New Method for Preparation of Coumarins and Quinolinones via Pd-Catalyzed Intramolecular Hydroarylation of C−C Triple Bonds

Chengguo Jia, Dongguo Piao, Tsugio Kitamura, and Yuzo Fujiwara*

Department of Chemistry and Biochemistry, Graduate School of Engineering, Kyushu University, Hakozaki, Fukuoka, 812-8581, Japan

yfujitcf@mbox.nc.kyushu-u.ac.jp

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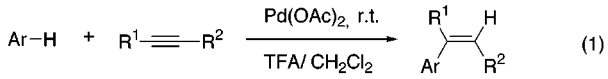
A new and general method has been developed for preparation of coumarins and quinolinones by intramolecular hydroarylation of alkynes. Various aryl alkynoates and alkynanilides undergo fast intramolecular reaction at room temperature in the presence of a catalytic amount of $Pd(OAc)_2$ in a mixed solvent containing trifluoroacetic acid (TFA), affording coumarins and quinolinones in moderate to excellent yields with more than 1000 turnover numbers (TON) to Pd. The methodology proved to tolerate a number of functional groups such as Br and CHO. On the basis of isotope experiments, a possible mechanism involving ethynyl chelation-assisted electrophilic metalation of aromatic C−H bonds by in-situ generated cationic Pd(II) species has been discussed. Also the involvement of vinylcationic species has been suggested.

Introduction

Catalytic activation of aromatic C−H bonds leading to new and useful reactions such as C−C bond formations remains a long-term challenge to chemists and is of considerable interest for the chemical and pharmaceutical industries.[1] It would provide simple, clean, and economic methods for making many useful aryl-substituted compounds directly from simple arenes since no prefunctionalization like halogenation is involved. A few examples of such reactions have been reported,[2,3] the catalytic hydroarylation of C−C multiple bonds through the metalation of aromatic C−H bonds by oxidative insertion of low valent transition metals[2a] and electrophilic Pd(II) substitution[3d] are typical examples, although there are many stoichiometric reactions of aromatic C−H bonds with transition-metal compounds.[1b,8]

Coumarins and quinolinones had stimulated a lot of interest due to their many applications as novel therapeutic agents and prompt the development of general and efficient methods for their preparations.[6] Recently, we have reported the efficient intermolecular hydroarylation of C−C triple bonds in the presence of Pd and Pt catalysts by simple arenes (eq 1).



(1)

We have found that the intramolecular version of this reaction is much faster than intermolecular one, providing coumarins and quinolinones in moderate to excellent yields (eq 2). Although intermolecular and intramolecular hydroarylation of C−C multiple bonds using aryl halides has been well developed,[4,5,6g] to our knowledge, few intramolecular reactions as shown in eq 2 have been reported. Herein we report on the novel intramolecular hydroarylation of activated alkynes, which proceeds with high efficiency (TON more than 1000 to Pd) and remarkable chemoselectivity (compatible to various functional groups) in the presence of a catalytic amount of Pd catalysts. The present reaction offers a unique, concise and straightforward route to coumarins and quinolinones

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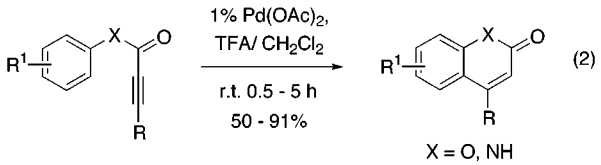
Table 1. Transition-Metal-Catalyzed Cyclization of 4′-*tert*-Butylphenyl Phenylpropiolate (1a) to 4-Phenyl-6-*tert*-butylcoumarin (2a)

entry	catalyst (mol %)	time (h)	yield[a] (%)
1	none	24	no reaction
2	$Pd(OAc)_2$ (1)	0.5	90
3	$Pd(OAc)_2$ (0.06)	60	32
4	$Pd(O_2CCF_3)_2(PPh3)_2$ (1)	0.5	92
5	$Pd(PPh_3)_4$ (1)	1	90
6	$PtCl_2$ (2)/AgOAc (4)	24	46
7	$Ni(OAc)_2$ (2)	24	41
8	$Rh_2(OAc)_4$ (2)	24	30
9[b]	$Pd(OAc)_2$ (1)/CF_3CO_2Na (5)	24	trace
10[b]	$Pd(O_2CCF_3)_2(PPh_3)_2$ (1)	24	trace

[a] The general procedure was followed, and the yields were determined by GC with diethyl phthalate as the internal standard. [b] Acetic acid was employed as the solvent.

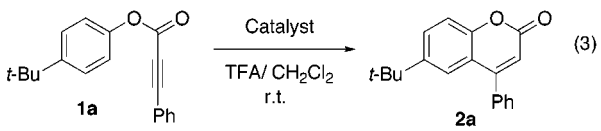
from commercially available simple alkynoic acids, phenols, and anilines.



(2)

Results and Discussion

Optimization of Catalytic Systems. Initially, we investigated the cyclization of the 4′−*tert*-butylphenyl phenylpropiolate (**1a**) to screen the catalytic systems (eq 3).

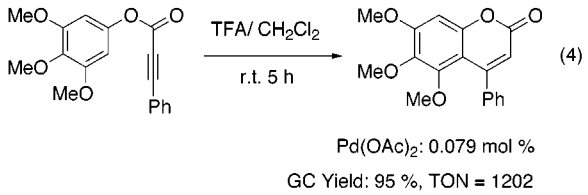


(3)

Treatment of **1a** in the presence of 1 mol % $Pd(OAc)_2$ and trifluoroacetic acid as solvent gave cleanly, within 30 min, **2a** as the sole product in 90% yield (entry 2 in Table 1). No side reaction was observed by analysis of the reaction mixture using ^1H NMR and ^{13}C NMR spectra and GC. Several transition metals such as Pd(II), Pt(II), Rh(II), and Ni(II) compounds, which are known to undergo electrophilic metalation of aromatic C−H bonds in stoichiometric reactions,[1a,3a,b,8] have been selected as catalysts for this reaction. The results are summarized in Table 1. Pd catalysts have been found to be the most active in the reaction (entries 2 and 5 in Table 1). The reaction with Pt(II), Ni(II), or Rh(II) catalysts is slow and incomplete within 24 h (entries 6−8 in Table 1). The catalytic activity of these transition metals decreases in the order Pd(II) > Pt(II) > Ni (II) > Rh(II) (entries 2, 3, and 6−8 in Table 1), in accordance with the activity difference in electrophilic metalation of aromatic C−H bonds by theses metal ions.[1a,8] The reaction is greatly enhanced by increasing the quantity of $Pd(OAc)_2$ (entries 2 and 3 in Table 1). Almost no reaction was observed in the absence of either a transition-metal catalyst or TFA (entries 1, 9, and 10 in Table 1). However, addition of a small amount of CH_2Cl_2 (one-third to TFA by volume) to the reaction system to improve the solubility of reactants has no detrimental effect on the reaction (Table 2).

Synthesis of Coumarins. As summarized in Table 2, various aryl alkynoates[7] undergo smoothly the intramolecular hydroarylation reactions over the catalytic system $Pd(OAc)_2$/TFA. The representative examples in Table 2 illustrate the generality of this reaction. In all cases, the cyclization is highly regioselective, affording kinetically favored six-membered rings.[9] Analysis of the crude reaction mixture using ^1H NMR and ^{13}C NMR spectra and GC separation indicated no any other regioisomers have been observed. The reaction exhibits high chemoselectivity with Br, CHO, or heterocyclic groups in the aromatic moiety (entries 7, 14, and 15 in Table 2) and with either terminal or internal C−C triple bonds, which all proved to be compatible. Most of the reactions (monitored by ^1H NMR spectrum) are very fast and complete within less than 30 min, especially for those substrates bearing electron-rich aromatic rings (entries 1−9 and 15 in Table 2), showing characteristics of electrophilic substitutions. Moreover, the reactivity of 3′-, 2′-, and 4′-methylphenyl phenylpropiolates (**1i**, **1j,** and **1k**) decreases in the order **1i** > **1j** > **1k** (entries 9, 10, and 11), revealing the same characteristics than in electrophilic substitutions. The slow cyclization reaction of **1k** can be improved by adding more catalysts (5%) to the reaction mixture (entries 11 and 12).

The efficiency of this intramolecular reaction (eq 2) can be seen from the cyclization of **1f** to **2f** (eq 4); TON of 1202 can be obtained in the presence of 0.079 mol % of $Pd(OAc)_2$ in 5 h at room temperature.



(4)

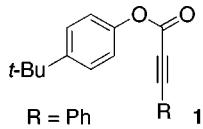
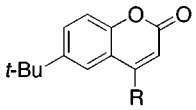
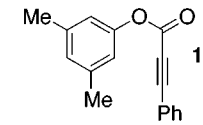
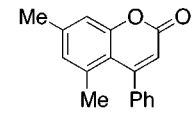
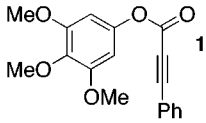
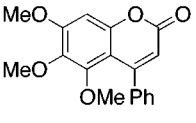
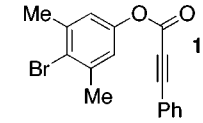
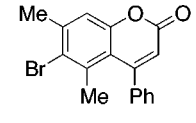
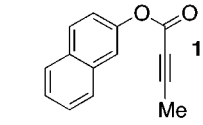
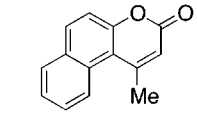
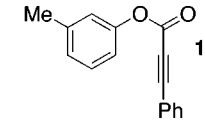
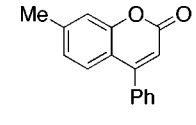
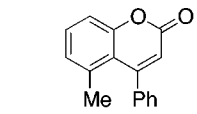
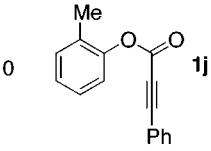
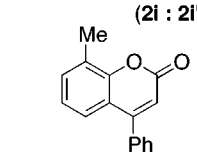
Compared with intermolecular reaction of phenols with acetylenes (Scheme 1 and Table 3), which also provide coumarins, the intramolecular reaction is more than 15 times faster, presumably because the electrophilic metalation of aromatic C−H bonds by Pd(II) species is assisted by ethynyl coordination. The intermolecular reaction can be enhanced by addition of trifluoroacetic anhydride (TFAA) or by using excess of phenol or alkyne (Table 3), but are generally lower yields.

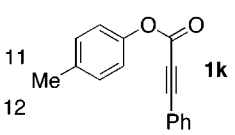
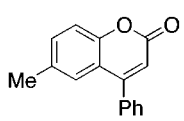
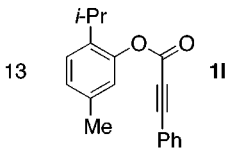
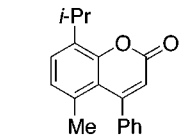
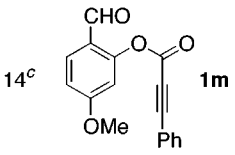
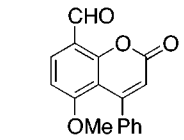
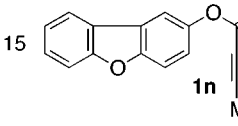
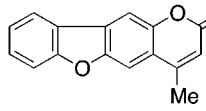
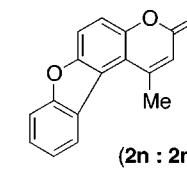
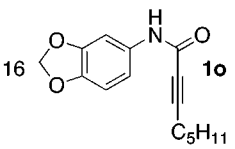
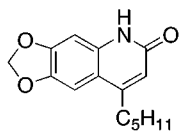
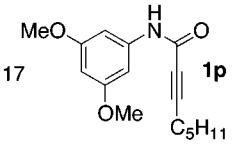
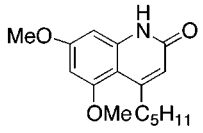
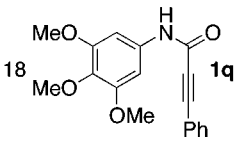
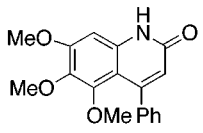
In connection with the intermolecular addition of arenes to C−C double bonds investigated recently (eq 1 in Scheme 2), we have found that the equimolar addition of the electron-rich phenols to 4-methoxycinnamic acid affords two 3,4-dihydrocoumarins (eqs 2 and 3 in Scheme 2), 3,4-dihydro-4-(4-methoxyphenyl)-5,6,7-trimethoxylcoumarin (**2r**), and 3,4-dihydro-4-(4-methoxyphenyl)-6,7-methylenedioxycoumarin (**2s**) in excellent yields at room temperature in the presence of 1 mol % $Pd(OAc)_2$. This reaction supplements our intramolecular reaction as a route to 3,4-dihydrocoumarins.

Synthesis of Quinolinones. The extension of this intramolecular addition to the synthesis of nitrogen-containing heterocycles, 2(1*H*)-quinolinones, has been made possible with the same catalytic system (entries 16, 17, and 18 in Table 2). The alkynanilides prepared from the corresponding alkynoic acid and anilines are readily cyclized in the presence of 1 mol % $Pd(OAc)_2$ in a mixed solvent containing TFA at room temperature,

(9) Endo-cyclization for the formation of six-membered rings is one of the most kinetically favored paths. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

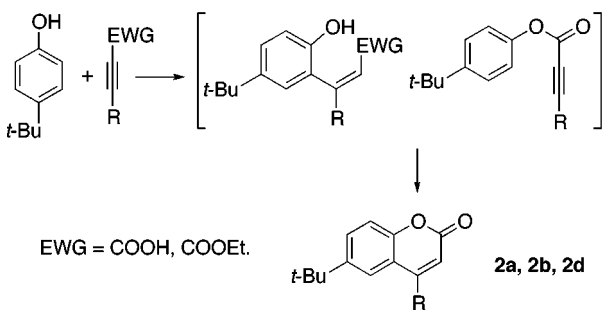
Table 2. Synthesis of Coumarins and Quinolin-2(*1H*)-ones from Pd-Catalyzed Intramolecular Addition Reactions of the Corresponding Aryl Alkynoates and Alkynanilides

Entry	Substrate	Time (h)	Product and Yield (%)[a]
1	 R = Ph	**1a** 0.5	 **2a** 70
2	R = Me	**1b** 0.5	**2b** 90
3	R = C_5H_{11}	**1c** 0.5	**2c** 71
4	R = H	**1d** 0.5	**2d** 60
5		**1e** 0.5	 **2e** 87
6		**1f** 0.5	 **2f** 91
7		**1g** 0.5	 **2g** 85
8		**1h** 0.5	 **2h** 65
9		**1i** 0.5	 **2i**  **2i'** 78 (**2i : 2i'** = 2:1)[b]
10		**1j** 5	 **2j** 79

Entry	Substrate	Time (h)	Product and Yield (%)[a]
11	 **1k**	10	 **2k** 50
12		2	(68)[c]
13	 **1l**	1	 **2l** 75
14[c]	 **1m**	1	 **2m** 71
15	 **1n**	0.5	 **2n**  **2n'** 75 (**2n : 2n'** = 1:3)[b]
16	 **1o**	1	 **2o** 91[d]
17	 **1p**	0.5	 **2p** 85[d]
18	 **1q**	0.5	 **2q** 82[d]

[a] Isolated yields following the general procedure. [b] The ratio was determined by ^{1}H NMR spectra. [c] 5% $Pd(OAc)_2$; yield was determined by ^{1}H NMR. [d] 2% $Pd(OAc)_2$.

Scheme 1. Formation of Coumarins via Pd-Catalyzed Intermolecular Addition of Arene to Alkyne



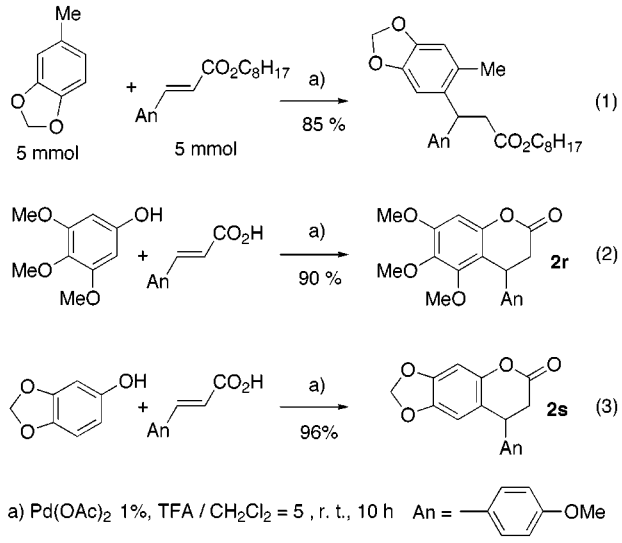
giving 2(1*H*)-quinolinones **2o**, **2p**, and **2q** in good yields. On the other hand, the intermolecular reaction of alkynoic acids and anilines did not afford 2(1*H*)-quinolinones, presumably because the amino groups in anilines are

Table 3. Synthesis of Coumarins by Pd-Catalyzed Intermolecular Reactions (Scheme 1)

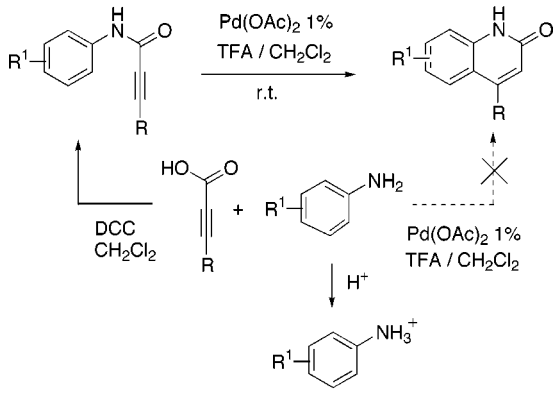
R	EWG	ratio phenol/alkyne	time (h)	product	yield[a] (%)
Ph	CO_2H	2	2	**2a**	60[b]
Me	CO_2H	2	2	**2b**	50[b]
Me	CO_2H	2	24	**2b**	12
H	CO_2Et	6	40	**2d**	71
H	CO_2Et	2	40	**2d**	51
H	CO_2Et	0.5[c]	40	**2d**	62

[a] The reaction was carried out in CH_2Cl_2/TFA (1 mL/5 mL) using 1 mmol of alkyne and 1% $Pd(OAc)_2$ at room temperature; the yields were based on alkyne. [b] TFAA (1 mmol) added. [c] Alkyne 5 mmol was used; yield was based on the phenol.

Scheme 2. Hydroarylation of Alkenes



Scheme 3. Formation of Quinolinones



converted in TFA to ammonium ions which act as electron-withdrawing groups and consequently deactivate the aromatic rings (Scheme 3). Therefore, the intramolecular addition process offers a unique and efficient method for the synthesis of 2(1*H*)-quinolinones.

Possible Mechanism. The *trans*-intermolecular hydroarylation of alkynes with various arenes over the same catalytic system provides a useful method for the preparation of *cis*-arylalkenes. However, the intermolecular reaction is slow in general; the present intramolecular reaction is at least 15 times faster than the intermolecular one, suggesting the electrophilic substitution of arenes by Pd(II) cationic species is assisted by the ethynyl-coordination. In fact, even relatively electron-deficient aromatic rings, such as those in 4′-*tert*-butylphenyl butynoate (**1b**) and 3′-methylphenyl phenylpropiolate (**1i**), can readily undergo the cyclization reactions (entries 2 and 9 in Table 2). The formation of various transition metal-alkyne complexes is well documented.[10] A possible mechanism is outlined in Scheme 4.

The cyclization reactions of 4′-*tert*-butylphenyl phenylpropiolate (**1a**) and 3′,4′,5′-trimethoxyl phenylpropynanilides (**1q**) in CF_3CO_2D as the solvent (eqs 2 and 3 in Scheme 5) reveal that deuterium atoms have incorporated to adducts as vinyl protons at the 3 position of **2a** and **2q** based on the ^1H NMR spectra of the adducts by comparison with the adducts from undeuterated TFA. These results are similar to those in the intermolecular reactions (eq 1 in Scheme 5),[2f,g] indicating possible formation of vinylpalladium complexes such as **C** in Scheme 4.

The highly electrophilic cationic palladium species are expected to be generated in situ through bonding weakly to trifluoroacetate anions by utilizing TFA as a solvent.[11] The cationic species should greatly enhance the metalation of aromatic C−H bonds and at the same time possibly activate C≡C bonds through coordination to generate the acceptors of aryl nucleophiles. A reasonable explanation for the requirement of a large excess of TFA as solvent is the reaction require highly cationic Pd(II) species to facilitate the formation of stable *σ*-aryl-Pd complexes such as **B** (Scheme 4). It has been proved that the acid loss from Pd or Pt trifluoroacetate complexes is irreversible under less acidic conditions,[11c] thus the presence of large excess of TFA is necessary to keep cationic Pd(II) species. Also, a strong acid like TFA would facilitate the hydrolysis of vinyl-M complexes such as **C** to give the final products (route (a) in Scheme 4).[12] Recently, we have found that the intermolecular reaction of phenylacetylene with pentamethylbenzene occurred without $Pd(OAc)_2$. This suggested that the involvement of vinylcationic species either generated from cationic Pd species or strong acid followed by electrophilic cyclization is also possible in the intramolecular reaction (route (b) in Scheme 4).[16]

Experimental Section

General Methods. All the reactions were performed in dry Pyrex tubes, and only under argon atmosphere when Pd(0) catalysts were used. All starting materials and solvents were used as received without further purification unless otherwise indicated. ^1H NMR and ^{13}C NMR spectra were recorded on a 300 FT-NMR (300 MHz) in $CDCl_3$ solution (TMS as an internal standard). The methyl protons of sodium 2,2-dimethyl-2-silapentane-5-sulfonate in a sealed tube containing D_2O are used as an internal standard when the reaction mixture (containing TFA) was directly subjected to ^1H NMR analysis. IR spectra were recorded either neat or as film on sodium chloride plates or as KBr pellets. Melting points were measured with YANACO micro melting apparatus and are uncorrected. The GC analysis was performed using a 2.0 m × 3 mm ∅ stainless steel column packed with Unisole 10T + H_3PO_4 (5 + 0.5)% on 80−100 mesh Uniport HP with a flame ionization detector. For thin-layer chromatography (TLC), Merck precoated aluminum plates were used and detected by a UV lamp.

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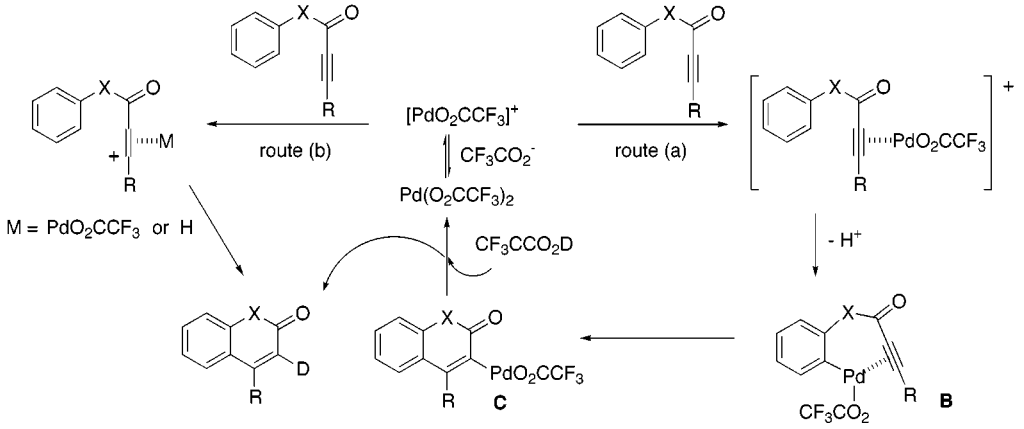
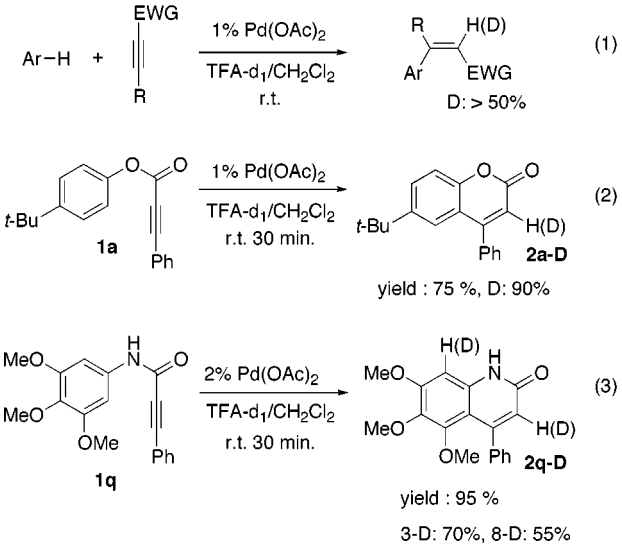
Scheme 4. Possible Mechanism for Intramolecular Hydroarylation of C−C Triple Bonds



Scheme 5. Isotope Reactions



Flash column chromatography was carried out on Wako silica gel, Wakogel C-300, 45−75 μm with hexanes−EtOAc mixtures (3/1 to 12/1, depending on the polarity of the reaction products) as eluent. The aryl alkynoates **1a**−**n** were readily prepared in 63−95% yields from the equimolar reaction of alkynoic acids and phenols in the presence of 1 equiv of dicyclohexylcarbodiimide and 10% of 4-(dimethylamino)pyridine at room temperature according to reported method.[7] The alkynanilides **1o**−**q** were prepared in the similar way, but in the absence of 4-(dimethylamino)pyridine. The detailed spectroscopic data for characterization of the compounds **1a**−**q** are provided in the Supporting Information.

General Procedure for the Preparation of Coumarins and Quinolinones. The aryl alkynoate or alkynanilide (1 mmol), a transition-metal catalyst (1−5 mol %), TFA (1.5 mL), and CH_2Cl_2 (0.5 mL) were mixed in a 25 mL dry Pyrex tube and stirred at room temperature. Stirring continued until the disappearance of the alkynoate as monitored by GC, TLC, or ^{1}H NMR. When the yield was determined by GC, diethyl phthalate was added to the reaction mixture as an internal standard. The reaction mixture was poured into a saturated NaCl aqueous solution and extracted with ether. The ethereal layer was washed with saturated NaCl solution, neutralized with $NaHCO_3$ solution, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the products were purified by flash column chromatography on silica gel and then recrystallization from the ethyl acetate−hexane mixtures provided the desired materials.

In the preparation of quinolinones, the products were precipitated by pouring the reaction mixture into the saturated NaCl solution. The precipitate was washed with water, aqueous $NaHCO_3$ solution, and hexane and then crystallized in a mixed solvent of hexane/chloroform or hexane/ethanol.

A Specific Example. 4-Methyl-6-*tert*-butylcoumarin (**2b**) was prepared from the cyclization of 4′-*tert*-butylphenyl butynoate (**1b**). In a 25 mL dry Pyrex tube, **1b** (0.22 g, 1 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), TFA (1.5 mL), and CH_2Cl_2 (0.5 mL) were mixed and stirred at room temperature for 30 min. The reaction mixture was poured into the saturated NaCl solution and extracted with ether, and the ethereal layer was neutralized and washed with saturated NaCl solution, neutralized with $NaHCO_3$, and dried over Na_2SO_4. Evaporation of solvent and column chromatography on silica gel with hexane/EtOAc as the eluent gave **2b** (0.198 g, 90%).

Intermolecular Reactions of Phenols with Alkynes (or with Alkenes). To a cold mixture of the phenol, $Pd(OAc)_2$, TFA (5 mL), and CH_2Cl_2 (1 mL) on an ice−water bath was added the alkyne (or alkenes) with stirring. After continuous stirring at the same temperature for 5 min, the mixture was warmed to room temperature. Stirring continued until no further increase of the reaction products or the disappearance of one starting material as monitored by GC, TLC, or ^{1}H NMR. When the yield was determined by GC, diethyl phthalate was added to reaction mixture as an internal standard. The workup of reaction mixtures was similar to that for an intramolecular reaction.

Characterization. 4-Phenyl-6-*tert*-butylcoumarin (2a): white crystals; mp 108.3−109.0 °C (*n*-hexane/EtOAc = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 9H, *tert*-butyl), 6.36 (s, 1H, vinyl), 7.35 (d, J = 8.4 Hz, 1H, aryl), 7.54 (m, 6H, aryl), 7.60 (dd, J = 2.4, 8.4 Hz, 1H, aryl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.23, 34.56, 114.99, 116.79, 118.20, 123.15, 128.40, 128.79, 129.47, 129.63, 135.35, 147.19, 152.19, 155.89, 161.00; IR ($CHCl_3$, cm^{-1}) 1726 (C=O). Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.94; H, 6.55.

4-Methyl-6-*tert*-butylcoumarin (2b): light yellow crystals; mp 123.5−124.0 °C (lit.[13] mp 123 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H, *tert*-butyl), 2.46 (d, J = 1.5 Hz, 3H, CH_3), 6.28 (d, J = 1.5 Hz, 1H, vinyl), 7.27 (d, J = 8.7 Hz, 1H, aryl), 7.57 (s, 1H, aryl), 7.60 (d, J = 8.7 Hz, 1H, aryl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.59, 31.33, 34.59, 114.84, 116.55, 119.20, 120.51, 129.33, 147.17, 151.46, 152.59, 161.01; IR ($CHCl_3$, cm^{-1}) 1729 (C=O).

4-Pentyl-6-*tert*-butylcoumarin (2c): 71% yield; colorless crystals; mp 112.6−113.1 °C (hexane/EtOAc = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3H, CH_3), 1.37 (s, 9H, *tert*-butyl), 1.42 (m, 4H, $2CH_2$), 1.73 (m, 2H, CH_2), 2.79 (t, J = 7.8 Hz, 2H, CH_2), 6.27 (s, 1H, vinyl), 7.27 (d, J = 8.7 Hz, 1H, aryl), 7.57 (dd, J = 2.1, 8.7 Hz, 1H, aryl), 7.60 (s, 1H, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.84, 22.32, 27.72, 31.33, 31.48, 31.55, 34.55, 113.62, 116.73, 118.53, 120.30, 129.10, 147.00, 151.68, 156.49, 161.21; IR ($CHCl_3$, cm^{-1}) 1735 (C=O). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.38; H, 8.89.

6-*tert*-Butylcoumarin (2d): light yellow crystals; mp 76.4−78.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H,

t-butyl), 6.41 (d, J = 9.6 Hz, 1H, vinyl), 7.27 (d, J = 8.7 Hz, 1H, aryl), 7.45 (d, J = 2.7 Hz, 1H, aryl), 7.60 (dd, J = 2.7, 8.7 Hz, 1H, aryl), 7.71 (d, J = 9.6 Hz, 1H, vinyl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.27, 34.46, 116.31, 116.36, 118.21, 124.08, 129.45, 143.87, 147.53, 151.99, 161.14; IR ($CHCl_3$, cm^{-1}) 1721 (C═O). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.05; H, 7.11.

4-Phenyl-5,7-dimethylcoumarin (2e): 87% yield; white crystals; mp 96.3−97.2 °C (*n*-hexane/EtOAc = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.18 (s, 1H, vinyl), 6.83 (s, 1H, aryl), 7.09 (s, 1H, aryl), 7.28 (m, 2H, aryl), 7.45 (m, 3H, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.27, 23.26, 115.49, 115.81, 116.11, 116.17, 127.35, 128.53, 129.57, 137.03, 139.61, 142.32, 155.19, 156.73, 160.49. IR ($CHCl_3$, cm^{-1}) 1733 (C═O). Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.55; H, 5.66.

4-Phenyl-5,6,7-trimethoxycoumarin (2f): 91% yield; brown crystals; mp 146.8−147.7 °C (hexane/EtOAc = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.06 (s, 1H, vinyl), 6.73 (s, 1H, aryl), 7.32 (m, 2H, aryl), 7.41 (m, 3H, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.20, 60.84, 61.02, 96.23, 107.22, 113.97, 127.15, 127.45, 127.97, 138.98, 139.40, 151.03, 151.64, 155.33, 156.85, 160.55; IR ($CHCl_3$, cm^{-1}) 1726 (C═O). Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.25; H, 5.23.

4-Phenyl-5,7-dimethyl-6-bromocoumarin (2g): 85% yield; yellow crystals; mp 162.3−163.3 °C (hexane/EtOAc = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 6.27 (s, 1H, vinyl), 7.29 (m, 2H, aryl), 7.47 (m, 3H, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.72, 24.78, 116.91, 117.40, 117.46, 125.78, 127.14, 128.92, 129.06, 136.88, 139.57, 142.71, 153.63, 156.10, 159.92; IR ($CHCl_3$, cm^{-1}) 1728 (C═O). Anal. Calcd for $C_{17}H_{13}O_2Br$: C, 62.03; H, 3.98. Found: C, 62.21; H, 4.18.

1-Methyl-3*H*-naphtho[2,1-*b*]pyran-3-one (2h): 65% yield; light yellow crystals; mp 181.0−182.0 °C (hexane/EtOAc = 5:1) (lit.[14] mp 182.0−183.0 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (s, 3H, CH_3), 6.37 (s, 1H, vinyl), 7.44 (d, J = 9.0 Hz, 1H, aryl), 7.54 (t, J = 8.1 Hz, 1H, aryl), 7.64 (t d, 1H, J = 2.1, 8.1, Hz, aryl), 7.91 (d, J = 8.1 Hz, 1H, aryl), 7.93 (d, J = 8.1 Hz, 1H, aryl), 8.58 (d, 1H, J = 9.0 Hz, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.36, 114.43, 116.45, 117.75, 124.97, 125.35, 127.80, 129.65, 130.18, 131.30, 133.60, 154.07, 154.60, 160.32; IR ($CHCl_3$, cm^{-1}) 1712 (C═O).

A mixture of two inseparable regioisomers, **4-phenyl-7-methylcoumarin (2i)** and **4-phenyl-5-methylcoumarin (2i′)**, was isolated from cyclization of **1i** in 78% yield (**2i/2i′** = 2/1): yellow crystals; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (s, 1.5H, 0.5CH_3), 2.43 (s, 3H, CH_3), 6.21 (s, 0.5H, vinyl), 6.26 (s, H, vinyl), 6.97−7.51 (m, 12H, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.30, 23.21, 113.60, 113.67, 115.29, 116.20, 116.89, 116.96, 117.10, 125.13, 126.41, 127.06, 128.02, 128.12, 128.37, 128.57, 129.38, 131.05, 135.05, 137.27, 139.13, 142.94, 153.96, 154.74, 155.40, 156.47, 159.89, 160.72. Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.22; H, 5.16.

4-Phenyl-8-methylcoumarin (2j): 79% yield; white crystals; mp 101.3−102.2 °C (hexane/EtOAc = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3H, CH_3), 6.37 (s, 1H, vinyl), 7.12 (t, J = 7.2 Hz, 1H, aryl), 7.32 (d, J = 8.1 Hz, 1H, aryl), 7.43 (d, J = 8.1 Hz, 1H, aryl), 7.45 (m, 2H, aryl), 7.52 (m, 3H, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.77, 114.87, 118.74, 123.59, 124.77, 126.68, 128.45, 128.77, 129.52, 133.22, 135.57, 152.49, 156.05, 160.89; IR ($CHCl_3$, cm^{-1}) 1724 (C═O). Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 80.50; H, 5.13.

4-Phenyl-6-methylcoumarin (2k): 50% yield; white crystals; mp 134.7−135.1 °C (hexane/EtOAc = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3), 6.35 (s, 1H, vinyl), 7.25 (s, 1H, aryl), 7.30 (d, J = 8.1 Hz, 1H, aryl), 7.36 (dd, J = 2.1, 8.1 Hz, 1H, aryl), 7.45 (m, 2H, aryl), 7.54 (m, 3H, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.88, 115.18, 117.01, 118.65, 126.66, 128.39, 128.82, 129.55, 132.88, 133.83, 135.35, 152.30, 155.58, 160.93; IR ($CHCl_3$, cm^{-1}) 1724. (C═O). Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.14; H, 5.11.

4-Phenyl-5-methyl-8-isopropylcoumarin (2l): 75% yield; light yellow crystals; mp 139.6−140.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, 6H, J = 6.9 Hz, 2CH_3), 1.79 (s, 3H, CH_3), 3.68 (m, 1H, CH), 6.25 (s, 1H, vinyl), 6.98 (d, J = 7.5 Hz, 1H, aryl), 7.27 (m, 2H, aryl), 7.35 (d, J = 7.5 Hz, 1H, aryl), 7.45 (m, 3H, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.69, 23.28, 26.51, 116.94, 117.62, 127.35, 127.94, 128.42, 128.54, 128.64, 134.63, 134.78, 139.83, 152.13, 157.16, 160.23; IR ($CHCl_3$, cm^{-1}) 1726 (C═O). Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.93; H, 6.51.

4-Phenyl-5-methoxy-8-formylcoumarin (2m): 71% yield; yellow crystals; mp 206.3−208.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (s, 3H, OCH_3), 6.25 (s, 1H, vinyl), 6.78 (d, J = 9.0 Hz, 1H, aryl), 7.28 (m, 2H, aryl), 7.42 (m, 3H, aryl), 8.11 (d, J = 9.0 Hz, 1H, aryl), 10.62 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.84, 106.69, 108.66, 116.21, 117.66, 126.82, 127.59, 128.27, 132.13, 138.96, 155.10, 157.22, 158.60, 161.91, 186.71. Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.44; H, 4.36.

A mixture of two inseparable regioisomers, **4-methyl-2*H*-benzofuro[3,2-*g*]-benzopyran-2-one (2n)**[15] and **4-methyl-2*H*-benzofuro[2,3-*f*]-benzopyran-2-one (2n′)**, were isolated in 75% total yield (**2n/2n′** = 1/3) from cyclization of **1n**: orange crystals; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 1H, 0.33CH_3), 2.91 (s, 3H, CH_3), 6.32 (s, 0.33H, vinyl), 6.36 (s, 1H, vinyl), 6.78 (d, J = 9.0 Hz, 1H, aryl), 7.33−7.72 (m, 8H, aryl), 7.91 (d, J = 7.8 Hz, 1H, aryl), 8.27 (d, J = 8.1 Hz, 1H, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.95, 25.78, 106.09, 107.98, 111.84, 112.33, 114.81, 115.59, 115.93, 116.14, 117.39, 118.94, 119.77, 120.55, 121.52, 122.82, 123.06, 123.19, 124.79, 127.55, 127.77, 129.03, 149.53, 151.32, 152.11, 152.23, 152.36, 152.95, 157.04, 157.65, 160.18, 160.83.

4-Pentyl-6,7-methylenedioxyquinolin-2(1*H*)-one (2o): 91% yield; white crystals; mp 229.1−230.3 °C (chloroform/hexane = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 6.9 Hz, 3H, CH_3), 1.39 (m, 4H, 2CH_2), 1.69 (m, 2H, CH_2), 2.75 (t, J = 7.8 Hz, 2H, CH_2), 6.03 (s, 2H, OCH_2), 6.47 (s, 1H, vinyl), 6.97 (s, 1H, aryl), 7.07 (s, 1H, aryl), 12.98 (br, 1H, NH, D/H exchangeable in D_2O/ $CDCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.92, 22.47, 28.53, 31.65, 32.78, 96.81, 101.68, 114.38, 116.77, 135.78, 144.43, 150.38, 153.03, 164.46; IR ($CHCl_3$, cm^{-1}) 1654 (C═O). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 68.85; H, 6.55; N, 5.38.

4-Pentyl 5,7-dimethoxyquinolin-2(1*H*)-one (2p): 85% yield; light yellow crystals; mp 180.3−181.6 °C (chloroform/hexane = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 7.1 Hz, 3H, CH_3), 1.37 (m, 4H, 2CH_2), 1.60 (m, 2H, CH_2), 2.97 (d, J = 7.6 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.24 (d, J = 2.1 Hz, 1H, aryl), 6.30 (s, 1H, vinyl), 6.53 (d, J = 2.1 Hz, 1H, aryl), 12.77 (br, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.08, 22.54, 30.36, 31.97, 37.16, 55.43, 55.65, 91.43, 94.71, 105.86, 116.88, 142.40, 155.41, 158.82, 161.82, 164.50; IR ($CHCl_3$, cm^{-1}) 1658 (C═O). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.52; H, 7.62; N, 5.04.

4-Phenyl 5,6,7-trimethoxyquinolin-2(1*H*)-one (2q): 82% yield; white crystals; mp 262.2−264.2 °C (chloroform/hexane = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.40 (s, 1H, vinyl), 6.80 (s, 1H, aryl), 7.35 (m, 5H, aryl), 13.17 (br, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.25, 60.74, 61.04, 94.46, 108.54, 119.74, 127.22, 127.51, 136.97, 138.63, 141.01, 150.89, 152.58, 156.63, 163.91; IR ($CHCl_3$, cm^{-1}) 1662 (C═O). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 68.14; H, 5.61; N, 4.28.

3,4-Dihydro-4-(4-methoxyphenyl)-5,6,7-trimethoxycoumarin (2r): 90% yield; off-white crystals; mp 96.7−97.4 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.02 (d, J = 8.7 Hz, 2H, aryl), 6.80 (d, J = 8.7 Hz, 2H, aryl), 6.51 (s, 1H, aryl), 4.53 (t, J = 4.8 Hz, 1H, CH), 3.86 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 2.97 (d, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.42, 158.57, 153.47, 150.38, 147.51, 138.87, 133.67, 127.67, 114.18, 111.20, 96.68, 60.97, 60.86, 55.98, 55.07, 37.25, 34.57; IR ($CHCl_3$, cm^{-1}) 1770 (C═O). Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.91. Found: C, 66.12; H, 5.85.

3,4-Dihydro-4-(4-methoxyphenyl)-6,7-methylenedioxycoumarin (2s): 96% yield; white crystals; mp 134.6−135.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, J = 8.7 Hz, 2H, aryl),

6.86 (d, J = 8.7 Hz, 2H, aryl), 6.62 (s, 1H, aryl), 6.38 (s, 1H, aryl), 5.92 (s, 2H, CH_2O_2), 4.16 (t, J = 6.3 Hz, 1H, CH), 3.78 (s, 3H, CH_3), 2.95 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.63, 158.90, 147.33, 146.01, 144.29, 132.29, 128.41, 118.31, 114.38, 107.14, 101.59, 98.95, 55.17, 39.71, 37.05; IR ($CHCl_3$, cm^{-1}) 1768 (C=O). Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.75. Found: C, 68.20; H, 4.84.

2′-Ethylhexyl 3-(2-Methyl-4,5-methylenedioxyphenyl)-3-(4-methoxyphenyl)propionate: light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, J = 7.2 Hz, 3H, CH_3), 0.87 (t, J = 7.2 Hz, 3H, CH_3), 1.10−1.45 (m, 9H, alkyl), 2.22 (s, 3H, CH_3), 2.92 (dd, J = 1.2, 7.8 Hz, 2H, CH_2C=O) 3.74 (s, 3H, OCH_3), 3.90 (d, J = 5.4 Hz, 2H, OCH_2), 4.61 (t, J = 7.8 Hz, 1H, CH), 5.86 (q, J = 2.4 Hz, 2H, CH_2O_2), 6.73 (s, 1H, aryl), 6.60 (s, 1H, aryl), 6.78 (d, J = 9.0 Hz, 2H, aryl), 7.08 (d, J = 9.0 Hz, 2H, aryl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.82, 14.03, 19.61, 22.87, 23.58, 28.83, 30.23, 38.65, 41.39, 42.01, 55.10, 66.68, 100.67, 106.81, 110.74, 113.82, 128.58, 129.10, 134.68, 135.26, 145.58, 145.83, 158.02, 171.99; IR (neat, cm^{-1}) 1734 (C=O). Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.03. Found: C, 73.42; H, 8.05.

Cyclization of 4′-*tert*-Butylphenyl Phenylpropiolate (1a) in TFA-d_1. In a 25 mL dry Pyrex tube, **1a** (0.27 g, 1 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), TFA-d_1 (1.5 mL), and CH_2Cl_2 (0.5 mL) were mixed and stirred at room temperature for 30 min. The reaction gave **2b**−**d** in 90% yield based on ^{1}H NMR spectra with ethyl phthalate as the internal standard. The ^{1}H NMR spectrum of **2a**−**d** is similar to that of 4-phenyl-6-*tert*-butylcoumarin (**2a**) except for the decrease in intensity of a singlet vinylic resonance at 6.36 ppm based on the integration of hydrogens of the *tert*-butyl group: 1.27 (s, 9H, *tert*-butyl), 6.36 (s, 0.1H, vinyl, 90% D-incorporated), 7.35 (d, J = 8.4 Hz, 1H, aryl), 7.54 (m, 6H, aryl), 7.60 (dd, J = 2.4, 8.4 Hz, 1H, aryl).

Cyclization 3′,4′,5′-Trimethoxyl Phenylpropynanilide (1q) in TFA-d_1. In a 25 mL dry Pyrex tube, **1q** (0.22 g, 1 mmol), $Pd(OAc)_2$ (4 mg, 0.01 mmol), TFA-d_1 (1.5 mL), and CH_2Cl_2 (0.5 mL) were mixed and stirred at room temperature for 30 min. The reaction gave **2q-D** in 95% yield based on ^{1}H NMR spectra with ethyl phthalate as the internal standard. The ^{1}H NMR spectrum of **2q-D** after workup is similar to that of 4-phenyl 5,6,7-trimethoxyquinolin-2(*1H*)-one (**2q**) except for the decrease in intensity of both a singlet vinylic resonance at 6.40 ppm and a singlet aryl resonance at 6.80 ppm based on the integration of hydrogens in methoxyl group: 3.25 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.40 (s, 0.3H, vinyl, 70% D-incorporated), 6.80 (s, 0.45 H, aryl, 55% D-incorporated), 7.35 (m, 5H, aryl), 13.17 (br, 1H, NH).

Supporting Information Available: Detailed spectroscopic data for characterization of starting materials **1a**−**q**. These materials are available free of charge via the Internet at http://pubs.acs.org.

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