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Oxidative carbonylation of phenylacetylene catalyzed by Pd(II) and Cu(I): Experimental tests of forty-one computer-generated mechanistic hypotheses

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Abstract

We describe an experimental study of the reaction mechanism of phenylacetylene oxidative carbonylation to methyl ester of phenylpropiolic acid catalyzed by Pd(II) and Cu(I), $PhC{\equiv}CH + CO + MeOH + 2NaOAc + 2CuCl_2 \rightarrow PhC{\equiv}CCOOMe + 2AcOH + 2NaCl + 2CuCl$, which was closely guided by recent computational research on the generation of reaction mechanisms. Our initial mechanistic studies of this reaction were based on informal (non-computer-generated) mechanistic hypotheses. When experiments at 20°C and 1 atm led us to reject four of five mechanistic possibilities for the reaction, we turned to formulating new hypotheses with the aid of the computer programs ChemNet, which generated a reaction network consisting of 233 elementary steps, and MECHEM, which uncovered 41 simplest hypothetical pathways from within the reaction network. Our subsequent analysis of these 41 hypothetical mechanisms suggested a highly informative experiment based on the CH_3OH/CH_3OD kinetic isotope effect. The ratio between the rates of ester formation in nondeuterated and deuterated methanol was close to unity, suggesting that O–H bond scission occurs after the rate-limiting transmetalation step $CuC{\equiv}CPh + PdCl_2 \rightarrow ClPdC{\equiv}CPh + CuCl$. This experiment led to rejecting 32 out of the 41 hypotheses. Four more mechanisms were rejected based on the results of preliminary experimental studies. Further work is needed to discriminate among the five remaining mechanisms. © 1998 Elsevier Science B.V.

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1. Introduction

Earlier we have argued for the merits of the following strategy in mechanistic studies of chemical reactions: preliminary experimental studies → formalized generation of multiple mechanistic hypotheses with the aid of computational techniques → experimental design → experimental testing of mechanistic hypotheses [1]. However, to our knowledge, the complete cycle of studies covering all

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M1:

$$PdCl_2 + CO + MeOH \underset{HCl}{\rightleftharpoons} ClPdCOOMe$$

$$\xrightarrow{PhC\equiv CH} ClPd{-}(Ph)C{=}CHCOOMe \longrightarrow HPdCl + PhC{\equiv}CCOOMe$$

M2:

$$CO + 2MeOH \xrightarrow{[Pd];\,-2H^+} (MeO)_2CO \xrightarrow{+PhC\equiv CH;\,-MeOH} PhC{\equiv}CCOOMe$$

M3:

$$CO + MeOH \xrightarrow{[Pd];\,CuCl_2} ClCOOMe \xrightarrow{+CuC\equiv CPh;\,-CuCl} PhC{\equiv}CCOOMe$$

M4:

$$PhC{\equiv}CH + CuCl \underset{HCl}{\rightleftharpoons} PhC{\equiv}CCu \xrightarrow{+2CuCl_2;\,-3CuCl} PhC{\equiv}CCl$$

$$PhC{\equiv}CCl + CO + MeOH \xrightarrow{[Pd]} PhC{\equiv}CCOOMe + HCl$$

M5:

$$PhC{\equiv}CH + CuCl \xrightarrow{-HCl} CuC{\equiv}CPh \underset{CuCl}{\overset{PdCl_2}{\rightleftharpoons}} ClPdC{\equiv}CPh \xrightarrow{CO}$$

$$ClPdCOC{\equiv}CPh \xrightarrow{MeOH} PhC{\equiv}CCOOMe + HCl + Pd(0)$$

Scheme 1.

stages from the computerized search in the hypothesis space to experimental studies has not yet been traversed in the elucidation of reaction mechanisms in organometallic chemistry and catalysis by metal complexes. This article reports the first study of this sort as applied to the synthesis of methyl ester of phenylpropiolic acid from phenylacetylene, CO and methanol catalyzed by Pd(II) catalyst in solution:

$$PhC{\equiv}CH + CO + MeOH + 2NaOAc + 2CuCl_2 \overset{PdCl_2,1atm,20^\circ C}{\rightarrow} PhC{\equiv}CCOOMe + 2AcOH + 2NaCl + 2CuCl \quad (1)$$

This reaction is noteworthy because it provides the simplest method for synthesizing esters of alkynylcarboxylic acids, which are useful symptoms for the synthesis of fine organic chemicals [2,3]. In addition to the target, the products of oxidative dimerization and oxidative chlorination are formed by reactions

$$PhC{\equiv}CH + 2NaOAc + 2CuCl_2 \rightarrow PhC{\equiv}CC{\equiv}CPh + 2CuCl + 2NaCl + 2AcOH \quad (2)$$

$$PhC{\equiv}CH + NaOAc + 2CuCl_2 \rightarrow PhC{\equiv}CCl + 2CuCl + NaCl + AcOH \quad (3)$$

Historically, our investigation of this reaction began with the understanding that we would follow the strategy whose merits we cited above. Not having a means to formally generate reaction mechanisms, Zung et al. [3] informally devised mechanistic hypotheses based on the literature data. Five hypotheses stemming from the literature [2,4,5] were submitted to experimental testing [3,6] (Scheme 1). As a result, one mechanism remained and four were rejected (including Heck's mechanism [4] and mechanisms involving the intermediate formation of dialkyl carbonate, chlorine carbonate, or PhC≡CCl) as inconsistent with the experimental evidence. The sole surviving pathway to PhC≡CCOOMe was mechanism M5 in Scheme 1.

We found it promising to try formulating mechanistic hypotheses with the aid of the computer programs ChemNet [7,8] and MECHEM [9–15], because a formalized procedure might prompt some new, undocumented mechanistic possibilities worth experimental testing. This recourse seemed still more advisable because of our growing realization that the density of simple plausible mechanisms is often beyond our (or anyone else's) ability to treat comprehensively without the aid of computers. Guided by our formulation of the problem, the computer programs provided us with 41 hypothetical mechanisms suggesting that more experiments are needed to confirm or disprove mechanism M5.

This paper presents the first well-documented protocol of an experimental study motivated by computer-generated mechanistic hypotheses, following the strategy described at the start of this section.

2. Previous experimental findings

Our previous experimental findings on the mechanism of alkynylcarboxylic acid synthesis resulted from previous work on discriminating among five informally advanced hypotheses. For our current work these findings served as prior experimental knowledge of the reaction. Therefore, we provide a brief summary of previous work on the mechanism of the oxidative carbonylation of 1-alkynes to alkynylcarboxylic acid esters in the $PdCl_2$–$CuCl_2$–CuCl system. For more details see Refs. [3,6].

(a) The kinetic curves of PhC≡CCOOMe, PhC≡CC≡CPh, PhC≡CCl and CO versus time clearly exhibit an induction period. The addition of CuCl leads to a decrease in the induction period.

(b) A similar reaction occurring in the presence of the solid PhC≡CCu(I), PhC≡CAg(I) or PhC≡CHg(II) complexes has no induction period.

(c) An increase in water concentration in the solution from 0.2 to 0.6 mol/l in the Cu(II)-based system results in a decrease of the induction period and an increase in the rates of $CuCl_2$ consumption and CuCl buildup. The rate of CO_2 formation increases and the yield of the ester decreases.

(d) The rates of the oxidative chlorination and carbonylation reactions behaved in the opposite manner: an increase in the $PdCl_2$ concentration decreased the chlorination rate and increased the carbonylation rate, whereas an increase in the concentration of $CuCl_2$ increased the chlorination rate and decreased the carbonylation rate.

(f) The formation of ClCOOMe by the reaction of MeOH with CO and $CuCl_2$ was not observed.

These observations are inconsistent with pathways M1 through M3. In the case of M3, the induction period in PhC≡CCOOMe, PhC≡CC≡CPh and PhC≡CCl formation, but not in CO consumption, could be observed.

Both pathways M4 and M5 conformed to the coherent picture of evidence (a)–(b). Newly designed kinetic experiments, carried out in methanol solution, took into account structural features of these

two mechanisms. Under the experimental conditions, the concentrations of active $PdCl_2$, CuCl and $CuCl_2$ complexes were proportional to the overall concentrations of Pd(II), Cu(I) and Cu(II). Mechanism M4 fails to account for the observed kinetics, but mechanism M5 succeeds, although several additional assumptions are needed. Taking into account the formation of PhC≡CCl, mechanism M5 can be rewritten thus:

$$\mathrm{PhC{\equiv}CH} + \mathrm{CuCl} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \sigma_1 + \mathrm{H^+} \tag{4.1}$$

$$\sigma_1 + \mathrm{CuCl_2} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \mathrm{X_1} \tag{4.2}$$

$$\mathrm{X_1} + \mathrm{CuCl_2} \overset{k_3}{\rightarrow} \mathrm{PhC{\equiv}CCl} + 3\mathrm{CuCl} \tag{4.3}$$

$$\sigma_1 + \mathrm{PdCl_2} \overset{k_4}{\rightarrow} \sigma_2 + \mathrm{CuCl} \tag{4.4}$$

$$\sigma_2 + \mathrm{CO} + \mathrm{MeOH} \overset{k_5}{\rightarrow} \mathrm{PhC{\equiv}CCOOMe} + \mathrm{Pd} \tag{4.5}$$

$$\mathrm{Pd} + 2\mathrm{CuCl_2} \overset{k_6}{\rightarrow} \mathrm{PdCl_2} + 2\mathrm{CuCl} \tag{4.6}$$

Here, X_1 is an intermediate species and σ_1 and σ_2 are intermediate σ-ethynyl complexes of Cu(I) and Pd(II). The concentrations of σ_1 and σ_2 were considered steady-state. Eq. (4.2) was treated as a pseudoequilibrium step. The concentrations of intermediates were considered too small to contribute to the material balance of Pd(II), Cu(I) and Cu(II). Under these assumptions, the laws for the initial rates of PhC≡CCOOMe and PhC≡CCl formation [1] were:

$$r^0_{\mathrm{PhC{\equiv}CCOOMe}} = \frac{k_{\mathrm{I}}[\mathrm{PhC{\equiv}CH}]_0[\mathrm{CuCl}]_0[\mathrm{PdCl_2}]_0}{[\mathrm{H^+}] + k_{\mathrm{II}}[\mathrm{CuCl_2}]_0^2 + k_{\mathrm{III}}[\mathrm{PdCl_2}]_0} \tag{5}$$

$$r^0_{\mathrm{PhC{\equiv}CCl}} = \frac{k_{\mathrm{IV}}[\mathrm{PhC{\equiv}CH}]_0[\mathrm{CuCl}]_0[\mathrm{CuCl_2}]_0^2}{[\mathrm{H^+}] + k_{\mathrm{II}}[\mathrm{CuCl_2}]_0^2 + k_{\mathrm{III}}[\mathrm{PdCl_2}]_0} \tag{6}$$

where $k_{\mathrm{I}} = k_4K_1$, $k_{\mathrm{II}} = k_3K_2/k_{-1}$, $k_{\mathrm{III}} = k_4/k_{-1}$ and $k_{\mathrm{IV}} = k_3K_1K_2$.

3. Mechanistic pathway generation

In this study, we used a procedure similar to that of an earlier paper [10], except that in the present case the computer-generated hypotheses motivated our further experimental work. The essence of this procedure is as follows. First, we use the ChemNet program to generate the reaction network. The elementary steps from the network are accepted by MECHEM as input; this network constitutes a reduced space within which MECHEM carries out its search for simpler pathways. This search for

[1] The mechanisms of chloroalkyne formation was studied earlier. See Refs. [16,17].

pathways is guided by constraints available in both MECHEM and ChemNet and by reaction transforms. This union of two programs allows one to avoid additional programming in either MECHEM or ChemNet and to join the constraints and other capabilities of the programs. MECHEM is not currently capable of restricting the search space by transforms, which is ChemNets task. However, MECHEM has a richer array of constraints and is specialized for finding simpler or simplest pathways. For the purposes of this study, we used the constraint on the overall stoichiometry.

Before inputting to MECHEM the reaction network of possible elementary steps, these can be corrected or even deleted or more steps may be added. However, if there is some more general rule that expresses the reasons for the implausibility of certain steps, it is easier to articulate this rule to MECHEM as a constraint rather than delete them manually.

MECHEM/ChemNet-generated mechanisms are perhaps better regarded as skeletal, because they do not consider the reversibility of steps, the full ligand environment of metal centers in conjectured species, rate-limiting steps and other important mechanistic and kinetic features.

3.1. ChemNet

ChemNet is a program for generating networks of reactions by applying user-formulated transforms that describe the essential features of the chemical transformations taking place in elementary steps [7,8]; the programs use of these transforms is further guided by other optional constraints. A distinctive feature of the program is the flexibility that it allows in formulating transforms: The complexity and generality of the transforms can vary considerably. The constraints and transforms in ChemNet permit expressing prior knowledge about the reaction mechanism, which may be founded on preliminary experimental work or literature data. The species and transforms are input by means of a graphical interface using a mouse and a keyboard.

The generation of elementary steps of the network proceeds by applying the transforms (or elementary-reaction templates) to the user-defined initial species, then to the enlarged ‘pot’ of initial species augmented by the newly-generated species, then to the still-larger pot and so on.

3.2. MECHEM

The computer program MECHEM is intended largely as an aid for the elucidation of reaction mechanisms. It is generally usable on any reaction, although so far its application has focused on catalysis (heterogeneous and homogeneous) [8–15]. Given the set of reaction starting materials, any observed products and intermediates, and user-defined constraints, the program searches comprehensively for all simplest reaction mechanisms, i.e. containing the fewest number of species and steps. The user can also override this default search behavior an d search for next-simplest mechanisms, e.g. by: (i) asking the program to generate mechanisms containing new steps or new species, i.e. that are absent from the simplest mechanisms and (ii) imposing more constraints, with which previously generated (simplest) mechanisms are inconsistent.

The prior knowledge about a reaction, whether empirical or theoretical, is expressed via a rich array of constraints that serve to discard implausible branches of the comprehensive search. Currently, MECHEM incorporates approximately 80 different types of constraints. MECHEMs main goal is to find all simplest mechanisms that are consistent with constraints formulated by the user. There are a number of user conveniences, such as an ability to inspect what partially-formed pathways the program is considering at the moment, as well as new auxiliary tools that can aid in the design of isotopic labeling experiments.

3.3. Computational procedure

The ChemNet transforms that we formulated for this reaction are as follows:

M–Cl + H–C≡C → M–C≡C + H–Cl	M = Cu(I)
M_1–C + M_2–Cl → M_1–Cl + M_2–C	M_1 = Cu(I); M_2 = Pd(II)
M–C≡C + C≡O → M–C(=O)–C≡C	M = Pd(II)
M–Cl + MeO–H → MeO–M + H–Cl	M = Pd(II), Cu(I)
M–O + C≡O → M–C(=O)–O	M = Pd(II)
M–C=O + MeO–H → M–H + MeO–C=O	M = Pd(II)
M_1 + Cl–M_2–Cl → M_1–Cl + M_2–Cl	M_1 = Pd(0) → Pd(I) or Pd(I) → Pd(II); M_2 = Cu(II)
M_1–OMe + M_2–Cl → M_1–Cl + M_2–OMe	M_1 = Cu(I); M_2 = Pd(II)
X–M–C → X–C + M	M = Pd(II) → Pd(O), X = C, O
M_1–Cl + M_2–Y → M_1–Y + M_2–Cl	M_1, M_2 = Pd(II), Y = H, C, O
M–C=O + C≡C → M–C=C–C=O	M = Pd(II)
M–C=C–H → M–H + C≡C	M = Pd(II)
M–C≡C + O–C(=O)–O → M–O + C≡C–C(=O)–O	M = Pd(II)

To illustrate how a transform works, consider transform 5 as an example. ChemNet expanded this transform into four elementary steps:

Cl**PdO**Me + **C≡O** → Cl**PdCOO**Me

Me**OPd**C≡CPh + **C≡O** → Me**OOCPd**C≡CPh

MeO**PdO**Me + **C≡O** → MeO**PdCOO**Me

H**PdO**Me + **C≡O** → H**PdCOO**Me

In these steps, the transform is highlighted in boldface. The species ClPdOMe, MeOPdC≡CPh, MeOPdOMe and HPdOMe became 'available' because ChemNet expanded other transforms into steps the products of which included these species. Carbon monoxide was defined as a starting material. The overall stoichiometry of the reaction in Eq. (1) was simplified to the reaction

$$PhC{\equiv}CH + CO + MeOH + 2CuCl_2 \rightarrow PhC{\equiv}CCOOMe + 2HCl + 2CuCl \qquad (1')$$

which conveys the essential chemistry of the reaction in Eq. (1) and makes it possible to avoid possible difficulties due to combinatorics. Besides the thirteen transforms listed above, we opted for the following settings:

- Starting materials: $PdCl_2$, HC≡CPh, CuCl, MeOH and CO.
- The maximum number of atoms in a conjectured species is 20 (considering Ph and Me as single 'pseudoatoms'; doing so we define methyl and phenyl groups as unchangeable fragments).
- The maximum number of carbon atoms in a conjectured species is three (the carbon atoms in Ph and Me groups are not counted).
- There is at most one metal atom in any conjectured species.
- There are at most three oxygen atoms in any conjectured species.
- There is at most one phenyl group in any conjectured species.
- The allowed oxidation states for Cu are Cu(I) and Cu(II) and for Pd they are Pd(0), Pd(I) and Pd(II).
- The maximum coordination number of Cu and of Pd is two.

Table 1
Mechanisms having 6 conjectured species and 7 steps (the table entries denote the Horiuti stoichiometric number of the step in the respective mechanism. A missing entry means that the step is not used in the mechanism)

Steps	No. of mechanism							
	1	2	3	4	5	6	7	8
(1) $CuCl_2$ + Pd → CuCl + PdCl	1	1	1	1	1	1	1	1
(2) $CuCl_2$ + PdCl → $PdCl_2$ + CuCl	1	1	1	1	1	1	1	1
(3) PhCCH + CuCl → HCl + CuCCPh	1	1	1		1	1	1	1
(4) $PdCl_2$ + MEOH → HCl + MeOPdCl	1	1	1	1				
(5) $PdCl_2$ + CuCCPh → CuCl + ClPdCCPh					1	1	1	1
(6) MeOOCPdCCPh → PhCCCOOMe + Pd	1	1				1		
(7) MeOPdCOCCPh → PhCCCOOMe + Pd			1		1			1
(8) Co + MeOPdCl → ClPd–COOMe	1			1				
(9) MeoPdCl + CuCCPh → CuCl + MeOPdCCPh		1	1					
(10) Co + MeOPdCCPh → MeOOCPdCCPh		1				1		
(11) CO + MeOPdCCPh → MeOPdCOCCPh			1		1			
(12) HPdCl → HCl + Pd				1			1	
(13) MeOH + ClPdCCPh → HCl + MeOPdCCPh					1	1		
(14) CO + ClPdCCPh → ClPdCOCCPh							1	1
(15) CuCCPh + ClPdCOOMe → CuCl + MeOOCPdCCPh	1							
(16) PhCCH + ClPdCOOMe → ClPd–CPh=CH–COOMe				1				
(17) ClPd–CPh=CH–COOMe → PhCCCOOMe + HPdCl				1				
(18) MeOH + ClPdCOCCPh → PhCCCOOMe + HPdCl							1	
(19) MeoH + ClPdCOCCPh → HCl + MeOPdCOCCPh								1

ChemNet conjectured 233 steps and 34 species [2]. These steps and species occasioned the following constraint in MECHEM: ''All conjectured mechanisms should be constructed from ChemNet-generated steps and species''. Thus, the 'space' of mechanisms was strongly restricted to those containing only steps from the network, but of course without requiring that any or all network steps appear in a mechanism found by MECHEM. The only additional significant constraint was the overall stoichiometry of the reaction in Eq. (1′) (other constraints were used to reduce the computer time but were not necessary for arriving at the output). After about 7 min on a Sun Ultra workstation, MECHEM found a set of eight simplest mechanisms containing 6 conjectured species (i.e. not stipulated as starting materials nor products) and 7 steps. Then we had MECHEM generate new mechanisms each containing at least one new step not contained in any of the 7-step/6-species mechanisms. This time, the program reported thirteen mechanisms containing 7 conjectured species and 8 steps (after about 5 h). Similarly, we obtained a set of 20 mechanisms having 6 conjectured species and 9 steps (after about 3 h). Overall, MECHEM generated the 41 mechanisms shown in Tables 1–3. Not all of the 5 informally conjectured mechanisms M1–M5 were among the newly generated forty-one mechanisms, because mechanisms involving the formation of ClCOOMe and PhC≡CCl (mechanisms M3 and M4) were explicitly prohibited by the transforms. As to the other informal mechanisms, there is no one-to-one correspondence between the old and new hypothetical mechanisms. For instance, mechanism M1 corresponds to mechanisms (4) from Table 1 and (7) from Table 2; mechanism M2 corresponds to mechanisms (9) and (12) from Table 3. There is no one-to-one correspondence because the informal mechanisms are more general and avoid some of the mechanistic details that are in the ChemNet/MECHEM-generated mechanisms. Before proceeding to the experimental study, the

[2] The generation of the set of the network took about 2 min on a Pentium PC (75 MHz, 8 Mb RAM).

Table 2
Mechanisms having 7 conjectured species and 8 steps

Steps	No. of the mechanism												
	1	2	3	4	5	6	7	8	9	10	11	12	13
(1) $CuCl_2 + Pd \rightarrow CuCl + PdCl$	1	1	1	1	1	1	1	1	1	1	1	1	1
(2) $CuCl_2 + PdCl \rightarrow PdCl_2 + CuCl$	1	1	1	1	1	1	1	1	1	1	1	1	1
(3) $PhCCH + CuCl \rightarrow HCl + CuCCPh$	1	1	1	1	1	1		1	1	1	1	1	1
(4) $PdCl_2 + CuCCPh \rightarrow CuCl + ClPdCCPh$				1	1	1		1		1	1	1	1
(5) $CuCl + MeOH \rightarrow HCl + CuOMe$	1	1	1	1	1	1	1						
(6) $MeOOCPdCCPh \rightarrow PhCCCOOMe + Pd$	1	1				1		1	1			1	
(7) $MeOPdCOCCPh \rightarrow PhCCCOOMe + Pd$			1	1	1					1	1		1
(8) $PdCl_2 + MeOH \rightarrow HCl + MeOPdCl$								1	1	1	1	1	
(9) $PdCl_2 + CuOMe \rightarrow CuCl + MeOPdCl$	1	1	1				1						
(10) $CO + MeOPdCl \rightarrow ClPd{-}COOMe$	1						1	1	1				
(11) $CO + MeOPdCCPh \rightarrow MeOOCPdCCPh$		1				1						1	
(12) $CO + MeOPdCCPh \rightarrow MeOPdCOCCPh$			1		1						1		
(13) $CO + ClPdCCPh \rightarrow ClPdCOCCPh$				1						1			1
(14) $CuCCPh + MeOPdCl \rightarrow CuCl + MeOPdCCPh$		1	1										
(15) $CuOMe + ClPdCCPh \rightarrow CuCl + MeOPdCCPh$					1	1							
(16) $MeOPdCl + ClPdCCPh \rightarrow PdCl_2 + MeOPdCCPh$											1	1	
(17) $CuCCPh + ClPdCOOMe \rightarrow CuCl + MeOOCPdCCPh$	1												
(18) $CuOMe + ClPdCOCCPh \rightarrow CuCl + MeOPdCOCCPh$				1									
(19) $PhCCH + ClPdCOOMe \rightarrow ClPd{-}CPh{=}CH{-}COOMe$							1						
(20) $ClPd{-}CPh{=}CH{-}COOMe \rightarrow PhCCCOOMe + HPdCl$							1						
((21) $HPdCl \rightarrow HCl + Pd$							1						
(22) $ClPdCOOMe + ClPdCCPh \rightarrow PdCl_2 + MeOOCPdCCPh$								1					
(23) $MeOPdCl + CuCCPh \rightarrow CuCl + MeOPdCCPh$									1				
(24) $ClPdCOOMe + MeOPdCCPh \rightarrow MeOPdCl + MeOOCPdCCPh$									1				
(25) $MeOPdCl + ClPd{-}CO{-}CCPh \rightarrow PdCl_2 + MeOPdCOCCPh$										1			
(26) $MeOH + ClPdCCPh \rightarrow HCl + MeOPdCCPh$													1
(27) $MeOPdCCPh + ClPdCOCCPh \rightarrow ClPdCCPh + MeOPdCOCCPh$													1

Table 3
Mechanisms having 6 conjectured species and 9 steps

Steps	No. of the mechanism																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
(1) PhCCH + CuCl → CuCCPh + HCl	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1
(2) $CuCl_2$ + Pd → CuCl + PdCl	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
(3) $CuCl_2$ + PdCl → $PdCl_2$ + CuCl	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
(4) $PdCl_2$ + CuCCPh → CuCl + ClPdCCPh	1	1		1		1	1	1	1	1		1	1	1	1		1	1	1	1
(5) $PdCl_2$ + MeOH → HCl + MeOPdCl			1	1	1	1	1	1	1	1	1	1	1	1						
(6) MeOOC–Pd–CCPh → Pd + PhCCCOOMe	1				1		1			1	1	1		1		1		1		1
(7) MeOPd–CO–CCPh → Pd + PhCCCOOMe		1	1	1		1		1							1		1		1	
(8) CO + MeOPdCl → ClPdCOOMe	1										1	1	1	1		1				1
(9) CO + ClPdCCPh → ClPdCOCCPh		1	1	1				1							1				1	
(10) 2(MeOPdCl) → $PdCl_2$ + $Pd(OMe)_2$					1	1	1	1	1	1	1									
(11) CuCl + MeOH → HCl + CuOMe															1	1	1	1	1	1
(12) $PdCl_2$ + CuOMe → CuCl + MeOPdCl																1	1	1	1	1
(13) MeOPdCl + ClPdCCPh → $PdCl_2$ + MeOPdCCPh				1								1					1	1		
(14) CuCCPh + MeOPdCl → CuCl + MeOPdCCPh			1								1					1				
(15) CO + $Pd(OMe)_2$ → MeOPdCOOMe					1				1	1										
(16) MeOH + ClPdCCPh → HCl + MeOPdCCPh	1	1																		
(17) $PdCl_2$ + MeOPdCCPh → ClPdCCPh + MeOPdCl	1	1																		
(18) ClPdCCPh + ClPdCOOMe → $PdCl_2$ + MeOOCPdCCPh	1																			1
(19) $PdCl_2$ + MeOPdCCPh → MeOPdCl + ClPdCCPh			1								1									
(20) MeOPdCl + ClPdCOCCPh → $PdCl_2$ + MeOPdCOCCPh			1																1	
(21) ClPdCOCCPh + MeOPdCCPh → ClPdCCPh + MeOPdCOCCPh				1											1					
(22) $Pd(OMe)_2$ + ClPdCCPh → MeOPdCl + MeOPdCCPh						1	1													
(23) CO + MeOPdCCPh → MeOPdCOCCPh						1											1			
(24) CO + MeOPdCCPh → MeOOCPdCCPh							1											1		
(25) MeOPdCOOMe → Pd + $(MeO)_2CO$									1				1							
(26) ClPdCCPh + $(MeO)_2CO$ → PhCCCOOMe + MeOPdCl									1				1							
(27) ClPdCCPh + MeOPdCOOMe → MeOPdCl + MeOOCPdCCPh										1				1						
(28) ClPdCOOMe + MeOPdCCPh → MeOPdCl + MeOOCPdCCPh												1				1				
(29) MeOPdCl + ClPdCOOMe → $PdCl_2$ + MeOPdCOOMe													1	1						
(30) ClPdCOCCPh + MeOPdCl → $PdCl_2$ + MeOPdCOCCPh		1																		
(31) $PdCl_2$ + MeOPdCOOMe → MeOPdCl + ClPdCOOMe					1															
(32) CuCCPh + ClPdCOOMe → CuCl + MeOOCPdCCPh					1															
(33) $Pd(OMe)_2$ + ClPdCOCCPh → MeOPdCl + MeOPdCOCCPh								1												
(34) ClPdCOOMe + ClPdCCPh → $PdCl_2$ + MeOOCPdCCPh											1									
(35) CuOMe + ClPdCCPh → CuCl + MeOPdCCPh															1					

Table 4
Initial rates of $PhC{\equiv}CCOOCH_3$ in CH_3OH and CH_3OD

Alcohol	No. of run	Initial rate, mol l^{-1} h^{-1}	Average rate	Standard deviation	r_H/r_D
CH_3OH	1	0.150	0.163	± 0.017	0.88 ± 0.17
	2	0.185			
	3	0.156			
	4	0.160			
CH_3OD	1	0.18	0.185	± 0.017	0.88 ± 0.17
	2	0.19			

new mechanisms corresponding to M1 and M2 were excluded from consideration. The remaining 37 mechanisms, which contain the step of palladium ethynyl complex formation, appeared indiscriminable by the available preliminary experimental evidence (a)–(f). Therefore, more experimentation was needed, as follows.

4. Experimental testing of hypothetical pathways

The remaining hypotheses could be tested by the dependence of rate laws on the methanol concentration or the carbon monoxide partial pressure. However, this is complicated because it is difficult to find a solvent that would allow varying the methanol concentration without changing the properties of the solution. Alternatively, one may choose a ligand to stabilize the catalyst when the CO partial pressure is varied within a broad range.

We devised another approach based on the CH_3OH/CH_3OD kinetic isotope effect (KIE). If a methanol molecule or a methoxy group is involved in the mechanism after the step of alkynyl-group transfer from Cu(I) to Pd(II), which is likely to determine the rate (e.g. mechanisms (5)–(8) in Table 1 and mechanism (13) in Table 2), then KIE should be close to unity. If the H–O bond cleavage in methanol occurs before or in a rate-limiting step, then the value of KIE should be ~ 3–4 [3]. The value of the kinetic isotope effect was calculated as the ratio between the formation rates of methyl ester of phenylpropiolic acid in CH_3OH and in CH_3OD (see Table 4).

The experiments showed that the value of KIE was approximately equal to unity (0.88 ± 0.17). Therefore, all the mechanisms except mechanisms (5)–(8) in Table 1 and mechanism (13) in Table 2 can be rejected.

Mechanism (13) in Table 2 is hardly plausible because it contains the step

$$MeOPdC{\equiv}CPh + ClPdCOC{\equiv}CPh \rightarrow ClPdC{\equiv}CPh + MeOPdCOC{\equiv}CPh$$

which by itself is not impossible. However, there is a more plausible alternative for forming palladium alkoxide: the MeO group can be donated by methanol, the concentration of which in the solution is far higher than the concentration of the $MeOPdC{\equiv}CPh$ complex, which merely serves as a source of MeO group. Hence, mechanism (13) (Table 2) can be safely excluded.

The mechanisms (5)–(8) in Table 1 are rather similar, except for the following features:

(1) The nucleophilic attack on the carbon atom of the carbonyl group may be internal (mechanism 5) or external (mechanism 7 and 8).

[3] The values of KIE mentioned here correspond to the D_2O/H_2O system [18,19]. We assume that these values should be close to those in the CH_3OD/CH_3OH system.

(2) CO may undergo insertion into the Pd–C (mechanisms 5 and 8) or Pd–OCH_3 (mechanism 6).

(3) The decomposition of a σ-organometallic complex may yield palladium hydride (mechanism 7) or Pd(0) (mechanisms 5, 6 and 8).

In the future, these features can be used to further discriminate the mechanisms, which all remain working hypotheses at this point.

5. Experimental section

Our experiments on phenylacetylene carbonylation in methanol were carried out in a glass constant-temperature reactor under vigorous stirring of the liquid and gas phases in the closed system. The volume of the consumed gas was measured by the volumetric method. The reacting mixture was analyzed by GLC. The products of carbonylation (PhC≡CCOOMe) and oxychlorination (PhC≡CCl) were analyzed on a 1 m column (diameter, 3 mm) filled with Porapak P (thermal conductivity detector; helium as a carrier gas; $T = 210$°C). The composition of the gas phase was analyzed by gas-adsorption chromatography with a 3 m column (diameter, 3 mm) filled with Activated Carbon AG-3 (0.25–0.5 mm fraction); $T = 140$°C.

All reagents except those mentioned below were either 'chemically pure' (CP) or of 'analytical grade' (AG) [4] and were used in experiments without additional purification. Phenylacetylene was of reagent grade (RG) and was distilled in vacuum before use. Carbon monoxide was prepared by the decomposition of formic acid (CP) in concentrated sulfuric acid (CP). Copper(II) dichloride $CuCl_2 \cdot 2H_2O$ was dried before use at 120°C to a constant weight. Copper(I) chloride (RG) was recrystallized from hot water, washed with acetone and dried at 80°C in nitrogen atmosphere. Nondeuterated methanol contained water at the concentration of 0.2 mol/l. Deuterated methanol contained at least 99% of CH_3OD.

The kinetic isotope effect study was carried out at 19°C and 1 atm of CO in methanol solutions having the following concentrations of the catalyst and buffer components, mol/l: CuCl, 0.3; $PdCl_2$, 1.4×10^{-3}; $CuCl_2$, 0.2; LiCl, 3; triethylamine, 0.5 and acetic acid, 0.35. The acetate triethylamine was used to maintain the constant concentration of H^+. The value of KIE was calculated as the ratio of the pseudo-steady-state rates of methyl phenylpropiolate formation (in nondeuterated and deuterated methanol), both averaged over the first 15 min after the start of the reaction.

In a typical run, the methanol solution of reactants and buffer components, prepared prior to a run, was loaded into a 25 ml reactor. The solution was prepared from 2 ml of methanol, $PdCl_2$ (0.5 mg, 2.8×10^{-3} mmol), LiCl (254 mg, 6 mmol), $CuCl_2$ (54 mg, 0.4 mmol), acetic acid (42 mg, 0.7 mmol), triethylamine (101 mg, 1 mmol) and ethyl benzoate (21 mg, 0.14 mmol, GLC standard). Immediately upon loading the solution, the reactor was rapidly purged with a large amount of carbon monoxide (0.5 l for 0.5 min). Then, phenylacetylene (41 mg, 0.4 mmol) was injected into the liquid phase of the reactor via microsyringe. Samples were withdrawn during the run and analyzed by GLC.

6. Conclusion

We have reported here our findings from the experimental study of the synthesis of methyl ester of phenylpropiolic acid from phenylacetylene, CO and methanol in the solution containing Pd(II)–Cu(I) catalyst. This study was closely guided by outputs of two computer programs which were responsible

[4] Russian standards of purity grades.

for generating an initial reaction network and then finding simpler pathways within this network. Both programs were guided by our formulation of the problem based on our initial understanding and on previous experiments. Thus, we have demonstrated a cycle consisting of preliminary experiments, computerized searches and experiment design motivated by the multiple (i.e. 41) working hypotheses generated by computer. After checking these hypothetical mechanisms against preliminary experimental evidence, we rejected four mechanisms, but 37 out of 41 mechanisms remained. Analysis of the remainder prompted highly discriminating KIE experiments, after which only five mechanisms remained. One of the five mechanisms is less plausible than the others. Four remaining mechanisms are indistinguishable on the basis of the experimental data and each can be accepted as a working hypothesis. All of them contain the main steps of the mechanism M5 (Scheme 1) that was informally devised without computer aid. Further study should allow finer discrimination among the remaining hypotheses. The implications of our results reach beyond this specific study: we propose that this human/computer methodology can be widely beneficial. Work is in progress to adduce further results in the context of model reactions of heterogeneous catalysis.

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