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Cp*Co(III)-Catalyzed Annulations of 2-Alkenylphenols with CO: Mild Access to Coumarin Derivatives

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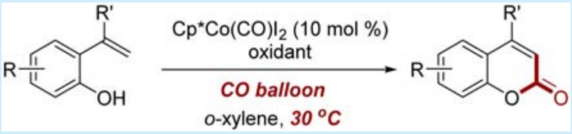
Ⓢ *Supporting Information*

ABSTRACT: Cp*Co(III)-catalyzed annulations of 2-alkenylphenols with CO for the synthesis of coumarin derivatives have been developed. The reaction features mild reaction conditions, broad substrate scope, and good functional group tolerance. Preliminary mechanistic studies were conducted, suggesting that C−H activation is the turnover limiting step. Furthermore, the efficiency of this reaction was demonstrated by the rapid total synthesis of three natural products herniarin, xanthyletin, and seselin.



Over the past few decades, transition-metal-catalyzed direct functionalization of relatively unreactive C−H bonds has considerably expanded the toolbox for organic synthesis,[1] providing an attractive alternative to traditional cross-coupling reactions with no prefunctionalization of starting materials necessitated. With the endeavor of many chemists, numerous metals are found to be effective in C−H activation reactions. In this regard, cobalt, as a cheap, earth-abundant, and low-toxic early transition metal, is particularly appealing.[2] Pioneered by Kanai,[3] and later advanced by the groups of Ackermann,[4] Ellman,[5] Glorius,[6] Chang,[7] and us,[8] Cp*Co(III) was found to be an interesting catalyst, which shows similar, and in some cases complementary, reactivities to its counterparts Cp*Rh(III) and Cp*Ir(III). Furthermore, the reactions initiated by Cp*Co(III) typically take place under relatively milder reaction conditions compared to other first-row cheap metals.

Coumarin and its derivatives[9] display good biological and pharmacological activities, such as antitumor,[10] anti-HIV,[11] antioxidant,[12] antibacterial,[11,13] antiinflammatory,[14] and anti-psychotic[9c] activity (Figure 1). They also exhibit good optical properties and, thus, are widely used in laser devices, light-emitting diodes, and fluorescent probes.[15] Synthetically, coumarins could be constructed by the condensation of phenols with various carbonyl compounds.[16] These methods usually occur under harsh conditions, and low regioselectivities are typically observed, which may lead to difficulty in product separation. Other transition-metal-catalyzed routes,[16c] such as Pd-catalyzed oxidative annulation of phenols with propargylic esters,[17] Pd-catalyzed carbonylative annulation of internal alkynes by *o*-iodophenols,[18] and ring-closing metathesis of esterified 2-vinylphenols using Grubbs' catalyst,[19] were also known.

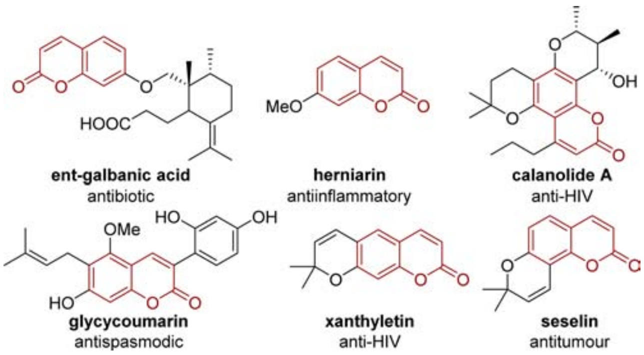


Figure 1. Selected naturally occurring bioactive coumarin derivatives.

The transition-metal-catalyzed direct cyclocarbonylation of 2-vinylphenols[20−23] represents an atom-economic and environmentally friendly method for coumarin synthesis. For example, Alper reported a Pd(II)-catalyzed oxidative cyclocarbonylation of 2-vinyphenols, with a relatively high pressure of CO applied (Scheme 1a).[21] Iwasawa disclosed an elegant Pd-catalyzed direct carboxylation of alkenyl C−H bonds with CO_2, which lead to a redox-neutral access to coumarins (Scheme 1b).[22] Mascareñas and Gulías realized a Cp*Rh(III)-catalyzed carbonylation of *o*-alkenyl phenols with CO, wherein a relatively high temperature was used (Scheme 1c).[23a] Very recently, we have developed a Cp*Co(III)-catalyzed aromatic C−H coupling with diazomalonates.[8] Herein, we would like to disclose our realization of a Cp*Co(III)-catalyzed annulation reaction of 2-alkenylphenols with CO (balloon pressure) under remarkably mild conditions (Scheme 1d).

At the outset of our studies, 2-(prop-1-en-2-yl)phenol (**1a**) was chosen as a model substrate (Table 1). The reaction of **1a** in the presence of Cp*Co(CO)I_2 (10 mol %) and AgOAc (2.5 equiv) under atmospheric CO at 50 °C in toluene for 20 h delivered the desired coumarin product **2a** in 14% yield (entry 1). Ag_2CO_3 is a superior oxidant for this transformation (entries 2 and 3). When the reaction was carried out in *o*-xylene or chlorobenzene, the yield could be doubled (entries 4−9). Interestingly, the use of Ag_2CO_3 (1.0 equiv) and $Cu(OAc)_2\cdot H_2O$ (1.0 equiv) as co-oxidants led to a good yield of 70%

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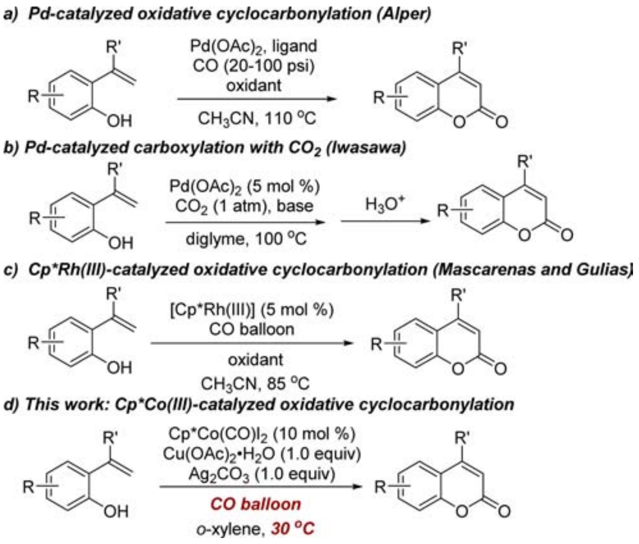
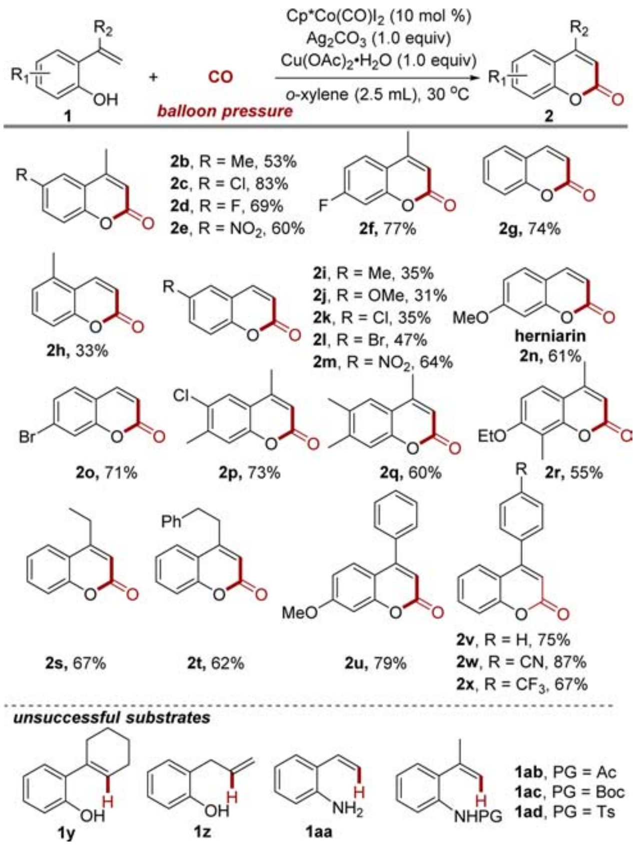
Scheme 1. Synthesis of Coumarins from 2-Alkenylphenols



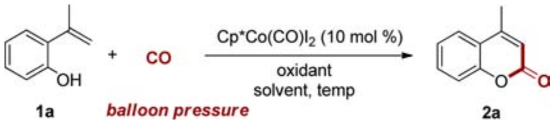
(entry 10).[24] To our delight, lowering the reaction temperature to 30 °C further improved the yield to 75% (entry 11). The use of 5 mol % catalyst gave a moderate yield of 61% (entry 12). Control experiments indicated that both the catalyst and oxidant were essential for the reaction (entries 13 and 14).

Scheme 2. $Cp^{*}Co(III)$-Catalyzed Annulations of 2-Alkenylphenols with CO



With the optimized conditions established (Table 1, entry 11), the substrate scope was then investigated. As shown in Scheme 2, a wide range of 2-vinylphenols bearing different substitutents, regardless of their electronic properties, underwent this reaction smoothly, giving the corresponding coumarins in 31–87% yields. Some commonly encountered functional groups such as halogen (**2c–d**, **2f**, **2k–l**, **2o–p**), nitro (**2e**, **2m**), methoxy (**2j**, **2n**, **2v**), cyano (**2w**), and trifluoromethyl (**2x**) were tolerated in this transformation, thus giving good opportunities for further functionalizations. Simple 2-hydroxyl styrenes were also suitable substrates (**2g–k**). However, relatively lower yields were observed, probably due to the ease of the rotation of vinyl group, which lead to the difficulty of a hydroxyl-directed metalation. It was found that the introduction of steric hindrance next to the vinyl group led to a diminished yield (**2h**). However, **1r** with an ortho methyl

Table 1. Optimization of the Reaction Conditions[a]

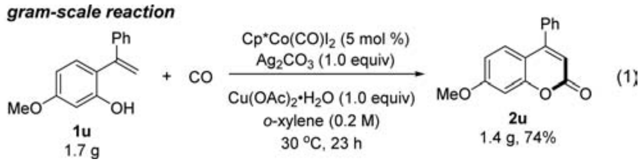


entry	oxidant (equiv)	solvent (M)	temp (°C)	yield (%)[b]
1	AgOAc (2.5)	toluene (0.1)	50	14
2	Ag_2CO_3 (2.5)	toluene (0.1)	50	27
3	$Cu(OAc)_2\cdot H_2O$ (2.5)	toluene (0.1)	50	19
4	Ag_2CO_3 (2.5)	DCE (0.1)	50	20
5	Ag_2CO_3 (2.5)	*o*-xylene (0.1)	50	41
6	Ag_2CO_3 (2.5)	mesitylene (0.1)	50	17
7	Ag_2CO_3 (2.5)	chlorobenzene (0.1)	50	39
8	Ag_2CO_3 (2.5)	trifluorotoluene (0.1)	50	27
9	Ag_2CO_3 (2.5)	*n*-hexane (0.1)	50	12
10	Ag_2CO_3 (1.0)/$Cu(OAc)_2\cdot H_2O$ (1.0)	*o*-xylene (0.2)	50	70
11	**Ag_2CO_3 (1.0)/$Cu(OAc)_2\cdot H_2O$ (1.0)**	***o*-xylene (0.2)**	**30**	**75 (78)**[c]
12[d]	Ag_2CO_3 (1.0)/$Cu(OAc)_2\cdot H_2O$ (1.0)	*o*-xylene (0.2)	30	61
13	–	*o*-xylene (0.2)	30	0
14[e]	Ag_2CO_3 (1.0)/$Cu(OAc)_2\cdot H_2O$ (1.0)	*o*-xylene (0.2)	30	0

[a] Reaction conditions: **1a** (0.2 mmol), $Cp^{*}Co(CO)I_2$ (10 mol %), oxidant, CO balloon, solvent, 20 h. [b] Yields are based on **1a**, determined by ^1H NMR spectroscopy by using 1-iodo-4-methoxybenzene as the internal standard. [c] Isolated yield. [d] $Cp^{*}Co(CO)I_2$ (5 mol %). [e] Without $Cp^{*}Co(CO)I_2$.

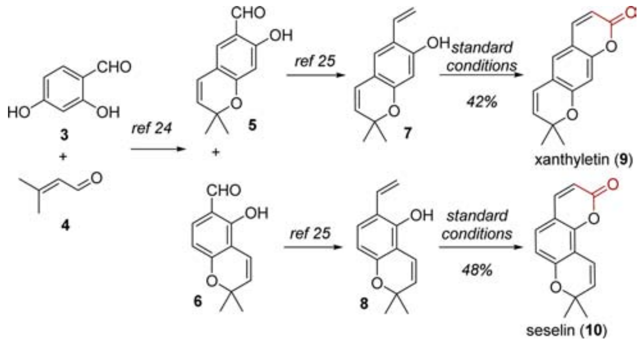
substitutent to the phenolic hydroxyl group (**2r**) gave a moderate yield of 55%. It should be noted that natural product herniarin can be assembled directly in 61% yield using this method (**2n**). A variety of diversely 1,1-disubstituted alkenes underwent reaction without difficulty (**2s−x**). However, the use of 1,1,2-trisubstituted alkene **1y** and 2-allylphenol **1z** showed no desired reactivity probably because of steric hindrance. An attempt to use nitrogen as a directing group also failed. Trivial consumption of **1aa−1ac** was found, which was suspected to be due to the unfavored low acidity of the corresponding N−H bonds. However, the more acidic substrate **1ad** furnished an indole product, with no insertion of CO observed.

As an indication of the possible practical potential of this catalyst system, a gram-scale reaction was conducted with 5 mol % of catalyst Cp*Co(CO)I_2 (eq 1). No significant erosion of yield (**2u**, 74%, 1.4 g) was observed compared to a small scale reaction.

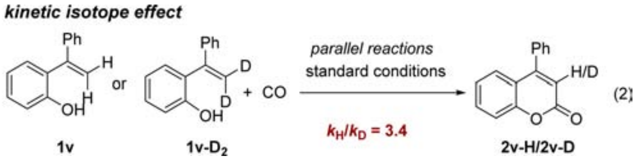


To further demonstrate the utility of this new strategy, we performed the total synthesis of the natural product xanthyletin (**9**) and seselin (**10**), which have shown promising biological activities. As shown in Scheme 3, the corresponding 2-vinylphenols **7** and **8** could be synthesized in two steps starting from commercially available β-resorcylaldehyde and prenal according to literature precedent.[25,26] We are delighted to find that, under the standard reaction conditions, xanthyletin and seselin could be obtained in 42% and 48% yield, respectively.

Scheme 3. Total Synthesis of Natural Products Xanthyletin and Seselin

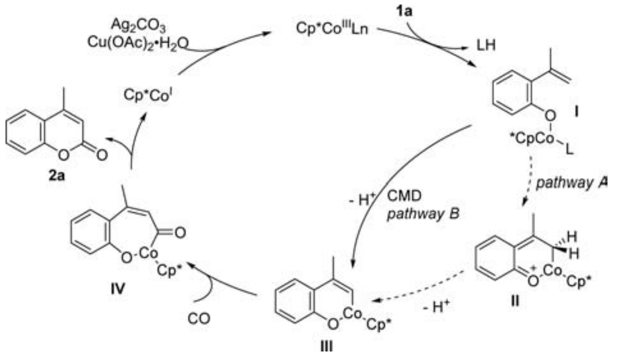


To gain some mechanistic information, the kinetic isotope effect (KIE) study was carried out (eq 2). A primary KIE value



of 3.4 was observed, indicating that C−H bond cleavage is the turnover-determining step. A proposed mechanism was outlined in Scheme 4. The active catalyst Cp*Co(III)Ln is generated by the reaction of Cp*Co(CO)I_2 with Ag_2CO_3 or $Cu(OAc)_2 \cdot H_2O$. The ligand replacement with 2-vinylphenol gives intermediate **I**. For the formation of the cyclometalated intermediate **III**, there are two possible pathways. An intramolecular electrophilic attack of the conjugated alkene to Cp*Co(III) followed by a base-assisted deprotonation would deliver the rearomatized intermediate **III** (pathway A). Alternatively, a concerted metalation deprotonation (CMD) process would also give **III** (pathway B). Based on the KIE experiment, we believe pathway B is more likely. Thereafter, CO coordination is followed by a migratory insertion to generate **IV**. The final coumarin product **2a** is formed upon reductive elimination. The resulting reduced Cp*Co^I is oxidized by the copper or silver salt to regenerate the active catalyst.

Scheme 4. Proposed Mechanism



In summary, we have developed a Cp*Co(III)-catalyzed direct cyclocarbonylation of 2-vinylphenols for the synthesis of coumarins. The reaction occurred under rather mild reaction conditions. Importantly, only balloon pressure CO was sufficient to maintain high reactivity. The substrate scope was generally good, and a variety of functional groups were well tolerated. The synthetic utility of this reaction is demonstrated by a practical gram-scale preparation and the facile synthesis of three natural products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02728.

Experimental procedures and full analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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