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Asymmetric organocatalytic reactions of *o*-hydroxycinnamaldehydes with organoboronic acids: a facile enantioselective access to chromanes and dihydrobenzopyranes

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ABSTRACT

Catalytic asymmetric 1,4-addition reactions of organoboronic acids to *o*-hydroxycinnamaldehydes, which afford chromanes and dihydrobenzopyranes, have been established using an organocatalyst derived from imidazolidinone. The chromanes have been obtained in high chemical yields and enantioselectivities and can be readily used to obtain a variety of chromane derivatives through subsequent transformations.

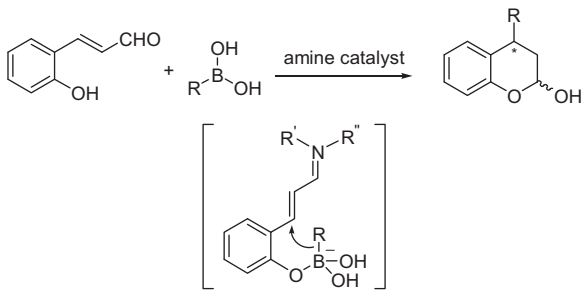
Chromanes (dihydrobenzopyranes) are ubiquitously found in numerous biologically active natural products. Molecules containing chromane scaffolds exhibit a broad range of bioactivities, such as antiviral, antitumor, antimicrobial, sex pheromone, and those of the central nervous system activity, and can be used as biodegradable agrochemicals and photo-active materials.[1]

Owing to the importance of their 'privileged' structures, numerous synthetic methods for chromanes have been reported, which have recently focused on the enantioselective synthetic approaches especially.[2,3] Consequently, the development of an efficient enantioselective synthetic method to obtain chromane scaffolds has attracted our attention. Herein, we report the first example of the asymmetric synthesis of chromanes and dihydrobenzopyranes from *o*-hydroxycinnamaldehydes and organoboronic acids using an organocatalyst.[4]

We recently developed novel catalytic asymmetric 1,4-addition reactions of arylvinyl and arylboronic acids to a γ-hydroxy α,β-unsaturated aldehyde using an organocatalyst that provide direct access to β-substituted γ-lactols.[4b] Encouraged by this result, we considered the possibility of carrying out this 1,4-addition reaction using *o*-hydroxycinnamaldehydes[3d,5] as aldehyde substrates; such a reaction could generate enantio-enriched chromanes and dihydrobenzopyranes.

In this reaction, we supposed that chiral amine catalyst should provide chiral environment for accessing enantioselective product through the formation of imminium intermediate, and organoboronic acid could be activated by the phenol –OH group which has served as nucleophile in other organocatalyzed asymmetric reactions (Scheme 1).[6]

We began our investigations with the goal of finding appropriate conditions for the 1,4-addition reaction of *o*-hydroxycinnamaldehyde **2a** to styrylboronic acid **3a** (Table 1). Diphenylprolinol silyl ether **1a** (Figure 1) was initially chosen as the catalyst for this 1,4-addition reaction because it provided the product in good yield with high enantioselectivity for the 1,4-addition reaction of 4-hydroxybut-2-enal to styrylboronic acid in previous research.[4b] This reaction was performed in CH_2Cl_2 at room temperature with 20 mol % of catalyst **1a**, 5 equiv of H_2O, and 1.5 equiv of styrylboronic acid **3a**, which



Scheme 1. Organocatalytic asymmetric 1,4-addition of organoboronic acids to *o*-hydroxycinnamaldehyde to generate chiral chromanes.

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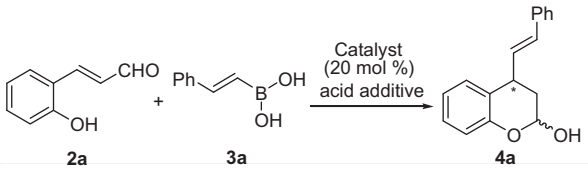
Table 1
Asymmetric 1,4-addition of *o*-hydroxycinnamaldehyde **2a** to styrylboronic acid **3a** by organocatalyst[a]



2a **3a** **4a**

Entry	Catalyst	Additive	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	er[c]
1[d]	**1a**	—	CH_2Cl_2	rt	12	97	51:49
2	**1b**	20 mol % CF_3CO_2H	CH_2Cl_2	rt	8	48	70:30
3	**1c**	20 mol % CF_3CO_2H	CH_2Cl_2	rt	18	46	79:21
4	**1c**	2 mol % CF_3CO_2H	CH_2Cl_2	rt	24	72	79:21
5	**1d**	2 mol % CF_3CO_2H	CH_2Cl_2	rt	24	65	78:22
6	**1e**	2 mol % CF_3CO_2H	CH_2Cl_2	rt	24	80	83:17
7	**1e**	2 mol % CF_3CO_2H	CH_2Cl_2	0	48	48	87:13
8	**1e**	2 mol % $CHCl_2CO_2H$	CH_2Cl_2	0	48	54	89:11
9[e]	**1e**	2 mol % $CHCl_2CO_2H$	CH_2Cl_2	0	72	86	89:11
10[e]	**1e**	2 mol % $CHCl_2CO_2H$	$CHCl_3$	0	72	83	92:8

[a] Unless otherwise specified, the reaction was carried out in solvent (0.3 M) with 1.5 equiv of styrylboronic acid **3a** relative to the *o*-hydroxycinnamaldehyde **2a** in the presence of 20 mol % catalyst and additive.
[b] Isolated yield after chromatographic purification.
[c] Determined by HPLC analysis after oxidation.
[d] 5.0 equiv of H_2O was added.
[e] 1.0 equiv of H_2O was added.

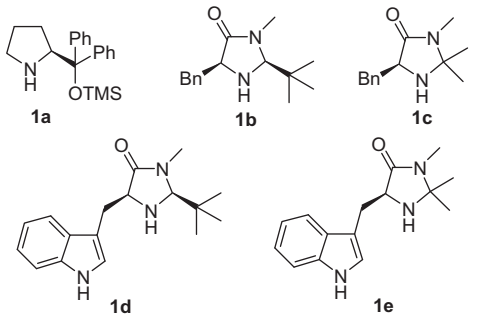


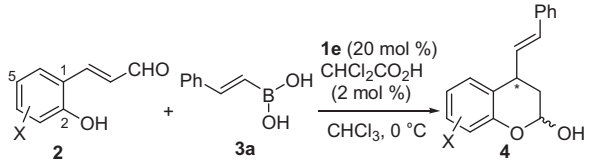
Figure 1. Chiral amine organocatalysts.

were the established reaction conditions in the addition reaction of hydroxybut-2-enal to styrylboronic acid. Under these conditions, catalyst **1a** afforded the desired product **4a** with good reactivity (97% yield, entry 1); however, a poor level of enantioselectivity was observed. Next, we used an imidazolidinone catalyst **1b** for this reaction with CF_3CO_2H (20 mol %) as an additive in CH_2Cl_2 at room temperature. The reaction proceeded to yield product **4a** with complete conversion of *o*-hydroxycinnamaldehyde **2a**, although the yield and enantioselectivity of **4a** were moderate (entry 2). Unlike previous results, wherein the second-generation MacMillan catalyst **1b** was superior to the first-generation MacMillan catalyst **1c** in terms of the reactivity and enantioselectivity in organocatalytic reactions,[7] catalyst **1c** exhibited higher enantioselectivity than catalyst **1b** in this reaction (entry 3). The amount of acid as an additive also had a considerable effect on the reaction. The reaction occurred in high yield without a loss of enantioselectivity when we used 0.1 equiv of acid relative to catalyst (entry 4).

Encouraged by this result, we investigated the application of other imidazolidinone catalysts, acid additives, solvents, and temperatures in order to improve both the reactivity and enantioselectivity in this reaction (entries 5–9). After the reaction conditions were optimized, we found that superior levels of enantioselectivity and yield were exhibited by catalyst **1e** (20 mol %) in $CHCl_3$ at 0 °C with $CHCl_2CO_2H$ (2 mol %) and H_2O (1.0 equiv) (83% yield, 92:8 er, entry 10).[8]

Having established the optimal reaction conditions for this asymmetric 1,4-addition reaction, we investigated the scope of this process. First, this reaction proved to be general for a variety of *o*-hydroxycinnamaldehydes **2**. As revealed in Table 2, the reactions proceeded in good yields and enantioselectivities for all *o*-hydroxycinnamaldehydes. In particular, 3-substituted *o*-hydroxycinnamaldehydes produced the corresponding chromanes **4** with high efficiency (entries 3, 5, and 6). It is supposed that the substituted group adjacent to hydroxy group promotes the formation of a lactol ring in this reaction and accelerates the reaction. However, *o*-hydroxycinnamaldehyde substrates that have a substituted group in only 5-position have been known to exhibit relatively lower reactivities (entries 2, 7, and 8).

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

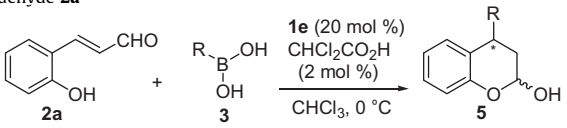


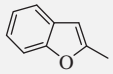
2 **3a** **4**

Entry	X	Product	Time (h)	Yield[b] (%)	er[c]	dr[d]
1	H	**4a**	72	83	92:8	3:1
2[e]	5-MeO	**4b**	72	65	80:20	3:1
3	3-MeO	**4c**	48	93	93:7	4:1
4	5-Cl	**4d**	72	85	85:15	4:1
5	3,5-DiCl	**4e**	72	99	85:15	4:1
6	3,5-DiBr	**4f**	72	91	85:15	4:1
7	5-CH_3	**4g**	77	66	86:14	3:1
8[e]	5-NO_2	**4h**	72	81	84:16	4:1

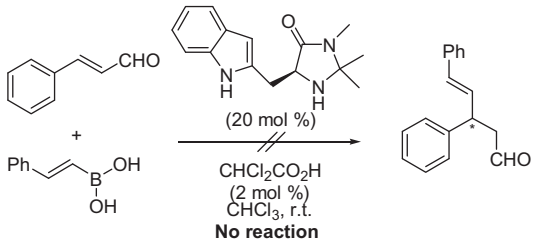
[a] Unless otherwise specified, the reaction was carried out in $CHCl_3$ (0.3 M) with 1.2 equiv of styrylboronic acid **3a** and 1.0 equiv of H_2O relative to the *o*-hydroxycinnamaldehyde **2a** in the presence of 20 mol % catalyst and 2 mol % additive at 0 °C.
[b] Isolated yield after chromatographic purification.
[c] Determined by HPLC analysis after oxidation.
[d] Determined by ^1H NMR.
[e] Performed at rt.

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



Entry	R	Product	Time (h)	Yield[b] (%)	er[c]	dr[d]
1	4-MeOC$_6$H$_4$CHCH	**5a**	72	80	93:7	2:1
2	4-MeC$_6$H$_4$CHCH	**5b**	72	63	92:8	3:1
3	4-ClC$_6$H$_4$CHCH	**5c**	72	55	91:9	3:1
4	4-FC$_6$H$_4$CHCH	**5d**	72	57	90:10	3:1
5		**5e**	72	90	78:22	5:1
6		**5f**	72	93	78:22	7:1
7		**5g**	72	64	78:22	9:1
8		**5h**	72	88	92:8	3:1

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



Scheme 2. Organocatalytic reaction of styrylboronic acid to cinnamaldehyde.

Next, we evaluated the scope of the use of organoboronic acids **3** using the general reaction conditions (Table 3). Arylvinyl boronic acids afforded the corresponding chromanes **5** in moderate to good yields and in high enantioselectivities (entries 1–4). Heteroaromatic boronic acids were also found to be a good substrate for this 1,4-addition reaction (entries 5–8). In particular, 2-*N*-Boc-pyrroleboronic acid afforded product **5h** in good yield and higher enantioselectivity than did the other heteroaromatic boronic acids (88% yield, 92:8 er, entry 8).

Finally, we confirmed the role of the phenol –OH group in 2-hydroxycinnamaldehyde by examining the reaction between cinnamaldehyde and styrylboronic acid under the same reaction conditions (Scheme 2). As expected, this reaction did not proceed. Thus, we can infer that in our organocatalytic 1,4-addition of organoboronic acids to *o*-hydroxycinnamaldehydes, organoboronic acid is activated by the phenol –OH group.

In summary, we described the organocatalytic asymmetric 1,4-addition reactions of organoboronic acids to *o*-hydroxycinnamaldehydes to afford chromanes and dihydrobenzopyranes in good yields and enantioselectivities. A variety of chromane derivatives can be readily obtained through the subsequent transformations of these products.[3e,f,9] Further application of this reaction to other substrates and to the preparation of biologically relevant compounds will be presented in due course.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.138.

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8. *General procedure for the synthesis of* **4** *and* **5**. An amber 2-dram vial equipped with a magnetic stir bar, containing catalyst **1e** (0.05 mmol) and organoboronic acid substrate **3** (0.30 mmol), was charged with chloroform (0.8 mL), 0.5 N $CHCl_2CO_2H$ in $CHCl_3$ (0.005 mmol), and H_2O (0.25 mmol), then placed in a bath of 0 °C. The solution was stirred for 5 min before addition of *o*-hydroxycinnamaldehydes **2** (0.25 mmol). The resulting suspension was stirred at constant temperature until complete consumption of *o*-hydroxycinnamaldehydes **2** was observed as determined by TLC. The resulting mixture was directly purified by silica gel chromatography to afford the desired compounds **4** and **5**.
4-Styryl-chroman-2-ol (**4a**). Prepared by the general procedure from *trans*-2-phenylvinylboronic acid **3a** (42 mg, 0.30 mmol), *o*-hydroxycinnamaldehyde **2a** (37 mg, 0.25 mmol) and catalyst **1e** (0.05 mmol), 0.5 N $CHCl_2CO_2H$ in $CHCl_3$ (10 μL, 0.005 mmol) and H_2O (4.5 μL, 0.25 mmol) in $CHCl_3$ (0.8 mL) at 0 °C for 72 h to provide the desired compound as awhite solid (52 mg, 83% yield, 92:8 er) after silica gel chromatography in 25% EtOAc/hexanes; mp 127–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.45 (m, 7H), 6.87–6.97 (m, 2H), 6.63 (d, J = 15.6 Hz, 0.75H), 6.59 (d, J = 16.0 Hz, 0.25H), 6.34 (dd, J = 8.0, 16.0 Hz, 0.25H), 6.21 (dd, J = 8.8, 15.6 Hz, 0.75H), 5.72 (br s, 0.75H), 5.60 (dt, J = 6.8, 13.6 Hz, 0.25H), 3.93 (dt, J = 6.0, 10.0 Hz, 0.75H), 3.80 (dt, J = 6.4, 8.4 Hz, 0.25H), 3.24 (d, J = 6.8 Hz, 0.25H), 3.12 (br s, 0.75H), 2.37 (ddd, J = 2.4, 6.4, 13.6 Hz, 0.25H), 2.21 (ddd, J = 3.6, 6.0, 13.6 Hz, 0.75H), 1.97–2.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4 (minor), 151.4 (major), 137.0 (major), 136.9 (minor), 132.5 (minor), 132.4 (major), 131.7 (major), 131.5 (minor), 129.3 (minor), 129.1 (major), 128.6 (major), 128.3 (minor), 128.1 (major), 127.5 (minor), 127.4 (major), 126.3 (minor), 126.2 (major), 124.1

(major), 123.5 (minor), 121.1 (major), 121.0 (minor), 117.1 (major), 117.0 (minor), 93.6 (minor), 91.3 (major), 38.3 (minor), 35.5 (minor), 34.3 (major), 33.8 (major); IR (KBr) 3436, 1584, 1492, 1448, 1229, 1204, 1175, 1100, 1011 cm^{-1}; MS *m*/*z* (%) 252 (M^+, 50), 234 (100), 207 (74), 178 (28), 131 (51), 91 (40); Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 81.22; H, 6.37. The enantioselectivity was determined by HPLC analysis of the chromanone compound using a Chiralcel AD-H column and AD-H guard column (5% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 220 nm); *R*-isomer t_r = 15.5 min and *S*-isomer t_r = 19.6 min. Oxidation of 4-styryl-chroman-2-ol **4a** (14 mg, 0.050 mmol) was performed in CH_2Cl_2 (0.3 mL) by adding of pyridinium chlorochromate (11 mg, 0.050 mmol) at room temperature. After 3 h, additional pyridinium chlorochromate (1.0 equiv) was added and after 6 h purification by silica gel chromatography in 10% EtOAc/hexanes was afforded chromanone compound (11 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.40 (m, 7H), 7.12–7.19 (m, 2H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.21 (dd, *J* = 7.6, 16.0 Hz, 1H), 3.94 (dd, *J* = 7.6, 13.6 Hz, 1H), 3.00 (dd, *J* = 5.6, 15.6 Hz, 1H), 2.88 (dd, *J* = 7.6, 15.6 Hz, 1H).

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