ORGANIC LETTERS

2011
Vol. 13, No. 16
4466–4469

Palladium(II)-Catalyzed Direct Intermolecular Alkenylation of Chromones

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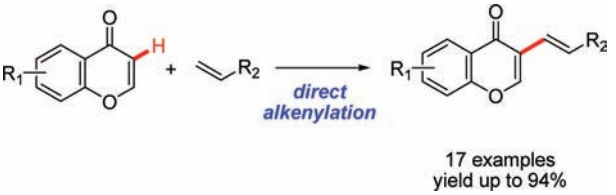
Received July 7, 2011

ABSTRACT



A new efficient method for the direct alkenylation of chromones via a palladium(II)-catalyzed C−H functionalization reaction was developed. The use of pivalic acid with $Cu(OAc)_3/Ag_2CO_3$ provided superior reactivity in the cross-coupling of chromones with alkene partners. This approach represents a significant advance over the existing two-step method and afforded various 3-vinylchromone derivatives, which are privileged structures in many biologically active compounds and versatile synthetic building blocks.

The chromone motif is an important constituent of natural products,[1] and this family of molecules has been extensively investigated due to their broad range of remarkable biological activities.[2] C-3 vinyl groups on chromones[3] are found in many pharmaceutically important compounds that have antimicrobial, antitumor, antiallergic, or anti-inflammatory activities.[4] The 3-vinylchromone scaffolds **2** have proven to be highly useful as versatile synthetic building blocks for the construction of more advanced structures, such as xanthones **3**[5] and 2-pyridone derivatives **4**,[6] as shown in Scheme 1. Consequently, vinylchromone derivatives **2** continue to attract the attention of synthetic chemists.[3−7] With the aim of constructing focused chemical libraries useful for chemical biology research and drug discovery, we were interested in developing an efficient method for the synthesis of various chromones bearing a functionalized vinyl unit at the C-3 position.

A general method for introducing C-3 vinyl groups into preformed chromones is via a Heck coupling reaction between 3-halochromones and alkene coupling partners.[8] This cross-coupling approach outweighs other synthetic methods due to its flexibility in the synthesis of structurally diverse 3-vinylchromone derivatives. Despite its flexibility, the overall coupling requires two discrete activation steps:

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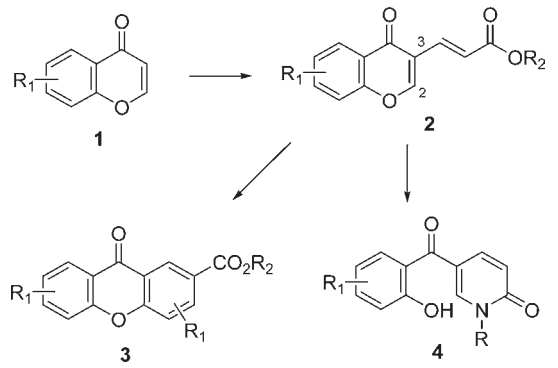
10.1021/ol2018278
Published on Web 07/28/2011

Scheme 1. Strategy for Building a Chromone-Related Chemical Library[a]



[a] Xanthones **3** and 2-pyridone derivatives **4** can be efficiently prepared from 3-vinylchromones **2** in a one-pot reaction.

(1) formation of 3-halochromone and (2) a palladium(0)-catalyzed Heck coupling reaction. Therefore, we were interested in exploring a direct coupling approach that would allow us to avoid prefunctionalizing the chromones and that would provide a more efficient process for the C-3 alkenylation of chromones under catalytic conditions. The direct transition metal-catalyzed functionalization of C−H bonds in heterocycles is an exceedingly valuable process in the context of contemporary organic synthesis.[9] In particular, direct arylation and vinylation of heterocycles has found widespread use in synthesis for the construction of complex frameworks.

Direct olefination of arenes, pyridine *N*-oxides, and indoles with alkene units via an oxidative palladium(II)-catalyzed process appears as a promising alternative to the conventional procedure.[10] In light of the advances in this area, we envisaged that in the event the nucleophilic attack of chromone on palladium proceeded, the C3-palladated species could be accessed in a catalytic one-step fashion, although the nucleophilic character of enolone systems is relatively weak compared with that of indole systems. The resulting intermediate could be further coupled with a suitable alkene to provide the desired 3-vinylchromone product. During these efforts, we established an efficient palladium catalytic protocol for the facile cross-coupling of chromones with a range of alkenes, and herein we report the details of this study.

To test the feasibility of this process, our efforts began by investigating the direct coupling reaction of chromone (**1a**) with *n*-butyl acrylate (**5a**) in the presence of $Pd(OAc)_2$ as a catalyst and $Cu(OAc)_2$ as an oxidant under conditions similar to those employed for the oxidative Heck coupling of indole.[8b] Unfortunately, no detectable coupling product was observed, probably because the innate nucleophilicity of chromone was insufficient to engage palladation under these conditions. Thus, a systematic investigation of more reactive catalytic systems was conducted with testing of different bases, solvents, oxidants, and temperatures to establish an optimal combination for the transformation (Tables 1S−3S in the Supporting Information). We found that the addition of certain bases was crucial, and the reactions that used 3 equiv of K_2CO_3 at 120 °C provided a noticeable product yield (Table 1, entry 2). Reactions conducted at other temperatures provided lower yields of the cross-coupled product.

Recent reports have described palladium−pivalic acid combinations that exhibit good reactivity in C−H activation reactions by lowering the energy of C−H bond cleavage and by acting as partial proton shuttles during catalysis.[11] These observations prompted us to evaluate the use of various carboxylic acids as sources of a catalytic carboxylate base to test for beneficial effects on the palladation of chromones. To our delight, the use of acetic acid as a solvent indeed promoted the reaction with an improved yield (31%) of 3-vinylchromone (Table 1, entry 2). The use of stronger acids, such as trifluoroacetic acid, did not positively influence the reaction outcome (entry 3). Gratifyingly, however, a marked increase in conversion was observed as the steric encumbrance of the acid increased from acetic acid to pivalic acid, and the use of pivalic acid with K_2CO_3 provided superior reactivity to furnish a 72% yield of the coupled product (entry 6). The reaction development efforts also focused on the appropriate choice of base−carboxylic acid combination. The use of Ag_2CO_3 in conjunction with pivalic acid as the solvent increased the reaction yield, and we successfully drove the coupling of chromone (**1a**) with *n*-butyl acrylate (**5a**) to achieve a 94% yield of product (entry 8). The control reactions performed without an oxidant and the screening of other base/oxidant combinations further demonstrated their critical role in effecting high cross-coupling conversion efficiency. For example, the reaction

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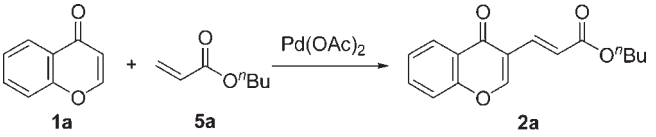
conducted in the presence of only Ag_2CO_3, which functioned as both a base and an oxidant, gave a lower product yield (entry 12).

Table 1. Development of the Direct Alkenylation of Chromone[a]



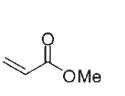
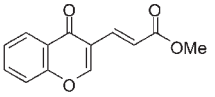
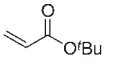
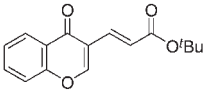
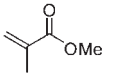
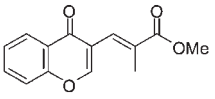
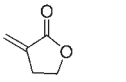
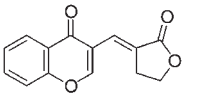
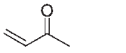
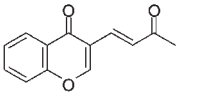
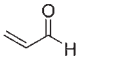
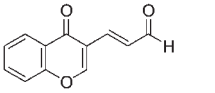
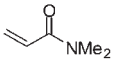
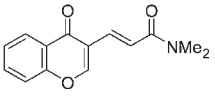
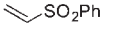
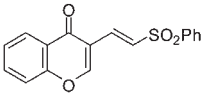
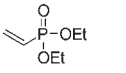
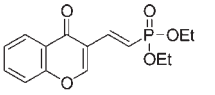
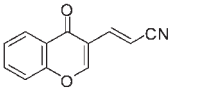
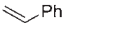
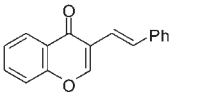
entry	oxidant (equiv)	solvent	base (equiv)	yield (%)[b]
1	$Cu(OAc)_2$ (3)	AcOH	none	8
2	$Cu(OAc)_2$ (3)	AcOH	K_2CO_3 (3)	31
3	$Cu(OAc)_2$ (3)	TFA	K_2CO_3 (3)	18
4	$Cu(OAc)_2$ (3)	$PhCO_2H$	K_2CO_3 (3)	trace
5	$Cu(OAc)_2$ (3)	$EtCO_2H$	K_2CO_3 (3)	37
6	$Cu(OAc)_2$ (3)	$^tBuCO_2H$	K_2CO_3 (3)	72
7	$Cu(OAc)_2$ (3)	$^tBuCO_2H$	Cs_2CO_3 (3)	54
8	$Cu(OAc)_2$ (3)	$^tBuCO_2H$	Ag_2CO_3 (3)	94
9	$Cu(OAc)_2$ (3)	$^tBuCO_2H$	AgOAc (3)	25
10	$Cu(OAc)_2$ (3)	$^tBuCO_2H$	AgO_2CF_3 (3)	76
11	$Cu(OAc)_2$ (3)	$^tBuCO_2H$	AgOTf (3)	22
12	none	$^tBuCO_2H$	Ag_2CO_3 (3)	74
13	$Cu(OAc)_2$ (3)	$^tBuCO_2H$	none	39

[a] Reactions were conducted with chromone (1 equiv), *n*-butyl acrylate (2 equiv), $Pd(OAc)_2$ (0.1 equiv), oxidant, and base at 120 °C for 24 h. [b] Yields are reported after isolation and purification by flash silica gel chromatography. TFA = trifluoroacetic acid.

With this optimized protocol in hand, studies of the coupling reaction were extended to include various functionalized alkenes summarized in Table 2. Reactions involving alkenes conjugated with methyl ester groups **5b** led to a good product yield (Table 2, entry 1). The acrylate ester bearing a bulky *tert*-butyl group **5c** also resulted in the formation of **2c** in high yield (entry 2). The reactions with methacrylate **5d** or lactone **5e** efficiently afforded the corresponding product **2d** or **2e**, respectively (entries 3 and 4). Alkenes conjugated with a ketone, aldehyde, amide, or sulfone group were all smoothly alkenylated on chromone (**1a**) in good yields (entries 5–8). A synthetically versatile precursor, chromone phosphonate **2j**, could be generated from vinyl phosphonate **5j** in 72% yield (entry 9). Acrylonitrile **5k** was also tolerated, and a 49% yield of **2k** was provided with 47% recovery of a starting material (entry 10). The sensitivity of both the rate and yield of the reaction to the electronic effects could be seen in the behavior of the alkenes. For example, reaction of the nonactivated alkene styrene **5l** with chromone (**1a**) provided only a moderate yield (entry 11).

To explore this coupling reaction further, we next turned our attention to the scope of chromone substrates (Figure 1). The 6-nitro, 6-methyl, or 7-methoxychromones were reacted with *n*-butyl acrylate (**5a**) to furnish the desired products with good yields. Of particular note was the use of bromochromone: synthetically versatile **2p** was

Table 2. Direct Alkenylation of Chromone with Various Alkenes[a]

entry	alkene		product		yield (%)[b]
1		**5b**		**2b**	94
2		**5c**		**2c**	92
3		**5d**		**2d**	52
4		**5e**		**2e**	63
5		**5f**		**2f**	89
6		**5g**		**2g**	78
7		**5h**		**2h**	82
8		**5i**		**2i**	71
9		**5j**		**2j**	72
10		**5k**		**2k**	49[c]
11		**5l**		**2l**	46

[a] Reactions were conducted with chromone (1 equiv), alkene (2 equiv), $Pd(OAc)_2$ (0.1 equiv), $Cu(OAc)_2$ (3 equiv), and $Ag_2(OAc)_2$ (3 equiv) at 120 °C for 24 h. [b] Yields are reported after isolation and purification by flash silica gel chromatography. [c] 47% of a starting material recovered.

isolated in 93% yield with an intact aryl bromo moiety to provide an opportunity for further functionalization. In addition, we were pleased to observe that the 2-phenylchromone (flavone) was readily derivatized through this oxidative alkenylation to afford 3-vinylflavone **2q** in 52% yield. This synthetic route would be useful in providing access to a set of highly functionalized flavone analogs.

A plausible mechanism for the palladation of chromone involves initiation by the nucleophilic attack of chromone on palladium, followed by deprotonation by the pivalate

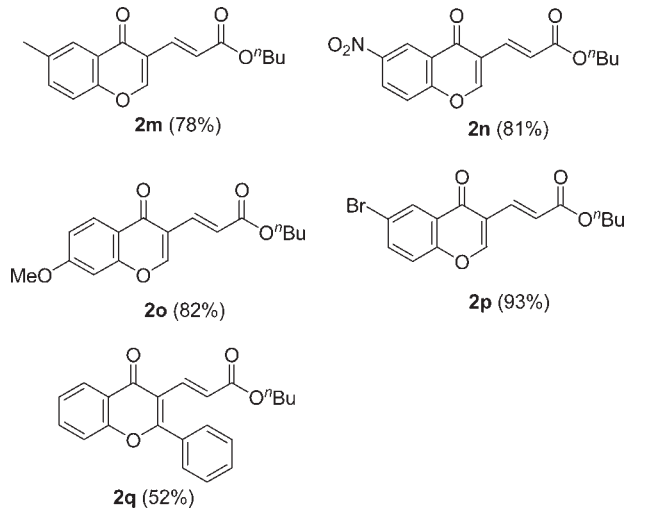


Figure 1. Direct alkenylation of substituted chromones.

ligand to give the palladium(II) intermediate **I** (Figure 2). The high reactivity of pivalic acid relative to other carboxylic acids may be derived from the increased basicity of its conjugate base.[12] Next, in the presence of an appropriate alkene substrate, the C3-palladated species inserts into the alkene, and reductive elimination provides the desired coupled product. In the case of the nonactivated alkene, the rate of insertion into an alkene was relatively slow, and a lower yield was obtained, presumably because of competitive oxidative decomposition of the remaining C3-palladated species. Finally, the oxidation of Pd(0) to Pd(II) using $Cu(OAc)_2/Ag_2CO_3$ completes the catalytic cycle.

In summary, we developed an efficient method for the intermolecular alkenylation of chromones via a palladium-catalyzed C−H functionalization reaction. This approach led to the construction of 3-vinylchromone scaffolds, which are privileged structures and prevalent motifs in many biologically active compounds. The beneficial effects associated with the use of pivalic acid in conjunction with $Cu(OAc)_3/Ag_2CO_3$ were clearly observed in the cross-coupling of chromones with alkene partners. This method represents an unprecedented example of C−H functionalization of chromones and a significant advance over the existing two-step method.

(12) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015.

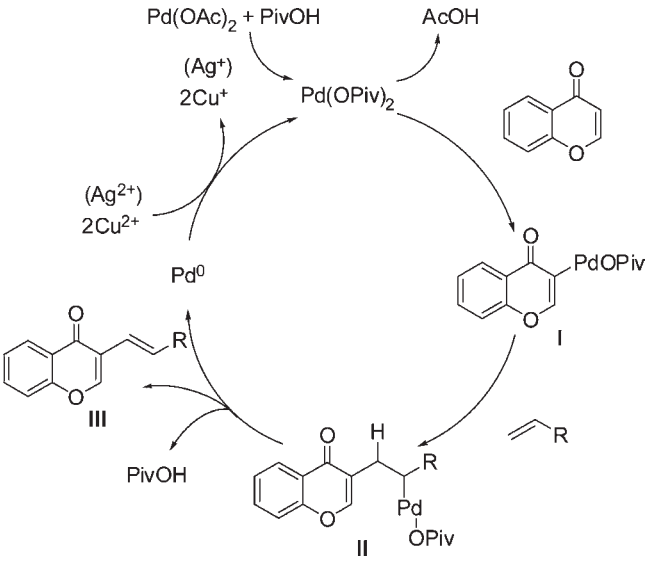


Figure 2. Proposed catalytic cycle for the direct alkenylation of chromone.

Acknowledgment. This research was supported by the National Research Foundation of Korea (NRF) through general research grants (NRF-2010-0022179 and 2011-0016436)

Supporting Information Available. Experimental procedures and characterization of all new compounds and biological evaluation data. This material is available free of charge via the Internet at http://pubs.acs.org.