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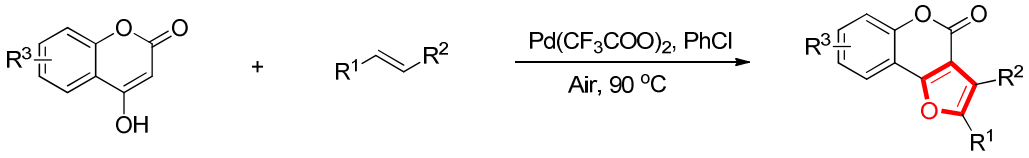
Graphic abstract

Atom-Economical ChemoselectiveSynthesis of Furocoumarins *via* Cascade Palladium Catalyzed Oxidative Alkoxylation of 4-Oxohydrocoumarins and Alkenes

Xian-chun Tan‡, Hai-yuan Zhao‡, Ying-ming Pan*, Na Wu, Heng-shan Wang, and Zhen-feng Chen*



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Atom-Economical Chemoselective Synthesis of Furocoumarins *via* Cascade Palladium Catalyzed Oxidative Alkoxylation of 4-Oxohydrocoumarins and Alkenes

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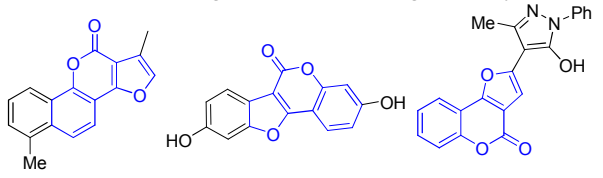
A novel and efficient procedure for the synthesis of furo[3,2-c]coumarins from readily available 4-oxohydrocoumarins and alkenes in the presence of a catalytic amount of $Pd(CF_3COO)_2$ has been developed. Atom-economical characteristics and mild conditions of this method are in accord with the concept of modern green chemistry.

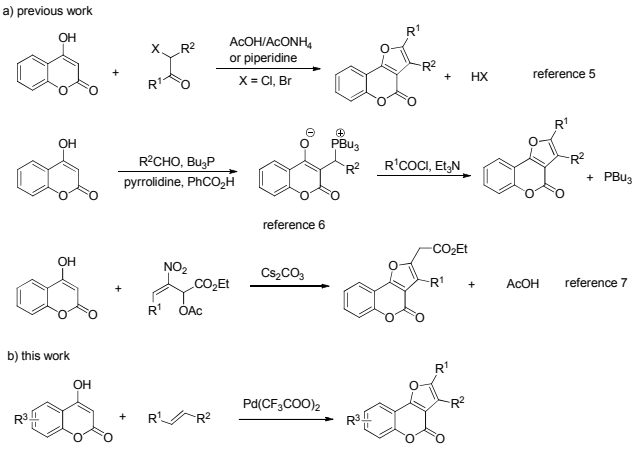
Coumarins are important structural units in several natural products, and feature widely in biologically active compounds.[1] Among them, furocoumarins are structural motif found in numerous pharmaceutically active compounds (Figure 1). Neo-tanshinlactone[2] and Coumestrol[3] exhibit high anti-tumor tissue-type as well as anti-breast cancer cell line selectivity. Pyrazolyl furocoumarin[4] showed good *in vitro* antifungal activity.



Neo-tanshinlactone **Coumestrol** **Pyrazolyl furocoumarin**

Figure 1. Bioactive furocoumarin analogues.

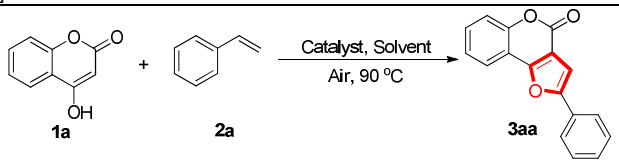
For this reason, considerable efforts have been expended to develop the synthetic methods of furocoumarins. Sameh and Risitano groups applied respectively a tandem O-alkylation/cyclisation of 4-hydroxycoumarin and haloketones to synthesize furo[3,2-c]coumarin derivatives.[5] Chen developed an efficient synthetic method *via* Michael–Oxa-Michael–aromatization protocol of nitroallylic acetates with 1,3-dicarbonyls mediated by base.[6] Lin group employed phosphorus zwitterions with acid chloride in a one-step procedure to approach furo[3,2-c]coumarins.[7] However, these methods require special materials, harsh reaction conditions, long reaction times or involving multistep synthetic operations, and all of them are not atom-economical (Scheme 1a). Therefore, an atom-economical, straightforward, convenient, and high regioselective route to synthesize furocoumarins with basic chemical materials is still highly attractive. To the best of our knowledge, the palladium-catalyzed synthesis of furo[3,2-c]coumarins directly from simple alkenes and 4-oxohydrocoumarins has not been reported so far. As a result of development on the transition-metal-catalyzed C–H functionalization of alkenes in our group,[8] herein, we developed a $Pd(CF_3COO)_2$ catalyzed aerobic oxidative alkoxylation of 4-oxohydrocoumarins and alkenes in a cascade sequence to afford the desired furocoumarins in good yields (Scheme 1b).



Scheme 1. Different approaches to furocoumarins and our work

In order to identify the optimal reaction conditions, 4-oxohydrocoumarin **1a** with styrene **2a** were chosen as model substrates. Initially, the reaction of **1a** (0.5 mmol) and **2a** (0.5 mmol) in the presence of 20 mol % $Pd(CF_3COO)_2$ in PhCl at 90 °C for 4 h gave the furo[3,2-c]coumarins **3aa** in 81% yield (Table 1, entry 1). In addition, in the presence of other catalysts such as $Sc(OTf)_3$, $Y(OTf)_3$, $Cu(OAc)_2$, $Rh(OH)_3$, $InCl_3$ and $AuBr_3$, most of the starting material **1a** was recovered (Table 1, entries 2–7). When other palladium catalysts such as $Pd_3(dba)_2$, $PdCl_2$ and $Pd(OAc)_2$ were used, the yield of **3aa** dramatically decreased to 45−69% (Table 1, entries 8−10). Further optimization suggested that solvents also had a strong effect on this process (Table 1, entries 11−15). The reactions were obviously restrained when they were performed in DMSO, DMF and DCE (Table 1, entries 11-13). The reactions in $PhCH_3$ and 1,4-dioxane yielded 60% and 40% of **1a**, respectively (Table 1, entries 14 and 15). Hence, it was concluded that the best conditions involved 20 mol % $Pd(CF_3COO)_2$ in PhCl at 90 °C .

Table 1. Optimization of the formation of substituted furo[3,2-c]coumarins[a]



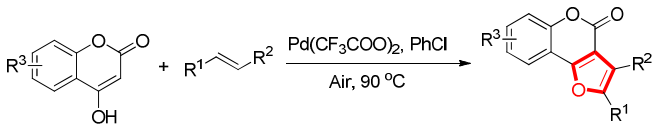
1a **2a** **3aa**

Entry	Catalyst	Solvent	Yield[b] (%)
1	$Pd(CF_3COO)_2$	PhCl	81
2	$Sc(OTf)_3$	PhCl	0
3	$Y(OTf)_3$	PhCl	0
4	$Cu(OAc)_2$	PhCl	0
5	$Rh(OH)_3$	PhCl	0
6	$InCl_3$	PhCl	0
7	$AuBr_3$	PhCl	0
8	$Pd_3(dba)_2$	PhCl	45
9	$PdCl_2$	PhCl	30
10	$Pd(OAc)_2$	PhCl	69
11	$Pd(CF_3COO)_2$	DMSO	20
12	$Pd(CF_3COO)_2$	DMF	0
13	$Pd(CF_3COO)_2$	DCE	25
14	$Pd(CF_3COO)_2$	$PhCH_3$	60
15	$Pd(CF_3COO)_2$	1,4-Dioxane	40

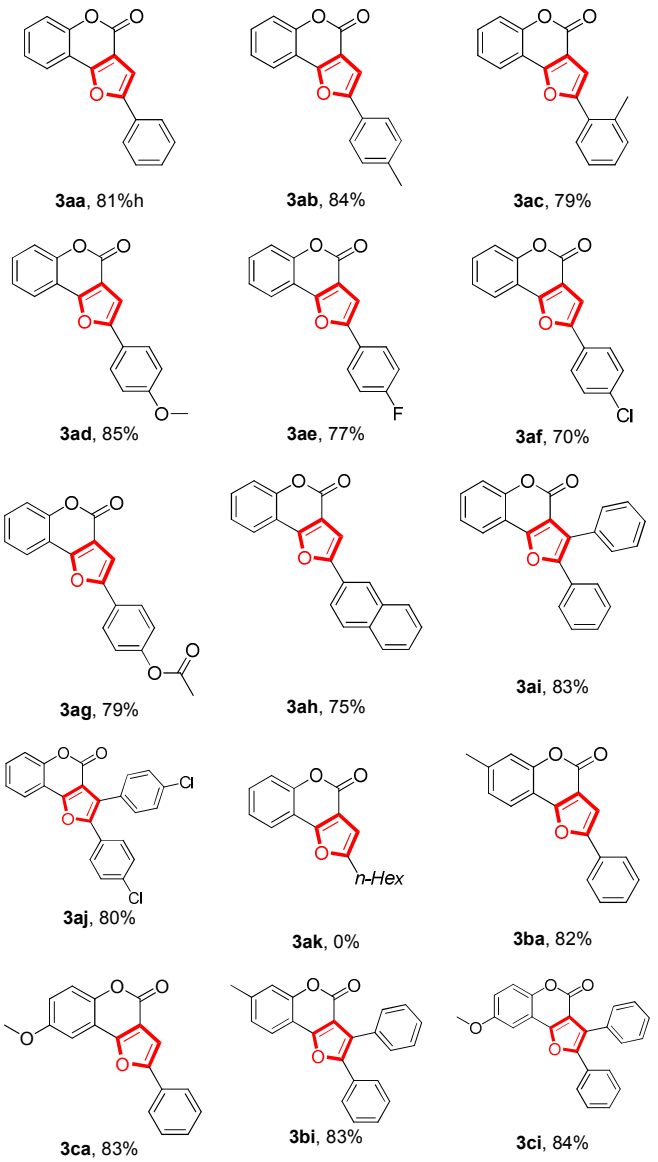
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (20 mol %), solvent (2 mL), 90 °C, 4 h. [b] Isolated yield of the pure product based on **1a**.

With the above optimized conditions in hand, the scope of the substrates was investigated. Typical results are shown in Table 2. To our delight, catalyzed by $Pd(CF_3COO)_2$, both aryl-substituted internal alkenes and terminal alkenes produced high yields of furo[3,2-c]coumarins under the optimized conditions. Terminal alkenes with differents substituted groups such as Me, OMe, F, Cl and $OCOCH_3$, all reacted smoothly afforded the target products in high yields (Table 2, entries **3ab**-**3ag**). In general, the desired products could be obtained in higher yields from electron rich alkenes than that from electron poor alkenes. The position of substituent on benzene ring seemed to have little influence on the product yield (Table 2, entry **3ac**). Terminal alkenes bearing polycyclic aromatic substituent, such as 2-vinylnaphthalene led to the corresponding 2-naphthalen-furo[3,2-c]coumarin **3ah** in 75% yield (Table 2, entry **3ah**). Additionally, the reaction of the internal alkenes **2i** and **2j** with 4-oxohydrocoumarin **1a** also gave the desired products **3ai** and **3aj** in 83% and 80% yields, respectively (Table 2, entries **3ai** and **3aj**). Unfortunately, when the aliphatic alkene was used, the reaction failed to afford the desired product (Table 2, entry **3ak**). Moreover, oxohydrocoumarin bearing substituent such as 6-methoxy-4-hydroxycoumarin and 7-methyl-4-hydroxycoumarin were found to afford the desired products in 82-84% yields (Table 2, entries **3ba**-**3ci**).

Table 2. Synthesis of substituted furo[3,2-c]coumarins from 4-oxohydrocoumarins and alkenes[a]

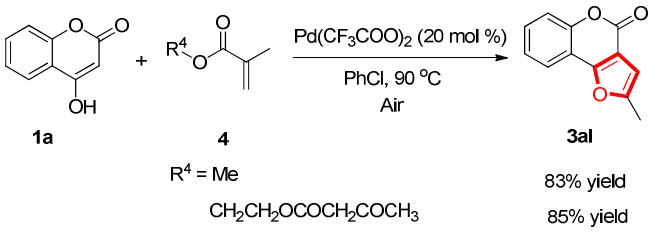


1 **2** **3**



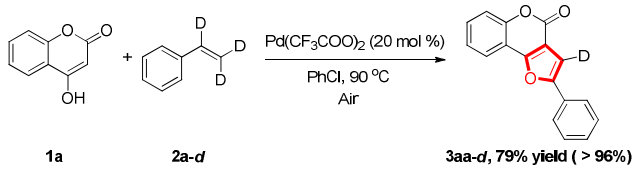
[a] Reactions conditions: 0.5 mmol of **1** and 0.5 mmol of **2** in the presence of 20 mol % of $Pd(CF_3COO)_2$, 2 mL of PhCl at 90 °C for 4 h. Isolated yields.

Surprisingly, the reaction of 4-oxohydrocoumarin **1a** with diffrent methacrylates **4** failed to afford the desired products but gave unexpected product **3al** in high yields (Scheme 2).



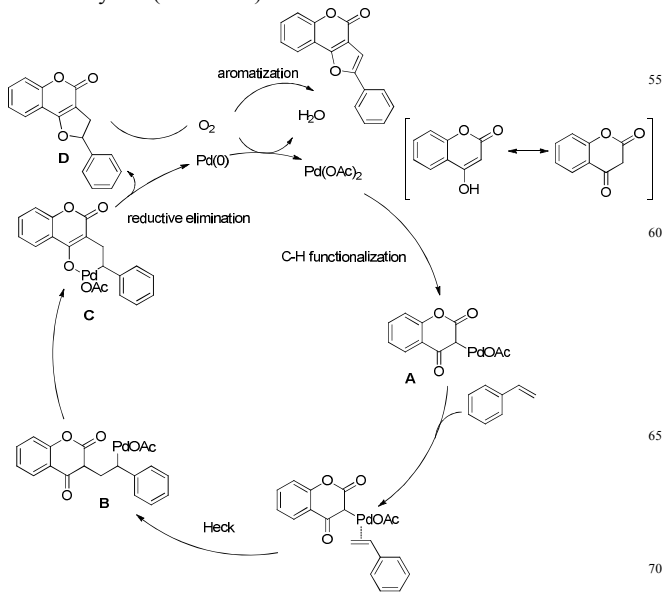
Scheme 2. Synthesis of 2-methyl-furo[3,2-c]coumarin **3al** from 4-hydroxycoumarin **1a** and methacrylates **4**.

To explore the possible reaction pathway, isotope deuterium-labeled styrene **2a-*d*** was used to react with 4-oxohydrocoumarin **1a** in PhCl at 90 °C for 4 h. The substituted furo[3,2-c]coumarin **3aa-*d*** was obtained in 79% yield. Over 96% of deuterium was incorporated in the product (Scheme 3).

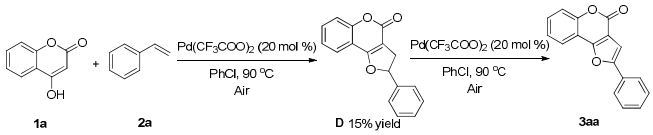


Scheme 3. Deuterium labeling experiment.

On the basis of the mechanism of previous reports[9] and our results, a plausible mechanism is provided in Scheme 4. α-Palladation of 1,3-ketone ester can provide **A**, followed by styrene coordination and Heck insertion to **B**. Reductive elimination to produce dihydro-furocoumarin **D**, which has been detected and isolated in our experiment. Finally, oxidative aromatization under air affords the desired product furocoumarins. Isolated dihydro-furocoumarin **D** reacted in the optimized conditions for another 2 h to afford the final furo[3,2-c]coumarin **3aa** in 95% yield (Scheme 5).



Scheme 4. Possible reaction mechanism.



Scheme 5. Isolated intermediate **D** and oxidation of **D.**

In summary, we have developed an efficient synthetic method to synthesis furo[3,2-c]coumarins from readily available 4-oxohydrocoumarins and alkenes. This operationally simple method gives a rapid access to the furo[3,2-c]coumarins. Atom-economical characteristics and mild conditions of the method are in accord with the concept of modern green chemistry.

Experimental Section

^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 500 MHz NMR spectrometer with $CDCl_3$ as solvent and recorded in ppm relative to an internal tetramethylsilane standard. General chemicals were purchased from commercial suppliers and used without further purification.

General experimental procedure for synthesis of furo[3,2-c]coumarins

The mixture of 4-hydroxycoumarin **1** (0.5 mmol), alkenes **2** (0.5 mmol) and $Pd(CF_3COO)_2$ (0.1 mmol) in PhCl (2 mL) was stirred at 90 °C for 4 h. The progress of the reaction was monitored by thin-layer chromatography. Upon completion, the mixture was then cooled and evaporated under reduced pressure. The target product **3** was purified by flash chromatography on silica gel using a mixture of ethyl acetate and petroleum ether.

Acknowledgements

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Notes and references

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† Electronic Supplementary Information (ESI) available: [general experimental procedures, and spectral data, NMR spectra and high resolution mass spectra for all compounds. See DOI: 10.1039/b000000x
‡ These authors contributed equally to this work.

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