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Enantioselective Michael Addition Reaction of *o*-Hydroxycinnamaldehydes with Organoboronic Acids using Hydroxy Group-Containing Organocatalysts

Yongcheon Lee and Sung-Gon Kim*

Department of Chemistry, College of Natural Science, Kyonggi University, Suwon 443-760, Korea
**E-mail: sgkim123@kgu.ac.kr*
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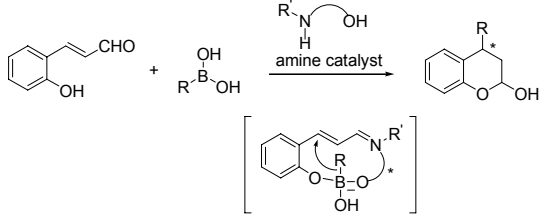
Chromanes and their derivatives are ubiquitously found in numerous biologically active natural products. Molecules containing chromane scaffolds exhibit a broad range of bioactivities, such as antiviral, antitumor, antimicrobial, and sex pheromone, and they can be used as biodegradable agrochemicals and photo-active materials.[1]

Owing to the importance of their structures, numerous synthetic methods for chromanes have been reported; the recent ones have focused on enantioselective synthetic approaches.[2,3] Hence, the development of an efficient enantioselective synthetic method for obtaining chromane scaffolds attracted our attention.

We recently developed a novel catalytic asymmetric 1,4-addition reaction of organoboronic acids with *o*-hydroxycinnamaldehydes using an imidazolidinone organocatalyst.[4] In due course, we aim to improve the enantioselectivity of this 1,4-addition reaction by using other organocatalysts; we suppose that a product with better enantioselectivity could be afforded by this reaction, which is possible if the intermediate is less fluxional and thereby provides a more selective chiral environment in the transition state (Scheme 1). Among possible catalysts, chiral amine catalysts having a hydroxy group provide the chiral environment necessary to yield the desired enantioselective product. This is because chiral amine catalysts lead the formation of imminium intermediate, and organoboronic acid could possibly be activated by the phenol -OH and amine catalyst -OH group. As a result, a less fluxional intermediate is simultaneously formed.

In an exploratory study for our hypothesis, we investigated several chiral amine catalysts (Figure 1) for their ability to promote the 1,4-addition reaction of *o*-hydroxycinnamaldehyde (**2a**) and styrylboronic acid (**3a**) (Table 1). First, α,α-diphenyl-L-prolinol TMS ether (**1a**)[5] was evaluated as the catalyst for the reaction, which was carried out in CH_2Cl_2 at room temperature with 10 mol % of catalyst **1a**, 1 equiv of *o*-hydroxycinnamaldehyde (**2a**), and 1.2 equiv of styrylboronic acid (**3a**). Under these conditions, catalyst **1a** afforded the desired product **4a** with good reactivity (75% yield, entry 1); however, a poor level of enantioselectivity (almost racemate) was observed. Next, we examined prolinol catalysts **1b-1d** for this reaction in CH_2Cl_2 at room temperature and found that α,α-diphenyl-L-prolinol (**1b**) is the best catalyst for this reaction. After the reaction conditions were optimized, we found that the highest regioselectivity and most satisfactory yield were obtained using catalyst **1b** (10 mol %) in $CHCl_3$ and toluene at room temperature with 1 N NaOH in H_2O (10 mol %) (87% yield, 72:28 er and 81% yield, 76:24 er, entries 7 and 8, respectively).



Scheme 1. Organocatalytic asymmetric 1,4-addition of organoboronic acid to *o*-hydroxycinnamaldehyde using organocatalyst having a hydroxy group

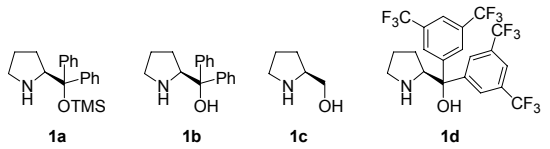
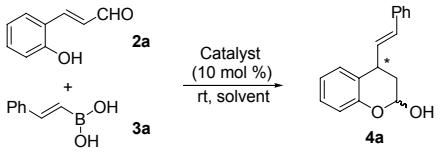


Figure 1. Chiral amine organocatalysts.

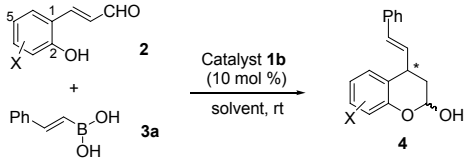
Table 1. Asymmetric 1,4-addition of *o*-hydroxycinnamaldehyde (**2a**) to styrylboronic acid (**3a**) by organocatalyst[a]



entry	catalyst	additive	solvent	time (h)	yield[b] (%)	er[c]
1	**1a**	-	CH_2Cl_2	12	75	51:49
2	**1b**	-	CH_2Cl_2	24	88	60:40
3	**1b**	2 eq. H_2O	CH_2Cl_2	24	94	63:37
4	**1c**	2 eq. H_2O	CH_2Cl_2	24	89	49:51
5	**1d**	2 eq. H_2O	CH_2Cl_2	36	10	66:34
6	**1b**	10 mol % 1 N NaOH in H_2O	CH_2Cl_2	24	88	67:33
7	**1b**	10 mol % 1 N NaOH in H_2O	$CHCl_3$	24	87	72:28
8	**1b**	10 mol % 1 N NaOH in H_2O	toluene	36	81	76:26

[a]Unless otherwise specified, the reaction was carried out in solvent (0.3 M) with 1.2 equiv of styrylboronic acid (**3a**) relative to the *o*-hydroxycinnamaldehyde (**2a**) in the presence of 10 mol % catalyst and additive. [b]Isolated yield after chromatographic purification. [c]Determined by HPLC using chiral column AD-H after oxidation.

Table 2. Organocatalytic asymmetric 1,4-addition of styrylboronic acid (**3a**) to *o*-hydroxycinnamaldehydes **2**[a]



entry	X	solvent	time (h)	yield[b] (%)	er[c]	dr[d]
1	H	$CHCl_3$	24	87	72:28	3:1
2	H	toluene	36	81	76:24	3:1
3	5-Cl	$CHCl_3$	24	70	72:28	4:1
4	5-Cl	toluene	36	80	80:20	4:1
5	5-CH_3	$CHCl_3$	24	88	74:26	3:1
6	5-CH_3	toluene	36	71	79:21	3:1
7	3,5-diCl	$CHCl_3$	24	94	69:31	4:1
8	3,5-diCl	toluene	48	76	76:25	4:1
9	3,5-diBr	$CHCl_3$	24	70	74:26	4:1
10	3,5-diBr	toluene	36	76	73:17	4:1
11	3-MeO	$CHCl_3$	36	75	76:24	4:1
12	5-NO_2	$CHCl_3$	24	60	73:27	4:1

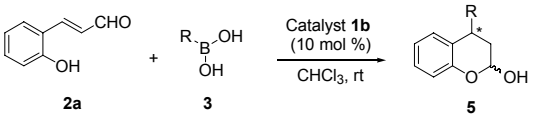
[a]Unless otherwise specified, the reaction was carried out in solvent (0.3 M) with 1.2 equiv of styrylboronic acid (**3a**) relative to the *o*-hydroxycinnamaldehyde **2** in the presence of 10 mol % catalyst and additive. [b]Isolated yield after chromatographic purification. [c]Determined by HPLC using chiral column AD-H after oxidation. [d]Determined by ^{1}H NMR.

Encouraged by these results, we investigated the scope of this process under the above mentioned optimized conditions. At first, this reaction proved to be applicable to a variety of *o*-hydroxycinnamaldehydes **2**. As can be inferred from Table 2, the reactions proceeded in good yields and moderate enantioselectivities for all *o*-hydroxycinnamaldehydes. In all cases, the reaction proceeded faster in $CHCl_3$ than in toluene, but enantioselectivity of the yielded product is slightly higher in toluene. In particular, 3,5-dibromo-substituted *o*-hydroxycinnamaldehyde afforded 1,4-addition adduct in good yield and higher enantioselectivity than did the other *o*-hydroxycinnamaldehydes (76% yield, 83:17 er, entry 10).

Next, we evaluated the scope for using organoboronic acids **3** under optimal reaction conditions (Table 3). 4-Methoxy and 4-fluorophenylallyl boronic acids afforded the corresponding chroman-2-ol **5** in good yields and high enantioselectivities (entries 1 and 2). However, the reaction of 4-chlorophenylallyl boronic acid and *o*-hydroxycinnamaldehyde (**2a**) proceeded to give the corresponding product in low yield (entry 3). Heteroaromatic boronic acids were also found to be a good substrate for this 1,4-addition reaction (entries 4-6). In particular, 2-furanboronic acid afforded the corresponding product in excellent yield, albeit with moderate enantioselectivity (98% yield, 62:38 er, entry 4).

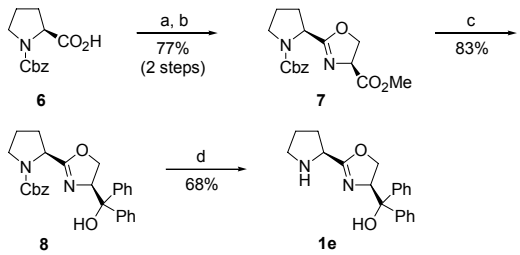
Although the above mentioned favorable results were obtained using our hypothesis, we were still not satisfied with them and therefore felt the need for a more efficient catalyst. We synthesized a new hydroxy group-containing pyrrolidine catalyst **1e** with oxazoline moiety, which could possibly afford not only additional chiral environment but also additional coordination

Table 3. Organocatalytic asymmetric 1,4-addition of organoboronic acids **3** to *o*-hydroxycinnamaldehyde (**2a**)[a]

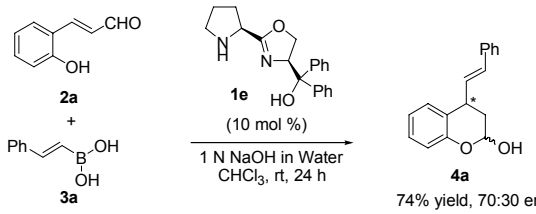


entry	R	time (h)	yield[b] (%)	er[c]	dr[d]
1	4-$MeOC_6H_4CHCH$	24	64	76:24	2:1
2	4-FC_6H_4CHCH	24	84	72:28	3:1
3	4-ClC_6H_4CHCH	36	30	76:24	3:1
4		24	98	62:38	5:1
5		24	87	78:22	7:1
6		24	74	68:32	3:1

[a]The reaction conditions were the same as those in Table 2. [b]Isolated yield after chromatographic purification. [c]Determined by HPLC using chiral column AD-H after oxidation. [d]Determined by ^{1}H NMR.



Scheme 2. Synthesis of catalyst **1e**. Reagents and conditions: (a) (*S*)-Serine methyl ester hydrochloride, EDC·HCl, Et_3N, THF (b) $(C_2H_5)_2NSF_3$, K_2CO_3, CH_2Cl_2 (c) PhMgBr, THF (d) H_2 (1 atm), 10% Pd/C, 1,4-cyclohexadiene, EtOH



Scheme 3. Asymmetric 1,4-addition of *o*-hydroxycinnamaldehyde (**2a**) to styrylboronic acid (**3a**) by organocatalyst **1e**

in the catalytic reaction. Catalyst **1e** was synthesized from Cbz-protected (*S*)-proline (Scheme 2). Formation of amide with Cbz-protected (*S*)-proline and (*S*)-serine methyl ester using an EDC coupling reagent followed by treatment of (diethylamino) sulfur trifluoride gave oxazoline compound **7**. Phenyl group addition to an ester yielded the corresponding alcohol **8**. Finally, removal of the Cbz group *via* catalytic hydrogenation gave the desired pyrrolidine catalyst **1e**.

To inspect the catalytic efficiency of the new pyrrolidine catalyst **1e**, we carried out the 1,4-addition reaction of *o*-hy-

droxycinnamaldehyde (**2a**) and styrylboronic acid (**3a**) under the optimized conditions to afford the corresponding product **4a** in 74% yield and 70 : 30 er (Scheme 3). However, contrary to our expectation, catalyst **1e** did not offer any advantages over catalyst **1b**.

In summary, we have demonstrated the enantioselective Michael addition reaction of *o*-hydroxycinnamaldehydes with organoboronic acids using hydroxy group-containing organocatalysts. In these reactions, α,α-diphenyl-L-prolinol (**1b**) afforded the corresponding 4-substituted chroman-2-ols in up to 98% yield and 83:17 er. We have also described a new hydroxy group-containing pyrrolidine catalyst **1e**, which exhibited catalytic ability similar to that of α,α-diphenyl-L-prolinol (**1b**) in a reaction of *o*-hydroxycinnamaldehyde (**2a**) with styrylboronic acid (**3a**).

Experiments

Synthesis of Catalyst 1e; (*S*)-Methyl 2-((*S*)-1-((benzyloxy) carbonyl)-pyrrolidin-2-yl)-4,5-dihydrooxazole-4-carboxylate (7). To a solution of **6** (2.50 g, 10.0 mmol) in THF (50 mL) was added Et_3N (3.48 mL, 25.0 mmol) and (*S*)-serine methyl ester hydrochloride (1.87 g, 11.0 mmol) followed by addition of *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl, 2.30 g, 12.0 mmol) at room temperature. After stirring for 12 hours, the reaction mixture was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with EtOAc. The combined organic layer were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash column chromatography (80% EtOAc/hexanes) to afford amide compound. The amide compound was dissolved in CH_2Cl_2 (70 mL) and allowed to cool down −78 °C. To this solution was added (diethylamino)sulfur trifluoride (1.45 mL, 11.0 mmol). After stirring for 30 minute at same temperature, the reaction mixture was quenched with K_2CO_3 (2.07 g, 15.0 mmol) and allowed to warm up room temperature. The reaction mixture was diluted with water and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash column chromatography (60% EtOAc/hexanes) to afford the title compound **7** (2.67 g, 77%) as a gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.41 (m, 2H), 5.04-5.24 (m, 2H), 4.32-4.58 (m, 3H), 3.78 (s, 3H), 3.47-3.68 (m, 3H), 1.89-2.38 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 170.7, 154.3, 136.8, 128.5, 128.1, 127.8, 69.9, 67.4, 67.0, 54.8, 62.6, 46.9, 30.4, 23.4; MS *m*/*z* (%) 332 (M^+, 25), 241 (10), 180 (28), 156 (40), 91 (100).

(*S*)-Benzyl 2-((*S*)-4,5-Dihydro-4-(hydroxydiphenyl-methyl) oxazol-2-yl)pyrrolidine-1-carboxylate (8). To a solution of **7** (1.04 g, 3.00 mmol) in THF (15 mL) was added PhMgBr (3.0 M solution in Et_2O, 2.50 mL, 7.50 mmol) at 0 °C. After stirring for 1 hour at room temperature, the reaction mixture was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with EtOAc. The combined organic layer were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash column chromatography (only EtOAc → 3% MeOH/EtOAc) to afford the title compound **8** (1.14 g, 83%) as a solid. mp 137 - 138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.67 (m, 15H), 5.12-5.37 (m, 3H), 4.16-4.59 (m, 3H), 3.99 (s, 1H), 3.48-3.51 (m, 2H), 1.83-2.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 154.9, 146.4, 136.6, 128.5, 128.3, 128.0, 126.7, 126.4, 125.9, 78.7, 73.0, 69.6, 67.2, 55.4, 46.9, 29.9, 23.7; MS *m*/*z* (%) 456 (M^+, 18), 348 (65), 243 (75), 207 (100), 105 (95), 70 (65).

((*S*)-4,5-Dihydro-2-((*S*)-pyrrolidin-2-yl)oxazol-4-yl)diphenylmethanol (1e). To a solution of **8** (640 mg, 1.40 mmol) in EtOH (14 mL) was added 1,4-cyclohexadiene (1.33 mL, 14.0 mmol) and 10% Pd/C (0.1 w/w, 65 mg). After stirring for 12 hours under H_2 atmosphere, Pd/C was filtered out and the reaction solvent was evaporated in vacuo. The residue was purified by flash column chromatography (3% MeOH/EtOAc → 5% MeOH/EtOAc) to afford the title compound **1e** (306 mg, 45%) as a solid. as a solid. mp 157 - 158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.57 (m, 10H), 4.10-4.88 (m, 3H), 3.54-3.81 (m, 3H), 2.78-2.96 (m, 2H), 1.39-1.85 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 145.3, 128.2, 127.0, 125.3, 81.1, 62.5, 60.4, 55.5, 46.9, 30.5, 25.7; MS *m*/*z* (%) 322 (M^+, 15), 262 (18), 210 (25), 183 (34), 139 (41), 105 (405), 70 (100).

Asymmetric Catalysis. An amber 2-dram vial equipped with a magnetic stir bar, containing catalyst (0.025 mmol), and organoboronic acid substrate **3** (0.30 mmol) was charged with chloroform or toluene (0.8 mL) and 1 N NaOH in H_2O (0.025 mmol) at room temperature. The solution was stirred for 5 min before addition of *o*-hydroxycinnamaldehydes **2** (0.25 mmol). The resulting suspension was stirred until complete consumption of *o*-hydroxycinnamaldehydes **2** was observed as determined by TLC. The resulting mixture was direct purified by silica gel chromatography to afford desired compounds **4** and **5** as described previously.[4] The enantioselectivity was determined by HPLC analysis of the chromanone product, which was prepared by oxidation (PCC, CH_2Cl_2), using a Chiralcel AD-H column and AD-H guard column.

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