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Requirement for an Oxidant in Pd/Cu Co-Catalyzed Terminal Alkyne Homocoupling To Give Symmetrical 1,4-Disubstituted 1,3-Diynes

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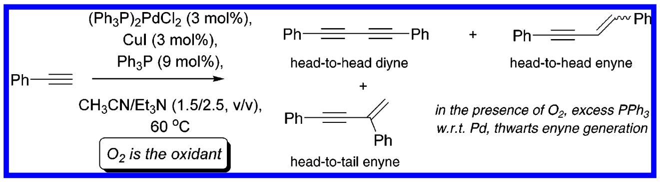
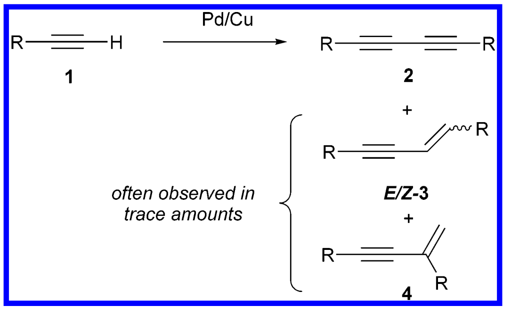


Palladium-catalyzed terminal alkyne dimerization, through oxidative homocoupling, is a useful approach to the synthesis of symmetrical 1,4-diynes. Recent investigations have suggested that this reaction might be accomplished in the absence of intentionally added stoichiometric oxidants (to reoxidize Pd(0) to Pd(II)). In this paper, we have fully addressed the question of whether oxygen (or added oxidant) is required to facilitate this process. The presence of a stoichiometric quantity of air (or added oxidant such as I_2) is essential for alkyne dimerization. Excess PPh_3 inhibits alkyne dimerization to enyne, which only occurs to a significant extent when the reaction is starved of oxidant. Theoretical studies shed more light on the requirement for an oxidant in the homocoupling reaction in order for the process to be theromodynamically favorable. The employment of I_2 as the stoichiometric oxidant appears to be the method of choice. The dual role of Cu both in transmetalation of alkynyl units to Pd(II) and in assisting reoxidation of Pd(0) to Pd(II) is suggested.

Palladium-catalyzed cross-coupling reactions are widely applied to the formation of C−C bonds.[1] Alkyne dimerization, through oxidative homocoupling, to give 1,3-diynes is important for a number of applications, particularly in the construction of linearly π-conjugated acetylenic oligomers and polymers,[2] natural products,[3] and molecular recognition processes.[4] Here, palladium catalysis has played a key role.[5] Traditional methods for oxidative homocoupling of terminal alkynes **1** to give symmetrical 1,4-disubsituted diynes **2** (Scheme 1) include Cadiot−Chodkiewicz,[6] Eglington,[7] Glaser,[8] Hay,[9] and Sonogashira couplings.[10] Catalytic systems mediated by palladium, Pd(0) or Pd(II), are arguably the most mild, efficient, and selective for the oxidative homocoupling reactions of **1** → **2**.[11] Common side products in these reactions are enynes *E*,*Z*-**3** and **4**, the former produced through head-to-head coupling and the latter through head-to-tail coupling.[12]

SCHEME 1. Homocoupling of Terminal Alkynes



Reported protocols for the oxidative homocoupling include (1) use of $(Ph_3P)_4Pd(0)$, CuI, Et_3N, and chloroacetone (as the reoxidant) in benzene;[13] (2) $(Ph_3P)_2PdCl_2$, CuI, Et_3N, or DABCO and bromoacetate (as the reoxidant) in THF;[14] (3) $(Ph_3P)_2PdCl_2$, CuI, and molecular iodine (as the reoxidant) in *i*-Pr_3N;[15] (4) $Pd(0)(dba)_2$ (dba

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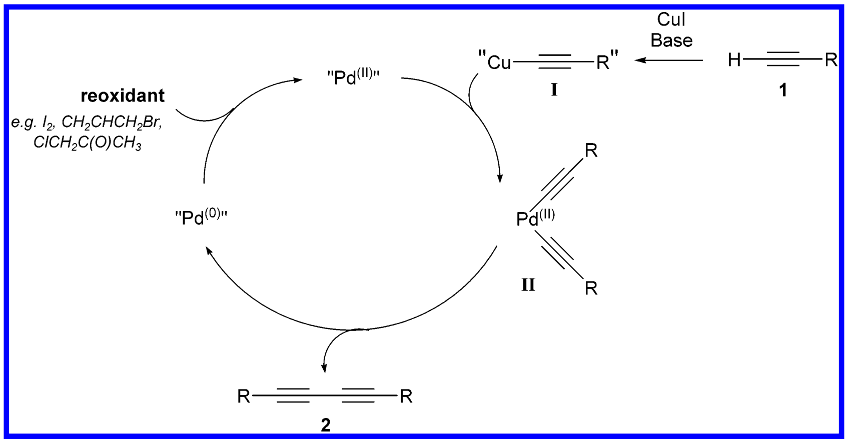
SCHEME 2. General Mechanism for the Pd(II) Homocoupling of Alkynes



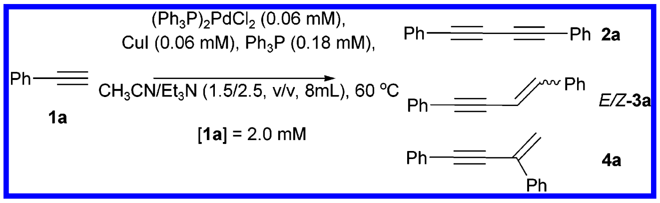
= *E*,*E*-dibenzylidene acetone), *n*-Bu$_4$NBr, NaOH, and allyl bromide (as the oxidant) in CH$_2$Cl$_2$.[16] Furthermore, the reaction may be conducted in the presence of air to give certain types of diynes.[17]

In all of the above cases, a stoichiometric amount of a reoxidant is required for successful homocoupling. The proposed mechanism for the Pd(II)-catalyzed homocoupling reaction is shown in Scheme 2. The formation of the alkynylcuprate **I**, by base-assisted deprotonation of **1** in the presence of CuI, and subsequent transmetalation with Pd(II), gives a dialkynylpalladium(II) species **II**. Final reductive elimination generates Pd(0) and diyne **2**. The Pd(0) species is reoxidized to Pd(II) with various oxidants to complete the catalytic cycle.

In a recent paper, a member of our group (I.J.S.F.) has reported the homocoupling of **1** to give **2** using a combination of (Ph$_3$P)$_2$PdCl$_2$ (3 mol %) and CuI (3 mol %) in a CH$_3$CN/Et$_3$N (1.5/2.5, v/v) solvent mixture, with additional Ph$_3$P (9 mol %) at room temperature.[18] The presence of phosphine was essential in eliminating the production of enyne byproducts *E*/*Z*-**3** and **4**. However, although an added oxidant was not required such as I$_2$ or chloroacetone, the question of whether air was promoting the homocoupling was unresolved. In this paper, we show conclusive evidence that stoichiometric quantities of air are required under the previously reported conditions. This is consistent with our (T.B.M.) previous findings.[17a] Importantly, theoretical calculations support the requirement for an oxidant in this reaction system. In its absence, H$_2$ would formally be produced, which we demonstrate is thermodynamically unfavorable. After screening several procedures for the oxidative homocoupling, vide supra, we have determined that the use of the I$_2$ system, developed by Burton and co-workers,[15] is the most versatile at the present time for the homocoupling of electron-deficient arylacetylenes, facilitating access to novel 1,4-diaryl-1,3-diynes.

To establish whether trace quantities of air were promoting the conversion of **1** → **2**, reactions were carried out under identical conditions to those reported, but in a nitrogen-filled glovebox (levels of O$_2$ were < 5 ppm) (Scheme 3).

SCHEME 3. Homocoupling of Phenylacetylene 1a to Diyne 2a



Specifically, phenylacetylene **1a** (2.0 mM) was added to a reaction vial containing (Ph$_3$P)$_2$PdCl$_2$ (0.06 mM, 3 mol %) and Ph$_3$P (0.18 mM, 9 mol %) in an CH$_3$CN/Et$_3$N mixture (1.5/2.5, v/v, total volume = 8 mL). The cocatalyst, CuI (0.06 mM, 3 mol %), was added last to initiate the reaction (there is not a Pd-catalyzed background reaction in the absence of CuI). Two reactions were carried out at temperatures of 25 and 60 °C.

GC/MS analysis of the reaction conducted at 25 °C after 0.25 h indicated the disappearance of a small amount of **1a** and the formation of **2a** (0.058 mM), but critically, no further change was seen after 24 h (concentration of **2a** = 0.058 mM ± 0.005 mM; samples withdrawn at 4, 8, 18, and 24 h). The total formation of **2a** can be accounted for by reduction of Pd(II) to Pd(0) in the first step of the catalytic cycle shown in Scheme 2 (theoretical amount of **2a** produced through the first turnover = 0.06 mM, overall theoretical conversion of **1a** → **2a** = 1 mM). A similar result was observed at 60 °C. Conducting the reaction in the presence of freshly prepared (Ph$_3$P)$_4$Pd (0.06 mM, 3 mol %), instead of (Ph$_3$P)$_2$PdCl$_2$ and additional Ph$_3$P, resulted in no turnover at all under the glovebox conditions.

The effect of air on the reaction of **1a** → **2a** was assessed using identical reactant/catalyst/cocatalyst concentrations as for the above glovebox reactions. Careful kinetic experiments were performed to monitor the disappearance of **1a** and appearance of **2a** with time, using the (Ph$_3$P)$_2$PdCl$_2$ precatalyst, in the presence and absence of additional Ph$_3$P ligand at 60 °C (Figures 1 and 2, respectively). A small quantity of air was introduced by opening the reaction vessel for 2 min, once all the components of the reaction mixture had been added (the reaction mixture was prepared under a stream of dried

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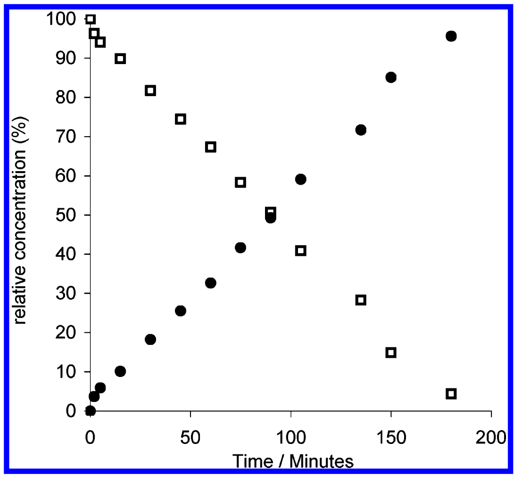

FIGURE 1. Concentration versus time plot for the conversion of **1a** (□, 2.0 mM) to **2a** (◆) in the presence of additional Ph_3P: reaction vessel opened to air for 2 min at t_0, where the relative concentrations of **1a** and **2a** refer to $[\mathbf{1a}]_t/[\mathbf{1a}]_0$ and $[\mathbf{2a}]_t/[\mathbf{1a}]_0$, respectively.

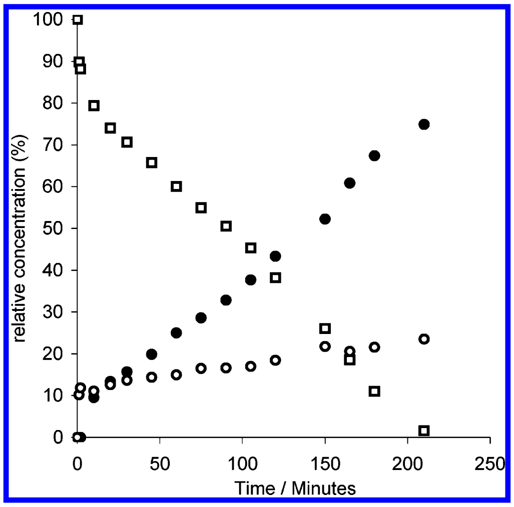

FIGURE 2. Concentration versus time plot for the conversion of **1a** (□, 2.0 mM) to **2a** (◆) and *E*/*Z*-**3a**+**4a** (○) in the absence of additional Ph_3P: reaction vessel opened to air for 2 min at t_0, where the relative concentrations of **1a**, **2a**, and *E*/*Z*-**3a**+**4a** refer to $[\mathbf{1a}]_t/[\mathbf{1a}]_0$, $[\mathbf{2a}]_t/[\mathbf{1a}]_0$, and $[E/Z\text{-}\mathbf{3a}+\mathbf{4a}]_t/[\mathbf{1a}]_0$, respectively.

N_2 using standard Schlenk techniques; dried solvents were degassed using three freeze−thaw-pump cycles). The reactions were then sampled using a gastight syringe, and all GC samples were quenched through a small plug of silica (analysis aliquot = 50 μL, 0.69 g of Kieselgel 60 silica; particle size 0.035−0.070 mm, 220−440 mesh), eluted with CH_2Cl_2 (~ 3 mL), and then stored at −30 °C prior to analysis by GC. The time-dependence of post-quenched samples showed no change after 72 h at this temperature, proving to be a reliable quenching procedure in this case.[19]

The initial rate seen in Figure 1 is somewhat faster than the overall rate, which is presumably associated with rapid reaction of the alkynylcuprate, derived from reaction of **1a** with CuI in the presence of Et_3N, with $(Ph_3P)_2PdCl_2$, to give $(Ph_3P)_nPd(0)$ (where n = 1−4) and diyne **2a**, through the intermediate species, $(Ph_3P)_nPd(\sigma\text{-alkynyl})_2$ (n = 1 or 2). Subsequent turnovers will be dependent on the efficiency of reoxidation of Pd(0) to Pd(II) by O_2 vide infra. Note that in this reaction we do not observe the formation of enynes *E*/*Z*-**3a** and **4a** and that the formation of $Ph_3P{=}O$ is only observed toward the latter stages of the reaction (by GC/MS).

TABLE 1. Isolated Yields of *p*-R-C_6H_4-C≡C-C≡C-C_6H_4-*p*-R Using O_2 or Anaerobic I_2 as Oxidant

entry	R	% yield (O_2)	% yield (I_2)
1	H, **2a**	80	81
2	CN, **2b**	22	31
3	CO_2Me, **2c**		73
4	CF_3, **2d**	41	66
5	Me, **2e**	42	52
6	SMe, **2f**	85	
7	OMe, **2g**	69	78
8	NMe_2, **2h**	80	59

In the absence of Ph_3P, one can see that the rate of enyne formation is faster in the initial stages (<2 min during which air is being introduced) as compared to the remaining course of the reaction (Figure 2). The O_2 concentration in solution is expected to be lower at this stage, and hence, the Pd(0) concentration will be higher, facilitating generation of the enyne byproducts (*E*/*Z*-**3a** and **4a**) probably via alkyne C−H oxidative addition, alkyne insertion into Pd−H, and C−C reductive elimination. This suggests that excess phosphine slows down/inhibits enyne generation, probably by tying up needed coordination sites on Pd(0) (Figure 1).

Overall, these reactions demonstrate that air (O_2) does promote the homocoupling process and that the role of excess phosphine is to thwart enyne generation. It is important to note, however, that if O_2 is bubbled through a solution of **1a** → **2a** at room temperature, under the standard conditions given above, we find that only low conversions to **2a** are seen (~20%). Furthermore, a number of other products are observed by GC/MS analysis, not least the formation of $Ph_3P{=}O$ in the early stages of the reaction, the production of other tri- and tetrameric acetylenic products, and the rapid production of palladium black. The separation of the minor side products from **2a** has so far proven unsuccessful.

To compare the use of O_2 and I_2 as oxidants, a series of symmetric para-R-substituted 1,4-diphenyl-1,3-butadiynes (**2b**−**h**) was prepared. Details of the synthesis and characterization are provided in the Supporting Information and the results are summarized in Table 1. The reactions with O_2 as the oxidant were easier to set up and the product was easier to isolate, but these often gave lower yields and incomplete reactions.

I_2 oxidation, in the absence of O_2, proved to be higher yielding in several cases (entries 1, 2, 4, 5, and 7; compounds **2a**, **2b**, **2d**, **2e**, and **2g**). Here, an extra synthetic step involving a sodium thiosulfate wash to remove any unreacted iodine gave purer products. The R = CF_3 product (entry 4, **2d**) was further characterized by single-crystal X-ray diffraction (see the Supporting Information), and the bond distances and angles are quite

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TABLE 2. Reaction Energies and Free Energies (kcal mol^{-1}) of Reactions (1) (ΔE_1 and $\Delta G1$), (2) (ΔE_2 and ΔG_2), and (3) (ΔE_3 and ΔG_3) Calculated with Different Theoretical Methods

		ΔE_1	ΔG_1	ΔE_2	ΔG_2	ΔE_3	ΔG_3
B3LYP	R = Me	0.9	−0.8	−57.9	−51.3	−58.3	−50.6
	R = Ph	−1.2	−1.3	−60.0	−51.8		
CCSD(T)	R = Me	3.7		−56.4		−60.1	

similar to those we recently found for the R = CO_2Me derivative.[20]

Computational Results

To investigate the thermodynamics of the homocoupling process, a series of density functional theory calculations were performed at the B3LYP level to optimize all the species in reactions (1)−(3). Frequency calculations at the same level of theory have also been performed to identify all stationary points as minima (zero imaginary frequencies). The 6-311++G** basis set was used in the calculations. On the basis of the optimized structures, single-point calculations at the CCSD(T) level, using the same basis set, were performed to calculate the reaction energies for R = Me. All calculations were performed using the Gaussian 98 package.[21]

The energetics of the following reactions have been theoretically evaluated for R = Me and Ph at the B3LYP level of density functional theory.

$$2RC\equiv CH \rightarrow RC\equiv C-C\equiv CR + H_2 \qquad (1)$$

$$2RC\equiv CH + {}^{1}/{}_{2}O_2 \rightarrow RC\equiv C-C\equiv CR + H_2O \qquad (2)$$

$$H_2 + {}^{1}/{}_{2}O_2 \rightarrow H_2O \qquad (3)$$

Table 2 gives the results of our energetic calculations. At the B3LYP level, reactions (1) are found to be almost energetically neutral. The high exothermicity of reactions (2) is clearly driven by the formation of H_2O because eq 2 is the sum of eqs 1 and 3. The CCSD(T) calculations for R = Me suggest that the B3LYP calculations slightly underestimate the endothermicity of reactions (1) by 2.8 kcal/mol. The experimental formation enthalpy and free energy of H_2O(g) are −57.8 and −54.6 kcal/mol, respectively.[22] Both the B3LPY and CCSD(T) calculations give comparable values. From these calculations, we conclude that reactions (1) are expected to be slightly endothermic and are thus not particularly favorable thermodynamically. The presence of oxidants, e.g., O_2, provides the thermodynamic driving force for alkyne homocoupling reactions.

Comments on the Reoxidation of Pd(0) to Pd(II). It being clear that an oxidant is required to carry out the homocoupling, it remains to consider the process by which the Pd(0) is reoxidized to Pd(II) under the reaction conditions. While direct reoxidation of Pd is feasible, it may be rather slow. Indeed, Figure 1 indicates a zero-order dependence of the reaction rate on alkyne concentration which would be consistent with the rate-determining step being Pd reoxidation. However, it is important to point out that Cu is widely used to accelerate the reoxidation of Pd(0) to Pd(II) with O_2 as in the industrially important Wacker process for the aerobic oxidation of alkenes to aldehydes.[23] Thus, Cu may well have a dual role in the alkyne homocoupling reaction, first being utilized to mediate alkynyl transfer to Pd(II) via transmetalation from a Cu-alkynyl species, and second in the redox sequence shown in eqs 4 and 5. Further studies of the role of Cu in these and related systems are in progress.

$$2Cu(I) + O_2 \rightarrow 2Cu(II) \qquad (4)$$

$$2Cu(II) + Pd(0) \rightarrow 2Cu(I) + Pd(II) \qquad (5)$$

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Supporting Information Available: Experimental procedures and characterization data for the diyne compounds, crystallographic data (CIF), and details of the kinetic studies by GC and GC/MS. This material is available free of charge via the Internet at http://pubs.acs.org.

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