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Palladium-Catalyzed Carbonylative Annulation of Internal Alkynes: Synthesis of 3,4-Disubstituted Coumarins

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The palladium-catalyzed annulation of internal alkynes by *o*-iodophenols in the presence of CO results in exclusive formation of coumarins. No isomeric chromones have been observed. The best reaction conditions utilize the 2-iodophenol, 5 equiv of alkyne, 1 atm of CO, 5 mol % $Pd(OAc)_2$, 2 equiv of pyridine, and 1 equiv of *n*-Bu_4NCl in DMF at 120 °C. The use of a sterically unhindered pyridine base is essential to achieve high yields. A wide variety of 3,4-disubstituted coumarins containing alkyl, aryl, silyl, alkoxy, acyl, and ester groups have been prepared in moderate to good yields. Mixtures of regioisomers have been obtained when unsymmetrical alkynes are employed. 2-Iodophenols with electron-withdrawing and electron-donating substituents and 3-iodo-2-pyridone are effective in this annulation process. The reaction is believed to proceed via (1) oxidative addition of the 2-iodophenol to Pd(0), (2) insertion of the alkyne triple bond into the aryl−palladium bond, (3) CO insertion into the resulting vinylic carbon−palladium bond, and (4) nucleophilic attack of the phenolic oxygen on the carbonyl carbon of the acylpalladium complex with simultaneous regeneration of the Pd(0) catalyst. This annulation process is the first example of intermolecular insertion of an alkyne occurring in preference to CO insertion.

Introduction

The development of methods for the formation of several carbon−carbon and/or carbon−heteroatom bonds in one reaction is one of the most important goals of the synthetic chemist, because such processes allow the assembly of complex molecular structures from relatively simple precursors in a single step. One of the fastest growing areas of research directed toward this goal is the development of transition-metal-catalyzed reactions involving the insertion of unsaturated molecules, such as alkenes, alkynes, and carbon monoxide, into a carbon−metal bond. For example, the palladium-catalyzed annulation of dienes and internal alkynes by aromatic and vinylic halides bearing a neighboring nucleophilic substituent has been developed in our laboratories in the last 15 years[1] as an efficient way to synthesize a wide variety of carbo- and heterocyclic compounds, including indoles,[2] isoquinolines,[3] benzofurans,[4] benzopyrans,[4] isocoumarins,[4,5] α-pyrones,[5,6] indenones,[7] naphthalenes,[8] and phenanthrenes.[9]

The insertion of CO into the aryl−palladium bond leading to the formation of an acylpalladium complex is now a ubiquitous process in organic synthesis.[10] Reactions of the resulting acylpalladium complexes with various nucleophiles are among the most useful methods of synthesis of aryl carbonyl compounds known. However, the consecutive insertion of CO and unsaturated hydrocarbons (alkenes and alkynes) into the aryl−palladium bond (Scheme 1) has received relatively little attention, and factors controlling the sequence of insertion are still not completely understood. On one hand, intramolecular versions of such processes in which a carbon−carbon double or triple bond is tethered to the aryl or vinylic iodide have been extensively studied.[11] The order of insertion in these processes depends on a variety of factors, such as the CO pressure, the nature of the multiple bond, the size of the ring formed, the reaction temperature, solvent, and other parameters. On the other hand, only a few examples of intermolecular three-component processes have been reported.[12] The pal-

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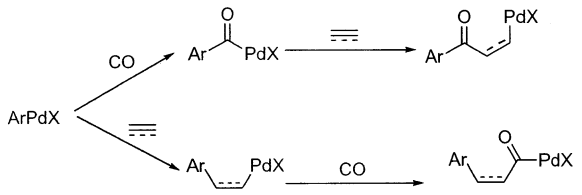
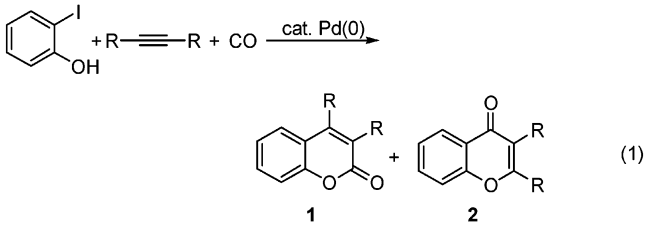
SCHEME 1



ladium-catalyzed reactions of 2-iodophenol with norbornene,[13] norbornadiene,[14] allenes,[15] and terminal alkynes[16] in the presence of CO produce coumaranone or chromone derivatives. Two examples of the palladium-catalyzed reactions of internal alkynes with aryl iodides and CO have been reported.[17] In all of the intermolecular reactions, insertion of CO always precedes insertion of the allene or alkyne, even when 1 atm of CO is employed, and the order of insertion of CO and norbornene can be controlled by the choice of the reaction temperature and phosphine ligand.

Our interest in palladium-catalyzed annulations of internal alkynes prompted us to explore the reaction of 2-iodophenols with internal alkynes in the presence of carbon monoxide (eq 1). This reaction appeared to be a potentially very efficient route to coumarins **1** or chromones **2**.



(1)

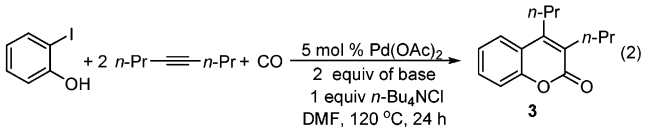
Naturally occurring coumarins possess interesting biological activity, including anticancer and HIV-1-specific reverse transcriptase inhibitor properties.[18] However, the existing methods for the synthesis of coumarins suffer major disadvantages. Two classical methods, the Perkin[19] and Pechman[20] reactions, require the use of stoichiometric amounts of strong acids and often high temperatures. Few functional groups in general can tolerate the harsh reaction conditions, and moreover, phenols with electron-withdrawing substituents fail to react. Many other syntheses of coumarins also utilize strong acidic or basic conditions, consist of several steps, and are often limited to the synthesis of monosubstituted coumarins.

Only a few Pd(0)-catalyzed approaches to the synthesis of coumarins have been reported,[14b,21] and the scope of these processes is very limited. A more general approach involves the Pd(II)-catalyzed reaction of phenols with 2-alkynoates.[22] Still, only polyoxygenated phenols have been used in this process, and the reaction is limited to the synthesis of 4-monosubstituted coumarins.

We have previously reported that the reaction of 2-iodophenol with internal alkynes in the presence of 1 atm of CO and a palladium catalyst results in the exclusive formation of coumarins **1**, without any traces of the isomeric chromones **2**.[23] Herein we report the full details of the synthesis of 3,4-disubstituted coumarins by the palladium-catalyzed carbonylative annulation of internal alkynes by 2-iodophenols.

Results and Discussion

Optimization of the Reaction Conditions. Initially, the reactions of 2-iodophenol with diphenylacetylene and 4-octyne under 1 atm of CO were run employing the standard conditions developed in our laboratories for the annulation of internal alkynes,[2,4] or the conditions usually employed in palladium-catalyzed carbonylation reactions.[11a,b,15,24] However, none of these systems afforded the desired product, except the reaction of 2-iodophenol with 4-octyne using NaOAc as a base at 120 °C, which afforded a small amount of 3,4-dipropylcoumarin (**3**) (eq 2). We, thus, chose the reaction of 2-iodophenol and 4-octyne under 1 atm of CO as a model system and thoroughly investigated the effect of various reaction parameters on the outcome of this reaction.



(2)

The nature of the base employed in the reaction proved to be the decisive factor determining the success of the reaction (Table 1). Only very low yields of the desired coumarin were obtained in reactions employing inorganic bases (entries 1−11). Moreover, with these bases, the presence or absence or nature of the phosphine ligand (entries 4−8) or variation in the amount of the alkyne employed (entries 6, 9, and 10) did not have any appreciable effect on the yield of **3**. Organic amines usually used in palladium-catalyzed carbonylation reactions, such as Et_3N or i-Pr_2NEt (entries 12 and 13), were completely ineffective in this reaction. Speculating that these amines can undergo β-hydride elimination upon

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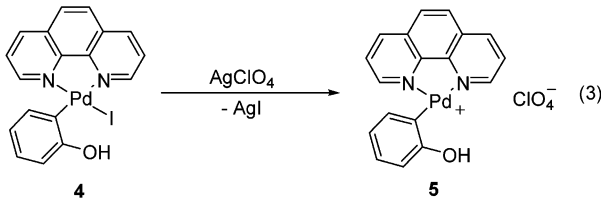
TABLE 1. Optimization of the Reaction Conditions on the Model System (Eq 2)[a]

entry	base	phosphine (amount, mol %)	amt of alkyne (equiv)	isolated yield of **3** (%)
1	TlOAc	PPh_3 (10)	2	9
2	$NaHCO_3$	PPh_3 (10)	2	12
3	Na_2CO_3	PPh_3 (10)	2	17
4	K_2CO_3	PPh_3 (10)	2	21
5	K_2CO_3		2	19
6	NaOAc	PPh_3 (10)	2	23
7	NaOAc		2	23
8	NaOAc	dppp (5)	2	21
9	NaOAc	PPh_3 (10)	1	26
10	NaOAc	PPh_3 (10)	5	25
11	Cs_2CO_3	PPh_3 (10)	2	30
12	Et_3N	PPh_3 (10)	2	12
13	*i*-Pr_2NEt	PPh_3 (10)	2	13
14	TMPP[b]	PPh_3 (10)	2	15
15	pyridine	PPh_3 (10)	2	37
16	pyridine		2	43
17	pyridine		3	50
18	pyridine		5	63
19	2,4,6-collidine	PPh_3 (10)	2	37
20	2,4,6-collidine		5	57
21	DTBMP[c]	PPh_3 (10)	2	20

[a] The following procedure was employed: 2-iodophenol (0.5 mmol), 4-octyne, the base (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), and $Pd(OAc)_2$ (5 mol %, 0.025 mmol) in DMF (10 mL) under 1 atm of CO were stirred at 120 °C for 24 h. [b] TMPP = 2,2,6,6-tetramethylpiperidine. [c] DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

coordination to the palladium atom, we tested a couple of amines lacking such hydrogens (entries 14 and 15). Only pyridine afforded a significantly better yield of the desired product. A further increase in the yield was achieved by removal of the phosphine ligand (entry 16) and an increase in the amount of 4-octyne (entries 17 and 18). A similar effect was observed when another relatively sterically unhindered pyridine, 2,4,6-collidine, was used as the base (entries 19 and 20). Use of the more sterically hindered base 2,6-di-*tert*-butyl-4-methylpyridine (entry 21) resulted in a significant decrease in the yield of **3**.

These results suggest that pyridine acts not only as a base, but also as a ligand, and perhaps its coordination to the palladium atom generates a more stable complex. Further support for this hypothesis has been obtained in experiments with bidentate pyridine ligands. Thus, when 2,2-bipyridyl was used as a base, only a 7% yield of **3** was obtained, and no coumarin **3** could be detected in the reaction employing 1,10-phenanthroline. However, the addition of $AgClO_4$ to the latter reaction results in the formation of coumarin **3** in 33% yield. These results can be rationalized by invoking the formation of complex **4** after oxidative addition of 2-iodophenol to the palladium(0) complex. Complex **4** lacks labile ligands that can easily dissociate to open a coordination site necessary for the reaction to proceed. The silver cation presumably removes the iodine atom from this complex, thus opening a coordination site and allowing the reaction to proceed (eq 3).



4 **5** (3)

Using 0.5 mmol of 2-iodophenol, 5 equiv of 4-octyne, and 2 equiv of pyridine as the base, other reaction parameters (catalyst precursor, solvent, and reaction temperature and time) have also been examined. Both $Pd(OAc)_2$ and $Pd(dba)_2$ are equally effective, while $Pd(PPh_3)_4$ afforded a slightly lower yield of **3**. The reactions run in other amide solvents, such as DMA or NMP, afforded slightly lower yields of the desired product, while DMSO proved to be completely ineffective, yielding the desired product in only 8% yield. Good yields of the desired product have been obtained only at 120 °C; only a 39% yield of **3** has been achieved after 48 h at 100 °C. The use of a higher pressure of CO proved to be detrimental to the process; no identifiable products could be isolated from the reaction mixture after 24 h at 120 °C under 5 atm of CO. The final optimized reaction conditions for the reaction of 2-iodophenol, 4-octyne, and carbon monoxide have thus been determined to be 0.5 mmol of 2-iodophenol, 5 equiv of 4-octyne, 5 mol % $Pd(OAc)_2$, 2 equiv of pyridine, and 1 equiv of *n*-Bu_4NCl in 5 mL of DMF at 120 °C for 24 h.

Scope and Limitations. The scope and limitations of this annulation reaction have been studied by allowing a wide variety of internal alkynes to react with various 2-iodophenols under our optimized reaction conditions. The results of this study are summarized in Table 2.

First, the carbonylative annulation of alkyl- and aryl-substituted acetylenes was investigated. Both dialkylalkynes (entries 1 and 2) and diarylalkynes (entries 3 and 4) afford coumarins in 55−63% yields, although a higher temperature was required with diphenylacetylene to drive the reaction to completion. A series of phenylalkylacetylenes, where the alkyl group is methyl, ethyl, or isopropyl, were also successfully employed in reactions with 2-iodophenol (entries 5−7). Mixtures of regioisomers were obtained in all cases with modest regioselectivity. The regioisomers were identified by comparison of the ^1H NMR chemical shifts of the hydrogens at C-5 in both isomers. The signal of this hydrogen is shifted upfield in 3-alkyl-4-phenylcoumarins relative to 4-alkyl-3-phenylcoumarins, because of the deshielding effect of the benzene ring.[25] Thus, it was determined that in all cases the major isomer is the 3-phenyl-4-alkylcoumarin. This pattern of alkyne insertion, in which the palladium atom adds to the more sterically hindered end of the triple bond, is consistent with results obtained in all of our previous annulation reactions.[1,2,3a,5]

Both the regioselectivity and the yields of the annulations of phenylalkylacetylenes are affected by the steric bulk of the alkyl substituent. An increase in the size of the alkyl group generally results in a decrease in the regioselectivity and the yield of the reaction (entries 5−8). However, the dependence of the yield on the size of the alkyl substituent is not linear. The yield of the coumarin decreases in the following order: Me ≅ Et > *i*-Pr ≫ *t*-Bu. The effect of the *tert*-butyl group is enormous. No product was obtained when 3,3-dimethyl-1-phenyl-1-butyne was employed as the alkyne (entry 8). The reaction with another alkyne bearing a *tert*-butyl group, 4,4-dimethyl-

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TABLE 2. Synthesis of Coumarins by the Palladium-Catalyzed Carbonylative Annulation of Internal Alkynes[a]

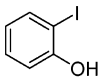
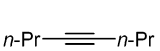
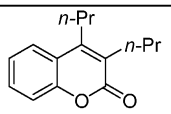
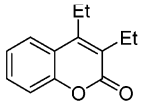
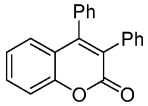
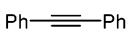
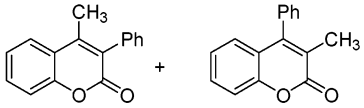
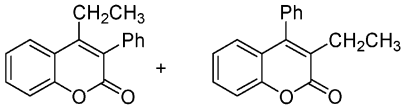
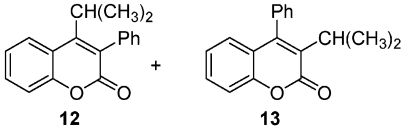
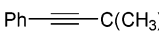
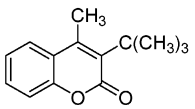
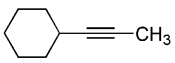
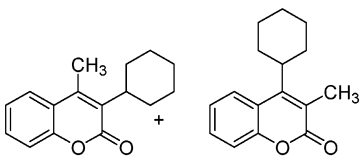
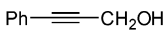
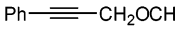
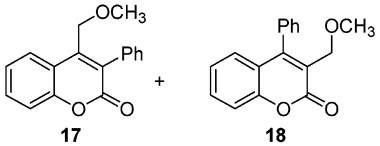
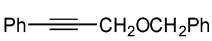
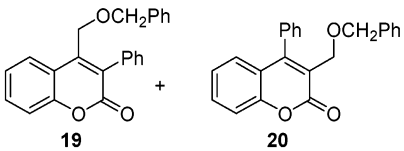
entry	phenol	alkyne	product(s)	% isolated yield (ratio)
1			 **3**	63
2			 **6**	55
3			 **7**	54
4			**7**	62[b]
5			 **8** **9**	72 (3.8:1)
6			 **10** **11**	78 (2.6:1)
7			 **12** **13**	62 (1.7:1)
8			--	0
9			 **14**	9
10			 **15** **16**	57 (2.8:1)
11			-- --	0
12			 **17** **18**	65 (3:1)
13			 **19** **20**	65 (3:1)

Table 2. (Continued)

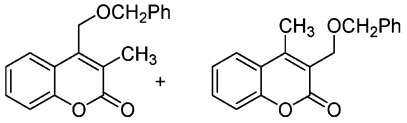
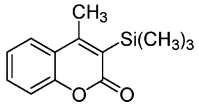
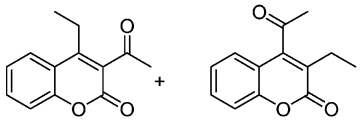
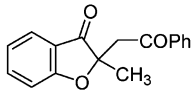
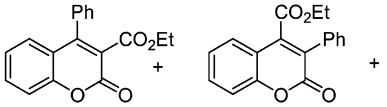
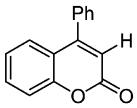
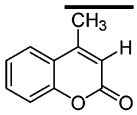
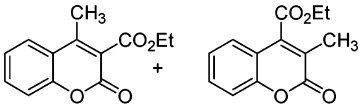
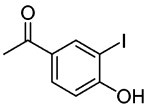
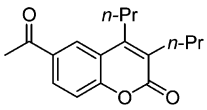
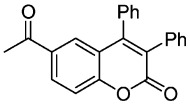
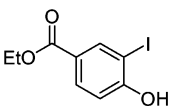
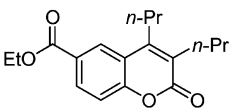
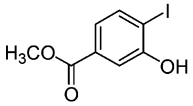
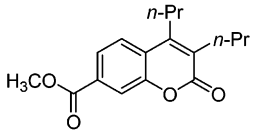
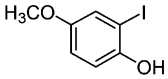
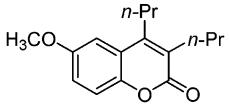
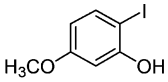
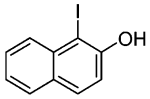
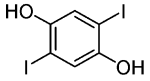
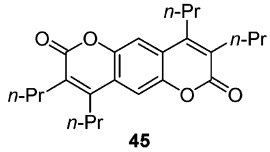
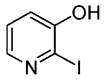
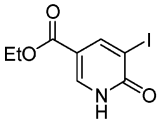
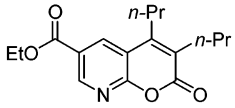
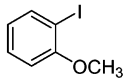
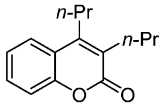
entry	phenol	alkyne	product(s)	% isolated yield (ratio)
14		$H_3C-\equiv-CH_2OCH_2Ph$	 **21** + **22**	45 (1:1.4)
15		$(H_3C)_3Si-\equiv-CH_3$	 **23**	43
16		$CH_3CH_2-\equiv-COCH_3$	 **24** + **25**	61 (9:1)
17		$H_3C-\equiv-COPh$	 **26**	75[c]
18		$Ph-\equiv-CO_2Et$	 **27** + **28** +	45 (1:3)
			 **29**	5
19		$H_3C-\equiv-CO_2Et$	 **30** +	24
			 **31** + **32**	22 (1:3.4)
20	 **33**	*n*-Pr—≡—*n*-Pr	 **34**	56
21		Ph—≡—Ph	 **35**	48
22	 **36**	*n*-Pr—≡—*n*-Pr	 **37**	59

Table 2. (Continued)

entry	phenol	alkyne	product(s)	% isolated yield (ratio)
23	 **38**	*n*-Pr—≡—*n*-Pr	 **39**	66[d]
24	 **40**	*n*-Pr—≡—*n*-Pr	 **41**	62[e]
25	 **42**	*n*-Pr—≡—*n*-Pr	--	0[f]
26	 **43**	*n*-Pr—≡—*n*-Pr	--	0[g]
27	 **44**	*n*-Pr—≡—*n*-Pr	 **45**	54
28	 **46**	*n*-Pr—≡—*n*-Pr	--	0
29	 **47**	*n*-Pr—≡—*n*-Pr	 **48**	70
30		*n*-Pr—≡—*n*-Pr	 **3**	27

[a] The following representative procedure for the carbonylative annulation of internal alkynes has been employed unless indicated otherwise: the 2-iodophenol (0.5 mmol), the alkyne (2.5 mmol), pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (5 mol %, 0.025 mmol), and DMF (5 mL) were placed in a 4 dram vial. The vial was purged with CO for 2 min and then connected to a balloon of CO, and the reaction mixture was stirred at 120 °C for 24 h. [b] The reaction was run at 135 °C. [c] The reaction was complete in 10 h. [d] The reaction was complete in 12 h. [e] The reaction was complete in 6 h. [f] 3-Methoxyphenol was obtained in 80% yield. [g] 2-Naphthol was obtained in 82% yield, and 12% of 1-iodo-2-naphthol was recovered.

2-pentyne (entry 9), resulted in only a 9% yield of the desired product. This unusual sensitivity of the annulation to steric hindrance is even more surprising considering that these alkynes have been among the best in our previous annulation reactions.[1,2,7a,8] The reaction temperature does not have any major effect on the regioselectivity. The carbonylative annulation of 1-phenyl-1-butyne at 120 °C affords coumarins **10** and **11** as a 2.6:1 mixture in 78% yield, while the analogous reaction run at 100 °C affords a 2.4:1 mixture in 47% yield. The carbonylative annulation of 1-cyclohexyl-1-propyne also produced a mixture of regioisomers (entry 10).

Alkynes bearing a variety of functional groups, such as alkoxy, silyl, acyl, and ester groups, have also been effectively annulated under our standard conditions (entries 12−19). Surprisingly, the propargylic alcohol

3-phenyl-2-propyn-1-ol failed to provide any coumarin in this process (entry 11). A significant amount of the starting acetylene was recovered from the reaction, along with a small amount (~0.2 mmol) of the corresponding formate. Protection of the hydroxyl group circumvents this problem. Thus, when 3-methoxy-1-phenyl-1-propyne was employed, the desired product was obtained in 65% yield as a 3:1 mixture of the regioisomers **17** and **18** (entry 12). More easily removed protecting groups, such as benzyl, can also be employed successfully in this process (entries 13 and 14).

Only one regioisomer has been obtained in the annulation of 1-trimethylsilyl-1-propyne, albeit in only 43% yield (entry 15). The improved regioselectivity is due to the steric bulk of the trimethylsilyl group. Unfortunately, the steric bulk also leads to a decrease in the overall yield of the coumarin, similar to the effect of a *tert*-butyl group (entries 8 and 9). However, it is noteworthy that the yield from the reaction of this silylacetylene with a longer C−Si bond is significantly higher than the yield from the reaction of 4,4-dimethyl-2-pentyne (entry 9).

Electron-deficient alkynes (alkynones and alkynoates) behave in these carbonylative annulation reactions quite differently from other alkynes. 3-Hexyn-2-one (entry 16) affords the desired coumarin in good yield with good regioselectivity (9:1). The major product is coumarin **24**, identified by comparison of its ^{1}H NMR spectrum with literature data.[26] The high regioselectivity of the annulation is clearly governed not only by steric factors (ethyl and acetyl groups are not very different in size), but also by electronic factors. Electronic factors apparently favor insertion of the alkyne into the aryl−palladium bond so that the palladium moiety ends up on the carbon next to the carbonyl group.

While the annulation of 3-hexyn-2-one was successful, none of the desired coumarin was observed in the annulation of 1-phenyl-2-butyn-1-one (entry 17). The major product isolated from the reaction mixture was identified as 2-benzoylmethyl-2-methyl-1-benzofuran-3(2*H*)-one (**26**), obtained in 75% yield. The structure of the product was confirmed by comparison of its ^{1}H and ^{13}C NMR spectra with those of 2-benzoylmethyl-2-*n*-butyl-1-benzofuran-3(2*H*)-one.[27] The mechanism for the formation of this interesting product will be discussed later.

Unexpected products were also observed in the reactions of 2-alkynoates. The carbonylative annulation of ethyl phenylpropiolate resulted in the formation of the desired coumarins **27** and **28** in a 1:3 ratio and 45% yield (entry 18). Here, the regioselectivity of the reaction is most likely determined by the size of the substituents on the carbon−carbon triple bond. Besides these two coumarins, a small amount of 4-phenylcoumarin (**29**) has also been detected by GC−MS and ^{1}H NMR spectroscopy, although we have been unable to isolate it in pure form and fully characterize it. This coumarin is likely the result of the in situ decarboalkoxylation of coumarin **27**.

The annulation of ethyl 2-butynoate (entry 19) also affords three coumarins, **30**−**32**, and the total yield of the annulation products is similar to that of the reaction of ethyl phenylpropiolate. In this case, however, the decarboxylated coumarin **30** is the major product (24% yield). Coumarin **31** has been identified by comparison of its ^{1}H NMR spectral data with literature data.[28] Thus, the selectivity of this reaction is only (**30** + **31**):**32** = (24 + 5):17 = 1.7:1. This result is similar to the result obtained with 1-benzyloxy-2-butyne (entry 14), and the regiochemistry is, therefore, most probably due only to the difference in size between the methyl and ethoxycarbonyl groups. Hence, unlike the reaction with 3-hexyn-2-one, no major electronic effects have been detected in the carbonylative annulation of alkynoates.

Various functionalized iodophenols have also been successfully employed in the carbonylative annulation of internal alkynes. Thus, the carbonylative annulation of 2-iodophenols bearing electron-withdrawing groups *para* to the hydroxyl group have proven to be nearly as successful as 2-iodophenol itself (entries 20−22). An electron-withdrawing group can also be introduced at C-7 of the coumarin (entry 23). Again, the yield is comparable to the yield obtained with the parent 2-iodophenol. In addition, the reaction of iodophenol **38** is much faster, reaching completion within 12 h. This result is consistent with the higher reactivity of an electron-poor aryl iodide in oxidative addition to Pd(0). These results are all the more important, because coumarins possessing electron-withdrawing groups cannot be prepared using classical methods, such as the Pechman reaction.[20]

On the other hand, an electron-donating group, such as a methoxy group, cannot be as easily introduced into the coumarin. When 2-iodo-4-methoxyphenol was allowed to react with 4-octyne, the desired coumarin was produced in 62% yield (entry 24). However, the annulation of 4-octyne with 2-iodo-5-methoxyphenol (entry 25) afforded none of the desired coumarin. The only product isolated from the reaction was 3-methoxyphenol, obtained in 80% yield. The same unusual behavior was observed in the reaction of 1-iodo-2-naphthol (entry 26), in which the only product was 2-naphthol, isolated in 82% yield, alongside 12% of the recovered starting material.

The reaction of 4-octyne with 2,5-diiodo-1,4-hydroquinone (**44**) (entry 27) shows that double annulation can be successfully accomplished using the standard reaction conditions, even without increasing the alkyne-to-iodophenol ratio beyond the usual 5:1 ratio. The yield of the doubly annulated product **45** (54%) is only slightly lower than the yield of coumarin **3** in the reaction with the parent 2-iodophenol (entry 1, 63%). This result and the absence of the product of monoannulation seem to indicate that the first pyrone ring activates the intermediate toward formation of the second pyrone ring.

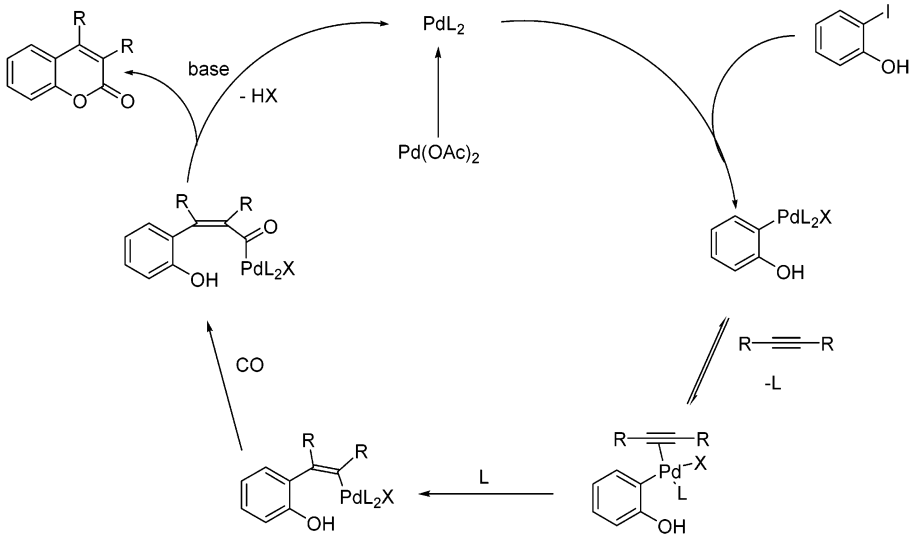
Heterocyclic analogues of 2-iodophenol were also examined in the carbonylative annulation. 3-Hydroxy-2-iodopyridine appeared to be unreactive in this process (entry 28). Only a small amount of a bipyridine coupling product was observed in the reaction, although the starting material almost completely disappeared. On the other hand, the substituted 3-iodo-2-pyridone **47** affords the azacoumarin **48** in 70% yield, the highest yield obtained thus far in the annulation of 4-octyne (entry 29).

(26) Clinging, R.; Dean, F. M.; Houghton, L. E. *J. Chem. Soc., Perkin Trans. 1* **1974**, 66.

(27) Kokubo, K.; Matsumasa, K.; Nishinaka, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 303.

(28) Awasthi, A. K.; Tewari, R. S. *Synthesis* **1986**, 1061.

SCHEME 2



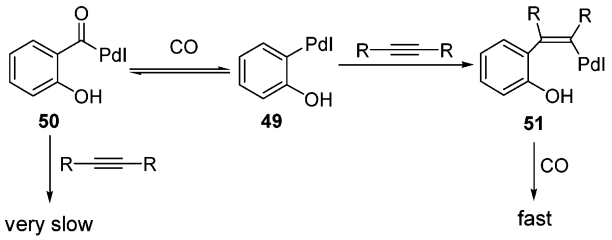
Surprisingly, 2-iodoanisole is also reactive in the carbonylative annulation, producing coumarin **3** in 27% yield (entry 30). Although this is only half of the yield obtained with 2-iodophenol, it is interesting to see that a free hydroxyl group is not necessary for the reaction to proceed.

Mechanism. A possible mechanism for the carbonylative annulation is shown in Scheme 2. First, $Pd(OAc)_2$ is reduced to a Pd(0) complex, which is the actual catalyst in the process. We believe that CO acts as the reducing agent in this reaction, since it is known to reduce Pd(II) to Pd(0) in the presence of alcohols and phenols.[29] The oxidative addition of 2-iodophenol to Pd(0) to form an arylpalladium complex starts the catalytic cycle. Dissociation of one of the neutral ligands from the palladium opens a coordination site, which is then occupied by the internal alkyne. Insertion of the alkyne into the aryl−palladium bond provides a vinylic palladium species. Insertion of CO into the vinyl−palladium bond gives rise to an acylpalladium complex. Finally, intramolecular nucleophilic attack on the carbonyl group of the latter complex by the phenolic oxygen produces the desired coumarin and regenerates Pd(0).

This process represents the first example of insertion of an internal alkyne into an aryl−palladium bond in preference to CO insertion. The reverse is true in all examples previously reported in the literature.[11a,17] In fact, Negishi determined the relative rates of various processes to be as follows: CO insertion ≅ intramolecular 5-*exo*- or 6-*exo*-alkyne carbopalladation > intramolecular 5-*exo*-alkyne acylpalladation > trapping of an acylpalladium with MeOH > intermolecular carbopalladation or acylpalladation.[11c] Thus, the preferential insertion of an alkyne and, moreover, the complete absence of products arising from the initial insertion of CO are quite surprising. Therefore, we attempted to establish the origins of such unusual behavior.

The observed order of insertion can be rationalized in two ways. The first explanation, shown in Scheme 3,

SCHEME 3



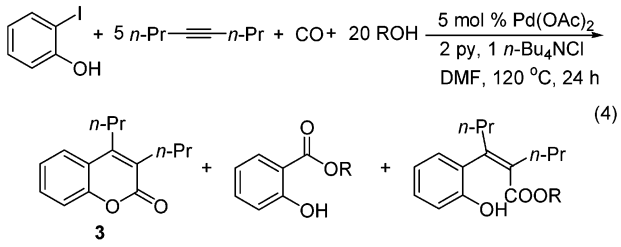
assumes that insertions of both CO and the alkyne readily occur under our reaction conditions. The alkyne inserts irreversibly to afford the vinylpalladium complex **51**, which then reacts with CO, eventually forming the coumarin. In contrast, CO inserts in a reversible fashion. Therefore, if the acylpalladium complex **50** reacts with the alkyne very slowly, or not at all, then, in the absence of any other reaction pathways, the palladium complex **50** could undergo decarbonylation, regenerating the original arylpalladium complex **49**. Eventually, most of the arylpalladium complex **49** reacts with the internal alkyne, affording the desired coumarin.

In the case shown in Scheme 3, insertion of the alkyne may be either faster or slower than the insertion of CO. On the other hand, it is possible that no insertion of CO into the aryl−palladium bond takes place under our reaction conditions. Indeed, our reaction conditions [$Pd(OAc)_2$, pyridine, *n*-Bu_4NCl] are quite different from the conditions usually employed in palladium-catalyzed carbonylations [$PdCl_2(PPh_3)_2$, Et_3N, no chloride source].[11a,b,15,24]

To establish whether the insertion of CO occurs under our standard conditions, we attempted to trap the acylpalladium complexes by reaction with a nucleophile. Initially, alcohols were used as external nucleophiles. Formation of three products is possible (eq 4). However, in all cases only coumarin **3** was isolated in yields comparable to the yield of the reaction without any alcohol present. For example, when 1-pentanol was used, **3** was obtained in 66% yield.

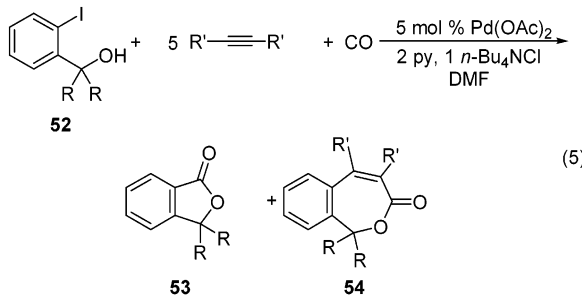
Since an attempt to use an external nucleophile failed, we employed an aryl iodide with an internal nucleophile. 2-Iodobenzyl alcohol was the obvious choice. If the

(29) (a) Rivetti, F.; Romano, U. *J. Organomet. Chem.* **1979**, *174*, 221. (b) Stromnova, T. A.; Vargaftik, M. N.; Moiseev, I. I. *J. Organomet. Chem.* **1983**, *252*, 113.



(4)

insertion of CO into the aryl−palladium bond occurs, the resulting acylpalladium complex should be easily trapped by the adjacent hydroxyl group, leading to formation of the five-membered ring lactone **53** (eq 5).[30] Alternatively, formation of the seven-membered ring lactone **54** might occur upon insertion of an alkyne and CO.



(5)

Under our standard carbonylative annulation conditions, the reaction of 2-iodobenzyl alcohol (**52a**, R = H) with 4-octyne was complete within 4 h, and both possible products **53a** (R = H) and **54a** (R = H, R′ = *n*-Pr) were isolated in 24% and 43% yields, respectively. The temperature has a remarkable effect on the chemoselectivity of this reaction (Table 3, entries 1−3). The yield of **54a** drops dramatically with a decrease in the reaction temperature, while the yield of **53a** increases. The nature of the alkyne is also a very important factor in determining the selectivity of the reaction. Thus, when diphenylacetylene was used (entry 4), the five-membered ring lactone **53a** was obtained in 46% yield, while the yield of the seven-membered ring lactone **54b** (R = H, R′ = Ph) was only 16%.

When the tertiary benzylic alcohol **52b** (R = Me) was employed in the reaction, only the five-membered ring lactone **53b** (R = Me) was obtained in 78% yield, and none of the product of the alkyne insertion was detected (entry 5). Apparently, the presence of two methyl groups forces the alcohol into a conformation in which the hydroxyl group is in close proximity to the iodine atom, and consequently, trapping of the acylpalladium intermediate is much more effective than in the case of 2-iodobenzyl alcohol.

These results suggest that CO does insert into the aryl−palladium bond under our reaction conditions. Moreover, the outcome of the reaction with alcohol **52b** shows that even at 120 °C the insertion of CO is faster than the insertion of an internal alkyne. Consequently, the ratio of products arising from the initial CO insertion to those of the initial alkyne insertion is determined by the relative rates of two processes, the reaction of acylpalladium complex **50** with either a nucleophile or some other species (alkene or alkyne) and insertion of

(30) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193.

TABLE 3. Carbonylative Annulation of Internal Alkynes with 2-Iodobenzylic Alcohols (Eq 5)

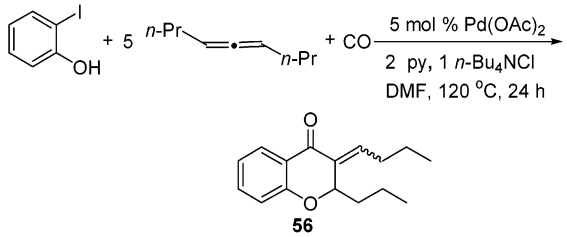
entry	R	R′	temp (°C)	time (h)	isolated yield (%) **53**	**54**
1	H	*n*-Pr	120	4	24	43
2	H	*n*-Pr	100	8	45	28
3	H	*n*-Pr	80	24	67	<5
4	H	Ph	120	4	46	16
5	Me	*n*-Pr	120	2	78	0

the alkyne into the aryl−palladium bond of complex **49**. The factors affecting the relative reactivity of one of these (or both) complexes change the ratio of the products of the initial CO insertion and the initial alkyne insertion.

The more favorable conformation of the hydroxyl group in **52b** than in **52a** apparently increases the rate of trapping of the acylpalladium complex corresponding to **50**. On the other hand, a decrease in the temperature slows insertion of the alkyne into the complex corresponding to **49**. Diphenylacetylene is less reactive than 4-octyne; thus, the yield of **53a** increases.

Thus, the apparent reason for the exclusive formation of coumarins in our process is the slow insertion of an internal alkyne into an acyl−palladium bond. Only in one case, the reaction of 2-iodophenol with 1-phenyl-2-butyn-1-one (Table 2, entry 17), have we observed a product apparently arising from the insertion of an internal alkyne into the acyl−palladium bond. Surprisingly, the product of this reaction is not a chromone, but a 1-benzofuran-3(2*H*)-one derivative **26**. A probable mechanism for its formation is shown in Scheme 4. Addition of the acylpalladium complex to the carbon−carbon triple bond generates a vinylpalladium intermediate that probably exists in equilibrium with the corresponding palladium enolate. The hydrolysis of this enolate by water present in DMF leads to enone **55**. Intramolecular Michael addition of the phenol then affords the final product **26**. No coumarins were detected in this reaction, while no products arising from the insertion of the alkyne into the acylpalladium bond were observed in the reaction with 3-hexyn-2-one (Table 2, entry 16). The origins of this complete reversal of the reactivity are not clear at this point.

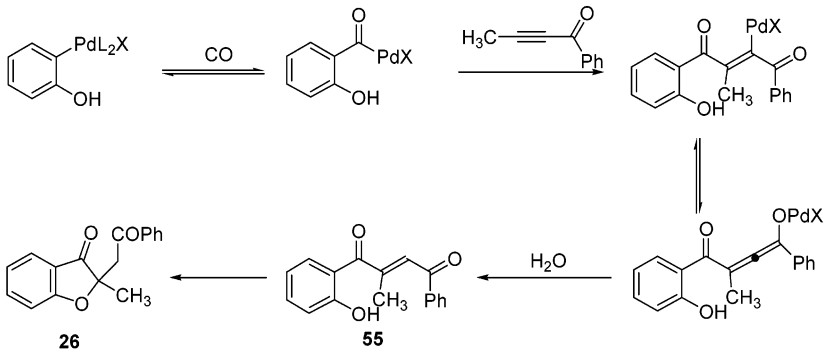
We were interested in seeing whether the unusual selectivity would be observed with other unsaturated compounds, such as allenes. However, only the product of initial CO insertion, 3-*n*-butylene-2-*n*-propyl-2,3-dihydro-4*H*-1-benzopyran-4-one (**56**), was obtained in the carbonylative annulation of 4,5-nonadiene under our standard annulation conditions (eq 6). The same order



(6)

of insertion has been observed by Alper under different reaction conditions.[15] This result shows that the carbon−carbon double bond of the allene easily inserts into the acyl−palladium bond under our reaction conditions, and

SCHEME 4



therefore, the unusual order of insertion in our chemistry is probably limited to internal alkynes.

Conclusions

An efficient palladium-catalyzed synthesis of 3,4-disubstituted coumarins has been developed. A wide variety of alkynes containing alkyl, aryl, silyl, alkoxy, acyl, and ester groups afford coumarins in moderate to good yields. The process is sensitive to the steric bulk of the alkynes, and alkynes bearing tertiary alkyl substituents generally fail to undergo annulation. Unsymmetrical alkynes produce mixtures of regioisomers with generally only modest selectivity. The regioselectivity of the process is governed by both steric and electronic factors. Substituted 2-iodophenols with both electron-donating and electron-withdrawing substituents, as well as substituted pyridinones, are effective in this process, thus creating a fast and efficient route to coumarins that are not easily accessible by classical methods.

This carbonylative annulation process represents the first example of a domino process in which the insertion of an internal alkyne into an aryl−palladium bond occurs prior to the insertion of CO. Trapping experiments suggest that the reason for this unusual selectivity is not the intrinsic inability of CO to undergo insertion under our reaction conditions, but the absence of any species able to react with the resulting acylpalladium complex faster than it undergoes decarbonylation.

Experimental Section

General Procedure for the Palladium-Catalyzed Synthesis of Coumarins. The 2-iodophenol (0.5 mmol), the alkyne (2.5 mmol), pyridine (79 mg, 1.0 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol %, 0.025 mmol), and DMF (5 mL) were placed in a 4 dram vial. The vial was purged with CO for 2 min, and then connected to a balloon of CO. The reaction mixture was stirred at 120 °C for 24 h, then allowed to cool to room temperature, diluted with EtOAc, washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel.

Data for 3,4-dipropyl-2*H*-1-benzopyran-2-one (3): white solid; mp 58−60 °C; ^1H NMR ($CDCl_3$) δ 7.59 (dd, J = 1.2, 8.0 Hz, 1H), 7.45 (ddd, J = 1.2, 8.0, 8.4 Hz, 1H), 7.25−7.32 (m, 2H), 2.79 (m, 2H), 2.61 (m, 2H), 1.55−1.70 (m, 4H), 1.11 (t, J = 7.6 Hz, 3H), 1.03 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.1, 152.8, 150.1, 130.5, 126.6, 124.7, 124.2, 120.0, 117.2, 30.7, 29.9, 23.1, 22.5, 14.7, 14.5; IR ($CHCl_3$, cm^{-1}) 3073, 2962, 2872, 1716; MS *m*/*z* (rel intens) 230 (67, M^+), 215 (77), 201 (66), 187 (100). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.05; H, 8.05.

Full characterization and spectral data for compounds **7**−**11**, **14**, **19**, **20**, **23**−**25**, **37**, **39**, **41**, and **48** can be found in ref 23. Full characterization and spectral data for all other coumarins prepared can be found in the Supporting Information.

Trapping of the Acylpalladium Complexes with an External Alcohol. 2-Iodophenol (110 mg, 0.5 mmol), 4-octyne (275 mg, 2.5 mmol), pyridine (79 mg, 1.0 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol %, 0.025 mmol), and DMF (5 mL) were placed in a 4 dram vial. The vial was purged with CO for 2 min and then connected to a balloon of CO. An alcohol (10 mmol) was added to the reaction mixture in one portion. The reaction mixture was stirred at 120 °C for 24 h, then allowed to cool to room temperature, diluted with EtOAc, washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The products were isolated by flash chromatography on silica gel.

Carbonylative Annulation of Internal Alkynes with 2-Iodobenzylic Alcohols. The 2-iodobenzylic alcohol (0.5 mmol), the alkyne (2.5 mmol), pyridine (79 mg, 1.0 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol %, 0.025 mmol), and DMF (5 mL) were placed in a 4 dram vial. The vial was purged with CO for 2 min and then connected to a balloon of CO. Upon completion of the reaction (for the reaction temperatures and times, see Table 3), the reaction mixture was cooled to room temperature, diluted with EtOAc, washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The products were isolated by flash chromatography on silica gel.

Data for 4,5-dipropyl-1,3-dihydrobenzo[*c*]oxepin-3-one (54a): colorless oil; ^1H NMR ($CDCl_3$) δ 7.37−7.48 (m, 3H), 7.31 (ddd, J = 1.2, 7.2, 7.6 Hz, 1H), 5.04 (d, J = 7.6 Hz, 1H), 4.81 (d, J = 7.6 Hz, 1H), 2.66−2.75 (m, 3H), 2.51−2.58 (m, 1H), 1.59−1.68 (m, 2H), 1.34−1.46 (m, 2H), 1.03 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.0, 143.5, 139.5, 135.7, 133.2, 129.5, 128.5, 128.3, 127.3, 68.3, 35.1, 34.2, 23.3, 22.5, 14.5, 14.4; IR ($CHCl_3$, cm^{-1}) 2959, 2872, 1707; MS *m*/*z* (rel intens) 244 (45, M^+), 216 (28), 201 (71), 173 (100); HRMS *m*/*z* calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1468.

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Supporting Information Available: Procedures for the preparation of starting materials and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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