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‘Anti-Wacker’-type hydroalkoxylation of diynes catalyzed by palladium(0)

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Abstract—The regioselective *trans* addition of acidic alcohols to conjugated diynes via a Pd(0)-diyne intermediate to give the alkoxylated enyne product, illustrates the first catalytic report involving electrophilic addition to unsaturated bonds by Pd(0).

The chemical nature of C–C unsaturated bonds is affected by transition metals. In the addition of H-nucleophiles to alkenes or alkynes, the electron density of unsaturated systems can be decreased by complexation of an electrophilic high oxidation state transition metal, e.g. Pd(II), thus activating the C–C multiple bonds for nucleophilic attack.[1] Processes based on this Wacker-type reaction have been exploited extensively in organic synthesis.

In our continuing study of palladium-catalyzed reactions, we focused on the addition of alcohol nucleophiles to C–C multiple bonds.[2] Typically, the addition of *O*-nucleophiles to alkynes proceeds by the catalytic action of Pd(II) salts[3,4] which are best interpreted as involving oxypalladation, a process similar to the nucleophilic attack in a Wacker-type reaction (Fig. 1A). Addition of alcohols to C–C triple bonds catalyzed by Pd(0) often involves the presence of carboxylic acids in hydropalladation reactions[5] which are initiated by the hydrido-palladium species formed in situ (Fig. 1B). On the other hand, the reaction involving a possible addition of an electrophile to the C–C multiple bond, with the aid of transition metals, has been limited to stoichiometric observations.[6] Catalytic reactions similar to Fig. 1C, however, have not been investigated. We report a Pd(0)-catalyzed hydroalkoxylation of internal conjugated diynes **2** using acidic alcohols which gives the hydroalkoxylated enyne products **3** in an unusual anti-Wacker-type process (Eq. (1)).

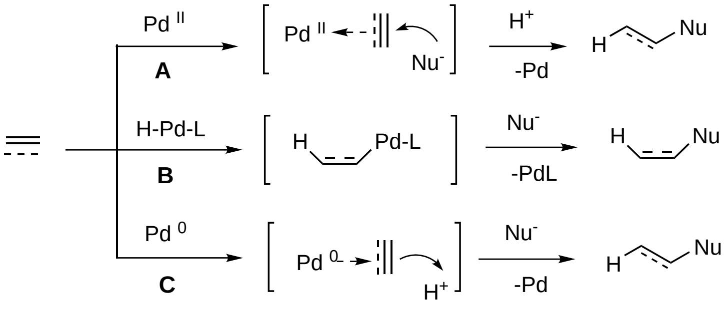
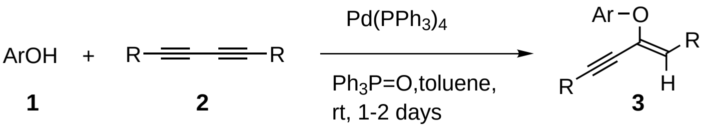


Figure 1. Pd-catalyzed functionalization of C–C multiple bonds.



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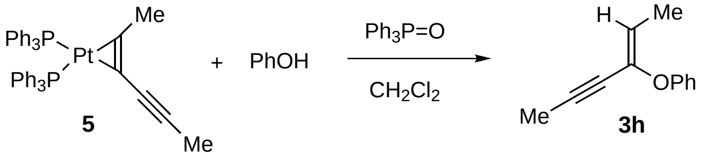
In an initial experiment, using mono-alkynes and phenols, no addition product was obtained in the presence of $Pd(PPh_3)_4$, as catalyst. But, when the substrate was changed to 5,7-dodecadiyne **2a**, addition of phenol **1a** occurred unexpectedly at 100°C in toluene to give enyne **3a** in 52% yield. Single addition of phenol to one of the triple bonds occurred exclusively, even in the presence of excess phenol, leaving free the other triple bond. Moreover, dimerization of the diyne was never observed under the reaction conditions.[7] After varying the reaction parameters, we observed that the P(*o*-tolyl)$_3$ and $Ph_3P{=}O$ ligands, increased the yield of **3a** to give 87 and 98% NMR yields, respectively, under mild room temperature conditions. The role of the additional ligands is not well understood as of this time. In the absence of Pd(0) catalyst, no reaction was observed. Several Pd(II) systems such as $Pd(OAc)_2$, $Pd(OAc)_2/PPh_3O$, $Pd(OAc)_2/CuCl_2$, $PdCl_2/CuCl/O_2$, $PdCl_2$, $PdCl_2/CH_3N$, $PdCl_2(CH_3CN)_2/PPh_3$, $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$/*p*-benzoquinone, were investigated but all gave no reaction, indicating the necessity of Pd(0) as the active catalyst.

As shown in Table 1, the reaction proceeds in a highly regio and stereoselective manner and the *Z*-phenoxyenyne **3** was isolated as the sole product in good to high yields. The reaction indicates an exclusive *trans* addition of phenol to one of the triple bonds. The *Z* configuration was confirmed by the observed $^3J_{CH} = 4.35$ Hz of **3i**[8] and by X-ray analysis of the Pt complex of **3h**, *cis*-Pt[$(PPh_3)_2$] [η^2-$CH_3C{\equiv}CC(OPh){=}CHCH_3$], **4**.[9] The observed exclusive formation of the *trans* adduct is in sharp contrast to the Pd(II)-catalyzed hydrostannation[10] and disilylation[11] of conjugated diynes, in which *cis* addition occurs.

The utility of the electron rich Pd(0) in the reaction indicates a mechanism involving addition of an electrophile to the diyne system. Such a process has been reported for platinum(0)[6] and osmium(II)[12] complexes. A remarkable observation was the noted increased nucleophilic character of Pt(0) complexes which were η^2-coordinated to a conjugated C–C multiple bonds compared to the non conjugated unsaturated system.[13] The electron rich transition metal with low oxidation state donates its electron density to the C–C multiple bond upon coordination. The conjugated diene or diyne system is a good acceptor of metal d electrons into its π^* orbitals, because of conjugation. Through π back bonding, the conjugated system becomes more electron rich and susceptible to electrophilic rather than nucleophilic addition. Indeed, the group of Casey[14] observed that, stoichiometrically, in the presence of excess CF_3COOH, electrophilic addition of H^+ to Pt[$(PPh_3)_2$][η^2-$CH_3C{\equiv}CC{\equiv}CCH_3$] **5** occurred selectively.

To shed light on the mechanism of the present reaction, a Pt(0) analogue was employed. In the presence of $Pt(PPh_3)_4$, the reaction of **1a** with **2a** gave **3a** after 5 days in ca. 15% yield. The low yield was expected due to the low reactivity of Pt compared to Pd. When the reaction started with the expected Pt(0)-diyne adduct **5** (Eq. (2)) and excess phenol in the presence of triphenylphosphine oxide, addition of phenol occurred to give **3h** in 34% yield, whose spectroscopic data matches those obtained by Pd(0) catalysis.



(2)

Table 1. Pd-catalyzed hydroalkoxylation of conjugated diynes **2**[a]

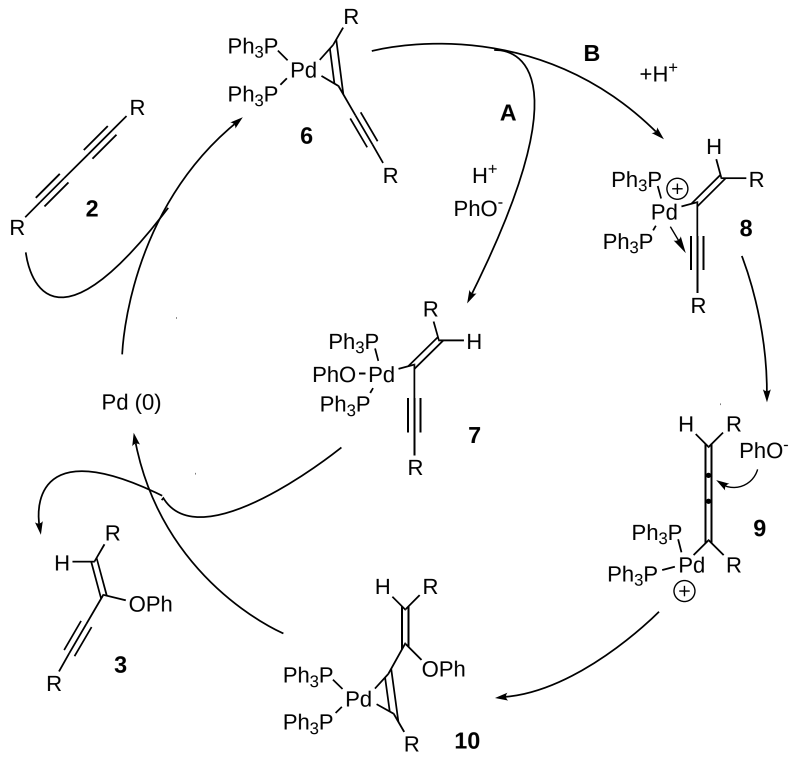
Entry	Alcohol **1**	Diyne **2**	Product **3**	Yield (%)[b]
1	PhOH **1a**	**2a** (R = Butyl)	**3a**	92
2	CF_3CH_2OH **1b**	**2a**	**3b**	71
3	2-Naphthol **1c**	**2a**	**3c**	91
4	4-Methoxyphenol **1d**	**2a**	**3d**	99
5	4-Methylphenol **1e**	**2a**	**3e**	86
6	2-Methylphenol **1f**	**2a**	**3f**	68
7	4-Triflouromethylphenol **1g**	**2a**	**3g**	80
8	**1a**	**2b** (R = Methyl)	**3h**	83
9	**1a**	**2c** (R = Phenyl)	**3i**[c]	40
10	**1a**	**2d** (R = Hexyl)	**3j**	92
11	**1a**	**2e** (R^1 = Phenyl; R^2 = Butyl)	**3k**/**3l**[d]	46/27

[a] Unless otherwise specified, the reaction of **1** (1.0 mmol) and **2** (0.5 mmol) was carried out in the presence of 5 mol% $Pd(PPh_3)_4$ and 10 mol% $Ph_3P{=}O$ in toluene at 25°C for 2–3 days.

[b] Isolated yield.

[c] Reaction performed at 60°C.

[d] **3k**: $PhC{\equiv}CC(OPh){=}CHButyl$; **3l**: $ButylC{\equiv}CC(OPh){=}CHPh$



Scheme 1. Two plausible mechanisms for enyne formation.

Plausible mechanisms are shown in Scheme 1.[15] Coordination of the Pd(0) species to one of the triple bonds would give the electron-rich η^2-coordinated Pd(0) complex **6.** Regioselective addition of a proton (route A) would give the neutral complex **7** followed by reductive elimination to give **3** and regeneration of Pd(0). An alternative process would involve the regioselective addition of a proton (route B) to afford **8**.[16] Rearrangement of **8** gives the σ-cumulenyl palladium complex **9**.[17] The attack of the phenoxide on the cumulene ligand of **9** (i.e. the side opposite to the bulky phosphine ligands) would occur to give **10**. Reductive elimination would then give **3** and Pd(0) is regenerated. The proposed mechanism is consistent with the absence of the double addition of phenol to the starting diyne or the second addition of phenol to the enyne **3** even over longer times and of higher temperature and also with the absence of the addition of phenol to mono-alkynes and conjugated enynes. This is primarily due to steric factors and the fact that efficient conjugation cannot be achieved in the enyne and mono-alkyne systems. Moreover, aliphatic alcohols do not add to the diyne system indicating the necessity of an acidic alcohol (phenols, naphthol **1c** and 2,2,2-trifluoroethanol **1b**), which is consistent with the importance of a proton source as proposed in the mechanism.

The present reaction, to the best of our knowledge, is the first *catalytic* report involving electrophilic addition to C–C multiple bonds by a transition metal with low oxidation state, in an unusual anti-Wacker-type process.

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