Synthesis of Isocoumarins and α-Pyrones via Palladium-Catalyzed Annulation of Internal Alkynes

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A number of 3,4-disubstituted isocoumarins and polysubstituted α-pyrones have been prepared in good yields by treating halogen- or triflate-containing aromatic and α,*β*-unsaturated esters, respectively, with internal alkynes in the presence of a palladium catalyst. Synthetically, the methodology provides an especially simple and convenient, regioselective route to isocoumarins and α-pyrones containing aryl, silyl, ester, *tert*-alkyl, and other hindered groups. The reaction is believed to proceed through a seven-membered palladacyclic complex in which the regiochemistry of the reaction is controlled by steric factors. A number of 3,4-disubstituted isocoumarins and polysubstituted α-pyrones have been prepared in good yields by treating halogen- or triflate-containing aromatic and α,*β*-unsaturated esters, respectively, with internal alkynes in the presence of a palladium catalyst. Synthetically, the methodology provides an especially simple and convenient regioselective route to isocoumarins and α-pyrones containing aryl, silyl, ester, *tert*-alkyl, and other hindered groups. The reaction is believed to proceed through a seven-membered palladacyclic complex in which the regiochemistry of the reaction is controlled by steric factors.

Introduction

Isocoumarins[1] and α-pyrones[2] are useful intermediates in the synthesis of a variety of important hetero- and carbocyclic molecules, including isocarbostyrils, isoquinolines, isochromenes, pyridones, and various aromatic compounds. These lactones also occur as structural subunits in numerous natural products that exhibit a wide range of biological activity.[3] Very recently, low molecular weight α-pyrones have been shown to be potent HIV-1 protease inhibitors.[4]

Although traditional approaches to the synthesis of these ring systems have been diverse,[1b,5,6] a number of organometallic approaches utilizing palladium have been reported over the past few years. Isocoumarins have been prepared by the ortho-thallation of benzoic acids and subsequent palladium-catalyzed olefination using simple olefins, allylic halides, and vinylic halides or esters.[7] Unsubstituted or 3-substituted isocoumarins have been prepared by the palladium-catalyzed coupling of 2-halobenzoate esters or 2-halobenzonitriles with alkenes,[8] vinylic stannanes,[9] or terminal alkynes[10] and subsequent cyclization or *π*-allylnickel cross-coupling and palladium-catalyzed cyclization.[11] Recently, 3-substituted isocoumarins have been synthesized by the palladium-catalyzed coupling of 2-(2′,2′-dibromovinyl)benzoates and organostannanes.[12] The cross-coupling of *o*-iodobenzoic acid and terminal alkynes produces either unsaturated phthalides[13] or 3-substituted isocoumarins[14] as major products. Pertinent to the present work, α-pyrones have been synthesized by the cyclization of open-chain 2,4-pentadienoic acids using lithium chloropalladite[15] or formed as unstable multiple-insertion products from the reaction of palladium complexes with internal alkynes.[16]

In 1989, Heck reported the direct formation of 3,4-diphenylisocoumarin in 56% yield from the palladium-

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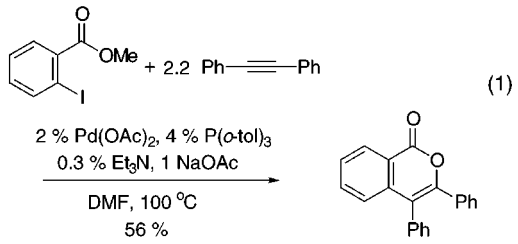
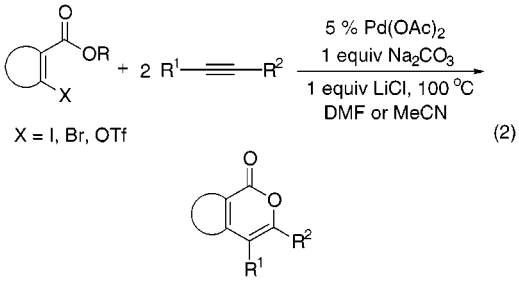
catalyzed coupling of methyl 2-iodobenzoate and diphenylacetylene (eq 1).[17] Di-*p*-anisylacetylene and 1-phenyl-1-hexyne afforded only 38% and 29% yields, respectively, of the corresponding isocoumarins. Because of our own interest in this type of annulation process,[18] we have extended this annulation methodology to a general synthesis of isocoumarins[19] and α-pyrones[20] and report those results here.



(1)

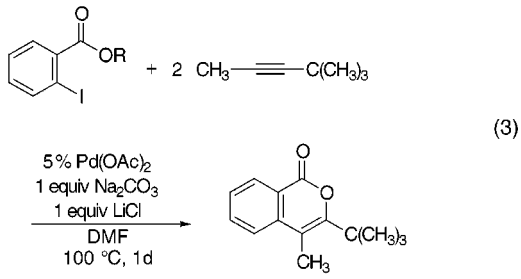
Results and Discussion

We have developed a simple procedure for the annulation of internal alkynes by appropriate halogen- or triflate substituted esters (eq 2). Our results using this procedure for the synthesis of isocoumarins are summarized in Table 1, entries 1−12.



(2)

Isocoumarins can be prepared from either *o*-iodo- or *o*-bromobenzoate esters, although the *o*-iodobenzoate esters generally afford shorter reaction times and higher yields (Table 1, entries 1 and 2). The corresponding aryl triflate was also treated with internal alkynes under these same conditions, but failed to produce any isocoumarin product, even after 6 days (Table 1, entry 3). Surprisingly, the nature of the R group on the ester had very little effect on the reaction rate or product yield as shown in eq 3. Even the neopentyl, phenyl, and *tert*-butyl

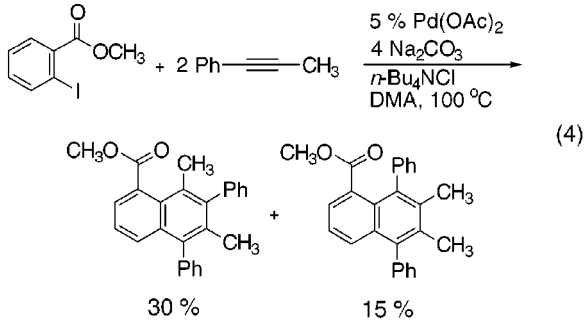


(3)

R = Me, 72 %; Et, 68 %; *i*-Pr, 71 %; *t*-Bu, 82 %; neopentyl, 64 %; phenyl, 75 %

o-iodobenzoate esters cyclized in approximately the same time and yield as the corresponding methyl ester. It is necessary to use an ester in this annulation process, as attempted annulation using the parent carboxylic acid, *o*-iodobenzoic acid, resulted in disappearance of the starting material and formation of only a trace amount of the desired product.

This annulation process is highly regioselective for alkynes containing tertiary alkyl, aryl, trialkylsilyl, or other hindered groups, with the only product having the more sterically demanding group in the position adjacent to the heteroatom (Table 1, entries 4−12). However, high-yielding, clean reactions are generally limited to these types of alkynes. Attempted annulation of less substituted alkynes, such as 4-octyne, lead to complex reaction mixtures. Highly substituted naphthalene derivatives were also formed in some cases, as in the reaction of 1-phenyl-1-propyne and methyl 2-iodobenzoate under slightly different reaction conditions (eq 4). The regiochemical assignment of the naphthalene isomers is based on ^{1}H NMR deshielding of the methyl group by the ester carbonyl group in the major isomer and the assumption that the second alkyne insertion proceeds regioselectively as described in our recent analogous polycyclic aromatic hydrocarbon chemistry.[18g]



(4)

Alkynes containing a terminal trimethylsilyl group can be annulated in good yield, albeit at a slower rate, by changing the solvent from dimethylformamide to acetonitrile, if the alkyne has a large group, such as a phenyl or 1-cyclohexenyl group, on the other end of the triple bond (Table 1, entries 7 and 8). Gas chromatographic analysis indicated that acetonitrile prevented desilylation of the alkyne under the reaction conditions. However, for similar alkynes having smaller alkyl groups on the opposite side of the triple bond, such as 1-(trimethylsilyl)-propyne, acetonitrile failed to prevent desilylation of the

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Table 1. Synthesis of Isocoumarins and α-Pyrones Via Annulation of Internal Alkynes (Eqs 2 and 8)[a]

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	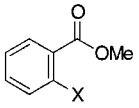	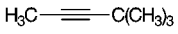		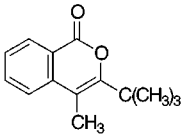	
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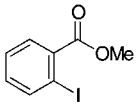
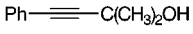
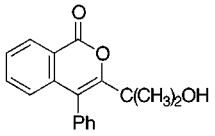
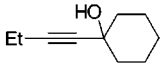
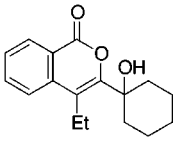
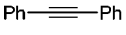
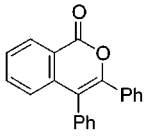
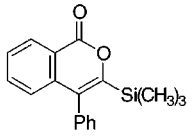
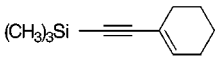
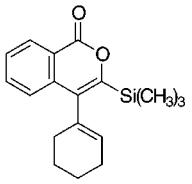
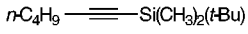
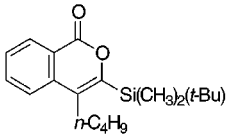
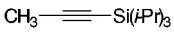
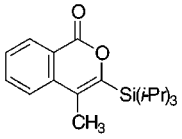
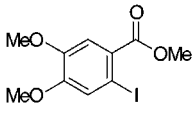
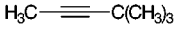
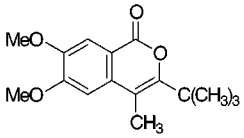
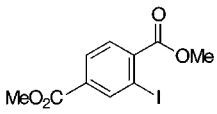
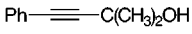
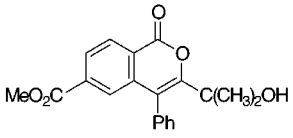
2	X = Br		96		31
3	X = OTf		144		0
4			40		77
5			48		63
6			216		74
7			84		63
8			84		51
9			30		72
10			24		76
11			20		76
12			7		70

Table 1 (Continued)

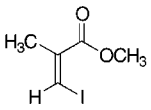
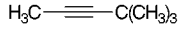
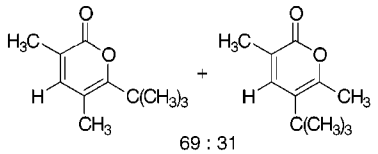
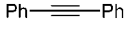
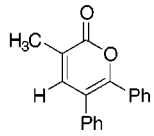
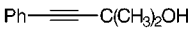
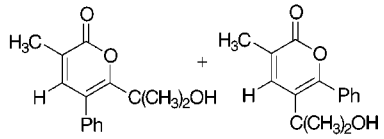
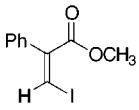
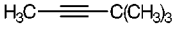
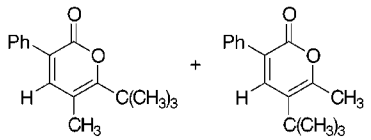
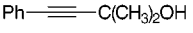
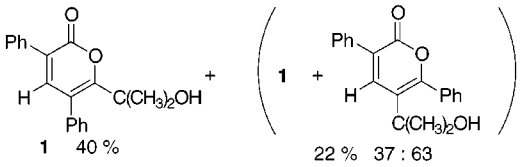
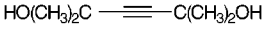
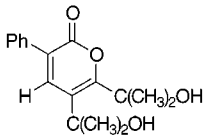
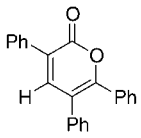
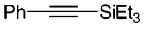
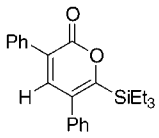
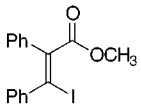
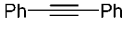
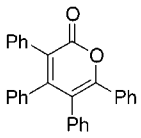
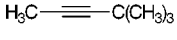
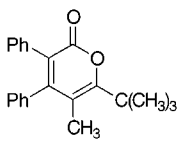
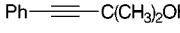
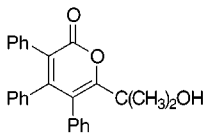
entry	ester	alkyne	time (h)	product(s)[b]	yield (%)[c]
13			28	 69 : 31	54
14			5		40
15			3		50 + 10
16			10		40 + 25
17			10	 1 40 % 22 % 37 : 63	
18			10		70
19			10		50
20			22		30
21			15		55
22			9		70
23			15		59

Table 1 (Continued)

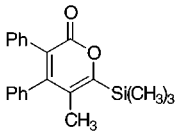
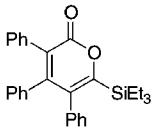
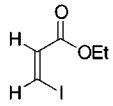
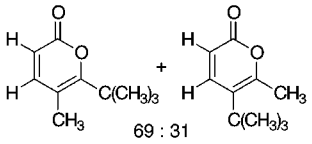
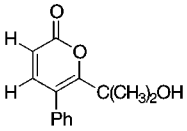
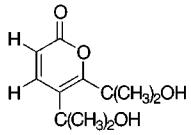
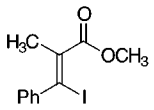
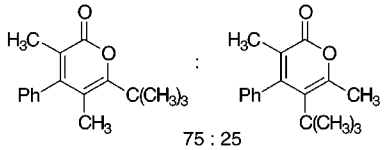
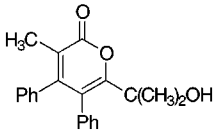
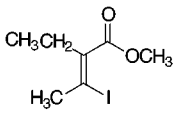
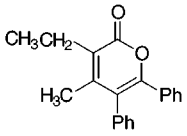
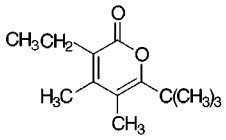
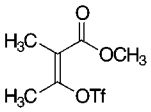
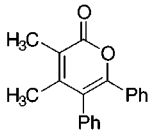
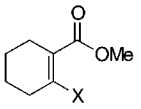
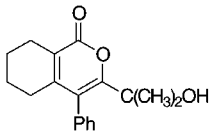
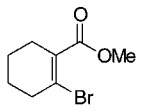
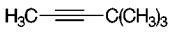
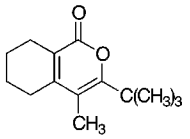
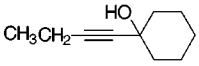
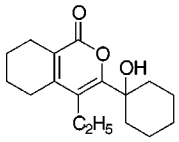
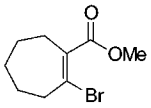
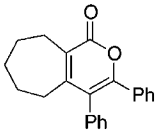
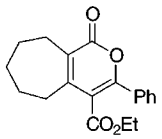
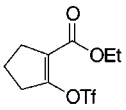
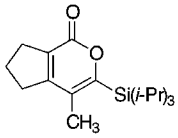
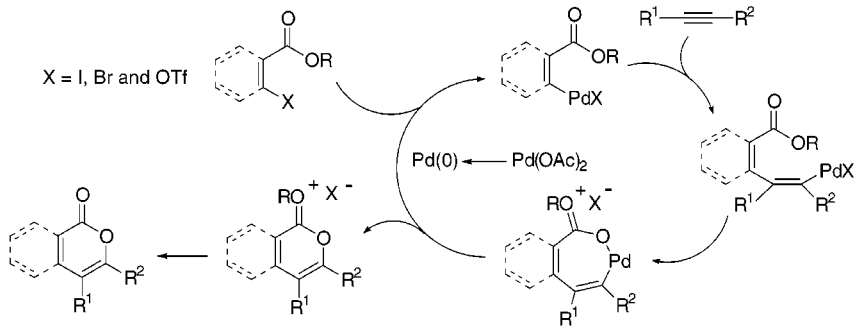
entry	ester	alkyne	time (h)	product(s)[b]	
24		$H_3C-\equiv-Si(CH_3)_3$	22		30
25		$Ph-\equiv-SiEt_3$	22		31
26		$H_3C-\equiv-C(CH_3)_3$	28	 69 : 31	22
27		$Ph-\equiv-C(CH_3)_2OH$	28		10
28		$HO(CH_3)_2C-\equiv-C(CH_3)_2OH$	6		10
29		$H_3C-\equiv-C(CH_3)_3$	100 °C, 32 h 120 °C, 50 h	 75 : 25	38
30		$Ph-\equiv-C(CH_3)_2OH$	100 °C, 32 h 120 °C, 32 h		20
31[d]		$Ph-\equiv-Ph$	12		51
32[e]		$H_3C-\equiv-C(CH_3)_3$	20		12
33		$Ph-\equiv-Ph$	9		12
		$Ph-\equiv-C(CH_3)_2OH$			
34	X = Br		20		71[f]
35	X = OTf		40		79

Table 1 (Continued)

entry	ester	alkyne	time (h)	product(s)[b]
36			48		65
37			36		70
38			8		56
39			7		77
40			21		64

[a] All of the reactions were run in the presence of 5 mol % of $Pd(OAc)_2$ (except entry 12, 10 mol % $Pd(OAc)_2$), 1 equiv of Na_2CO_3, 1 equiv of LiCl, 5 ml of DMF (except entries 6−8, 5 mL of CH_3CN) at 100 °C. [b] A colon (:) indicates that the products were inseparable, and a plus sign (+) indicates that they were separated. [c] Yields refer to isolated compounds purified by chromatography. All of these compounds gave satisfactory ^1H NMR, ^{13}C NMR, HRMS, and IR spectra. [d] This reaction was run in the presence of 2.5 equiv of LiCl. [e] This reaction was run in the presence of 3.0 equiv of LiCl. [f] This reaction was run in the presence of 2.0 equiv of Na_2CO_3.

Scheme 1



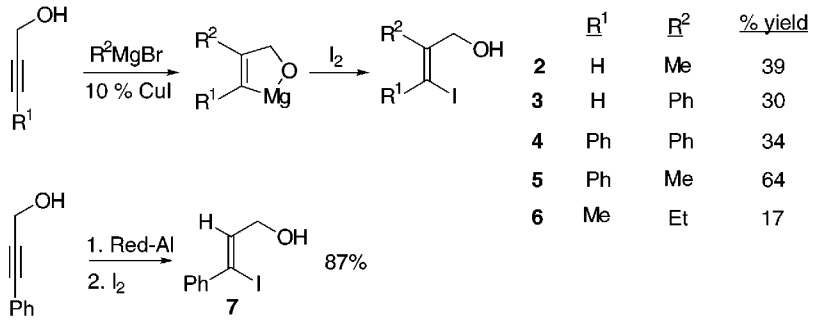
alkyne and hence resulted in low product yields. Therefore, progressively more steric hindrance had to be introduced into the silyl moiety of these alkynes in order to maintain clean, high-yielding reactions (Table 1, entries 9 and 10). While the majority of the isocoumarin reactions have been run on only a 0.5 mmol scale, the transformation depicted in entry 10 of Table 1 was increased to 5.0 mmol, which resulted in an almost identical yield (72% versus 76%).

The regiochemistry has been established for the products of entries 7[21] and 10[7] of Table 1 by comparison with known compounds following desilylation (see below). On the basis of these results, the regiochemistry indicated in Table 1 is assumed for all other products containing a tertiary center.

The annulation of 4,4-dimethyl-2-pentyne by *β*-naphthyl 2-iodobenzoate resulted in a 73% yield of 3-*tert*-butyl-4-methylisocoumarin and recovery of 53% of *β*-naphthol. On the basis of these results, we believe that this annulation process proceeds as shown in Scheme 1 by a sequence involving (1) reduction of $Pd(OAc)_2$ to the actual catalyst Pd(0), (2) oxidative addition of the starting halide or triflate to Pd(0), (3) aryl- or vinylpalladium coordination to the alkyne and subsequent insertion to form a vinylpalladium intermediate, (4) attack of the carbonyl oxygen on the vinylpalladium intermediate to form a seven-membered palladacyclic complex, and (5) regeneration of the Pd(0) catalyst by reductive elimination and formation of the salt. Loss of the R group of the ester is thought to occur either during the reaction by either an S_N1 or S_N2 process or during the aqueous workup, but the real path for this step is unclear.

(21) Beautement, K.; Clough, J. M. *Tetrahedron Lett.* **1984**, *25*, 3025.

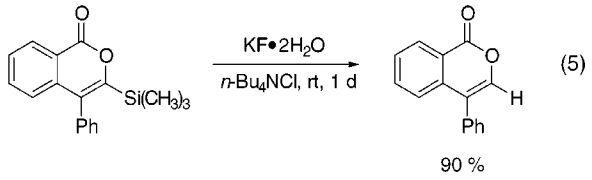
Scheme 2



	R^1	R^2	% yield
2	H	Me	39
3	H	Ph	30
4	Ph	Ph	34
5	Ph	Me	64
6	Me	Et	17

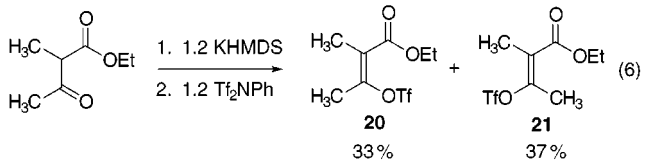
	R^1	R^2		% yield		% yield
2	H	Me	**8**	90	**14**	77
3	H	Ph	**9**	71	**15**	42
4	Ph	Ph	**10**	86	**16**	50
5	Ph	Me	**11**	88	**17**	88
6	Me	Et	**12**	95	**18**	24
7	Ph	H	**13**	77	**19**	24

Although the process is limited to the annulation of hindered internal alkynes, the methodology proves to be very convenient and general for the synthesis of 4-substituted isocoumarins as well, via the silylated products, since the silyl moiety can readily be cleaved at room temperature in the presence of potassium fluoride dihydrate and tetra-*n*-butylammonium chloride (eq 5).[22]



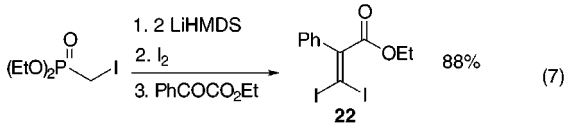
(5)

We next examined the possibility of preparing α-pyrones by this same methodology. The starting materials for our α-pyrone synthesis, *β*-iodo-substituted propenoates, were synthesized by the reactions shown in Scheme 2. (*Z*)-*β*-Iodo-substituted 2-propenols **2**−**6** were synthesized by the CuI-catalyzed Grignard addition across the triple bond of an appropriate propargylic alcohol and subsequent quenching by I_2.[23] Alcohol **7** was prepared by the reaction of 3-phenyl-2-propyn-1-ol with Red-Al [$NaAlH_2(OCH_2CH_2OMe)_2$], followed by quenching with I_2.[24] Oxidation of the (*Z*)-*β*-iodo-substituted 2-propenols with 20 equiv of MnO_2 in CH_2Cl_2 at room temperature afforded the corresponding aldehydes **8**−**13**.[25] The resulting (*Z*)-*β*-iodo-substituted 2-propenals were subjected to a second oxidation by 20 equiv of MnO_2, 5.2 equiv of NaCN, and 1.5 equiv of AcOH in MeOH at room temperature to provide the desired (*Z*)-methyl *β*-iodo-substituted 2-propenoates **14**−**19**.[25] The triflates **20** and **21** were synthesized from the corresponding *β*-keto ester (eq 6).[26] The stereochemistry of the triflates **20** and **21** was assigned by ^1H NMR spectral analysis based on the fact that the chemical shift of a methyl group cis to an ester group appears further downfield due to the deshielding effect of an ester group.[27]



(6)

The diiodide **22** was synthesized in 88% yield according to a literature procedure (eq 7).[28]



(7)

Methyl (*Z*)-3-bromo-3-iodo-2-phenyl-propenoate (**23**) was prepared according to the reactions shown in Scheme 3.[25,29]

The palladium-catalyzed annulation of a variety of internal alkynes using the above-mentioned vinylic iodides and triflates has been carried out as shown in eq 8. The reaction conditions chosen are those used for the

(22) Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.
(23) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1.
(24) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236.
(25) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
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(28) Bonnet, B.; Gallic, Y.; Ple, G.; Duhamel, L. *Synthesis* **1993**, 1071.
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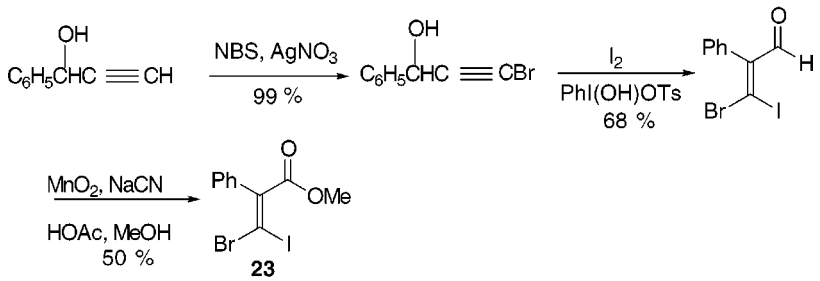
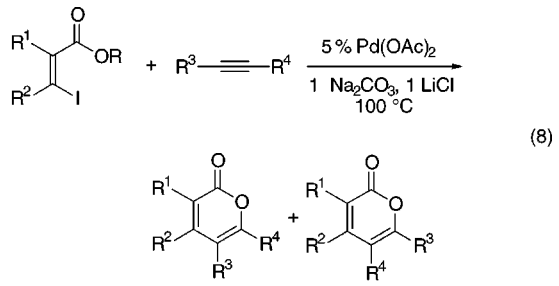
Scheme 3



23

synthesis of isocoumarins. The results are summarized in Table 1, entries 13−40.

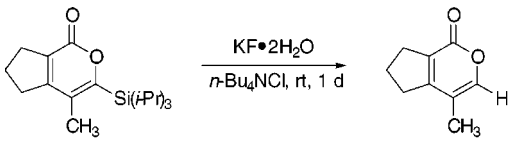


(8)

From the results, we can make the following observations. (1) Methyl (*Z*)-3-iodo-2-methyl-2-propenoate (Table 1, entries 13−15) gives slightly lower yields than methyl (*Z*)-3-iodo-2-phenyl-2-propenoate (Table 1, entries 16−20). Both give a mixture of regioisomers when 4,4-dimethyl-2-pentyne or 2-methyl-4-phenyl-3-butyn-2-ol are employed as the alkyne. (2) Methyl (*Z*)-3-iodo-2,3-diphenyl-2-propenoate (Table 1, entries 21−25) generally gives good yields of just one regioisomer. (3) Ethyl (*Z*)-3-iodo-2-propenoate (Table 1, entries 26−28) gives only very low yields of products. (4) Methyl (*Z*)-3-iodo-2-methyl-3-phenyl-2-propenoate (Table 1, entries 29 and 30) gives lower yields of products and a slower reaction rate compared with the first two esters mentioned above. (5) Trialkylsilyl-substituted α-pyrones in which C−Si bonds are available for further functionalization can be obtained in modest yields from the corresponding silylalkynes (Table 1, entries 20, 24, and 25). (6) The triflate **20**, which is easily prepared, gives the desired product in only a very low yield (Table 1, entry 33). (7) Cyclic vinylic bromides and triflates afford the desired bicyclic α-pyrones in very good yields (Table 1, entries 34−40).

From the above findings, we conclude that vinylic substrates with an organic substituent in the 2-position generally give α-pyrones in good yields (Table 1, entries 13−25). Second, the presence of a hydrogen β to the iodide in the starting material lowers the yields of the palladium reactions, presumably due to β-hydride elimination in the vinylic palladium intermediate, although we have no solid evidence that this is the source of the problem. For example, three of the esters used in this study, which have a β-hydrogen, namely ethyl (*Z*)-3-iodo-2-propenoate and esters **18** and **20**, usually gave α-pyrones in low yields (Table 1, entries 26−28 and 31−33). Third, esters with a phenyl group adjacent to the iodo group gave α-pyrones in poor yields. For example, ester **17** gave only low yields of products (Table 1, entries 29 and 30) and ester **19** failed to give any α-pyrones at all. These observations might be explained by the above-mentioned β-hydride elimination reaction (for ester **19**) and/or steric hindrance about the C−I bond, which retards the oxidative addition reaction and subsequent insertion of the internal alkynes. It should be pointed out that we did not observe any methyl 3-phenylpropynoate, the β-hydride elimination product of the vinylic palladium intermediate from ester **19**, despite careful chromatography of the products from the reactions of ester **19** and diphenylacetylene or 4,4-dimethyl-2-pentyne. However, ester **16**, which has a phenyl group adjacent to the iodo group, gave α-pyrones in good yields, perhaps due to activation by the phenyl group in the 2-position during the oxidative addition step. Fourth, an alkyl or aryl substituent in the 3-position increases the regioselectivity during the carbopalladation step, resulting, in most cases, in the formation of just one regioisomer (Table 1, entries 22−25, 30, and 32). Finally, in contrast to acyclic vinylic triflates (Table 1, entry 33), cyclic vinylic triflates and even analogous bromides can be used to annulate onto internal alkynes to afford bicyclic α-pyrones in good yields as a single regioisomer (Table 1, entries 34−40).

Once again, the silyl-substituted pyrones provide a novel route to other highly substituted pyrones by simple desilylation (eq 9).



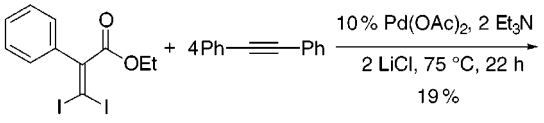
85 %

(9)

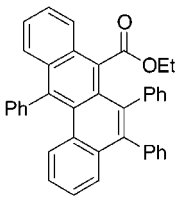
The regiochemistry was established for the products of entries 16 and 17 of Table 1 by NOESY spectroscopy. For the minor product of entry 16, there was an NOE interaction between C_4−H and C_5−$C(CH_3)_3$ and no interaction between C_4−H and C_6−CH_3. This compound was therefore assigned the structure shown in Table 1. The major product of entry 17 was assigned the structure shown due to the lack of an observable NOE interaction between C_4−H and the methyl hydrogens. The above assignments are consistent with our previous work, i.e., the bulkier group of the alkyne ends up bonded to the carbon atom attached to the oxygen in the pyrone product, which was also presumably the carbon to which the palladium species was originally attached.[18] The rest of the products in Table 1 have been assigned by analogy with the above observations.

On the basis of the above results, we believe that this α-pyrone synthesis proceeds by the same mechanism as that proposed for the synthesis of isocoumarins (Scheme 1).

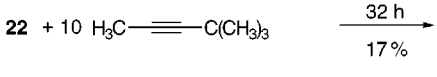
To extend the above chemistry to a double annulation process, dihalo-substituted esters **22** and **23** were prepared (eq 7 and Scheme 3). When compounds **22** or **23**



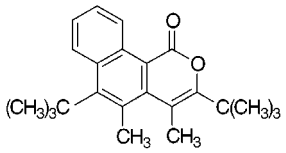
22 (10)



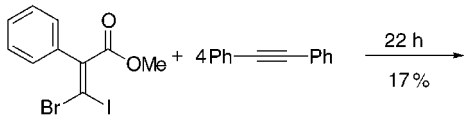
24



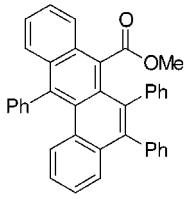
(11)



25



23 (12)



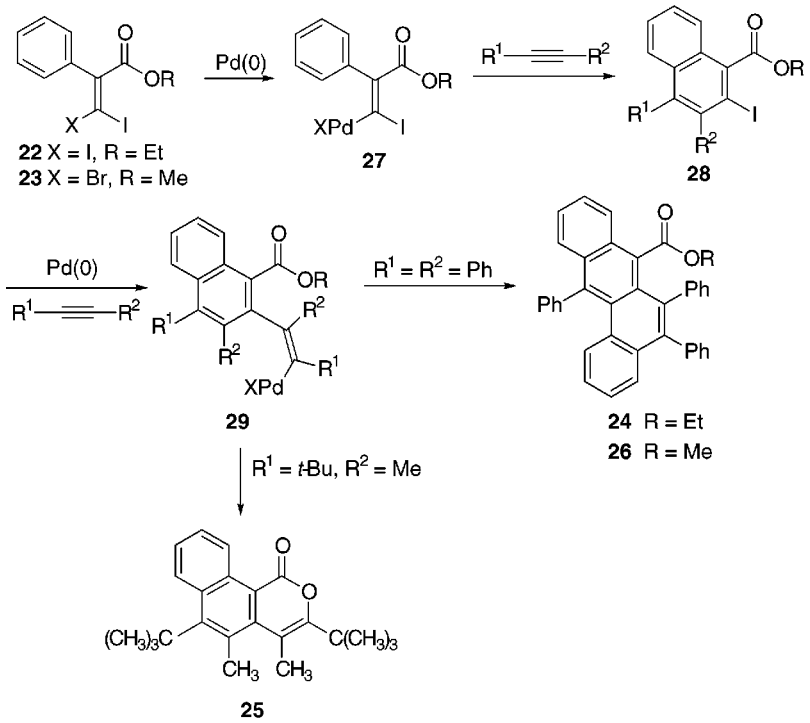
26

were reacted with diphenylacetylene or 4,4-dimethyl-2-pentyne in the presence of 10% $Pd(OAc)_2$, 2 equiv of Et_3N and 2 equiv of LiCl at 75 °C for 22−32 h, the double annulation products **24**−**26** were formed in 17−19% yields (eqs 10−12) with the formation of four new carbon−carbon and/or carbon−oxygen bonds.[30]

The formation of compounds **24**−**26** can be explained by the reactions shown in Scheme 4. The oxidative addition of Pd(0) to compound **22** or **23** affords vinylpalladium intermediate **27** in which the halogen trans to the carbonyl group undergoes preferential insertion. This is consistent with the known reactivity of such halogens toward Pd oxidative addition.[31] Vinylpalladium intermediate **27** undergoes insertion of a molecule of internal alkyne and subsequent substitution onto the adjacent phenyl ring to form intermediate **28**.[18g,h] Vinylpalladium intermediate **29** is then formed by oxidative addition of Pd(0) to compound **28** and subsequent insertion of a second molecule of internal alkyne. When diphenylacetylene is employed, compound **24** or **26** is obtained. When 4,4-dimethyl-2-pentyne is used, compound **25** is produced. The formation of compounds **24** and **26** indicates that the production of aromatic rings is easier than that of α-pyrones.

In conclusion, a useful synthesis of 3,4-disubstituted isocoumarins and a variety of 3,4,6-tri- and 3,4,5,6-tetrasubstituted α-pyrones has been developed using the palladium-catalyzed annulation of internal alkynes via appropriate halogen- and/or triflate-substituted esters. The procedure utilizes readily available starting materials. The reactions proceed under relatively mild conditions and give good yields. Although the reaction is somewhat limited in scope synthetically, it is suited for the synthesis of the 4-substituted ring systems via the corresponding silyl alkynes. The above chemistry has also been extended to the synthesis of polycyclic aromatic compounds by employing geminal dihalo-substituted esters.

Scheme 4



Experimental Section

General Methods. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F) and visualized with short wavelength UV light (254 nm) and basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O].

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous Na_2CO_3 and LiCl were purchased from Fisher Scientific. $Pd(OAc)_2$ was donated by Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Ltd. The following starting materials for the annulation reactions were made according to literature procedures: 1-(*tert*-butyldimethylsilyl)-1-hexyne,[32] ethyl (*Z*)-3-iodo-2-propenoate,[33] methyl (*Z*)-2-bromocyclohex-1-ene-1-carboxylate,[34] methyl (*Z*)-2-bromocyclohept-1-ene-1-carboxylate,[34] methyl 2-trifluoromethanesulfonyloxy-1-cyclohexene-1-carboxylate,[35] ethyl 2-trifluoromethanesulfonyloxy-1-cyclopentene-1-carboxylate,[35] and methyl 2-(trifluoromethanesulfonyloxy)-benzoate.[36] The preparation and characterization of the other aryl and vinylic esters used in this study are included in the Supporting Information.

General Procedure for the Synthesis of Isocoumarins and α-Pyrones. $Pd(OAc)_2$ (3 mg, 0.013 mmol), Na_2CO_3 (26.5 mg, 0.25 mmol), DMF (5 mL), LiCl (10.6 mg, 0.25 mmol), the alkyne (0.5 mmol), and the ester (0.25 mmol) were placed in a 2 dram vial (the isocoumarins and bicyclic pyrones were prepared on twice this scale). The vial was heated in an oil bath at 100 °C for the necessary period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with ether, washed with saturated NH_4Cl, dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography (EtOAc/hexanes) on a silica gel column.

3-*tert*-Butyl-4-methylisocoumarin (Entries 1−3, Table 1). The reaction mixture was chromatographed using 15:1 *n*-hexane/EtOAc to yield a white solid: mp 94−96 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.34 (s, 3H), 7.45 (dt, J = 0.9, 7.8 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.73 (dt, J = 1.2, 8.1 Hz, 1H), 8.10 (dd, J = 0.9, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.9, 29.6, 37.2, 107.3, 120.1, 122.4, 127.0, 129.1, 134.3, 139.8, 159.2, 162.5; IR ($CHCl_3$) 1720 cm^{-1}; HRMS *m*/*z* 216.1150 (calcd for $C_{14}H_{16}O_2$, 216.1150).

The product characterization data for all other isocoumarins prepared appears in the Supporting Information.

6-*tert*-Butyl-3,5-dimethyl-2*H*-pyran-2-one (30) and 5-*tert*-Butyl-3,6-dimethyl-2*H*-pyran-2-one (31) (Entry 13, Table 1). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a light yellow inseparable liquid (**30**:**31** = 69:31). Compound **30** (major isomer): ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.39 (s, 3H), 2.70 (d, J = 1.0 Hz, 3H), 7.25 (d, J = 1.2 Hz, 1H). Compound **31** (minor isomer): ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 2.13 (s, 3H), 2.50 (d, J = 1.0 Hz, 3H), 6.91 (d, J = 1.2 Hz, 1H). Additional spectral data for the product mixture: ^{13}C NMR ($CDCl_3$) δ 15.9, 16.4, 17.2, 20.4, 28.9, 30.8, 32.3, 37.4, 104.1, 109.7, 121.4, 121.9, 123.3, 141.5, 147.0, 156.3, 163.8, 164.2; IR ($CHCl_3$) 1699 cm^{-1}; HRMS 180.1147 (calcd for $C_{11}H_{16}O_2$ 180.1150).

The physical characterization data for all other α-pyrones prepared appear in the Supporting Information.

General Procedure for the Palladium-Catalyzed Double Annulation Reactions. $Pd(OAc)_2$ (6 mg, 0.026 mmol), Et_3N (53 mg, 0.50 mmol), DMF (5 mL), LiCl (21.2 mg, 0.50 mmol), the alkyne (1 mmol for diphenylacetylene and 2.5 mmol for 4,4-dimethyl-2-pentyne), and the dihaloalkene (0.25 mmol) were placed in a 2 dram vial. The vial was heated in an oil bath at 75 °C for the necessary period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with ether, washed with saturated NH_4Cl, dried over anhydrous Na_2SO_4, and decanted. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography (EtOAc/hexanes) on a silica gel column. The following compounds were prepared by the above procedure.

7-Ethoxycarbonyl-5,6,12-triphenylbenz[*a*]anthracene (24, Eq 10). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a brown solid: mp 193−195 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J = 7.2 Hz, 3H), 3.31 (q, J = 7.2 Hz, 2H), 6.66−7.27 (m, 23H); ^{13}C NMR ($CDCl_3$) δ 13.6, 61.3, 125.1, 126.36, 126.40, 126.46, 126.54, 126.9, 127.0, 127.06, 127.14, 127.2 (2C), 127.4, 127.5, 128.3, 130.1, 130.3, 130.5 (2C), 130.9, 131.5, 133.6, 134.8, 134.9, 135.5, 135.6, 136.3, 143.5, 144.2, 145.6, 146.7, 168.4; IR ($CHCl_3$) 1720 cm^{-1}; HRMS 528.2084 (calcd for $C_{39}H_{28}O_2$ 528.2089).

3,6-Di-*tert*-butyl-4,5-dimethyl-1*H*-naphtho[1,2-*c*]pyran-1-one (25, Eq 11). The reaction mixture was chromatographed using 1:20 EtOAc/hexanes to yield a light yellow solid: mp 140−142 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 1.77 (s, 9H), 2.36 (s, 3H), 2.48 (s, 3H), 7.48 (t, J = 7.7 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 8.42 (d, J = 8.4 Hz, 1H), 9.74 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.8, 29.1, 33.6, 37.6, 39.6, 107.6, 113.1, 124.5, 126.3, 126.4, 126.8, 128.5, 130.2, 132.0, 147.0, 155.0, 161.6, 162.1; IR ($CHCl_3$) 1706 cm^{-1}; HRMS 336.2094 (calcd for $C_{23}H_{28}O_2$ 336.2089).

7-Methoxycarbonyl-5,6,12-triphenylbenz[*a*]anthracene (26, Eq 12). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a brown solid: mp 217−219 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 3.02 (s, 3H), 6.66−6.75 (m, 8H), 6.84−7.03 (m, 11H), 7.22−7.25 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 52.0, 125.1, 126.40, 126.46, 126.48, 126.88, 126.97 (2C), 127.1, 127.2, 127.4, 128.2, 128.3, 128.4, 130.1, 130.3, 130.6, 130.9, 131.3, 131.6, 133.5, 133.6, 134.76, 134.84, 135.3, 135.6, 136.2, 143.1, 144.8, 145.8, 146.9, 168.8; IR ($CHCl_3$) 1715 cm^{-1}; HRMS 514.1936 (calcd for $C_{38}H_{26}O_2$ 514.1933).

Acknowledgment. We gratefully acknowledge partial financial support from the Petroleum Research Fund, administered by the American Chemical Society; Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for the palladium compounds; and Merck for Academic Development Awards in 1997 and 1998.

Supporting Information Available: The preparation of the starting materials, product characterization data for the isocoumarin and α-pyrone products, and ^{1}H and ^{13}C NMR spectra for all new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) The following dihalides failed to give any double annulation products: $Br_2C{=}CPhCO_2Et$, $Br_2C{=}C(CO_2Et)_2$, and $I_2C{=}C(CO_2Et)_2$.

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