

Insights into the elementary steps in Negishi coupling through kinetic investigations

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The Negishi coupling has been widely applied in organic synthesis, while relevant mechanistic studies are relatively rare. To obtain an understanding of the fundamental steps in the Negishi coupling, oxidative addition, transmetalation and reductive elimination, the kinetic investigation has served as one of the most important strategies. In this review, insights into the elementary steps in the Negishi coupling through kinetic investigations are summarized.

Introduction

Transition metal-catalyzed coupling reaction involving organic halides and organometallics has been one of the most important approaches to construct C–C and C–Heteroatom bonds.^{1,2} Due to the wide application of this powerful strategy in the chemical community, the 2010 Nobel Prize in Chemistry was awarded jointly to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their outstanding contributions to palladium-catalyzed cross-couplings.

Since the 1970s, the Negishi coupling has been widely employed in the synthesis of biaryls and Ar-alkyls.^{3–7} It is generally defined as Pd or Ni-catalyzed cross-coupling reactions between organic halides as the electrophile and organozinc, organoaluminium or organozirconium as the nucleophile.⁸ Because of the diversity of the preparation methods and tolerance toward many functional groups, organozinc reagents are more effective and useful than the other two metal reagents.^{9–24}

Moreover, the related mechanistic studies have attracted more and more attention.^{12,25–44} Generally, the mechanism for transition-metal catalyzed cross-coupling reactions is described as an accepted catalytic cycle involving three elementary steps: (1) oxidative addition of R–X to a low valent transition metal Mcat. to afford a [R–Mcat.–X] intermediate; (2) transmetalation between [R–Mcat.–X] and an organometallic reagent R'M to form [R–Mcat.–R']; (3) reductive elimination of [R–Mcat.–R'] to produce R–R'. The oxidative addition step investigations were mainly revealed from some individual stoichiometric experiments.^{45–58} Among these studies, catalytic intermediates, which could be stabilized by special ligands, were prepared and

characterized by NMR and X-ray diffraction. For the transmetalation step, exploration has always been focused on the Suzuki coupling^{59–63} or Stille coupling,^{64–68} in which the transmetalation is normally rate-limiting step.

The Negishi coupling was proposed to undergo an analogous pathway while the mechanistic investigations for the Negishi coupling are relatively rare. On one hand, the proposed intermediates in the Negishi coupling are difficult to isolate or detect.⁶⁹ On the other hand, various preparation methods for organozinc reagents involving different additives sometimes resulted to kinetic or selectivity differentiation, which made the mechanism of the Negishi coupling more complex. In most cases, DFT calculations were preferred to elucidate the mechanism for the Negishi coupling.^{26,70,71}

With the development of modern analytical techniques, kinetic studies for mechanistic investigations have attracted more and more attention. In earlier studies, reaction rates could be obtained from NMR, GC or HPLC according to the product distribution, which have provided important information for mechanistic insights; however, the active intermediates are difficult to capture from a live catalytic cycle. For some facile transformations, *in situ* IR, *in situ* UV-Vis or *in situ* Raman is preferred. NMR could be also a powerful tool when a proper reaction model was employed. Jutand and co-workers have elucidated a thorough understanding of Pd, Fe or Cu chemistry through kinetic investigation by electrochemical tools.⁷² Blackmond employed Reaction Calorimetry in the mechanistic studies of Pd-catalyzed coupling reactions.⁷³ Recently, ESI-MS has also been helpful in capturing intermediates.³² All of these kinetic techniques have been used cooperatively in mechanistic studies and will play more important roles in the future.

Recently, our group has been working on mechanistic studies through kinetic use of *in situ* IR.^{33,34,41,74–78} Insights into the elementary steps from transition metal-catalyzed coupling between ArI and organozinc or a newly developed oxidative coupling model have been revealed. Herein, this review

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summarizes mechanistic aspects of the Negishi coupling through detailed kinetic investigation from different reaction models. In addition, different kinetic and structure features of organozinc reagents which aggravate the difficulty of mechanistic studies for the Negishi coupling are also introduced.

Oxidative addition

In mechanistic studies for transition-metal catalyzed coupling reactions oxidative addition is the most extensively investigated.^{79–84} However, in Negishi-type coupling reactions, effects of organozinc reagents or Lewis acid on oxidative addition, such as ZnX_2 , is rarely discussed. Recently, it has been reported that $Zn(II)X_2$ could promote the oxidative addition of thioimidates to Pd(0) by forming an electron-deficient complex between ZnX_2 and thioimide.⁸⁵ Anderson and Vicic also revealed that $ZnBr_2$ could abstract the halide of the oxidative addition product $R-Ni-X$ to form an ionic intermediate.²⁷

Moreover, the carbon anion in organozinc reagents could be regarded as a Lewis base, which might coordinate with transition metals to influence the catalyst activity. It has been established that bases play important roles in oxidative addition. Jutand and co-workers reported that the acetate ion could coordinate to the Pd(0) center to form $[Pd(PPh_3)_2OAc]^-$, which was identified through CV and NMR to be the active species to undergo oxidative addition.^{86,87} In $Pd(P^tBu_3)_2$ -catalyzed amination of chloroarenes, effects of Lewis bases and halides were discussed, indicating that $[(P^tBu_3)Pd(OR)]^-$ could be the active catalyst when different haloarenes were employed.⁸⁸ The promotion to oxidative addition from bases was also demonstrated by other groups.⁸⁹

Recently, our group has revealed that alkylzinc reagents from Grignard reagents might play a key role in oxidative addition in Pd/thioamide pincer ligand-catalyzed Negishi couplings of aryl iodides with alkylzinc reagents.^{75,77} Using pincer-Pd **1** catalyzed coupling of ethyl 2-iodobenzoate and cyclohexylzinc(II) chloride ($CyZnCl$) as the model reaction, preliminary kinetic studies were performed. An induction period could be clearly observed (Fig. 1, blue), indicating that the reactive species is not catalyst **1**. The stoichiometric reaction between **1** and ArI did not occur unless excess $CyZnCl$ is present, suggesting that $CyZnCl$ is involved in the formation of active species to promote the oxidative addition step. Supported by NMR and IR, further exploration suggested that the anionic complex **2** could be formed when complex **1** reacted with RM (RM = $RMgX$ or $RZnX$). If catalyst **1** (0.5 mol%) was mixed with $CyMgBr$ (2.5 mol%) for 2 min followed by adding $CyZnCl$ and aryl iodide to this resulted mixture, the induction period disappeared and the reaction was fast even at a lower temperature ($-20\text{ }^\circ\text{C}$) (Fig. 1, green and purple). Supported by other NMR and X-ray information, the alkylated Pd ate complex was confirmed as the active catalyst to react with ArI in oxidative addition in this Negishi coupling reaction.

Consequently, the oxidative addition in the Negishi coupling is not as simple as we expected due to the complexity of the reaction components. The organozinc reagent, as the transmetalating reagent, should not be overlooked in the oxidative addition step.

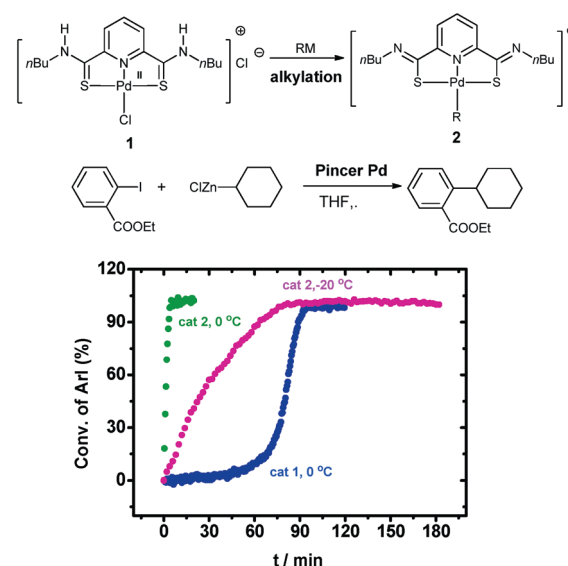


Fig. 1 Catalyst **1** or **2** catalyzed Negishi coupling. Reaction conditions: [ethyl *o*-iodobenzoate] = 0.29 M, [cyclohexylzinc chloride] = 0.65 M, [**1**] = 1.6 mM, Blue: no additive, $0\text{ }^\circ\text{C}$. Green: [$CyMgCl$] = 8 mM, $0\text{ }^\circ\text{C}$; Purple: [$CyMgCl$] = 8 mM, $-20\text{ }^\circ\text{C}$.

Transmetalation

Transmetalation is a key step to introduce a σ -bonded carbon atom into the coordination sphere of the transition metal center. In the mechanistic investigation of Negishi couplings, transmetalation has received more attention than other elementary steps. However, the organozinc reagent, compared to other organometallic reagents, such as organotin or organoboron reagents, is much more reactive in the transmetalation step as a “hard” nucleophile.⁸ Therefore, most knowledge about the transmetalation step were obtained from the Suzuki or Stille couplings.^{90,91} For the Negishi coupling, the transmetalation has been rarely investigated until recent efforts by Espinet and our group.^{34,41,44,70,92}

Espinet and co-workers reported the first detailed experimental observations of transmetalation of an alkylzinc reagent with $R-Pd-X$, revealing different behavior for $ZnMe_2$ and $ZnMeCl$.⁴⁴ Employing the coupling reactions of $ZnMe_2$ or $ZnMeCl$ with $Rf-I$ ($Rf = 3,5$ -dichloro-2,4,6-trifluorophenyl) catalyzed by $trans$ - $PdRfCl(PPh_3)_2$ to afford $Rf-Me$ as a model, the transmetalation was investigated by ^{19}F NMR. As shown in Fig. 2(A), when $ZnMe_2$ was used as the nucleophile, $trans$ - $PdRfCl(PPh_3)_2$ reacted quickly and $trans$ - $[PdRfMe(PPh_3)_2]$ was produced. Then $trans$ - $[PdRfMe(PPh_3)_2]$ could undergo an isomerization to give cis - $[PdRfMe(PPh_3)_2]$ slowly. However, the major way to consume $trans$ - $[PdRfMe(PPh_3)_2]$ was another transmetalation with additional $ZnMe_2$, affording $[PdMe_2(PPh_3)_2]$ and $ZnRfMe$. When $ZnMeCl$ was employed, the transmetalation proceeded with a relatively slower rate (Fig. 2(B)). It was observed that cis - $[PdRfMe(PPh_3)_2]$ was formed initially and then underwent isomerization to produce $trans$ - $[PdRfMe(PPh_3)_2]$. The existence of $ZnClRf$ in the early stage indicated that another side transmetalation between $trans$ - $[PdRfMe(PPh_3)_2]$ and $ZnMeCl$ occurred. All of these results indicated that ZnR_2 and $ZnRX$ behave with

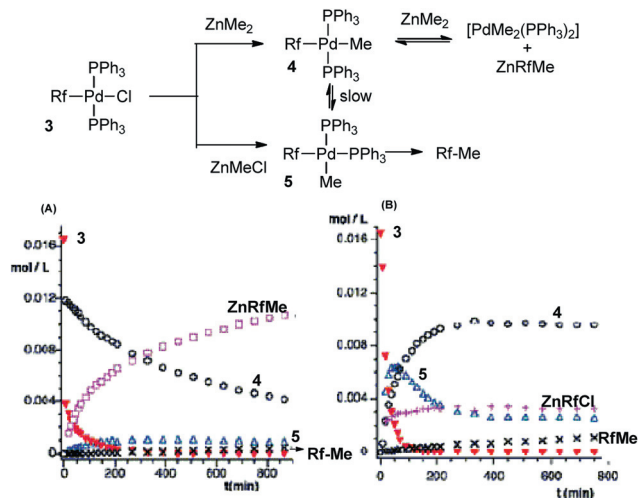


Fig. 2 Different kinetics of ZnMe_2 (A) and ZnMeCl (B) in the transmetalation step. *Reaction conditions:* (A) $[3] = 1.65 \times 10^{-2}$ M, $[\text{ZnMe}_2] = 0.33$ M; (B) $[3] = 1.65 \times 10^{-2}$ M, $[\text{ZnMeCl}] = 0.33$ M. Reprinted (adapted) with permission from *J. Am. Chem. Soc.*, 2007, **129**, 3508–3509. Copyright (2007) American Chemical Society.

different kinetic features in the transmetalation step. Moreover, the kinetic data also suggested a powerful transmetalating activity of alkylzinc reagent. For the overall transformation, the *cis-trans* isomerization was another limited factor for the next reductive elimination step. The model reaction they selected was the key for ^{19}F NMR kinetic observation, in which the reductive elimination of $[\text{Rf-Pd-Me}]$ was a relatively tough process and beneficial for product detection. Thus, the kinetic investigation should be performed based on a proper model reaction.

Following previous research, Espinet and co-workers conducted a further study between *trans*- $[\text{PdClMe}(\text{PMePh}_2)_2]$ and ZnMeCl .⁷⁰ The transmetalation of ZnMeCl with *trans*- $[\text{PdClMe}(\text{PMePh}_2)_2]$ was carried out at 223 K and 203 K and monitored by ^{31}P NMR spectroscopy. *trans*- $[\text{PdMe}_2(\text{PMePh}_2)_2]$ was accumulated initially and then its concentration decreased, meanwhile, the concentration of its *cis* isomer increased continuously. The kinetic results indicated that the transmetalation of *trans*- $[\text{PdClMe}(\text{PMePh}_2)_2]$ and ZnMeCl afforded the *trans* isomer kinetically, while its *cis* isomer was a thermodynamic product. Actually, when *trans*- $[\text{PdMe}_2(\text{PMePh}_2)_2]$ was isolated it was fairly stable and the isomerization from *trans* to *cis* was negligible. So it was proposed that in the experimental conditions, additional ZnCl_2 could promote the transformation from *trans* isomer to $[\text{PdClMe}(\text{PMePh}_2)_2]$. A similar promotion could also be attributed to the transformation from *cis* isomer to $[\text{PdClMe}(\text{PMePh}_2)_2]$. In other words, the transmetalation between $[\text{PdClMe}(\text{PMePh}_2)_2]$ and ZnMeCl to form *trans*- $[\text{PdMe}_2(\text{PMePh}_2)_2]$ and *cis*- $[\text{PdMe}_2(\text{PMePh}_2)_2]$ was a quick reversible process (Fig. 3). Combined with DFT calculation, this reversible transmetalation was supported.

Recently, a totally different kinetic observation was reported about the transmetalation of *trans*- $[\text{PdClMe}(\text{PMePh}_2)_2]$ with ZnMe_2 (Fig. 4) by NMR.⁹² As ZnMe_2 bears a better nucleophilicity, this transformation was considerably fast, affording *trans*-

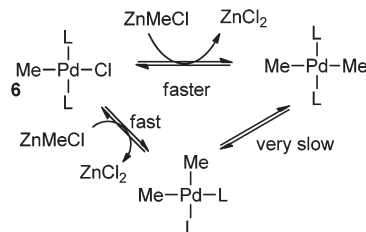


Fig. 3 Transmetalation between *trans*- $[\text{PdClMe}(\text{PMePh}_2)_2]$ 6 and ZnMeCl .

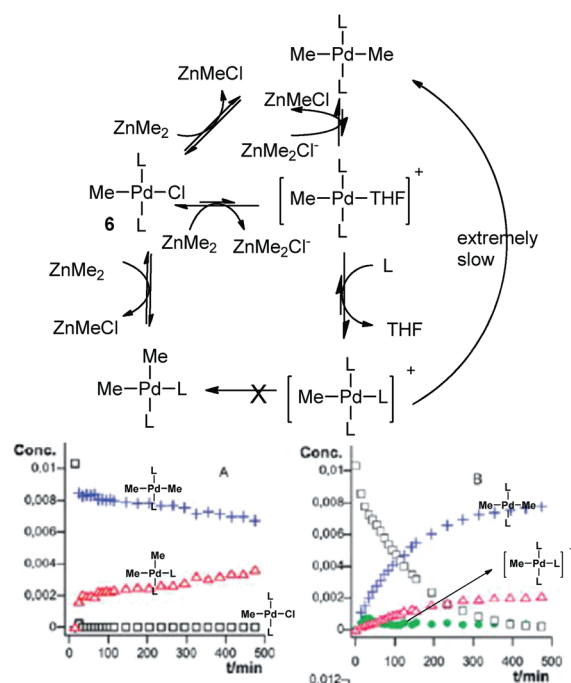
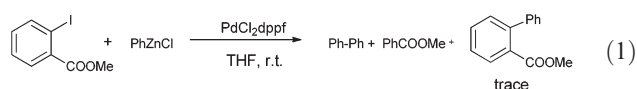


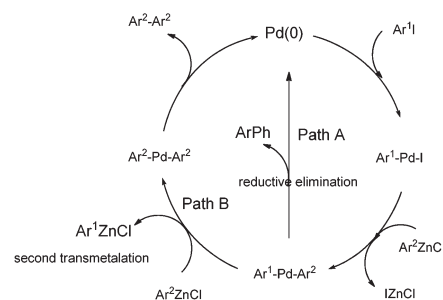
Fig. 4 Transmetalation between *trans*- $[\text{PdClMe}(\text{PMePh}_2)_2]$ and ZnMe_2 . *Reaction conditions:* $[6] = 0.01$ M, $[\text{ZnMe}_2] 0.21$ M, (A) $[\text{PMePh}_2] = 0$ M, (B) $[\text{PMePh}_2] = 6.0 \times 10^{-4}$ M. Reprinted (adapted) with permission from *J. Am. Chem. Soc.*, 2011, **133**, 13519–13526. Copyright (2011) American Chemical Society.

$[\text{PdMe}_2(\text{PMePh}_2)_2]$ (Fig. 4(A), blue), followed by the isomerization from the *trans* to the *cis* isomer took place. However, when a tiny amount of ligand PMePh_2 was added, the consumption of *trans*- $[\text{PdClMe}(\text{PMePh}_2)_2]$ was sharply inhibited (Fig. 4(B)). Moreover, the rate of the transmetalation was affected only slightly when more ligands were added and a cationic species $[\text{PdMe}(\text{PMePh}_2)_3]^+$ could be observed (Fig. 4(B), green). They proposed that an active intermediate should exist in such a low concentration that was out of a detection limit, while this species could be quenched by additional ligand to form another species with lower activity toward the transmetalation. *trans*- $[\text{PdMe}(\text{PMePh}_2)_2(\text{THF})]^+$ was postulated to be formed because ZnMe_2 could act as a Cl^- scavenger of *trans*- $[\text{PdClMe}(\text{PMePh}_2)_2]$. This cation was respected as the most plausible active intermediate to proceed the following transformation at a high rate. In the presence of additional ligand, $[\text{PdMe}(\text{PMePh}_2)_3]^+$ was formed and inhibited the transformation. This conclusion was also supported by DFT studies. Their results suggested that the transmetalation

step could be accelerated by using coordinative solvent or weak ligands in Negishi coupling.



The kinetic investigations by Espinet and co-workers provided profound understanding towards the transmetalation step for alkylzinc reagents. As Espinet illustrated, the intermediate R^1-M-R^2 could undergo transmetalation with another organozinc reagent. Similar results were also reported by our group employing an arylzinc reagent.⁴¹ Using palladium-catalyzed cross coupling of methyl 2-iodobenzoate and PhZnCl as a model, ethyl benzoate and Ph-Ph were observed to be generated in the same amount (Fig. 5, eqn (1)). Through *in situ* IR (Fig. 5(A)) and NMR (Fig. 5(B)), ArZnCl 7 was detected and accumulated at the same rate as the consumption of ArI. Therefore, we proposed that a second transmetalation step between [Ar-Pd-Ph] and PhZnCl existed to produce ArZnCl and [Ph-Pd-Ph] (Scheme 1 path B). The proposed mechanism was further demonstrated by DFT calculations and stoichiometric experiments. These results could explain why the homocoupling product of the arylzinc reagent was observed in the Negishi coupling. The selectivity in this transformation depended on the competition between reductive elimination of [Ar¹-Pd-Ar²] and the second transmetalation to a great extent. Based on these results, controlling factors about this competition were further disclosed by DFT calculations. It has been revealed that when Ar¹ bears a *para*-substituent, the activation energy for the reductive elimination is slightly increased, while the activation energy for the second transmetalation increases as much as 3 kcal mol⁻¹. Namely, when using *para*-substituted Ar¹I, reductive elimination of [Ar¹-Pd-Ar²] is



Scheme 1 Proposed mechanism for Pd-catalyzed Negishi coupling of ArI and PhZnCl.

favored. When Ar¹ has an *ortho* substituent, the barrier of reductive elimination is increased by 2–4 kcal mol⁻¹, while the barrier of the second transmetalation is reduced by an ester group (by 2.7 kcal mol⁻¹) and methoxyl group (by 0.7 kcal mol⁻¹). This result could probably attribute to the Zn–O coordination in the transition state. When *ortho*-methyl or *ortho*-isopropyl Ar¹ is utilized, energy barriers for both two steps increase. Moreover, the steric effect is more significant in the reductive elimination transition state than in the transmetalation transition state. In that case, *ortho* substituent in Ar¹I favors the second transmetalation reaction and leads to the dehalogenation and homocoupling of Ar²ZnCl. When Ar² bears an *ortho* substitute, (COOMe, OMe, isopropyl and 2,4,6-trimethyl), the free energy of activation of the second transmetalation is significantly increased by 5–13 kcal mol⁻¹, and the second transmetalation is totally hampered. These results indicated that an *ortho* substituent in ArZnX significantly disfavors a second transmetalation. In all, this work profoundly provided an important strategy for modifying the selectivity of the cross-coupling and homocoupling product through employing different substrates in Pd-catalyzed Negishi coupling.

The above kinetic investigations have provided some important information for the mechanism from a qualitative aspect. Moreover, quantitative measurements for the elementary steps could also be gained from kinetic studies.

In Ni-catalyzed Negishi coupling reactions, the transmetalation was rarely studied because the associated intermediates were unstable for stoichiometric experiments. Recently, by using Ni-catalyzed oxidative homocoupling of an arylzinc reagent as a model, 2-chloro-1,2-diphenylethanone (desyl chloride) as the oxidant, we revealed our quantitative investigation of transmetalation between [R-Ni-Ar] and arylzinc from a catalytic cycle.³⁴ Through *in situ* IR, the first-order kinetic behavior on the concentration of arylzinc was confirmed (Fig. 6(A)) from a live catalytic circumstance. And the reaction rate was independent of the concentration of the oxidant (Fig. 6(B)). These results suggest that:

$$\text{rate} = k_{\text{obs}} [\text{ArZnCl}]$$

The rate law showed that arylzinc is involved in the rate-limiting step, suggesting that the transmetalation might be the slowest step. When using varied oxidants, different reaction rates were observed (Fig. 6(C)), indicating that the oxidant R–Cl is also involved in the rate-limiting step. As shown in Scheme 2, the

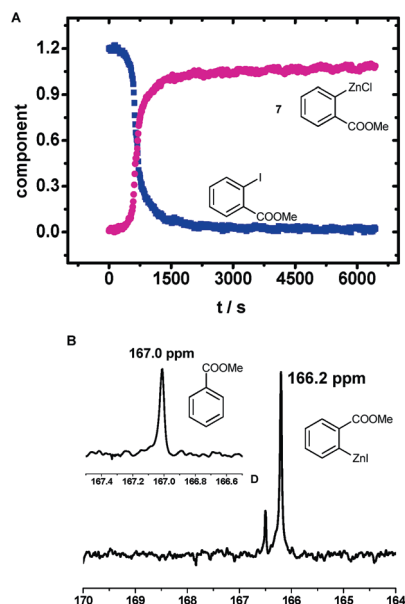


Fig. 5 Pd-catalyzed Negishi coupling of PhZnCl and ArI. Reaction conditions: methyl 2-iodobenzoate (0.5 mmol), PhZnCl (1.0 mmol), (A) PdCl₂dppf (0.025 mmol), (B) PdCl₂(dppf) (0.015 mmol), 5 min. Reprinted (adapted) with permission from *J. Am. Chem. Soc.*, 2009, **131**, 10201–10210. Copyright (2009) American Chemical Society.

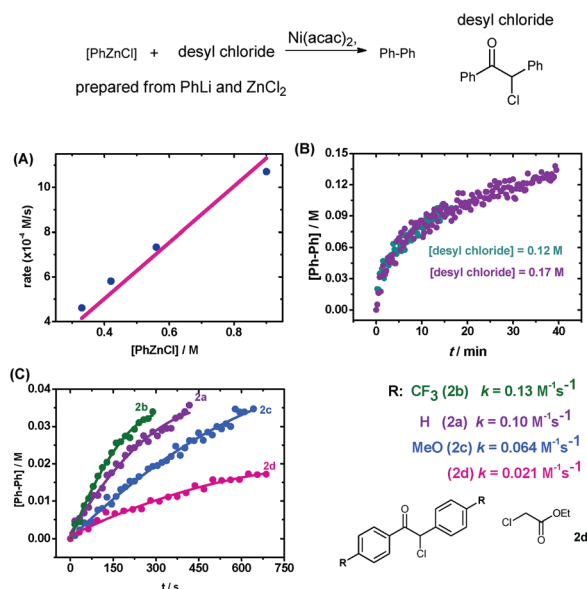
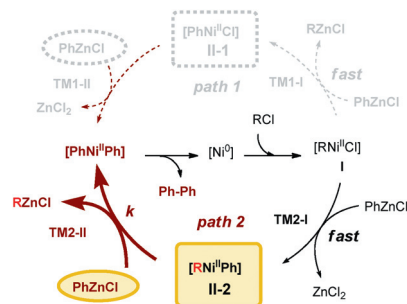


Fig. 6 Kinetic studies of Ni-catalyzed oxidative homocoupling of arylzinc. Reaction conditions: $[\text{Ni(acac)}_2] = 6.5 \times 10^{-5} \text{ M}$, 0°C (A) $[\text{desyl chloride}] = 0.175 \text{ M}$, $[\text{PhZnCl}] = 0.33\text{--}0.90 \text{ M}$; (B) $[\text{desyl chloride}] = 0.12 \text{ M}$ and 0.17 M , $[\text{PhZnCl}] = 0.38 \text{ M}$; (C) $[\text{oxidant}] = 0.10 \text{ M}$, $[\text{PhZnCl}] = 0.30 \text{ M}$, 10°C . Reprinted (adapted) with permission from *J. Am. Chem. Soc.*, 2010, **132**, 9607–9609. Copyright (2010) American Chemical Society.

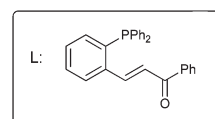
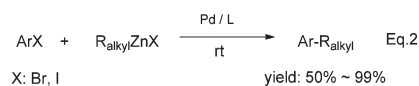


Scheme 2 Proposed mechanism for Ni-catalyzed oxidative homocoupling of PhZnCl.

reaction was postulated to undergo through two possible pathways. After the oxidative addition of $[\text{Ni}^0]$ to R-Cl to produce $[\text{R-Ni-Cl}]$, the PhZnCl reagent may transmetalate with R or Cl to form $[\text{R-Ni-Ph}]$ or $[\text{Ph-Ni-Cl}]$, respectively. Independent of pathway, the second transmetalation is regarded to be slower than the first transmetalation. And only in path II, R was involved in the second transmetalation TM2-II, in which the rate constant is dependent on the concentration of $[\text{R-Ni-Ph}]$. Hence, the second transmetalation between arylzinc and $[\text{R-Ni-Ph}]$, not $[\text{Ph-Ni-Cl}]$ was established to be rate-limiting. Based on these results, the activation enthalpy for this transmetalation was shown to be $14.6 \text{ kcal mol}^{-1}$ according to Eyring plot. However, through stoichiometric experiments, the activation parameters of transmetalation of arylzinc reagent are difficult to obtain.

Reductive elimination

Reductive elimination is an essential step for bond formation. Similar to oxidative addition, most of the knowledge about reductive elimination came from stoichiometric experiments by using some special ligands or substrates to stabilize the key intermediate for analysis by NMR or other tools. In the Negishi coupling reaction, organozinc reagents, as “hard” nucleophiles, promote a fast transmetalation step, so that the reductive elimination or oxidative addition is more likely to be the rate-limiting step. Thus, the Negishi coupling reaction could be treated as a proper model to discuss reductive elimination if the oxidative addition is fast. Recently, a quantitative understanding of reductive elimination from a catalytic Negishi coupling reaction was revealed by our group through kinetic investigations.^{33,78}



(2)

It has been established that electron-deficient ligands can promote the reductive elimination step.⁹³ Our earlier research reported an efficient Pd-catalyzed Negishi-coupling with a phosphine/olefin compound as the ligand (eqn (2)).⁷⁶ High efficiency, selectivity and good tolerance of $\beta\text{-H}$ were gained. Pd/P-olefin-catalyzed cross-coupling of ethyl 2-iodobenzoate and $\text{C}_{12}\text{H}_{25}\text{ZnCl}$ (from Grignard reagent) was employed as a model for kinetic studies to elucidate the quantitative measurement of the reductive elimination step.⁷⁸

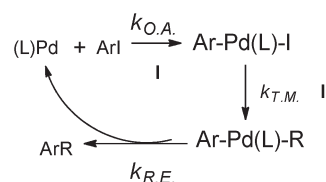
As shown in Scheme 3, the mechanism for this model reaction could be proposed to follow these three elementary steps. According to *steady-state approximation* for ArPd(II)I and ArPd(II)R , the rate law could be deduced.

$$\frac{d[\text{ArPd(II)I}]}{dt} = k_{\text{O.A.}}[\text{ArI}][\text{Pd(0)}] - k_{\text{T.M.}}[\text{ArPd(II)I}][\text{RZnCl}] = 0$$

$$\frac{d[\text{ArPd(II)R}]}{dt} = k_{\text{T.M.}}[\text{ArPd(II)I}][\text{RZnCl}] - k_{\text{R.E.}}[\text{ArPd(II)R}] = 0$$

The mass balance of Pd can be illustrated as below ($[\text{Pd}]_{\text{total}}$ is the total Pd concentration)

$$[\text{Pd}]_{\text{total}} = [\text{Pd(0)}] + [\text{ArPd(II)I}] + [\text{ArPd(II)R}]$$



Scheme 3 Proposed mechanism for Pd-catalyzed Negishi coupling of ArI and RZnCl.

For the whole catalytic reaction, the reaction rate can be written as:

$$\text{rate} = -\frac{d[\text{ArI}]}{dt} = k_{\text{O.A.}}[\text{ArI}][\text{Pd}(0)]$$

$$= \frac{[\text{Pd}]_{\text{total}}}{(1/k_{\text{O.A.}}[\text{ArI}]) + (1/k_{\text{T.M.}}[\text{RZnCl}]) + (1/k_{\text{R.E.}})}$$

It has been confirmed that the catalyst could decay in the overall reaction, so the kinetic behaviour became more complex. Different kinetic regimes were employed to analyse the kinetic data: zero-order kinetic (reductive elimination might be rate-limiting), first-order kinetic on ArI (oxidative addition might be rate-limiting) and complex kinetic.

Take the complex kinetic regime as an example, the rate of oxidative addition and transmetalation are in the same range, which is much slower than the reductive elimination ($k_{\text{R.E.}} \gg k_{\text{O.A.}} \times [\text{ArI}]$, $k_{\text{R.E.}} \gg k_{\text{T.M.}} \times [\text{RZnCl}]$). The rate law could be simplified as:

$$\text{rate} = \frac{[\text{Pd}]_{\text{total}}}{(1/k_{\text{O.A.}}[\text{ArI}]) + (1/k_{\text{T.M.}}[\text{RZnCl}])}$$

$$= \frac{k_{\text{O.A.}}k_{\text{T.M.}}[\text{ArI}][\text{RZnCl}][\text{Pd}]_{\text{total}}}{k_{\text{O.A.}}[\text{ArI}] + k_{\text{T.M.}}[\text{RZnCl}]}$$

According to the rate law, kinetic simulation could be used to obtain the rate constants as shown in Fig. 7 and Table 1.

$$([\text{RZnCl}] = [\text{RZnCl}]_0 - [\text{ArI}]_0 + [\text{ArI}]), [\text{Pd}]_{\text{total}}$$

$$= [\text{Pd}]_0 \times (1 - k_{\text{decay}})^{94}$$

No matter which kinetic regime was chosen, the rate constant for reductive elimination of $\text{Csp}^3\text{-Pd-Csp}^2$ was determined about four orders of magnitude greater than those reported by

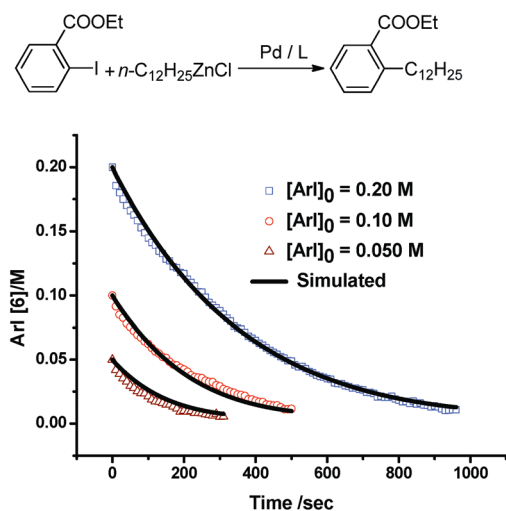


Fig. 7 The simulated curve and the experimental data of reaction between ArI and $\text{R}_{\text{alkyl}}\text{ZnCl}$. Reaction conditions: $[\text{ArI}] = 0.05\text{--}0.20\text{ M}$, $[\text{Pd}] = 1.0 \times 10^{-3}\text{ M}$, $15\text{ }^\circ\text{C}$. Reprinted (adapted) with permission from *Chem.-Eur. J.*, 2009, 3823–3829. Copyright (2009) John Wiley and Sons.

Table 1 Rate constants determined by fitting the experimental data of Fig. 7 with Dynafit

	$k_{\text{O.A.}} (\text{M}^{-1} \text{s}^{-1})$	$k_{\text{T.M.}} (\text{M}^{-1} \text{s}^{-1})$	$k_{\text{decay.}} (\text{s}^{-1})$	$k_{\text{R.E.}} (\text{s}^{-1})$
Constant	10.8	2.50	2.55×10^{-3}	$\gg 0.5^a$
Error	0.51	0.57	2.1×10^{-4}	

^a Under these conditions, the rate of reductive elimination is deemed to be much faster than oxidative addition or transmetalation, so $k_{\text{R.E.}}$ is expressed as $\gg k_{\text{O.A.}} \times [\text{ArI}]_0$ or $k_{\text{T.M.}} \times [\text{RZnCl}]_0$.

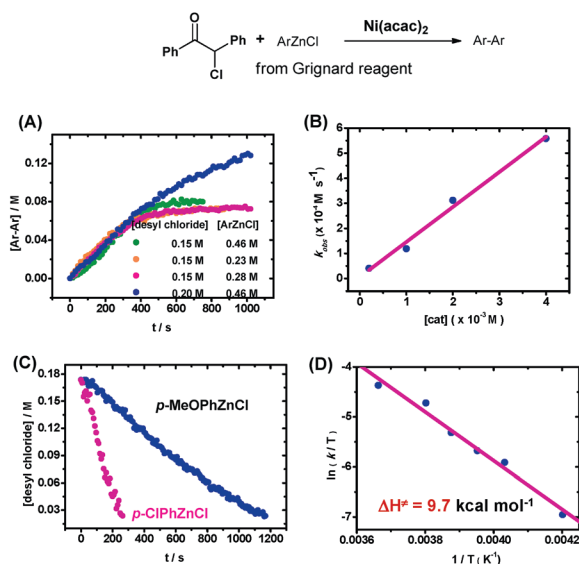


Fig. 8 Kinetic studies of Ni-catalyzed oxidative homocoupling of arylzinc. Reprinted (adapted) with permission from *J. Am. Chem. Soc.*, 2009, 131, 9892–9893. Copyright (2009) American Chemical Society.

Hartwig and about five orders of magnitude greater than those reported by Espinet. Hence, the results elucidated the promotion of olefin ligand on reductive elimination and provide significant insights into ligand design for C–C bond formation. Although the accurate rate constant for reductive elimination was not gained, the estimated range of this value was also significant from quantitative aspect.

In the above-mentioned Ni-catalyzed oxidative homocoupling of arylzinc reagents, when the arylzinc reagent was prepared from Grignard reagent, the reaction was unexpectedly fast and exhibited a zero-order kinetic behavior. This result encouraged us to gain insights into the reductive elimination of $[\text{Ar-Ni-Ar}]$, which is a vacant area for the elementary steps.³³ With desyl chloride as the oxidant, Ni-catalyzed oxidative homocoupling of ArZnCl (from Grignard reagent) was selected as the kinetic model. The reaction rate was unvaried when using different concentrations of the oxidant or arylzinc reagent (Fig. 8(A)), and first order kinetic on $[\text{Ni}]$ was observed (Fig. 8(B)) indicating that the rate law is:

$$\text{Rate} = k_{\text{obs}} = k \times [\text{Ni}]_t$$

These results showed that neither the oxidative addition nor transmetalation is rate-limiting. When using different arylzinc

reagents, the reaction rate changed. All of these kinetic results confirmed that the reductive elimination is the rate-limiting step. Therefore, temperature-dependent experiments led to quantitative investigation for reductive elimination of [Ar–Ni–Ar] and the Eyring plot revealed the enthalpy of this step as 9.7 kcal mol⁻¹. This small value suggests that the reductive elimination of [Ar–Ni–Ar] is too fast to be studied under stoichiometric experiments.

Organozinc reagents

It has been mentioned that different ways to prepare organozinc reagent have been developed.³ The most widely applied one is the transmetalation of RMgX or RLi with ZnX₂. For alkyl halides, the zinc insertion process was also widely used. Boron–zinc exchange to afford functionalized dialkylzinc reagents is another attractive methodology. Recently, Knochel has made a great contribution to the preparation of zinc reagents, leading to a more widely application of zinc reagents in synthesis.^{14–16,95}

The organozinc reagents from different preparation methods possess different reactivity and stability. The resulted or additional inorganic salts also affect the reactivity of organozinc reagent. Recently, more and more research groups have observed differences and begin to seek insights into the structure and reactivity of organozinc reagents. Kinetic investigations of the organozinc reagents from different reaction models were also discussed to reveal the nature of the organozinc reagents.

As described above, Espinet and co-workers have studied the different transmetalation of ZnMe₂ and ZnMeCl. Our group also revealed the unprecedented difference in transmetalation step of arylzinc reagent generated from Grignard reagent and aryl lithium reagent (Fig. 9).⁷⁴ The remarkable kinetic variation in Ni-catalyzed oxidative homocoupling of arylzinc reagents suggested a much more facile transmetalation step when arylzinc from Grignard reagent was used. X-ray analysis of arylzinc from Grignard reagent showed a structure of dichloro-bridged Zn–Mg complex, suggesting that MgCl₂ plays an important role in the activity of this arylzinc reagent (Fig. 10). The similar structure of alkylzinc reagent from the corresponding Grignard reagent was also confirmed by Hevia and co-workers.³¹

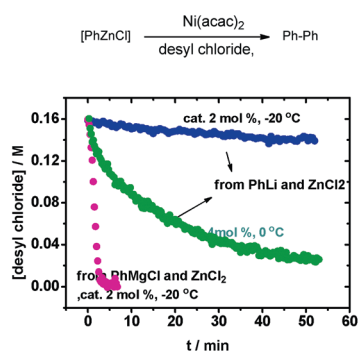


Fig. 9 Kinetic variation of arylzinc from different preparation methods. Reprinted (adapted) with permission from *J. Am. Chem. Soc.*, 2009, **131**, 16656–16657. Copyright (2009) American Chemical Society.

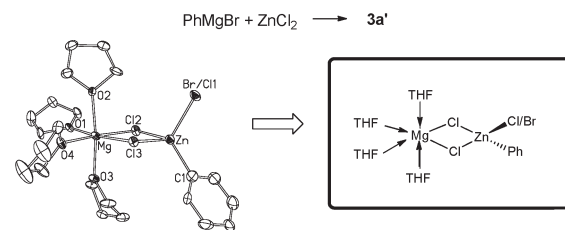


Fig. 10 X-ray analysis of PhZnX prepared from PhMgX. Reprinted (adapted) with permission from *J. Am. Chem. Soc.*, 2009, **131**, 16656–16657. Copyright (2009) American Chemical Society.

Knochel's group has compared the basicity of different organozinc reagents and their stability toward acidic protons in palladium-catalyzed cross-coupling of organozinc reagent with unsaturated aryl halides. The relative kinetic basicity of the organozinc compounds was established to be arylzinc halide > alkylzinc halide > benzylic zinc halide.⁹⁶

Through electrospray ionization mass spectrometry (ESI-MS), electrical conductivity measurements, and NMR, Koszinowski and co-workers investigated the effect of LiX on organozinc reagent. They proposed that lithium organozincate complexes LiRZnX₂ could be formed when LiX was mixed with pure alkylzinc reagent.^{30,35,36,42} Organ and co-workers postulated a higher-order zincate of the type Li_mZn(ⁿBu)Br₃^{(2–m)+} as the active transmetalating agent in Pd/NHC-catalyzed alkyl–alkyl coupling.³² Mass spectrometry and NMR spectroscopy identified the species and clarified that highly polar solvent could stabilize the higher order zincate.

Conclusions

As an efficient protocol towards C–C bond formations, the Negishi coupling has been widely used in both laboratory and industry, in which most efforts were devoted to methodology exploration. Recently, mechanistic investigation has attracted more and more attention due to its importance. As an important aspect in mechanistic study, the kinetic approach served as a powerful tool to elucidate the elementary steps of the Negishi coupling. Moreover, it is crucial to investigate the elementary steps from the conditions close to the live reaction conditions as much as possible. It is believed that detailed understanding of the Negishi coupling would further promote the development of the Negishi coupling, which will also provide significant and suggestive clues on the mechanism.

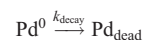
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This process was regarded to be a unimolecular transformation and exhibit a first-order kinetic behavior on $[\text{Pd}^0]$. The decomposition rate should be expressed as: $\text{rate}_{\text{decay}} = k_{\text{decay}} \times [\text{Pd}^0]$.

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