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Regioselective palladium-catalyzed olefination of coumarins *via* aerobic oxidative Heck reactions†

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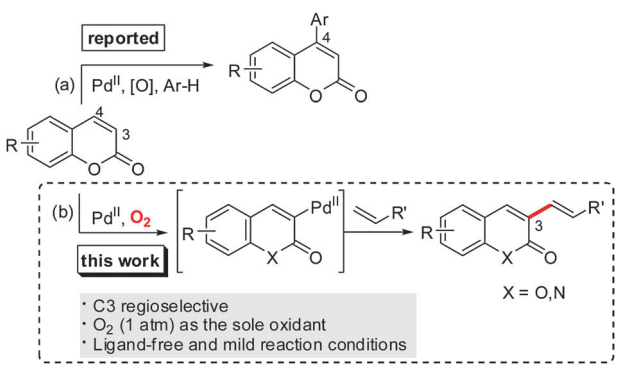
Pd-catalyzed oxidative Heck reactions of coumarins were developed *via* simultaneous C–H functionalization at the C3 position of coumarins under aerobic conditions.

In recent years, notable progress has been made toward enhancing the efficiency of direct C–H bond activation in (hetero)arenes.[1] The current approach is advantageous in that it enables the direct formation of target molecules without requiring prefunctionalization of the starting materials, thereby minimizing undesired waste in fewer reaction steps. Since the discovery of direct olefination of benzene by Fujiwara,[2] substantial progress has been made with oxidative Heck reactions toward improving the reaction efficiency as promising alternatives to conventional procedures.[3] The scope of these reactions has remained limited, however, due to difficulties associated with controlling a single C–H bond in the presence of electronically or sterically similar C–H bonds.[4]

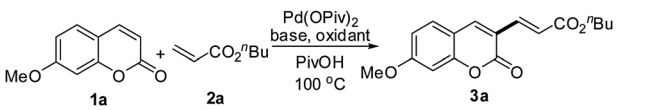
Coumarin derivatives exhibit a broad range of biological activities[5] and have been extensively investigated for their outstanding optical properties.[6] Over the course of developing efficient coumarin synthetic methods, our group recently described a Pd(II)-catalyzed direct arylation of coumarins using simple arenes, thereby permitting the construction of a variety of 4-arylcoumarins (Scheme 1a).[7] This finding prompted us to explore the feasibility of the expeditious synthetic approach for the installation of an olefin at the C3 position of coumarins to extend the π-electron system, yielding enhanced optical properties. Herein, we describe a regioselective Pd(II)-catalyzed C–H olefination of coumarins with the use of 1 atm O_2 as the stoichiometric oxidant in the absence of a co-oxidant.

We explored the prospects of the proposed Pd-catalyzed coupling reaction by investigating the reactivity of 7-methoxycoumarin (**1a**) and *tert*-butyl acrylate (**2a**) as model substrates. We were pleased to observe that the coupling product **3a** was obtained using a catalytic system comprising both $Pd(OPiv)_2$ and Cu(OAc), albeit in a 20% yield (entry 1). The functionalization



Scheme 1 Regioselective oxidative coupling of coumarins.

Table 1 Optimization of alkenylation conditions[a]



Entry	Oxidant (equiv.)	Additive (equiv.)	Base	Yield[b] (%)
1	$Cu(OAc)_2$ (3)	—	—	20
2	Ag_2CO_3 (3)	—	—	35
3	$Cu(OAc)_2$ (3)	—	Ag_2CO_3	30
4	$Cu(OAc)_2$ (3)	—	K_2CO_3	40
5	TEMPO (1.2)	—	K_2CO_3	75
6	Air (1 atm)	—	K_2CO_3	76
7	**O_2 (1 atm)**	—	**K_2CO_3**	**81**
8	O_2 (1 atm)	—	CsOPiv	65
9	O_2 (1 atm)	$Cu(OAc)_2$ (0.1)	K_2CO_3	59
10	O_2 (1 atm)	HPMoV (0.1)	K_2CO_3	63
11	O_2 (1 atm)	PPh_3 (0.2)	K_2CO_3	44
12	O_2 (1 atm)	Xantphos (0.2)	K_2CO_3	40
13	O_2 (1 atm)	Ethyl nicotinate (0.2)	K_2CO_3	45

[a] Reactions were conducted with coumarin, *tert*-butyl acrylate (2.0 equiv.), $Pd(OPiv)_2$ (0.2 equiv.), and base (3 equiv.) in PivOH at 100 °C for 9 h. [b] Yields are reported after isolation and purification by flash silica gel chromatography. Piv = pivaloyl, TEMPO = 2,2,6,6-tetramethylpiperidin-1-yl)oxyl, HPMoV = molybdovanadophosphoric acid, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

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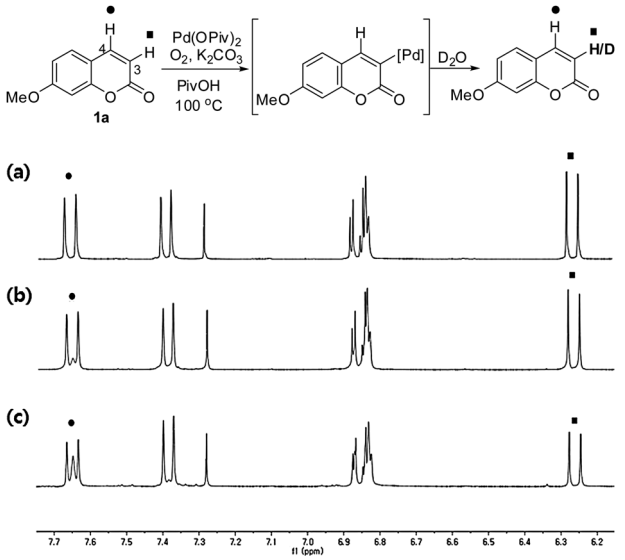


Fig. 1 Pd-catalyzed H/D exchange experiments analysed by ^{1}H NMR: (a) without D_2O (0% exchange); (b) after 3 h (16% exchange); (c) after 12 h (41% exchange).

occurred selectively at the C3 position of the coumarin core. Among the Pd species screened, $Pd(OPiv)_2$ was most effective in promoting the reaction. Both the base and the solvent were found to fundamentally influence the efficiency of the reaction, with K_2CO_3 and pivalic acid[8] being the optimal base and solvent, respectively. The oxidant's properties were also critical to the reaction efficiency, and the use of TEMPO dramatically improved the catalytic efficiency (entry 5). Recent advances in palladium-catalyzed aerobic oxidation reactions suggested that the resulting Pd–H or Pd(0) species in this coupling reaction could be oxidized by employing an environmentally benign terminal oxidant, such as air or O_2.[9] To our delight, the C3-alkenylation process worked well when the reaction was carried out in the open air (entry 6, 76%). A slightly higher product yield was obtained under an O_2 atmosphere (entry 7, 81%). Ligands, such as PPh_3, Xantphos, pyridine or ethyl nicotinate, which have been used in other Pd-catalyzed aerobic reactions[10] led to lower yields under the reaction conditions (entries 11–13 and the ESI†). In addition, no beneficial effects were observed in the presence of electron-transfer mediators, such as $Cu(OAc)_2$ (entry 9) or HPMoV

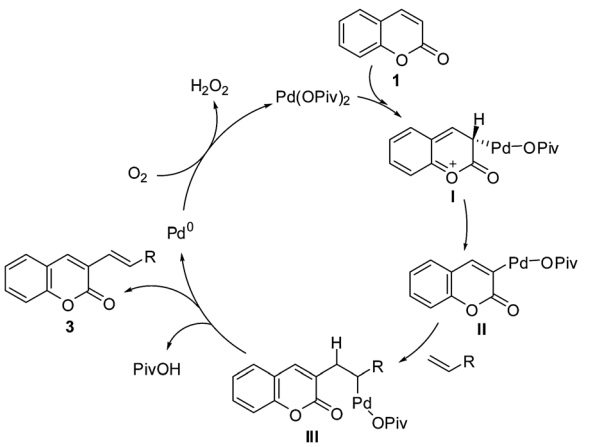
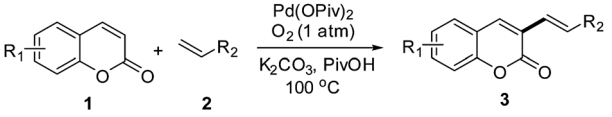
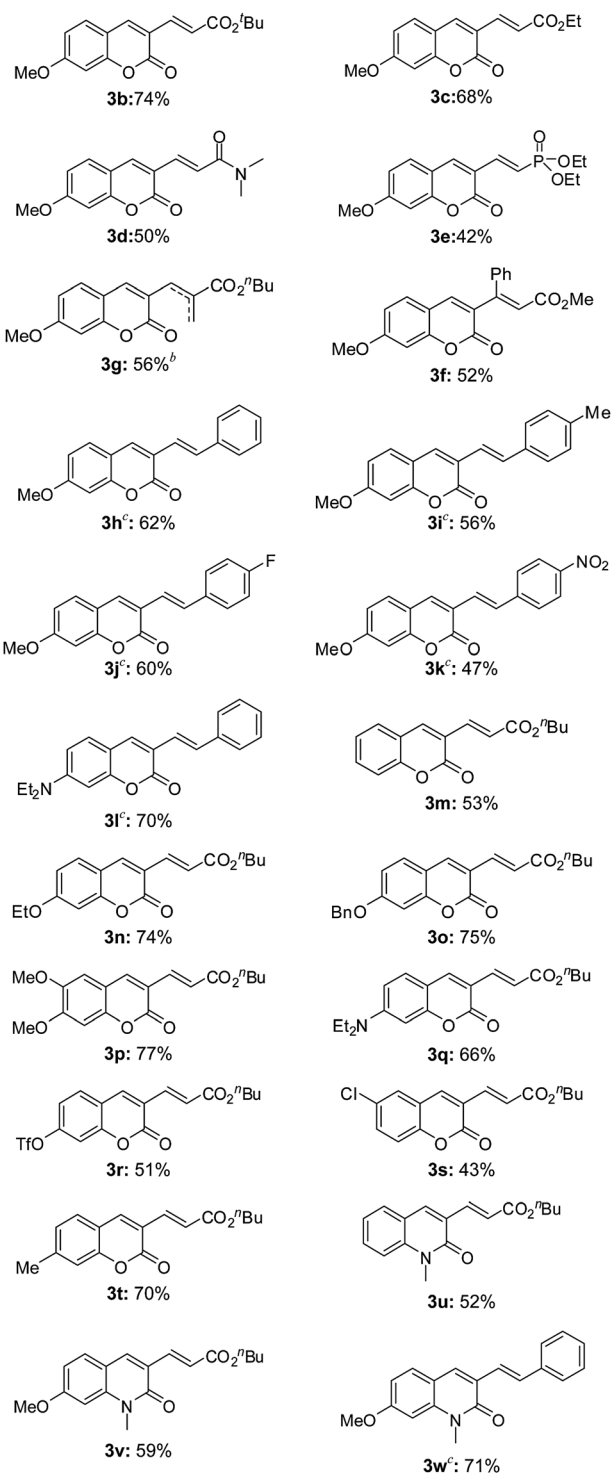


Fig. 2 Proposed mechanistic pathways underlying the present reactions.

Table 2 Direct C3-olefination of the coumarins with various alkenes[a]





[a] Reactions were conducted with coumarin, alkene (2.0 equiv.), $Pd(OPiv)_2$ (0.2 equiv.), and K_2CO_3 (3 equiv.) in PivOH at 100 °C under an O_2 atmosphere for 3–9 h. [b] A 1 : 1 mixture of isomers was produced. [c] Reactions were conducted at 120 °C. Yields are reported after isolation and purification by flash silica gel chromatography.

(entry 10).[11] The optimized catalytic conditions allowed for the direct installation of olefins at the C-3 position with the use of 1 atm O_2 as the sole oxidant, presenting an efficient and sustainable approach to the synthesis of a variety of fluorescent 3-vinylcoumarin derivatives (Table 1).

To elucidate the present alkenylation process, a mechanistic analysis of the initial interaction of Pd(II) with coumarin **1a** was carried out by means of a H/D exchange experiment.[12] A significant level of deuterium incorporation (after 12 h, 41% D) was observed at the C3 position of coumarin (**1a**) when the reaction mixture was treated with D_2O (20 equiv.) as a deuterium source under the optimized conditions and in the absence of alkene, as shown in Fig. 1 (see the ESI† for the full spectra).

Based on the above observations, we proposed a mechanism for the present reaction pathway (Fig. 2). Electrophilic palladation of coumarin at the C3 position with the Pd(II) species was favorable due to the more nucleophilic 3-position, thereby affording the intermediate **II**. In the presence of an alkene substrate, the C3-palladated species **II** inserted into the olefin, and the subsequent reductive elimination of a Pd/alkyl intermediate **III** provided the desired coupled product **3**. Finally, the reoxidation by molecular oxygen regenerated the Pd(II) catalyst to complete the catalytic cycle.

With the optimized conditions in hand, we next investigated the substrate scope of both the coumarin and the arene substrate (Table 2). The present C3-alkenylation process was amenable to the presence of a variety of functional groups. For example, alkene substrates conjugated with the ester (**3b** and **3c**), amide (**3d**), or phosphonate (**3e**) groups all smoothly coupled with 7-methoxycoumarin at the C3 position. When 2-methyl substituted methyl arylate was employed as a substrate, a mixture of regioisomers **3g** (1 : 1) formed. Methyl cinnamate also readily reacted with the coumarin to afford the corresponding desired product (**3f**). The addition of the styryl group to the 3 position of the coumarin core was expected to induce a red-shift in the emission wavelength by extending the π-electron system.[13] To our delight, a variety of styrene substrates were compatible with the coupling reaction conditions, and modest to good yields of the desired products were obtained (**3h**, **3i**, **3j**, **3k**, and **3l**). The scope of the coumarin substrates was subsequently examined, and a relatively broad range of functional groups (*e.g.*, alkyl, chloro, methoxy, ethoxy, benzoxy, triflate, and diethylamino) on the coumarin core were compatible with the coupling conditions. Substitution with an electron-donating OMe group at the 7-position enhanced the reaction efficiency (**3a** *vs.* **3m**). Notably, a coumarin bearing a triflate substituent yielded the synthetically versatile **3r** with an intact triflate moiety under the reaction conditions. We further investigated additional substrates and were pleased to observe that quinolinones also worked well in the optimized system, leading to the formation of **3u**, **3v** and **3w**.

In summary, we developed an efficient method for the direct C–H olefination of coumarins *via* a palladium catalyzed oxidative Heck reaction. The choice of palladium catalyst source and base were important factors for achieving a high reaction efficiency, and O_2 was successfully utilized as the sole oxidant. This approach led to the construction of a variety of 3-vinyl and 3-styryl coumarin scaffolds, which are privileged structures and prevalent motifs in many biologically active compounds and fluorophores.

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