

## Cross-Coupling

# Synergistic Catalysis in the Sonogashira Coupling Reaction: Quantitative Kinetic Investigation of Transmetalation\*\*

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The formation of a  $C_{sp}-C_{sp_2}$  bond is the key step for the construction of arylalkyne and conjugated enyne moieties, which widely exist in natural products, medicine molecules, agrochemicals, and organic functional materials.<sup>[1]</sup> The Sonogashira coupling between aryl or vinyl halides and terminal alkynes is one of the most efficient tools to furnish the above-mentioned motif. This named reaction is well-known as a Pd-catalyzed process, and its scope and parameters such as Pd precursors, ligands, additives etc. have been extensively studied during the past 40 years.<sup>[1b-d,h,j-m]</sup> However, scarce examples regarding the detailed reaction mechanism have been reported.<sup>[2]</sup> And to our knowledge, no quantitative kinetic information about the transmetalation step of the Sonogashira coupling has been obtained by in situ measurements has been reported to date.

The general catalytic cycle of transition-metal-catalyzed cross-coupling reactions, such as Negishi coupling, Suzuki coupling, Stille coupling, and Sonogashira coupling etc. includes three elementary steps: oxidative addition, transmetalation, and reductive elimination.<sup>[1h,j,o]</sup> Although numerous efforts have been focused on the methodology development during the past three decades, very few have been devoted to the kinetic investigations, especially for the transmetalation step.<sup>[3]</sup> Espinet et al. have studied the organotin-reagents-related transmetalation step of the Stille coupling in the past few years.<sup>[3h-l]</sup> Recently, transmetalations of the organozinc reagents in the Negishi coupling were also investigated.<sup>[3m-o,4]</sup> Herein, we communicate our direct kinetic investigation of a Sonogashira coupling reaction by using in situ IR spectroscopy. In this reaction, transmetalation is assigned as the rate-limiting step. The quantitative kinetic measurement of the transmetalation step for the  $C_{sp}-C_{sp_2}$

coupling reaction has been performed by using in situ measurements. Meanwhile, palladium and copper are demonstrated to be the synergistic catalysts in the Sonogashira coupling reaction.

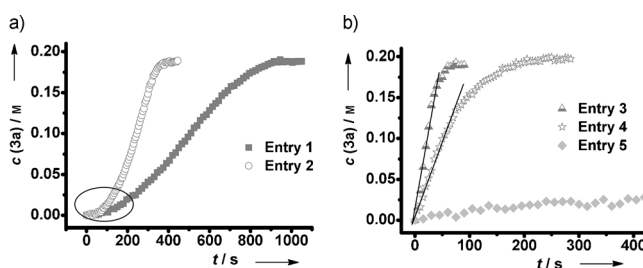
Owing to the interest in the mechanism of the Sonogashira coupling reaction, we firstly used some classic conditions for the coupling of aryl iodide **1a** and phenylacetylene **2a** monitored by in situ IR spectroscopy. The results are compiled in Table 1 and Figure 1.

The reactions proceeded smoothly and gave even quantitative yields under these typical conditions (Table 1, entries 1–4). However, the kinetic behaviors were distinct.

**Table 1:** Kinetic investigation of the Sonogashira coupling reaction.<sup>[a]</sup>

Entry	[Pd]	Base and solvent	T	Yield [%] <sup>[b]</sup>
1	[PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> ]	Et <sub>3</sub> N	25 °C	quant.
2	[PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> ]	<i>i</i> Pr <sub>2</sub> NH	25 °C	quant.
3	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	<i>i</i> Pr <sub>2</sub> NH	25 °C	quant.
4	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	<i>i</i> Pr <sub>2</sub> NH	0 °C	quant.
5	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	Et <sub>3</sub> N	0 °C	20

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol), [Pd] (1 mol%), and Cul (2 mol%) in 5 mL of solvent. [b] Determined by GC with naphthalene as the internal standard.



**Figure 1.** Kinetic profiles of Table 1 monitored by in situ IR spectroscopy. a) [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] was used as the catalyst precursor. b) [Pd(PPh<sub>3</sub>)<sub>4</sub>] was used as the catalyst precursor.

The reaction using *i*Pr<sub>2</sub>NH was much faster and more effective than that using Et<sub>3</sub>N (Figure 1a). Meanwhile, the inductive periods existed in both reactions. It could be rationalized that the Pd<sup>II</sup> species should be reduced to the active Pd<sup>0</sup> catalyst at the beginning of the reaction.<sup>[5]</sup> When [Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>4</sub>] was employed instead of [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>], the inductive period disappeared, and the reaction proceeded

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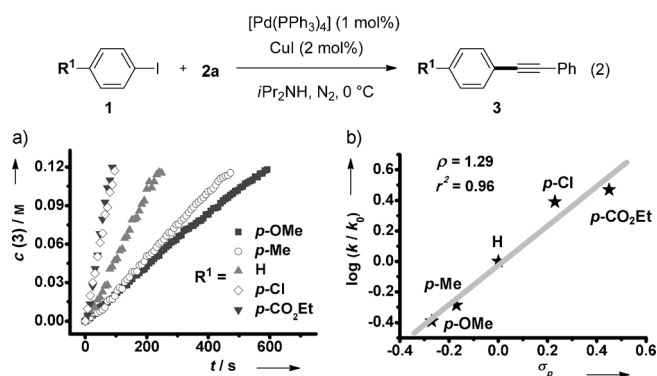
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much faster even at 0 °C in *i*Pr<sub>2</sub>NH (Figure 1b, entries 3 and 4). However, Et<sub>3</sub>N was less effective under the same conditions (Figure 1b, entry 5). It was noteworthy that these three Pd<sup>0</sup>-catalyzed reactions all exhibited zero-order kinetics, which apparently indicated that reductive elimination might be the rate-limiting step in this transformation.

Detailed kinetic investigations of the Sonogashira coupling reactions were further performed in *i*Pr<sub>2</sub>NH at 0 °C [Eq. (1) in Figure 2]. In Figure 2a the kinetic profiles at varying initial concentrations of **1a** are shown. The nearly identical initial rates indicated that this reaction was zero-order dependent on *c*(**1a**). This result could rule out the oxidative addition of ArI with the Pd catalyst as the rate-limiting step. Meanwhile, Figure 2b showed the kinetic plots of the reactions when *c*(**2a**) was varied. The almost perfectly overlaying initial kinetic rates revealed that this Sonogashira coupling was also independent on the concentration of the terminal alkyne *c*(**2a**). Furthermore, kinetic measurements with different concentrations of the [Pd] catalyst were investigated. A linear relationship was observed in Figure 2c when plotting the initial rate versus *c*([Pd]). This result suggested that the reaction was first-order dependent on the concentration of the Pd catalyst in the tested Pd concentration range. Thus far, all the above kinetic observations suggested that reductive elimination might be the rate-limiting step.

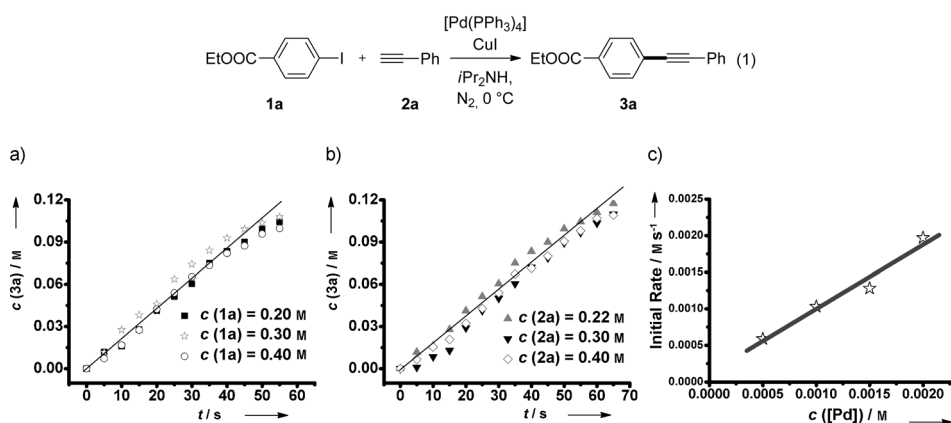
However, when we tried to further reveal the relationship between the electronic effect of substituent and rate-limiting step, we faced a puzzle. As shown in Figure 3a, the more electron-withdrawing the substituent on the electrophile ArI **1** was, the faster the reaction proceeded. This result was unanticipated. The reversed trend was observed when the substituents on the nucleophile alkynes **2** were investigated (Figure 4a). The more electron-withdrawing group the alkyne had, the slower the reaction occurred. Although the electronic effects on the reductive elimination to form a C–C bond had been revealed to some extent,<sup>[6]</sup> there are rare examples for the reductive elimination to form a C<sub>sp</sub>–C<sub>sp2</sub>



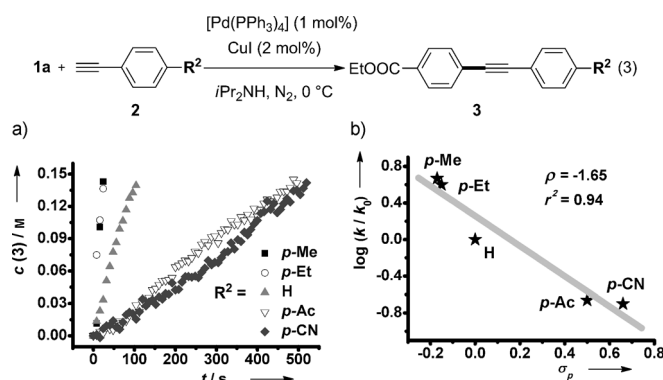
**Figure 3.** a) Kinetic profiles of different aryl iodides **1** monitored by in situ IR spectroscopy. b) The Hammett correlation plot. The rate constant *k* was obtained by fitting the linear plot of *c*(**3**) versus time. Plotting  $\log(k/k_0)$  versus the substituent constant  $\sigma_p$  for these substrates gave a linear relation (correlation coefficient  $r^2 = 0.96$ , positive slope  $\rho = 1.29$ ).

bond. At the beginning, we assumed if the reductive elimination is rate-limiting, the electronic effects on varying the substituents of only one, the electrophile or the nucleophile, should follow the same trend when the other is constant. The results of the experiments shown in Figures 3a and 4a were just different from the speculation. This puzzle enforced us to reappraise the catalytic cycle of the Sonogashira coupling reaction.

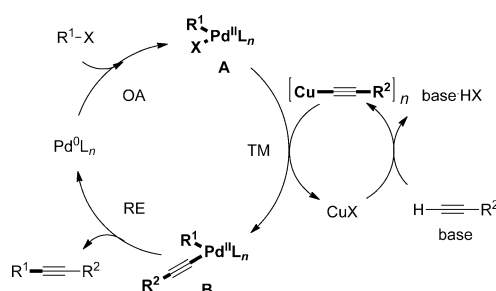
In fact, different from other Pd-catalyzed cross-coupling reactions, the Sonogashira coupling usually also required Cu salt as a cocatalyst.<sup>[7]</sup> In the above-mentioned kinetic experiments, CuI (2 mol%) was also employed. Two synergistic catalytic cycles are generally proposed for the Sonogashira coupling reaction (Scheme 1).<sup>[1b,j,l,m]</sup> For the Pd-catalyzed Sonogashira coupling, one usually considers that ArI is the electrophile, and the terminal alkyne is the nucleophile. In this way, when the kinetic data showed the reaction was independent on both *c*(electrophile ArI) and *c*(nucleophile alkyne), reductive elimination as the rate-limiting step could be easily envisioned. However, a careful analysis of the catalytic cycle reveals the terminal alkyne is not the direct nucleophile of the Pd-catalyzed cycle! The proposed copper–acetylide is the nucleophile for the Pd-catalyzed cycle, and is also the catalytic species for the Cu-catalyzed cycle.<sup>[8]</sup> Therefore, the zero-order kinetic dependences of *c*(ArI) and *c*(alkyne) cannot suggest reductive elimination is the rate-limiting step in this case. The rate-limiting transmetalation of copper–acetylide with the R<sup>1</sup>PdX complex **A** could also lead to the zero-order kinetic behavior.



**Figure 2.** a) Kinetic profiles of different initial concentrations of **1a** (from 0.2 M to 0.4 M). Reaction conditions: **2a** (0.22 M), [Pd(PPh<sub>3</sub>)<sub>4</sub>] (0.002 M), CuI (0.004 M), carried out in *i*Pr<sub>2</sub>NH (5 mL) at 0 °C. b) Kinetic profiles of different initial concentrations of **2a** (from 0.22 M to 0.4 M). Reaction conditions: **1a** (0.20 M), [Pd(PPh<sub>3</sub>)<sub>4</sub>] (0.002 M), CuI (0.004 M), carried out in *i*Pr<sub>2</sub>NH (5 mL) at 0 °C. c) Kinetic profiles of different [Pd(PPh<sub>3</sub>)<sub>4</sub>] loadings (from 0.25 mol% to 1.0 mol%) with CuI (0.004 M), **1a** (0.20 M), and **2a** (0.22 M), carried out in *i*Pr<sub>2</sub>NH (5 mL) at 0 °C. Reactions were monitored by in situ IR spectroscopy.



**Figure 4.** a) Kinetic profiles of different terminal aryl alkynes **2** monitored by in situ IR spectroscopy. b) The Hammett correlation plot. The rate constant  $k$  was obtained by fitting linear plot of  $c(\text{3})$  versus time. Plotting  $\log(k/k_0)$  versus  $\sigma_p$  for these substrates gave a linear relation (correlation coefficient  $r^2 = 0.94$ , negative slope  $\rho = -1.65$ ).

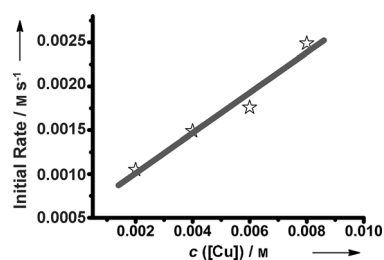


**Scheme 1.** Catalytic cycle of the Sonogashira coupling reaction that is synergistically catalyzed by Pd and Cu. OA = oxidative addition, TM = transmetalation, RE = reductive elimination.

When assuming transmetalation is the rate-limiting step in this Sonogashira cross-coupling, the kinetics and electronic effect of the substituent then can be fit well. The Hammett correlation plots in Figures 3b and 4b revealed insights into the transmetalation of the copper–acetylide with  $[\text{ArPdIL}_n]$ . The positive  $\rho$  (1.29) value indicates that the  $[\text{ArPdIL}_n]$  acts as an electrophile (Figure 3b), while the negative  $\rho$  ( $-1.65$ ) value indicates that the copper–acetylide acts as a nucleophile (Figure 4b). The electron-withdrawing substituent on  $\text{ArI}$  **1** would enhance the electrophilicity of  $\text{Pd}^{\text{II}}$  complex **A**, which would be more easily attacked by the nucleophile copper–acetylide. Meanwhile, the electron-donating substituent on arylacetylenes **2** would enhance the nucleophilicity of the copper–acetylide, which would more easily react with  $\text{Pd}^{\text{II}}$  complex **A**.

What is the rate-limiting step, reductive elimination or transmetalation? From the speculated catalytic cycle for synergistic catalysis in Scheme 1, the dependence of the kinetic behavior on the Cu salt could give the answer. If reductive elimination is the rate-limiting step, the dependence of the kinetic behavior on the Cu salt should be zero-order. If transmetalation is the rate-limiting step, the kinetic dependence on the Cu salt should be first-order.

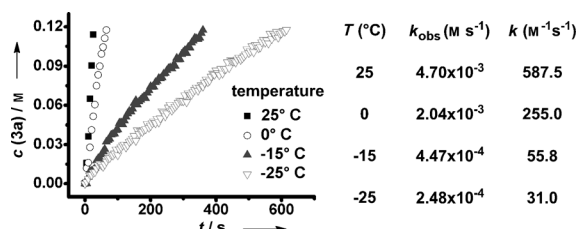
In fact, the first-order kinetic dependence on the concentration of Cu salt indeed indicated that transmetalation is the rate-limiting step (Figure 5).<sup>[9]</sup> To our knowledge, this is the



**Figure 5.** Kinetic profiles of different  $\text{CuI}$  loadings (from 1.0 mol% to 4.0 mol%) with  $[\text{Pd}(\text{PPh}_3)_4]$  (0.002 M), **1a** (0.20 M), and **2a** (0.22 M), carried out in  $i\text{Pr}_2\text{NH}$  (5 mL) at  $0^\circ\text{C}$ . Reactions were monitored by in situ IR spectroscopy.

first time that a first-order kinetic dependence on the Cu salt is determined in a “live” Sonogashira cross-coupling. Notably, the first-order kinetic dependence on both palladium catalyst and copper catalyst established the synergistic catalysis in this Sonogashira coupling reaction. Moreover, if transmetalation is rate-limiting, the catalyst resting states should be  $\text{Pd}^{\text{II}}$  complex **A** and copper–acetylide respectively. The  $^{31}\text{P}$  NMR experiments confirmed that the  $\text{Pd}^{\text{II}}$  complex **A** was indeed the resting state in this reaction (see Figure S11 in the Supporting Information).

Moreover, after it was confirmed that transmetalation is the rate-limiting step, we believed that this model Sonogashira coupling reaction might provide a good opportunity to quantitatively measure the rate constant and activation enthalpy for the transmetalation of the  $\text{C}_{\text{sp}}\text{--C}_{\text{sp}^2}$  bond formation. The model kinetic reaction of **1a** and **2a** was carried out at different temperatures (Figure 6). As trans-



**Figure 6.** Kinetic profiles of the reaction of **1a** with **2a** to **3a** at different temperatures monitored by in situ IR spectroscopy. Conditions:  $[\text{Pd}(\text{PPh}_3)_4]$  (1 mol%),  $\text{CuI}$  (2 mol%),  $i\text{Pr}_2\text{NH}$ ,  $\text{N}_2$ .

metalation is the rate-limiting step and the reaction shows first-order dependence on both  $c([\text{Pd}(\text{PPh}_3)_4])$  and  $c(\text{CuI})$ , the transmetalation rate constant  $k = k_{\text{obs}}/[c([\text{Pd}(\text{PPh}_3)_4]) \times c(\text{CuI})]$ . The transmetalation rate constants for the  $\text{C}_{\text{sp}}\text{--C}_{\text{sp}^2}$  bond formation were obtained from  $587.5 \text{ M}^{-1}\text{s}^{-1}$  at  $25^\circ\text{C}$  to  $31.0 \text{ M}^{-1}\text{s}^{-1}$  at  $-25^\circ\text{C}$  (Figure 6). The plot of  $\ln(k/T)$  versus  $1/T$  allowed us to calculate the activation parameters, and the activation enthalpy was determined as  $8.5 \text{ kcal mol}^{-1}$  (see Figure S10 in the Supporting Information). Compared to the oxidative coupling of arylzinc reagents for  $\text{C}_{\text{sp}^2}\text{--C}_{\text{sp}^2}$  bond formation,<sup>[4]</sup> the value of activation enthalpy in this case is lower. It means that this type of Sonogashira coupling reaction, which is synergistically catalyzed by palladium and copper, is a facile transformation.

In conclusion, the transmetalation step of the Sonogashira coupling reaction is established as the rate-limiting step. This well-known cross-coupling is demonstrated to be a Pd-catalyzed and Cu-catalyzed synergistic process, which exhibits a first-order kinetic dependence on the [Pd] and [Cu] catalysts, respectively. To our knowledge, it is also the first quantitative in situ measurement of the kinetics of the transmetalation step for a  $C_{sp}-C_{sp_2}$  bond formation from a catalytic reaction. The activation enthalpy is determined as  $8.5 \text{ kcal mol}^{-1}$  for the transmetalation. We believe that these quantitative investigations provide a useful insight into the nature of catalytic reactions, which will be helpful for the understanding of the mechanisms and for the synthetic applications.

### Experimental Section

General procedure: A three-necked reaction vessel was fitted with a magnetic stirring bar. The IR probe was inserted through an adapter into the middle neck; the other two necks were capped by septa for injections and a nitrogen line. CuI (0.02 mmol) was added, and the reactor was allowed to be vacuumed and purged with nitrogen for three times. After that  $iPr_2NH$  (5.0 mL), phenylacetylene **2a** (1.1 mmol), and ethyl-4-iodobenzoate **1a** (1.0 mmol) were added in by using syringes. The mixture was allowed to stir at  $0^\circ\text{C}$ . Then the data collection was started, followed by addition of  $[Pd(PPh_3)_4]$  (0.01 mmol) to start the reaction. In situ IR spectra were recorded over the course of the reaction.

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