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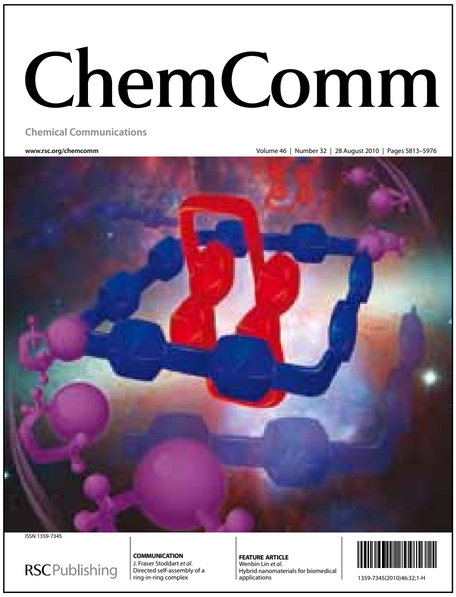

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ARTICLE TYPE

Quantitative Kinetic Investigation on Transmetalation of ArZnX in a Pd-Catalysed Oxidative Coupling

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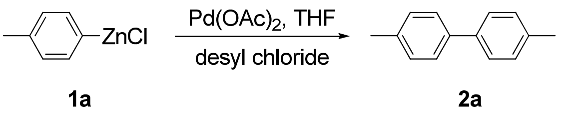
Transmetalation is the rate-limiting step. The [R-Pd-Ar] was suggested to be the resting species from the kinetic studies. Quantitative measurement of the transmetalation of ArZnCl with [R-Pd-Ar] from a live Pd-catalysed oxidative coupling reaction was conducted and the corresponding activation enthalpy was determined as 12.3 kcal/mol.

Transmetalation is one of the most important elementary reactions in transition-metal-catalysed coupling reactions. It involves the transfer of an organo group from one metal to the other and introduces a σ-bonded carbon atom into the coordination sphere of the transition metal centre.[1] Up to now, transmetalation step has been investigated in many reports. However, most of the explorations focused on the Stille reaction[2-11] and Suzuki–Miyaura reaction[12-18], in which transmetalation has been assigned to be the rate-limiting step. Compared with the organoboron reagents and organotin reagents, the organozinc reagents exhibit higher reactivity in Pd-catalysed coupling reactions and the transmetalation of organozinc reagents with $R^1M_{cat}X$ is generally considered to be a facile process.[19] Therefore, it is more difficult to quantitatively obtain the kinetic data of transmetalation from Pd-catalysed Negishi couplings. Espinet and co-workers have sequentially reported the experimental and computational results on the transmetalation of $[R_{alkyl}PdCl]$ with the $ZnMe_2$ or ZnMeCl through stoichiometric experiments.[20-22] However, it is usually not the rate determining step within a catalytic cycle which makes the rate constants for transmetalation from a "live" catalytic process difficult to be measured quantitatively and accurately. Hence, detailed quantitative kinetic data of transmetalation in Pd-catalysed Negishi-type reaction were still rare.

With Ni-catalysed oxidative coupling as a proper kinetic model, our group has successfully revealed the transmetalation of arylzinc with nickel catalyst,[19] which offered an opportunity to quantitatively acquire the kinetic data of transmetalation of arylzinc from a live catalytic reaction. With this idea in mind, this work reported a quantitative kinetic investigation of transmetalation between arylzinc and [R-Pd-Ar] from Pd-catalysed oxidative homo-coupling reactions.

The Pd-catalysed homo-coupling of ArZnCl was investigated as the kinetic model reaction to reveal the quantitative measurement of transmetalation, in which desyl chloride was applied as the oxidant (Eq.1).



(Eq. 1)

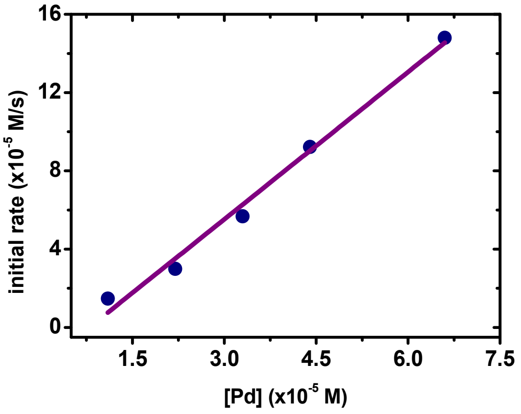


Fig.1 Dependence of the initial rates on catalyst concentrations for the homo-coupling of **1a**. Reaction conditions: **1a** (0.35 M in THF, 4.0 mL), $Pd(OAc)_2$ (1.1×10^{-5} M–6.6×10^{-5} M in THF), 2-chloro-1,2-diphenylethanone **(3a)** (7.5×10^{-2} M in THF, 0.3 mmol), -20 °C.

The dependence of the initial rates on catalyst concentrations was first tested by using **1a** as the substrate with different palladium concentrations. Monitored by *in-situ*IR, the reaction rates were measured (Fig.1). A linear relationship was obtained by plotting the initial rates *vs* $[Pd(OAc)_2]$, suggesting that the reaction is first-order dependent on $[Pd(OAc)_2]$. This indicated that the rate-limiting step of the Pd-catalysed oxidative homo-coupling of **1a** might be involved in the catalytic cycle.

Then, the kinetic studies with different concentrations of **1a** and **3a** were performed to confirm the rate-limiting step. A linear line was obtained by plotting initial rates *vs* [**1a**], demonstrating that this reaction exhibited a first-order kinetic behaviour on [**1a**] (Fig.2). Meanwhile, initial rates were identical when the reactions were carried out with different concentrations of **3a**, which indicated that the reaction was zero-order on [**3a**] (Fig.3). These kinetic results revealed that the transmetalation step should be the rate-limiting step and only [ArZnCl] was involved in the rate law when the concentration of Pd catalyst was identical (Eq.2).

$$\text{rate} = k_{obs}\times[\text{ArZnCl}] \quad (\text{Eq.2})$$

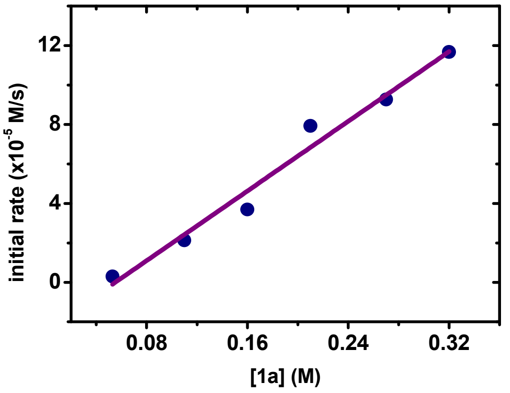


Fig.2 Dependence of the initial rates on concentrations of **1a**. Reaction condition: 2-chloro-1,2-diphenylethanone (**3a**) (5.0×10^{-2} M in THF, 0.3 mmol), *p*-MeC_6H_4ZnCl (**1a**) (0.053 M–0.32 M in THF, 6.0 mL) , $Pd(OAc)_2$ (3.3×10^{-5} M in THF), 30 °C.

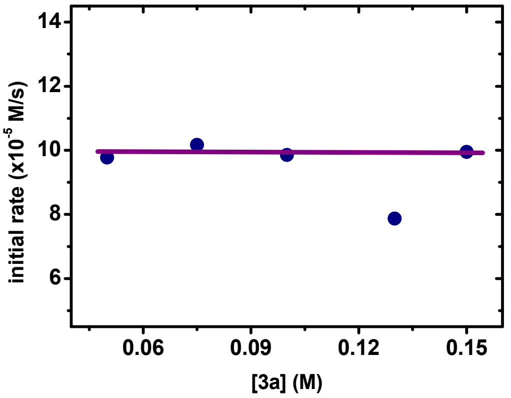


Fig.3 Kinetic profiles of the homo-coupling of **1a** under different concentrations of **3a**. Conditions: *p*-MeC_6H_4ZnCl (**1a**) (0.31 M in THF, 4.0 mL), 2-chloro-1,2-diphenylethanone (**3a**) (0.050M–0.15 M in THF), $Pd(OAc)_2$ (3.3×10^{-5} M in THF), 10 °C.

As shown in Scheme 1, there are two theoretical paths for this reaction. For path 1, oxidative addition of RCl to Pd(0) affords [R-Pd-Cl], the subsequent transmetalation between **1a** and **TM-I** furnishes the intermediate [Ar-Pd-R]. Then, the second transmetalation between **1a** and **II-1** forms [Ar-Pd-Ar], and the reductive elimination of [Ar-Pd-Ar] produces Ar-Ar. For path 2, oxidative addition of RCl to Pd(0) affords [R-Pd-Cl], the subsequent transmetalation between **1a** and **TM-I** furnishes the intermediate [Ar-Pd-Cl]. Then, the second transmetalation between **1a** and **II-2** forms [Ar-Pd-Ar], and the reductive elimination of [Ar-Pd-Ar] produces Ar-Ar.

From the data described above, this reaction exhibited a first-order kinetic behaviour on [**1a**], suggesting that either **TM-I** or **TM-II** was the rate-limiting step. According to the Scheme 1, the two intermediates **II-1** and **II-2** resulting from **TM-I** would have a phenyl anion as a δ donor, which would make them more electronegative and slow down the second transmetalation step.[19] Thus, **TM-II** should be the rate-limiting step. Moreover, the intermediates **II-1** and **II-2** are crucial in distinguishing the two paths. If the reaction follows Path1, the transmetalation between **1a** and Pd-R would be the rate-limiting step, and the initial rate would vary by employing different oxidants (R-Cl). If Path 2 was followed, the transmetalation between **1a** and Pd-Cl would be the rate-limiting step, and the reaction rate would not be affected by different oxidants (R-Cl).

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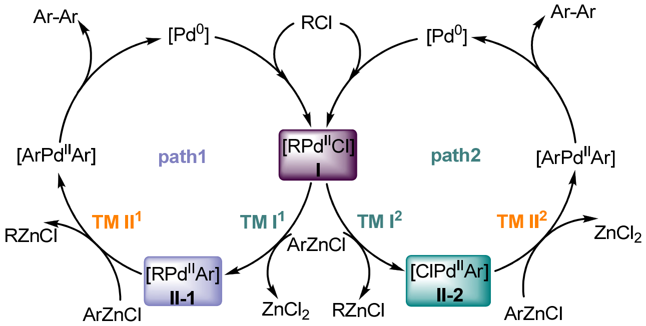
Consequently, the kinetic investigations of the homo-coupling of **1a** under different substituted oxidants (R-Cl) were then carried out. When CF_3 substituted oxidant (**3b**) was utilized, the reaction displayed first order on arylzinc and zero order on oxidant, suggesting that transmetalation is the rate limiting step when **3b** was the oxidant in Pd-catalyzed homocoupling of arylzinc reagent (Figure S7-1). Same kinetic behavior was also determined when Me substituted oxidant (**3c**) was employed. On the basis of the above kinetic results, we then investigated the reaction rate by using different oxidants under identical conditions. As shown in Fig.4, when employing different oxidants (**3a**, **3b**, **3c**), varied initial rates could be observed, demonstrating that **II-1** was involved in the rate-limiting step, which should be assigned to **TM II^1** in path 1.



Scheme 1 Pd-catalysed oxidative homo-coupling reaction

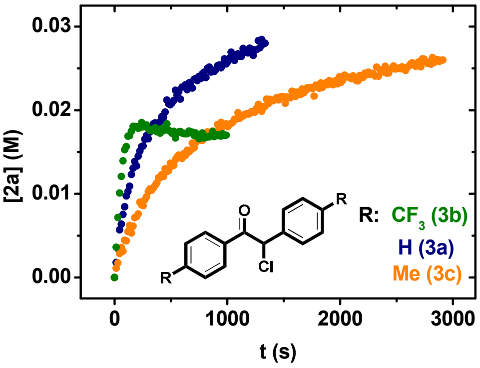


Fig.4 Kinetic profiles of homo-coupling reaction of **1a** under different oxidants. Conditions: *p*-MeC_6H_4ZnCl (**1a**) (0.27 M in THF, 4.0 mL), oxidants (**3a**, **3b**, **3c**) (5.0×10^{-2} M in THF, 0.2 mmol), $Pd(OAc)_2$ (2.8×10^{-5} M in THF), 10 °C.

We have confirmed that the transmetalation **TM II^1** is the rate-limiting step, which provided an opportunity to quantitatively measure the activation energy of this transmetalation step from the Pd-catalysed oxidative homo-coupling. Then, the kinetic investigations were carried out at different temperatures. Plotting the $\ln(k_{obs}/T)$ *vs* $1/T$ (Fig.5) gives a smooth linear relationship, allowing the calculation of the activation energy for this transformation. According to the Eyring Equation, the activation enthalpy was determined to be 12.3 kcal/mol.

In order to gain further insights into the substituent effects, we investigated the reaction in the presence of different *para*–substituted arylzinc reagents including *p*-MeOC_6H_4ZnCl, *p*-MeC_6H_4ZnCl, PhZnCl, *p*-BrC_6H_4ZnCl and *p*-ClC_6H_4ZnCl. Initial rates have been obtained. Plotting the $\log(k/k_H)$ *vs* σ_p gave a linear free energy relationship with a ρ value of -2.37, suggesting that electron-rich arylzinc reagents displayed higher reaction rates than electron-deficient arylzinc reagents (Fig.6**)**. The result further supported that the transmetalation is the rate-limiting step.

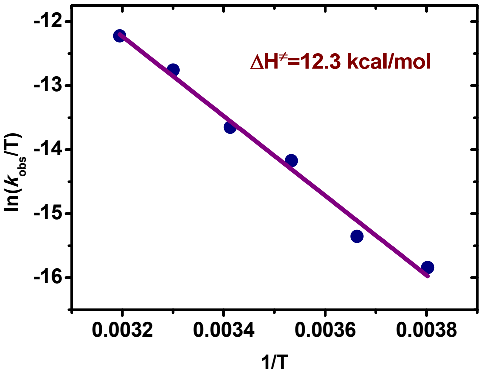


Fig.5 Eyring plots for the homocoupling of *p*-MeC_6H_4ZnCl (**1a**). Reaction conditions: 2-chloro-1,2-diphenylethanone (**3a**) (7.5×10^{-2} M in THF, 0.3 mmol), *p*-MeC_6H_4ZnCl (0.31 M in THF, 4.0 mL), $Pd(OAc)_2$ (3.3×10^{-5} M in THF).

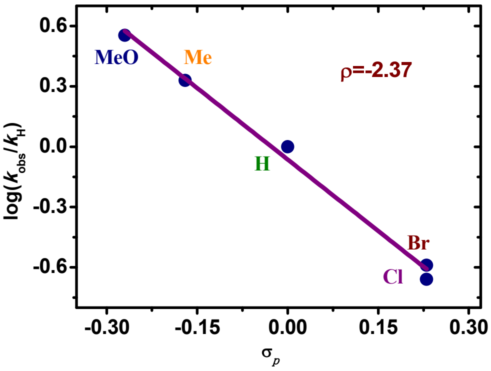


Fig.6 Hammett plot for the homo-coupling reaction with different *para*-substituted arylzinc reagents. Reaction conditions: 2-chloro-1,2-diphenylethanone (**3a**) (7.5×10^{-2} M in THF, 0.3 mmol), *p*-substituted ArZnCl (MeO, Me, H, Br, Cl) (0.30 M in THF, 4.0 mL), $Pd(OAc)_2$ (2.8×10^{-5} M in THF), 10°C.

In summary, the kinetic studies of palladium-catalysed Negishi-type oxidative homo-coupling reaction of ArZnCl have been quantitatively investigated. The *in-situ*IR experiments confirmed that the transmetalation between **1a** and Pd-R is the rate-limiting step. The corresponding activation enthalpy $\Delta H^{\neq}$ (12.3 kcal/mol) for this transmetalation is obtained quantitatively.

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Notes and references

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† Electronic Supplementary Information (ESI) available: detailed experimental procedures and kinetic parameters detected by a Mettler Toledo ReactIR™ 15 spectrometer. See DOI:10.1039/b000000x/

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