

Transmetalation is the Rate-Limiting Step: Quantitative Kinetic Investigation of Nickel-Catalyzed Oxidative Coupling of Arylzinc Reagents

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Abstract: Transmetalation is the rate-limiting step! The transmetalation between arylzinc reagents and ArNi^{II}R was confirmed as the rate-limiting step in the nickel-catalyzed oxidative coupling reactions. It was proved to be an excellent model allowing the first quantitative measurement of the kinetic rate constants of transmetalation from a live catalytic system. Rate constants from 0.04 to 0.31 M⁻¹ s⁻¹ were obtained for different arylzinc reagents under the conditions, and the activation enthalpy $\Delta H^\ddagger$ was 14.6 kcal/mol for PhZnCl. The substituent effect on the transmetalation was also gained for the first time from the catalytic reaction.

Transmetalation is one of the elementary reactions in organometallic chemistry and involves an organometallic reagent R²M as a nucleophile to react with another metal intermediate. For example, as shown in eq 1, the transmetalation of R²M with XM_{cat}R¹, which appears in most cross-coupling reactions, results in another intermediate, R²M_{cat}R¹, and MX.¹



For clarification regarding different organometallic reagents, a number of named reactions (e.g., Negishi coupling,² which involves RZnX) are prosperous in the cross-coupling field. Cross-coupling reactions have already been extensively studied and widely applied on both academic laboratory and industrial scales during the past three decades.³ However, only scarce efforts have been devoted to kinetic investigations of transmetalation, especially for Negishi coupling.⁴ Undoubtedly, gaining insights into a reaction is of benefit to its application. Herein, we report the first quantitative measurement of kinetic rate constants of transmetalations involving organozinc reagents from a “live” catalytic system.

In general, the transmetalation of organozinc reagents with R¹M_{cat}X is considered to be a facile process.⁵ To quantitatively and accurately measure the rate constants from a “live” catalytic process, the precondition is that transmetalation should be the rate-limiting step.^{5,6} However, to the best of our knowledge, few examples of “traditional Negishi coupling reactions” in which the transmetalation is the rate-limiting step have been reported.^{4c}

Recently, we uncovered dramatic differences between “arylzinc” reagents originating from ArMgCl and ArLi.⁷ When desyl chloride (**2a**) was used as the oxidant, the oxidative coupling of arylzinc **1** formed from ArLi was much slower than that of the one formed from ArMgCl. As shown in Figure 1, the oxidative coupling

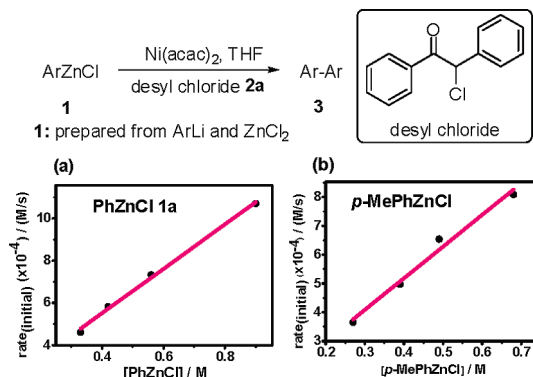
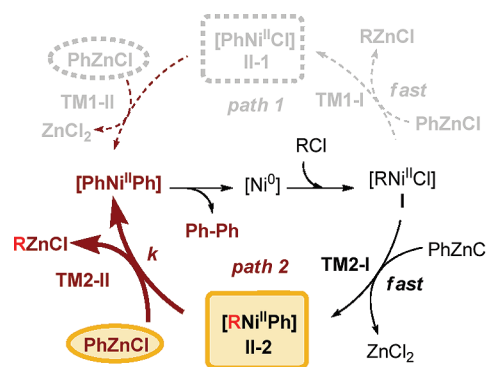


Figure 1. Linear relationship between initial rate and arylzinc concentration.

reaction of **1** was first-order in [**1**] and zeroth-order in [**2a**] (see the Supporting Information), suggesting that the rate-limiting step should be the transmetalation; this provided us the opportunity to quantitatively investigate this step from the catalytic system.

The speculated pathways for the oxidative coupling of **1a**, including the oxidative addition of Ni⁰ with **2a**, the consequent double transmetalations **TM-I** and **TM-II**, and the final reductive elimination to obtain biphenyl (**3a**), are illustrated in Scheme 1.

Scheme 1. Speculated Mechanism of the Model Reaction



The first-order kinetic dependence on [**1a**] indicated that either **TM-I** or **TM-II** was the rate-determining step. The two intermediates **II-1** and **II-2** resulting from **TM-I** would have a phenyl anion as a δ donor, which should make them more electronegative than the intermediate **I**. Thus, one could reasonably deduce that **TM-I** should be faster than **TM-II**. Thus, **TM-II** should be the rate-limiting step.

As described in Scheme 1, if the reaction proceeds along path 1, then **TM1-II**, the transmetalation between **1a** and Ni–Cl, would

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be the rate-limiting step. This reaction rate would not be affected if the oxidant RCl were varied. If the reaction proceeds along path 2, then **TM2-II**, the transmetalation between **1a** and R–Ni, would be the rate-limiting step, and the reaction rate would vary if different oxidants RCl were employed.

Therefore, we investigated the kinetic behaviors of the oxidative coupling of **1a** using the different oxidants **2a**, **2b**, **2c**, and **2d** (Figure 2). The completely different reaction rates shown in Figure 2 clearly revealed that the reaction proceeds along path 2 and **TM2-II** is the rate-limiting step. In addition, we also obtained the quantitative rate constants. The rate constant for **2b** was $0.13 \text{ M}^{-1} \text{ s}^{-1}$, which was larger than that for **2a**. The rate constant for **2c** was $0.064 \text{ M}^{-1} \text{ s}^{-1}$, which was smaller than that for **2a**. In addition, the reaction employing the other oxidant **2d** was the slowest, with a rate constant of $0.021 \text{ M}^{-1} \text{ s}^{-1}$.⁸

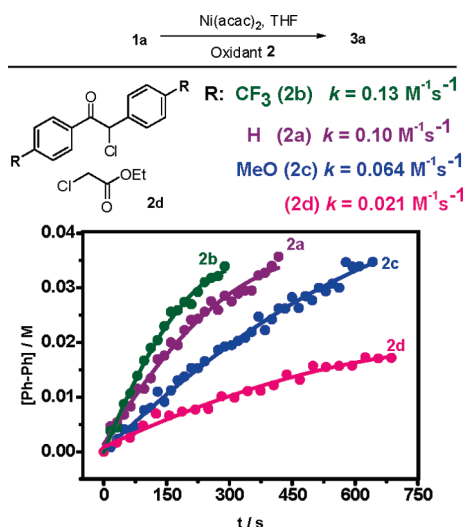


Figure 2. Kinetic profiles of the transmetalation with different oxidants.

After it was confirmed that the transmetalation **TM2-II** is the rate-limiting step, our model reaction provided an opportunity to quantitatively measure the rate constant and the activation parameters. The kinetic investigation of the oxidative coupling of **1a** was carried out at different temperatures. As shown in Figure 3, the perfect linear kinetic profiles at different reaction temperatures further confirmed the first-order kinetic behavior of the reaction. Plotting $\ln(k/T)$ versus $1/T$ also allowed us to calculate the activation parameters, and the activation enthalpy $\Delta H^\ddagger$ was found to be 14.6 kcal/mol. Because **TM2-II** is the rate-limiting step, we could assume that this $\Delta H^\ddagger$ value was for the transmetalation. According to the kinetic investigation in our previous report, $\Delta H^\ddagger$ for the reductive elimination of PhNiPh is 9.7 kcal/mol.⁵ The energy

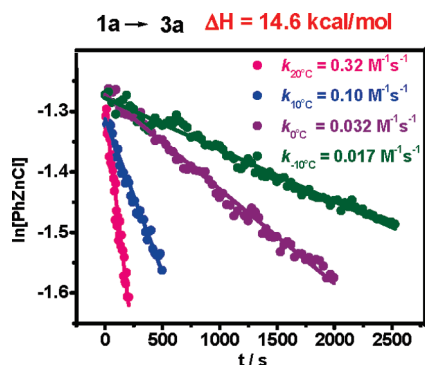


Figure 3. Plots of $\ln[2a]$ vs t at different temperatures.

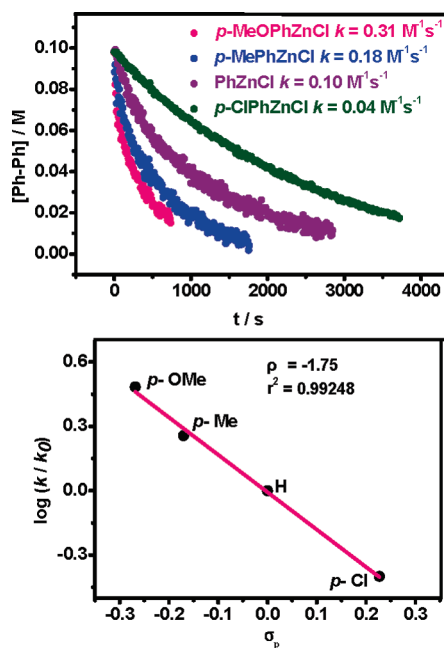


Figure 4. (top) Kinetic profiles of different compounds **1** and (bottom) the Hammett correlation plot.

difference at least discloses that the transmetalation between PhZnCl **1a** and [Ni–R] is much slower than the subsequent reductive elimination.

We further investigated the transmetalation reactions using different ArZnCl, all of which were prepared from the corresponding ArLi using ZnCl₂; the results are exhibited in Figure 4. The rate constant of the transmetalations of *p*-MePhZnCl, *p*-MeOPhZnCl, and *p*-ClPhZnCl were 0.18, 0.31, and $0.04 \text{ M}^{-1} \text{ s}^{-1}$, respectively. Plotting $\log(k/k_0)$ versus σ_p for these substrates indeed gave a rather linear relation (correlation coefficient $r^2 = 0.99248$), and the negative slope (-1.75) can be associated with a developing positive charge in the transition state.

In conclusion, the transmetalation of ArZnCl with RNi^{II}Ar was confirmed as the rate-limiting step in the oxidative coupling reactions. It was proved to be an excellent model allowing the first quantitative measurement of the kinetic rate constants of transmetalation from a live catalytic system. The activation enthalpy $\Delta H^\ddagger$ for transmetalation was obtained for the first time, and the substituent effect on the transmetalation was also measured for the first time from the catalytic reaction. These quantitative measurements for the transmetalation of arylzinc reagents will provide guiding significance in improving the selectivity of the cross-coupling reactions in synthetic applications.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (20702040, 20832003, 20972118).

Supporting Information Available: Experimental details and kinetic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (8) For the oxidative coupling reaction using **2d** as the oxidant, the kinetic investigation revealed that the reaction displayed zeroth-order kinetic behavior in [**2d**] (see the Supporting Information).

JA1045296