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Boronic Acid Accelerated Three-Component Reaction for the Synthesis of α-Sulfanyl-Substituted Indole-3-acetic Acids

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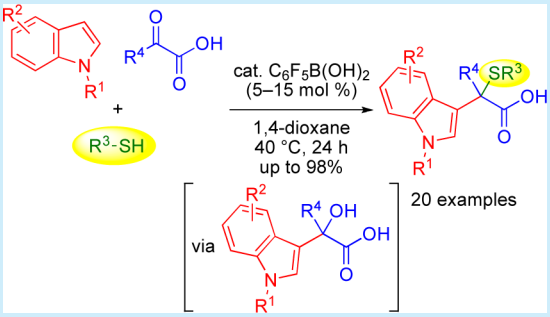
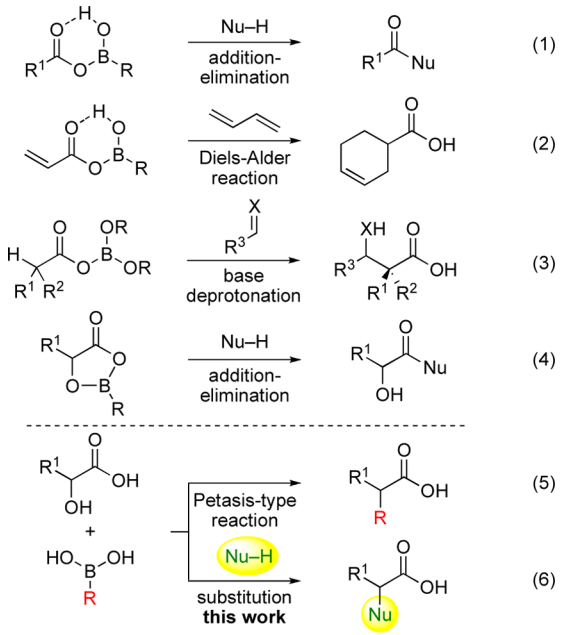
Supporting Information

ABSTRACT: Boronic acid was used to accelerate a three-component reaction of indoles, thiols, and glyoxylic acids for the synthesis of α-sulfanyl-substituted indole-3-acetic acids. Boronic acid catalysis to activate the α-hydroxy group in α-hydroxycarboxylic acid intermediates and intramolecular assistance by free carboxylic acid were the keys to accelerating the product formation.



Boronic and boric acid catalyzed transformations of carboxylic acids are frequently applied in the field of organic synthesis. The most widely investigated transformation is the direct activation of carboxylic acids to afford amides and esters (Scheme 1, eq 1).[1,2] Diels–Alder and [3 + 2] cycloaddition reactions of carboxylic acids are also accelerated by boronic and boric acid catalysts, as exemplified by chemoselective electrophilic activation of carboxylic acid in the presence of ester in a Diels–Alder reaction (Scheme 1, eq 2).[3] A different activation mode was recently introduced, in which nucleophilic activation of carboxylic acids was achieved using $BH_3{\cdot}SMe_2$ as a borane catalyst in the presence of DBU as the base (Scheme 1, eq 3).[4] Boronic acid is also useful to activate α-hydroxycarboxylic acid in the formation of amides[5] and esters[6] (Scheme 1, eq 4).

Scheme 1. Activation Modes of Carboxylic Acids with Boronic and Boric Acids



Although activation of carboxylic acids by boronic and boric acid derivatives is well developed, activation of an *α-hydroxy group* of carboxylic acids with boron-based catalysts is rarely described.[7] To this end, we were interested in Petasis-type borono-Mannich reactions,[8] in which stoichiometric amounts of boronic acids act as nucleophiles to form α-arylated acetic acids (Scheme 1, eq 5). Because electron-deficient boronic acids are less prone to act as nucleophiles,[9] we envisioned that electron-deficient boronic acids would promote the activation of α-hydroxy groups without the concomitant formation of Petasis-type products (Scheme 1, eq 6).[8b] In conjunction with our recent interests in the activation of unactivated hydroxy groups,[10] including modification of thiols with α-hydroxycarboxylic acids,[11] here we present boronic acid accelerated substitution of the α-hydroxy group of carboxylic acids in a three-component reaction of indoles, glyoxylic acids, and thiols. We further demonstrated chemoselective activation of the carboxylic acid over the corresponding ester.

To evaluate the feasibility of this mode of activating an α-hydroxy group with boronic acids, we selected a three-component reaction of indoles, thiols, and glyoxylic acids because this combination yields α-sulfanyl-substituted indole-acetic acids, a core structure of many bioactive compounds.[12] Although the synthesis of related sulfur-containing indole derivatives using metal or acid catalysts has been reported,[13] multicomponent reactions to generate compounds containing

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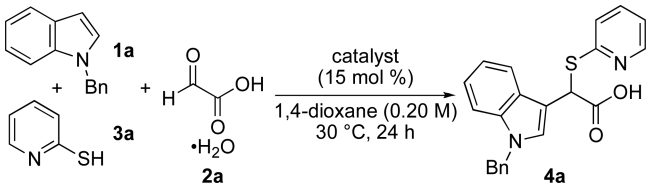
free carboxylic acids have not yet been described. We began screening various catalysts using *N*-benzylindole **1a**, glyoxylic acid monohydrate **2a**, and 2-mercaptopyridine **3a** as model substrates to facilitate monitoring of the reaction progress (Table 1). The desired reaction did not proceed without a

Table 1. Optimization of Reaction Conditions[a]



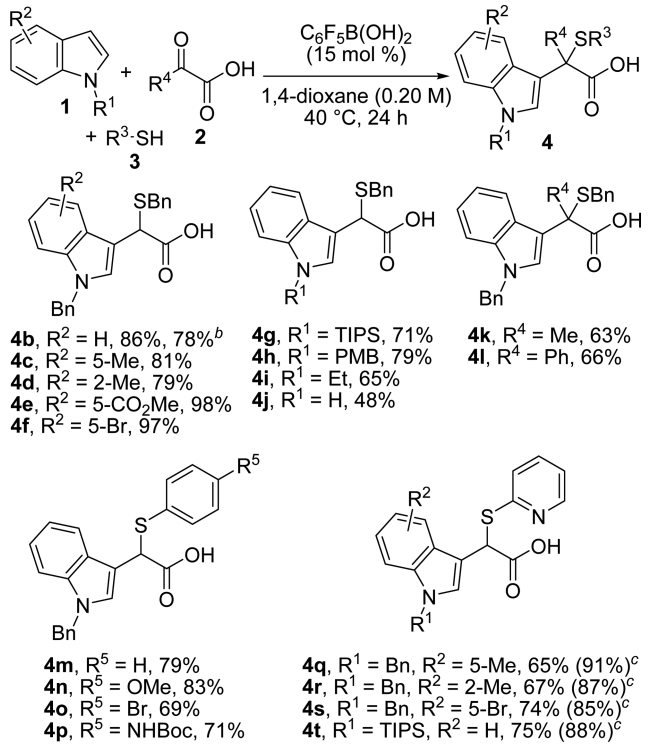
entry	catalyst	yield (%)[b]
1	none	n.d.
2	AcOH	n.d.
3	H_3PO_4	3
4	CF_3CO_2H	7
5	*p*-TsOH·H_2O	40
6	CF_3SO_3H	8
7	$B(OH)_3$	18
8	$EtB(OH)_2$	20
9	$PhB(OH)_2$	15
10	4-$MeOC_6H_4B(OH)_2$	16
11	3,5-$(CF_3)_2C_6H_3B(OH)_2$	68
12	$C_6F_5B(OH)_2$	82
13	$(C_6F_5)_3B$	8
14[c]	$C_6F_5B(OH)_2$	90
15[c,d]	$C_6F_5B(OH)_2$	92 (73)[e]

[a]Reaction conditions: **1a**/**2a**/**3a** (1:1:1) and catalyst (15 mol %) in 1,4-dioxane (0.20 M) at 30 °C for 24 h. [b]Determined by ^1H NMR analysis of the crude mixture. [c]At 40 °C. [d]**1a**/**2a**/**3a** (1:1.5:1.2). [e]Isolated yield. n.d. = not detected.

catalyst (entry 1), and even the use of stronger acids did not promote the reaction well (entries 2−6). On the other hand, boric acid (pK_a = 9.2) as well as ethyl- and phenylboronic acids afforded the desired product **4a**, albeit in low yields (entries 7−9). To improve the reactivity, we evaluated several arylboronic acids and found that electron-deficient arylboronic acids promoted the reaction in high yield (entries 10−12), whereas strongly Lewis acidic tris(pentafluorophenyl)borane provided **4a** in low yield (entry 13), suggesting that the formation of boronate ester was important for promoting the desired reaction. Further optimization of the temperature (entry 14) and substrate ratio gave **4a** in 92% yield (entry 15).[14,16]

Having determined the optimized conditions, we next examined the substrate scope (Scheme 2). We selected benzyl mercaptan **3b** to study the scope of indole **1** with glyoxylic acids **2**. Product **4b** was obtained in good yield, even at 1.0 mmol scale and 5 mol % catalyst loading, with slightly modified reaction conditions.[15] Various substituted indoles **1c**−**f** gave the products **4c**−**f** in good yields. Indoles having several *N*-protecting groups **1g**−**1i** were tolerated, and even unprotected indole **1j** gave the product **4j**, albeit in moderate yield. Pyruvic acid **2b** and phenylglyoxylic acid **2c** were also suitable to generate products **4k** and **4l** containing quaternary carbon centers in good yields. The substrate scope of thiol **3** was studied with 4-substituted benzenethiols and 2-mercaptopyridine; electron-rich thiols afforded a better yield of the desired product **4**. Notably, acid-sensitive *N*-Boc protective groups were tolerated to give **4p** in good yield, suggesting the

Scheme 2. Substrate Scope[a]

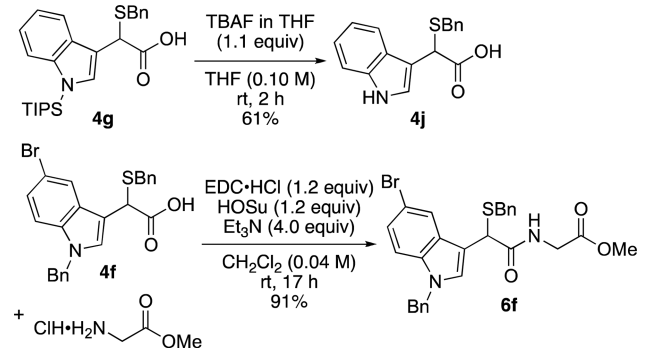


[a]Reaction conditions: at 0.20 mmol scale, **1**/**2**/**3** (1:1.5:1.2) in 1,4-dioxane (0.20 M) at 40 °C for 24 h using $C_6F_5B(OH)_2$ (15 mol %) as catalyst. [b]At 1.0 mmol scale, **1a**/**2a**/**3b** (1.3:1.5:1.0) in 1,4-dioxane (0.20 M) at 60 °C for 24 h using 5 mol % of catalyst. [c]Determined by ^1H NMR analysis of the crude mixture.

mildness of the current reaction conditions compared with conventional strongly acidic conditions used for related α-substitution reactions.[13a−c]

Next, transformation of the product **4** was performed (Scheme 3). *N*-TIPS-protected indole was deprotected to

Scheme 3. Transformation of the Products



give *N*-unprotected product **4j**. Amide bond formation of **4f** was achieved with glycine methyl ester hydrochloride to give the desired product **6f** in 91% yield.

To clarify the accelerating effects of boronic acids, we monitored the reaction progress. In the absence of the catalyst, α-hydroxycarboxylic acid intermediate **7a** formed slowly (Scheme 4), and the structure of **7a** was confirmed after in situ transformation to the corresponding ester.[15] Product **4a** also formed very slowly and only after the formation of **7a**

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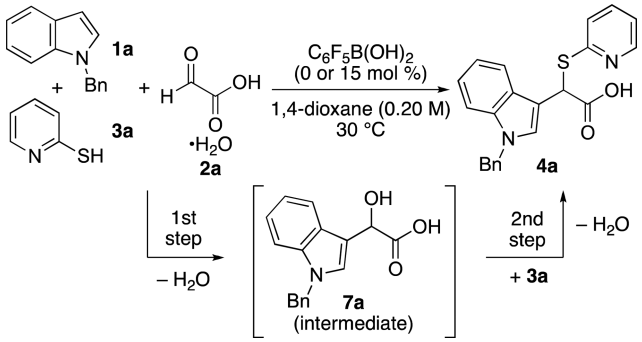
Scheme 4. Monitoring the Reaction Progress



(Figure 1a), suggesting that the formation of **4a** (the second step) was slower than that of **7a** (the first step) without a

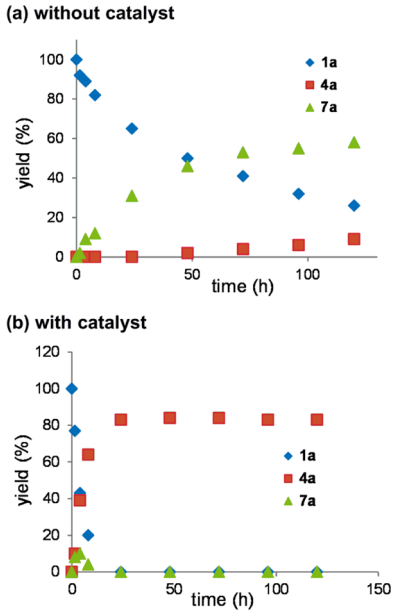


Figure 1. Reaction progress (a) without catalyst and (b) with catalyst.

catalyst. On the other hand, addition of the boronic acid catalyst significantly accelerated the formation of **4a**, and only a trace amount of the intermediate **7a** was observed during the reaction (Figure 1b). These results indicate that the second step was faster than the first step in the presence of the catalyst and suggest that the boronic acid catalyst accelerated the second step.

To elucidate how the boronic acid catalyst accelerated the second step, we explored plausible reaction mechanisms in the presence of the catalyst using DFT calculations (Figure 2).[15] The calculated activation energies suggest that the reaction via acyclic boronate **TS1** was favored over that via cyclic boronate **TS2**, most probably because the carboxylic acid moiety assists in eliminating the α-hydroxy group during the transition state of acyclic boronate.

To obtain experimental evidence for the carboxylic acid assisted activation of the intermediate, we examined the chemoselective reaction with glyoxylic acid in the presence of the corresponding ester (Table 2). The boronic acid catalyst produced high chemoselectivity with carboxylic acid **4a** over ester **5a′**, whereas rather strong acids (*p*-toluenesulfonic acid and phosphoric acid) promoted the reaction more slowly but

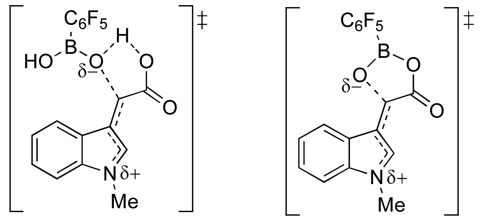
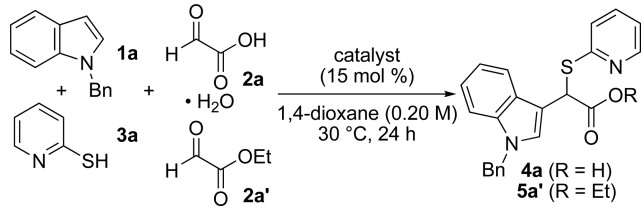


Figure 2. Comparison of transition state energies.

Table 2. Chemoselective Reaction between Glyoxylic Acid and Its Ethyl Ester[a]



entry	catalyst	4a (%)[b]	5a′ (%)[b]	4a/5a′
1	$C_6F_5B(OH)_2$	84	2	42:1
2	*p*-TsOH·H_2O	37	17	2.2:1
3	H_3PO_4 (1 equiv)	14	2	7:1

[a]Reaction conditions: **1a**/**2a**/**2a′**/**3a** (1:1:1:1) in 1,4-dioxane (0.20 M) at 30 °C for 24 h. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture.

maintained the chemoselectivity in favor of carboxylic acid. These results support the proposed reaction mechanism by which the carboxylic acid moiety functions to facilitate elimination of the α-hydroxy group.[17]

In summary, we developed a novel boronic acid accelerated three-component reaction of indoles, thiols, and glyoxylic acids, providing a unique class of α-sulfanyl-substituted indole derivatives containing free carboxylic acids via the formation of α-hydroxycarboxylic acids. We also demonstrated that simultaneous activation of the α-hydroxy group with a boronic acid catalyst and internal carboxylic acid is key to promoting the reaction. Although the scope is currently limited to indole derivatives, this strategy could be further extended in principle to other substitution reactions of α-hydroxy carboxylic acids. The exploration of such reactions is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02727.

Detailed experimental procedures and characterization data of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) Isolated yield of **4a** was reduced due to the instability of **4a** upon isolation. However, we were able to isolate the corresponding methyl ester **5a** in 89% yield after in situ transformation of **4a**.[15]

(15) See Supporting Information for details.

(16) We also examined effects of water on reactivity under the catalytic conditions, and complete removal of water from the reaction mixture was found unnecessary but excess amounts of water could reduce the reactivity, possibly because of the inhibition of formation of boronate esters with hydroxycarboxylic acid intermediate as well as formation of glyoxylic acid from its hydrate.[15]

(17) Comparison of transition state energies of α-hydroxycarboxylic acid intermediate and its ester with boronic acid catalyst revealed that activation of ester was more energetically unfavorable than that of carboxylic acid.[15] In addition, addition of 1 equiv of $^{i}Pr_2NEt$ diminished the reactivity, suggesting that acidic condition is important for promoting the reaction.[15]

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