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Enantioselective Synthesis of Chromenes by the Palladium-Catalyzed Asymmetric Redox-Relay Heck Reaction

Ze-Zhen Jiang,[a,b] Ang Gao,[b] Hao Li,[a,b] Di Chen,[b] Chang-Hua Ding,*[b] Bin Xu,*[a] and Xue-Long Hou*[b]

Dedication ((optional))

Abstract: A palladium-catalyzed asymmetric redox-relay Heck reaction of 4*H*-chromenes and arylboronic acids has been successfully developed. The reaction proceeded in moderate to good yields with good to high enantioselectivities. The resulting product is an advanced intermediate of bio-active compound BW683C.

Chromene and chroman rings are key heterocycles present in a variety of natural occurring products and bio-active molecules such as (S)-Candenatenin E,[1a] Hilgartene,[1b] BW683C,[1c] and tephrowatsin E[1d] (Figure 1). Thus the development of efficient synthetic methods to access these motifs has received a tremendous amount of attention, and many strategies have been reported.[2] However, the catalytic asymmetric synthesis of 2*H*-chromene derivatives are limited. The main strategies are based on the enantioselective addition of aryl boronates to in-situ generated pyrylium ions,[3] the intramolecular asymmetric Brønsted acid-catalyzed allylic etherification,[4] and the 6-*endo*-trig Pd-catalyzed asymmetric allylic substitution.[5] You's group reported an iridium-catalyzed asymmetric allylic etherification and the subsequent Ru-catalyzed ring-closing metathesis reaction for enantioselective synthesis of chromene.[6] In spite of these significant advancement, some problems exit such as the limitation of intramolecular approach[4,5] or the need of multiple step reactions.[6] Therefore, the development of new approaches to this important motifs is still in great demand. In connection with our studies on palladium-catalyzed asymmetric Heck reaction,[7] we envisioned that the enantioselective Heck of 4*H*-chromene would provide an attractive access to optically active chromenes. While Pd-catalyzed intermolecular Heck reaction has been well developed,[8-10] the alkenes suitable for the asymmetric intermolecular Heck reaction are limited. Cyclic alkenes such as 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran are most commonly used substrates in asymmetric Heck reaction. Surprisingly, the report of using their analogue, 4*H*-chromene, as substrate for asymmetric Heck reaction is not available so far. Herein, we reported our preliminary results to this end.

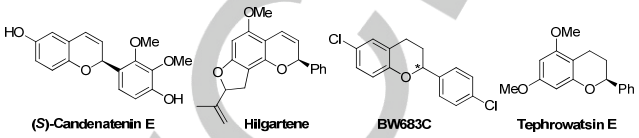
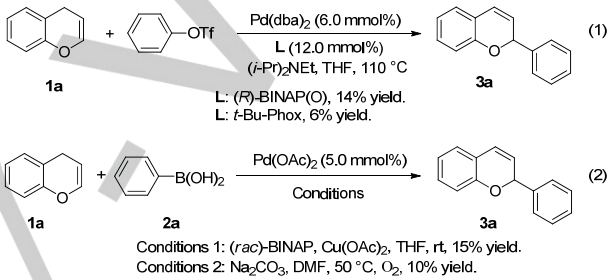


Figure 1. Chromene and chroman rings in bio-active compounds.



Initially, we examined the Heck reaction of 4*H*-chromene (**1a**) with phenyl trifluoromethanesulfonate in the presence of two catalyst systems which show high efficiency in the Mizoroki-Heck reaction (eq 1).[11] Unfortunately, 2-phenyl-2*H*-chromene (**3a**) was obtained in very low yield and an extensive optimization of reaction conditions couldn't lead to a better result. Then, the Pd-catalyzed oxidative Heck reaction between 4*H*-chromene (**1a**) with phenyl boronic acid (**1a**) was conducted in the presence of catalytic $Pd(OAc)_2$ (eq 2).[12] The yield of **3a** was also very low and the extensive exploration couldn't improve the reaction. Inspired by the Pd-catalyzed redox-relay Heck reaction of Sigman group,[10] $Pd(CH_3CN)_2Cl_2$ and PyrOx **L1** were used as the catalyst for the reaction of 4*H*-chromene (**1a**) with phenyl boronic acid (**2a**) (eq 3). Pleasingly, the reaction afforded product **3a** in 20% yield with 96% ee (eq 3 and entry 1, table 1). It is noted that alkenols are usually used as substrates in the Pd-catalyzed redox-relay Heck reaction.[10] The result herein represents a new application of the catalyst system in the Pd-catalyzed intermolecular Heck reaction. The promising results promoted us to carry out further investigations. Studies on the influence of reaction temperature indicated that performing the reaction at higher temperature afforded a better yield of **3a** but lower enantioselectivity (entries 1–4, table 1). When the reaction was conducted at a temperature of 80 °C, enantioselectivity of product **3a** was significantly reduced to 40% ee (entry 4, table 1). Control experiments revealed the importance of the presence of oxygen because only 5% of **3a** was observed when the reaction was carried out under argon (entry 5 vs entry 3, table 1). Absence of 3 Å MS also led to a yield decrescence of **3a** (entry 6 vs entry 3, table 1). The yield of **3a** was increased significantly from 29% to 61%, whereas the enantioselectivity was also increased from 91% to 93%, when the reaction was run by using 12 mol% of $Cu(OTf)_2$ (entry 7 vs entry 2, table 1). Performing the reaction using 20 mol% of $Cu(OTf)_2$ didn't afforded better results

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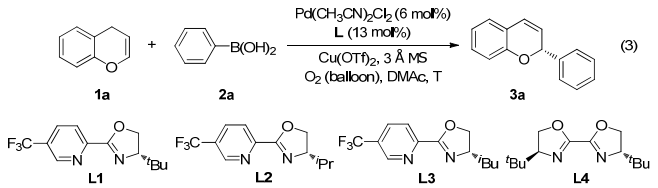
(entry 8 vs entry 7, table 1). Switching the ratio of **1a/2a** from 100/120 to 150/100 further increased the yield of **3a** to 81% while the enantioselectivity was unchanged (entries 9 vs entry 7, Table 1). A solvent screen showed the reaction proceeded well in DMF and DMSO (entries 10 and 11, Table 1), but the reaction did not proceed in toluene (entry 12, table 1). Other solvents, such as CH_3CN and THF, gave inferior results (entries 13 and 14, Table 1). Use of other bidentate nitrogen ligands **L2**-**L4** didn't improve the reaction (entries 15–17, Table 1) [for more optimization of reaction conditions, such as the effect of palladium salt, copper salt, and ligand on the reaction, see Supporting Information].

Table 1. Optimization of Reaction Conditions for Pd-Catalyzed Asymmetric Redox-Relay Heck Reaction of 4*H*-Chromene (**1a**) and Phenylboronic Acid (**2a**)[a]

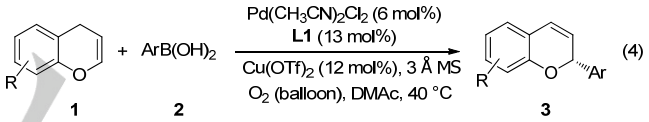


entry	Ligand	$Cu(OTf)_2$ (mol%)	Solvent	T (^oC)	yield/%[b]	ee/%[c]
1	**L1**	6	DMAc[g]	rt	20	96
2	**L1**	6	DMAc	40	29	91
3	**L1**	6	DMAc	60	80	87
4	**L1**	6	DMAc	80	71	40
5[d]	**L1**	6	DMAc	60	5	87
6[e]	**L1**	6	DMAc	60	72	87
7	**L1**	12	DMAc	40	61	93
8	**L1**	20	DMAc	40	62	93
9[f]	**L1**	12	DMAc	40	81	93
10	**L1**	12	DMF	40	52	95
11	**L1**	12	DMSO	40	67	89
12	**L1**	12	toluene	40	nr	--
13	**L1**	12	CH_3CN	40	5	79
14	**L1**	12	THF	40	42	76
15	**L2**	12	DMAc	40	71	84
16	**L3**	12	DMAc	40	61	80
17	**L4**	12	DMAc	40	76	11

[a] Entries 1-8: molar ratio of **1a**/**2a**/[Pd]/**L** = 100/120/6/13. [b] Isolated yield. [c] Determined by chiral HPLC. [d] under argon instead of O_2. [e] in the absence of 3 Å MS. [f] entries 9-17 molar ratio of **1a**/**2a** = 150/100. [g] DMAc: dimethylacetamide

With the above optimum conditions established, the substrate scope of this Pd-catalyzed asymmetric redox-relay Heck reaction was examined (eq 4 and Table 2). In general, the reaction proceeded smoothly for a variety of 4*H*-chromene **1** and arylboronic acids **2**, leading to the corresponding allylic alkylation products **3** in 49–88% yields with 57–95% ee. The reaction tolerated various substituents at the *para*, *meta*, or *ortho* positions of the phenyl group of boronic acid **2** (entries 2–8). The substituent at the *ortho*-position of the phenyl ring of arylboronic acid **3d** showed a diminished effect on the yield and enantioselectivity of the reaction (entry 4). The reaction of arylboronic acid **2f**, bearing bromide as substituent which is suitable for further transformation, could be used to provide 2*H*-chromene **3f** in 53% yield with 93% ee (entry 6). The reaction also worked well for arylboronic acid **2g** with ester group on the phenyl ring, affording the corresponding product **3g** in 49% yield with 95% ee (entry 7). The presence of bulky groups such as 1-naphtyl or 2-naphthyl at the boronic acids **2** had little influence on the reaction (entries 9 and 10). A halide atom as a substituent at the 6-position of 4*H*-chromene **1** exerted limited effects on the enantioselectivity (entries 11–13). Notably, the reaction of 4*H*-chromene **1d** with boronic acid **2k** provided 2*H*-chromene **3m** with 93% ee, which has been reported to be transformed into BW683C by the Pt-catalyzed hydrogenation.[6] A methyl groups as a substituent at the 6- and 7- positions of 4*H*-chromene **1** have negative effects on the enantioselectivity (entries 14 and 15). However, substantial amounts of unknown side product were observed for the arylboronic acids with an electron-withdrawing group on the aromatic ring, thus resulting in a poorer yield of the Heck product, although with high ee value (entries 7, 16-18). The absolute configuration of product **3f** was determined to be (*R*) by comparison of optical rotation to that of literature[6].

Table 2. Substrate Scope for Palladium-Catalyzed Asymmetric Redox-Relay Heck Reaction of 4*H*-Chromenes **1** and Arylboronic Acids **2**[a]



entry	R (**1**)	Ar (**2**)	yield (**3**,%)[b]	ee (%)[c]
1	H (**1a**)	Ph (**2a**)	81 (**3a**)	93
2	H (**1a**)	*p*-Me-C_6H_4 (**2b**)	76 (**3b**)	91
3	H (**1a**)	*m*-Me-C_6H_4 (**2c**)	84 (**3c**)	94
4	H (**1a**)	*o*-Me-C_6H_4 (**2d**)	51 (**3d**)	83
5	H (**1a**)	*p*-F-C_6H_4 (**2e**)	80 (**3e**)	92
6	H (**1a**)	*p*-Br-C_6H_4 (**2f**)	53 (**3f**)	93
7	H (**1a**)	*p*-MeOCO-C_6H_4 (**2g**)	49 (**3g**)	95
8	H (**1a**)	*p*-MeO-C_6H_4 (**2h**)	88 (**3h**)	82
9	H (**1a**)	1-naphthyl (**2i**)	63 (**3i**)	91
10	H (**1a**)	2-naphthyl (**2j**)	70 (**3j**)	92
11	6-F (**1b**)	*p*-MeO-C_6H_4 (**2h**)	84 (**3k**)	85
12	6-Br (**1c**)	*p*-MeO-C_6H_4 (**2h**)	71 (**3l**)	85
13	6-Cl (**1d**)	*p*-Cl-C_6H_4 (**2k**)	62 (**3m**)	92
14	6-Me (**1e**)	*p*-MeO-C_6H_4 (**2h**)	71 (**3n**)	83
15	7-Me (**1f**)	*p*-MeO-C_6H_4 (**2h**)	62 (**3o**)	66

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16	H (**1a**)	*p*-CF_3-C_6H_4 (**2l**)	21 (**3p**)	93
17	H (**1a**)	*p*-CN-C_6H_4 (**2m**)	37 (**3q**)	91
18	H (**1a**)	*p*-Ac-C_6H_4 (**2n**)	45 (**3r**)	92

[a] Molar ratio of **1**/**2**/$Pd(CH_3CN)_2Cl_2$/**L1**/$Cu(OTf)_2$ = 150:100:6:13:12. [b] Isolated yield. [c] Determined by chiral HPLC.

In conclusion, we have realized a palladium-catalyzed asymmetric redox-relay Heck reaction of 4*H*-chromenes and arylboronic acids in moderate to good yields with good to high enantioselectivities. The resulting products contain core structure of many natural products and bio-active compound. The usefulness of the method is demonstrated by the product **3m** reported to be converted into BW683C.[6] Further studies of extension of the method and applications in organic synthesis are in progress.

Experimental Section

General procedure for the palladium-catalyzed asymmetric redox-relay Heck reaction of 4*H*-chromenes 1 and arylboronic acids 2:

A 10 mL dry Schlenk tube equipped with a stir bar was flame dried and flushed with argon. $Pd(CH_3CN)_2Cl_2$ (3.1 mg, 0.012 mmol), **L1** (7.1 mg, 0.026 mmol), $Cu(OTf)_2$ (8.6 mg, 0.024 mmol) and 3Å MS (30 mg) were added into the dry Schlenk tube. The flask was evacuated via vacuum and refilled with O_2 three times, then DMAc (2 mL) was added using a syringe. The resulting mixture was stirred for 30-40 minutes. Then, 4*H*-Chromenes **1** (0.3 mmol, 1.5 equiv) and aryl boronic acid **2** (0.2 mmol, 1.0 equiv) were added. The resulting mixture was stirred for another 18 h to 24 h at 40 °C. After the reaction was completed, the reaction mixture was diluted with EtOAc (2 mL) and H_2O (5 mL). The aqueous phase was extracted with EtOAc (3×5 mL). The organic phase was dried with anhydrous Na_2SO_4 and then filtered through a 0.5 inch plug of silica gel (eluting with EtOAc) to remove the solid. The crude reaction mixture was concentrated under reduced pressure. The resulting crude product was purified by flash column silica gel chromatography (eluting with petroleum ether/ethyl acetate 100/1) to provide product **3**.

Keywords: palladium • redox-relay Heck reaction • asymmetric catalysis • 4*H*-chromene • boronic acid

Acknowledgements

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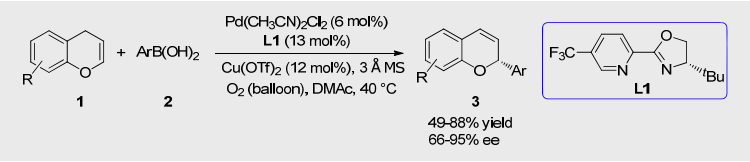

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