Communication

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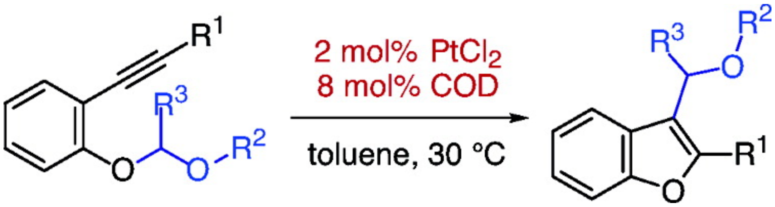

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Synthesis of 2,3-Disubstituted Benzofurans by Platinum−Olefin-Catalyzed Carboalkoxylation of *o*-Alkynylphenyl Acetals

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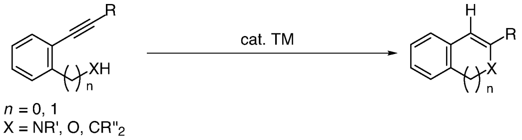
It is well known that the transition metal-catalyzed annulation of *o*-alkynylarylamines, alcohols, and other derivatives produces the corresponding heterocycles and carbocycles in high yields (eq 1).[1] Furthermore, it is becoming popular that the 2,3-disubstituted indoles and benzofurans shown in eq 2 can be synthesized from *o*-alkynylanilines, phenols, and their derivatives through the external addition of organopalladium species to the triple bond (eq 2).[2] However, intramolecular annulation accompanied by migration of the second functional group Y, attached to the first functional group X, is rare (eq 3).[3−6] This type of sequential addition of the two functional groups is important from a synthetic point of view, since 2,3-disubstituted indoles ($n = 0$, R at C2, Y at C3, X = N) and benzofurans ($n = 0$, X = O) constitute an often valuable structural framework of biologically active natural products.[7] Previously, the synthesis of indoles (R at C2, allyl at C3, ref 3; or R at C2, acyl at C3, ref 4) and benzofurans (R at C2, allyl at C3, ref 5; or R at C2, propargyl/allenyl at C3, ref 6) was accomplished through reaction of the type shown in eq 3. We report that the $PtCl_2$-catalyzed cyclization reaction of *o*-alkynylphenyl acetals **1** in the presence of 1,5-cyclooctadiene (COD) produces 3-(α-alkoxyalkyl)benzofurans **2** in good to high yields (eq 4).[8]



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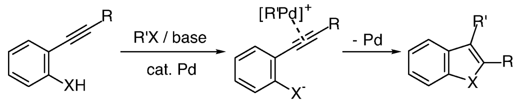

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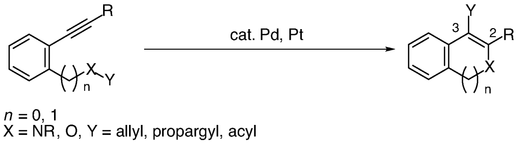

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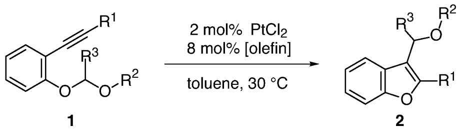

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Table 1. Carboalkoxylation of **1a** Catalyzed by the Platinum−Olefin System[a]

entry	Pt	olefin (mol %)	yield of **2a**/%[b]	recovery of **1a**/%[b]
1	$PtCl_2$	COD (8)	93 (91)[c]	
2	$PtCl_2$	none	24	68
3	$PtCl_2$	1-hexene (16)	90	trace
4	$PtCl_2$	cyclooctene (16)	84	16
5	$PtCl_2$	β-pinene (16)	51	48
6	$PtCl_2$	norbornadiene (8)	50	50
7	$PtCl_2$	styrene (16)	40	60
8	$PtCl_2$(cod)	none	0	quant.

[a] The reaction of **1a** (0.3 mmol) was carried out in the presence of 2 mol % of $PtCl_2$ and olefin in toluene at 30 °C for 1 h. [b] The yield was determined by ^{1}H NMR using 1,4-dioxane as an internal standard. [c] Isolated yield.

Table 2. Platinum-Catalyzed Carboalkoxylation of *o*-Alkynylphenyl Acetals **1**[a]

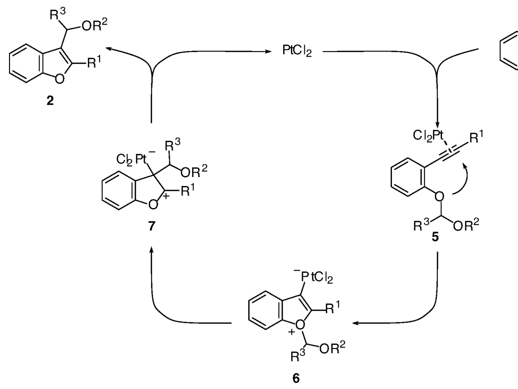
entry	**1**	R^1	R^2	R^3	time/h	**2**	yield/%[b]
1	**1a**	*n*-Hex	Et	Me	1	**2a**	91
2	**1b**	$(CH_2)_4Cl$	Et	Me	1	**2b**	92
3	**1c**	cyclohexyl	Et	Me	2.5	**2c**	94
4	**1d**	*t*-Bu	Et	Me	24	**2d**	trace
5	**1e**	*p*-$(MeO)C_6H_4$	Et	Me	24	**2e**	90
6	**1f**	Ph	Et	Me	3	**2f**	88
7	**1g**	*p*-$(CF_3)C_6H_4$	Et	Me	4 days	**2g**	61
8[c]	**1h**	*n*-Pr	Me	H	22	**2h**	92
9[c]	**1i**	Ph	Me	H	24	**2i**	73
10[d]	**1j**	*n*-Pr	Bn	H	20	**2j**	94
11[d]	**1k**	Ph	Bn	H	48	**2k**	83
12[e]	**1l**	Ph	TBS	H	4 days	**2l**	61

[a] The reaction of **1** was carried out in the presence of 2 mol % of $PtCl_2$ and 8 mol % of COD in toluene at 30 °C. [b] Isolated yield. [c] 20 mol % of $PtCl_2$ and 80 mol % of COD were used. [d] 10 mol % of $PtCl_2$ and 40 mol % of COD were used. [e] 100 mol % of $PtCl_2$ and 80 mol % of COD were used.

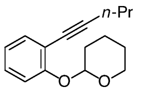
The reaction of acetaldehyde ethyl *o*-(1-octynyl)phenyl acetal **1a** in the presence of 2 mol % of $PtCl_2$ and 8 mol % of COD in toluene proceeded at 30 °C, and 1 h later 3-(1-ethoxyethyl)-2-hexylbenzofuran **2a** was produced in 91% yield (Table 1, entry 1). The use of COD as an additive is very important for facilitating this migration, as shown in Table 1. The reaction in the absence of COD gave **2a** in 24% yield (entry 2). The reaction using 1-hexene or cyclooctene, instead of COD, gave **2a** in a similar yield, while the use of β-pinene, norbornadiene, or styrene resulted in lower yields (entries 3−7). Interestingly, $PtCl_2$(cod) did not promote the reaction at all (entry 8). Other transition metal complexes, such as $PtBr_2$, PtI_2, K_2PtCl_4, $PdCl_2$, $NiCl_2$, $Yb(OTf)_3$, $[RhCl(cod)]_2$, and $Pd(PPh_3)_4$, also did not promote the reaction. The reaction of **1a** using acetonitrile as solvent produced **2a** in 60% yield along with a small amount of unknown byproducts. The results of the reaction of **1** are summarized in Table 2. The reaction of substrates bearing 4-chlorobutyl (**1b**) and cyclohexyl (**1c**) groups at the alkynyl terminus proceeded very smoothly, while the reaction of **1d** having a *tert*-butyl group was sluggish (entries 2−4). The reaction of **1e**, which had an electron-rich aromatic group at the R^1 position, gave the desired product in a high yield, while the reaction of **1g**, which had an electron-deficient aromatic group, proceeded slowly, producing **2g** in a moderate yield (entries 5−7). The reaction of the MOM ethers (**1h** and **1i**) and the BOM ethers (**1j** and **1k**) proceeded smoothly with use of slightly higher amounts of the platinum catalyst (entries 8−11); the reaction of **1h** using 2 mol % of $PtCl_2$ and 8 mol % of COD proceeded very slowly and it took 5 days, giving **2h** in 50% yield along with 50% yield of recovered **1h**.[9]

10.1021/ja055202f CCC: $30.25

Scheme 1. Plausible Mechanism

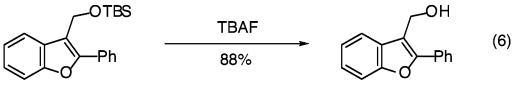


The reaction of TBS ether **1l** was promoted by the use of a stoichiometric amount of the platinum catalyst (entry 12). The reaction of **1m** bearing a THP group did not proceed at all. The benzyl ether **2k** and TBS ether **2l** were converted to the corresponding aldehyde **3** and alcohol **4** in good yields, respectively (eqs 5 and 6).



1m

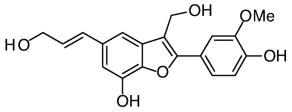
2k **3** (5)



2l **4** (6)

A plausible mechanism for the platinum-catalyzed reaction of **1** is illustrated in Scheme 1. Platinum chloride is coordinated by the triple bond of the substrate **1**. Nucleophilic attack of the oxygen atom of the phenyl acetal moiety of **5** would give the cyclized intermediate **6**. Migration of the α-alkoxyalkyl group of **6** to the carbon bonded to platinum atom would produce the intermediate **7**. Elimination of platinum chloride gives the product **2**. COD probably works as an activating agent to disconnect Pt−Cl bonds of polymeric platinum chloride and to generate a reactive platinum catalyst.[10] However, since PtCl$_2$(cod) itself did not promote the present reaction at all, a real active species might be a platinum oligomer (Table 1, entry 8).

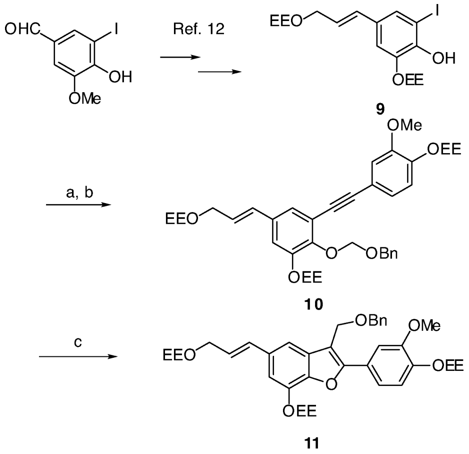
We applied the present reaction for the synthesis of vibsanol **8**, which was isolated from *Viburnum awabuki*. It is well known that



8 vibsanol

8 works as an inhibitor of lipid peroxidation.[11,12] The precursor of carboalkoxylation, *o*-alkynylaryl benzyl acetal **10**, was synthesized from the *o*-iodophenol **9**, prepared from iodovaniline according to the reported procedures.[12] The carboalkoxylation of **10** proceeded smoothly, giving the desired vibsanol precursor **11** in 76% yield (Scheme 2). Accordingly, a formal synthesis of **8** was accomplished through platinum−olefin-catalyzed carboalkoxylation methodology.

Scheme 2. Synthesis of Vibsanol Precursor **11** via Carboalkoxylation[a]



[a] Reagents and conditions: (a) BOMCl, NaH, THF, 0 °C, quantitative; (b) [4-(1-ethoxyethyl)-3-methoxyphenyl]acetylene, Pd(PPh$_3$)$_4$,CuI, Et$_3$N, THF, room temperature, 64%; (c) 20 mol % PtCl$_2$, 80 mol % COD, toluene, 30 °C, 76%.

In conclusion, we are in a position to synthesize 3-(α-alkoxyalkyl)-2-substitued benzofurans in an efficient and atom-economic manner. The present result suggests that a cation-stabilizing group Y may undergo transition metal-catalyzed intramolecular 1,3-transfer from X to the C3 position of the heterocycles containing X. We are now investigating the full scope of this type of transformation.

Supporting Information Available: Experimental details and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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