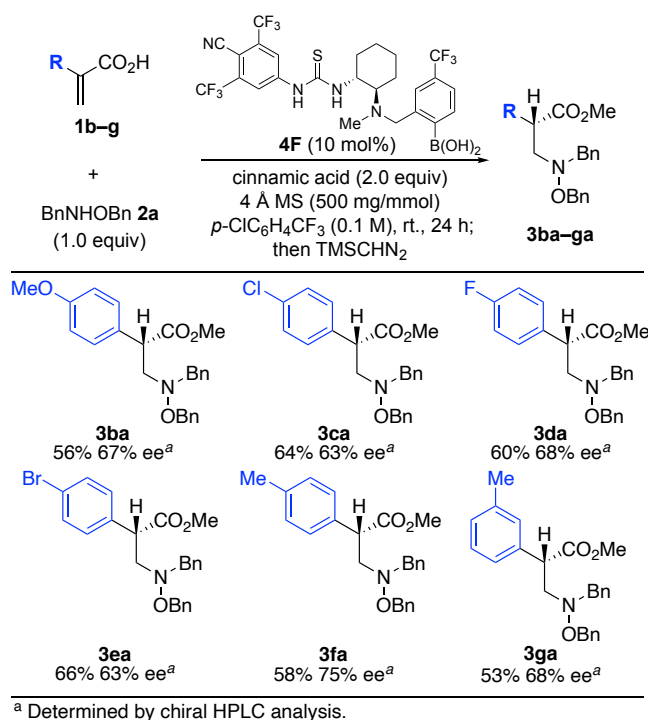
Scheme 2. Scope of α-arylacrylic acids

After establishing the optimized conditions, we investigated the reaction scope of the carboxylic acids **1b–g** (Scheme 2). Although 2-alkylacrylic acids did not undergo Michael addition, the reaction was applicable to a range of 2-arylacrylic acids bearing either an electron-withdrawing group (EWG) or electron-donating group (EDG) at the *p*-position (**1b–1f**), affording the corresponding products **3ba–fa** in reasonable yield and selectivity. In addition, **1g** possessing methyl group at the *m*-position furnished the Michael adduct **3ga** in similar yield and selectivity.

To further examine the scope of nucleophiles, a range of hydroxylamine derivatives **2b–h** was studied using **1a** as the common substrate (Scheme 3). Regarding the effect of the electron density of the nitrogen atom, the EDG of **2b** enhanced both reactivity and selectivity. In contrast, the EWG of **2c** significantly decreased the reactivity and slightly decreased the selectivity. Change of the *N*-Bn group of **2a** to linear and branched alkyl groups of **2d–g** revealed that the bulkier substituent tends to afford higher enantioselectivity (**3ad, 3ae, 3af** > **3ag**). However, the bulkiness of the *O*-alkyl group of **2** is likely not important for the selectivity (**3aa** vs **3ah**). Finally, the chiral fragment **3cf** of the Akt inhibitor, *Ipatasertib*, was concisely synthesized from carboxylic acid **1c** and *O*-benzyl-*N*-isopropylhydroxylamine **2f**.

Scheme 3. Scope of the nucleophiles

Reaction conditions and products:

Ph—CH=C(CO₂H) **1a** + R¹NHOR² **2b–h** (1.0 equiv) → **4F** (10 mol%), cinnamic acid (2.0 equiv), 4 Å MS (500 mg/mmol), *p*-ClC₆H₄CF₃ (0.1 M), rt., 24 h; then TMSCHN₂ → **3ab–ah, 3cf**

3ab
80%, 74% ee[a]
(24 h)

3ac
32%, 66% ee[a]
(48 h)

3ad
60%, 70% ee[a]
(24 h)

3ae
78%, 64% ee[a]
(24 h)

3af
61%, 70% ee[a]
(24 h)

3ag
67%, 42% ee[a]
(24 h)

3ah[b]
50%, 79% ee[a]
(24 h)

3cf[c]
49%, 61% ee[a]
(24 h)

[a] Ee values were determined by chiral HPLC analysis.
[b] Nucleophile was added slowly with a syringe pump over 24 h.
[c] Instead of **1a**, **1c** was used as substrate.

To demonstrate the synthetic applicability of aza-Michael addition-asymmetric protonation, we explored the total asymmetric synthesis of the natural product, (–)-*nakinadine* B. This molecule was isolated from Okinawan marine sponge *Amphimedon* sp by the Kobayashi group,[12a] and it possesses modest cytotoxicity against L1210 murine leukemia and the KB human epidermoid. It possesses a chiral core structure of a β^2-amino acid with a long aliphatic chain bearing pyridine at a terminal position. Till date, two studies have accomplished the asymmetric total synthesis of the natural product. However, both synthetic routes are slightly lengthy due to the additional steps required for the protection and deprotection of the carboxy groups. Therefore, our method is an ideal synthetic tool for accessing the natural product and its derivatives. In fact, the reaction of **1a** with **2i** in the presence of **4F** (20 mol%) and cinnamic acid (2 equiv.) affords the desired carboxylic acid **5**. The subsequent treatment of **5** with TMSCHN₂ afforded methyl ester **3ai** in 46% and 70% ee. Notably, the addition of **2i** to the reaction did not have any detrimental effect on the outcomes, whereas a pyridine moiety of **2i** may inactivate the catalyst and substrate by interacting with the boron atom and the carboxy group, respectively. The final Pd/C-catalyzed hydrogenation of the crude product **5** yielded (–)-nakinadine B in 28% yield in two steps (Scheme 4). The spectroscopic data of a synthetic sample including specific rotation $[\alpha]_D$ are consistent with those of the natural product.[12b] We have thus achieved the catalytic and direct asymmetric synthesis of target molecule in the shortest step.
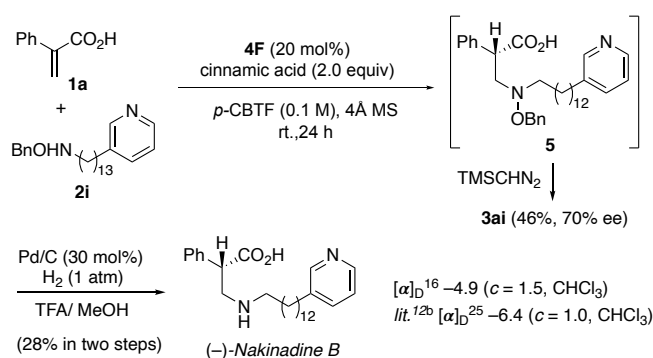
Scheme 4. Synthetic application to (–)-nakinadine *B*

To rule out the possibility of direct asymmetric protonation of carboxylic acids **3** via either the corresponding enol or enolate during the CAAP reaction, the racemic product **3aa-CO₂H** was exposed to the reaction conditions, resulting in the recovery of methyl ester **3aa** without changing the enantioselectivity (50:50) (Scheme 5). Therefore, we confirmed that no α-deprotonation of products **3** occurred under the catalytic conditions.
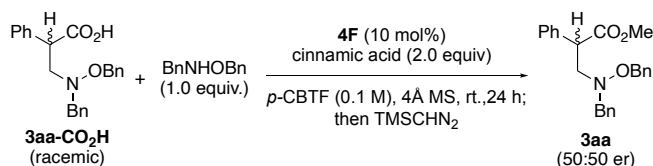
Scheme 5. Control experiment with product **3aa-CO₂H**

In addition, we confirmed the stereochemistry of α-protonation in the CAAP reaction. For this, the product **3aa** was converted to a known compound **6**[14] as shown in Scheme 6. By comparing the specific rotation $[\alpha]_D$ of product **6** with that of an authentic sample, the absolute configuration of **3aa** was unambiguously determined to be *S*.
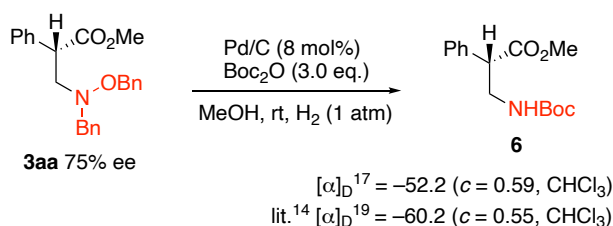

Scheme 6. Determination of the absolute configuration of **3aa**

Based on these results, a plausible catalytic cycle is shown in **Figure 1**. We presumed that complex **A**, which comprises a catalyst and two molecules of cinnamic acid, initially forms in a resting state. This occurs because the less demanding cinnamic acid preferentially coordinates to the catalyst boron atom due to the bulkiness of atropic acid **1a**. After one molecule of cinnamic acid is replaced by **1a**, the nucleophile BnNHOBn attacks the coordinated atropic acid from the upper site through the hydrogen bonding interaction with the carbonyl group of the cinnamic acid ligand (**int B** to **int C**). Since the acidity of the catalyst thiourea moiety is very important for achieving good

yield and enantioselectivity of product **3**, we speculate that the aza-Michael addition of BnNHOBn is probably a late-determining step. Subsequently, the resulting enolate **int C** can be intramolecularly protonated from the upper side by an ammonium proton of the nucleophile to generate **int D** in a enantioselective manner.[4e],[15] Finally, the catalytic cycle is completed by the following ligand exchange of **int D** with another cinnamic acid, providing the desired product **3a** along with complex **A**. However, nonstereoselective reactions can also proceed with less demanding nucleophiles, leading to the racemic product or antipode (*R*)-isomer via **Int E** or **Int F**. This may be one of the reasons for the reduced enantioselectivity, when small-sized nucleophiles are used.

In conclusion, we have developed an aza-Michael addition– asymmetric protonation reaction to α,β-unsaturated carboxylic acids using a thiourea–boronic acid hybrid catalyst. Various substituents on the nucleophile can be applied to the reaction. Furthermore, this method provides an efficient synthetic tool for the catalytic asymmetric synthesis of natural products and pharmaceuticals. Further mechanistic studies and more comprehensive systems are under development in our laboratory.
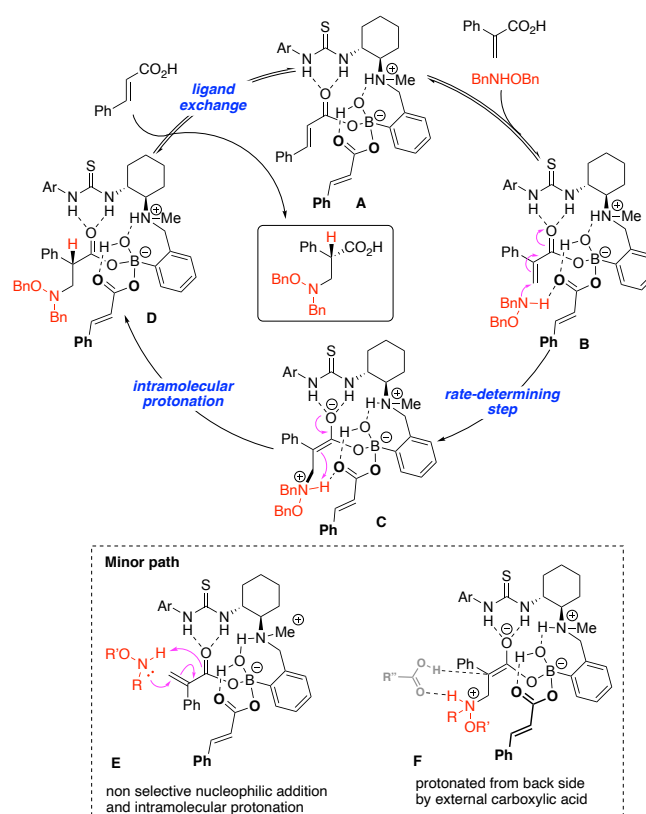
Figure 1. Proposed mechanism

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