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Atom Economy. Palladium-Catalyzed Formation of Coumarins by Addition of Phenols and Alkynoates via a Net C−H Insertion

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Abstract: A strategy to achieve ortho substitution of phenols initiated by an ortho-palladation to create coumarins was examined. Indeed, treatment of alkynoates with electron-rich phenols in the presence of a palladium catalyst and an acid does generate coumarins. The scope of the reaction with respect to the phenol and the alkynoates is defined. With unsymmetrical aromatic substrates, generally good regioselectivity that reflects the HOMO coefficients can be observed. In the course of these studies, numerous important naturally occurring coumarins have been synthesized, including fraxinol methyl ether, ayapin, herniarin, xanthoxyletin, and alloxanthoxyletin. The fact that a Pd(0) is the precatalyst rather than a Pd(+2) species and that an acid that reduces Pd(+2) salts, formic acid, functions better than other carboxylic acids raises doubts about the initial working hypothesis. A novel mechanism involving a palladium phenoxide formed from a hydridopalladium carboxylate and phenol is invoked to rationalize the results.

Introduction

The conversion of aromatic C−H bonds into C−C bonds classically has involved Friedel−Crafts reactions that most normally require stoichiometric quantities of the Lewis acids, although recent advances notably with rare earth triflates are addressing this problem.[1] The harshness of the conditions has led to increasing use of a two-step protocol—formation of a C−X bond by electrophilic aromatic substitution followed by replacement of the C−X bond with a C−C bond by a transition-metal-catalyzed coupling reaction. Formation of substituted arenes by direct substitution of an aromatic C−H bond with a C−C bond under mild conditions where nothing else is needed catalytically streamlines this process. Our efforts directed toward the synthesis of the coumarin natural products inspired us to envision utilizing such a process to directly prepare coumarins by the reaction of phenols with alkynoates. The general biological importance of coumarins makes the development of milder strategies for their direct synthesis significant. Since the first isolation of coumarin in 1820, over 1400 natural coumarins have been isolated. Their biological activities include anticoagulation, antibiotic, antipsoriasis, antitumor, anti-HIV, etc. Surprisingly, despite their importance, few mild ways for their direct synthesis exist. The most common is undoubtedly the Pechmann condensation and its variants; however, harshness of the quite strong acid conditions limits its scope. Our initial approach to this problem focused on the well-documented electrophilic metalation (*ortho*-palladation) of the aromatic ring.[2] Furthermore, the insertion of an alkyne into the palladium−aryl bond, a carbopalladation, has also been reported.[3] We thus turned our attention to the use of palladium catalysts to accomplish the transformation.

Results

Our preliminary catalytic system[4] employed palladium(+2) acetate, in acetic acid, as the catalyst.[5] However, under these conditions no coupling occurred between electron-rich phenol[6] **1** and ethyl propynoate (**2**) (Table 1, entries 1,2). Remarkably, conducting the reaction using formic acid in place of acetic acid afforded 5,7-dimethoxycoumarin (**3**)[7] in 40% yield (entry 3), which could be improved to 62% by lowering the palladium acetate loading to 10 mol % (entry 5). The dramatic difference in the reactivity of palladium acetate in formic acid, compared to acetic acid, led us to conjecture that perhaps the formic acid was reducing the palladium(+2) salt to palladium(0).[8] In support of this deduction, using 5 mol % of $(dba)_3Pd_2{\cdot}CHCl_3$ as catalyst, in formic acid, afforded 88% yield of coumarin **3** (entry 11).

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(4) For a preliminary communication of the results described in this section, see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *118*, 6305.

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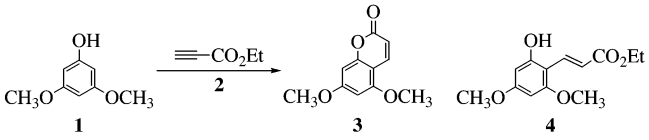
10.1021/ja0286573 CCC: $25.00

Table 1. Palladium Catalyzed Preparation of 5,7-Dimethoxycoumarin

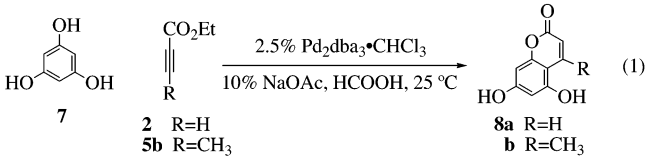


entry	Pd source (mol %)	mol % NaOAc	solvent, temp, °C	3	4
1	$Pd(OAc)_2$ (30)	50	CH_3CO_2H, 25		
2	$Pd(OAc)_2$ (30)	50	CH_3CO_2H, 70		
3	$Pd(OAc)_2$ (30)	50	HCOOH, 50	40	
4		20	HCOOH, 50		
5	$Pd(OAc)_2$ (10)	20	HCOOH, 50	62	
6	$Pd(OAc)_2$ (10)	20	1:1 HCOOH/DMF, 35	35	
7	$Pd(OAc)_2$ (10)	20	1 equiv of HCOOH/CH_2Cl_2, 50	18	
8	$Pd(OAc)_2$ (10)	20	1:1 HCOOH/CH_2Cl_2, 25	42	
9	$Pd(OAc)_2$ (10)	20	1:1 HCOOH/PhH, 50	45	16
10	$Pd(OAc)_2$ (20)	40	1:1 HCOOH/EtOAc, 50		
11	$Pd_2(dba)_3$ (5)	20	HCOOH, 50	88	
12	$Pd_2(dba)_3$ (2.5)	20	HCOOH, 25	77	
13	$Pd_2(dba)_3$ (5.0)	20	CH_3CO_2H, 25	41	
14	$Pd_2(dba)_3$ (5.0)	20	TFA/DMF, 25		

Returning to acetic acid as solvent, now with a palladium(0) catalyst, decreased the isolated yield of **3** (entry 13). Since formic acid is a slightly stronger acid than acetic acid, this difference in the acidity could be the source of the enhanced reactivity in formic acid. However, use of a stronger acid, trifluoroacetic acid ($pK_a = -0.25$), did not afford any of the desired coumarin (entry 14). This is consistent with formic acid serving the role of a reductant.

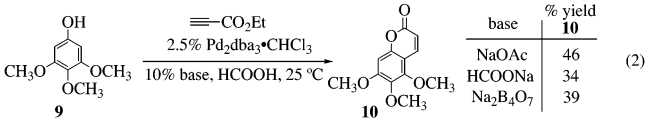
The tolerance of the palladium-catalyzed coumarin-forming reaction to substitution on the alkynoate was examined by using alkynes **5a**−**g** (Table 2). The palladium-catalyzed reactions proceed well with unsubstituted (**2**) as well as aryl- and alkyl-substituted (**5a**−**e**, **h**) alkynoates. Most notably is the successful coupling reaction of methyl 6-cyanohex-2-ynoate (**5d**) with phenol **1**. The traditional Pechmann cyclization precludes the use of nitrile groups as they can be hydrolyzed under the strongly acidic reaction conditions. In contrast to such strong acid conditions, these reactions are best performed in the presence of sodium acetate which presumably plays the role of a general base cocatalyst to promote shuttling of protons required in these reactions (vide infra). On the other hand, silyl-substituted alkynoate **5e** also participates in the palladium-catalyzed coupling, but in this case the isolated coumarin (**3**) no longer contains the silyl group. The removal of the silyl group presumably occurs by protonolysis[10] of the sp carbon−silicon bond prior to coumarin formation. The palladium-catalyzed reaction fails to proceed with alkynoates substituted with potential nucleophiles, such as carboxylic acids (**5f**) or free alcohols (**5g**). In both cases, the phenol is recovered unreacted and the β-ketoester derived from hydration of the alkynoate is isolated.

Despite the lower catalyst loading, the palladium(0) system was generally more efficient than the palladium(+2) catalyst. For example, the reaction of **1** with ethyl carbonate protected alkynol **5c** (Table 2, entries 4 and 5) produced coumarin **6c** in 58% yield with the $Pd_2(dba)_3$ catalyst and 41% using $Pd(OAc)_2$. Using the optimized palladium(0) catalyzed conditions, we also found that it is not necessary that the phenol be substituted with methyl ethers. Thus, phloroglucinol (**7**) reacts with ethyl propynoate (**2**) and ethyl butynoate (**5b**), catalyzed by $Pd_2(dba)_3$, to afford 5,7-dihydroxy coumarins **8a**[11] and **8b**[12] in 79% and 83% yield, respectively (eq 1).



(1)

Increasing the electron richness of the aromatic ring, as in the case of 3,4,5-trimethoxyphenol **9,** has somewhat of a deleterious effect. Thus, fraxinol methyl ether (**10**), a coumarin isolated from *Pelargonium reniforme* and *Pelargonium sidoides*,[13] could be prepared in 46% yield by the $Pd_2(dba)_3$ catalyzed addition of phenol **9** to ethyl propynoate (eq 2). In contrast, the Pechmann condensation of 3,4,5-trimethoxyphenol (**9**) is often complicated by mixtures of coumarins and chromones,[14] which can be circumvented using a four-step protocol from **9**.[15a] Envisioning that increased acid sensitivity in the fomation of **10** due to its increased electron richness may be responsible for the lower yields led to examination of any base effect. However, varying the base from sodium acetate to sodium formate or sodium tetraborate had only a minor, albeit deleterious, effect on the isolated yield of **10**.



base	% yield 10
NaOAc	46
HCOONa	34
$Na_2B_4O_7$	39

(2)

The question of regioselectivity is of both synthetic and mechanistic interest. An initial test case was sesamol (**11**) whose coumarin analogue **12** is ayapin,[16] a naturally occurring coumarin exhibiting hemostatic and antibiotic activity.[17] Preparation of ayapin (**12**) by the reaction of sesamol (**1**) with ethyl 3,3-diethoxypropanoate using the traditional Pechmann condensa-

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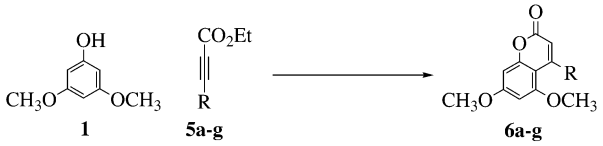
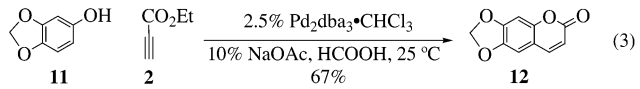
Table 2. Palladium-Catalyzed Preparation of 4-Substituted 5,7-Dimethoxycoumarins



1 **5a-g** **6a-g**

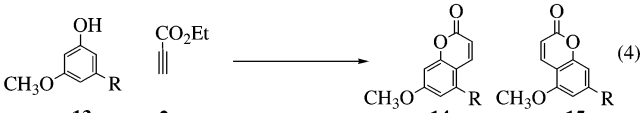
entry	R	reaction conditions	% yield (product)
1	**a,** C_6H_5	10% $Pd(OAc)_2$, 20% NaOAc, HCOOH, 35 °C	69 (**6a**)
2	**b,** CH_3	10% $Pd(OAc)_2$, 20% NaOAc, HCOOH, 35 °C	51 (**6b**)
3		2.5% $Pd_2(dba)_3$, 10% NaOAc, HCOOH, 25 °C	63 (**6b**)
4	**c,** $(CH_2)_2OCO_2Et$	10% $Pd(OAc)_2$, HCOOH, 25 °C	41 (**6c**)
5		2.5% $Pd_2(dba)_3$, HCOOH, 25 °C	58 (**6c**)
6	**d,** $(CH_2)_3CN$	2.5% $Pd_2(dba)_2$ HCOOH, 25 °C	67 (**6d**)
7	**e,** $Si(C_6H_5)(CH_3)_2$	10% $Pd(OAc)_2$, 20% NaOAc,HCOOH, 25 °C	53 (**4**)
8	**f,** $(CH_2)_2CO_2t$-Bu	10% $Pd(OAc)_2$, 20% NaOAc,HCOOH, 50 °C	
9	**g,** CH_2OH	10% $Pd(OAc)_2$, 20% NaOAc,HCOOH, 50 °C	
10		2.5% $Pd_2(dba)_3$, 10% NaOAc,HCOOH, 35 °C	

tion is complicated by formation of an ayapin dimer.[18] Thus, a three-step synthesis in which the coumarin ring is formed by a Wittig reaction[16d] or a four-step synthesis using an intramolecular Claisen condensation is used to prepare coumarin **12**.[16e] Using the palladium-catalyzed coumarin formation, ayapin (**12**) is available in a single step from sesamol (**11**) and ethyl propynoate (**2**) in 67% yield (eq 3). In this reaction, the coumarin formation occurred with complete regioselectivity for the addition of the alkynoate to form the linear coumarin product.



11 **2** 2.5% Pd_2dba_3•$CHCl_3$, 10% NaOAc, HCOOH, 25 °C, 67% **12** (3)

One way to interpret the result of eq 3 considers the addition of the alkynoate to sesamol (**11**) to have occurred selectively to the sterically less demanding ortho position. To further examine the factors responsible for the regioselectivity of coumarin formation, the palladium-catalyzed coupling of 3-methoxyphenols **13a,b** with ethyl propynoate (**2**) was examined (eq 4). Palladium(+2) acetate catalyzed reaction of phenol **13a** produced a 7.4:1 mixture of herniarin (**14a**),[19] a coumarin possessing antiinflammatory activity,[20] to the regioisomeric coumarin **15a.**[21] Switching to the palladium(0) catalyst system diminished both the yield and regioselectivity of the reaction.



13 **2** **14** **15** (4)

R	conditions	isolated yield (%) 14	15
a H	10% $Pd(OAc)_2$, HCOOH, 35 °C	52	7
	2.5% $Pd_2(dba)_3$, 10% NaOAc, HCOOH, 25 °C	44	8
b CH_3	2.5% $Pd_2(dba)_3$, 10% NaOAc, HCOOH, 25 °C	72	10

The reaction of orcinol monomethyl ether (**13b**) showed a similar 7.2:1 regioselectivity for coumarin formation of coumarins **14b**[22] and **15b**,[22a] i.e., ortho to the sterically more demanding methyl group (eq 4). In comparison, the two-step modified Pechmann condensation of **13a** with 3-ethoxyacryloyl chloride affords a 9:1 mixture of **14a** and **15a** in slightly lower yield.[18b] The fact that the presence of the methyl group did not significantly alter the regioselectivity suggests that electronic effects (vide infra) have a greater impact on the regioselectivity than do steric factors. The regioselectivity of the reaction was confirmed by NOE experiments on the product coumarins as summarized in Figure 1.

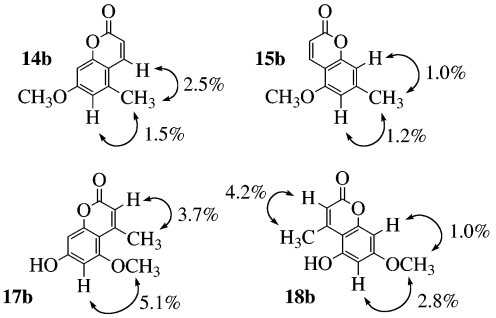


Figure 1. Confirmation of regioselectivity of coumarin formation by NOE.

The coumarin formation starting from 5-methoxyresorcinol (**16**) represents a more challenging example of regioselectivity. Palladium-catalyzed reaction of **16** with ethyl propynoate (**2**) produced a 71% yield of a 1.2:1 mixture of regioisomeric coumarins **17a**[23] and **18a**[24] (eq 5). The palladium-catalyzed reaction of **16** and ethyl butynoate (**5b**) afforded a 62% yield

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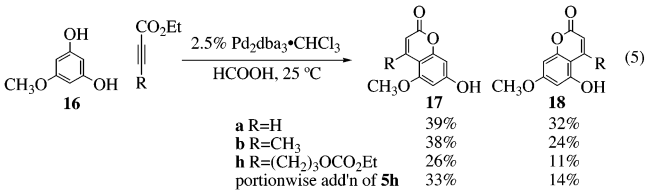
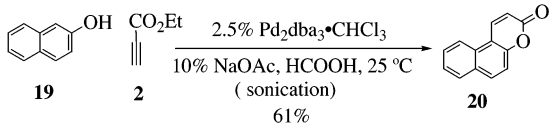
of coumarins **17b** and **18b**[21c,25] with a slightly improved regioselectivity of 1.6:1. In contrast, the traditional Pechmann condensation of ethyl acetoacetate and **16** affords a 65% yield of a 1.1:1 mixture of hydroxycoumarins **17b**:**18b**.[25] The regiochemistry of the products was confirmed by NOE experiments (Figure 1). Unfortunately, irradiation of the 4-methyl substituent showed enhancement of only the 3-hydrogen. Irradiation of the methoxy group, however, clearly confirms the regiochemistry of the products. Reaction of **16** with the sterically more demanding alkynoate (**5h**) is more regioselective, affording a 2.4:1 mixture of coumarins **17h**:**18h** in 37% combined yield. This yield could be improved to 47% by portionwise addition of 2.5 equiv of the alkynoate, without deterioration of the regioselectivity (2.4:1).



(5)

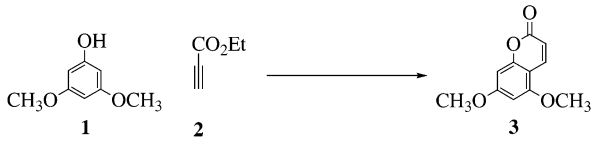
β-Naphthol (**19**) is reported to be an unsuitable substrate for the traditional Pechmann condensation.[26] Therefore, preparation of 5,6-benzocoumarins have generally relied on multistep sequences based on formylation of **19** followed by addition to the aldehyde.[27] Alternatively, a two-step protocol involving addition of **19** to triethyl orthoacrylate followed by dehydrogenation is reported to afford **20**.[28] Utilizing the palladium-catalyzed reaction, benzocoumarin **20**[29] is prepared in 46% yield as a single regioisomer, by the reaction of **19** with ethyl propynoate (**2**) (eq 6). Sonication of the reaction mixture, which increases the solubility of β-naphthol (**19**) in formic acid, improved the isolated yield of **20** to 61%. Surprisingly, all attempts to react β-naphthol (**19**) with substituted alkynoates **5a** and **b** failed to produce any of the desired 4-substituted benzocoumarins.



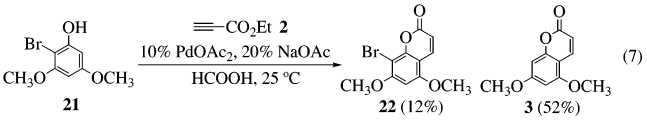
(6)

The potential utility of bromocoumarins for further elaboration led to consideration of the chemoselectivity with respect to aryl bromides.[30] As shown in eq 7, palladium acetate catalyzed reaction of bromophenol **21**[31] with ethyl propynoate (**2**) afforded a 1:5 mixture of brominated **22** and debrominated **3** coumarin products. Thus, bromine, ortho to the hydroxyl group suffers hydrogenolysis competitive with coumarin formation.

Table 3. Alternative Metals for Coupling of Phenols and Alkynoates

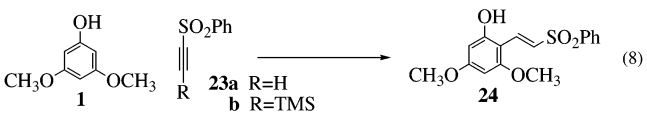


entry	reaction conditions	% yield **3**
1	10% $Ni(OAc)_2$, 40% NaOAc, HCOOH, 50 °C	
2	10% $PtCl_2$, 40% NaOAc, HCOOH, 50 °C	49
3	1% $(PPh_3)RhCl$, CH_3CN, 70 °C	
4	10% $RuCl_3$, 30% NH_4PF_6, THF, 60 °C	
5	10% $CpRu(CH_3CN)_3PF_6$, acetone, 25 °C	
6	1eq $In(OTf)_3$, THF, 25 °C	
7	1eq $Hg(OAc)_2$, THF, 25 °C	
8	1eq AgBF4, THF, 25 °C	92
9	1eq $Ag(O_2CCF_3)$, THF, 25 °C	65
10	10% $AgBF_4$, THF, 25 °C	30
11	10% $AgBF_4$, 10% *o*-DPPB, THF, 25 °C	40
12	10% $AgBF_4$, 10% *o*-DPPPy,10% HOAc, THF, 25 °C	7
13	10% AgBF4, 10% *o*-DPPPy,10% CSA, THF, 25 °C	59



(7)

As expected, electron-deficient phenols, such as 2-acetylphenol, fail to participate in the palladium-catalyzed coumarin formation. In contrast to 3-methoxy-5-methylphenol (**13b**) (eq 4), no coupling is observed between 3-methylphenol and ethyl propynoate (**2**). Similarly, while 3-methoxyphenol (**13a**) reacts with ethyl propynoate (eq 4), changing the phenol to 4-methoxyphenol failed to produce any coupling reaction with the same alkynoate. The reaction of 3-acetamidophenol with ethyl propynoate, however, produces a complex mixture in which both reactants have been consumed. Thus far, the palladium-catalyzed reaction has been limited to the addition of phenols to alkynoate esters. Changing the acceptor to 3-butyn-2-one failed to produce any coupling products in the Pd_2dba_3-catalyzed coupling with 3,5-dimethoxyphenol (**1**). Similarly, the reaction of **1** with phenylacetylene also resulted in recovery of the starting phenol. However, $Pd(OAc)_2$ catalyzed addition of **1** to ethynyl sulfone **23a**[32] did produce an 18% yield of (*E*)-vinyl sulfone **24** (eq 8). The analogous Pd_2dba_3-catalyzed reaction produced only a trace of **24**. The instability of ethynyl sulfone **23a** to the acidic reaction conditions prompted us to utilize trimethylsilyl protected alkyne **23b**. However, under the reaction conditions examined, no coupling products between **23b** and **1** were isolated.



(8)

Other metal catalysts were screened for their ability to catalyze the coupling of 3,5-dimethoxyphenol (**1**) and ethyl propynoate (**2**) (Table 3). The other group 10 metals, nickel and platinum, were examined under conditions similar to those

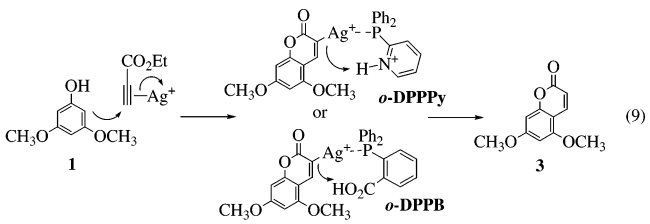
(25) (a) Terán, C.; Miranda, R.; Santana, L.; Teijeira, M.; Uriarte, E. *Synthesis* **1997**, 1385. (b) Gia, O.;
(26) Sethna, S. M.; Shah, N. M. *Chem. Rev.* **1945**, *36*, 1.
(27) (a) Black, M.; Cadogan, J. I. G.; McNab, H.; MacPherson, A. D.; Roddam, V. P.; Smith, C.; Swenson, H. R. *J. Chem. Soc.* **1997**, 2483. (b) Taylor, R. T.; Cassell, R. A. *Synthesis* **1982**, 672. (c) Narasimhan, N. S.; Mali, R. S. *Tetrahedron* **1975**, *31*, 1005. (d) Shriner, R. L. *Org. React.* **1942**, *1*, 1.
(28) Panetta, J. A.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 946.
(29) Das Gupta, A. K.; Chatterje, R. M.; Das Carp. K. R. *J. Chem. Soc. C* **1969**, 2618. For an additional alternative, see: Subba Raju, K. V.; Srimannarayana, G.; Subba Rao, N. V. *Tetrahedron Lett.* **1977**, 473.
(30) For examples of palladium-catalyzed hydrogenolysis of aryl halides and triflates with formates, see: (a) Pews, R. G.; Hunter, J. E.; Wehmeyer, R. M. *Tetrahedron Lett.* **1991**, *32*, 7191. (b) Anwer, M. K.; Sherman, D. B.; Roney, J. G.; Spatola, A. F. *J. Org. Chem.* **1989**, *54*, 1284. (c) Dolk, R.; Schmidt, S. J.; Kruse, L. I. *Tetrahedron Lett.* **1988**, *29*, 1581. (d) Numazawa, M.; Kimura, K.; Ogata, M.; Nagaoka, M. *J. Org. Chem.* **1985**, *50*, 5421. For a review, see: Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91.
(31) Kiehlmann, E.; Lauener, R. W. *Can. J. Chem.* **1989**, *67*, 335.
(32) Bhattacharya, S. N.; Josiah, B. M.; Walton, D. R. M. *Organomet. Chem. Synth.* **1971**, *1*, 145; *Chem. Abstr.* **1971**, *75*, 36214.

used in the palladium-catalyzed reaction (entries 1 and 2). The nickel catalyst failed to produce any of the desired coumarin. However, platinum(+2) chloride afforded the coumarin in only slightly lower yield than the palladium(+2)-catalyzed reaction (see Table 1, entry 5).[33] Rhodium and ruthenium catalysts (Table 3, entries 3−5) proved completely ineffective, mainly resulting in consumption of the alkynoate.

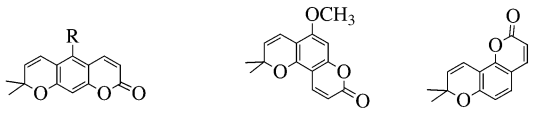
Electrophilic metal reagents, which are known to mediate additions of nucleophiles to alkynes, were also examined. Indium(+3) triflate failed to produce any of the desired coumarin (entry 6).[34] Similarly, no reaction occurred between phenol **1** and alkynoate **2** in the presence of mercury(+2) acetate.[35a] After these experiments, a similar thallium(+3) polyphosphoric acid mediated coumarin formation was reported.[35b] This result suggests that a strong acid may be required in combination with these electrophilic metals, such as indium(+3) and mercury-(+2), to promote the addition of phenols to alkynoates.

The silver(+1) promoted coupling of phenol **1** and alkynoate **2** was also examined (entries 8−10).[36] Carrying out the reaction in the presence of stoichiometric silver(+1) tetrafluoroborate (entry 8) or trifluoroacetate (entry 9) afforded coumarin **2** in 92% and 65%, respectively. However, unlike other silver-catalyzed reactions,[37] lowering the amount of silver(+1) to 10 mol % dramatically reduced the yield to 30% (entry 10).

We postulated that the reaction was promoted by coordination of silver(+1) to the alkyne, followed by nucleophilic addition of the phenol (eq 9). This mechanism would result in the formation of the vinyl silver intermediate, which could be stable enough to prevent turnover of the silver. We therefore examined the possibility that this problem could be alleviated by the use of phosphine ligands *o*-DPPB and *o*-DPPPy. These phosphines could potentially serve not only as ligands for silver(+1) but also as facilitators of protonation of the silver−sp^2 carbon bond. Addition of these ligands did slightly enhance the catalytic activity of the silver(+1) salt (entries 11−13), affording the coumarin in 59% yield in the presence of 10% silver tetrafluoroborate and a strong acid, camphorsulfonic acid (entry 13). It remains unclear, however, if they are acting as depicted in eq 9 or simply serving as a general acid source. Another important distinction between the palladium-catalyzed and the silver(+1)-mediated coumarin forming reaction is that the latter does not tolerate substitution on the alkynoate. For example, the reaction of **1** with ethyl butynoate (**5b**) proceeds smoothly under palladium catalysis (see Table 2). Conversely, the silver-mediated process is completely unproductive.

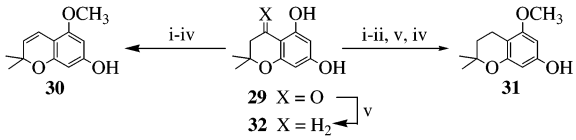


Synthesis of the Xanthoxyletins. The pyranocoumarins, several of which have been isolated from natural sources, display a wide range of pharmacological actions including anticancer[38] and anti-HIV activity.[23,39] Xanthoxyletin (**26**) and its angular isomer alloxanthoxyletin (**27**) are examples of this class of coumarins, which have been isolated from a number of plant sources[40] and even from a marine organism.[41]



25 R=H xanthyletin
26 R=OCH_3 xanthoxyletin
27 alloxanthoxyletin
28 seslin

In our initial approach to the xanthoxyletins, we wanted to examine the palladium-catalyzed coumarin-forming reaction between chroman-4-one **29**[42] and ethyl propynoate (**2**). Unfortunately, the reaction of phenol **29** with **2** was unsuccessful; both in the presence of Pd_2dba_3 and $Pd(OAc)_2$, **29** was recovered unchanged.



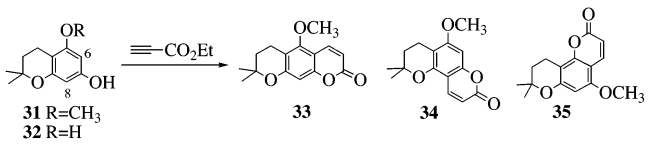
(10)

i. TsCl, K_2CO_3 ii. MeI, K_2CO_3 iii. BH_3 then $NaHSO_4$ iv. KOH, EtOH v. Zn^o, HCl

The presence of the electron-withdrawing ketone functionality was presumably responsible for the lack of reactivity of **29**. Our initial solution to this problem was to convert the chrom-4-one into the chromene functionality present in the natural product. To this end, selective tosylation of the less hindered oxygen, followed by methylation of the remaining phenol, afforded a selectively protected chrom-4-one. Reduction of the ketone with borane followed by the acidic elimination of the resulting borate provided the chromene, which was deprotected with ethanolic potassium hydroxide to afford the desired phenol **30**. Disappointingly, reaction of **30** with ethyl propynoate (**2**), catalyzed by Pd_2dba_3 or $Pd(OAc)_2$, did not afford any of the desired coumarins. In this case, unlike the reaction of chrom-4-one **29**, chromene **30** was consumed under the reaction conditions. Analysis of the crude reaction mixture indicated that the chromene olefin was not stable to the reaction conditions.

(33) For an example of Pt(+2)-catalyzed addition to alkynes, see: Katoaka, Y.; Matsumoto, O.; Tani, K. *Organometallics* **1996**, *15*, 5246 and references therein.
(34) For examples of carboindination of alkynes, see: (a) Klaps, E.; Schmid, N. *J. Org. Chem.* **1999**, *64*, 7537. (b) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4095.
(35) (a) For Hg(+2)-mediated addition to alkynes, see: (a) Subramanian, R. S.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1990**, 1469. Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1997**, *62*, 4746. Carollo, L.; Floris, B. *J. Organomet. Chem.* **1999**, *583*, 80 and references therein. (b) For Tl-(+3) mediated addition, see: Shamsuddin, K. M.; Jamshed Ahmed Siddiqui, M. *J. Chem. Res. Synop.* **1998**, 392.
(36) For silver(+1) catalyzed addition to alkynes, see: Kotora, M.; Neghsi, E. *Synthesis* **1997**, 121. (b) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Synlett* **1995**, 871.
(37) Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5728 and references therein.
(38) (a) Guntatilaka, A. A. L.; Kingston, D. G. I.; Wijertane, E. M. K.; Bandara, B. M. R.; Hofmann, G. A.; Johnason. R. K. *J. Nat. Prod.* **1994**, *57*, 518. (b) Magiatis, P.; Melliou, E.; Skaltsounis, A.; Mitaku, S.; Leonce, S.; Renard, P.; Pierre, A.; Alassi, G. *J. Nat. Prod.* **1998**, *61*, 982 and references therein.
(39) Takeuchi, Y.; Xie, L.; Cosentino, L. M.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2573.
(40) (a) Mohan, P. S.; Ramesh, M.; Shanmugam, P. *J. Nat. Prod.* **1985**, *48*, 501. (b) Lasak, E. V.; Pinhey, J. T. *Aust. J. Chem.* **1969**, *22*, 2175. c. King, F. E.; Housely, J. R.; King, S. J. *J. Chem. Soc.* **1954**, 1392. (c) Tsukayama, M.; Sakamoto, T.; Horie, T.; Masamura, M.; Nakayama, M. *Heterocycles* **1981**, *16*, 955.
(41) Tillekeratne, L. M. V.; De Silva, E. D.; Mahindaratne, M. P. D.; Schmitz, F. J.; Gunasekera, S. P.; Alderslade, P. *J. Nat. Prod.* **1989**, *52*, 1303.
(42) (a) Timár, T.; Jászberényl, J. C. *J. Heterocycl. Chem.* **1988**, *25*, 871. (b) Wolfrom, M. L.; Koos, E. W.; Bhat, H. B. *J. Org. Chem.* **1967**, *32*, 1056. (c) Sowmithran, D.; Rajendra Prasad, R. J. *Synthesis* **1985**, 545.

Table 4. Regioselectivity of Pyranocoumarin Formation



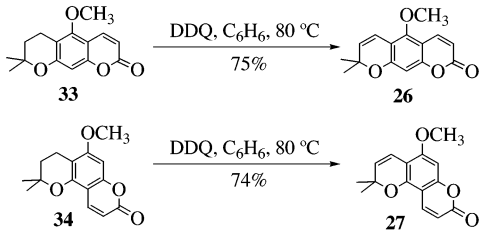
31 R=CH_3
32 R=H

33 **34** **35**

entry	phenol	conditions	yield	**33**:**34**:**35**
1	**31**	10% $Pd(OAc)_2$, 20% NaOAc, HCOOH, 25 °C	63%	1.0:3.3:0
2		1eq AgBF4, THF, 25 °C	54%	1.0:4.3:0
3	**32**	2.5% $Pd_2(dba)_3$, HCOOH, 30 °C then CH_3I, K_2CO_3, acetone	56%	1.0:6.6:1.3
4		2.5% $Pd_2(dba)_3$, 10% NaOAc, HCOOH, 25 °C then CH_3I, K_2CO_3, acetone	68%	1.0:2.8:0

To avoid this complication, the differentially protected chromone derived from **29** was subjected to a Clemmenson reduction, followed by deprotection of the tosyl group to afford chroman **31**.[43] Reaction of phenol **31** with ethyl propynoate (**2**), catalyzed by palladium(+2) acetate, produced a 1:3.3 mixture of dihydroxanthoxyletin (kanzanol Q, **33**) and dihydroalloxanthoxyletin (**34**) (Table 4, entry 1). The regiochemistry of the coumarin formation was established by conversion of **33** and **34** to the natural products (eq 11 and 12). The silver-mediated addition of ethyl propynoate to **2** also favored reaction at the 8-position of the chroman (Table 4, entry 2). Similar selectivity for reaction at the 8-position of **31** has been observed in other electrophilic reactions, including the Pechmann condensation (42% yield, ratio 1:6:trace).[43a]

Unprotected chroman-4-one **29** was similarly reduced to afford chroman **32**.[44] Chroman **32** offers an additional regioselectivity issue, since addition of the alkynoate to the 6-position can lead either to **33** or to **35,** depending on which hydroxyl group cyclizes onto the intermediate cinnamate ester. The reaction of **32** with ethyl propynoate catalyzed by Pd_2dba_3, and subsequent methylation of the crude reaction mixture, afforded a mixture of three coumarins **33**:**34**:**35** (Table 4, entry 3). The regioselectivity of addition to the 8-position versus the 6-position (2.9:1) is similar to that obtained for reaction with phenol **31** (entry 1). Addition of 10 mol % tetrabutylammonium chloride to the reaction mixture did not have any observable impact on the yield or selectivity of the reaction. In contrast, addition of 10 mol % sodium acetate increased the yield to 68% while maintaining the regioselectivity for addition to the 8-position to produce dihydroalloxanthoxyletin (**34**) (entry 4). Notably, under the latter conditions, only two out of the three possible regioisomeric coumarins were produced.



(43) (a) Matsui, T.; Nishimura, S.; Nakayama, M.; Hayashi, S.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1975. (b) Lahey, F. N.; Stick, R. V. *Aust. J. Chem.* **1973**, *26*, 2291.

(44) Bridge, W.; Heyes, R. G.; Robertson, A. *J. Chem. Soc.* **1937**, 279.

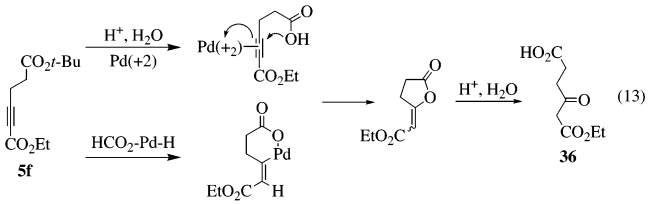
The DDQ oxidation[42] of the chromans **33** and **34**, to the chromenes, completes the synthesis of xanthoxyletin (**26**) and alloxanthoxyletin (**27**) (eq 11 and 12). Using the palladium-catalyzed coumarin synthesis, alloxanthoxyletin (**27**) is available in four steps, and 36% overall yield, from chrom-4-one **29**. The regioisomeric coumarin xanthoxyletin (**26**) is also produced in 13% overall yield.

Discussion

The initial mechanistic proposal was based on the notion that an electron-rich phenol could be ortho-palladated by an electrophilic palladium(+2) source.[3] Therefore, the first phenols examined in the palladium-catalyzed coumarin forming reaction all possessed strong electron-donating groups. Indeed, the coupling reaction of phenols **1**, **7**, **9**, **11**, and **16**, all of which contain at least two activating groups, with a variety of alkynoates, afford coumarins in good to excellent yields (46−88%). On the other hand, the electron-deficient 2-acetylphenol failed to produce any coumarin product. These results clearly indicate that the reaction is favored by electron-donating substituents on the phenol; however, it was unclear how electron rich the phenol had to be for the reaction to proceed.

The successful reaction of phenols **13a** and **13b** with ethyl propynoate (**2**) (eq 4) indicates that only a single additional electron-donating substituent is required. The failure of 3-methylphenol to participate in the palladium-catalyzed reaction clearly demonstrates that at least one additional strong electron-donating group, such as methoxy, is required and that alkyl is not a strong enough activating substituent. Moreover, the position of the electron-donating group is also important, as demonstrated by the difference in reactivity between *m*-methoxy (**13a**) and *p*-methoxy phenols. 3-Methoxyphenol (**13a**) reacts with ethyl propynoate (**2a**) at the position para to the methoxy group (eq 4), while 4-methoxyphenol fails to react with the same alkynoate.

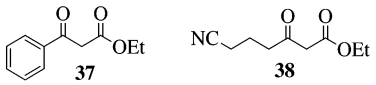
The palladium-catalyzed reactions proceed well with unsubstituted (**2**) as well as aryl and alkyl substituted (**5a**−**e**, **h**) alkynoates. However, the palladium catalyzed reaction fails to proceed with alkynoates substituted with potential nucleophiles, such as carboxylic acids (**5f**) or free alcohols (**5g**). In these cases, the β-keto ester derived from hydration of the alkynoate is isolated.



The failure of alkynoate **5f** to react with 3,5-dimethoxyphenol (**1**) may arise from palladium(+2)-catalyzed intramolecular addition of the homopropargylcarboxylic acid, resulting from acidic deprotection of the *tert*-butyl ester, to the alkynoate (eq 13).[45] Alternatively, insertion of palladium(0) into the carboxylic

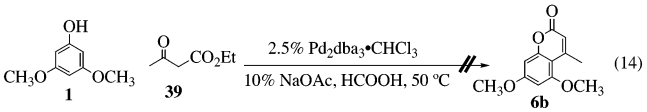
(45) (a) Arcardi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, *57*, 976. (b) Yanagihara, N.; Lambert, C.; Iritani, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753. (c) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323. A similar reaction is reported for propargyl alcohols in the presence of carbon dioxide: Iritani, K.; Yanagihara, N.; Utimoto, K. *J. Org. Chem.* **1986**, *51*, 5501.

acid O−H bond, followed by hydropalladation−reductive elimination, leads to a similar methylene lactone.[46] Presumably, the intermolecular addition of formic acid to the other alkynoates is also occurring;[47] however, the addition of phenol is competitive. Indeed, with alkynoates **5a** and **5d** the corresponding β-keto esters, **37** and **38**, were detected along with the coumarins.



37 **38**

The isolation of β-keto esters **37** and **38** from the reactions depicted in Table 2 raises the possibility that they were intermediates in the palladium-catalyzed coumarin formation. To examine this possibility, phenol **1** was reacted with ethyl acetoacetate (**29**) under the standard palladium-catalyzed conditions (eq 14). Coumarin **6b** was not obtained in this reaction, thus excluding β-keto esters as intermediates in the mechanism of the palladium-catalyzed coumarin formation.

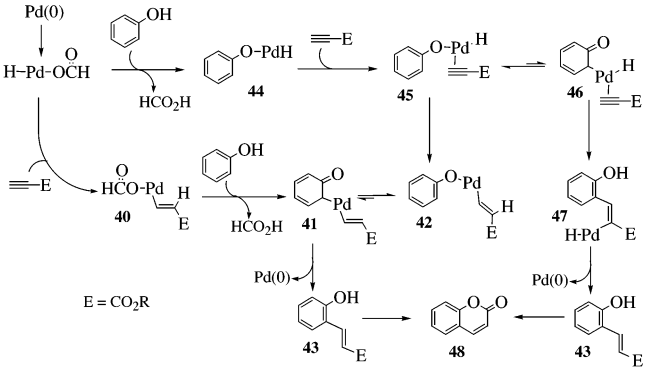


1 **39** **6b** (14)

The palladium-catalyzed coumarin formation proceeds with excellent (>95:5, eqs 3 and 6) to moderate regioselectivity (1.2−2.4:1, eq 5). In an attempt to rationalize the origin of the regioselectivity of addition, ab intio (HF-6-31G**) calculations were performed to determine both the atomic charges and the HOMO of the phenols. In general, reactions of aromatic compounds with *hard* (high lying LUMO's) electrophiles are charged controlled, while reactions with *soft* (low lying LUMO's) electrophiles are under frontier molecular orbital (FMO) control. The calculated atomic charges are not consistent with the experimentally determined regioselectivity. For example, in the case of sesamol (**11**) the greatest amount of negative charge is found at the 2-position (atomic charge = −0.44), while reaction occurs selectively at the 6-position (atomic charge = −0.29) (eq 3). On the other hand, the observed regioselectivity fits well with the calculated HOMO of the phenols. In accord with the observed regioselectivity, the HOMO coefficient at the 6-position of sesamol (**11**) is significantly larger than that at the 2-position.

Our original mechanistic proposal was based on the idea than an electrophilic palladium(+2) source could ortho-palladate[48] an electron-rich phenol. Several experimental observations led to the exclusion of this mechanism of coumarin formation. First, insertion of alkynoates into aryl carbon−palladium bonds is reported to proceed with regioselectivity opposite to that observed in the coumarin formation.[46] Second, a number of results suggest that the reaction involves a palladium(0) rather than a palladium(+2) catalyst. The reaction does not proceed with a palladium(+2) source in acetic acid. However, changing the solvent to formic acid, which may reduce palladium(+2) to palladium(0), leads to a productive coupling reaction (see Table 1). Indeed, in the absence of substrate, treatment of palladium acetate with formic acid led to the formation of palladium black. Furthermore, a palladium(0) source, Pd_2dba_3, is an effective catalyst in both acetic and formic acid, although the latter solvent gave better results. Finally, reaction with 2-bromophenol produced the debrominated coumarin as the major product (eq 7). The fact that 8-bromocoumarin (**22**) is isolated in this reaction suggests that coumarin formation is competitive with oxidative addition of palladium into the aryl bromide bond. This observation also led us to exclude a mechanism, similar to that proposed for silver(+1) or thallium(+3), in which coordination of the palladium(+2) to the alkyne activates it for nucleophilic addition of the phenol.

Scheme 1. Mechanistic Proposals for Palladium Catalyzed Coumarin Formation



A mechanistic rational derives from the effectiveness of Pd_2dba_3, in formic acid, to promote the cycloisomerization of enynes.[7] Since this reaction involves the hydropalladation of an alkyne, the formation of HPdX from palladium(0) and formic appears likely. Furthermore, other palladium(0) catalyzed additions of phenols and alcohols to alkynes, in the presence of acid, have been described.[45] These reactions are proposed to involve hydropalladation by a HPdX species, to produce a vinylpalladium intermediate, which is then carbonylated. In support of this proposal, a hydridopalladium species (HPd−O_2CF_3) has recently been observed in the ^{1}H NMR of a mixture of $Pd(PPh_3)_4$ and trifluoroacetic acid.[46a]

Similarly, the proposed mechanism for the coumarin formation involves the formation of a hydridopalladium intermediate from the reaction of palladium(0) and formic acid (Scheme 1). One mechanistic possibility involves addition of the hydridopalladium complex to the alkynoate (a hydropalladation) to form a vinylpalladium intermediate **40**. The regiochemistry of the hydropalladation is consistent with that observed for the hydropalladation of ethyl octynoate. The different polarization of the H−PdX bond compared to C−PdX bond accounts for the different regioselectivity of addition to alkynoates for the two processes. The fact that protonation of Pd(0) is highly reversible supports this argument. Nucleophilic addition of phenol on **40** affords either the C-bound (**41**) or O-bound (**42**) vinylpalladium complex. In any case, **41** and **42** are interconvertible by a keto−enol type tautomerization. In a related system, CO has been reported to insert into intermediates such as **42** to afford α,β-unsaturated esters.[46b] In the absence of carbon monoxide, reductive elimination of **41** regenerates the palladium(0) catalyst and initially affords *E*-cinnamate ester **43**. Olefin *E*−*Z* isomerization of **43** followed by lactonization

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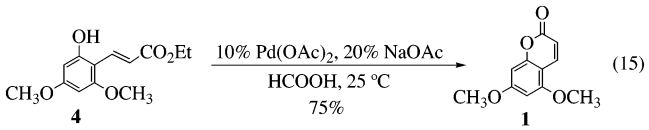
affords coumarin **48**. In support of the isomerization, subjecting cinnamate ester **4** to the reaction conditions affords coumarin **1** in 75% yield (eq 15).



(15)

Alternatively, the hydridopalladium intermediate can undergo exchange with the phenol to produce hydridopalladium phenoxide **44**.[49] Coordination of the alkyne to **44** affords **45,** which can undergo either hydrometalation or carbometalation of the alkyne. Hydrometalation of the alkyne generates intermediate **42**, whose conversion to coumarin **48** has already been discussed. Carbometalation of the alkynoate, perhaps via **46**, generates the vinyl hydridopalladium intermediate **47**, which can undergo a reductive elimination to regenerate palladium(0) and afford cinnamate ester **43**.

The equilibrium between an O- (**41** or **45**) and C-bonded (**42** or **46)** phenol is consistent with the preference for addition of the alkynoate to the position ortho to the hydroxyl group. In some coupling reactions, such as with sesamol (**11**) (eq 3), the alkynoate addition occurs with exceptional selectivity for one of the ortho positions. The ab intio calculations strongly suggest that the regioselectivity of coumarin formation is FMO controlled. This is not unexpected, since both palladium(+2) (as in **41**) and the palladium-coordinated alkynoate (as in **45**) would be predicted to have low-lying LUMO's. This further suggests that, like in most FMO controlled electrophilic aromatic substitutions, the addition of the phenol to the alkynoate is both the regiochemistry- and rate-determining step.

Conclusion

In conclusion, the combination of palladium catalysts and formic acid is an effective system for the catalytic *ortho* vinylation of phenols with activated alkynes. This catalyst system provides a new atom economic synthesis of coumarins through the simple addition of phenols with alkynoate esters, the first criterion for an atom economical reaction. While the yields are not quantitative, they are higher than for other coumarin syntheses. This is demonstrated by the application of the palladium-catalyzed coumarin synthesis to the efficient preparation of various coumarin natural products including faxinol methyl ether, ayapin, herniarin, xanthoxyletin, and alloxanthoxyletin. The mechanism of this new reaction appears to involve a palladium(0) species. Several mechanistic possibilities involving hydridopalladium intermediates are presented. Much like electrophilic aromatic substitutions, the coumarin formation with unsymmetrical phenols appears to be frontier molecular orbital directed.

Experimental Section

All reactions were performed under a nitrogen atmosphere unless otherwise indicated. Solvents were generally freshly distilled before use: methylene chloride, benzene, and toluene from calcium hydride; DMF from barium oxide; THF and diethyl ether from sodium benzophenone ketyl; acetone from cacium sulfate. Methanol was distilled from magnesium methoxide. Acetic acid, formic acid, and 95% ethanol were used as obtained. All phenols were obtained from Aldrich or Fluka and recrystallized or distilled prior to use. Palladium acetate, $Pd(OAc)_2$, was recyrstallized from hot acetic acid under a nitrogen atmosphere. Tris(dibenzylidideneacetone) monochloroform complex, $Pd_2dba_3{\cdot}CHCl_3$, was prepared according to the literature.[50]All other reagents were used as obtained unless otherwise noted.

5,7-Dimethoxycoumarin (3). The procedures described for preparation of 5,7-dimethoxycoumarin (**3)** from 3,5-dimethoxyphenol (**1)** are representative of those used to prepare subsequent coumarins.

Method A. To a mixture of 3,5-dimethoxyphenol (**1)** (50 mg, 0.324 mmol), palladium acetate (7 mg, 0.032 mmol), and sodium acetate (5 mg, 0.065 mmol) under a nitrogen atmosphere, formic acid (3 mL) was added and the resultant mixture placed into a preheated to 50 °C in an oil bath. After 2 min at this temperature, ethyl propynoate (**2)** (66 μL, 0.649 mmol) was added and the resulting brown solution stirred at 50 °C for 14 h. The reaction mixture was cooled to room temperature, diluted with methylene chloride (10 mL), and washed with water (15 mL), 5% aqueous sodium bicarbonate (15 mL), and brine (15 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a brown solid. Flash chromatography eluting with methylene chloride afforded 51 mg (62%) of 5,7-dimethoxycoumarin (**3)**.

Method B. To a mixture of 3,5-dimethoxyphenol (**1)** (2.00 g, 13.0 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (0.34 g, 0.325 mmol), and sodium acetate (0.11 g, 0.725 mmol) under a nitrogen atmosphere formic acid (13 mL) was added followed by ethyl propynoate **2** (2.6 mL, 26 mmol). The resulting brown/purple solution was stirred at room temperature for 16 h, then diluted with methylene chloride (20 mL), and washed with water (25 mL), 5% aqueous sodium bicarbonate (25 mL), and brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a brown solid. Flash chromatography eluting with methylene chloride followed by recrystallization from CH_2Cl_2/pentanes afforded 2.51 g (77%) of 5,7-dimethoxycoumarin (**3)** as a slightly yellow solid, mp 143−145 °C (lit.[6] mp 143−144 °C). IR(film): 2931, 1723, 1616, 1228, 1152, 1113, 827 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, $J = 9.6$ Hz, 1 H), 6.41 (d, $J = 2.2$ Hz, 1 H), 6.27 (d, $J = 2.2$ Hz, 1 H), 6.15 (d, $J = 9.6$ Hz, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1, 161.8, 157.3, 157.1, 139.0, 111.0, 104.2, 94.9, 93.1, 56.1, 55.9.

5,7-Dihydroxycoumarin (8a). Using method B, phloroglucinol (**7)** (100 mg, 1.30 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (41 mg, 0.04 mmol), sodium acetate (7 mg, 0.08 mmol), and ethyl propynoate (**2)** (100 μL, 1.59 mmol) were reacted in formic acid (0.8 mL) at room temperature for 16 h. After 16 h, the brown solid which precipitated from the reaction mixture was collected by suction filtration and recrystallized from hot water to afford **8a** (140 mg, 79%) as a light yellow solid, mp 270−272 °C (lit. mp[11c] 280 °C). IR(KBr): 3246, 1686, 1641, 1618, 1479, 1375, 1292, 1152, 1070 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.75 (br s, 2 H), 7.95 (d, $J = 9.9$ Hz, 1 H), 6.23 (d, $J = 2.1$ Hz, 1 H), 6.12 (d, $J = 2.1$ Hz, 1 H), 5.91 (d, $J = 9.9$ Hz, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.1, 160.8, 158.8, 157.3, 156.1, 107.0, 101.2, 98.9, 93.1.

4-Methyl-5,7-dihydroxycoumarin (8b). Using *method B*, phloroglucinol **7** (100 mg, 1.30 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (41 mg, 0.04 mmol), sodium acetate (7 mg, 0.08 mmol) and ethyl butynoate **5b** (100 μL, 1.50 mmol) were reacted in formic acid (0.8 mL) at room temperature for 16h. After 16h, the brown solid which precipitated from the reaction mixture is collected by suction filtration and recrystallized from hot water to afford **8b** (135 mg, 83%) as a light yellow solid, mp 282−4 °C (lit.[12a] mp 284−285 °C). IR(KBr): 3158, 1669, 1622, 1558, 1386, 1300, 1160, 1097, 1024 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 6.25 (d, $J = 1.8$ Hz, 1H), 6.16 (d, $J = 1.8$ Hz, 1H), 5.83 (s, 1H), 4.2−3.8 (br s, 2H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7, 160.7, 158.5, 157.0, 155.6, 109.4, 102.7, 98.6, 95.1, 24.0.

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6,7-(Methylenedioxy)coumarin (Ayapin, 12). Using method B, phenol **11** (200 mg, 1.45 mmol), Pd_2dba_3·$CHCl_3$ (38 mg, 0.036 mmol), sodium acetate (12 mg, 0.14 mmol), and ethyl propynoate **2** (290 μL, 2.9 mmol) were reacted in formic acid (1.5 mL) at room temperature for 16 h. Flash chromatography eluting with 30% ethyl acetate:hexanes followed by recrystallization from carbon tetrachloride afforded **12** (128 mg, 67%) as a tan solid, mp 225−227 °C (lit.[16a] mp 223 °C). IR(film): 2938, 1723, 1634, 1453, 1333, 1272, 1223, 1100, 1038 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 9.8 Hz, 1 H), 6.81 (s, 2 H), 6.26 (d, J = 9.8 Hz, 1 H), 6.06 (s, 2 H).

Dihydroxanthoxyletin (Kanzanol Q, 33), Dihydroalloxanthoxyletin (34), and 5-Methoxydihydroseslin (35). From 2,2-Dimethyl-7-hydroxy-5-methoxychroman (31). (a) Silver Mediated. To a solution of phenol **31** (86 mg, 0.417 mmol) and silver tetrafluoroborate (89 mg, 0.96 mmol) in THF (0.4 mL) was added ethyl propynoate (84 μL, 0.83 mmol) and the resulting orange solution was stirred at room temperature for 2 h. After 2 h, the reaction mixture was diluted with ether (10 mL) and the precipitated silver removed by filtration. The filtrate was washed with 1 N sodium hydroxide (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography eluting with 2:1 petroleum ether:diethyl ether afforded **33** (11 mg, 10%) and **34** (47 mg, 44%).

(b) Palladium-Catalyzed. To a test tube containing phenol **31** (50 mg, 0.242 mmol), palladium acetate (5 mg, 0.022 mmol), and sodium acetate (4 mg, 0.05 mmol) was added formic acid (0.3 mL) and the solution stirred at room temperature for 5 min. To this solution was added methyl propynoate (50 μL, 0.49 mmol), and the solution was stirred at room temperature for 8 h. The reaction mixture is then diluted with ether (5 mL), washed with 1M sodium hydroxide (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated to afford a yellow solid. Flash chromatography eluting with 2:1 petroleum ether:diethyl ether afforded **33** (9 mg, 15%) and **34** (30 mg, 48%).

From 5,7-Dihydroxy-2,2-dimethylchroman (32). To a solution of chroman **32** (100 mg, 0.51 mmol), $Pd_2(dba)_3$ (14 mg, 0.013 mmol), and sodium acetate (4 mg, 0.05 mmol) in formic acid (0. 5 mL) was added ethyl propynoate (**2**) and the reaction mixture stirred at room temperature. Two additional equivalents of ethyl propynoate (**2,** 50 μL, 0.49 mmol) were added after 3 and 6 h, and stirring was continued for a total of 10 h. After 10 h, the reaction mixture was flushed through a pad of silica eluting with 1% methanol/methylene chloride and the filtrate concentrated in vacuo to afford a brown solid (390 mg). The solid was taken into acetone (5 mL) and treated with potassium carbonate (211 mg, 1.53 mmol) followed by iodomethane (48 μL, 0.77 mmol), and the resulting suspension was heated at reflux for 6 h. The reaction mixture was cooled to room temperature, the potassium salts were removed by filtration and the filtrate concentrated in vacuo. Flash chromatography eluting with 2:1 petroleum ether:diethyl ether gave **33** (22 mg, 18%) and **34** (62 mg, 50%).

The identical reaction of chroman **32** (200 mg, 0.51 mmol), $Pd_2(dba)_3$ (25 mg, 0.024 mmol), and ethyl propynoate **2** (3 additions of 95 μL, 0.96 mmol) in formic acid (2 mL) in the absence of sodium acetate afforded **33** (15 mg, 6% yield), **34** (100 mg, 40%), and **35** (21 mg, 8%).

33: mp 140−144 °C (lit.[52a] mp 143 °C). IR (film): 2928, 2856, 1734, 1618, 1560, 1457, 1385, 1256, 1139, 1120, 829, 825 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, J = 9.8 Hz, 1 H), 6.54 (s, 1 H), 6.17 (d, J = 9.8 Hz, 1 H), 3.84 (s, 3 H), 2.76 (t, J = 6.8 Hz, 2 H), 1.80 (t, J = 6.8 Hz, 2 H), 1.35 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 158.5, 155.3, 154.2, 138.6, 112.0, 111.6, 106.6, 100.9, 75.7, 62.0, 31.8, 26.8, 17.0.

34: mp 150−154 °C (lit.[52b] mp 155 °C). IR (film): 2963, 2849, 1730, 1619, 1366, 1252, 1160, 1112, 819, 796 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, J = 9.6 Hz, 1 H), 6.34 (s, 1 H), 6.10 (d, J = 9.6 Hz, 1 H), 3.85 (s, 3 H), 2.60 (t, J = 6.8 Hz, 2 H), 1.79 (t, J = 6.8 Hz, 2 H), 1.34 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0, 161.1, 155.2, 150.8, 139.2, 110.4, 105.6, 103.7, 90.4, 75.6, 55.7, 31.7, 26.5, 16.5. Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found C, 69.95; H, 6.39.

35: mp 155−158 °C (lit.[53] mp 162−163 °C). IR (film): 2973, 2855, 1730, 1602, 1367, 1205, 1140, 1112, 819 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J = 9.6 Hz, 1 H), 6.18 (s, 1 H), 6.12 (d, J = 9.6 Hz, 1 H), 3.83 (s, 3 H), 2.79 (t, J = 6.8 Hz, 2 H), 1.82 (t, J = 6.8 Hz, 2 H), 1.35 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9, 158.1, 155.1, 154.0, 139.1, 109.9, 103.4, 101.5, 95.6, 76.0, 55.8, 31.7, 26.6, 15.3.

Xanthoxyletin 26. A solution of **33** (22 mg, 0.08 mmol) in benzene (1 mL) was treated with DDQ (97 mg, 0.44 mmol) and the resulting brown solution heated at reflux for 20 h. The reaction mixture was cooled to room temperature and diluted with ether (15 mL), washed with 1 N sodium hydroxide (10 mL), water (10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography eluting with 1:1 ether:pentanes and recrystallization from ethanol afforded xanthoxyletin **26** (16 mg, 75%), mp 130−132 °C (lit. mp[54] 134−135 °C). IR (film): 2927, 2855, 1727, 1614, 1462, 1370, 1240, 1140, 1024 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, J = 9.6 Hz, 1 H), 6.61 (d, J = 10.0 Hz, 1 H), 6.34 (s, 1 H), 6.16 (d, J = 9.6 Hz, 1 H), 5.55 (d, J = 10.0 Hz, 1 H), 3.87 (s, 3 H), 1.46 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 157.5, 155.5, 152.8, 138.5, 115.8, 112.3, 111.3, 107.4, 100.8, 77.9, 63.6, 28.1, 14.1.

Alloxanthoxyletin (27). A solution of **34** (43 mg, 0.167 mmol) in benzene (5 mL) was treated with DDQ (189 mg, 0.79 mmol) and the resulting brown solution heated at reflux for 16 h. The reaction mixture was diluted with ether (15 mL), washed with 1 N sodium hydroxide (15 mL), water (15 mL), and brine (15 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography eluting with 1:1 ether: pentanes and recrystallization from hexanes afforded alloxanthoxyletin (**27**) (33 mg, 76%), mp 113−6 °C (lit.[40c] mp 114−115 °C). IR (film): 2977, 2850, 1738, 1615, 1370, 1120 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, J = 9.6 Hz, 1 H), 6.61 (d, J = 10.0 Hz, 1 H), 6.34 (s, 1 H), 6.16 (d, J = 9.6 Hz, 1 H), 5.55 (d, J = 10.0 Hz, 1 H), 3.87 (s, 3 H), 1.46 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5, 158.2, 155.8, 150.2, 138.6, 116.0, 111.1, 106.4, 103.7, 91.5, 77.7, 55.9, 27.9, 15.3.

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Supporting Information Available: Experimental procedures for **6a−d**, **8**, **14a,b**, **17a,b,h**, **18a,b,h**, **20**, **22**, **24**, and **29−32** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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