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Cascade Reactions: A New Synthesis of 2-Benzofuran-2-ylacetamides by Sequential Pd(0)-Catalyzed Deallylation−Pd(II)-Catalyzed Aminocarbonylative Heterocyclization of 1-(2-Allyloxyaryl)-2-yn-1-ols

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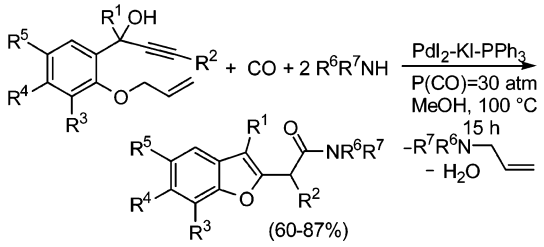

A general and efficient synthesis of 2-benzofuran-2-ylacetamides **5** starting from 1-(2-allyloxyaryl)-2-yn-1-ols **1**, amines **4**, and CO, in the presence of catalytic amounts of PdI_2 in conjunction with PPh_3 and KI, has been developed based on the "sequential homobimetallic catalysis" concept, that is, a process in which two different complexes of the same metal, but in two different oxidation states, promote two catalytic cycles in sequence. The first cycle corresponds to a Pd(0)-catalyzed aminodeallylation of **1** with formation of the free phenol **2**, which then undergoes Pd(II)-catalyzed aminocarbonylative heterocyclization to give the final product **5**.

Introduction

We have recently described the first example of "sequential homobimetallic catalysis", that is, a process in which two different complexes of the same metal, but in two different oxidation states, promote two catalytic cycles in sequence.[1] Thus, 1-(2-allyloxyaryl)-2-yn-1-ols **1** were selectively converted into 2-benzofuran-2-ylacetic esters **3** through Pd(0)-catalyzed carbonylative deallylation to give β,γ-unsaturated esters and the free phenols **2**, followed by in situ PdI_2-catalyzed cyclization−alkoxycarbonylation of the latter to give **3**, as depicted in Scheme 1 (unreactive ligands are omitted for clarity). The possibility to obtain free phenols **2** in situ, by deallylation of **1**, was particularly important, since phenols **2**, with R^2 = alkyl, were known to be unstable and therefore difficult to obtain at the pure state.[2] On the other hand, the use of isolable phenols **2** (with R^2 = H or aryl) led to the corresponding benzofurans **3** in lower yields with respect to the sequential procedure starting from *O*-allyl phenols **1**.

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(1) (a) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *Adv. Synth. Catal.* **2006**, *348*, 1101−1109. (b) Gabriele, B.; Mancuso, R.; Salerno, G.; Veltri, L. *Chem. Commun.* **2005**, 271−273.

(2) Pflieger, D.; Muckensturm, B. *Tetrahedron Lett.* **1990**, *31*, 2299−2300.

(3) Benzofuran-2-ylacetamides are an interesting class of compounds. Recently, some 2-benzofuran-2-ylacetamide derivatives have shown interesting anticonvulsant activity: Kohn, H. K.; Sawhney, N.; LeGall, P.; Conley, J. D.; Robertson, D. W.; Leander, J. D. *J. Med. Chem.* **1990**, *33*, 919−926.

(4) To the best of our knowledge, no general methodology for the synthesis of 2-benzofuran-2-ylacetamides by annulation of acyclic precursors has been reported thus far. The classical syntheses of 2-benzofuran-2-ylacetamides are based on amination of benzofuran-2-ylacetyl chorides (obtained from the corresponding acids): (a) Foster, R. T.; Robertson, A.; Healy, T. V. *J. Chem. Soc.* **1939**, 1594−1601. (b) Dean, F. M.; Halewood, P.; Mongkolsuk, S.; Robertson, A.; Whalley, W. B. *J. Chem. Soc.* **1953**, 1250−1261 and on rearrangement of 2-diazoacetylbenzofurans in the presence of ammonia: (c) McGookin, A.; Roberston, A.; Whalley, W. *J. Chem. Soc.* **1940**, 787−795. (d) Wagner, R. B.; Tome, J. M. *J. Am. Chem. Soc.* **1950**, *72*, 3477−3478. (e) Trofimov, F. A.; Mukhanove, T. I.; Grinov, A. N. *Chem. Heterocycl. Compd. (N.Y., NY, U.S.)* **1973**, *9*, 552−554.

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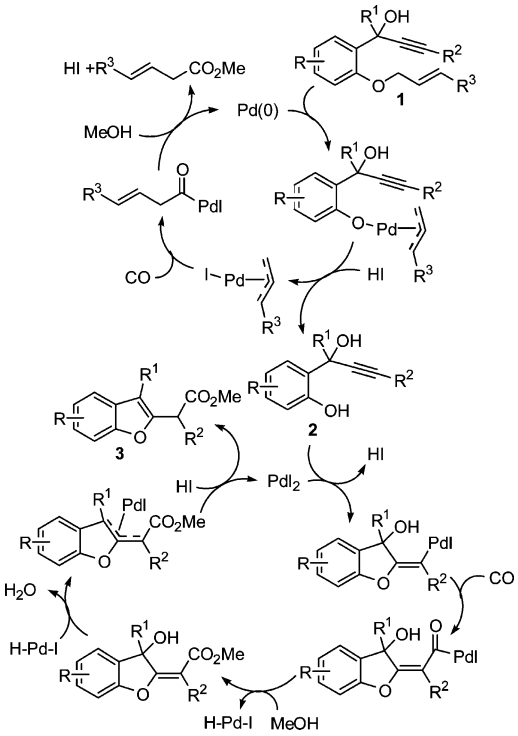
SCHEME 1



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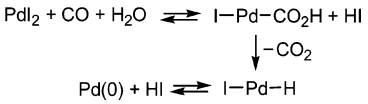
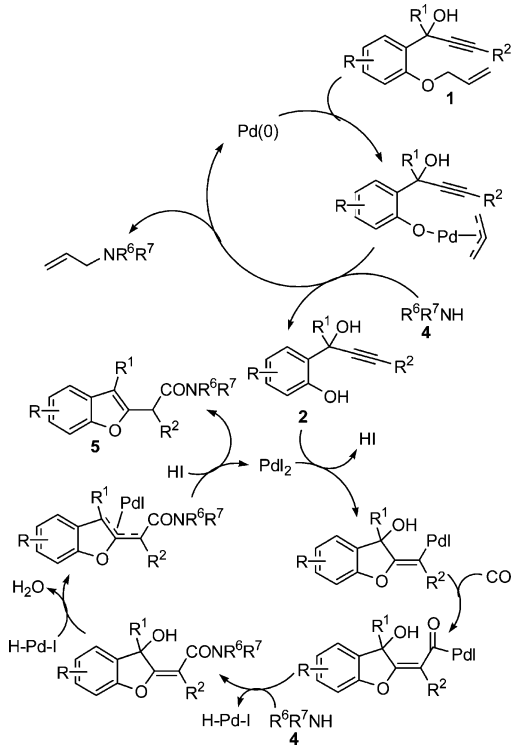
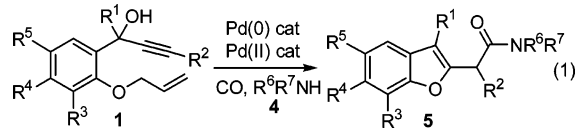


SCHEME 3



Reactions were carried out in MeOH at 100 °C under 30−90 atm of carbon monoxide in the presence of catalytic amounts of PdI_2 (1 mol % with respect to **1**) in conjunction with 100−200 equiv of KI, 4 equiv of PPh_3, and 200 equiv of H_2O. The presence of water was necessary to generate in situ the Pd(0) species promoting the deallylation cycle, according to Scheme 2. On the other hand, ligands PPh_3 and I^- were needed to stabilize the Pd(0) species (catalyst of the first cycle) and the Pd(II) species (catalyst of the second cycle), respectively.

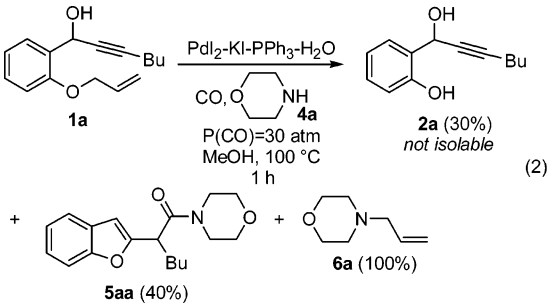
To expand the synthetic scope of the reaction, we have investigated the possibility to use amines **4** as the nucleophiles for the direct synthesis of the corresponding 2-benzofuran-2-ylacetamides **5**,[3,4] according to eq 1.



Results and Discussion

We first tested the reactivity of 1-(2-allyloxyphenyl)hept-2-yn-1-ol **1a** ($R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Bu$) in the presence of 2 equiv of morpholine **4a** under conditions similar to those employed for the synthesis of benzofuranacetic esters **3**, namely, anhydrous MeOH as the solvent (**1a** concentration = 0.22 mmol/mL of MeOH) at 100 °C under 30 atm of CO in the presence of PdI_2 in conjunction with KI, PPh_3, and H_2O (PdI_2/KI/PPh_3/**1a**/**4a**/H_2O molar ratio = 1:10:4:100:200:200). We found that, in agreement with the higher nucleophilicity of morpholine with respect to methanol, the substrate conversion rate was significantly higher with respect to the analogous reaction carried out in the absence of morpholine,[1] and thus **1a** conversion was quantitative after only 1 h reaction time. According to our hypotheses, the reaction led to the formation of 2-benzofuran-2-yl-1-morpholin-4-ylhexan-1-one **5aa** in 40% GLC yield (Table 1, entry 1).

The GLC−MS analysis of the reaction crude also suggested the presence in the reaction mixture of the deallylated substrate, that is, the free phenol **2a** ($R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Bu$, ca. 30%), which, however, according to its instability,[2] could not be isolated at the pure state from the reaction crude. The formation of unidentified heavy compounds was detected by TLC analysis (these materials were chromatographically immobile) and accounted for the remaining part of the converted substrate. Interestingly, an equimolar amount of 4-allylmorpholine **6a** with respect to **1a** was detected in the reaction mixture, thus showing that in this case the π-allylpalladium intermediate of the first cycle directly undergoes external nucleophilic attack by **4a** (eq 2 and Scheme 3, to be compared with Scheme 1).[5]



As shown by the results reported in entry 2, the presence of PPh_3 was essential for the reaction to occur; in fact, the substrate **1a** remained unconverted working in the absence of PPh_3. This is in agreement with what we already observed in the formation

TABLE 1. Reactions of 1-(2-Allyloxyphenyl)hept-2-yn-1-ol 1a with CO and Morpholine 4a in the Presence of the PdI_2−KI−PPh_3 Catalytic System[a]

entry	PdI_2/KI/PPh_3/**1a**/**4a**/H_2O molar ratio	solvent	T (°C)	P_{CO} (atm)	time (h)	yield of **5aa**[b] (%)
1	1:10:4:100:200:200	MeOH	100	30	1	40
2	1:10:0:100:200:200	MeOH	100	30	1	0[c]
3	1:10:4:100:200:0	MeOH	100	30	1	40
4	1:100:4:100:200:0	MeOH	100	30	1	42
5	1:200:4:100:200:0	MeOH	100	30	1	50
6	1:10:4:100:200:0	MeOH	80	30	1	10
7	1:100:4:100:200:0	MeOH	100	15	1	30
8	1:100:4:100:200:0	MeOH	100	60	1	38
9	1:10:4:100:200:0	MeOH	100	30	15	69
10	1:10:4:100:200:0	dioxane	100	30	15	25
11	1:10:4:100:200:0	DME	100	30	15	16
12	1:10:4:100:200:0	DMA	100	30	15	25
13	1:10:4:100:200:0	MeCN	100	30	15	42

[a] All reactions were carried out with a substrate concentration of 0.22 mmol of **1a**/mL of solvent (2 mmol scale based on **1a**). Unless otherwise noted, substrate conversion was quantitative. [b] GLC yield based on starting **1a**. [c] Substrate conversion was 0%.

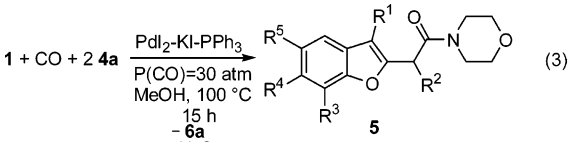
TABLE 2. Synthesis of 2-Benzofuran-2-ylacetamides 5aa−ja Starting from 1-(2-Allyloxyaryl)-2-yn-1-ols 1, Morpholine 4a, and CO, in the Presence of the PdI_2–KI−PPh_3 Catalytic System[a]

entry	**1**	R^1	R^2	R^3	R^4	R^5	**5**	yield of **5**[b] (%)
14	**1a**	H	Bu	H	H	H	**5aa**	87
15	**1b**	H	Ph	H	H	H	**5ba**	66
16	**1c**	H	*t*-Bu	H	H	H	**5ca**	46
17[c]	**1c**	H	*t*-Bu	H	H	H	**5ca**	60
18[d]	**1c**	H	*t*-Bu	H	H	H	**5ca**	27
19	**1d**	Me	Bu	H	H	H	**5da**	65
20	**1e**	Ph	Bu	H	H	H	**5ea**	66
21	**1f**	H	Bu	OMe	H	H	**5fa**	80
22	**1g**	H	Bu	H	OMe	H	**5ga**	80
23	**1h**	H	Bu	H	H	OMe	**5ha**	80
24	**1i**	H	Ph	H	H	OMe	**5ia**	65
25	**1j**	H	Bu	H	H	Cl	**5ja**	80

[a] Unless otherwise noted, all reactions were carried out in anhydrous MeOH (0.22 mmol of **1**/mL of MeOH, 2 mmol scale based on **1**) in the presence of PdI_2, KI, PPh_3, and morpholine **4a** (PdI_2/KI/PPh_3/**1**/**4** molar ratio = 1:200:4:100:200) at 100 °C and under 30 atm of CO for 15 h. Substrate conversion was quantitative in all cases. [b] Isolated yield based on starting **1a**. [c] The reaction was carried out with a KI/PdI_2 molar ratio of 100. [d] The reaction was carried out with a KI/PdI_2 molar ratio of 10.

of benzofuran-2-acetic esters[1] and confirms the role played by PPh_3 in stabilizing the Pd(0) species promoting the deallylation cycle. On the contrary, the presence of H_2O in the present process turned out to be unnecessary for promoting the formation of Pd(0), as shown by comparing entry 3 with entry 1. This effect must be ascribed to the presence of the amine, whose partial oxidative carbonylation may be responsible for the in situ formation of Pd(0) from PdI_2 and CO.[6] The effect on the yield of **5aa** of the KI/PdI_2 molar ratio, reaction temperature, and carbon monoxide pressure was also tested (entries 4−8). A significantly higher selectivity toward **5aa** was observed by increasing the KI/PdI_2 ratio to 200 (entry 5).

The detection of intermediate **2a** in the reaction mixture after 1 h also suggested the possibility to improve the yield of **5aa** by simply increasing the reaction time. Indeed, under the same conditions of entry 3, but after 15 h, the yield of **5aa** reached 69% (entry 9). The reaction was much slower in aprotic solvents, such as 1,4-dioxane, 1,2-dimethoxyethane (DME), *N*,*N*-dimethylacetamide (DMA), or acetonitrile, as shown by the results reported in entries 10−13. On the other hand, by carrying out the reaction under the same conditions as those in entry 9, but with a KI/PdI_2 molar ratio of 200, the GLC yield of **5aa** was as high as 93% (87% isolated, Table 2, entry 14, and eq 3).



(3)

aa R^1=R^3=R^4=R^5=H, R^2=Bu: 87%
ba R^1=R^3=R^4=R^5=H, R^2=Ph: 66%
ca R^1=R^3=R^4=R^5=H, R^2=*t*-Bu: 60%
da R^1=Me, R^2=Bu, R^3=R^4=R^5=H: 65%
ea R^1=Ph, R^2=Bu, R^3=R^4=R^5=H: 66%
fa R^1=R^4=R^5=H, R^2=Bu, R^3=OMe: 80%
ga R^1=R^3=R^5=H, R^2=Bu, R^4=OMe: 80%
ha R^1=R^3=R^4=H, R^2=Bu, R^5=OMe: 80%
ia R^1=R^3=R^4=H, R^2=Ph, R^5=OMe: 65%
ja R^1=R^3=R^4=H, R^2=Bu, R^5=Cl: 80%

The generality of the process was then verified by varying the nature of substituents R^1 (at the benzylic position), R^2 (on

(5) Although there could be the possibility that deallylation occurred by direct nucleophilic attack by morpholine **4a** on the allyl group of **1a** with formation of **2a** and **6a**, we have verified that this was not the case. In fact, **1a** remained unconverted when it was reacted with **4a** in MeOH under nitrogen at 100 °C for 15 h. This confirms that deallylation is indeed Pd-catalyzed according to Scheme 2.

(6) For a recent monograph on oxidative carbonylations, see: Gabriele, B.; Salerno, G.; Costa, M. *Top. Organomet. Chem.* **2006**, *18*, 239−272.

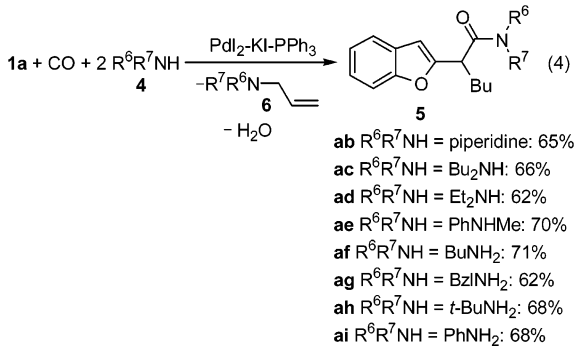
TABLE 3. Synthesis of 2-Benzofuran-2-ylacetamides 5ab−ai Starting from 1-(2-Allyloxyphenyl)hept-2-yn-1-ol 1a, Amines 4, and CO, in the Presence of the PdI_2–KI−PPh_3 Catalytic System[a]

entry	PdI_2/KI/PPh_3/**1a**/**4** molar ratio	solvent	**4**	R^6R^7NH	time (h)	**5**	yield of **5**[b] (%)
26	1:200:4:100:200	MeOH	**4b**	piperidine	15	**5ab**	65
27	1:200:4:100:200	MeOH	**4c**	Bu_2NH	15	**5ac**	46
28	1:100:4:100:200	MeOH	**4c**	Bu_2NH	15	**5ac**	66
29	1:200:4:100:200	MeOH	**4d**	Et_2NH	15	**5ad**	62
30	1:200:4:100:200	MeOH	**4e**	PhNHMe	15	**5ae**	61[c]
31	1:100:4:50:100	MeCN	**4e**	PhNHMe	24	**5ae**	70
32	1:200:4:100:200	MeOH	**4f**	$BuNH_2$	15	**5af**	35[d]
33	1:100:4:50:100	MeCN	**4f**	$BuNH_2$	24	**5af**	71
34	1:200:4:100:200	MeOH	**4g**	$BnNH_2$	15	**5ag**	22[e]
35	1:100:4:50:100	MeCN	**4g**	$BnNH_2$	24	**5ag**	62
36	1:200:4:100:200	MeOH	**4h**	*t*-$BuNH_2$	15	**5ah**	26[f]
37	1:100:4:50:100	MeCN	**4h**	*t*-$BuNH_2$	24	**5ah**	68
38	1:200:4:100:200	MeOH	**4i**	$PhNH_2$	15	**5ai**	10[g]
39	1:100:4:50:100	MeCN	**4h**	$PhNH_2$	24	**5ai**	68

[a] Unless otherwise noted, all reactions were carried out with a substrate concentration of 0.22 mmol of **1a**/mL of solvent (2 mmol scale based on **1**) in the presence of PdI_2, KI, PPh_3, and R^6R^7NH **4** at 100 °C and under 30 atm of CO. Substrate conversion was quantitative in all cases. [b] Isolated yield based on starting **1**. [c] The reaction also led to the formation of 2-benzofuran-2-ylhexanoic acid methyl ester **3a** in 24% isolated yield. [d] The reaction also led to the formation of **3a** in 36% isolated yield. [e] The reaction also led to the formation of **3a** in 42% isolated yield. [f] The reaction also led to the formation of **3a** in 41% isolated yield. [g] The reaction also led to the formation of **3a** in 67% isolated yield.

the triple bond), and R^3−R^5 (on the aromatic ring) (eq 3). The results are shown in Table 2, entries 15−25. As can be seen, good isolated yields in the corresponding 2-benzofuran-2-ylacetamides **5aa**−**ja** were consistently obtained.[7] In the case of 1-(2-allyloxyphenyl)-4,4-dimethylpent-2-yn-1-ol **1c**, the product selectivity was higher working with a KI/PdI_2 molar ratio of 100 (entry 17) rather than 200 (entry 16).

The effect of the nature of the amine was also tested, using **1a** as the model substrate (eq 4). Cyclic and acyclic dialkylamines (such as piperidine **4b**, dibutylamine **4c**, and diethylamine **4d**) behaved similarly to morpholine, as shown by Table 3, entries 26−29. On the other hand, less nucleophilic secondary amines (such as *N*-methylaniline **4e**) and primary amines (such as butylamine **4f**, benzylamine **4g**, *tert*-butylamine **4h**, and aniline **4i**), led, under the usual conditions (in MeOH as the solvent), to mixtures of the corresponding 2-benzofuran-2-ylacetamides **5ae**−**ai** and 2-benzofuran-2-ylhexanoic acid methyl ester **3a**, because of the competition between the amine and MeOH as the nucleophile (entries 30, 32, 34, 36, 38). We accordingly carried out the reactions in a non-nucleophilic solvent such as MeCN. To compensate for the lower reactivity in this latter solvent as compared with MeOH (Table 1, entries 9 and 13), carbonylations were performed with a substrate-to-catalyst ratio of 50 rather than 100 for 24 h. Under these conditions, 2-benzofuran-2-ylacetamides **5ae**−**ai** were selectively obtained in good isolated yields (entries 31, 33, 35, 37, 39).



Conclusions

In conclusion, we have reported a new and convenient method for the synthesis of important heterocyclic derivatives, such as 2-benzofuran-2-ylacetamides **5**, starting from readily available 1-(2-allyloxyaryl)-2-yn-1-ols **1**, amines **4**, and CO. Carbonylation reactions are carried out under relatively mild conditions in the presence of a PdI_2-based catalytic system. The generality of the process has been verified by varying the nature of the substrate **1** as well as the nature of the amine **4**. Mechanistically, the process is an example of "sequential homobimetallic catalysis": a PPh_3-stablized Pd(0) complex (generated in situ under the reaction conditions) catalyzes the deallylation of **1**, with formation of the free phenol **2**, which then acts as the substrate in a second catalytic cycle, consisting of a PdI_4^{2-}-catalyzed aminocarbonylative heterocyclization of **2** to give the final product **5**.

Experimental Section

Preparation of Substrates. Substrates were prepared as described in the literature.[1] 2-Benzofuran-2-ylhexanoic acid methyl ester **3a** was characterized by comparison with literature data.[1]

General Procedure for the Synthesis of 2-Benzofuran-2-ylacetamides 5 (Tables 1−3). A 250-mL stainless steel autoclave was charged with PdI_2 (8.0 or 16.0 mg, 2.22×10^{-2} or 4.44×10^{-2} mmol), KI (370.0 or 740.0 mg, 2.23 or 4.46 mmol), PPh_3 (23.3 or 46.5 mg, 8.88×10^{-2} or 1.77×10^{-1} mmol), and a solution of **1** (2.22 mmol) in anhydrous MeOH or MeCN (10.1 mL). Anhydrous **4** (4.44 mmol) was then added, and the autoclave was sealed, purged at room temperature several times with CO with stirring (10 atm), and eventually pressurized at 30 atm. After being stirred at 100 °C for the required time, the autoclave was cooled and degassed. The solvent was evaporated, and products were purified by column chromatography on silica gel: **5aa** (9:1 hexane/

(7) It is worth noting that unprotected 2-(1-hydroxy-3-phenylprop-2-ynyl)phenol **2b** was sufficiently stable during the purification procedure to be isolated at the pure state.[1a] However, its carbonylation reaction, carried out under the same conditions as those in entry 15 (Table 2), but in the absence of PPh_3, led to the corresponding 2-benzofuran-2-ylacetamide **5ba** in only 34% isolated yield. See the Experimental Section for details.

acetone, pale yellow oil, 580 mg, 87%); **5ba** (9:2 hexane/AcOEt, yellow solid, mp 127−128 °C, 470 mg, 66%); **5ca** (95:5 hexane/acetone, colorless solid, mp 108−109 °C, 400 mg, 60%); **5da** (9:1 hexane/acetone, colorless oil, 455 mg, 65%); **5ea** (8:2 hexane/acetone, yellow solid, mp 96−97 °C, 550 mg, 66%); **5fa** (8:2 hexane/acetone, yellow oil, 590 mg, 80%); **5ga** (9:1 hexane/acetone, yellow oil, 586 mg, 80%); **5ha** (9:1 hexane/acetone, pale yellow oil, 588 mg, 80%); **5ia** (8:2 hexane/acetone, yellow solid. The product thus obtained could be further purified by dissolving it in MeOH followed by crystallization with hexane, to give a colorless solid, mp 114−116 °C, 506 mg, 65%); **5ja** (8:2 hexane/acetone, yellow solid, mp 61−63 °C, 595 mg, 80%); **5ab** (9:1 hexane/acetone, yellow solid, 52−53 °C, 430 mg, 65%); **5ac** (9:1 hexane/acetone, yellow oil, 501 mg, 66%); **5ad** (9:1 hexane/Et_2O, yellow oil, 395 mg, 62%); **5ae** (8:2 hexane/AcOEt, yellow oil, 500 mg, 70%); **5af** (8:2 hexane/Et_2O, yellow solid, mp 61−62 °C, 451 mg, 71%); **5ag** (8:2 hexane/acetone, yellow solid, mp 68−69 °C, 443 mg, 62%); **5ah** (8:2 hexane/AcOEt, yellow solid, mp 95−96 °C, 435 mg, 68%); **5ai** (9:1 hexane/acetone, yellow solid, mp 118−120 °C, 465 mg, 68%).

Carbonylation of 2-(1-Hydroxyphenylprop-2-ynyl)phenol 2b to 2-Benzofuran-2-ylacetamide 5ba (Note 7). A 250-mL stainless steel autoclave was charged with PdI_2 (8.0 mg, 2.22×10^{-2} mmol), KI (737.4 mg, 4.44 mmol), and a solution of **2b** (497.4 mg, 2.22 mmol) in anhydrous MeOH (10.1 mL). Anhydrous morpholine **4a** (386.9 mg, 4.44 mmol) was then added, and the autoclave was sealed, purged at room temperature several times with CO with stirring (10 atm), and eventually pressurized at 30 atm. After being stirred at 100 °C for 15 h, the autoclave was cooled and degassed. The solvent was evaporated, and the product **5ba** was purified by column chromatography on silica gel (9:1 hexane/AcOEt, yellow solid, mp 127−128 °C, 242 mg, 34%).

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Supporting Information Available: General experimental methods, characterization data, and copy of ^1H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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