doi:10.1246/cl.2012.705
Published on the web June 23, 2012

Cascade Synthesis of 3-Alkenylcoumarins by Palladium-catalyzed Reaction of Phenols and Ethyl Propiolate

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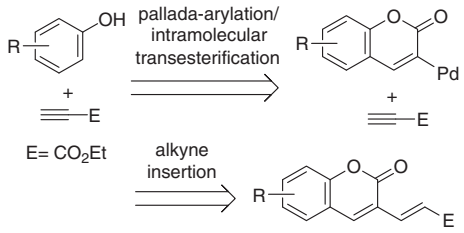
A highly effective cascade process giving 3-alkenylcoumarins is furnished by a series of reactions involving palladaarylation of ethyl propiolate with phenols, intramolecular transesterification to 3-coumarylpalladium species, its alkyne insertion, and protonation. [Pd(OAc)$_2$(dppe)] is an effective catalyst for the synthesis of 3-alkenylcoumarins from phenols and ethyl propiolate.

Direct functionalization of C–H bonds forming new C–C bonds has attracted much attention as a significant subject in organic synthesis,[1] because such direct functionalization of C–H bonds does not require any prefunctionalization of the C–H bonds transforming into reactive C–halogen bonds, and consequently it reduces reaction steps to furnish highly efficient synthetic processes. Hydroarylation of alkynes can formally be regarded as a reaction where both aryl and hydrogen moieties of an aromatic compound add across a triple bond. It is a highly efficient reaction with high atom economy and provides aromatic alkenes through a direct introduction of a double bond into an aromatic C–H bond.[2] Very recently, we have further developed a direct synthesis of arylbutadienes by means of C–H bond functionalization methodology,[3] where two molecules of ethyl propiolate are formally incorporated into an aromatic C–H bond.

On the other hand, coumarin and its derivatives widely occur in nature, particularly in plants, and most of them show useful biological activities.[4] In addition to the biological properties, a coumarin unit is an important chromophore of organic materials, indicating many applications to cosmetics, optical brighteners, and dispersed fluorescent and laser dyes.[4] Due to the useful applications much attention has been paid to the synthesis of functionalized coumarin derivatives.[4] Especially, the outstanding fluorescence of the coumarin chromophore has been clarified by introduction of unsaturated substituents at the 3 position, bringing about the extension of the π system.[5] Very recently, it has been reported 3-alkenylcoumarins bearing electron-withdrawing groups on the alkenyl moiety serve as useful intermediates in the synthesis of 6*H*-dibenzo[*b*,*d*]pyran-6-one, which is an important core of many natural products.[6]

Introduction of a substituent at the 3 position of coumarins has been achieved so far by the following reactions: Heck-type Pd-catalyzed cross-coupling reactions using 3-bromocoumarins,[5a] the Friedel–Crafts acylation of coumarin-3-acetic acid followed by reduction and dehydration,[7] the Horner–Emmons reaction of coumarylmethylphosphonate derived from salicylaldehyde,[8] the Knoevenagel condensation reaction of 2-hydroxybenzaldehydes with diethyl 2-pentenedicarboxylate,[9] and the conventional reactions of 3-formylcoumarin such as the Horner–Wadsworth–Emmons reaction, the Wittig reaction, and the Knoevenagel condensation.[6] However, there are several drawbacks in these methods. Each of the above-mentioned reactions required a complicated substrate as a starting material, and required several synthetic steps to introduce the unsaturated substituent at the 3 position of coumarins. It would be the best synthetic process if target 3-alkenylcoumarins could be prepared by one-pot synthesis using simple substrates. Thus, we considered a cascade process affording the alkenylcoumarins, as illustrated in Scheme 1. Synthesis of 3-alkenylcoumarins may be furnished by insertion of an alkyne into a coumarin–palladium bond of a coumarylpalladium complex, which is formed by coumarin synthesis from a phenol and propiolates. In this paper, we report a highly efficient cascade synthesis of 3-alkenylcoumarins directly from phenols and ethyl propiolate with the aid of [Pd(OAc)$_2$(dppe)] [dppe: 1,2-bis(diphenylphosphino)ethane] as a catalyst.

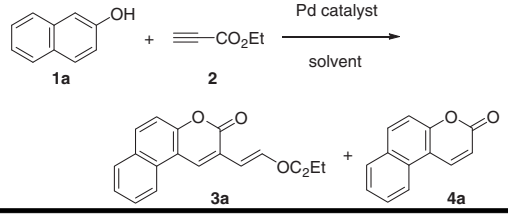


Scheme 1.

Although we already have suitable reaction conditions for the synthesis of coumarins,[10] it is essential to use a bidentate phosphine ligand to promote the alkyne insertion of the intermediate coumarylpalladium complex.[3] First, we examined the reaction of 2-naphthol (**1a**) and ethyl propiolate (**2**) to optimize the reaction conditions. The results are given in Table 1. When the reaction of **1a** (2 mmol) with **2** (2 mmol) was carried out in the presence of a catalytic amount (0.5 mol %) of [Pd(OAc)$_2$(dppe)] in TFA (0.5 mL) and CH_2Cl_2 (1 mL) at 30 °C for 5 h, alkenylcoumarin **3a** was obtained in 44% yield, together with coumarin **4a** in 26% yield (Entry 1). The yield and selectivity of **3a** were improved by using an excessive quantity of **2** to **1a** (Entries 2 and 3), giving the highest yield (82%) of **3a** (Entry 3). In order to search for a better ligand, we screened the following ligands: 1,3-bis(diphenylphosphino)propane (dppp), 1,1-bis(diphenylphosphino)methane (dppm), 1,1′-bis(diphenylphosphino)ferrocene (dppf), 1,2-bis(diphenylphosphino)benzene (dppbz), and (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP). Unfortunately, better yield and selectivity were not obtained (Entries 4–8).

By using the optimized conditions (Table 1, Entry 3) in hand, a wide range of phenol derivatives **1** were converted into the corresponding 3-alkenylcoumarin derivatives **3**. The results

Table 1. Optimization of the reaction conditions[a]



Entry	**1a** /mmol	**2** /mmol	Pd catalyst	**3a** /%	**4** /%
1	2	2	[Pd(OAc)$_2$(dppe)]	44	26
2	1.2	2	[Pd(OAc)$_2$(dppe)]	59	35
3	1.2	6	[Pd(OAc)$_2$(dppe)]	82	10
4	1.2	6	[Pd(OAc)$_2$(dppp)]	16	10
5	1.2	6	[Pd(OAc)$_2$(dppm)]	9	27
6	1.2	6	[Pd(OAc)$_2$(dppf)]	8	33
7	1.2	6	[Pd(OAc)$_2$(dppbz)]	57	19
8	1.2	6	[Pd(OAc)$_2$(*R*-BINAP)]	11	4

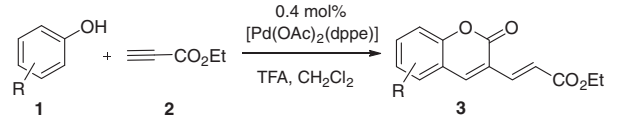
[a]Reaction conditions: Pd catalyst (0.005 mmol), **1a**, **2**, TFA (0.5 mL), CH_2Cl_2 (1 mL), 30 °C, 5 h. Yields (%) represent isolated ones by column chromatography. See Supporting Information (SI) for details.[13]

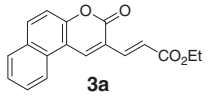
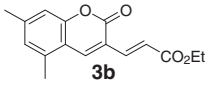
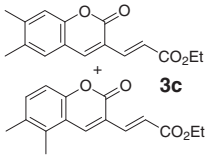
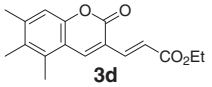
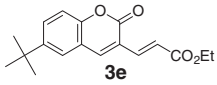
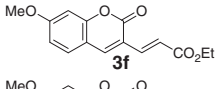
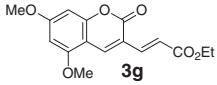
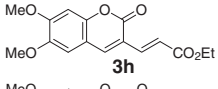
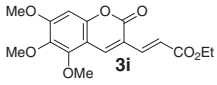
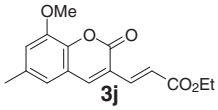
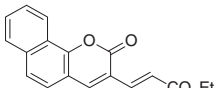
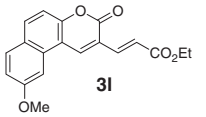
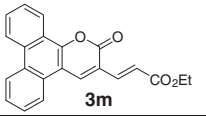
are given in Table 2. The reaction of 3,5-dimethylphenol (**1b**) afforded alkenylcoumarin **3b** in 47% yield, together with the formation of coumarin **4b** (Entry 2). Interestingly, 3,4-dimethylphenol (**1c**), 3,4,5-trimethylphenol (**1d**), and 4-*tert*-butylphenol (**1e**) reacted highly selectively to give the corresponding coumarins **3c**–**3e** in 94, 77, and 61% yields, respectively (Entries 3–5). In the case of **1c**, a regioisomeric mixture (1:1) of **3c** was formed. Next, we examined the reaction of alkoxyphenols under similar conditions (Entries 6–10). The reaction of 3-methoxyphenol (**1f**) gave alkenylcoumarins **3f** in 39% yield. A similar reaction with 3,5-dimethoxyphenol (**1g**) afforded alkenylcoumarin **3g** in 39% yield. A better yield (57%) of alkenylcoumarin **3h** was obtained in the case of 3,4-dimethoxyphenol (**1h**), albeit coumarin **4d** was also formed. The reaction of 3,4,5-trimethoxyphenol (**1i**) selectively gave the corresponding alkenylcoumarin **3i** in 70% yield. Similarly, the reaction of 2-methoxy-4-methylphenol (**1j**) gave alkenylcoumarin **3j** selectively in 48% yield. This alkenylcoumarin-formation reaction was applied to polycyclic phenols such as 1-naphthol (**1k**), 7-methoxy-2-naphthol (**1l**), and phenanthrol (**1m**) (Entries 11–13). Differently from 2-naphthol (**1a**), 1-naphthol (**1k**) resulted in a low selectivity to give alkenylcoumarin **3k** and coumarin **4e** in 50 and 28% yields, respectively. The reaction of **1l** gave alkenylcoumarin **3l** in 71% yield, together with coumarin **4f** (6%). The reaction of **1m** afforded alkenylcoumarin **3m** selectively in 58% yield.

The presence of a substituent at the terminal position of propiolate **2** inhibited the reaction. For example, the reaction of ethyl phenylpropiolate did not occur at all.

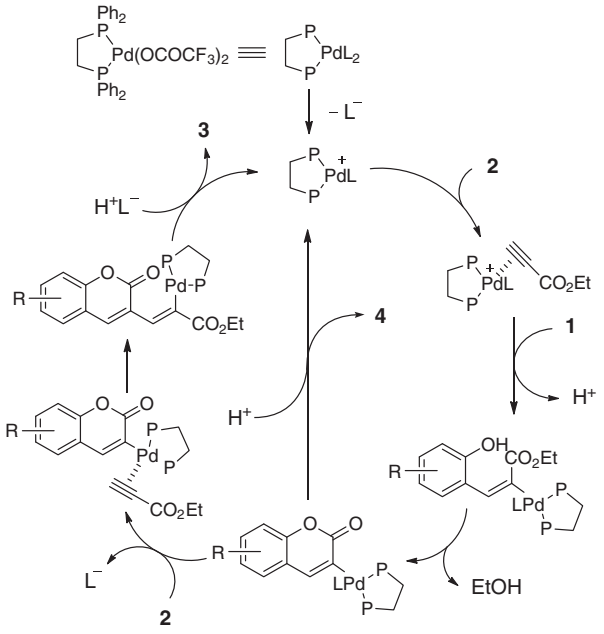
A possible mechanism for the reaction of phenols **1** with **2** in the presence of a palladium complex is shown in Scheme 2. First, [Pd(OAc)$_2$(dppe)] is thought to undergo ligand exchange with TFA in TFA to form a cationic palladium species,[11] which coordinates with ethyl propiolate (**2**) to activate it. Next, the activated **2** reacts with phenol **1** via electrophilic aromatic

Table 2. Scope for Pd-catalyzed alkenylcoumarin formation[a]



Entry	**1**	Solv.[b]	Time /h	Product	Yield /%[c]
1	**1a**	A	5	 **3a**	82 (**4a**: 10)
2	**1b**	B	12	 **3b**	47 (**4b**: 24)
3	**1c**	B	12	 **3c**	94
4	**1d**	A	12	 **3d**	77
5	**1e**	B	12	 **3e**	61
6	**1f**	B	12	 **3f**	39
7	**1g**	B	5	 **3g**	39 (**4c**: 21)
8	**1h**	C	5	 **3h**	57 (**4d**: 22)
9	**1i**	A	12	 **3i**	70
10	**1j**	A	12	 **3j**	48
11	**1k**	A	12	 **3k**	50 (**4e**: 28)
12	**1l**	A	5	 **3l**	71 (**4f**: 6)
13	**1m**	A	5	 **3m**	58

[a]Reaction conditions: Pd catalyst (0.005 mmol), **1** (1.2 mmol), **2** (6 mmol), TFA, CH_2Cl_2, 30 °C. [b]Solvent A: TFA (0.5 mL), CH_2Cl_2 (1 mL); solvent B: TFA (0.5 mL), CH_2Cl_2 (0.5 mL); solvent C: TFA (0.25 mL), CH_2Cl_2 (0.75 mL). [c]Isolated yields by column chromatography. The yield of coumarin **4** is shown in a parenthesis. See SI for details.[13]



Scheme 2.

substitution and immediately cyclizes by intramolecular transesterification to give a 3-coumarylpalladium species. Although the protonation of this coumarylpalladium species produces coumarin **4**, the coordination with **2** makes a new route to 3-alkenylcoumarin **3**. In this complex, the bidentate phosphine ligand (dppe) plays an important role. The presence of this bidentate ligand forces the *cis* relationship between the coumaryl group and **2** and this structural relation favors the insertion of alkyne **2** into the C–Pd bond. If a bidentate ligand is not present, alkyne **2** will be located *trans* to the coumaryl group due to steric hindrance, where the coumarylpalladium intermediate undergoes protonation to yield coumarin **4**.[10] To confirm this postulation, we examined the reaction in the presence of $Pd(OAc)_2$ without any bidentate phosphine ligands. The reaction of **1a** with **2** was conducted in the presence of 0.4 mol % $Pd(OAc)_2$ in TFA and CH_2Cl_2 at 30 °C for 5 h. The products isolated were **3a** and **4** in 20 and 56% yields, respectively. Apparently this result indicates that the presence of the bidentate ligand is essential for this alkenylcoumarin formation. Finally, the protonation of the resulting (coumarylvinyl)palladium species gives 3-alkenylcoumarin **3**, regenerates the cationic palladium species, and closes the catalytic cycle.[12]

In summary, we have demonstrated for the first time an effective cascade process involving pallada-arylation of ethyl propiolate (**2**) with phenols **1**, intramolecular transesterification to 3-coumarylpalladium species, its alkyne insertion, and protonation leading to 3-alkenylcoumarins **3**. In this reaction, two molecules of **2** are formally incorporated into the *ortho* C–H bond of **1**. [$Pd(OAc)_2$(dppe)] is an effective catalyst for the synthesis of 3-alkenylcoumarins **3** from phenols **1** and ethyl propiolate (**2**). Due to the wide applications of 3-alkenylcoumarins, this efficient synthetic method will be attractive in biological and material fields.

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12 A referee suggested the possibility of direct coupling of coumarin **4** with **2**, but the reaction of **4a** with **2** resulted in the recovery of **4a** under the present conditions.

13 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

