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Transient and Recyclable Halogenation Coupling (TRHC) for Isoflavonoid Synthesis with Site Selective Arylation

Jie-Ping Wan,*[a] Zhi Tu†[a] and Yuyun Wang†[a]

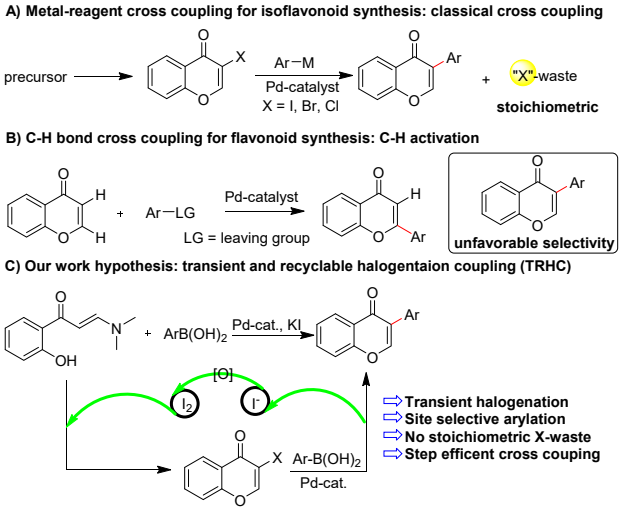
†These authors contributed equally

Abstract: The transient and recyclable C-H iodination has been designed for the synthesis of isoflavonoids via the domino reactions of *o*-hydroxyphenyl enaminones and aryl boronic acids in the presence of catalytic KI and Pd-catalyst. Instead of the conventional cross coupling strategy employing pre-halogenated substrates, this method transforms raw C-H bond by means of a transient C-H halogenation to smoothly relay the subsequent C-arylation. Consequently, such method avoids the pre-functionalization for C-halogen bond installation as well as the generation of stoichiometric halogen-containing waste following the cross coupled product, disclosing a intriguing new coupling protocol to forge C-C bond in the virgin area between classical C-X (X = halogen) bond cross coupling and the C-H activation.

The transition metal-catalyzed cross coupling reactions act as the predominant method in constructing C-C and C-heteroatom bonds. Their applications are irreplaceable in both the laboratory investigation and many industries associated with organic synthesis. Interestingly, most of the classical cross coupling reactions such as Ullmann, Suzuki, Heck, Negishi, Goldberg, Buckwald-Hartwig, Sonogashira, Hiyama, Cadiot-Chodkiewicz, Stille and Kumada coupling, the carbonylation coupling as well as cyanation coupling etc share a common feature: employing C(sp^2)-X or C(sp)-X bond as the key transformation group.[1] While benefiting the efficiency and synthetic power associated with the reactive C-X bond, people also suffers from the additional labors and chemical consumption resulting from the pre-functionalization generating C-X bond. Moreover, the generation of stoichiometric halogen-waste from the C-X substrate is another major challenge. Over the past several decades, new coupling modes such as the transition-metal-catalyzed C-H activation,[2] dehydrative coupling,[3] dehydrogenative and/or oxidative coupling[4] have been developed as more environmentally benign tactics. These couplings transform directly natural C-H bond, and are thus free of the aforementioned substrate pre-functionalization and halogen waste production. However, due to the intrinsic stability of most C-H bonds, the scope of efficient coupling on C-H bond is yet far insufficient. In this context, developing new coupling strategy beyond these known modes is highly urgent task of modern organic synthesis.

Isoflavonoids are important natural products with widespread application in treating diseases, drug discovery, food industry and health care.[5] Besides natural resources, the major route accessing isoflavonoids is the Suzuki,[6] Neghishi,[7] Stille[8] and other coupling reactions[9] using prior prepared 3-halochromones (Scheme 1A). The reactions employing unfunctionalized chromones with aryl reactant, however, do not provide isoflavonoid. Instead, flavones were the products in such reactions as determined by the inherent regioselectivity (Scheme 1B).[10] Therefore, the isoflavonoids are hitherto typical targets which are not accessible by C-H bond coupling. Actually, the synthesis of 3-vinyl,[11] 3-perfluoroalkyl,[12] 3-akynyl,[13] 3-alkyl,[14] 3-chalcogenyl[15] 3-acyloxyl chromones[16] etc, have been successively realized by coupling the C(sp^2)-H bond of chromones or proper precursors, but never equivalent arylation. These known results confirm the challenge of synthesizing isoflavonoids by C-H arylation. Therefore, it is inarguably significant to establish alternative coupling method for isoflavonoid synthesis by directly transform raw C-H bond and avoids the aforementioned shortcomings of the C-X bond-based cross coupling.

In light of the known transformation of *o*-hydroxyphenyl enaminone to 3-halochromone,[9,17] we envisage that it can be utilized to design a catalytic and selective formal C-H arylation for isoflavonoids synthesis by catalytically recycling the halogenation. Herein, we wish to report for the first time the selective arylation of 2-hydroxyphenyl enaminones for the synthesis of isoflavonoids with relayed KI and Pd-catalysis wherein the transient and recyclable halogenation takes place in the presence of a terminal oxidant (Scheme 1C), thus disclosing a new coupling mode for C-C bond formation alongside the classical C-X bond-based cross coupling and C-H activation.



Scheme 1. Coupling reactions providing isoflavonoids and flavonoids

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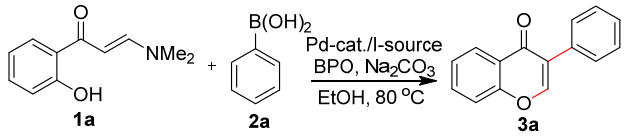
To start the exploration, enaminone **1a** and phenyl boronic acid **2a** were selected for reaction. To optimize the conditions, comprehensive experiments on screening the iodo-source, Pd-catalyst, temperature, base additive, reaction medium as well as reagent loading were conducted (see SI). According to the typical results (Table 1), KI was found as the hitherto best iodo-source in 40 mol% loading (entries 1-2 and 5-6, Table 1).[18] No product **3a** was formed in the absence of iodo-reagent (entry 7, Table 1), confirming the indispensable role of an iodo-reagent in leading this arylation. As a Pd(0) catalyst, $Ph(PPh_3)_4$ displayed evidently better activity than $Pd(OAc)_2$ and $Pd(PPh_3)_2Cl_2$ (entries 2-4, Table 1). Increasing the loading of the catalyst (entry 8, Table 1) and varying the species of base additive (entries 9-10, Table 1), however, did not further improve the yield of **3a**.

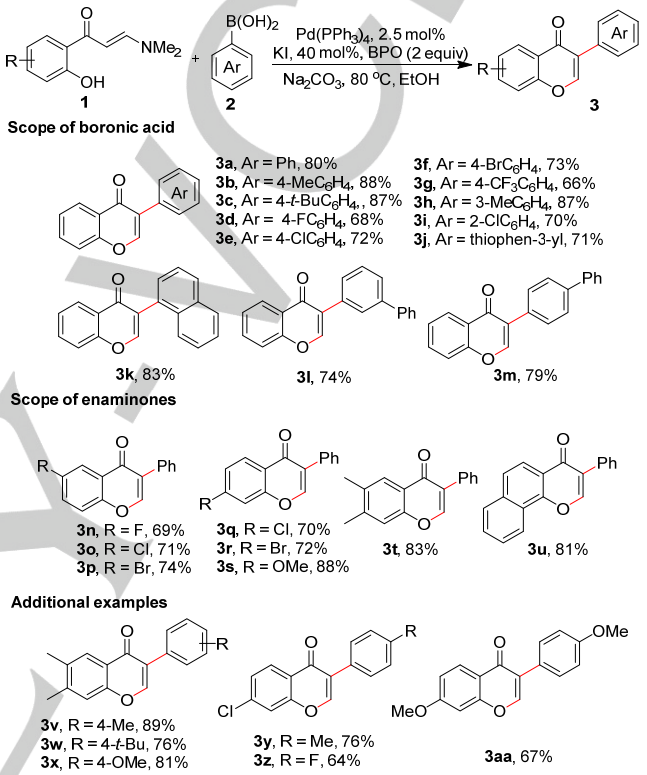
Table 1 Typical results on condition optimization[a]



entry	catalyst	"I"-source	base	Yield (%)[b]
1[c]	$Pd(PPh_3)_2Cl_2$	KI	Na_2CO_3	53
2	$Pd(PPh_3)_2Cl_2$	KI	Na_2CO_3	69
3	$Pd(PPh_3)_4$	KI	Na_2CO_3	80
4	$Pd(OAc)_2$	KI	Na_2CO_3	55
5	$Pd(PPh_3)_4$	NaI	Na_2CO_3	74
6	$Pd(PPh_3)_4$	Bu_4NI	Na_2CO_3	63
7	$Pd(PPh_3)_4$	-	Na_2CO_3	0
8[d]	$Pd(PPh_3)_4$	KI	Na_2CO_3	78
9	$Pd(PPh_3)_4$	KI	K_2CO_3	50
10	$Pd(PPh_3)_4$	KI	NaOH	37

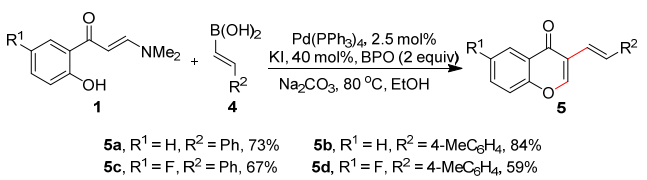
[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.3 mmol), Pd-catalyst (2.5 mol%), KI (0.4 equiv.), BPO (0.5 mmol), base (0.5 mmol) in EtOH (2.0mL), stirred at 80 °C in sealed tube for 24h. [b]Yield of isolated product based on **1a**. [c]The loading of KI was 0.2 equiv. [d]The loading of $Pd(PPh_3)_4$ was 5 mol%.

To illustrate the application of this new coupling protocol, enaminones and aryl boronic acids containing diverse substituents were utilized for the reaction, respectively. Generally, this method displayed satisfactory tolerance to both components. In the reactions employing different aryl boronic acids, electron donating groups such as alkyls (**3b**, **3c** and **3h**, Scheme 2), electron withdrawing groups such as halogen (**3d-3f** and **3i**, Scheme 2) and trifluoromethyl (**3g**, Scheme 2) were employed smoothly for the expected reaction. In addition, the heteroaryl (**3j**, Scheme 2), fused aryl (**3k**, Scheme 2) and biaryl (**3l** and **3m**, Scheme 2) boronic acids were also practical substrates. A tendency found in these data was that the electron enriched aryl boronic acids generally afforded the products with higher yields than those reactions using electron deficient aryl boronic acids. As for the reaction of different enaminones **1**, satisfactory application scope was also demonstrated by the efficient synthesis of products containing halogen (**3n-3r**, Scheme 2), alkoxyl (**3s**, Scheme 2), dialkyl (**3t**, Scheme 2) and fused aryl (**3u**, Scheme 2) substructure in the chromone core. The positive effect of the electron donating substituent in the phenyl ring of **1** to the product yield was also observed. Furthermore, as expected, the reactions using both substituted boronic acids and 2-hydroxyphenyl chromones also accordingly gave rise to the diversely functionalized isoflavonoids with efficiency (**3v-3z** and **3aa**, Scheme 2).



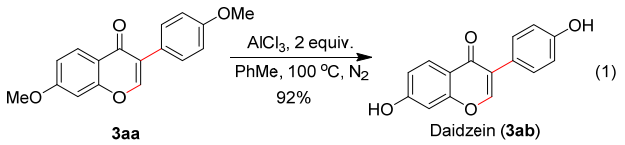
Scheme 2. Scope the isoflavonoid synthesis by recyclable halogenation coupling. Conditions: enaminone **1** (0.25 mmol), **2** (0.3 mmol), $Pd(PPh_3)_4$ (2.5 mmol%), KI (0.1 mmol), BPO (0.5 mmol), Na_2CO_3 (0.5 mmol) in EtOH (2.0 mL), sealed and stirred at 80 °C for 24h.

Moreover, besides aryl boronic acids, the reactions of vinyl boronic acids **4** were also investigated. Delightfully, the 3-vinyl chromones **5** could be practically synthesized by this step economical cross coupling mode with good to excellent yields (Scheme 3), revealing further the high potential of this coupling method.

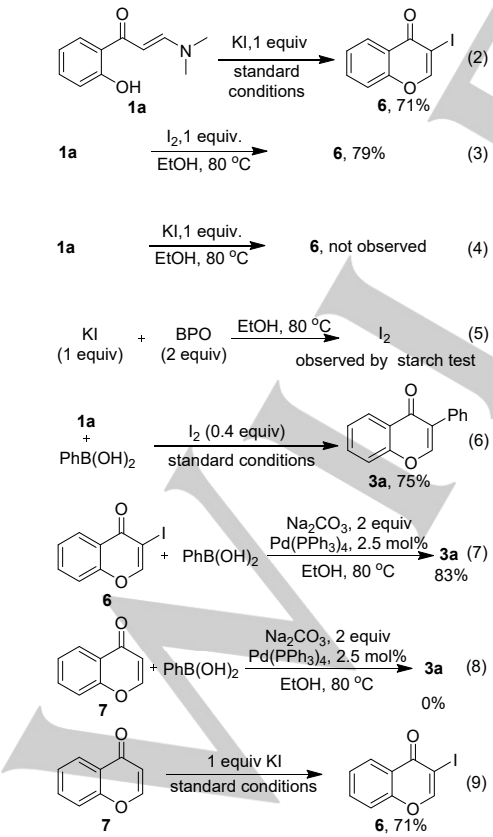


Scheme 3. Transient C-H halogenation coupling for 3-vinyl chromone synthesis

Notably, the important isoflavonoid natural product Daidzein (**3ab**) could be easily accessed from **3aa** with high efficiency via a typical $AlCl_3$ promoted demethylation(Eq 1).

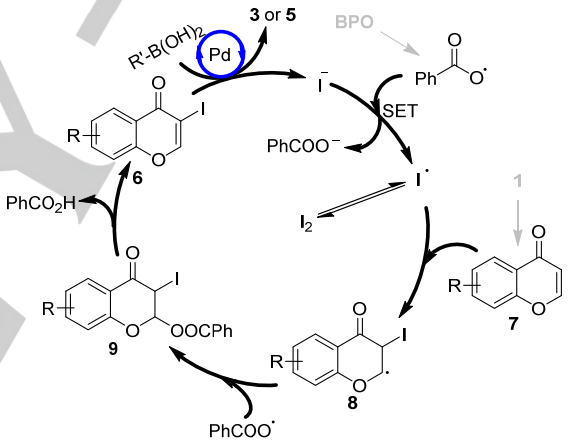


To testify the reaction mechanism, a series of control experiments were then conducted. Because the absence of iodine reagent was proved to provide no target product, we first explored the possible iodo-species mediating the reaction. In the designed entries, the reaction of KI with enaminone **1a** in the presence of BPO as well as the reaction employing directly I_2 without BPO both gave iodinated chromone **6** with high yield (Eq 2 and 3). On the other hand, without BPO, KI along was not able to react with **1a** to give **6** (eq 4), and the oxidation of KI to molecular iodine by BPO was confirmed by a classical starch test (Eq 5). Moreover, alternate KI with molecular iodine afforded efficiently the target product **3a** under the standard conditions (Eq 6). These results indicated that the molecular iodine was the active species or precursor during the reaction, and **6** was a key intermediate in the reaction. Later on, the 3-iodochromone **6** and the unsubstituted chromone **7** was employed to react with phenyl boronic acid under the Pd-catalyzed conditions, respectively. The former led to smooth synthesis of **3a** (Eq 7). The latter one, on the contrary, didn't enable the formation of this product (Eq 8). These results further supported the fact that the *in situ* and recyclable formation of iodinated intermediate **6** was a key point in the isoflavonoid synthesis. Additionally, the



reaction of chromone **7** with KI provided 3-iodochromone **6** under the standard catalytic conditions (eq 9), suggesting that **7** was the key intermediate in the formation of **6**.

With the results in hand, the reaction mechanism is proposed. As outlined in Scheme 4, the reaction starts from the single electron transfer (SET) between the iodine anion and the in situ generated carboxyl radical resulting from the thermo-induced homo-cleavage of BPO[16] to afford iodine radical. Besides the reversible formation of molecular iodine, the iodine radical can incorporate the in situ generated chromone **7** via radical addition, which gives rise to free radical spcies **8**. The chain termination of **8** with the benzoyloxyl radical leads to the formation of intermediate **9**. The β-elimination of a benzoic acid from **9** then provides the 3-iodochromone intermediate **6**. The subsequent Pd-catalyzed Suzuki-type coupling between the C(sp^2)-I bond and the aryl/vinyl boronic acids then yields products **3** or **5**, respectively. Most notably, the simultaneously released iodine anion can be repeatedly oxidized to iodine radical, thus enables the recyclable halogenation and the successive arylation/vinylation, offering this new cross coupling strategy in the presence of only catalytic loading of iodide salt.



Scheme 4. The proposed reaction mechanism by recyclable C-H halogenation

To sum up, by means of a rationally designed transient and recyclable halogenation coupling tactic, the synthesis of isoflavonoids and 3-vinyl chromones have been efficiently achieved via the Pd(0)/KI-co-catalyzed reactions of *o*-hydroxyphenyl enaminones and aryl/vinyl boronic acids. The present method employs catalytic amount of KI to enable the arylation and vinylation with C(sp^2)-H substrate, which discloses a new coupling tactic in constructing C-C bonds. Besides free of substrate pre-functionalization and no stoichiometric halogen waste, this present coupling tactic directs unconventional site selectivity to the chromone C3-postion because previously known Pd-catalyzed arylation of chromones naturally takes place in the C2 position, demonstrating additional value of such a cross coupling approach in switching the reaction selectivity.

Experimental Section

General procedure for the synthesis of isoflavonoids 3

Enaminone **1** (0.25 mmol) and aryl boronic acid **2** (0.3 mmol) were dissolved in EtOH (2 mL) in in a 10 mL sealed tube. Subsequently, KI (0.1 mmol), BPO (0.5 mmol), Na_2CO_3 (0.5 mmol) and $Pd(PPh_3)_4$ (2.5%mmol) were added. The tube was sealed with Teflon cap and stirred at 80 ^oC for 24 hours. After cooling sown to room temperature, the mixture was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography by using mixed EtOAc and petroleum ether(v/v = 1:15) to give pure product.

Procedure for the synthesis of Daidzein (3ab)

Compound **3aa** (0.25 mmol) and $AlCl_3$ (0.5 mmol) were employed in a 10 mL sealed tube with 2 mL toluene. The tube was filled with N_2 and sealed with Teflon cap. The vessel was stirred at 100 ^oC for 12 hours with oil bath heating. After cooling dow to room temperature, water (10 mL) was added, and the resulting suspension was extracted with ethyl acetate (3 × 10 mL). The organic phase was combined and dried with anhydrous Na_2SO_4. After filtration, the solution was subjected to reduced pressure to remove the solvent. The resulting residue was employed to flash column chromatography via the elution of mixed EtOAc and petroleum ether (v/v = 1:1) to give pure product **3ab**.

Acknowledgements

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Keywords: transient • recyclable • halogenation • selective arylation • isoflavonoids

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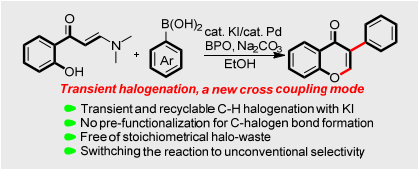
Layout 1:

COMMUNICATION

A transient and recyclable C-H bond halogenation is designed for the synthesis of isoflavonoids via site selective arylation using o-hydroxyphenyl enaminones and aryl boronic acids. This work discloses a new cross coupling protocol in step-economical and sustainable manner.



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