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A facile route to isoflavone quinones *via* the direct cross-coupling of chromones and quinones†

Youngtaek Moon and Sungwoo Hong*

A straightforward and efficient method for the palladium-catalyzed direct cross-coupling of chromones with various quinones has been developed to rapidly construct isoflavone quinone structural motifs.

The family of isoflavone quinones has been extensively investigated due to its broad range of remarkable biological activities.[1] Isoflavone quinone scaffolds are useful and versatile building blocks and, therefore, provide target systems for synthetic chemists. Despite significant synthetic efforts, existing methods for preparing the scaffolds suffer from multiple steps, and harsh reaction conditions.[2] In view of the high synthetic utility of isoflavone quinone derivatives, the most straightforward method for synthesizing the compounds would involve a direct cross-coupling of chromones with quinones *via* C–H bond functionalization.[3]
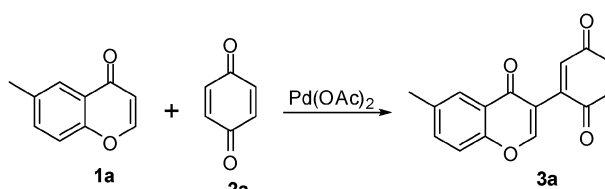
Although some notable advances in the direct C–H functionalization of quinones have been made, C–C bond formation in quinones often remains a challenge due to the unique electronic properties of the structures.[4] These difficulties have pushed synthetic strategies toward pre-functionalizing the quinone substrates[5] or investigating other reaction modes, such as cross-coupling of quinones with organoboron compounds as coupling partners.[6] With these types of reactions, reoxidation steps are often necessary to revert to the quinone oxidation state.

We were interested in exploring a direct coupling approach that would allow us to avoid pre-functionalization of the chromones and quinones, thereby providing a more efficient process for coupling chromones and quinones under catalytic conditions. During these investigations, we established an efficient palladium catalytic protocol for the facile cross-coupling of chromones with a range of quinones, and herein we report the details of this study.

The feasibility of this process was tested *via* the direct coupling of 6-methylchromone (**1a**) with 1,4-benzoquinone (**2a**) in the presence of Pd(OAc)$_2$ and Cu(OAc)$_2$ in pivalic acid. Unfortunately, no detectable coupling product was observed. Thus, a systematic investigation of more reactive catalytic systems

Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, 305-701, Korea.
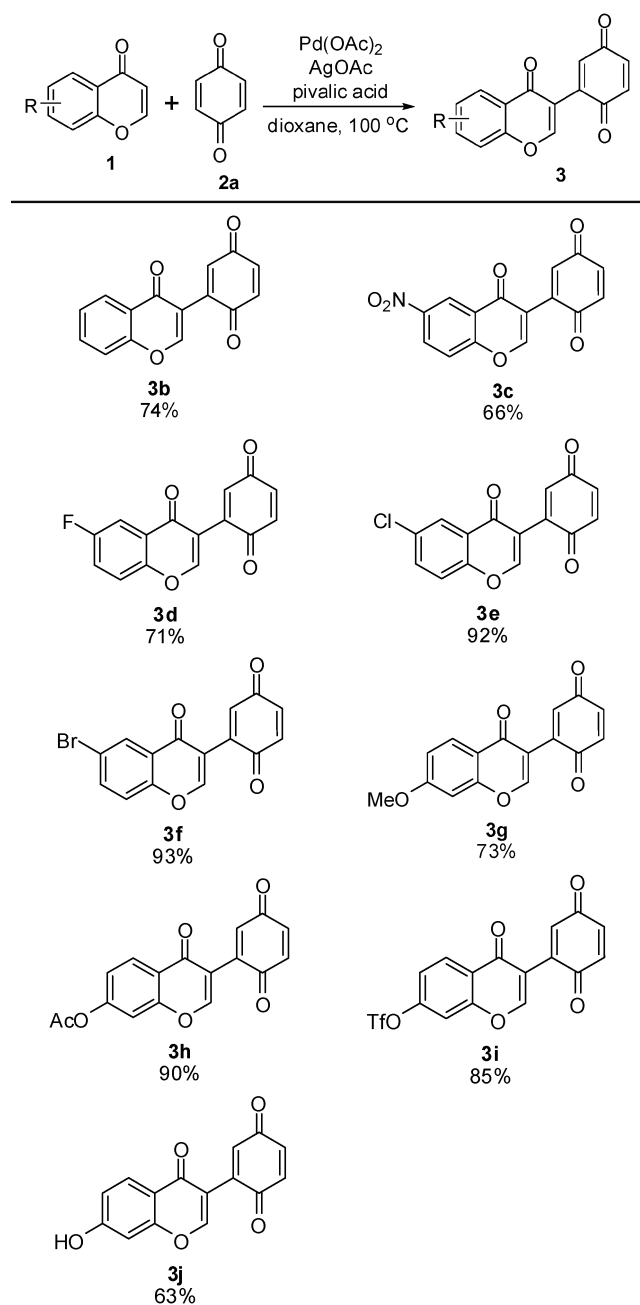*E-mail: hongorg@kaist.ac.kr; Fax: +82-42-350-2810;*
Tel: +82-42-350-2811

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was conducted by testing different solvents, oxidants and temperatures to establish an optimal combination for achieving the transformation. To our delight, the replacement of Cu^{2+} with Ag$^+$ was crucial, and the reactions that used Ag$_2$CO$_3$ at 100 °C provided a noticeable product yield (Table 1, entry 2). Reactions conducted at other temperatures provided lower yields of the cross-coupled product. Among the palladium sources tested, Pd(OAc)$_2$ afforded the best catalytic reactivity. The use of AgOAc with dioxane as the solvent provided a 46% product yield (entry 5). Introduction of the base K$_2$CO$_3$ negatively affected the reaction (entry 6). A combination of AgOAc and acetic acid as an additive promoted the reaction and improved the yield (52%) (entry 7). On the other hand, stronger acids, such as trifluoroacetic acid, did not improve the reaction outcome (entry 9). Pivalic acid provided a superior reactivity, furnishing a 67% yield of the coupled product (entry 8). The high reactivity of pivalic acid relative to other carboxylic acids may be derived from the increased basicity of its conjugate base.[7] Interestingly, variations in the amount of AgOAc present

Table 1 Development of direct C–C coupling between a benzoquinone and a chromone[a]

Entry	Oxidant (equiv.)	Additive (equiv.)	Solvent	Yield[b] (%)
1	Cu(OAc)$_2$ (3)	None	PivOH	—
2	Ag$_2$CO$_3$ (3)	None	PivOH	20
3	AgOAc (3)	None	PivOH	41
4	AgOAc (3)	None	TFA	Trace
5	AgOAc (3)	None	Dioxane	46
6	AgOAc (3)	K$_2$CO$_3$ (2)	Dioxane	Trace
7	AgOAc (3)	AcOH (2)	dioxane	52
8	AgOAc (3)	PivOH (2)	Dioxane	67
9	AgOAc (3)	TFA (2)	Dioxane	28
10[c]	AgOAc (3)	PivOH (2)	Dioxane	77
11[c]	AgOAc (2.5)	PivOH (2)	Dioxane	89

[a] Reactions were conducted with chromone (1 equiv.), benzoquinone (2 equiv.), Pd(OAc)$_2$ (0.2 equiv.), an oxidant and a base at 100 °C under N$_2$ for 12–24 h. [b] Yields are reported after isolation and purification by flash silica gel chromatography. [c] Benzoquinone (4 equiv.) was used. TFA = trifluoroacetic acid.

influenced the reaction outcomes, and the use of 2.5 equiv. AgOAc provided the best product yields. An excess of benzoquinone (4 equiv.) was needed to ensure complete conversion of a chromone. A combination of these strategies led to the identification of optimized conditions involving the treatment of a chromone (1 equiv.) with benzoquinone (4 equiv.) in the presence of the Pd(OAc)$_2$ catalyst (0.2 equiv.), AgOAc (2.5 equiv.), and PivOH (2 equiv.) in dioxane at 100 °C (entry 11). Under the optimized reaction conditions, the direct cross-coupling

of 6-methyl chromone (**1a**) and 1,4-benzoquinone (**2a**) proceeded efficiently to provide the best isolated yield of 89%.

With the optimized protocol in hand, we next investigated the generality of this transformation by extending it to a variety of chromone substrates (Table 2). The reaction scope

Table 2 Direct coupling of various chromones with 1,4-benzoquinone[a]

3b 74%

3c 66%

3d 71%

3e 92%

3f 93%

3g 73%

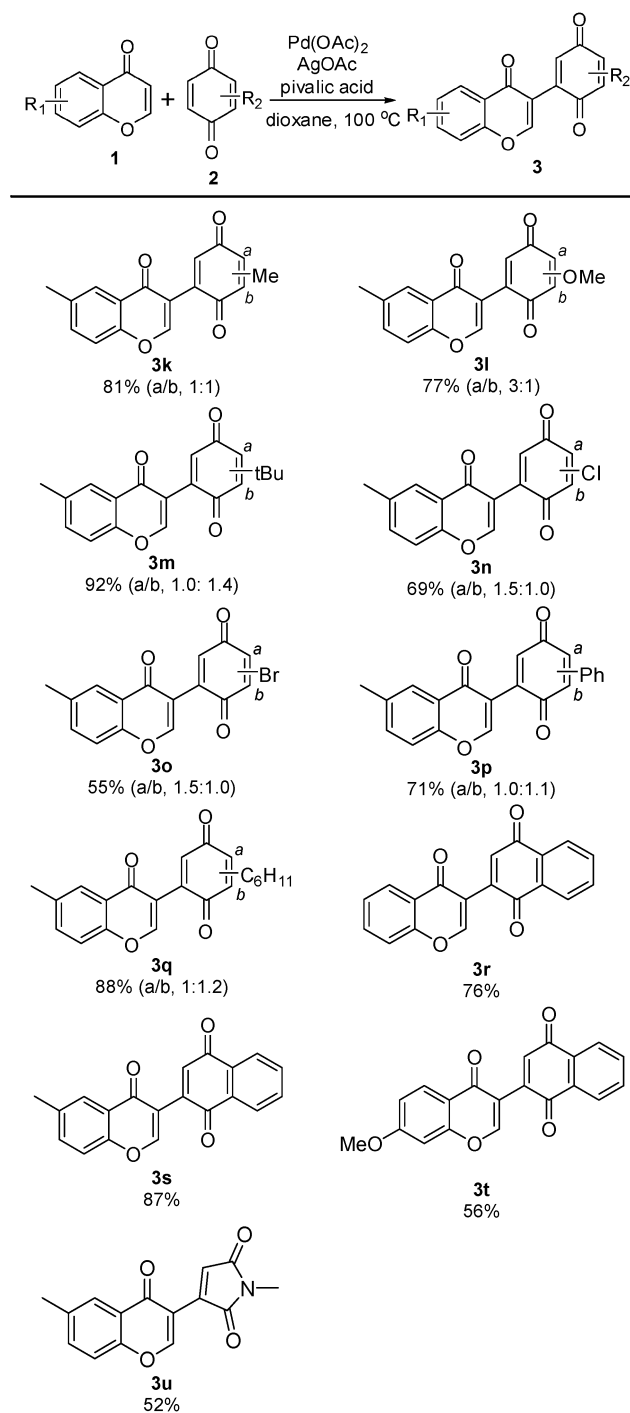**3h** 90%

3i 85%

3j 63%

[a] Reactions were conducted with chromone (1 equiv.), benzoquinone (4 equiv.), Pd(OAc)$_2$ (0.2 equiv.) and AgOAc (2.5 equiv.) at 100 °C under N$_2$ for 12–24 h. Yields are reported after isolation and purification by flash silica gel chromatography.

Table 3 Scope of the quinones with respect to C–C coupling of chromones[a]

3k 81% (a/b, 1:1)

3l 77% (a/b, 3:1)

3m 92% (a/b, 1.0: 1.4)

3n 69% (a/b, 1.5:1.0)

3o 55% (a/b, 1.5:1.0)

3p 71% (a/b, 1.0:1.1)

3q 88% (a/b, 1:1.2)

3r 76%

3s 87%

3t 56%

3u 52%

[a] Reactions were conducted with chromone (1 equiv.), quinone (4 equiv.), Pd(OAc)$_2$ (0.2 equiv.) and AgOAc (2.5 equiv.) at 100 °C under N$_2$ for 12–24 h. Yields are reported after isolation and purification by flash silica gel chromatography. Ratios were determined by ^{1}H NMR spectroscopy.

with respect to the chromone derivatives was extensive. Chromones with a broad range of functional groups including, alkyl, fluoride, bromide, chloride, nitro, methoxy, hydroxy, triflate, and ester smoothly underwent dehydrogenative coupling with 1,4-benzoquinone (**2a**) in moderate to good yields under the optimal conditions. In some cases, the moderate yields were attributed to the poor solubility of the products (*e.g.*, **3c** and **3d**). The obtained product **3g** was reported to exhibit potent biological activities.[2b] Of particular note are the chromones bearing bromo or triflate groups, which yielded the synthetically versatile **3f** and **3i** in excellent yields with intact bromo or triflate moieties, thereby providing an opportunity for the further formation of C–C or C–heteroatom bonds.

To explore this coupling reaction further, we turned our attention to the scope of quinone substrates (Table 3). Regiochemical issues come into play in the context of unsymmetric quinones. Reactions involving 1,4-benzoquinone substituted with a methyl group produced a 1 : 1 mixture of the isomers **3k** in an 81% combined yield. Analogous results were obtained with the phenyl-, bulky *tert*-butyl- or long-chain alkyl-substituted benzoquinones (**3m**, **3p** and **3q**). The dependence of the regioselectivity on the electronic effects could be seen from the benzoquinone substituent behaviors. For example, a more electron-rich methoxy substituent on the benzoquinone donated electron density to the π-system, and this led to the preferred coupling adduct of the regioisomers **3l** in a 3 : 1 ratio. The chloro or bromo groups had less influence, and the coupling products **3n** and **3o** were obtained in a 1.5 : 1 ratio. A reversal in regioselectivity was observed, albeit small, for the sterically bulky *tert*-butyl- and long-chain alkyl-substituted benzoquinones, probably because bulky groups partially impede complex formation between the neighboring carbonyl oxygen and Pd.[8] Two other notable variations in the substrate included 1,4-naphthoquinone and *N*-methylmaleimide. As a coupling partner, 1,4-naphthoquinone reacted with similar efficiencies under the optimal conditions to afford the corresponding products, **3r**, **3s** and **3t**. In a similar manner, the reaction of *N*-methylmaleimide afforded the corresponding product, **3u**, in a 52% yield.

The catalytic cycle of the coupling reaction can be initiated by electrophilic palladation at C3 of the chromone. In the presence of quinone substrates, the C3-palladated species next inserts into the quinone, and subsequent reductive elimination provides the desired coupled product.[9] Finally, the oxidation of Pd(0) to Pd(ɪɪ) using AgOAc completes the catalytic cycle.

In summary, we developed an efficient method for preparing isoflavone quinones *via* a palladium-catalyzed direct C–C coupling reaction. This approach provides facile and affordable access to isoflavone quinone structural motifs, which are privileged and prevalent structures in many biologically active compounds. The beneficial effects associated with the use of AgOAc were clearly observed in this cross-coupling reaction. This method represents an unprecedented example of the direct coupling of chromones with quinones and a significant advance over existing methods.

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