Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers

Supporting Information

Transmetalation of Ar^1ZnX with $[Ar^2\text{-}Pd\text{-}X]$ is the Rate-Limiting Step: Kinetic Insights from a Live Pd-Catalyzed Negishi Coupling

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Analytical methods and reagents.

All reactions and manipulations were conducted in a nitrogen-filled self-prepared three-necked micro reactor. IR spectra were recorded on a Mettler Toledo React IR™ 15 spectrometer using a diamond comb. Yields of Ar^1-Ar^2 were obtained from GC and naphthalene was added as internal standard. All glasswares were oven dried at 120 °C for more than 1 hour prior to use. THF was dried and distilled from sodium/benzophenone ketyl in nitrogen atmosphere. Anhydrous $ZnCl_2$ was from commercial source (Alfa Aesar 98+%) and used without further purification. $Pd(OAc)_2$ was commercial available. All arylzinc reagents were prepared from the corresponding aryl lithium with $ZnCl_2$ and the concentration was based on the titration by I_2 / LiCl.[1]

Preparation of arylzinc reagents.

To a 100 mL Schlenk flask was added aryl bromide (20 mmol) and THF (7.5 mL) in nitrogen atmosphere. The mixture was allowed to stir at -78 °C for 5 min. Butyllithium (2.4 M solution in hexanes J&K, 21 mmol) was added slowly via a syringe. 2 h later, the solution of $ZnCl_2$ (24 mmol, in 30 mL THF (as the solvent)) was injected to the flask. The mixture temperature was allowed to increase to room temperature. After stirring for about 1 h, the arylzinc reagent concentration was identified basing on the titration by I_2 / LiCl.[1]

General procedure of Pd-catalyzed Negishi cross-coupling reactions.

In an oven dried self-prepared three-necked micro reactor with a magnetic stirrer, naphthalene (64 mg) as the internal standard was added. The reactor was allowed to be vacuumed and purged with nitrogen for several times. The arylzinc reagent (0.35 M in THF, 4.0 mL) and ethyl 4-iodobenzoate (0.50 mmol, 138 mg) were added in via a syringe. The mixture was allowed to stir at 10 °C and recorded by React IR. At the same time, $Pd(OAc)_2$ (5.2×10^{-6} M in THF, 100 μL) was added quickly in by a micro syringe. The course of the reaction could be observed from the characteristic IR absorption of ethyl 4-iodobenzoate or product. When ethyl 4-iodobenzoate was consumed completely, or the product did not increase, the reaction was quenched by diluted hydrochloric acid and the yield of product was determined by GC.

Other reactions followed the same procedure under different reaction conditions.

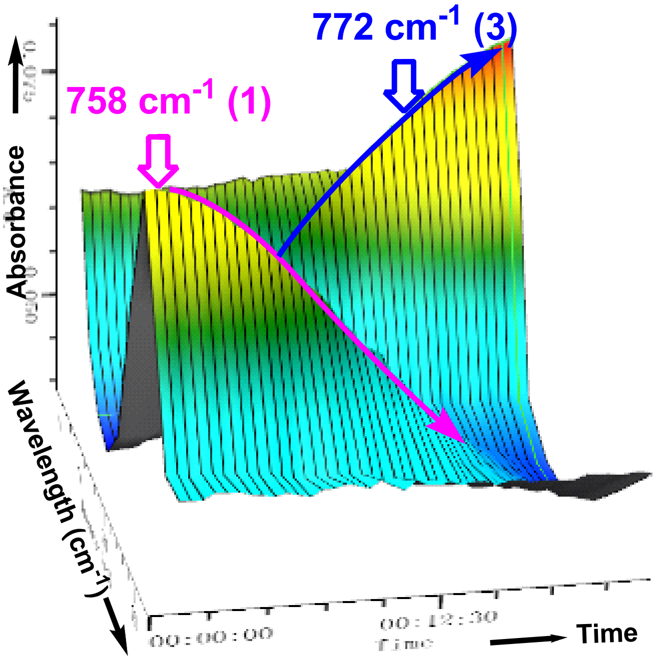


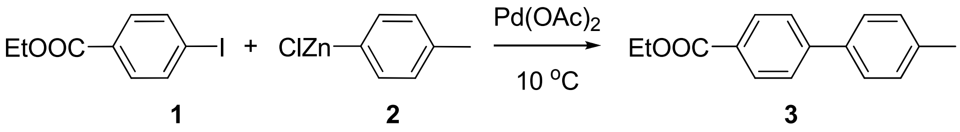
Figure S1. The characteristic IR absorptions of **3** and **2**.

Following general procedure, the course of the reactions was observed from the characteristic IR absorption of product (**3**).

Pd-catalyzed Negishi cross-coupling of *p*-tolylzinc(II) chloride with ethyl 4-iodobenzoate.

Following the general procedure, Pd-catalyzed Negishi cross-couplings of *p*-tolylzinc(II) chloride with ethyl 4-iodobenzoate were carried out under different catalyst loadings. The TON increased up to 290,000 as shown in Table S1.

Table S1. Pd-catalyzed Negishi coupling between **1** and **2** under different catalyst loadings.[a]

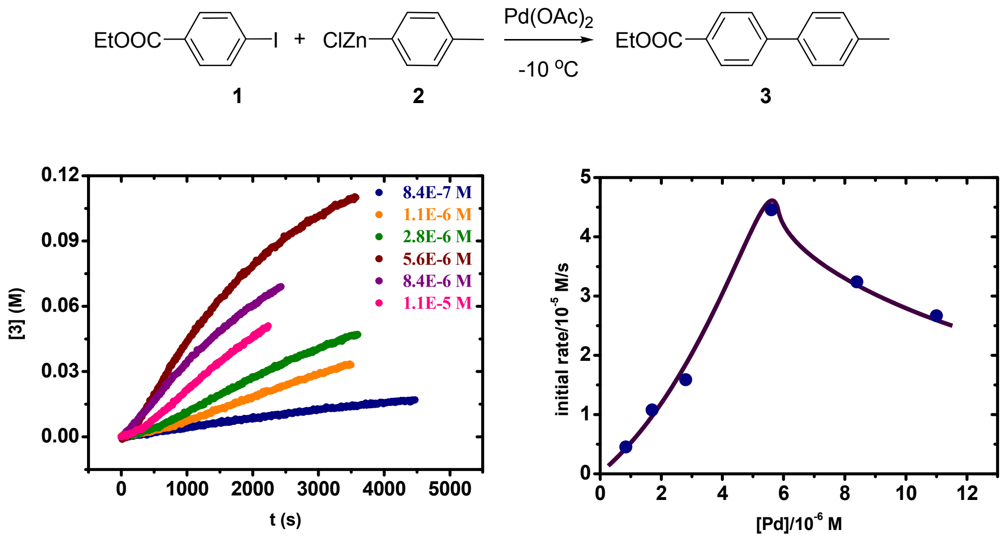


entry	cat / mol%	yield/%	TON
1	3.3E-4	97	289706
2	6.7E-4	73	109013
3	1.0E-3	92	91591
4	1.3E-3	99	73920
5	1.8E-3	94	52640
6	2.2E-3	96	43008
7	2.9E-3	96	33083
8	3.6E-3	76	21280
9	4.5E-3	85	19040
10	5.5E-3	82	14694

[a] ethyl 4-iodobenzoate (1.0 mmol, 0.25 M in THF), *p*-Me C_6H_4ZnCl (0.34 M in THF, 4.0 mL), 10 °C, GC yields with naphthalene as the internal standard.

Kinetic studies of Pd-catalyzed Negishi cross-coupling of *p*-tolylzinc(II) chloride with ethyl 4-iodobenzoate under different concentrations of catalyst.

I

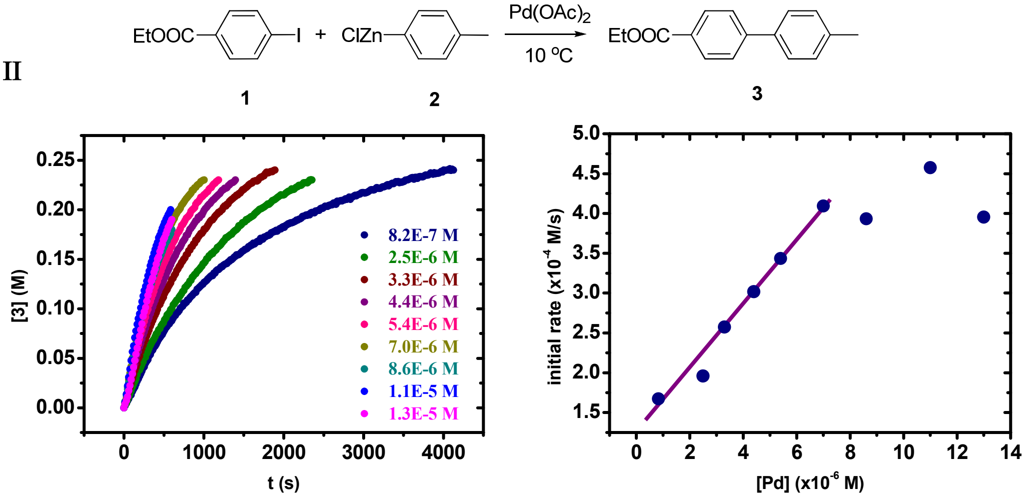


(A)

(B)

Figure S2-I. Kinetic profiles of the Negishi cross-coupling of *p*-MeC_6H_4ZnCl (0.28 M in THF, 4.0 mL) with ethyl 4-iodobenzoate (0.12 M in THF, 0.5 mmol) under different concentrations of $Pd(OAc)_2$ (8.2×10^{-7} M – 1.1×10^{-5} M), -10 °C, N_2.

II



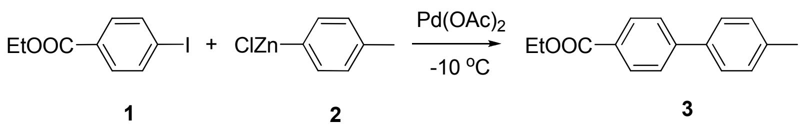
(A)

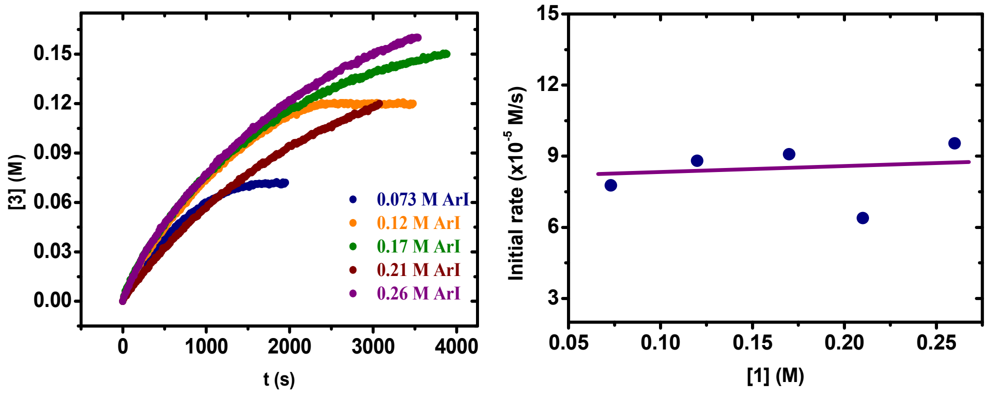
(B)

Figure S2-II. Kinetic profiles of the Negishi cross-coupling of *p*-MeC_6H_4ZnCl (0.34 M in THF, 4.0 mL) with ethyl 4-iodobenzoate (0.25 M in THF, 1.0 mmol) under different concentrations of $Pd(OAc)_2$ (8.2×10^{-7} M – 1.3×10^{-5} M in THF), 10 °C, N_2.

Following general procedure, kinetic experiments of Pd-catalyzed coupling between **1** and **2** under different concentrations of Pd have been carried out. According to Figure S1, it was revealed that when the concentration of Pd < 8.6×10^{-6} M, plotting the initial rates *vs* [Pd] obtained a linear relationship, suggesting that the reaction was first-order dependent on Pd concentration([Pd] ≦7.0×10^{-6} M) (Figure S2-II (**B**)). Higher concentration of Pd resulted in a complicated kinetic dependence. In that regards, the following kinetic experiments were performed under lower Pd concentration ([Pd] ≦7.0×10^{-6} M).

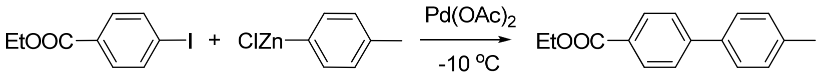
Kinetic studies of Pd-catalyzed Negishi cross-coupling of *p*-tolylzinc(II) chloride with ethyl 4-iodobenzoate under different concentrations of ethyl 4-iodobenzoate and arylzinc.



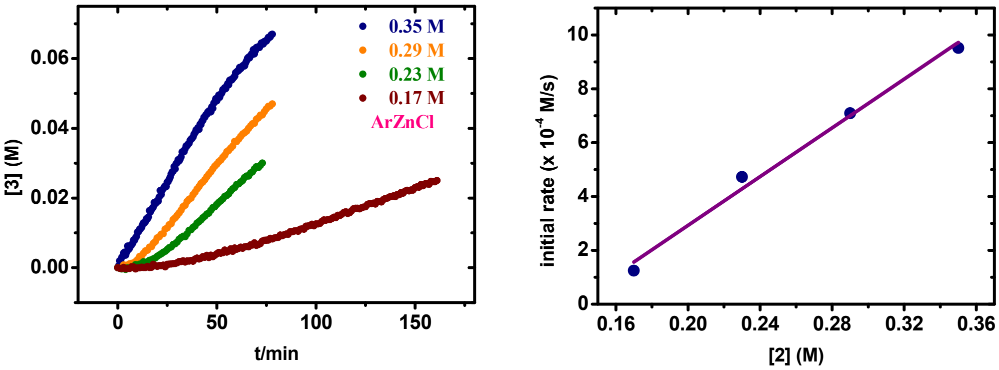


(**A**) (**B**)

Figure S3. Kinetic profiles of the Negishi cross-coupling between **1** (0.073 M – 0.26 M in THF) and **2** (0.33 M in THF, 4.0 mL), $Pd(OAc)_2$ (5.2×10^{-6} M in THF), -10 °C.



1 **2** **3**

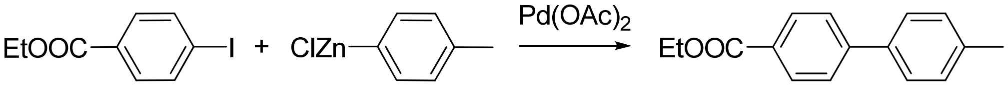


(A) (B)

Figure S4. Kinetic profiles of the Negishi cross-coupling of **1** (0.082 M in THF), **2** (0.17 M – 0.35 M in THF, 6.0 mL), $Pd(OAc)_2$ (6.6×10^{-6} M in THF), -10 °C.

Following the general procedure, the Negishi cross-coupling reactions with different concentrations of ethyl 4-iodobenzoate and *p*-MeC_6H_4ZnCl were carried out and the kinetic profiles were shown in the Figure S3 and Figure S4, respectively. It was clearly shown that the initial rates were identical when varying the concentrations of ethyl 4-iodobenzoate. In other words, the reaction displayed zero-order kinetic behavior of ethyl 4-iodobenzoate. Plotting the initial rates *vs* concentration of arylzinc obtained a linear relationship (Figure S4), suggesting that the reaction was first-order dependent on *p*-MeC_6H_4ZnCl.

Kinetic studies of Pd-catalyzed Negishi cross-coupling of *p*-tolylzinc(II) chloride with ethyl 4-iodobenzoate at different temperatures.



1 **2** **3**

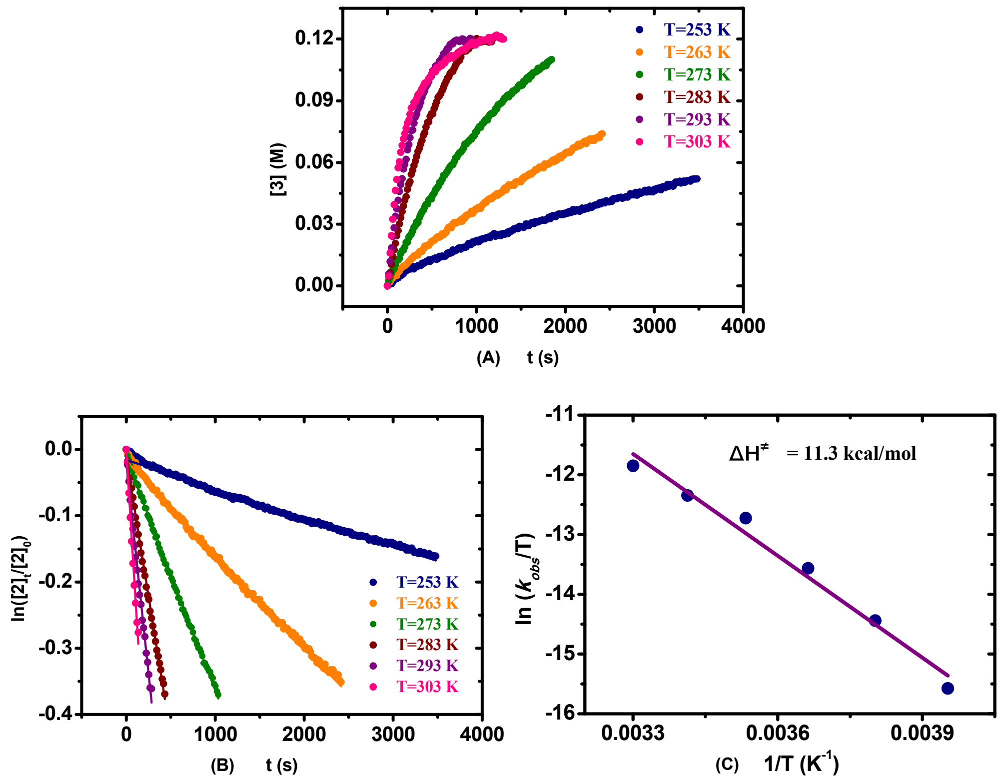


Figure S5 Kinetic investigation of Pd-catalyzed Negishi cross-coupling of **2** with ethyl **1** at different temperatures. **1** (0.12 M in THF), **2** (0.25 M in THF, 4.0 mL), $Pd(OAc)_2$ (5.2×10^{-6} M in THF), N_2. **(A)** Kinetic plots of [**3**] *vs* t. **(B)** Kinetic plots of ln ($[\mathbf{2}]_t/[\mathbf{2}]_0$) *vs* t. **(C)** Plots of ln (k_{obs}/T) *vs* (1/T).

Following the general procedure, these reactions were carried out under different temperature. According to the concentration of product, the concentration of *p*-Me C_6H_4ZnCl could be derived as the formula:

$$[\mathbf{2}] = [\mathbf{2}]_{t=0} - [\mathbf{3}]$$

The rate constants k_{obs} could be obtained plotting ln ($[\mathbf{2}]_t/[\mathbf{2}]_0$) *vs* t (Figure S5 (**B**)). Plots of ln (k_{obs}/T) *vs* (1/T) gave a linear relationship. According to Eyring Equation, activation enthalpy $\Delta H^{\neq}$ could be obtained (Table S2).

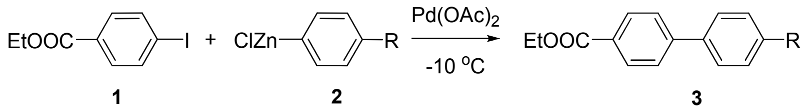
Table S2. Kinetic parameters.

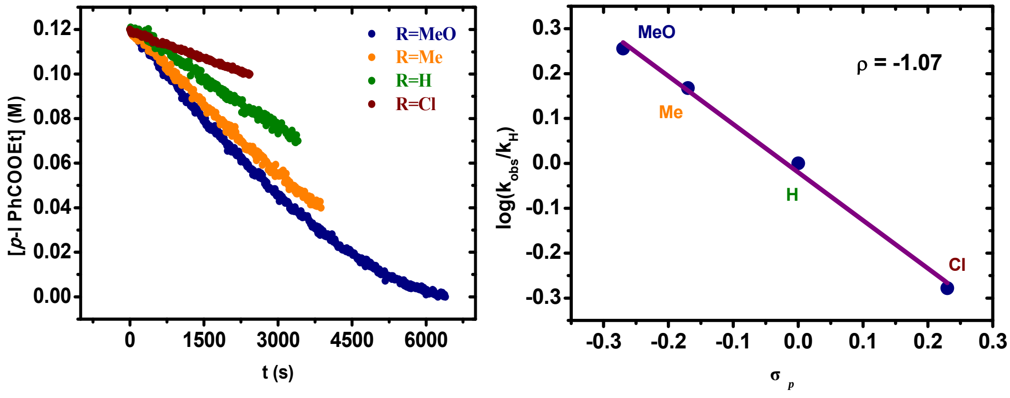
According to Eyring Equation:

$$\ln\frac{k}{T} = -\frac{\Delta H^{\neq}}{R}\times\frac{1}{T} + \ln\frac{k_B}{h} + \frac{\Delta S^{\neq}}{R}$$

T (K)	k_{obs} (s^{-1})	1/T (K^{-1})	ln(k_{obs}/T)	ΔH$^{\neq}$ (kcal/mol)
253	4.4E-5	0.00395	-15.57508	**11.3**
263	1.4E-4	0.00380	-14.44061	
273	3.5E-4	0.00366	-13.56435	
283	8.4E-4	0.00353	-12.72579	
293	12.7E-4	0.00341	-12.34667	
303	21.6E-4	0.00330	-11.85053	

Kinetic studies of Pd-catalyzed Negishi cross-coupling of ethyl 4-iodobenzoate with different arylzinc reagents.





(A)

(B)

Figure S6 (**A**) Kinetic profiles of [ethyl 4-iodobenzoate] *vs* t in Pd(OAc)$_2$-catalyzed Negishi cross-coupling of different arylzinc reagents. Ethyl 4-iodobenzoate (0.12 M in THF), ArZnCl (0.31 M in THF, 4.0 mL), Pd(OAc)$_2$ (5.2×10^{-6} M in THF), -10 °C. (**B**) Hammett correlation.

Pd-catalyzed Negishi cross-coupling reactions with *p*-MeOC$_6$H$_4$ZnCl, *p*-Me C$_6$H$_4$ZnCl, PhZnCl and *p*-ClC$_6$H$_4$ZnCl were carried out according to the general procedure. As shown in Figure S6, a linear free energy relationship was observed with a calculated ρ-value of -1.07. The electron-efficient arylzinc reagent displayed faster reaction rates than electron-deficient arylzinc reagent. The result further supported that the transmetalation was the rate-limiting step.

References

(1) Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890-891.