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Cascade Reactions: Sequential Homobimetallic Catalysis Leading to Benzofurans and β,γ-Unsaturated Esters

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Abstract: The concatenation between a Pd(0)-promoted deallylation catalytic cycle and a Pd(II)-promoted heterocyclization catalytic cycle (an example of what we have named "sequential homobimetallic catalysis") has been shown to occur starting from 1-(2-allyloxyphenyl)-2-yn-1-ols **1** to afford 2-benzofuran-2-ylacetic esters **2** and β,γ-unsaturated esters in high yields under carbonylative conditions. In view of the conceptual as well as the synthetic importance of the process, the mechanistic aspects and the synthetic scope of the reaction have been investigated in detail. All the experimental evidence is in agreement with the sequential homobimetallic mechanism, and the reaction has proven to be of general synthetic applicability.

Keywords: benzofurans; carbonylation; palladium; sequential catalysis; β,γ-unsaturated esters

Introduction

The concatenation between different catalytic cycles, in which the product of the first cycle becomes the substrate of the second cycle and so on (sequential or tandem catalysis, Figure 1) is rather frequent in biological systems, where a substrate can be subsequently transformed into the final product through a sequence of biosynthetic steps catalyzed by different enzymes, but it is not so commonly observed in chemical systems.

Compared to the huge number of examples of single catalytic processes promoted by an organometallic catalyst, relatively few examples of sequential catalytic cycles promoted by different metal systems (sequential heterobimetallic catalysis) have appeared in the literature.[1] However, to the best of our knowledge, the first example of a concatenation of different catalytic cycles promoted by the same metal, but in different oxidation states ("sequential homobimetallic catalysis"), is represented by the Pd(0)-catalyzed deallylation/Pd(II)-catalyzed carbonylative heterocyclization reaction of 1-(2-allyloxyphenyl)-2-yn-1-ols **1** leading to benzofuran derivatives **2**, which has recently been communicated by us [Eq. (1)].[2]

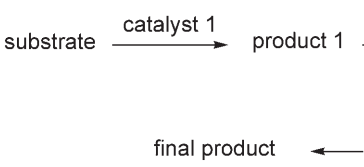
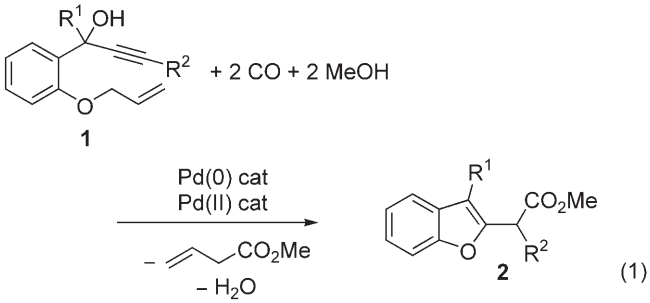


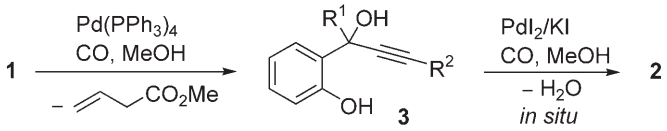
Figure 1. Sequential catalysis.



(1)

In this process, the first catalytic cycle (consisting of deallylation of **1**, with simultaneous allylic carbonylation) is promoted by a Pd(0) complex, and affords a product (the free phenol **3**) that acts as the substrate of the second catalytic cycle (consisting of a carbonylative heterocyclization leading to **2**), promoted by a Pd(II) species (Scheme 1).

We now report a complete account on this kind of reactivity. In view of the conceptual as well as the



Scheme 1. Sequential homobimetallic catalysis leading to benzofurans **2.**

synthetic importance of the process,[3,4] the mechanistic aspects and the synthetic scope of the reaction have been investigated in detail.

Results and Discussion

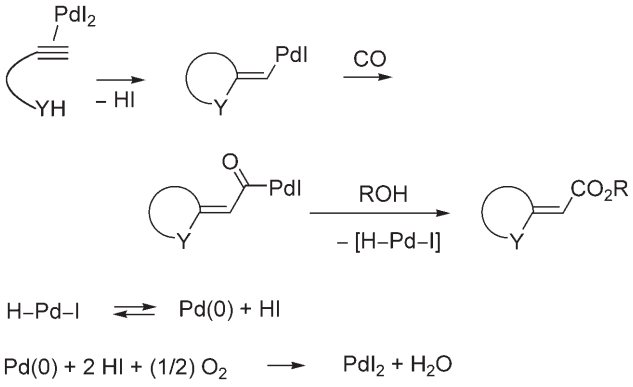
Our investigations were initially focused on the possibility to synthesize benzofuran-2-acetic esters (an important class of benzofuran derivatives, with important biological activity)[4] in one step starting from 2-(1-hydroxyalk-2-ynyl)phenols **3**, through the PdI_2-catalyzed heterocyclization-alkoxycarbonylation-reduction sequence shown in Scheme 2.

This mechanistic hypothesis was based on our previous studies on the PdI_2-catalyzed carbonylation reactions leading to heterocycles.[5] In particular, we have reported several examples of *exo-dig* type heterocyclization-alkoxycarbonylation processes catalyzed by PdI_2 in conjunction with an excess of KI under oxidative conditions, with oxygen as the oxidant, as exemplified in Scheme 3.

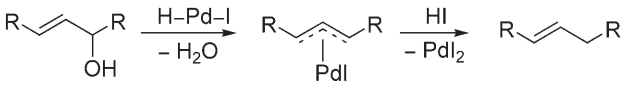
On the other hand, we have also recently showed that an H–Pd–I species is able to promote the reduction of an allylic alcohol function through the formation of a π-allyl complex, with elimination of water, followed by protonolysis, according to Scheme 4.[6]

We therefore reasoned that the PdI_2/KI-catalyzed carbonylation of 2-(1-hydroxyalk-2-ynyl)phenols **3**, carried out in the absence of oxygen, could directly afford benzofurans **2** through initial heterocyclization-alkoxycarbonylation followed by the reduction by H–Pd–I of the allyl alcohol moiety of the resulting intermediate (Scheme 2). Free phenols **3**, however, with R^2 = alkyl, were, according to the literature, difficult to obtain in the pure state owing to their instability and tendency to polymerize.[7] This was confirmed by our attempts to prepare 2-(1-hydroxyhept-2-ynyl)phenol (R^1 = H, R^2 = Bu), which were unsuccessful. One possibility to bypass this inconvenience was to protect the phenolic –OH group with a suitable function, removable in situ under the reaction conditions. Our choice fell on the allyl group, potentially removable through oxidative addition to Pd(0) followed by cleavage by HI and carbonylation (Scheme 5).

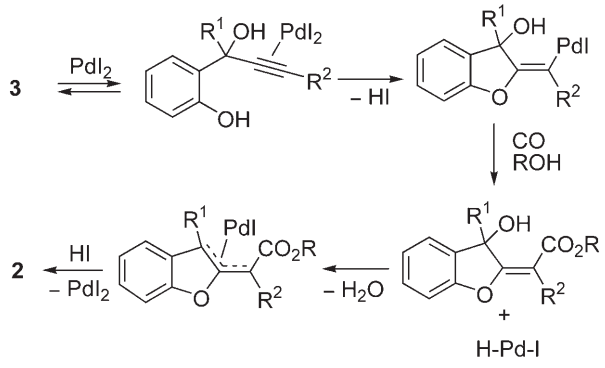
We therefore needed the presence of *both* a Pd(0) catalyst, able to promote the deallylation-carbonylation cycle, *and* a Pd(II) catalyst (PdI_4^{2-}), able to promote the heterocyclization-methoxycarbonylation-reduction cycle, i.e., a sequential catalysis in which a suitable Pd(0) complex catalyzed the formation of the substrate undergoing the subsequent reaction, catalyzed by PdI_2 (*sequential homobimetallic catalysis*). The model substrate we used to test this possibility was 1-(2-allyloxyphenyl)hept-2-yn-1-ol (**1a**; R^1 = H,



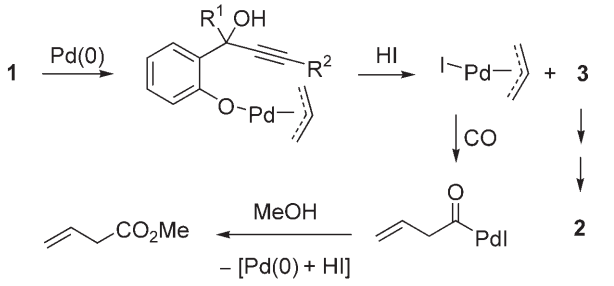
Scheme 3.



Scheme 4.

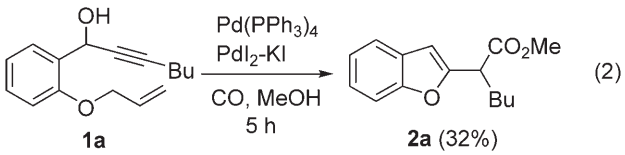


Scheme 2.



Scheme 5.

R^2 = Bu), which was initially reacted in MeOH at 100 °C under 15 atm of CO in the presence of $Pd(PPh_3)_4$ (1 mol %), PdI_2 (1 mol %) and KI (KI:PdI_2 molar ratio = 10). After 5 h, 2-benzofuran-2-ylhexanoic acid methyl ester (**2a**) was indeed formed in 32 % GLC yield at ca. 50 % substrate conversion, thus confirming the validity of our hypotheses [Eq. (2) and Table 1, entry 1].



(2)

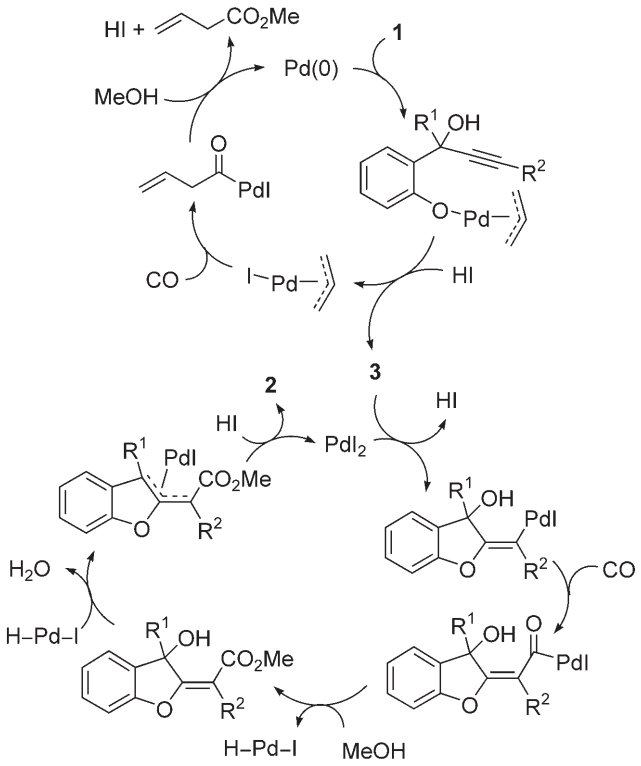
The GLC and GC/MS analysis of the reaction crude showed the formation of but-3-enoic acid methyl ester as co-product, in agreement with Scheme 1. The two sequential catalytic cycles eventually leading to the benzofuran are depicted in Scheme 6.

In agreement with our hypotheses, the reaction carried out in the absence of $Pd(PPh_3)_4$ led to the formation of only small amounts of **2a** (3 %), while the

Table 1. Reactions of 1-(2-allyloxyphenyl)hept-2-yn-1-ol (**1a**) with CO (15 atm) in MeOH at 100 °C in the presence of Pd catalysts.[a]

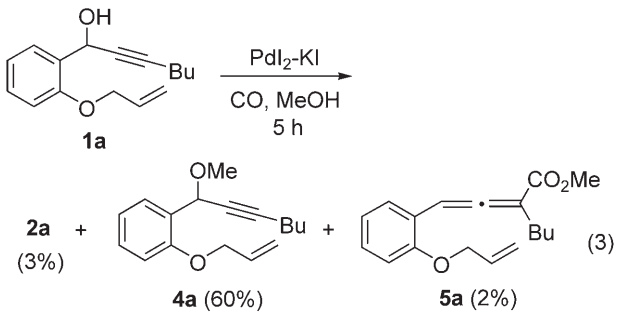
Entry	$Pd(PPh_3)_4$:PdI_2:KI:Ligand:**1a** Molar Ratio	Ligand	H_2O:PdI_2 Molar Ratio	Conv. of **1a** [%][b]	Yield of **2a** [%][c]	Yield of **4a** [%][b]	Yield of **5a** [%][b]
1	0.5:0.5:10:0:100	-	0	50	32		
2	0:1:10:0:100	-	0	80	3	60	2
3	1:0:0:0:100	-	0	30			
4	0:1:10:4:100	PPh_3	200	44	33	2	
5	0:1:10:5:100	PPh_3	200	62	30	traces	
6	0:1:10:3:100	PPh_3	200	49	22	4	
7	0:1:10:2:100	PPh_3	200	100	10	71	8
8	0:1:10:1:100	PPh_3	200	95	5	52	4
9	0:1:10:0:100	-	200	100	11	66	6
10	0:1:10:4:100	PBu_3	200	20	8		
11	0:1:10:3:100	PBu_3	200	15	2	4	0
12	0:1:10:4:100	PCy_3	200	100	2	60	20
13	0:1:10:4:100	$(o\text{-}MeC_6H_4)_3P$	200	100	2	65	10
14	0:1:10:4:100	$(p\text{-}MeC_6H_4)_3P$	200	48	20	traces	
15	0:1:10:2:100	dppe	200	0			
16	0:1:10:1:100	dppe	200	0			
17	0:1:10:4:100	$P(OBu)_3$	200	21	7	2	
18	0:1:10:4:100	$P(OPh)_3$	200	85	4	65	
19	0:1:10:4:100	$P(O\text{-}iPr)_3$	200	100	4	20	62
20	0:1:10:4:100	$AsPh_3$	200	100	2	12	60
21	0:1:10:4:100	$SbPh_3$	200	90	0	85	0
22	0:1:10:2:100	bipy	200	100	8	20	60
23	0:1:10:4:100	bipy	200	100	4	50	40
24	0:1:10:8:100	bipy	200	100		85	3
25	0:1:10:4:100	phen	200	100		85	3
26	0:1:10:4:100	$(2\text{-}Py)PPh_2$	200	40	25	traces	
27	0:1:2:4:100	PPh_3	200	49	20	traces	
28	0:1:100:4:100	PPh_3	200	52	46	1	
29	0:1:200:4:100	PPh_3	200	52	32		
30	0:1:100:4:100	PPh_3	1000	56	29	8	
31	0:1:10:4:100	PPh_3	0	38	traces	17	
32[d]	0:1:100:4 :100	PPh_3	200	71	59		
33[d,e]	0:1:100:4:100	PPh_3	200	100	98 (91)		
34[d,e]	0:1:100:4:100	PPh_3	0	100	8	83	2
35[d,e]	0:1:100:0:100	-	200	100	7	85	2

[a] Unless otherwise noted, all reactions were carried out in MeOH (0.22 mmol of **1a**/mL of MeOH, 2 mmol scale based on **1a**) under 15 atm (at 25 °C) of CO for 5 h.
[b] Based on starting **1a**, by GLC.
[c] GLC yield (isolated yield) based on **1a**.
[d] The reaction was carried out under 30 atm (at 25 °C) of CO.
[e] Reaction time was 15 h.



Scheme 6. Sequential homobimetallic catalysis leading to benzofurans **2**: the two sequential cycles.

main reaction product turned out to be 1-allyloxy-(1-methoxyhept-2-ynyl)benzene (**4a**), still bearing the allyloxy group (60% yield, deriving from etherification of the alcoholic function of **1a**, entry 2) [Eq. (3)]. 4-

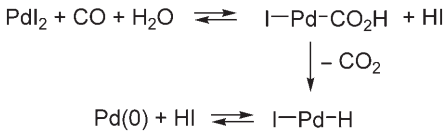


(3)

(2-Allyloxyphenyl)-2-butylbuta-2,3-dienoic acid methyl ester (**5a**) (2%, from Tsuji-type carbonylation[8] of the propargylic function of **1a**) was also detected in the reaction mixture under these conditions. This result confirms that practically no deallylation occurred in the absence of the Pd(0) catalyst.

On the other hand, when the reaction was carried out in the presence of $Pd(PPh_3)_4$ alone, partial decomposition of the substrate was observed with formation of unidentified heavy product (entry 3). This result proves that, in the absence of the Pd(II) catalyst, the free phenol intermediate does not undergo the heterocylization reaction, and goes through decomposition instead.

Interestingly, we have found that a PPh_3-stabilized Pd(0) complex could be formed in situ directly from PdI_2 and PPh_3 working in MeOH in the presence of small amounts of H_2O. In fact, under these conditions, formation of an I–Pd–CO_2H species (from the reaction between PdI_2, CO and H_2O)[9] occurs, whose decarboxylation[10] affords H–Pd–I in equilibrium with Pd(0) and HI (Scheme 7).

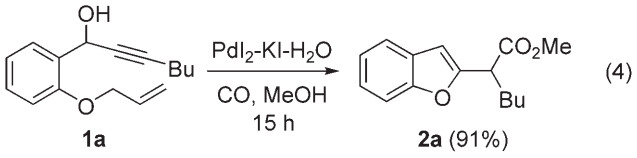


Scheme 7.

Actually, the use of PdI_2 (1 mol%) in conjunction with 10 equivs. of KI, 4 equivs. of PPh_3 and 200 equivs. of H_2O (at 100°C and under 15 atm of CO, as in the previous experiments) led to a 33% yield of **2a** together with a 2% yield of **4a** at 44% substrate conversion (entry 4). The use of a higher amount of PPh_3 led to similar results (entry 5). On the other hand, the use of a lower amount of PPh_3 led to less satisfactory results, as shown by entries 6–8. In the absence of PPh_3, the yields of **2a**, **4a** and **5a** were 11, 66 and 6%, respectively (entry 9). This means that the presence of PPh_3 is essential for stabilizing the Pd(0) complex, responsible for the initial deallylation reaction. We next tested the effect of the nature of other ligands on the reaction. The results obtained, reported in entries 10–26, clearly indicate PPh_3 as the ligand of choice. The results obtained by changing the KI:PdI_2 and H_2O:PdI_2 ratio with 4 mol of PPh_3 per mol of PdI_2 are shown in entries 27–31. The optimal molar ratio was found to be H_2O:KI:PdI_2 = 200:100:1 (substrate conversion = 52% after 5 h, yields of **2a**, **4a** and **5a** = 46, 1 and 0%, respectively, entry 28). It is interesting to note that, according to the fact that the presence of H_2O is necessary to generate the Pd(0) species responsible for *in situ* deallylation, the reaction carried out in the absence of water afforded **4a** as the main product (17%) with only traces of **2a** (entry 31). The effect of rising the CO pressure from 15 to 30 atm was also tested. As can be seen by comparing the results reported in entries 28 and 32, working with P_{CO} = 30 atm had a beneficial effect both on substrate conversion rate and product selectivity.

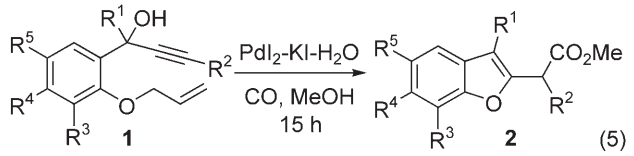
The next experiments were aimed at achieving complete substrate conversion in order to maximize

the yield of **2a**. Under the optimized conditions found before (PdI_2:KI:PPh_3:H_2O:**1a** = 1:100:4:200:100, T = 100 °C, P_{CO} = 30 atm, **1a** concentration = 0.22 mmol per mL of anhydrous MeOH), the conversion of **1a** reached 100% after 15 h, benzofuran **2a** being obtained in a GLC yield as high as 98% [91% isolated, Eq. (4) and entry 33]. To further confirm our mechanistic hypotheses, the same reaction was carried out in the absence of water: **2a** was obtained in only 8% yield, while the main reaction product was the methyl ether **4a** (83% yield; the allene **5a** was also formed in 2% yield, entry 34). Similar results were observed when the reaction was carried out in the presence of water but in the absence of PPh_3 (entry 35).



(4)

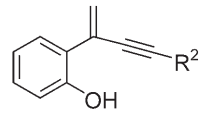
Our methodology could be successfully applied to a variety of differently substituted substrates, as shown in Eq. (5) and Table 2. All the tested substrates afforded the corresponding benzofurans in good to excellent isolated yields (62–91%), working under 30–90 atm of CO. Thus, the triple bond could also be terminal (entries 36 and 37) or substituted with a very bulky alkyl group (entries 38, 42–45) or conjugated with a phenyl group (entries 39, 46–49, 51–53, 56, 58, 60, 62).[11] An additional alkyl (entries 40–49), phenyl (entries 50–53) or even alkynyl substituent (entry 54) could be present at the benzylic position. Finally, π-donors (entries 55–60) as well as electron-withdrawing (entries 61 and 62) groups could be present on the aromatic ring.



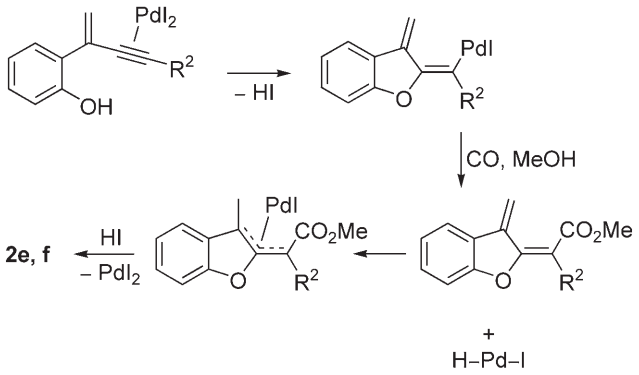
(5)

a $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Bu$: 91%
b $R^1 = R^2 = R^3 = R^4 = R^5 = H$: 70%
c $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = t$-Bu: 80%
d $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Ph$: 82%
e $R^1 = Me$, $R^2 = Bu$, $R^3 = R^4 = R^5 = H$: 83%
f $R^1 = Me$, $R^2 = t$-Bu, $R^3 = R^4 = R^5 = H$: 80%
g $R^1 = Me$, $R^2 = Ph$, $R^3 = R^4 = R^5 = H$: 81%
h $R^1 = Ph$, $R^2 = Bu$, $R^3 = R^4 = R^5 = H$: 74%
i $R^1 = R^2 = Ph$, $R^3 = R^4 = R^5 = H$: 81%
j R^1 = 1-hexynyl, $R^2 = Bu$, $R^3 = R^4 = R^5 = H$: 80%
k $R^1 = R^4 = R^5 = H$, $R^2 = Bu$, $R^3 = OMe$: 84%
l $R^1 = R^4 = R^5 = H$, $R^2 = Ph$, $R^3 = OMe$: 82%
m $R^1 = R^3 = R^5 = H$, $R^2 = Bu$, $R^4 = OMe$: 80%
n $R^1 = R^3 = R^5 = H$, $R^2 = Ph$, $R^4 = OMe$: 62%
o $R^1 = R^3 = R^4 = H$, $R^2 = Bu$, $R^5 = OMe$: 87%
p $R^1 = R^3 = R^4 = H$, $R^2 = Ph$, $R^5 = OMe$: 71%
q $R^1 = R^3 = R^4 = H$, $R^2 = Bu$, $R^5 = Cl$: 88%
r $R^1 = R^3 = R^4 = H$, $R^2 = Ph$, $R^5 = Cl$: 79%

Interestingly, in the case of substrates **1e** and **1f**, bearing a methyl group at the benzylic position, enyne by-products **6e** and **6f** (ensuing from deallylation and dehydration of the tertiary alcoholic group) could be isolated after 15 h reaction time. These compounds proved to be possible intermediates in the formation of benzofurans **2**, as shown by the results obtained by prolonging the reaction time to 24 h (entries 41 and 43, to be compared with entries 40 and 42, respectively). In the case of substrate **1f**, rising the CO pressure from 30 to 60 atm also had a beneficial effect on product selectivity (entries 44 and 45, to be compared with entries 42 and 43, respectively). That enynes **6e** and **6f** could also afford **2e** and **2f** is conceivable, since the dienic intermediates ensuing from heterocyclization-alkoxycarbonylation can easily undergo reduction by H–Pd–I (Scheme 8).



6e R^2 = Bu
6f R^2 = *t*-Bu



Scheme 8.

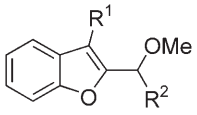
In the case of substrates **1g** and **1i** (bearing an alkyl or phenyl substituent at the benzylic position and with the triple bond conjugated with a phenyl group), an undesired methoxylation by-reaction, with formation of 2-methyoxymethylbenzofurans **7g** and **7i**, respectively, was observed (entries 46–48, 51 and 52).

This by-reaction results from methanol attack on the allylic carbocation (stabilized by the alkyl or

Table 2. Reactions of 1-(2-allyloxyphenyl)-2-yn-1-ols **1** with CO in MeOH at 100 °C in the presence of PdI_2-KI-H_2O.[a]

Entry	**1**	R^1	R^2	R^3	R^4	R^5	P_{CO} [atm]	Time [h]	Yield of **2** [%][b]
36	**1b**	H	H	H	H	H	30	15	70
37	**1b**	H	H	H	H	H	60	15	70
38	**1c**	H	*t*-Bu	H	H	H	30	15	80
39	**1d**	H	Ph	H	H	H	30	15	82
40	**1e**	Me	Bu	H	H	H	30	15	62[c]
41	**1e**	Me	Bu	H	H	H	30	24	83
42	**1f**	Me	*t*-Bu	H	H	H	30	15	62[d]
43	**1f**	Me	*t*-Bu	H	H	H	30	24	74[e]
44	**1f**	Me	*t*-Bu	H	H	H	60	15	79[f]
45	**1f**	Me	*t*-Bu	H	H	H	60	24	80
46	**1g**	Me	Ph	H	H	H	30	15	55[g]
47	**1g**	Me	Ph	H	H	H	60	15	70[h]
48[i]	**1g**	Me	Ph	H	H	H	60	15	75[j]
49[i]	**1g**	Me	Ph	H	H	H	90	15	81
50	**1h**	Ph	Bu	H	H	H	30	15	74
51	**1i**	Ph	Ph	H	H	H	30	15	63[k]
52[i]	**1i**	Ph	Ph	H	H	H	60	24	73[l]
53[i]	**1i**	Ph	Ph	H	H	H	90	24	81
54	**1j**	1-hexynyl	Bu	H	H	H	30	15	80
55	**1k**	H	Bu	OMe	H	H	30	15	84
56	**1l**	H	Ph	OMe	H	H	30	15	82
57	**1m**	H	Bu	H	OMe	H	30	15	80
58	**1n**	H	Ph	H	OMe	H	30	15	62
59	**1o**	H	Bu	H	H	OMe	30	15	87
60	**1p**	H	Ph	H	H	OMe	30	15	71
61	**1q**	H	Bu	H	H	Cl	30	15	88
62	**1r**	H	Ph	H	H	Cl	30	15	79

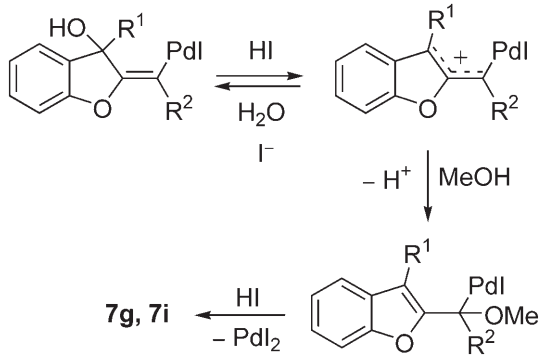
[a] Unless otherwise noted, all reactions were carried out in MeOH (0.22 mmol of **1** per mL of MeOH, 2 mmol scale based on **1**) in the presence of PdI_2 (1 mol%), KI, PPh_3, and H_2O (PdI_2:KI:PPh_3:H_2O molar ratio = 1:100:4:200) at 100 °C. Substrate conversion was quantitative in all cases.
[b] Isolated yield based on starting **1**.
[c] The reaction also led to the formation of 2-(1-methylenehept-2-ynyl)phenol (**6e**) (20%).
[d] The reaction also led to the formation of 2-(4,4-dimethyl-1-methylenepent-2-ynyl)phenol (**6f**) (17%).
[e] The reaction also led to the formation of **6f** (6%).
[f] The reaction also led to the formation of **6f** (2%).
[g] The reaction also led to the formation of 2-(methoxyphenylmethyl)-3-methylbenzofuran **7g** (26%).
[h] The reaction also led to the formation of **7g** (14%).
[i] The KI:PdI_2 molar ratio was 200.
[j] The reaction also led to the formation of **7g** (9%).
[k] The reaction also led to the formation of 2-(methoxyphenylmethyl)-3-phenylbenzofuran **7i** (21%).
[l] The reaction also led to the formation of **7i** (7%).



7g R^1 = Me, R^2 = Ph
7i R^1 = R^2 = Ph

phenyl R^1 group and by conjugation with the R^2 phenyl group) ensuing from HI-promoted elimination of water from the vinylpalladium intermediate, as shown in Scheme 9.

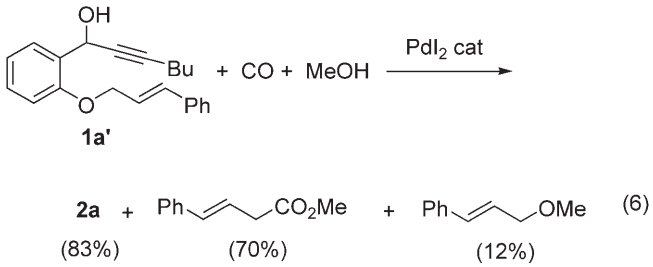
The methoxylation by-reaction could be easily curtailed by working at higher CO pressures (which favor the CO insertion at the level of the vinylpalladi-



Scheme 9.

um intermediate) and by rising the KI:PdI_2 molar ratio (which, on the other hand, increases the concentration of iodide anions, thus making the formation of the allylic carbocation less favored), as shown by entries 47–49 (to be compared with entry 46) and 52 and 53 (to be compared with entry 51).

The nature of the allylic protecting group could also be changed, as shown by the results obtained with 1-[2-(3-phenylallyloxy)phenyl]hept-2-yn-1-ol (**1a**′), which, under the usual conditions, afforded **2a** in 83% yield. As expected on the basis of the sequential mechanism, the reaction also led to the formation of 4-phenylbut-3-enoic acid methyl ester (70% yield), together with small amounts of (3-methoxypropenyl)-benzene (by direct MeOH attack on the phenyallylpalladium complex) [12%, Eq. (6)]. Thus, the present



methodology can permit one to couple the heterocyclization-carbonylation of the 1-oxy-(2-hydroxy-2-ynyl)benzene moiety of the substrate with the substitutive carbonylation of the allyloxy moiety of the same substrate, thus achieving two synthetically important goals *in the same catalytic process.*

Conclusions

In conclusion, we have shown that two different complexes of palladium, with palladium in different oxidation states, may efficiently catalyze two catalytic cycles in ordered sequence ("sequential homobimetallic catalysis"). Thus, the concatenation of a Pd(0)-catalyzed carbonylative deallylation catalytic cycle with a Pd(II)-catalyzed carbonylative heterocyclization catalytic cycle has allowed to obtain benzofuran-2-acetic esters and β,γ-unsaturated esters simultaneously in one step starting from the same substrate, easily prepared from commercially available products through a few simple synthetic steps.

Experimental Section

General Remarks

Melting points were determined with a Reichert Thermovar apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on a Bruker DPX Avance 300 spectrometer in $CDCl_3$ solutions at 300 MHz and 75 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with a Perkin–Elmer Paragon 1000 PC FT-IR spectrometer. Mass spectra were obtained using a Shimadzu QP-2010 GC-MS apparatus at 70 eV ionization voltage. Microanalyses were carried out with a Carlo Erba Elemental Analyzer Model 1106. All reactions were analyzed by TLC on silica gel 60 F_{254} and by GLC using a Shimadzu GC-2010 gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase (HP-5). Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

Substrates were prepared, purified and characterized as described in the Supporting Information. Characterization data for products **2a–2r**, **4a**, **5a**, **6e**, **6f**, **7g**, and **7i** can also be found in the Supporting Information.

General Procedure for Carbonylation of 1-(2-Allyloxyphenyl)-2-yn-1-ols 1a–r to Benzofuran-2-acetic Esters 2a–r and Separation of Products (Tables 1 and 2, entries 33, 36–39, 41, 45, 49, 50, 53–62)

A 250 mL stainless steel autoclave was charged with PdI_2 (7.2 mg, $2.0\cdot10^{-2}$ mmol), KI (332.0 mg, 2.0 mmol), PPh_3 (21.0 mg, $8.0\cdot10^{-2}$ mmol) and a solution of **1** (2.0 mmol) in anhydrous MeOH (9.1 mL). Water (72 μL, 4.0 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 (**1a, 1a**′, **1c–e**, **1h**, **1j–r**), 60 atm (**1b**, **1f**), or 90 atm (**1g**, **1i**). After stirring at 100 °C for 15 h (**1a**, **1a**′, **1b–d**, **1g, 1h**, **1j–r**) or 24 h (**1e, 1f**, **1i**), the autoclave was cooled and degassed. The solvent was evaporated and products were purified by column chromatography on silica gel: **2a** (1:1 hexane-CH_2Cl_2, colorless oil, 449.5 mg, 91%); **2b** (8:2 hexane-AcOEt, yellow oil, 265.8 mg, 70%); **2c** (8:2 hexane-AcOEt, pale yellow solid, mp 60–61 °C, 395.4 mg, 80%); **2d** (8:2 hexane-acetone, yellow oil, 438.1 mg, 82%); **2e** (9:1 hexane-AcOEt, pale yellow oil, 431.2 mg, 83%); **2f** (8:2 hexane-AcOEt, yellow oil, 416.8 mg, 80%); **2g** (9:1 hexane-AcOEt, yellow oil, 453.4 mg, 81%); **2h** (95:5 hexane-AcOEt, pale yellow oil, 478.1 mg, 74%); **2i** (8:2 hexane-AcOEt, yellow oil, 555.8 mg, 81%); **2j** (9:1 hexane-acetone, yellow oil, 520.6 mg, 80%); **2k** (8:2 hexane-AcOEt, yellow oil, 463.7 mg, 84%); **2l** (8:2 hexane-AcOEt, yellow oil, 486.6 mg, 82%); **2m** (8:2 hexane-AcOEt, yellow oil, 440.9 mg, 80%); **2n** (8:2 hexane-AcOEt, yellow oil, 368.3 mg, 62%); **2o** (8:2 hexane-AcOEt, yellow oil, 481.5 mg, 87%); **2p** (8:2 hexane-AcOEt, yellow oil, 419.3 mg, 71%); **2q** (7:3 hexane-AcOEt, pale yellow oil, 493.2 mg, 88%); **2r** (8:2 hexane-acetone, yellow oil, 476.8 mg, 79%).

Carbonylation of 1-(2-Allyloxyphenyl)-hept-2-yn-1-ol 1a to a Mixture of 2-Benzofuran-2-ylhexanoic Acid Methyl Ester (2a), 1-Allyloxy-(1-methoxyhept-2-ynyl)benzene (4a), and 4-(2-Allyloxyphenyl)-2-butylbuta-2,3-dienoic Acid Methyl Ester (5a) and Separation of Products (Table 1, entry 7)

A 250 mL stainless steel autoclave was charged with PdI_2 (7.2 mg, $2.0 \cdot 10^{-2}$ mmol), KI (33.5 mg, 0.2 mmol), PPh_3 (10.5 mg, $4.0 \cdot 10^{-2}$ mmol) and a solution of **1a** (489.0 mg, 2.0 mmol) in anhydrous MeOH (9.1 mL). Water (72 μL, 4.0 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 15 atm. After stirring at 100 °C for 5 h, the autoclave was cooled and degassed. The solvent was evaporated and products were purified by column chromatography on silica gel using 6:4 hexane-CH_2Cl_2 as eluent. Order of elution: **2a** (yellow oil, 49.6 mg, 10 %), **4a** (yellow oil, 367.2 mg, 71 %), **5a** (yellow oil, 45.8 mg, 8 %).

Carbonylation of 2-(2-Allyloxyphenyl)-oct-3-yn-2-ol (1e) to a Mixture of 2-(3-Methylbenzofuran-2-yl)-hexanoic Acid Methyl Ester (2e) and 2-(1-Methylenehept-2-ynyl)phenol (6e) and Separation of Products (Table 2, entry 40)

A 250 mL stainless steel autoclave was charged with PdI_2 (7.2 mg, $2.0 \cdot 10^{-2}$ mmol), KI (332.0 mg, 2.0 mmol), PPh_3 (21.0 mg, $8.0 \cdot 10^{-2}$ mmol) and a solution of **1e** (516.5 mg, 2.0 mmol) in anhydrous MeOH (9.1 mL). Water (72 μL, 4.0 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 stirring at 100 °C for 15 h, the autoclave was cooled and degassed. The solvent was evaporated and products were purified by column chromatography on silica gel using 9:1 hexane-AcOEt as eluent. Order of elution: **6e** (yellow oil, 80.5 mg, 20 %), **2e** (yellow oil, 323.6 mg, 62 %).

Carbonylation of 2-(2-Allyloxyphenyl)-5,5-dimethylhex-3-yn-2-ol (1f) to a Mixture of 3,3-Dimethyl-2-(3-methylbenzofuran-2-yl)butanoic Acid Methyl Ester (2f) and 2-(4,4-Dimethyl-1-methylenepent-2-ynyl)phenol (6f) and Separation of Products (Table 2, entry 42)

A 250 mL stainless steel autoclave was charged with PdI_2 (7.2 mg, $2.0 \cdot 10^{-2}$ mmol), KI (332.0 mg, 2.0 mmol), PPh_3 (21.0 mg, $8.0 \cdot 10^{-2}$ mmol) and a solution of **1f** (516.5 mg, 2.0 mmol) in anhydrous MeOH (9.1 mL). Water (72 μL, 4.0 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 stirring at 100 °C for 15 h, the autoclave was cooled and degassed. The solvent was evaporated and products were purified by column chromatography on silica gel using 8:2 hexane-AcOEt as eluent. Order of elution: **2f** (yellow oil, 323.2 mg, 62 %), **6f** (yellow oil, 67.4 mg, 17 %).

Carbonylation of 2-(2-Allyloxyphenyl)-4-phenylbut-3-yn-2-ol (1g) to a Mixture of (3-methylbenzofuran-2-yl)phenylacetic Acid Methyl Ester (2g) and 2-(Methoxyphenylmethyl)-3-methylbenzofuran (7g) and Separation of Products (Table 2, entry 46)

A 250 mL stainless steel autoclave was charged with PdI_2 (7.2 mg, $2.0 \cdot 10^{-2}$ mmol), KI (332.0 mg, 2.0 mmol), PPh_3 (21.0 mg, $8.0 \cdot 10^{-2}$ mmol) and a solution of **1g** (556.5 mg, 2.0 mmol) in anhydrous MeOH (9.1 mL). Water (72 μL, 4.0 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 stirring at 100 °C for 15 h, the autoclave was cooled and degassed. The solvent was evaporated and products were purified by column chromatography on silica gel using 9:1 hexane-AcOEt as eluent. Order of elution: **7g** (yellow oil, 132.3 mg, 26 %), **2g** (yellow oil, 307.7 mg, 55 %).

Carbonylation of 1-(2-Allyloxyphenyl)-1,3-diphenylprop-2-yn-1-ol (1i) to a Mixture of Phenyl-(3-phenylbenzofuran-2-yl)acetic Acid Methyl Ester (2i) and 2-(Methoxyphenylmethyl)-3-methylbenzofuran (7i) and Separation of Products (Table 2, entry 51)

A 250 mL stainless steel autoclave was charged with PdI_2 (7.2 mg, $2.0 \cdot 10^{-2}$ mmol), KI (332.0 mg, 2.0 mmol), PPh_3 (21.0 mg, $8.0 \cdot 10^{-2}$ mmol) and a solution of **1i** (680.5 mg, 2.0 mmol) in anhydrous MeOH (9.1 mL). Water (72 μL, 4.0 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 stirring at 100 °C for 15 h, the autoclave was cooled and degassed. The solvent was evaporated and products were purified by column chromatography on silica gel using 95:5 hexane-AcOEt as eluent. Order of elution: **7i** (yellow oil, 132.6 mg, 21 %), **2i** (yellow oil, 430.1 mg, 63 %).

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[11] In contrast to **1a**, 2-(1-hydroxyprop-2-ynyl)phenol (**3b**) and 2-(1-hydroxy-3-phenylprop-2-ynyl)phenol (**3d**), bearing a triple bond terminal or conjugated with a phenyl group, respectively, were sufficiently stable to be prepared in the pure state, according to the literature.[12,13] These substrates, as expected, afforded the corresponding benzofurans **2** working in the absence of PPh_3 and H_2O. Thus, under the same conditions of entry 37, but in the absence of PPh_3 and H_2O, **3b** led to **2b** in 40% yield at total substrate conversion. On the other hand, under the same conditions of entry 39, but in the absence of PPh_3 and H_2O, **3d** gave **2d** in 61% yield after 3 h at total substrate conversion. From a practical point of view, however, the procedure employing unprotected **3b** and **3d** is less convenient than that employing the corresponding protected substrates **1b** and **1d**, since a considerable higher excess of the corresponding alkynylmagnesium reagents is necessary for carbonyl alkynylation (see Supporting Information for details) and also in view of the higher yields of **2b** and **2d** obtained when starting from **1b** (70%, entry 37) or **1d** (82%, entry 39) respectively, rather than from **3b** or **3d** (40% and 61%, respectively, as we have seen).

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