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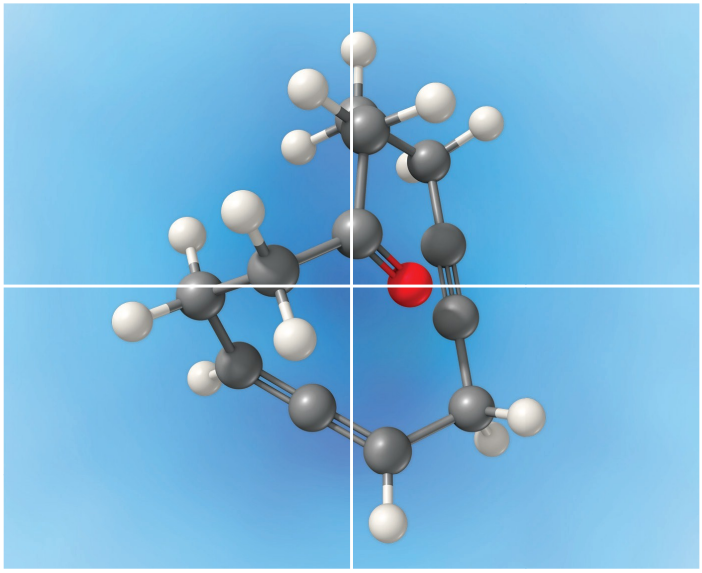

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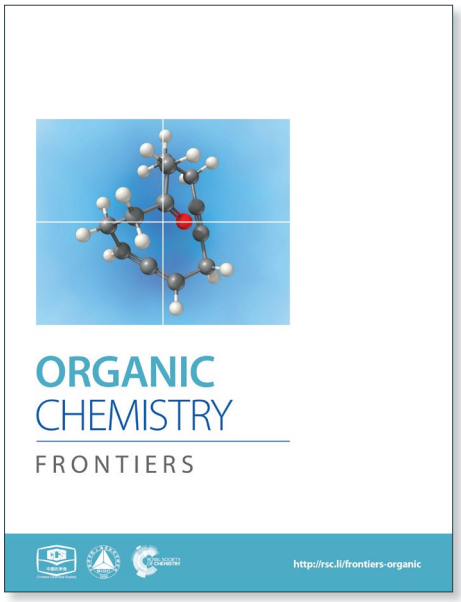

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Journal Name

ARTICLE

Regioselective palladium(II)-catalyzed aerobic oxidative Heck-type C3 alkenylation of sulfocoumarins

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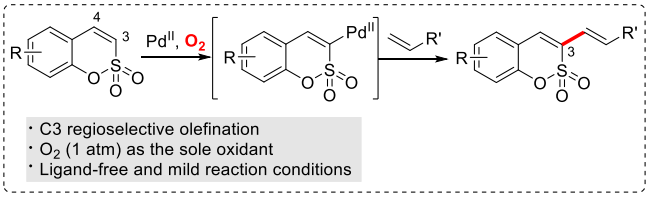
An efficient method for the direct C–H olefination of sulfocoumarins with a wide range of alkenes was developed. Moreover, O_2 was successfully utilized as the sole oxidant for the oxidative Heck reaction. This approach enables the rapid generation of various 3-alkenylated sulfocoumarins.

Sulfocoumarins (1,2-benzoxathiine 2,2-dioxides) are bioisostere of coumarins, where the carbonyl group in the coumarin ring is replaced by a sulfonyl group. Sulfocoumarin has been reported to be an important structural motif that inhibits the metalloenzyme, carbonic anhydrase.[1] Consequently, the development of efficient methods for the rapid derivatization of sulfocoumarin has been the subject of intensive research.[2] Despite significant synthetic efforts, an approach to functionalize this scaffold via C–H bond activation has not yet been reported.

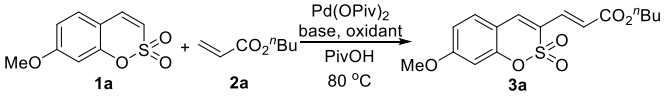
Since Fujiwara's discovery of the direct olefination of benzene, [3] substantial progress has been achieved in the field of oxidative Heck reactions.[4] Our group and Lee's group recently developed Pd(II)-catalyzed oxidative Heck reactions of coumarins and phosphacoumarin, respectively.[5] These works prompted us to explore the feasibility of an expeditious synthetic approach to install an olefin into the sulfocoumarins. We speculated that the C3-palladated species could be accessed in a catalytic fashion because of the inherent nucleophilic characteristics of the 3-position of sulfocoumarins. Herein, we describe a regioselective Pd(II)-catalyzed C–H olefination of sulfocoumarins using 1 atm O_2 as the only oxidant,[6] which enables the construction of various 3-vinyl and 3-styryl sulfocoumarins.



Scheme 1 Regioselective oxidative Heck reactions of sulfocoumarins.

We studied the feasibility of the proposed strategy by investigating the possibility of C–H activation/olefination of sulfocoumarin (**1a**) with *n*-butyl acrylate (**2a**): the representative catalyst screening data for the conversion are listed in Table 1. The reaction utilized a $Pd(OPiv)_2$ catalyst combined with Ag_2CO_3 to exclusively afford the C3-alkenylated product, presumably via an electrophilic palladation pathway (entry 1, 33%). Among the Pd species screened, $Pd(OPiv)_2$ displayed the best catalytic efficiency. Both the base and the solvent were found to fundamentally affect the reaction efficiency; K_2CO_3 and pivalic acid were the optimal base and solvent, respectively. The properties of the oxidant were also critical for the reaction efficiency, and the use of $Cu(OAc)_2$ dramatically improved the catalytic reactivity (entry 3). Based on recent advances in palladium-catalyzed aerobic oxidation reactions, an intensive screen was conducted to promote the reactions using environmentally benign and economical oxidants.[7] We therefore surveyed the capabilities of air and O_2 as oxidizing agents. Indeed, we were pleased to observe that the C3-alkenylation process proceeded in the air conditions (entry 6, 76%) and the yields were higher than those obtained using the Pd(II)/Cu(II) catalytic system. When the reaction was subjected to treatment with 1 atm O_2 as the only oxidant, an excellent product yield was obtained. Thus, this method presents an efficient and sustainable approach to the synthesis of various 3-vinylsulfocoumarin derivatives Under the optimized reaction conditions, the C3 alkenylation of **1a** in the presence of $Pd(OPiv)_2$ (0.1 equiv) K_2CO_3 (3 equiv) in pivalic acid at 80 °C, afforded the product **3a** in the highest yield (93%).

Table 1 Optimization of alkenylation conditions[a]



entry	oxidant (equiv)	base (equiv)	yield (%)[c]
1	Ag_2CO_3 (3)	-	33
2	Oxone (1.2)	K_2CO_3	34

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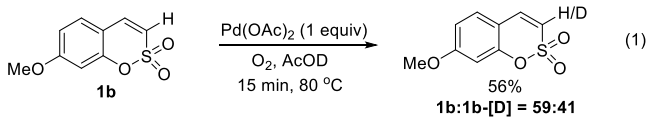
†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

3	$Cu(OAc)_2$ (3)	K_2CO_3	61
4	$AgNO_3$ (3)	K_2CO_3	75
5	DDQ (1)	K_2CO_3	14
6	air (1 atm)	K_2CO_3	76
7	O_2 (1 atm)	K_2CO_3	94
8	N_2	K_2CO_3	15
9[b]	O_2 (1 atm)	K_2CO_3	95 (93[d])

[a]Reactions were conducted with sulfocoumairn, butyl acrylate (2.0 equiv), $Pd(OPiv)_2$ (0.2 equiv), and base (3 equiv) in PivOH at 80 °C for 8 h. [b] butyl acrylate (1.1 equiv), $Pd(OPiv)_2$ (0.1 equiv), and base (3 equiv). [c]Yields were determined using ^{1}H NMR analysis of the crude reaction mixture. [d]Isolation yield. Piv = pivaloyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

To gain some insight into the present alkenylation, a mechanistic analysis of the initial interaction of a Pd catalyst with sulfocoumarin **1b** was performed using H/D exchange experiments.[8] A significant level of deuterium incorporation (after 15 min, 41% D) was observed at the C3 position of sulfocoumarin (**1b**) when the reaction mixture was treated with AcOD as a deuterium source under the optimized conditions and in the absence of alkene, as shown in Figure 1 (see the Supporting Information for the full spectra).



Based on our observations, a plausible catalytic mechanism for the alkenylation of sulfocoumarin involves the aforementioned electrophilic palladation pathway at the C3 position, followed by H-abstraction by the pivalate ligand to provide the intermediate **II**. In the presence of an alkene substrate, the C3-palladated species **II** inserts into the olefin, and the subsequent C–Pd β-hydride elimination of intermediate **III** provides the desired coupled product **3**. Finally, the reoxidation of Pd(0) to Pd(II) by molecular oxygen completes the catalytic cycle.

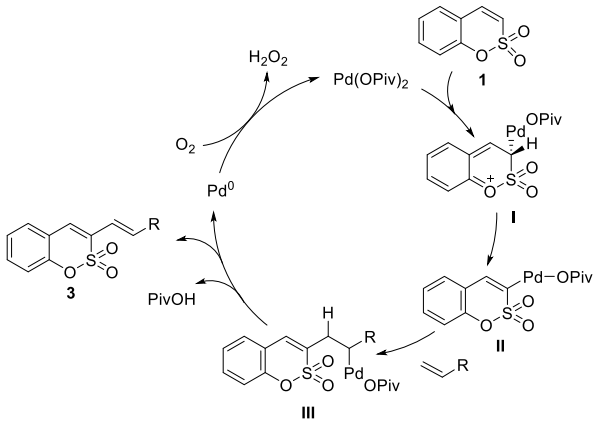
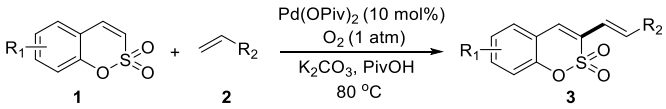
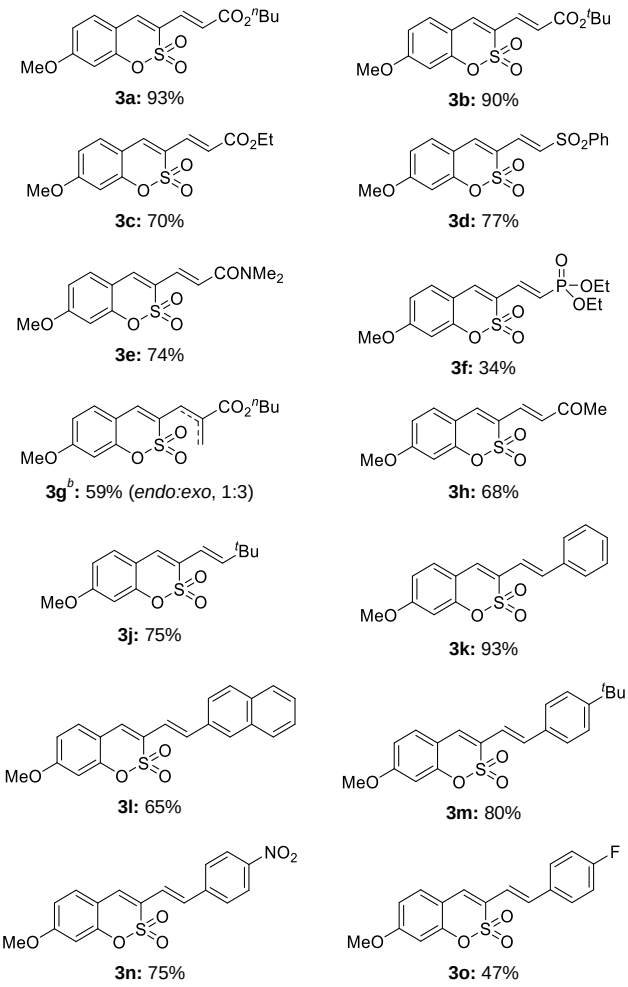


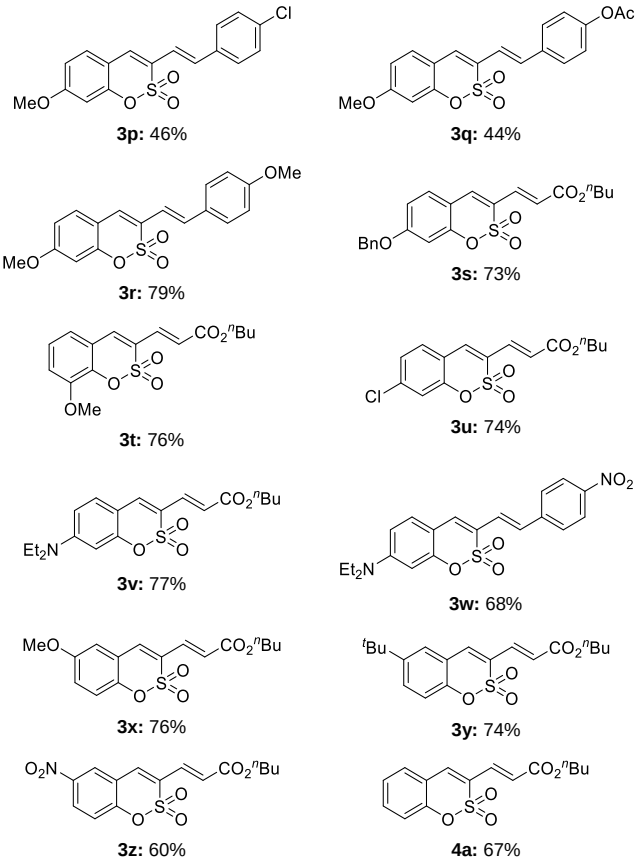
Figure 2 Proposed mechanistic pathways of the present reactions.

Both sulfocoumarin and alkene substrates were next investigated to extend the utility and generality of this methodology. In general, the present C3-alkenylation process was amenable to alkene substrates conjugated with a variety of functional groups from electron-donating to electron-withdrawing groups, as described in Table 2. For example, alkene substrates conjugated with ester (**3a**, **3b**, and **3c**), sulfonate (**3d**), amide (**3e**), or phosphonate (**3f**) groups smoothly coupled with 7-methoxy sulfocoumarin at the C3 position. When 2-methyl substituted methyl acrylate was employed as a substrate, a mixture of regioisomers **3g** (*endo:exo*, 1:3) formed. The addition of the styryl group to the 3 position of the sulfocoumarin core was expected to induce a red-shift in the emission wavelength by extending the π-electron system.[9] To our delight, various styrene substrates were compatible with the coupling reaction conditions, and modest to good yields of the desired products were obtained (**3k-3q**, **3w**). For broad utility, the scope of the sulfocoumarin substrates was examined, and a broad range of functional groups (e.g., methoxy, benzoxy, chloro, diethylamino, alkyl, and nitro) on the sulfocoumarin core were compatible with the coupling conditions. Substitution with an electron-donating OMe group at the 7-position enhanced the reaction efficiency (**3a** vs **4a**).

Table 2 Direct C3-olefination of sulfocoumarins with various alkenes.[a]

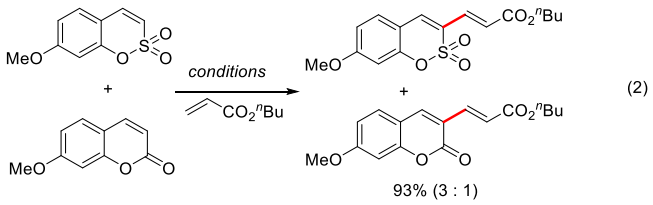






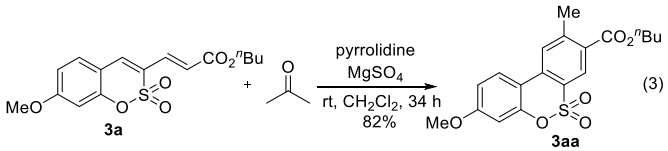
[a] Reactions were conducted with coumarin, alkene (2.0 equiv), $Pd(OPiv)_2$ (0.2 equiv), and K_2CO_3 (3 equiv) in PivOH at 80 °C under an O_2 atmosphere for 3-36 h. [b] A 1:3 mixture of isomers was produced.

The C–H alkenylation of phosphacoumarin is less reactive compared to coumarin and sulfacoumarin counterparts, and the use of AgOAc as an oxidant was required to get comparable reactivity. When a competition experiment between sulfacoumarin and coumarin substrates was carried out under the optimized conditions, sulfacoumarin substrate reacts preferentially over coumarin in a ratio of 3:1 (eq 2).



(2)

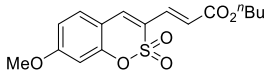
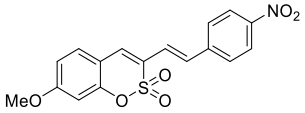
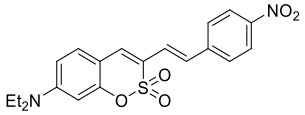
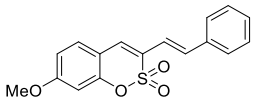
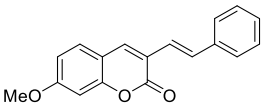
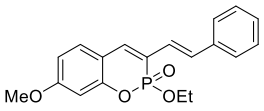
To showcase the applicability of the developed method, the present strategy was employed as a straightforward synthetic route to benzosulfocoumarin (eq 3). When 3-alkenylated sulfocoumarin **3a** was treated with acetone and pyrrolidine in the presence of $MgSO_4$, the desired benzosulfocoumarin (**3aa**) was produced in an 82% yield via the inverse electron demand Diels-Alder reaction.[10]



(3)

We next examined the photophysical and spectroscopic properties of 3-alkenylsulfocoumairns, and some of new derivatives exhibited promising photonic luminescence (Table 3). The introduction of electron-donating NEt_2 at position 7 on the sulfocoumairn core ring and *p*-nitro group on styrene gave rise to notably red-shifted maxima and increased the value of Φ_F. The comparison of the photophysical properties indicated that the coumarin core possesses higher photoluminescence efficiencies than those of sulfacoumarin and phosphacoumarin counterparts.

Table 3 Photophysical properties [a]

compd	λ_{abs} (nm)[a]	λ_{em} (nm)[b]	ϕ_F[c]
	350	391	0.0007
	376	520	0.1222
	454	661	0.1624
	357	414	0.0005
	360	460	0.8307
	355	435	0.03

[a]Only the longest absorption maxima are shown. [b]Excited at the maximum excitation wavelength. [c] fluorescence quantum yield.

In summary, we developed a new protocol for effecting the direct C–H olefination of sulfocoumarins via a palladium-catalyzed oxidative Heck reaction using O_2 as the sole oxidant. The reaction scope exhibits broad utility and functional group tolerance with complete regioselectivity. This simple and efficient approach offers convenient access to a variety of 3-vinyl and 3-styryl sulfocoumarin scaffolds, which are privileged structures in many biologically active compounds. In addition, our synthetic strategy led to the discovery of new sulfocoumarin-based derivatives that show promising photonic luminescence.

Acknowledgements

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