ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

Pd(II)-Catalyzed Fujiwara–Moritani Reactions for the Synthesis and Functionalization of Substituted Coumarins

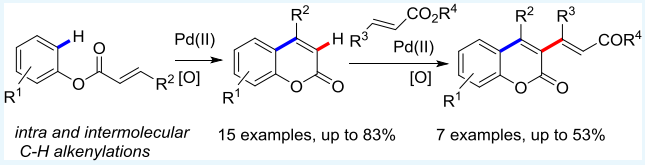
Verónica Ortiz-de-Elguea, Asier Carral-Menoyo, Lorena Simón-Vidal, Mikel Martinez-Nunes, Iratxe Barbolla, Marta G. Lete, Nuria Sotomayor,* and Esther Lete*

Cite This: *ACS Omega* 2021, 6, 29483–29494

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Highly substituted coumarins, privileged and versatile scaffolds for bioactive natural products and fluorescence imaging, are obtained via a Pd(II)-catalyzed direct C–H alkenylation reaction (Fujiwara–Moritani reaction), which has emerged as a powerful tool for the construction and functionalization of heterocyclic compounds because of its chemical versatility and its environmental advantages. Thus, a selective 6-*endo* cyclization led to 4-substituted coumarins in moderate yields. Selected examples have been further functionalized in C3 through a second intermolecular C–H alkenylation reaction to give coumarin-acrylate hybrids, whose fluorescence spectra have been measured.

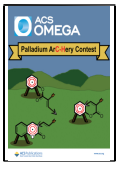


INTRODUCTION

Coumarins (2*H*-chromen-2-nes or benzo-α-pyrones) are privileged scaffolds of a large variety of natural products[1,2] (e.g., pestalasins A-E[3,4] and lamellarins[5,6]) and/or synthetic molecules, as exemplified by the antioxidant umbelliferone,[7] choleretic and antispasmodic hymecromone (4-methylumbelliferone),[8] anti-inflammatory toddaculin,[9] or anti-HIV agent 4-propylcoumarins[10] (Figure 1). Owing to their outstanding optical properties, these coumarin fluorophores have found applications as fluorescent probes and tracers in biology, laser dyes, solar energy collectors, etc.[11−13] Additionally, coumarins are widely used as additives in food and cosmetics,[14,15] as well as agrochemicals,[16] and pharmaceuticals.[17] In particular, 4-arylcoumarins, a subgroup of flavonoids, have received great attention because they exhibit important biological activities, such as anti-HIV,[18] antibacterial,[19] antiprotozoal,[20] and cytotoxic properties.[21] For example, 5,7,4′-trimethoxy and 5,7-dimethoxy-4-phenylcoumarins have been tested for their anti-inflammatory activity, specifically as COX inhibitors, which opens the door to future developments as these enzymes are also associated with cancer and neuropsychiatric diseases such as schizophrenia.[22] The introduction of a fused heterocyclic moiety into the coumarin core usually leads to compounds with promising or even unprecedented properties.[23] For example, furo[3,2-*g*]coumarins (e.g., psoralen, xanthoxin, or bergapten) are used in treatment of several skin disorders (psoriasis and vitiligo).[24] Therefore, the development of synthetic methods to construct and functionalize the coumarin core has attracted much attention over the past decades. Classical approaches for the preparation of coumarin derivatives usually involve the acid- or base-catalyzed condensation reactions of phenol derivatives with esters of acrylic acids (the Pechmann reaction) or with carbonyl compounds (Perkin, Wittig reaction, or Knoevenagel-type reactions).[25−27] Some milder methods that do not use phenol precursors have also been developed, such as the PIDA/I_2-mediated reactions of substituted phenyl acrylic acids[28] and visible-light induced synthesis of functionalized coumarins.[29]

Transition-metal-catalyzed, particularly palladium–catalyzed, inter- or intramolecular heteroannulation reactions[30,31] represent an excellent alternative for the construction of the coumarin framework.[32] Representative examples include the intramolecular Mizoroki–Heck reaction of *o*-halophenyl 3-alkenoates,[33] the tandem intermolecular Heck/cyclization between aryl halides and acrylates,[34−36] or the Suzuki cross-coupling/cyclization of 2-(pinacolboronate)phenol and β-brominated dehydroaminoacids.[37] In addition, palladium-catalyzed intermolecular carbonylative cyclization of *o*-halophenols with alkynes[38,39] or salicylic aldehydes with benzyl chlorides[40] has been reported. More recently, Gilmour *et al.*[41] has reported a Pd(0)-catalyzed cascade annulation of 2-halophenols with β-borylacrylates as ambiphilic C3-synthons to generate C3 and C4-substituted coumarins. However, the transition-metal-catalyzed oxidative coupling reactions[42] are even more attractive strategies for the synthesis of heterocyclic scaffolds as coumarins, as they avoid the use of preactivated coupling partners (halides, triflates, boronates, etc.). In this

Received: July 2, 2021
Accepted: October 12, 2021
Published: October 25, 2021



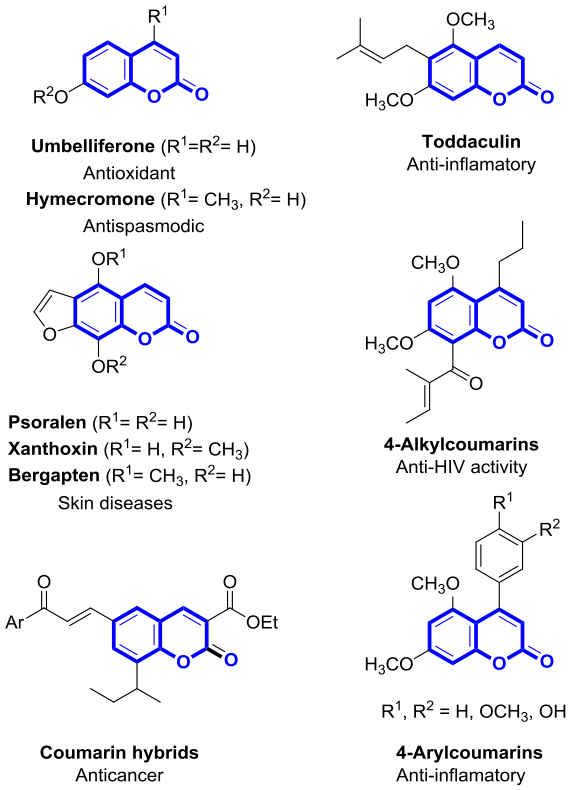
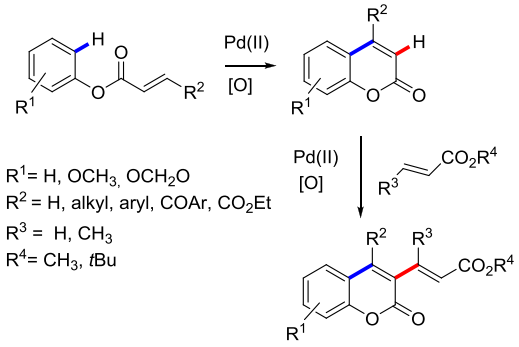


Figure 1. Selected bioactive compounds with the coumarin core.

context, the oxidative cyclocarbonylation[43] or carboxylation[44] of 2-vinylphenols are efficient procedures for the synthesis of 4-substituted coumarins. The inter- or intramolecular hydroarylation of alkynes provides a direct and simple route to these heterocycles from phenols and propiolates or aryl propiolates, respectively.[45] The formation of coumarins by addition of phenols and alkynoates via palladium(II)-catalyzed C−H insertion is an excellent example to illustrate the potential of this methodology.[46] The palladium(II)-catalyzed intermolecular C−H alkenylation reaction of phenols and acrylates followed by intramolecular C−O formation, first reported by Kitamara *et al.*[47] in 2005 and later developed by Maiti *et al.*[48] and Shi *et al*,[49] has given good results mainly for the synthesis of coumarins with no substituents at the pyrane ring. A related tandem dehydrogenation/oxidative Heck reaction starting from 4-phenylcyclohexanone to generate the intermediate phenol has also been reported.[50] Therefore, we decided to investigate the intramolecular C−H alkenylation variant[51,52] of aryl alkenoates and cinnamates to prepare 4-alkyl and 4-aryl-substituted coumarins with alkoxy groups at the aromatic ring, a structural feature common to biologically active coumarins (Scheme 1). The strategy involves a 6-*endo*-trig cyclization, which could be accomplished by controlling the positional selectivity of C−H activation, as we have previously demonstrated in the Pd(II)-catalyzed intramolecular 6-*endo* C−H alkenylation of *N*-arylacrylamides[53] and *N*-substituted *N*-allylanilines[54] for the construction of quinolone and dihydroquinoline cores, respectively. The effect of the substitution patterns of the benzene ring and the alkene on the reactivity and regioselectivity would be investigated. In addition, as conjugation of coumarin nucleus with an unsaturated moiety at the C-3 position can play a pivotal role in the anticancer activity of these heterocycles,[55] we

Scheme 1. Synthesis of Coumarins via C−H Alkenylation

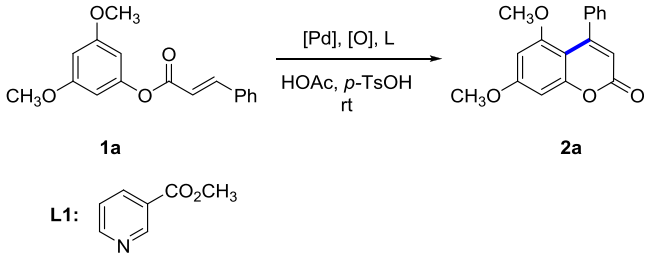


decided to carry out an intermolecular alkenylation reaction on the coumarin ring with α,β-unsaturated esters to generate new coumarin-acrylate hybrids.

RESULTS AND DISCUSSION

We started the study of the reaction conditions (palladium catalyst and oxidant) using cinnamate **1a** as the model substrate (Table 1). We selected the reaction conditions that

Table 1. Optimization of 6-*Endo* Cyclization of 1a



entry	[Pd]	[O]	L	t (h)	**2a** (%)
1	$Pd(OAc)_2$[a]	$Cu(OAc)_2$[b]	-	30	-[c]
2	$Pd(OAc)_2$[a]	*p*-BQ[b]	-	30	-[c]
3	$Pd(OAc)_2$[a]	$PhCO_3tBu$[d]	-	24	9
4	$Pd(dba)_2$[a]	$PhCO_3tBu$[d]	-	24	5
5	$PdCl_2(CH_3CN)_2$[a]	$PhCO_3tBu$[d]	-	8	10[e]
6	$PdCl_2(CH_3CN)_2$[a]	$PhCO_3tBu$[d]	-	24	-[f]
7	$PdCl_2(CH_3CN)_2$[a]	$PhCO_3tBu$[d]	-	4[g]	-[f]
8	$PdCl_2(CH_3CN)_2$[a]	$PhCO_3tBu$[d]	L1[a]	24	23
9	$PdCl_2(CH_3CN)_2$[h]	$PhCO_3tBu$[d]	-	24	25
10	$PdCl_2(CH_3CN)_2$[a]	$PhCO_3tBu$[d]	-	24[i]	25
11	$PdCl_2(CH_3CN)_2$[a]	F+[d,j]	-	24	74

[a]5 mol %. [b]1 equiv. [c]Starting material was recovered. [d]$Cu(OAc)_2$ (5 mol %) was used as a co-oxidant. [e]Conversion: 31%. [f]Decomposition. [g]The reaction was carried out under reflux. [h]10 mol %. [i]2% wt. PT aqueous solution was used as solvent instead of HOAc. [j]*N*-Fluoro-2,4,6-trimethylpyridinium triflate (1.2 equiv) was used as the oxidant

had been previously employed for the 6-*endo* cyclization of *N*-aryl acrylamides to quinolones[53] as a starting point, carrying out the reactions at room temperature in acetic acid and in the presence of *p*-TsOH (1 equiv) as an additive. The presence of this acid has been shown to be a determinant to increase the reactivity in this type of reaction.[53,54,56,57] However, when palladium acetate was used as the catalyst using copper acetate or *p*-benzoquinone as oxidants, no conversion at all was observed after 30 h at rt, recovering unreacted **1a** (Table 1, entries 1 and 2). The use of *t*-butyl perbenzoate in combination with copper acetate as an oxidant was required

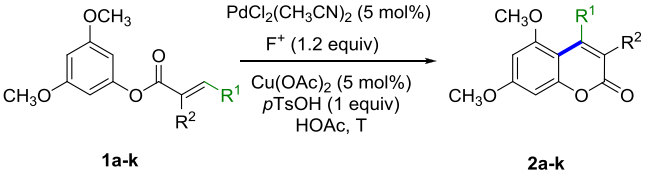
https://doi.org/10.1021/acsomega.1c03469
ACS Omega 2021, 6, 29483−29494

to obtain some reactivity, although low yields of the corresponding coumarin **2a** were isolated, observing also the formation of decomposition products (Table 1, entries 3 and 4). A change in the palladium catalyst to bis(acetonitrile)-dichloropalladium(II) resulted in a low conversion of the substrate (69% of **1a** was recovered) after 8 h, but with a low isolated yield of **2a** (Table 1, entry 5). A longer reaction time or higher reaction temperature was detrimental due to decomposition of the substrate (Table 1, entries 6 and 7). The use of a pyridine ligand (**L1**), a higher catalyst loading (10 mol %), or the use of an aqueous medium for the reaction resulted in increased but still low isolated yields (Table 1, entries 8−10). In no case, open-ring or decarboxylated products could be observed in isolable quantities. It was necessary to use a stronger oxidant such as *N*-fluoro-2,4,6-trimethylpyridinium triflate (F^+) to obtain a complete conversion after 24 h, affording coumarin **2a** in good isolated yield (Table 1, entry 11). This oxidant has been successfully employed in related intermolecular C−H alkenylation reactions in which the use of weaker oxidants gave low reactivity.[58−60] It is noteworthy that the reaction was completely regioselective toward the formation of the 6-*endo* cyclization product (coumarin **2a**), not observing the formation of the corresponding 5-*exo* cyclization product, benzofuran-2(3*H*)-one. Finally, a control experiment was carried out and in the absence of palladium, the reaction did not take place and unreacted **1a** was recovered after 24 h at rt.

These reaction conditions were applied to a series of cinnamates and enoates **1b−1k**. The results are summarized in Table 2.

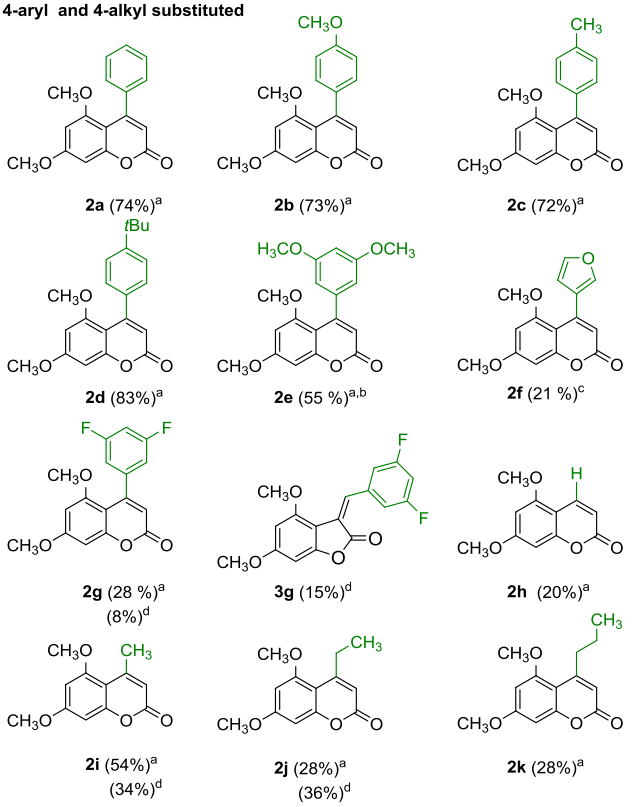
As shown, the results obtained were highly dependent on the substrate employed. Different substitution patterns on the aromatic ring at C4 are tolerated, and coumarins **2b−d** were obtained in good isolated yields (Table 2). Nevertheless, the obtention of **2e** required the use of a higher catalyst loading (10 mol %). A heteroaromatic ring, such as furan, could also be introduced at C4, although in a lower yield (**2f**, 21%). When an electron-deficient aryl group was introduced, **2g** was obtained in a much lower yield (28%). Interestingly, when the reaction temperature was increased to 70 °C, the regioselectivity of the reaction was lost, isolating both the 6-*endo* and 5-*exo* cyclization products (**2g** and **3g**, respectively) in low yields, together with decomposition products. Under these reaction conditions, unsubstituted or 4-alkyl substituted coumarins **2h−k** were obtained only in moderate to low yields (Table 2), though no starting material could be recovered. An increase of the reaction temperature to 70 °C did not improve the results. It was also shown that the reaction conditions are not compatible with the presence of acyl groups on the alkene (**1l** R^1 = CO_2Et; **1m** R^1 = COAr) or with the substitution on the α-position of the alkene (**1n** and **1o** R = Ph and CH_3, respectively). In these cases, complex mixtures of products were obtained, not isolating coumarins **2l−2o**. These results show that it is possible to access the coumarin framework via 6-*endo* cyclization, but this procedure is not as efficient as it was shown for the synthesis of quinolones from the corresponding amides.[53] This difference in reactivity could be attributed to the instability of the esters in acidic media, leading to decomposition when long reaction times are required. Consequently, the reaction conditions were re-evaluated to use an alternative solvent to acetic acid, using in this case pent-5-enoate **1j** as the model substrate (Table 3).

Table 2. Synthesis of 4-Substituted Coumarins 2a−g



1a-k **2a-k**

4-aryl and 4-alkyl substituted



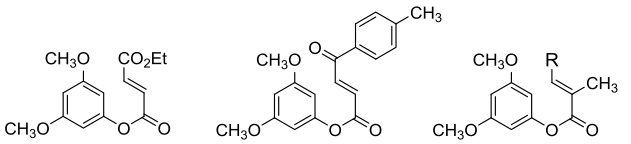
2a (74%)[a] **2b** (73%)[a] **2c** (72%)[a]

2d (83%)[a] **2e** (55 %)[a,b] **2f** (21 %)[c]

2g (28 %)[a] (8%)[d] **3g** (15%)[d] **2h** (20%)[a]

2i (54%)[a] (34%)[d] **2j** (28%)[a] (36%)[d] **2k** (28%)[a]

4-acyl and 3,4-disubstituted: non compatible



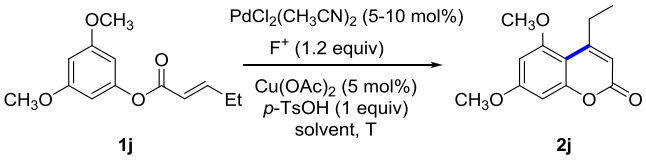
1l[e] **1m**[e] **1n**[e] R = Ph **1o**[e] R = CH_3

[a]Yield (%) of the pure isolated compound (rt, 6−24 h). [b]10 mol % of the catalyst was used; 79% conversion. [c]75% conversion. [d]Yield (%) of the pure isolated compound (70 °C, 24 h). [e]Decomposition.

The change of acetic acid for a non-protic solvent, such as dichloromethane, led to a low conversion at room temperature (Table 3, entry 1). The use of an apolar solvent, such as mesitylene, in combination with a smaller proportion of acetic acid[61] led to an increase of the isolated yield of **2j**, although in a longer reaction time (Table 3, entry 2). The reactivity could be recovered at 40 °C, with slight erosion of the yield (Table 3, entry 3). When the reaction was carried out in mesitylene, the presence of *p*-TsOH was essential, as no reactivity was observed even after 96 h at rt in its absence (Table 3, entry 4). Finally, a moderate yield of **2j** could be obtained at 70 °C (Table 3, entry 5). The use of these reaction conditions (mesitylene, 70 °C) resulted in a significant increase in the

https://doi.org/10.1021/acsomega.1c03469
ACS Omega 2021, 6, 29483−29494

Table 3. Cyclization Reaction Conditions for 1j

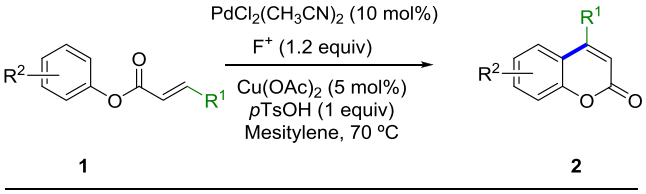


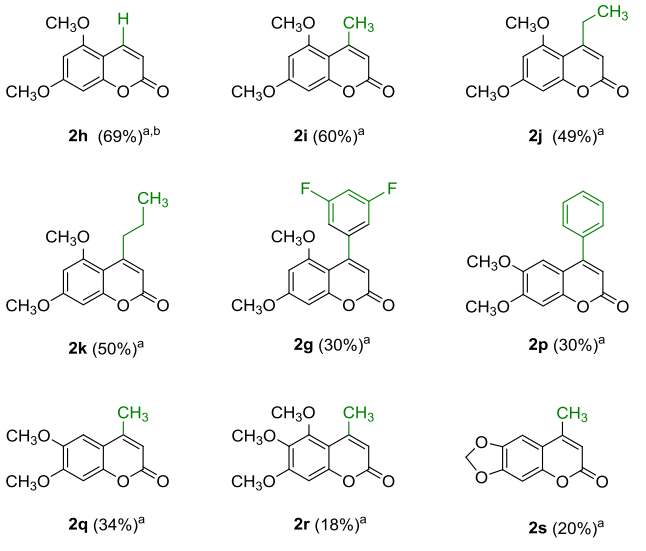
entry	solvent	T (°C)	t (h)	**2j** (%)
1[a]	CH_2Cl_2	rt	24	8[b]
2[c]	mesitylene/HOAc 4:1	rt	96	37
3[c]	mesitylene/HOAc 4:1	40	24	33
4[c]	mesitylene	rt	96	-[d]
5[c]	mesitylene	70	24	49

[a]5 mol% of catalyst. [b]Conversion: 17%. [c]10 mol% of catalyst. [d]No *p*-TsOH was added; no reaction.

yield of coumarin **2h** (69% *vs* 20%) and 4-alkyl substituted coumarins **2i**−**2k** (Table 4). The yield of 4-aryl substituted

Table 4. Synthesis of 4-Substituted Coumarins in Mesitylene





[a]Yield (%) of the pure isolated compound. [b]5 mol% of catalyst.

coumarin **2g** could not be improved under these conditions, although in this case, the formation of the 5-*exo* product **3g** was not observed by NMR. Finally, the extension to different substitution patterns in the aromatic ring was also studied (Table 4). It was clear that an electron-rich aromatic ring is a determinant to obtain reactivity under these conditions.

Two mechanistic pathways could be proposed for this type of oxidative alkenylation reaction. On one hand, arene metalation with an electrophilic Pd(II) species would give an aryl-Pd(II) species **I**, followed by *syn*-migratory insertion onto the alkene to give **II**, and *syn* elimination, after isomerization to **III**, to afford coumarin **2**.[53] Alternatively, the alkene could be first activated by the palladium catalyst (**IV**), followed by *anti*-addition of the aromatic ring to give also **III**, and *syn* elimination would lead to **2** (Scheme 2). In both cases, an electron-rich aromatic ring would be more reactive. As shown on Table 4, 6,7-dialkoxycoumarins **2p**, **2q**, and **2s** could be obtained regioselectively, although in lower yields, as the 5,6,7-trimethoxy-substituted coumarin **2r**, but no unreacted substrate was recovered. Although other aromatic substitution patterns were tested, no reactivity was observed with 3,5-dimethylphenyl, 3-methoxyphenyl, and 3-methoxy-5-methyl cinnamates, while complex mixtures of products were formed when using the corresponding (*E*)-but-2-enoates (see the Supporting Information for the substrates tested, **1t**−**1y**).

The selective functionalization of the coumarin skeleton is also an important issue as, in addition to the biological properties, the extension of the conjugation could affect, for instance, their photophysical properties.[62,63] Thus, several procedures have been developed for the C3 alkenylation of coumarins. For instance, palladium-catalyzed decarboxylative couplings have been described for the functionalization of coumarins with cinnamic acids[64] and for the reaction of coumarin-3-carboxylic acid with acrylates.[65] In addition, the selective C3 alkenylation of non-substituted coumarins has also been efficiently accomplished through the oxidative Heck reaction.[66] Thus, we decided to study the derivatization of selected 4-substituted coumarins through a second intermolecular C−H alkenylation reaction.

First, we tested the conditions used for the 6-*endo*-cyclization, but no intermolecular alkenylation reaction with *t*-butyl acrylate was observed. After some experimentation, we found that the best results were obtained using the reaction conditions previously developed for the alkenylation of quinolones.[53] However, in most cases, conversions were low and 30−40% of the starting material was recovered (Table 5). When longer reaction times or higher temperatures were used, complex mixtures of products were isolated. We tried to optimize the reaction conditions by changing the oxidant or the palladium source, but the results could not be improved (see the Supporting Information). As shown in Table 5, C4 aryl- and methyl-substituted coumarins **2a,d,e,i** could be alkenylated with methyl or *t*-butyl acrylate using palladium acetate in the presence of silver acetate and pivalic acid obtaining alkenylated coumarins **4a**−**f** in moderate yields (Table 5, entries 1−6). Substitution on the β-position of the alkene is also possible, obtaining **4g** in moderate yield (Table 5, entry 7).

As 3-vinyl and 3-styryl coumarins[62,63] can be interesting fluorophores, the absorption and emission properties of selected coumarins **2a,d,e** and **4a**−**d** were also studied (see Table 6, Figure 2, and the Supporting Information). All coumarins showed UV−vis absorption, only one absorption band around $\lambda_{max.}$ = 375 nm for 4-aryl coumarins **2a,d,e** and around $\lambda_{abs.}$ = 300 nm for their C3 alkenylated derivatives **4a**−**d**. This shift to a lower wavelength upon introduction of the acrylate moiety reflects the loss of coplanarity of the aromatic ring and the coumarin nucleus, thus decreasing delocalization. C3 alkenylation in the coumarin core leads to considerable changes in the fluorescence properties of coumarins **4a**−**d**, whose maximum emission were more blue-shifted than those of coumarins **2** ($\lambda_{em.}$ = 452−480 nm vs $\lambda_{em.}$ = 435−446 nm) and presented higher Stoke shifts (up to 180) (Table 6).

https://doi.org/10.1021/acsomega.1c03469
ACS Omega 2021, 6, 29483−29494

Scheme 2. Mechanistic Pproposals for the 6-*Endo* Cyclization: Arene Metalation *vs* Alkene Activation

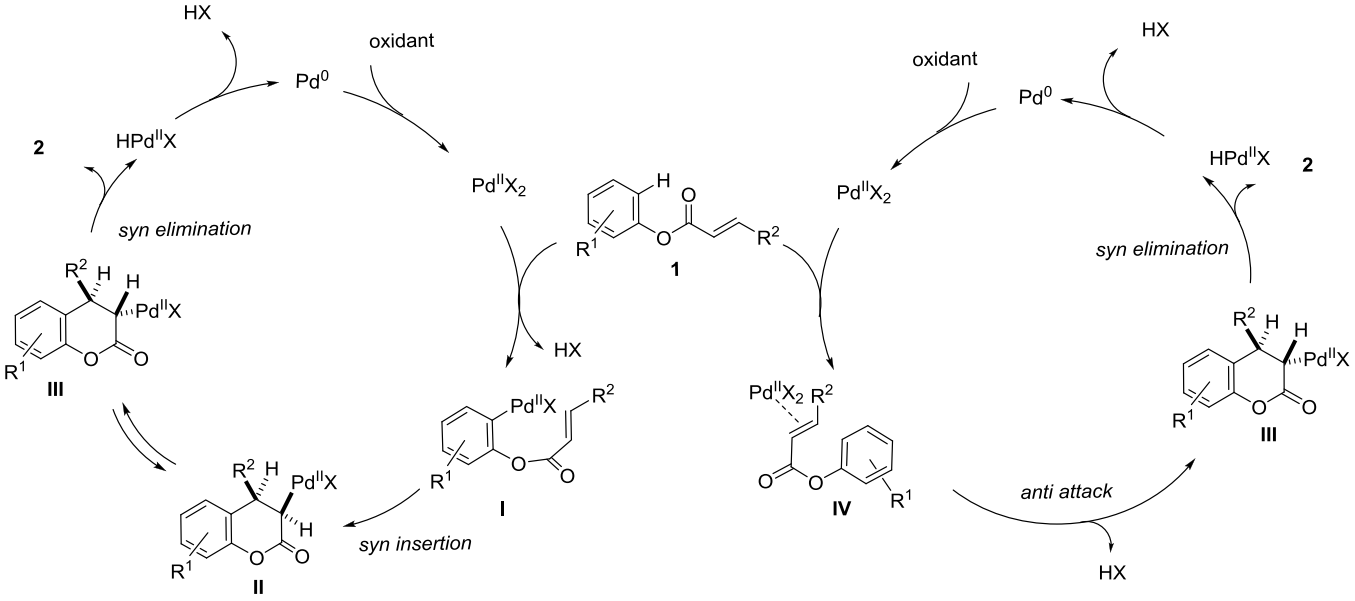
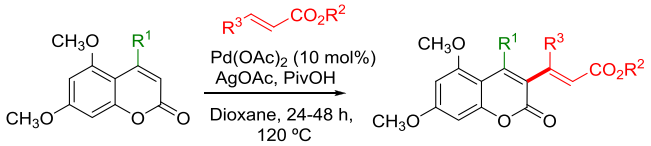


Table 5. Intermolecular C−H Alkenylation of Coumarins 2



entry	2	R^1	R^2	R^3	4	yield (%)[a]
1	**2a**	Ph	CH_3	H	**4a**	31
2	**2a**	Ph	*t*-Bu	H	**4b**	31
3	**2d**	4(*t*Bu)C_6H_4	CH_3	H	**4c**	52
4	**2e**	3,4(OMe)C_6H_4	CH_3	H	**4d**	28
5	**2i**	CH_3	CH_3	H	**4e**	45
6	**2i**	CH_3	*t*-Bu	H	**4f**	53
7	**2i**	CH_3	CH_3	CH_3	**4 g**	44

[a]Yield (%) of the pure isolated compound; in all cases, 30−40% of the unreacted starting material was also recovered.

Table 6. Absorption and Emission Maxima of Selected Coumarins 2 and 4

entry	compd	λ_{abs}[a] (nm)	λ_{em}[b] (nm)	ΔStoke[c] (nm)
1	**2a**	375	435	60
2	**2d**	377	441	64
3	**2e**	376	446	70
4	**4a**	301	453	152
5	**4b**	302	452	150
6	**4c**	300	480	180
7	**4d**	300	455	155

[a]The maximum absorption wavelength in acetonitrile (2.3 mM). [b]Excited at the maximum absorption wavelength in acetonitrile (2.3 mM). [c]Stoke shift = $\lambda_{em} - \lambda_{abs}$.

Fluorescent organic dyes with large Stoke shift are essential for biological applications.[67−69]

In conclusion, it has been shown that 4-aryl-substituted coumarins can be obtained in moderate to good yields via palladium(II)-catalyzed C−H alkenylation reactions. 4-Aryl-substituted derivatives can be obtained in acetic acid at room temperature, while mesitylene at 70 °C is required to obtain moderate yields of 4-alkyl-substituted coumarins, avoiding decomposition in an acidic medium. However, the procedure is limited to an electron-rich aromatic ring for the cyclization to proceed efficiently. The coumarin skeleton can be further functionalized via C3 intermolecular alkenylation. Additionally, the fluorescence spectra of selected coumarins have been measured to provide perspective for potential applications.

EXPERIMENTAL SECTION

General Experimental Methods. Melting points were measured in unsealed capillary tubes. The NMR spectra were obtained at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C or at 500 MHz for ^{1}H and 125.7 MHz for ^{13}C using $CDCl_3$ as solvent and internal standard at 20−25 °C. Distortionless enhancement by polarization transfer (DEPT) experiments and 2D correlation experiments (COSY, heteronuclear single-quantum coherence (HSQCed), or heteronuclear multiple bond correlation (HMBC)) were used when necessary for the assignments of individual ^{13}C and ^{1}H resonances. Electron impact (EI, 70 eV), chemical ionization (CI, 230 eV), or electrospray ionization (ESI^+) sources were used for obtaining the mass spectra. A TOF detector was employed for the obtention of exact mass. The IR spectra were obtained using an ATR instrument. The fluorescence spectra were measured using a Jasco FP-6500 spectrofluorimeter using acetonitrile as solvent at 2.3 mM. The emission spectra were acquired by irradiating the sample at its maximum absorbance. Both excitation and emission spectra were collected with a 3 nm slit bandwidth and were recorded at 25 °C. TLC was carried out with 0.2 mm-thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography was carried out on silica gel (230−400 mesh). All solvents used in reactions were purified according to standard procedures. Palladium catalysts were purchased from Aldrich and were used without further purification: $Pd(OAc)_2$, 98% purity, and $PdCl_2(CH_3CN)_2$, 99% purity.

Intramolecular Alkenylation of Enoates 1 and Synthesis of Coumarins 2: General Procedure. 1-Fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (1.2 mmol), $Cu(OAc)_2$ (0.05 mmol), *p*-TsOH (1 mmol), and

https://doi.org/10.1021/acsomega.1c03469
ACS Omega 2021, 6, 29483−29494

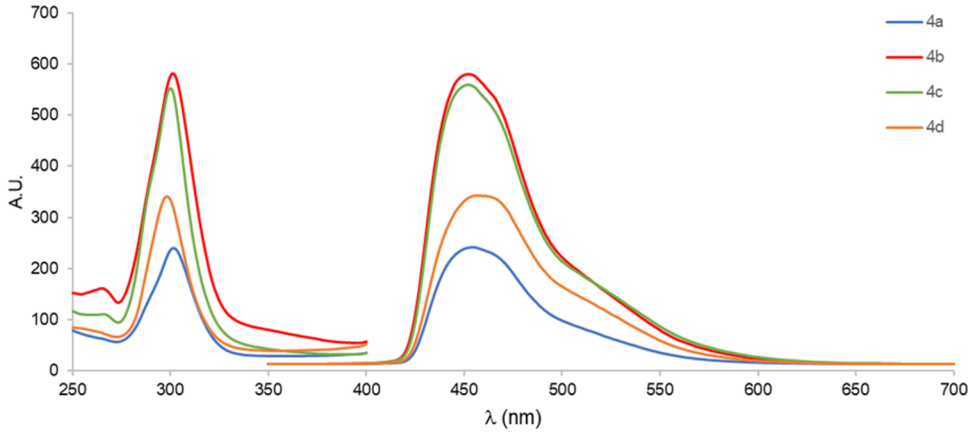


Figure 2. Excitation and emission spectra of coumarins **4a**−**d** at 2.3 mM in acetonitrile.

$PdCl_2(CH_3CN)_2$ (0.05 or 0.1 mmol) were added sequentially over a solution of the corresponding enoate **1** (1 mmol) in HOAc or mesitylene (4 mL). The mixture was stirred at room temperature or at 70 °C for 4−24 h. The solvent was removed under vacuum and the residue was dissolved in EtOAc (5 mL). The solution was washed with a 2 M aqueous solution of Na_2CO_3 (2 × 15 mL) and brine (2 × 15 mL). The aqueous phase was re-extracted with EtOAc (10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/EtOAc) afforded coumarins **2**.

*5,7-Dimethoxy-4-phenyl-2H-chromen-2-one (**2a**).* Coumarin **2a** was prepared from **1a** (101.7 mg, 0.36 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (130.7 mg, 0.43 mmol), $Cu(OAc)_2$ (3.3 mg, 0.018 mmol), *p*-TsOH (69.1 mg, 0.36 mmol), and $PdCl_2(CH_3CN)_2$ (4.7 mg, 0.018 mmol) in HOAc (1.4 mL). The mixture was stirred at room temperature for 24 h, and after the work-up, flash column chromatography (silica gel, hexane/EtOAc 8/2) afforded **2a** (75 mg, 74%) as a solid, whose data are coincidental with those reported:[46] mp (CH_2Cl_2): 164−166 °C [lit.[46] mp (CH_2Cl_2/hexanes) 164−165 °C]; IR (ATR) 1713 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.42 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.01 (s, 1H, H_3), 6.23 (d, J = 2.3 Hz, 1H, H_6), 6.53 (d, J = 2.3 Hz, 1H, H_8), 7.22−7.30 (m, 2H, $H_{3'}$, $H_{5'}$), 7.32−7.41 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 55.4 (OCH_3), 55.8 (OCH_3), 93.6 (C_8), 95.8 (C_6), 103.6 (C_{4a}), 112.7 (C_3), 127.1 ($C_{2'}$, $C_{6'}$), 127.3 ($C_{3'}$, $C_{5'}$), 127.9 ($C_{4'}$), 139.8 ($C_{1'}$), 155.7 (C_4), 157.2 (C_{8a}), 158.2, 163.4 (C_5, C_7), 160.9 (CO); MS (CI) *m/z* (rel intensity) 284 (MH^+ + 1, 18), 283 (MH^+, 100), 282 (34), 254 (7); HRMS (CI) Calcd. for $C_{17}H_{15}O_4$ [MH^+]: 283.0965; found, 283.0958.

*5,7-Dimethoxy-4-(4-methoxyphenyl)-2H-chromen-2-one (**2b**).* Coumarin **2b** was prepared from **1b** (117.6 mg, 0.37 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (131.2 mg, 0.45 mmol), $Cu(OAc)_2$ (3.5 mg, 0.019 mmol), *p*-TsOH (72.2 mg, 0.37 mmol), and $PdCl_2(CH_3CN)_2$ (4.9 mg, 0.019 mmol) in HOAc (1.5 mL). The mixture was stirred at room temperature for 6 h, and after the work-up, flash column chromatography (silica gel, hexane/EtOAc 7/3) afforded **2b** (85.5 mg, 73%) as a solid, whose data are coincidental with those reported:[70] mp (CH_2Cl_2): 153−155 °C [lit.[70] mp (methanol) 151−152 °C]; IR (ATR) 1716 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.46 (s, 3H, OCH_3), 3.84 (s, 6H, 2 × OCH_3), 5.95 (s, 1H, H_3), 6.22 (d, J = 2.4 Hz, 1H, H_6), 6.48 (d, J = 2.4 Hz, 1H, H_8), 6.88 (d, J = 8.8 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.19 (d, J = 8.8 Hz, 2H, $H_{2'}$, $H_{6'}$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 55.3 (OCH_3), 55.4 (OCH_3), 55.7 (OCH_3), 93.6 (C_8), 95.7 (C_6), 103.6 (C_{4a}), 112.5 (C_3), 112.7 ($C_{3'}$, $C_{5'}$), 128.7 ($C_{2'}$, $C_{6'}$), 132.0 ($C_{1'}$), 155.5 (C_4), 157.2 (C_{8a}), 158.3 ($C_{4'}$), 159.6, 163.3 (C_5, C_7), 160.9 (CO); MS (CI) *m/z* (rel intensity) 314 (MH^+ + 1, 20), 313 (MH^+, 100), 312 (60), 284 (18); HRMS (CI) Calcd. for $C_{18}H_{17}O_5$ [MH^+]: 313.1071; found, 313.1061.

*5,7-Dimethoxy-4-(p-tolyl)-2H-chromen-2-one (**2c**).* Coumarin **2c** was prepared from **1c** (105.9 mg, 0.36 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (123.2 mg, 0.43 mmol), $Cu(OAc)_2$ (3.2 mg, 0.018 mmol), *p*-TsOH (67.5 mg, 0.36 mmol), and $PdCl_2(CH_3CN)_2$ (4.6 mg, 0.018 mmol) in HOAc (1.4 mL). The mixture was stirred at room temperature for 24 h, and after the work-up, flash column chromatography (silica gel, petroleum ether/EtOAc t 8/2) afforded **2c** (75.9 mg, 72%) as a solid, whose data are coincidental with those reported:[70] mp (CH_2Cl_2): 131−133 °C [lit.[70] mp (ethanol/water) 131−133 °C]; IR (ATR) 1712 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.42 (s, 3H, CH_3), 3.47 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.00 (s, 1H, H_3), 6.25 (d, J = 2.4 Hz, 1H, H_6), 6.53 (d, J = 2.4 Hz, 1H, H_8), 7.15−7.21 (m, 4H, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 21.3 (CH_3), 55.4 (OCH_3), 55.8 (OCH_3), 93.6 (C_8), 95.8 (C_6), 103.6 (C_{4a}), 112.7 (C_3), 127.2 ($C_{2'}$, $C_{6'}$), 128.0 ($C_{3'}$, $C_{5'}$), 136.9 ($C_{4'}$), 137.8 ($C_{1'}$), 155.8 (C_4), 157.2 (C_{8a}), 158.3, 161.0 (C_5, C_7), 163.3 (CO); MS (ESI^+) *m/z* (rel intensity) (MH^+ + 1, 15), 297 (MH^+, 100); HRMS (ESI^+) Calcd. for $C_{18}H_{17}O_4$ [MH^+]: 297.1127; found, 297.1132.

*4-[4-(tert-Butyl)phenyl]-5,7-dimethoxy-2H-chromen-2-one (**2d**).* Coumarin **2d** was prepared from **1d** (122.0 mg, 0.36 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (124.4 mg, 0.43 mmol), $Cu(OAc)_2$ (3.3 mg, 0.018 mmol), *p*-TsOH (68.2 mg, 0.36 mmol), and $PdCl_2(CH_3CN)_2$ (4.7 mg, 0.018 mmol) in HOAc (1.4 mL). The mixture was stirred at room temperature for 24 h, and after the work-up, flash column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **2d** (101.0 mg, 83%) as a solid: mp (CH_2Cl_2): 176−178 °C; IR (ATR) 1718 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 9H, $C(CH_3)_3$), 3.43 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.02 (s, 1H, H_3), 6.25 (d, J = 2.4 Hz, 1H, H_6), 6.53 (d, J = 2.4 Hz, 1H, H_8), 7.19−7.22 (m, 2H, $H_{3'}$, $H_{5'}$), 7.39−7.42 (m, 2H, $H_{2'}$, $H_{6'}$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 31.3 ($C(CH_3)_3$), 34.7 ($C(CH_3)_3$), 55.5 (OCH_3), 55.8 (OCH_3), 93.6 (C_8), 95.8 (C_6), 103.7 (C_{4a}),

https://doi.org/10.1021/acsomega.1c03469
ACS Omega 2021, 6, 29483−29494

112.5 (C_3), 124.2 ($C_{2'}$, $C_{6'}$), 127.0 ($C_{3'}$, $C_{5'}$), 136.8 ($C_{4'}$), 151.1 ($C_{1'}$), 155.8 (C_4), 157.2 (C_{8a}), 158.3, 161.0 (C_5, C_7), 163.3 (CO); MS (ESI^+) *m/z* (rel intensity) 340 (MH^+ + 1, 17), 339 (MH^+, 100); HRMS (ESI^+) Calcd. for $C_{21}H_{23}O_4$ [MH^+]: 339.1596; found, 339.1600.

*4-(3,5-Dimethoxyphenyl)-5,7-dimethoxy-2H-chromen-2-one (**2e**).* Coumarin **2e** was prepared from **1e** (115.6 mg, 0.34 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (116.5 mg, 0.40 mmol), $Cu(OAc)_2$ (3.0 mg, 0.017 mmol), *p*-TsOH (63.9 mg, 0.34 mmol), and $PdCl_2(CH_3CN)_2$ (8.6 mg, 0.034 mmol) in HOAc (1.4 mL). The mixture was stirred at room temperature for 24 h, and after the work-up, flash column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **2e** (63.9 mg, 55%, 79% conversion) as a solid: mp (CH_2Cl_2): 126−128 °C; IR (ATR) 1718 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.49 (s, 3H, OCH_3), 3.81 (s, 6H, 2 × OCH_3), 3.87 (s, 3H, OCH_3), 6.02 (s, 1H, H_3), 6.25 (d, J = 2.4 Hz, 1H, H_6), 6.41 (d, J = 2.3 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.49 (t, J = 2.3 Hz, 1H, $H_{4'}$), 6.52 (d, J = 2.4 Hz, 1H, H_8); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 55.5 (2 × OCH_3), 55.6 (OCH_3), 55.8 (OCH_3), 93.6 (C_8), 95.9 (C_6), 100.0 ($C_{4'}$), 103.5 (C_{4a}), 105.4 ($C_{2'}$, $C_{6'}$), 112.4 (C_3), 141.7 ($C_{1'}$), 155.5 (C_4), 157.1 (C_{8a}), 158.2 (C_7), 160.0 ($C_{3'}$, $C_{5'}$), 160.9 (C_5), 163.4 (CO); MS (ESI^+) *m/z* (rel intensity) 344 (MH^+ + 1, 16), 343 (MH^+, 100); HRMS (ESI^+) Calcd. for $C_{19}H_{19}O_6$ [MH^+]: 343.1182; found, 343.1180.

*4-(Furan-3-yl)-5,7-dimethoxy-2H-chromen-2-one (**2f**).* Coumarin **2f** was prepared from **1f** (98.1 mg, 0.36 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (124.1 mg, 0.43 mmol), $Cu(OAc)_2$ (3.2 mg, 0.018 mmol), *p*-TsOH (68.0 mg, 0.36 mmol), and $PdCl_2(CH_3CN)_2$ (4.6 mg, 0.018 mmol) in HOAc (1.4 mL). The mixture was stirred at room temperature for 24 h, and after the work-up, flash column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **2f** (20.6 mg, 21%, 75% conversion) as a solid: mp (CH_2Cl_2): 153−155 °C; IR (ATR) 1714 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.67 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.09 (s, 1H, H_3), 6.30 (d, J = 2.4 Hz, 1H, H_6), 6.49−6.52 (m, 2H, H_8, $H_{4'}$), 7.45 (t, J = 1.8 Hz, 1H, $H_{5'}$), 7.56−7.57 (m, 1H, $H_{2'}$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 55.3 (OCH_3), 55.8 (OCH_3), 93.6 (C_8), 95.7 (C_6), 103.4 (C_{4a}), 112.1 ($C_{4'}$), 112.5 (C_3), 125.0 ($C_{3'}$), 140.3 ($C_{2'}$), 142.0 ($C_{5'}$), 146.7 (C_4), 157.3, 158.2, 160.8 (C_{8a}, C_5, C_7), 163.3 (CO); MS (ESI^+) *m/z* (rel intensity) 274 (MH^+ + 1, 12), 273 (MH^+, 100); HRMS (ESI^+) Calcd. for $C_{15}H_{13}O_5$ [MH^+]: 273.0763; found, 273.0769.

*4-(3,5-Difluorophenyl)-5,7-dimethoxy-2H-chromen-2-one (**2g**).* Coumarin **2g** was prepared from **1g** (87.5 mg, 0.27 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (94.9 mg, 0.33 mmol), $Cu(OAc)_2$ (3.0 mg, 0.016 mmol), *p*-TsOH (79.3 mg, 0.27 mmol), and $PdCl_2(CH_3CN)_2$ (8.5 mg, 0.032 mmol) in mesitylene (1.1 mL). The mixture was stirred at 70 °C for 24 h, and after the work-up, flash column chromatography (silica gel, hexane/EtOAc 8/2) afforded **2g** (25.8 mg, 30%) as a solid: mp (CH_2Cl_2): 170−172 °C; IR (ATR) 1724 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.48 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.97 (s, 1H, H_3), 6.23 (d, J = 2.4 Hz, 1H, H_6), 6.51 (d, J = 2.4 Hz, 1H, H_8), 6.72−6.91 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 55.6 (OCH_3), 55.8 (OCH_3), 93.7 (C_8), 95.8 (C_6), 102.8 (C_{4a}), 103.2 (t, J = 25.2 Hz, $C_{4'}$), 110.9−112.7 (m, $C_{2'}$, $C_{6'}$), 112.7 (C_3), 142.8 (t, J = 10.1 Hz, $C_{1'}$), 153.0 (C_4), 157.1 (C_{8a}), 157.9 (C_5), 160.3 (C_7), 162.2 (dd, J = 248.1, 13.2 Hz, $C_{3'}$, $C_{5'}$), 163.8 (CO); MS (EI) *m/z* (rel intensity) 319.1 (M^+ + 1, 19), 318.1 (M^+, 100), 291.1 (16), 290.1 (93), 275.1 (39), 247 (12), 188 (14), 175 (15), 69 (10); HRMS (CI) Calcd. for $C_{17}H_{13}F_2O_4$ [MH^+]: 319.0776; found, 319.0770.

*5,7-Dimethoxy-2H-chromen-2-one (**2h**).* Coumarin **2h** was prepared from **1h** (94.4 mg, 0.45 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (157.4 mg, 0.54 mmol), $Cu(OAc)_2$ (4.1 mg, 0.023 mmol), *p*-TsOH (131.6 mg, 0.45 mmol), and $PdCl_2(CH_3CN)_2$ (5.9 mg, 0.023 mmol) in mesitylene (1.8 mL). The mixture was stirred at 70 °C for 4 h, and after the work-up, flash column chromatography (silica gel, hexane/EtOAc 7/3) afforded **2h** (64.9 mg, 69%) as a white solid, whose data are coincidental with those reported:[46] mp (CH_2Cl_2): 144−146 °C [lit.[46] mp (CH_2Cl_2/pentanes) 143−145 °C]; IR (ATR) 1724 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.82 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.15 (d, J = 9.7 Hz, 1H, H_3), 6.28 (d, J = 2.1 Hz, 1H, H_6), 6.41 (d, J = 2.1 Hz, 1H, H_8), 7.96 (d, J = 9.7 Hz, 1H, H_4); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 55.8 (OCH_3), 55.9 (OCH_3), 92.8 (C_8), 94.8 (C_6), 104.0 (C_{4a}), 110.9 (C_3), 138.7 (C_4), 156.8 (C_{8a}), 157.0, 163.7 (C_5, C_7), 161.5 (CO); MS (EI) *m/z* (rel intensity) 207 (M^+ + 1, 12), 206 (M^+, 100), 178 (79), 163 (48), 135 (22); HRMS (CI) Calcd. for $C_{11}H_{11}O_4$ [MH^+]: 207.0652; found, 207.0658.

*5,7-Dimethoxy-4-methyl-2H-chromen-2-one (**2i**).* Coumarin **2i** was prepared from **1i** (84.2 mg, 0.38 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (131.5 mg, 0.45 mmol), $Cu(OAc)_2$ (3.4 mg, 0.018 mmol), *p*-TsOH (72.1 mg, 0.38 mmol), and $PdCl_2(CH_3CN)_2$ (9.8 mg, 0.036 mmol) in mesitylene (1.5 mL). The mixture was stirred at 70 °C for 24 h, and after the work-up, flash column chromatography (silica gel, hexane/EtOAc 7/3) afforded **2i** (50.3 mg, 60%) as a white solid, whose data are coincidental with those reported:[46] mp (CH_2Cl_2): 166−168 °C [lit.[46] mp (methanol): 168−170 °C; IR (ATR) 1740 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.50 (d, J = 1.2 Hz, 3H, CH_3), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.91 (br s, 1H, H_3), 6.26 (d, J = 2.4 Hz, 1H, H_6), 6.39 (d, J = 2.4 Hz, 1H, H_8); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 24.2 (CH_3), 55.6 (OCH_3), 55.7 (OCH_3), 93.4 (C_8), 95.4 (C_6), 104.8 (C_{4a}), 111.3 (C_3), 154.5 (C_{8a}), 156.9 (C_4), 159.1, 162.8 (C_5, C_7), 161.0 (CO); MS (EI) *m/z* (rel intensity) 221 (M^+ + 1, 13), 220 (M^+, 100), 193 (11), 192 (91), 178 (10), 177 (73), 149 (13); HRMS (CI) Calcd. for $C_{12}H_{13}O_4$ [MH^+]: 221.0808; found, 221.0811.

*4-Ethyl-5,7-dimethoxy-2H-chromen-2-one (**2j**).* Coumarin **2j** was prepared from **1j** (61.0 mg, 0.26 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (94.3 mg, 0.31 mmol), $Cu(OAc)_2$ (2.4 mg, 0.013 mmol), *p*-TsOH (49.9 mg, 0.26 mmol), and $PdCl_2(CH_3CN)_2$ (6.8 mg, 0.026 mmol) in mesitylene (1 mL). The mixture was stirred at 70 °C for 24 h, and after the work-up, flash column chromatography (silica gel, hexane/EtOAc 7/3) afforded **2j** (29.8 mg, 49%) as a solid, whose data are coincidental with those reported:[71] mp (CH_2Cl_2): 141−143 °C [lit.[71] mp (EtOH:H_2O) 146−148 °C]; IR (ATR) 1710 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.21 (t, J = 7.3 Hz, 3H, CH_3), 2.94 (q, J = 7.3 Hz, 2H, CH_2), 3.84 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.00 (s, 1H, H_3), 6.30 (d, J = 2.4 Hz, 1H, H_6), 6.45 (d, J = 2.4 Hz, 1H, H_8); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 13.5 (CH_3), 29.4 (CH_2), 55.7 (OCH_3), 55.8 (OCH_3), 93.6 (C_8), 95.6 (C_6), 104.3 (C_{4a}), 109.7 (C_3), 157.2 (C_{8a}), 158.8 (C_4), 159.9, 162.6

https://doi.org/10.1021/acsomega.1c03469
ACS Omega 2021, 6, 29483−29494

(C_5, C_7), 161.4 (CO); MS (EI) *m/z* (rel intensity) 235 (M^+ + 1, 15), 234 (M^+, 100), 207 (12), 206 (86), 205 (16), 191 (52), 161 (12), 103 (11); HRMS (CI) Calcd. for $C_{13}H_{15}O_4$ [MH^+]: 235.0965; found, 235.0966.

*5,7-Dimethoxy-4-propyl-2H-chromen-2-one (**2k**).* Coumarin **2k** was prepared from **1k** (77.0 mg, 0.31 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (112.4 mg, 0.37 mmol), $Cu(OAc)_2$ (2.9 mg, 0.015 mmol), *p*-TsOH (59.4 mg, 0.31 mmol), and $PdCl_2(CH_3CN)_2$ (8.0 mg, 0.030 mmol) in mesitylene (1.2 mL). The mixture was stirred at 70 °C for 24 h, and after the work-up, flash column chromatography (silica gel, hexane/EtOAc 7/3) afforded **2k** (37.9 mg, 50%) as a solid, whose data are coincidental with those reported:[72] mp (CH_2Cl_2): 109−111 °C [lit.[72] mp ($CHCl_3$) 113.5−115 °C]; IR (ATR) 1713 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.00 (t, J = 7.3 Hz, 3H, $CH_2-CH_2-C\underline{H}_3$), 1.52−1.69 (m, 2H, $CH_2-C\underline{H}_2-CH_3$), 2.82−2.88 (m, 2H, $C\underline{H}_2-CH_2-CH_3$), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.96 (s, 1H, H_3), 6.30 (d, J = 2.4 Hz, 1H, H_6), 6.45 (d, J = 2.4 Hz, 1H, H_8); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 14.0 ($CH_2-CH_2-\underline{C}H_3$), 22.8 ($CH_2-\underline{C}H_2-CH_3$), 38.5 ($\underline{C}H_2-CH_2-CH_3$), 55.7 ($OCH_3$), 55.8 ($OCH_3$), 93.6 ($C_8$), 95.6 ($C_6$), 104.3 ($C_{4a}$), 110.7 ($C_3$), 157.3 ($C_{8a}$), 158.2 ($C_4$), 158.7, 162.6 ($C_5$, C_7), 161.3 (CO); MS (EI) *m/z* (rel intensity) 249.1 (M^+ + 1, 15), 248.1 (M^+, 100), 233.1 (36), 220.1 (63), 205.1 (41), 192.1 (56), 191.1 (28), 178 (15), 177.1 (25), 161.1 (22), 146 (15), 91 (10), 77.1 (12), 69 (14); HRMS (CI) Calcd. for $C_{14}H_{17}O_4$ [MH^+]: 249.1121; found, 249.1123.

*6,7-Dimethoxy-4-phenyl-2H-chromen-2-one (**2p**).* Coumarin **2p** was prepared from **1p** (60 mg, 0.21 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (75.9 mg, 0.25 mmol), $Cu(OAc)_2$ (2.2 mg, 0.010 mmol), *p*-TsOH (40.2 mg, 0.21 mmol), and $PdCl_2(CH_3CN)_2$ (5.6 mg, 0.021 mmol) in mesitylene (1.0 mL). The mixture was stirred at 70 °C for 24 h, and after the work-up, flash column chromatography (silica gel, hexane/EtOAc 7/3) afforded **2p** (17.8 mg, 30%) as an oil, whose data are coincidental with those reported:[73] IR (ATR): 1715 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.77 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.26 (s, 1H, H_3), 6.88 (s, 1H, H_8), 6.94 (s, 1H, H_5), 7.46−7.56 (m, 5H, Ph); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 56.3 (OCH_3), 56.4 (OCH_3), 100.3 (C_8), 107.5 (C_5), 111.4 (C_{4a}), 112.4 (C_3), 128.3, 128.9, 129.7 ($C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$), 135.8 ($C_{1'}$), 146.1 (C_4), 150.2 (C_{8a}), 152.9, 155.6 (C_6, C_7), 161.4 (CO); MS (EI) *m/z* (rel intensity): 282 (M^+, 100), 254 (23), 239 (16), 207 (27), 168 (10), 155 (12), 139 (15), 127 (17); HRMS (ESI^+) Calcd. for $C_{17}H_{15}O_4$ [MH^+]: 283.0965; found, 283.0957.

*6,7-Dimethoxy-4-methyl-2H-chromen-2-one (**2q**).* Coumarin **2q** was prepared from **1q** (60.1 mg, 0.27 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (98.9 mg, 0.33 mmol), $Cu(OAc)_2$ (5.1 mg, 0.027 mmol), *p*-TsOH (52.2 mg, 0.27 mmol), and $PdCl_2(CH_3CN)_2$ (7.1 mg, 0.027 mmol) in mesitylene (1.3 mL). The mixture was stirred at 70 °C for 24 h, and after the work-up, flash column chromatography (silica gel, hexane/EtOAc 7/3) afforded **2q** (20.3 mg, 34%) as a solid, whose data are coincidental with those reported:[71] mp (CH_2Cl_2): 128−129 °C [lit.[71] mp (EtOH:H_2O) 128−129 °C]; IR (ATR): 1715 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.41 (d, J = 1.0 Hz, 3H, CH_3), 3.94 (s, 6H, 2 × OCH_3), 6.17 (d, J = 1.0 Hz, 1H, H_3), 6.85 (s, 1H, H_5), 6.94 (s, 1H, H_8); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 18.9 (CH_3), 56.3 (OCH_3), 56.4 (OCH_3), 100.1 (C_8), 105.2 (C_5), 112.4 (C_{4a}), 112.5 (C_3), 146.2 (C_4), 149.2 (C_{8a}), 152.3, 159.1 (C_6, C_7), 161.5 (CO); MS (EI) *m/z* (rel intensity): 220 (M^+, 100), 192 (10), 149 (14), 1201 (10); HRMS (ESI^+) Calcd. for $C_{12}H_{13}O_4$ [MH^+]: 221.0808; found, 221.0820.

*5,6,7-Trimethoxy-4-methyl-2H-chromen-2-one (**2r**).* Coumarin **2r** was prepared from **1r** (674 mg, 0.24 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (88.3 mg, 0.31 mmol), $Cu(OAc)_2$ (4.4 mg, 0.024 mmol), *p*-TsOH (48.8 mg, 0.24 mmol), and $PdCl_2(CH_3CN)_2$ (6.2 mg, 0.024 mmol) in mesitylene (1.0 mL). The mixture was stirred at 70 °C for 72 h, and after the work-up, flash column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **2r** (13.0 mg, 18%) as an oil, whose data are coincidental with those reported:[74] IR (ATR): 1735 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.56 (d, J = 1.1 Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.04 (d, J = 1.1 Hz, 1H, H_3), 6.64 (s, 1H, H_8); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 23.0 (CH_3), 56.2 (OCH_3), 61.0 (OCH_3), 61.3 (OCH_3), 96.2 (C_8), 108.1 (C_{4a}), 113.0 (C_3), 139.2 (C_6), 151.3 (C_{8a}), 151.6 (C_4), 153.6, 156.3 (C_5, C_7), 160.1 (CO); MS (EI) *m/z* (rel intensity): 250 (M^+, 90), 235 (100), 207 (75), 163 (39), 149 (14), 69 (17), 53 (14), 51 (13); HRMS (ESI^+) Calcd. for $C_{13}H_{15}O_5$ [MH^+]: 251.0914; found, 251.0939.

*4-Methyl-6,7-methylenedioxy-2H-chromen-6-one (**2s**).* Coumarin **2s** was prepared from **1s** (61.5 mg, 0.30 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (101.1 mg, 0.35 mmol), $Cu(OAc)_2$ (5.1 mg, 0.015 mmol), *p*-TsOH (57.7 mg, 0.30 mmol), and $PdCl_2(CH_3CN)_2$ (8.0 mg, 0.027 mmol) in mesitylene (1.5 mL). The mixture was stirred at 70 °C for 96 h, and after the work-up, flash column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **2s** (13.0 mg, 20%) as a solid, whose data are coincidental with those reported:[75] mp (CH_2Cl_2): 120−122 °C; IR (ATR): 1735 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.37 (s, 3H, CH_3), 6.07 (s, 2H, OCH_2O), 6.17 (s, 1H, H_3), 6.83 (s, 1H, H_5), 6.96 (s, 1H, H_8); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 19.1 (CH_3), 98.4 (OCH_2O), 102.1 (C_8), 102.3 (C_5), 112.2 (C_{4a}), 113.8 (C_3), 144.9 (C_4), 150.6 (C_{8a}), 150.9, 152.4 (C_6, C_7), 161.2 (CO); MS (EI) *m/z* (rel intensity): 204 (M^+, 100), 176 (72), 96 (15); HRMS (ESI^+) Calcd. for $C_{11}H_9O_4$ [MH^+]: 205.0495; found, 205.0523.

*(Z)-3-(3,5-Difluorobenzylidene)-4,6-dimethoxybenzofuran-2(3H)-ne (**3g**).* Compound **3g** was obtained from **1g** (123.8 mg, 0.39 mmol), 1-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (135.5 mg, 0.46 mmol), $Cu(OAc)_2$ (3.6 mg, 0.019 mmol), *p*-TsOH (74.6 mg, 0.39 mmol), and $PdCl_2(CH_3CN)_2$ (5.1 mg, 0.019 mmol) in HOAc (1.5 mL). The mixture was stirred at 70 °C for 24 h, and after the work-up, flash column chromatography (silica gel, hexane/EtOAc 8/2) afforded **2g** (9.8 mg, 8%) and **3g** (18.3 mg, 15%) as a solid: mp (CH_2Cl_2): 202−204 °C; IR (ATR): 1774 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.85 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.26 (d, J = 2.0 Hz, 1H, H_5), 6.32 (d, J = 2.0 Hz, 1H, H_7), 6.79−6.88 (m, 1H, $H_{4'}$), 7.49−7.63 (m, 1H, $H_{2'}$, $H_{6'}$), 7.80 (s, 1H, C═C$\underline{H}$−Ar); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 55.8 (OCH_3), 55.9 (OCH_3), 89.3 (C_7), 94.3 (C_5), 104.7−105.8 (m, C_{3a}, $C_{4'}$), 113.5−113.9 (m, $C_{2'}$, $C_{6'}$), 122.6 (C_3), 136.4 (C═$\underline{C}$H−Ar), 136.9 (t, J = 10.0 Hz, $C_{1'}$), 155.1 (C_{7a}), 157.0 (C_4), 162.6 (dd, J = 247.5, 13.0 Hz, $C_{3'}$, $C_{5'}$), 163.1 (C_6), 165.8 (CO); MS (EI) *m/z* (rel intensity) 319 (M^+ + 1, 19), 318 (M^+, 100), 275 (28), 188 (12), 175 (11), 69

https://doi.org/10.1021/acsomega.1c03469
ACS Omega 2021, 6, 29483−29494

(10); HRMS (ESI$^+$) Calcd. for $C_{17}H_{13}F_2O_4$ [MH$^+$]: 319.0776; found, 319.0783.

C3 Intermolecular C−H Alkenylation of Coumarins 2: General Procedure. Over a solution of coumarins **2** (1 mmol) in 1,4-dioxane (5 mL), AgOAc (3 mmol), PivOH (10 mmol), and $Pd(OAc)_2$ (0.1 or 0.2 mmol) were added. The mixture was stirred vigorously for 5 min, and then the corresponding acrylate (2 or 4 mmol) was added. The reaction was heated at 120 °C for 24−48 h, and then the reaction was allowed to cool down to room temperature. The mixture was filtered through diatomaceus earth and the filtrate was concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/EtOAc) afforded coumarins **4**.

*Methyl (E)-3-(5,7-Dimethoxy-2-oxo-4-phenyl-2H-chromen-3-yl)acrylate (**4a**).* Coumarin **4a** was prepared from **2a** (83.2 mg, 0.29 mmol), AgOAc (0.15 g, 0.88 mmol), PivOH (0.30 g, 2.95 mmol), methylacrylate (0.06 mL, 0.59 mmol), and $Pd(OAc)_2$ (6.6 mg, 0.029 mmol). The reaction was heated at 120 °C for 24 h, and after this, additional amounts of methyl acrylate (0.06 mL, 0.59 mmol) and $Pd(OAc)_2$ (6.6 mg, 0.029 mmol) were added, and it was heated again at 120 °C for 24 h. After the work-up, flash column chromatography (silica gel, hexane/EtOAc 7/3) afforded **4a** (33.4 mg, 31%) as a solid: mp (CH_2Cl_2) 194−196 °C; IR (ATR): 1710 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.29 (s, 3H, CH═CH−COOC$\underline{H}_3$), 3.65 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.15 (d, J = 2,4 Hz, 1H, H_6), 6.49 (d, J = 2,4 Hz, 1H, H_8), 7.06−7.15 (m, 4H, $H_{2'}$, $H_{4'}$, $H_{6'}$, CH═C$\underline{H}$−COOCH$_3$), 7.34−7.47 (m, 3H, $H_{3'}$, $H_{5'}$, C$\underline{H}$═CH−COOCH$_3$); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 51.4 (CH═CH−COO$\underline{C}$H$_3$), 55.7 (OCH_3), 55.9 (OCH_3), 93.1 (C_8), 96.0 (C_6), 104.7 (C_{4a}), 115.7 (C_3), 121.9 (CH═$\underline{C}$H−COOCH$_3$), 127.1 ($C_{2'}$, $C_{6'}$), 127.8 ($C_{3'}$, $C_{5'}$), 127.9 ($C_{4'}$), 137.2 ($\underline{C}$H═CH−COOCH$_3$), 137.7 ($C_{1'}$), 155.8 (C_4), 156.0 (C_{8a}), 159.1, 164.4 (C_5, C_7) 159.2 ($\underline{C}$O), 168.4 (COOCH$_3$); MS (CI) m/z (rel intensity) 368 (MH$^+$ + 1, 19), 367 (MH$^+$, 100), 336 (7), 335 (41); HRMS (ESI$^+$) Calcd. for $C_{21}H_{19}O_6$ [MH$^+$]: 367.1176; found, 367.1180.

*tert-Butyl (E)-3-(5,7-Dimethoxy-2-oxo-4-phenyl-2H-chromen-3-yl)acrylate (**4b**).* Coumarin **4b** was prepared from **2a** (82.4 mg, 0.29 mmol), AgOAc (0.15 g, 0.88 mmol), PivOH (0.30 g, 2.92 mmol), *tert*-butyl acrylate (85 μL, 0.58 mmol), and $Pd(OAc)_2$ (6.6 mg, 0.029 mmol). The reaction was heated at 120 °C for 24 h, and after the work-up, flash column chromatography (silica gel, CH_2Cl_2) afforded **4b** (37.3 mg, 31%, 44% conversion) as a solid: mp (CH_2Cl_2) 148−150 °C; IR (ATR): 1732 (COO), 1706 (COO*t*Bu) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (s, 9H, C(CH$_3$)$_3$), 3.31 (s, 3H, OCH_3), 3.89 (OCH_3), 6.17 (d, J = 2.4 Hz, 1H, H_6), 6.52 (d, J = 2.4 Hz, 1H, H_8), 7.02−7.15 (m, 4H, $H_{2'}$, $H_{4'}$, $H_{6'}$, CH═C$\underline{H}$−COO*t*Bu), 7.35−7.47 (m, 3H, $H_{3'}$, $H_{5'}$, C$\underline{H}$═CH−COO*t*Bu); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 28.1 (C($\underline{C}$H$_3$)$_3$), 55.7 (OCH_3), 55.9 (OCH_3), 79.9 ($\underline{C}$(CH$_3$)$_3$), 93.1 (C_8), 96.0 (C_6), 104.8 (C_{4a}), 115.9 (C_3), 124.4 (CH═$\underline{C}$H−COO*t*Bu), 127.1 ($C_{3'}$, $C_{5'}$), 127.7 ($C_{4'}$), 127.9 ($C_{2'}$, $C_{6'}$), 135.9 ($\underline{C}$H═CH−COO*t*Bu), 137.8 ($C_{1'}$), 155.4, 155.9 (C_4, C_{8a}), 159.1, 159.2 (C_5, C_7), 164.2 (CO), 166.9 ($\underline{C}$OO*t*Bu); MS (ESI$^+$) m/z (rel intensity) 410 (MH$^+$ + 1, 9), 409 (MH$^+$, 45), 354 (16), 353 (100); HRMS (ESI$^+$) Calcd. for $C_{25}H_{25}O_6$ [MH$^+$]: 409.1651; found, 409.1653.

*Methyl (E)-3-{4-[4-(tert-Butyl)phenyl]-5,7-dimethoxy-2-oxo-2H-chromen-3-ylacrylate (**4c**).* Coumarin **4c** was prepared from **2d** (85.0 mg, 0.25 mmol), AgOAc (0.13 g, 0.75 mmol), PivOH (0.26 g, 2.51 mmol), methyl acrylate (45 μL, 0.50 mmol), and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol). The reaction was heated at 120 °C for 24 h, and after this, additional amounts of methyl acrylate (45 μL, 0.50 mmol) and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) were added, and it was heated again at 120 °C for 24 h. After the work-up, flash column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **4c** (55.4 mg, 52%, 63% conversion) as a solid: mp (CH_2Cl_2): 159−162 °C; IR (ATR): 1726 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.40 (s, 9H, C(CH$_3$)$_3$), 3.28 (s, 3H, COOCH$_3$), 3.67 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.16 (d, J = 2.4 Hz, 1H, H_6), 6.50 (d, J = 2.4 Hz, 1H, H_8), 7.04−7.06 (m, 2H, $H_{3'}$, $H_{5'}$), 7.16 (d, J = 15.8 Hz, 1H, CH═C$\underline{H}$−COOCH$_3$), 7.24 (d, J = 15.8 Hz, 1H, C$\underline{H}$═CH−COOCH$_3$), 7.44−7.47 (m, 2H, $H_{2'}$, $H_{6'}$); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 31.3 (C($\underline{C}$H$_3$)$_3$), 34.7 ($\underline{C}$(CH$_3$)$_3$), 51.4 (COOCH$_3$), 55.8 (OCH_3), 55.8 (OCH_3), 93.1 (C_8), 96.1 (C_6), 105.0 (C_{4a}), 115.7 (C_3), 121.8 (CH═$\underline{C}$H−COOCH$_3$), 124.7 ($C_{3'}$, $C_{5'}$), 126.9 ($C_{2'}$, $C_{6'}$), 134.6 ($C_{1'}$), 137.4 ($\underline{C}$H═CH−COOCH$_3$), 150.8 ($C_{4'}$), 156.0 (C_4, C_{8a}), 156.3, 159.2 (C_5, C_7), 164.3 (CO), 168.3 ($\underline{C}$OOCH$_3$); MS (ESI$^+$) m/z (rel intensity) 424 (MH$^+$ + 1, 24), 423 (MH$^+$, 100), 391 (20), 318 (11); HRMS (ESI$^+$) Calcd. for $C_{25}H_{27}O_6$ [MH$^+$]: 423.1808; found, 423.1801.

*Methyl (E)-3-[4-(3,5-Dimethoxyphenyl)-5,7-dimethoxy-2-oxo-2H-chromen-3-yl]acrylate (**4d**).* Coumarin **4d** was prepared from **2e** (69.2 mg, 0.20 mmol), AgOAc (0.10 g, 0.61 mmol), PivOH (0.21 g, 2.02 mmol), methyl acrylate (36 μL, 0.40 mmol), and $Pd(OAc)_2$ (4.5 mg, 0.020 mmol). The reaction was heated at 120 °C for 24 h, and after this, additional amounts of methyl acrylate (36 μL, 0.40 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.020 mmol) were added, and it was heated again at 120 °C for 24 h. After the work-up, flash column chromatography (silica gel, petroleum ether/EtOAc 6/4) afforded **4d** (24.2 mg, 28%, 57% conversion) as a solid: mp (CH_2Cl_2) 207−209 °C; IR (ATR): 1722 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.40 (s, 3H, COOCH$_3$), 3.69 (s, 3H, OCH_3), 3.81 (s, 6H, 2 × OCH_3), 3.88 (s, 3H, OCH_3), 6.19 (d, J = 2.4 Hz, 1H, H_6), 6.28−6.29 (m, 2H, $H_{2'}$, $H_{6'}$), 6.49−6.51 (m, 2H, H_8, $H_{4'}$), 7.15−7.27 (m, 2H, C$\underline{H}$═C$\underline{H}$−COOCH$_3$); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 51.5 (COOCH$_3$), 55.5 (2 × OCH_3), 55.9 (OCH_3), 56.0 (OCH_3), 93.1 (C_8), 96.1 (C_6), 99.8 ($C_{4'}$), 104.6 (C_{4a}), 105.5 ($C_{2'}$, $C_{6'}$), 115.5 (C_3), 122.0 (CH═$\underline{C}$H−COOCH$_3$), 137.2 ($\underline{C}$H═CH−COOCH$_3$), 139.5 ($C_{1'}$), 155.5 (C_4), 156.0 (C_{8a}), 159.2, 160.6 (C_5, C_7), 164.4 (CO), 168.2 ($\underline{C}$OOCH$_3$); MS (ESI$^+$) m/z (rel intensity) 428 (MH$^+$ + 1, 19), 427 (MH$^+$, 100), 396 (10), 395 (56), 353 (24); HRMS (ESI$^+$) Calcd. for $C_{23}H_{23}O_8$ [MH$^+$]: 427.1393; found, 427.1393.

*Methyl (E)-3-(5,7-Dimethoxy-4-methyl-2-oxo-2H-chromen-3-yl)acrylate (**4e**).* Coumarin **4e** was prepared from **2i** (81.3 mg, 0.37 mmol), AgOAc (0.19 g, 1.11 mmol), PivOH (0.38 g, 3.69 mmol), methyl acrylate (0.07 mL, 0.74 mmol), and $Pd(OAc)_2$ (8.5 mg, 0.04 mmol). The reaction was heated at 120 °C for 48 h, and after the work-up, flash column chromatography (silica gel, hexane/EtOAc 6/4) afforded **4e** (50.7 mg, 45%) as a solid: mp (CH_2Cl_2) 199−201 °C; IR (ATR): 1713 cm^{-1} (COO, COOCH$_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.72 (s, 3H, CH_3), 3.79 (s, 3H, COOCH$_3$), 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.30 (d, J = 2,4 Hz, 1H, H_6), 6.40 (d, J = 2,4 Hz, 1H, H_8), 7.07 (d, J = 15,7 Hz, 1H, CH═C$\underline{H}$−COOCH$_3$), 7.82 (d, J = 15,7 Hz, 1H, C$\underline{H}$═CH−COOCH$_3$); ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz): δ 19.7

https://doi.org/10.1021/acsomega.1c03469
ACS Omega 2021, 6, 29483−29494

(CH_3), 51.7 (CH=CH−COO$\underline{C}H_3$), 55.8 (OCH_3), 55.9 (OCH_3), 93.1 (C_8), 96.0 (C_6), 106.5 (C_{4a}), 115.5 (C_3), 123.1 (CH=$\underline{C}$H−COOCH_3), 136.3 ($\underline{C}$H=CH−COOCH_3), 154.5 (C_4), 155.8 (C_{8a}), 159.0, 163.5 (C_5, C_7), 159.8 (CO), 168.4 (COOCH_3); MS (CI) *m/z* (rel intensity) 306 (MH^+ + 1, 14), 305 (MH^+, 100), 274 (10), 273 (85); HRMS (CI) Calcd. for $C_{16}H_{17}O_6$ [MH^+]: 305.1020; found, 305.1021.

*tert-Butyl (E)-3-(5,7-Dimethoxy-4-methyl-2-oxo-2H-chromen-3-yl)acrylate (**4f**).* Coumarin **4f** was prepared from **2i** (60 mg, 0.27 mmol), AgOAc (0.14 g, 0.82 mmol), PivOH (0.28 g, 2.72 mmol), *tert*-butyl acrylate (0.08 mL, 0.54 mmol), and $Pd(OAc)_2$ (6.2 mg, 0.03 mmol). The reaction was heated at 120 °C for 24 h, and after the work-up, flash column chromatography (silica gel, hexane/EtOAc 7/3) afforded **4f** (49.8 mg, 53%) as a solid: mp (CH_2Cl_2): 159−161 °C; IR (ATR): 1716 (COO), 1695 (COO*t*Bu) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.51 (s, 9H, $C(CH_3)_3$), 2.69 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.28 (d, J = 2.4 Hz, 1H, H_6), 6.38 (d, J = 2.4 Hz, 1H, H_8), 6.97 (d, J = 15.7 Hz, 1H, CH=C$\underline{H}$−COO*t*Bu), 7.71 (d, J = 15.7 Hz, 1H, C$\underline{H}$=CH−COO*t*Bu); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 19.6 (CH_3), 28.2 ($C(\underline{C}H_3)_3$), 55.7 (OCH_3), 55.9 (OCH_3), 80.3 ($\underline{C}(CH_3)_3$), 93.1 (C_8), 95.9 (C_6), 105.5 (C_{4a}), 115.6 (C_3), 125.4 (CH=$\underline{C}$H−COO*t*Bu), 135.0 ($\underline{C}$H=CH−COO*t*Bu), 154.0 (C_{8a}), 155.7 (C_4), 159.1, 159.7 (C_5, C_7), 163.4 (COO), 167.3 (COO*t*Bu); MS (CI) *m/z* (rel intensity) 347.1 (MH^+, 6), 346.1 (20), 292.1 (10), 291 (52), 290.1 (100), 274.1 (10), 273.1 (63), 262.1 (12), 245.1 (72); HRMS (CI) Calcd. for $C_{19}H_{23}O_6$ [MH^+]: 347.1489; found, 347.1507.

*Methyl (E)-3-(5,7-Dimethoxy-4-methyl-2-oxo-2H-chromen-3-yl)but-2-enoate (**4g**).* Coumarin **4g** was prepared from **2i** (52.1 mg, 0.24 mmol), AgOAc (0.12 g, 0.71 mmol), PivOH (0.24 g, 2.37 mmol), methyl crotonate (0.05 mL, 0.47 mmol), and $Pd(OAc)_2$ (5.4 mg, 0.024 mmol). The reaction was heated at 120 °C for 48 h. After the work-up, flash column chromatography (silica gel, hexane/EtOAc 7/3) afforded **4g** (33.5 mg, 44%) as a solid: mp (CH_2Cl_2): 153−155 °C; IR (ATR): 1706 cm^{-1} (COO, $COOCH_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.39 (d, J = 1.3 Hz, 3H, C($C\underline{H}_3$)=CH($COOCH_3$)), 2.48 (s, 3H, C−CH_3), 3.73 (s, 3H, C(CH_3)=CH−($COOC\underline{H}_3$)), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.76−5.79 (m, 1H, C(CH_3)=C$\underline{H}$($COOCH_3$)), 6.31 (d, J = 2,4 Hz, 1H, H_6), 6.43 (d, J = 2,4 Hz, 1H, H_8); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 19.4 (C($\underline{C}H_3$)=CH($COOCH_3$)), 20.7 (C−$\underline{C}H_3$), 51.1 (C(CH_3)=CH($COO\underline{C}H_3$)), 55.7 (OCH_3), 55.8 (OCH_3), 93.2 (C_8), 95.8 (C_6), 104.8 (C_{4a}), 111.4 (C_3), 121.6 (C(CH_3)=$\underline{C}$H($COOCH_3$)), 148.8 ($\underline{C}$-(CH_3)=CH($COOCH_3$)), 152.6 (C_4), 155.8 (C_{8a}), 159.4, 159.5 (C_5, C_7), 162.6 (CO), 166.5 (C(CH_3)=CH−($\underline{C}OOCH_3$)); MS (ESI^+) *m/z* (rel intensity) 319 (MH^+, 100), 288 (17), 287 (71); HRMS (ESI^+) Calcd. for $C_{17}H_{19}O_6$ [MH^+]: 319.1176, found, 319.1171.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c03469.

Preparation procedures for the substrates **1**, additional substrates tested in the cyclization, additional essays for the intermolecular alkenylation reaction of **2i**, copies of the ^1H and ^{13}C NMR spectra of compounds **2**−**4**, and the fluorescence spectra for selected compounds **2** and **4** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Nuria Sotomayor − *Departamento de Química Orgánica e Inorgánica, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU, Bilbao 48080, Spain;* orcid.org/0000-0003-3079-6380; Email: nuria.sotomayor@ehu.es

Esther Lete − *Departamento de Química Orgánica e Inorgánica, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU, Bilbao 48080, Spain;* orcid.org/0000-0001-8624-6842; Email: esther.lete@ehu.es

Authors

Verónica Ortiz-de-Elguea − *Departamento de Química Orgánica e Inorgánica, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU, Bilbao 48080, Spain*

Asier Carral-Menoyo − *Departamento de Química Orgánica e Inorgánica, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU, Bilbao 48080, Spain*

Lorena Simón-Vidal − *Departamento de Química Orgánica e Inorgánica, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU, Bilbao 48080, Spain*

Mikel Martinez-Nunes − *Departamento de Química Orgánica e Inorgánica, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU, Bilbao 48080, Spain*

Iratxe Barbolla − *Departamento de Química Orgánica e Inorgánica, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU, Bilbao 48080, Spain; Instituto Biofisika (UPV/EHU-CSIC), Leioa 48940, Spain*

Marta G. Lete − *CIC bioGUNE, Derio 48170, Spain;* orcid.org/0000-0002-9654-7881

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c03469

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Ministerio de Economía y Competitividad (FEDER CTQ2016-74881-P), Ministerio de Ciencia e Innovación (PID2019-104148GB-I00), and Gobierno Vasco (IT1045-16) are gratefully acknowledged for their financial support. A.C.-M. wishes to thank Gobierno Vasco for a grant. Technical and human support provided by Servicios Generales de Investigación SGIker (UPV/EHU, MINECO, GV/EJ, ERDF and ESF) is also acknowledged.

■ REFERENCES

(1) Estévez-Braun, A.; González, A. G. Coumarins. *Nat. Prod. Rep.* **1997**, *14*, 465−475.

(2) Vazquez-Rodriguez, S.; Matos, M.; Borges, F.; Uriarte, E.; Santana, L. Bioactive Coumarins from Marine Sources: Origin, Structural Features and Pharmacological Properties. *Curr. Top. Med. Chem.* **2015**, *15*, 1755−1766.

(3) Xu, J.; Kjer, J.; Sendker, J.; Wray, V.; Guan, H.; Edrada, R.; Müller, W. E. G.; Bayer, M.; Lin, W.; Wu, J.; Proksch, P. Cytosporones, coumarins, and an alkaloid from the endophytic fungus *Pestalotiopsis* sp. isolated from the Chinese mangrove plant *Rhizophora mucronata*. *Bioorg. Med. Chem.* **2009**, *17*, 7362−7367.
(4) Rateb, M. E.; Ebel, R. Secondary metabolites of fungi from marine habitats. *Nat. Prod. Rep.* **2011**, *28*, 290−344.
(5) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. Lamellarins and Related Pyrrole-Derived Alkaloids from Marine Organisms. *Chem. Rev.* **2008**, *108*, 264−287.
(6) Fukuda, T.; Ishibashi, F.; Iwao, M. Lamellarin alkaloids: Isolation, synthesis, and biological activity. In *The Alkaloids: Chemistry and Biology*; Vol. *83*, Knolker, H. J. Ed.; Elsevier: London, 2020; pp. 1−112.
(7) Garg, S. S.; Gupta, J.; Sharma, S.; Sahu, D. An insight into the therapeutic applications of coumarin compounds and their mechanisms of action. *Eur. J. Pharm. Sci.* **2020**, *152*, 105424.
(8) Nagy, N.; Kuipers, H. F.; Frymoyer, A. R.; Ishak, H. D.; Bollyky, J. B.; Wight, T. N.; Bollyky, P. L. 4-Methylumbelliferone treatment and hyaluronan inhibition as a therapeutic strategy in inflammation, autoimmunity, and cancer. *Front. Immunol.* **2015**, *6*, 123.
(9) Kumagai, M.; Watanabe, A.; Yoshida, I.; Mishima, T.; Nakamura, M.; Nishikawa, K.; Morimoto, Y. Evaluation of Aculeatin and Toddaculin Isolated from *Toddalia asiatica* as Anti-inflammatory Agents in LPS-Stimulated RAW264 Macrophages. *Biol. Pharm. Bull.* **2018**, *41*, 132−137.
(10) McKee, T. C.; Fuller, R. W.; Covington, C. D.; Cardellina, J. H.; Gulakowski, R. J.; Krepps, B. L.; McMahon, J. B.; Boyd, M. R. New Pyranocoumarins Isolated from *Calophyllum lanigerum* and *Calophyllum teysmannii*. *J. Nat. Prod.* **1996**, *59*, 754−758.
(11) Duval, R.; Duplais, C. Fluorescent natural products as probes and tracers in biology. *Nat. Prod. Rep.* **2017**, *34*, 161−193.
(12) Tasior, M.; Kim, D.; Singha, S.; Krzeszewski, M.; Ahn, K. H.; Gryko, D. T. π-Expanded coumarins: synthesis, optical properties and applications. *J. Mater. Chem. C* **2015**, *3*, 1421−1446.
(13) Cao, D.; Liu, Z.; Verwilst, P.; Koo, S.; Jangjili, P.; Kim, J. S.; Lin, W. Coumarin-Based Small-Molecule Fluorescent Chemosensors. *Chem. Rev.* **2019**, *119*, 10403−10519.
(14) Ungureanu, I. M.; Van Ommeren, E.; Givaudan, S. A. Switzerland Off-taste masking sweetener. PCT Int. Appl. WO 2010100158 A1 20100910, Sep. 10, 2010; *Chem. Abstr.* 2010, *153*, 381750.
(15) Orlow, S. J.; Komatsu, L. N. (New York University, USA) Coumarins as melanogenesis modifiers for cosmetics and pharmaceuticals. PCT Int. Appl. WO 2012103487 A1 20120802, Jan. 27, 2017; *Chem. Abstr.* 2012, *157*, 305798.
(16) Guan, A.-Y.; Liu, C.-L.; Li, M.; Zhang, H.; Li, Z.-N.; Li, Z.-M. Design, synthesis and structure-activity relationship of novel coumarin derivatives. *Pest Manage. Sci.* **2011**, *67*, 647−655.
(17) Stefanachi, A.; Leonetti, F.; Pisani, L.; Catto, M.; Carotti, A. Coumarin: A Natural, Privileged and Versatile Scaffold for Bioactive Compounds. *Molecules* **2018**, *23*, 250−284.
(18) Yu, M.; Liu, X.; De Clercq, E. NF-κB: the inducible factors of HIV-1 transcription and their inhibitors. *Mini-Rev. Med. Chem.* **2009**, *9*, 60−69.
(19) Verotta, L.; Lovaglio, E.; Vidari, G.; Finzi, P. V.; Neri, M. G.; Raimondi, A.; Parapini, S.; Taramelli, D.; Riva, A.; Bombardelli, E. 4-Alkyl- and 4-phenylcoumarins from *Mesua ferrea* as promising multidrug resistant antibacterials. *Phytochemistry* **2004**, *65*, 2867−2879.
(20) Pierson, J.-T.; Dumètre, A.; Hutter, S.; Delmas, F.; Laget, M.; Finet, J.-P.; Azas, N.; Combes, S. Synthesis and antiprotozoal activity of 4-arylcoumarins. *Eur. J. Med. Chem.* **2010**, *45*, 864−869.
(21) Combes, S.; Barbier, P.; Douillard, S.; McLeer-Florin, A.; Bourgarel-Rey, V.; Pierson, J.-T.; Fedorov, A. Y.; Finet, J. P.; Boutonnat, J.; Peyrot, V. Synthesis and Biological Evaluation of 4-Arylcoumarin Analogues of Combretastatins. Part 2. *J. Med. Chem.* **2011**, *54*, 3153−3162.
(22) Revankar, H. M.; Bukhari, S. N. A.; Kumar, G. B.; Qin, H.-L. Coumarins scaffolds as COX inhibitors. *Bioorg. Chem.* **2017**, *71*, 146−159.
(23) Medina, F. G.; Marrero, J. G.; Macías-Alonso, M.; González, M. C.; Córdova-Guerrero, I.; Teissier García, A. G.; Osegueda-Robles, S. Coumarin heterocyclic derivatives: chemical synthesis and biological activity. *Nat. Prod. Rep.* **2015**, *32*, 1472−1507.
(24) Rodrigues, J. L.; Rodrigues, L. R. Biosynthesis and heterologous production of furanocoumarins: perspectives and current challenges. *Nat. Prod. Rep.* **2021**, *38*, 869−879.
(25) Garazd, M. M.; Garazd, Y. L.; Khilya, V. P. Neoflavones. 2. Methods for synthesizing and modifying 4-arylcoumarins. *Chem. Nat. Compd.* **2005**, *41*, 245−271.
(26) Fedorov, A. Y.; Nyuchev, A. V.; Beletskaya, I. P. Catalytic methods of creation and functionalization of the coumarin skeleton. *Chem. Heterocycl. Comp.* **2012**, *48*, 166−178.
(27) Vekariya, R. H.; Patel, H. D. Recent Advances in the Synthesis of Coumarin Derivatives via Knoevenagel Condensation: A Review. *Synth. Commun.* **2014**, *44*, 2756−2788.
(28) Li, J.; Chen, H.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. Synthesis of coumarins via PIDA/I_2-mediated oxidative cyclization of substituted phenylacrylic acids. *RSC Adv.* **2013**, *3*, 4311−4320.
(29) Singh, J.; Sharma, A. Visible Light-Induced Synthesis of Functionalized Coumarins. *Adv. Synth. Catal.* **2021**, *363*, 3411−3438.
(30) de Meijere, A.; Bräse, S.; Oestreich, M. Eds. *Metal-Catalyzed Cross-Coupling Reactions and More 3 Volume Set*; Wiley-VCH: Wenheim, Germany, 2014.
(31) Larhed, M. Ed. *Science of Synthesis: Cross Coupling and Heck-Type Reactions 3, Metal-Catalyzed Heck-Type Reactions and C−C Cross-Coupling via C−H Activation*; Thieme: Stuttgart, Germany, 2013.
(32) Priyanka, S. R. K.; Katiyar, D. Recent Advances in Transition-Metal-Catalyzed Synthesis of Coumarins. *Synthesis* **2016**, *48*, 2303−2322.
(33) Catellani, M.; Chiusoli, G. P.; Marzolini, G.; Rossi, E. Designing a catalytic synthesis of 4-methylcoumarin from *ortho*-iodophenyl 3-butenoate: ring closure and isomerization control. *J. Organomet. Chem.* **1996**, *525*, 65−69.
(34) Battistuzzi, G.; Cacchi, S.; De Salve, I.; Fabrizi, G.; Parisi, L. M. Synthesis of Coumarins in a Molten *n*-Bu_4NOAc/*n*-Bu_4NBr Mixture through a Domino Heck Reaction/Cyclization Process. *Adv. Synth. Catal.* **2005**, *347*, 308−312.
(35) Ulgheri, F.; Marchetti, M.; Piccolo, O. Enantioselective Synthesis of (*S*)- and (*R*)-Tolterodine by Asymmetric Hydrogenation of a Coumarin Derivative Obtained by a Heck Reaction. *J. Org. Chem.* **2007**, *72*, 6056−6059.
(36) Chen, J.; Liu, W.; Zhou, L.; Zhao, Y. Palladium catalyzed Heck-arylation/cyclization cascade: An environmentally benign and efficient synthesis of 4-arylcoumarins in water. *Tetrahedron Lett.* **2018**, *59*, 2526−2531.
(37) Queiroz, M.-J. R. P.; Abreu, A. S.; Calhelha, R. C.; Carvalho, M. S. D.; Ferreira, P. M. T. New strategies for the synthesis of heteroannulated 2-pyridinones, substituted 2-quinolinones and coumarins from dehydroamino acid derivatives. *Tetrahedron* **2008**, *64*, 5139−5146.
(38) Kadnikov, D. V.; Larock, R. C. Palladium-Catalyzed Carbonylative Annulation of Internal Alkynes: Synthesis of 3,4-Disubstituted Coumarins. *J. Org. Chem.* **2003**, *68*, 9423−9432.
(39) Kadnikov, D. V.; Larock, R. C. Palladium-catalyzed carbonylative annulation of terminal alkynes: synthesis of coumarins and 2-quinolones. *J. Organomet. Chem.* **2003**, *687*, 425−435.
(40) Wu, X.-F.; Wu, L.; Jackstell, R.; Neumann, H.; Beller, M. A general palladium-catalyzed carbonylative synthesis of chromenones from salicylic aldehydes and benzyl chlorides. *Chem. − Eur. J.* **2013**, *19*, 12245−12248.
(41) Wienhold, M.; Molloy, J. J.; Daniliuc, C. G.; Gilmour, R. Coumarins by Direct Annulation: β-Borylacrylates as Ambiphilic C3-Synthons. *Angew. Chem., Int. Ed.* **2021**, *60*, 685−689.

https://doi.org/10.1021/acsomega.1c03469
ACS Omega 2021, 6, 29483−29494

(42) Lei, A.; Shi, W.; Liu, W.; Zhang, H.; He, C. *Oxidative Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2016, DOI: 10.1002/9783527680986.
(43) Ferguson, J.; Zeng, F.; Alper, H. Synthesis of Coumarins via Pd-Catalyzed Oxidative Cyclocarbonylation of 2-Vinylphenols. *Org. Lett.* **2012**, *14*, 5602−5605.
(44) Sasano, K.; Takaya, J.; Iwasawa, N. Palladium(II)-Catalyzed Direct Carboxylation of Alkenyl C−H Bonds with CO_2. *J. Am. Chem. Soc.* **2013**, *135*, 10954−10957.
(45) Yamamoto, Y. Synthesis of Heterocycles via Transition-Metal-Catalyzed Hydroarylation of Alkynes. *Chem. Soc. Rev.* **2014**, *43*, 1575−1600.
(46) Trost, B. M.; Toste, F. D.; Greenman, K. Atom Economy Palladium-Catalyzed Formation of Coumarins by Addition of Phenols and Alkynoates via a Net C-H Insertion. *J. Am. Chem. Soc.* **2003**, *125*, 4518−4526.
(47) Aoki, S.; Oyamada, J.; Kitamura, T. Formation of Coumarins by Palladium(II)-Catalyzed Reaction of Phenols with Ethyl Acrylates. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 468−472.
(48) Sharma, U.; Naveen, T.; Maji, A.; Manna, S.; Maiti, D. Palladium-Catalyzed Synthesis of Benzofurans and Coumarins from Phenols and Olefins. *Angew. Chem., Int. Ed.* **2013**, *52*, 12669−12673.
(49) Zhang, X.-S.; Li, Z.-W.; Shi, Z.-J. Palladium-Catalyzed Base-Accelerated Direct C−H Bond Alkenylation of Phenols to Synthesize Coumarin Derivatives. *Org. Chem. Front.* **2014**, *1*, 44−49.
(50) Kim, D.; Min, M.; Hong, S. One-pot catalysis of dehydrogenation of cyclohexanones to phenols and oxidative Heck coupling: expedient synthesis of coumarins. *Chem. Commun.* **2013**, *49*, 4021−4023.
(51) Suna, E.; Shubin, K. Intramolecular Coupling via C(sp^2)-H Activation. In *Science of Synthesis. Cross Coupling and Heck-Type Reactions 3. Metal-Catalyzed Heck-Type Reactions and C-H Couplings via C-H Activation*; Larhed, M., Ed.; Georg Thieme Verlag: Stuttgart, 2013; pp. 643−653.
(52) Carral-Menoyo, A.; Sotomayor, N.; Lete, E. Palladium-catalysed Heck-type alkenylation reactions in the synthesis of quinolines. Mechanistic insights and recent applications. *Catal. Sci. Technol.* **2020**, *10*, 5345−5361.
(53) Ortiz-de-Elguea, V.; Sotomayor, N.; Lete, E. Two consecutive Palladium(II)-promoted C-H alkenylation reactions for the synthesis of 3-alkenylquinolones. *Adv. Synth. Catal.* **2015**, *357*, 463−473.
(54) Carral-Menoyo, A.; Sotorríos, L.; Ortiz-de-Elguea, V.; Diaz-Andrés, A.; Sotomayor, N.; Gómez-Bengoa, E.; Lete, E. Intramolecular Palladium(II)-Catalyzed 6-endo C−H Alkenylation Directed by the Remote *N*-Protecting Group: Mechanistic Insight and Application to the Synthesis of Dihydroquinolines. *J. Org. Chem.* **2020**, *85*, 2486−2503.
(55) Sandhu, S.; Bansal, Y.; Silakari, O.; Bansal, G. Coumarin hybrids as novel therapeutic agents. *Bioorg. Med. Chem.* **2014**, *22*, 3806−3814.
(56) Carral-Menoyo, A.; Misol, A.; Gómez-Redondo, M.; Sotomayor, N.; Lete, E. Palladium(II)-Catalyzed Intramolecular C−H Alkenylation for the Synthesis of Chromanes. *J. Org. Chem.* **2019**, *84*, 2048−2060.
(57) Carral-Menoyo, A.; Ortiz-de-Elguea, V.; Martinez-Nunes, M.; Sotomayor, N.; Lete, E. Palladium-Catalyzed Dehydrogenative Coupling: An Efficient Synthetic Strategy for the Construction of the Quinoline Core. *Mar. Drugs* **2017**, *15*, 276.
(58) García-Rubia, A.; Urones, B.; Gómez-Arrayás, R.; Carretero, J. C. Pd^{II}-Catalyzed C-H Olefination of *N*-(2-Pyridyl)sulfonyl Anilines and Arylalkylamines. *Angew. Chem., Int. Ed.* **2011**, *50*, 10927−10931.
(59) Urones, B.; Gomez-Arrayas, R.; Carretero, J. C. Pd^{II}-Catalyzed Di-*o*-olefination of Carbazoles Directed by the Protecting *N*-(2-Pyridyl)sulfonyl Group. *Org. Lett.* **2013**, *15*, 1120−1123.
(60) García-Rubia, A.; Laga, E.; Cativiela, C.; Urriolabeitia, E. P.; Gómez-Arrayás, R.; Carretero, J. C. Pd-Catalyzed Directed *ortho*-C-H Alkenylation of Phenylalanine Derivatives. *J. Org. Chem.* **2015**, *80*, 3321−3331.
(61) Schiffner, J. A.; Oestreich, M. All-Carbon-Substituted Quaternary Carbon Atoms in Oxindoles by an Aerobic Palladium-(II)-Catalyzed Ring Closure onto Tri- and Tetrasubstituted Double Bonds. *Eur. J. Org. Chem.* **2011**, 1148−1154.
(62) Gordo, J.; Avó, J.; Parola, A. J.; Lima, J. C.; Pereira, A.; Branco, P. S. Convenient Synthesis of 3-Vinyl and 3-Styryl Coumarins. *Org. Lett.* **2011**, *13*, 5112−5115.
(63) Avó, J.; Martins, S.; Parola, A. J.; Lima, J.; Ramalho, J.; Branco, P.; Pereira, A. A Family of Styryl Coumarins: Synthesis, Spectroscopic, Photophysical and Photechemical Properties. *ChemPlusChem* **2013**, *78*, 789−792.
(64) Wang, X.; Li, S.; Pan, Y.; Wang, H.; Chen, Z.; Huang, K. Regioselective Palladium-Catalyzed Decarboxylative Cross-Coupling Reaction of Alkenyl Acids with Coumarins: Synthesis of 3-Styrylcoumarin Compounds. *J. Org. Chem.* **2015**, *80*, 2407−2412.
(65) Jafarpour, F.; Zarei, S.; Barzegar Amiri Olia, M.; Jalalimanesh, N.; Rahiminejadan, S. Palladium-Catalyzed Decarboxylative Cross-Coupling Reactions: A Route for Regioselective Functionalization of Coumarins. *J. Org. Chem.* **2013**, *78*, 2957−2964.
(66) Min, M.; Kima, Y.; Hong, S. Regioselective palladium-catalyzed olefination of coumarins via aerobic oxidative Heck reactions. *Chem. Commun.* **2013**, *49*, 196−198.
(67) Lavis, L. D.; Raines, R. T. Bright Ideas for Chemical Biology. *ACS Chem. Biol.* **2008**, *3*, 142−155.
(68) Lavis, L. D.; Raines, R. T. Bright Building Blocks for Chemical Biology. *ACS Chem. Biol.* **2014**, *9*, 855−866.
(69) Gao, Z.; Hao, Y.; Zheng, M.; Chen, Y. A fluorescent dye with large Stokes shift and high stability: synthesis and application to live cell imaging. *RSC Adv.* **2017**, *7*, 7604−7609.
(70) Boland, G. M.; Donnelly, D. M. X.; Finet, J.-P.; Rea, M. D. Synthesis of neoflavones by Suzuki arylation of 4-substituted coumarins. *J. Chem. Soc. Perkin. Trans. 1* **1996**, *21*, 2591−2597.
(71) Prateeptongkum, S.; Duangdee, N.; Thongyoo, P. Facile Iron(III) Chloride Hexahydrate Catalyzed Synthesis of Coumarins. *ARKIVOC* **2015**, *2015*, 248−258.
(72) Sekino, E.; Kumamoto, T.; Tanaka, T.; Ikeda, T.; Ishikawa, T. Concise Synthesis of Anti-HIV-1 Active (+)-Inophyllum B and (+)-Calanolide A by Application of (−)-Quinine-Catalyzed Intramolecular Oxo-Michael Addition. *J. Org. Chem.* **2004**, *69*, 2760−2767.
(73) Crecente-Campo, J.; Pilar Vázquez-Tato, M.; Seijas, J. A. Microwave-Promoted, One-Pot, Solvent-Free Synthesis of 4-Arylcoumarins from 2-Hydroxybenzophenones. *Eur. J. Org. Chem.* **2010**, 4130−4135.
(74) Tang, B.-C.; Wang, M.; Ma, J.-T.; Wang, Z.-X.; Wu, Y.-D.; Wu, A.-X. Palladium-Acid Co-Catalyzed Cleavage of Alkynoates to Construct Dibenzo[*c,h*]xanthene Derivatives. *Adv. Synth. Catal.* **2018**, *360*, 4023−4028.
(75) Zhao, B.; Xu, B. Visible-Light Promoted Oxidative Cyclization of Cinnamic Acid Derivatives using Xanthone as the Photocatalyst. *Org. Biomol. Chem.* **2021**, *19*, 568−573.

https://doi.org/10.1021/acsomega.1c03469
ACS Omega 2021, 6, 29483−29494