Effective Pd-Nanoparticle (PdNP)-Catalyzed Negishi Coupling Involving Alkylzinc Reagents at Room Temperature
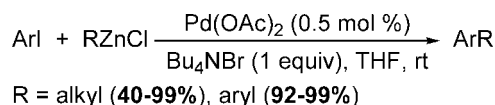
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ABSTRACT

$$ArI + RZnCl \xrightarrow[\text{Bu}_4\text{NBr (1 equiv), THF, rt}]{\text{Pd(OAc)}_2\ (0.5\ \text{mol \%})} ArR$$

R = alkyl (**40-99%**), aryl (**92-99%**)

Pd(OAc)$_2$ is an efficient catalyst precursor for Negishi coupling in the presence of Bu$_4$NBr. Secondary and primary alkylzinc reagents with β-H and arylzinc reagents all reacted with aryl iodides at temperatures as low as $-20\ °C$, giving moderate to good yields. One example of coupling between alkynylzinc reagents and aryl iodides was tested and the yield was good. Preliminary kinetic studies indicated that the process involved PdNPs as the active catalytic species.

Negishi coupling, one of the most efficient methods to construct carbon–carbon bonds, was first developed in 1977.[1,2] From then on, extensive investigations have been carried out to extend the scope and application of the method. Reactions involving alkenyl-, aryl-, and alkynylzinc reagents and in some cases alkylzinc reagents[3] have been achieved with high yields and good functional group tolerance. Recently, by employing sterically hindered and/or electronically rich ligands, some efficient processes involving Csp^3-coupling were developed.[4–14] In addition, employing olefin-type ligands with Pd and Ni was proven by Knochel et al.[15–19] to be an effective manner to facilitate Csp^3-related couplings.

During the past two decades, there have been increasing amounts of literature about nanoparticles (NPs) of transition metals which could catalyze reactions efficiently with low loadings.[20–23] Stabilizers of NPs are often used to prevent them from further agglomeration and precipitation from the reaction system, and meanwhile allow the reactants to access their surfaces. Among the stabilizers, commercially available and inexpensive tetraalkylammonium halides are common.[24–27] Pincer–Pd complexes, palladacyles, and ligand free Pd precursors such as Pd(OAc)$_2$ and Pd/C have been investigated or proposed to form PdNPs by reduction or thermal decomposition followed by aggregation, mostly in Heck, Suzuki, and Sonogashira reactions.[23,28–52] To the best of our

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knowledge, there have been few reports about application of PdNPs in the Negishi reaction. Ligand-free Pd(OAc)$_2$-catalyzed Negishi couplings under homeopathic conditions from 25 to 100 °C to prepare biaryls were reported once.[53] Fu et al. had demonstrated an elegant example of Negishi couplings between alkyl electrophiles and organozirconium reagents under "ligandless" conditions in 2004.[54] Recently, we discovered that ligand-free Pd(OAc)$_2$ could efficiently promote Negishi reactions of alkyl-, aryl-, and alkynylzinc reagents. Herein, we communicate our results.

When the reaction of ethyl 2-iodobenzoate **1a** with *n*-dodecylzinc chloride **2a** was monitored by in situ IR, we surprisingly found that the reaction proceeded quickly and produced ethyl 2-dodecylbenzoate **3a** in high yield using Pd(OAc)$_2$ as a catalyst precursor and a stoichimetric amount of Bu$_4$NBr as an additive. Pd(OAc)$_2$ (0.5 mol %) promoted

Table 1. PdNP-Catalyzed Negishi Coupling of Aryl Iodides with Primary Alkylzinc Reagents[a]

$$\text{ArI} + \text{RZnCl} \xrightarrow[\text{Bu}_4\text{NBr (1 equiv), THF, rt}]{\text{Pd(OAc)}_2\ (0.5\ \text{mol \%})} \text{ArR}$$

entry	ArI	RZnX	product	yield[b]
1	(1a)	*n*-BuZnCl (2b)	(3b)	79%
2	1a	(2c)	(3c)	99%
3	1a	(2d)	(3d)	95%
4	1a	(2e)	(3e)	85%
5	(1b)	2c	(3h)	45%
6	(1c)	2b	(3f)	95%
7	(1d)	2b	(3g)	0

[a] Reaction conditions: aryl iodide (1 mmol), alkylzinc reagent (2 mmol), Pd(OAc)$_2$ (0.005 mmol), Bu$_4$NBr (1 mmol) at rt. [b] Isolated yield.

the reaction to completion in 32 s at 25 °C, and gave 92% yield (see Figure 1 in the Supporting Information). Importantly, alkylzinc reagents with β-H tend to undergo β-H elimination to give dehalogenated byproducts in many cases, but in our system, only 8% of ethyl benzoate (determined by GC) was detected.

Without further optimization, the substrate scope of the reaction involving aryl iodides and primaryl alkylzinc reagents was examined. At 25 °C, 0.5 mol % of Pd(OAc)$_2$ promoted the Csp^3–Csp^2 coupling smoothly. Ethyl 2-iodobenzoate **1a** reacted with primary alkylzinc chlorides in excellent yields (Table 1, entries 1–4). Ethyl 4-iodobenzoate **1b** gave moderate yield (Table 1, entry 5). However, the reaction involving the electron-rich electrophile 2-iodoanisole **1d** was unsatisfactory (Table 1, entry 7).
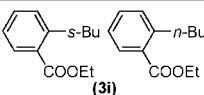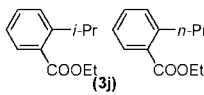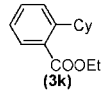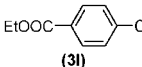
When secondary cyclohexylzinc chloride **2i** was utilized as the nucleophile, coupling with **1a** proceeded smoothly in 98% yield (Table 2, entry 4). The reaction of *sec*-butylzinc chloride **2f** and **1a** produced the desired product in 96% isolated yield, yet the selectivity (ratio of ethyl 2-*sec*-butylbenzoate and ethyl 2-butylbenzoate) was poor (Table

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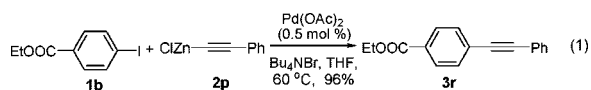**Table 2.** PdNP-Catalyzed Negishi Coupling of Aryl Iodides with Secondary Alkylzinc Reagents[a]

entry	ArI	Zinc reagent	product	yield[b]
1	1a	sec-BuZnCl (2f)	s-Bu / n-Bu (COOEt) (3i)	96% (53 : 47)[c]
2	1a	(sec-Bu)₂Zn (2g)	3i	95% (81 : 19)[c]
3	1a	(i-Pr)₂Zn (2h)	i-Pr / n-Pr (COOEt) (3j)	99% (74 : 26)[c]
4	1a	CyZnCl (2i)	Cy (COOEt) (3k)	98%
5	1a	(Cy)₂Zn (2j)	3k	94%
6	1b	2j	EtOOC—Cy (3l)	57%

[a] Reaction conditions: aryl iodide (1 mmol), alkylzinc reagent (2 mmol), Pd(OAc)₂ (0.005 mmol), Bu₄NBr (1 mmol) at rt. [b] Isolated yield. [c] The data in parentheses are ratios of isomerized to unisomerized product, determined by GC. For example, the ratio between ethyl sec-butylbenzoate and ethyl n-butylbenzoate was 53:47 (entry1).

Table 3. PdNP-Catalyzed Negishi Coupling of Aryl Iodides with Arylzinc Reagents[a]

$$ArI + Ar'ZnX \xrightarrow[\text{Bu}_4\text{NBr (1 equiv), THF, rt}]{\text{Pd(OAc)}_2 \text{ (0.5 mol \%)}} ArAr'$$

entry	ArI	Ar'ZnX	Ar'ZnX	yield[b]
1	1b	(2k)	(3m)	99%
2	1b	(2l)	(3n)	99%
3	1b	OMe (2m)	OMe (3o)	99%
4	MeO— (1e)	2k	(3p)	92%
5	1e	2l	(3q)	95%

[a] Reaction conditions: aryl iodide (1 mmol), arylzinc reagent (2 mmol), Pd(OAc)₂ (0.005 mmol), Bu₄NBr (1 mmol) at rt. [b] Isolated yield.

2, entry 1) as a result of β-H elimination/alkene reinsertion preceding reductive elimination. However, under otherwise identical conditions, (s-Bu)₂Zn **2g** gave 95% product along with improved selectivity (Table 2, entry 1 vs entry 2). Similar results were obtained when (iPr)₂Zn **2h** was employed as the nucleophile (Table 2, entry 3). The reaction of **1a** with Cy₂Zn **2j** gave a satifactory yield, while a moderate yield was obtained when ethyl 4-iodobenzoate **1b** was used as the electrophile.

For reactions between aryl iodides and arylzinc reagents, both electron-deficient and electron-rich aryl iodides were suitable substrates, and arylzinc reagents with ortho substituents also gave excellent yields (Table 3, entries 2, 3, and 5).

When the reaction of phenylethynylzinc chloride **2p** with ethyl 4-iodobenzoate **1b** was tested, no product was detected at 25 °C. Raising the temperature to 60 °C improved the yield to 96% (eq 1). Currently, there are not enough data to rationalize the reactivity differences between alkynylzinc reagents and arylzinc or alkylzinc nucleophiles.
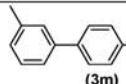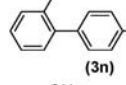
$$\text{EtOOC—}\bigcirc\text{—I} + \text{ClZn—}\!\!\equiv\!\!\text{—Ph} \xrightarrow[\text{Bu}_4\text{NBr, THF,}]{\text{Pd(OAc)}_2 \text{ (0.5 mol \%)}} \text{EtOOC—}\bigcirc\text{—}\!\!\equiv\!\!\text{—Ph} \quad (1)$$
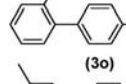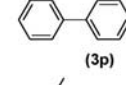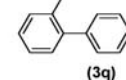1b · 2p · 60 °C, 96% · 3r

To gain some preliminary understanding of this Pd(OAc)₂-catalyzed Negishi coupling, we further followed the progress

of the reactions between ethyl 2-iodobenzoate **1a** and CyZnCl **2i** in the presence of 0.5 mol % of Pd(OAc)₂ using in situ IR. The conversion of **1a** at 25 °C reached 60% after only 30 s, and 100% after 2 min (Figure 1, black line). A similar kinetic plot was obtained at a reaction temperature of 0 °C (Figure 1, red line). Surprisingly, the reaction proceeded smoothly even at −20 °C, and reached 100% conversion of **1a** after 30 min with 97% GC yield (Figure 1, blue line).

Figure 1. Conversion of **1a** vs time curve for the reaction of **1a** [0.33 M] with **2i** [0.65 M], with 0.5 mol % Pd(OAc)₂ as the catalyst precursor in the presence of 1 equiv of Bu₄NBr monitored by in situ IR at different temperatures.

At −20 °C, the rate increased during the first 15 min and a sigmoidal curve throughout the reaction was observed. To probe whether Pd(NPs) were involved in the transformation above, a quantitative ligand poisoning experiment, shown to be an effective method to establish the presence of NPs in the reaction system,[55] was conducted. PPh₃ (0.5 equiv) [vs Pd(OAc)₂)] was added to the reaction system with [Pd(OAc)₂]

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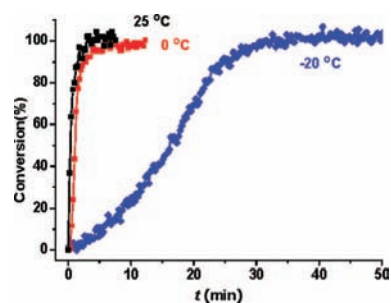(54) Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82–83.
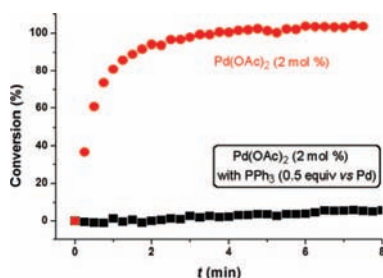
Figure 2. Conversion of **1a** vs time curve for the reaction of **1a** [0.33 M] with **2i** [0.65 M], with 2 mol % of Pd(OAc)$_2$ as the catalyst precursor in the presence of 1 equiv of Bu$_4$NBr monitored by in situ IR at rt. Black line: 1 mol % PPh$_3$ was present.
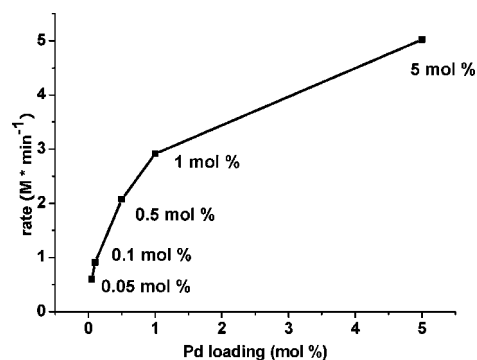

Figure 3. Rate vs Pd loading curve for reactions of **1c** [0.16 M] and **2i** [0.29 M] with different concentrations of Pd(OAc)$_2$ in the presence of 1 equiv of Bu$_4$NBr monitored by in situ IR at −20 °C.

= 1.45 mM, [CyZnCl] = 0.65 M in 3 mL of THF, and the mixture was stirred for 5 min. After that, 0.92 mmol of **1a** was added to initiate the reaction. The reaction rate was much slower than the control without PPh$_3$ (Figure 2), the convesion was less than 10% after 8 min, and only 4% cross-coupled product together with 6% ethyl benzoate was detected by GC. The results strongly supported PdNPs as being the active catalytic species.

Generally, PdNPs are proposed to form by aggregation of naked Pd(0) reduced from soluble Pd(II) species. The process usually involves multipile naked Pd(0) interactions, and the amount of active Pd on the surface of the PdNPs is not first order in the concentration of the original Pd(II) complex. As a result, the rate of the reaction catalyzed by PdNPs is not first order in the concentration of the catalyst precursor, while in homogeneous catalytic systems, the reaction rate is usually first order in catalyst concentration.[36,51,56–58] Kinetic studies of the reaction between **1c** and **2i**, carried out with [**1a**] = 0.16 M, [**2i**] = 0.29 M, [Bu$_4$NBr] = 0.16 M, and [Pd(OAc)$_2$] = 0.08−8 mM (0.05−5 mol %) at −20 °C, indicated that the rate was not first order in [Pd(OAc)$_2$] (Figure 3), further supporting the notion that this system is heterogeneous rather than homogeneous. Indeed, the reaction with 5 mol % of Pd(OAc)$_2$ was only 1.7-fold faster than the one with 1 mol % of Pd(OAc)$_2$ (Figure 3). Though further lowering the catalyst loading reduced the reaction rate, the reaction was still fast even with only 0.05 mol % of Pd(OAc)$_2$.

Bu$_4$NBr has been used as an additive in many "ligand free" palladium catalytic systems, and was speculated to stablize the PdNPs from further aggregation.[59] To test the effect of Bu$_4$NBr in our system, we compared the reactions of methyl 2-iodobenzoate **1c** with CyZnCl **2i** in the presence of 0.5 mol % of Pd(OAc)$_2$ at −20 °C with or without Bu$_4$NBr. Though the yields were almost the same, the kinetic profiles

of the two reactions monitored by in situ IR were obviously different (see Figure 2 in the Supporting Information). With 1 equiv of Bu$_4$NBr, the reaction rate decreased when the conversion reached ca. 72%, while the reaction rate decreased from ca. 44% conversion without Bu$_4$NBr. Moreover, the maxmium reaction rate with Bu$_4$NBr was around 3 times faster than that without Bu$_4$NBr. The differences indicated that the Pd catalyst in the reaction system without Bu$_4$NBr was more prone to aggregate and lose reactivity. In addition, we examined the reaction of **1a** with **2i** using Pd(OAc)$_2$ loadings of 0.1, 0.01, and even 0.001 mol % at room temperature in the absence of Bu$_4$NBr. Although reproducibility of conversion vs time varied somewhat over 3 runs at each concentration, reproducible isolated yields of 92%, 91%, and 94% were obtained at 0.01 mol % loading, and up to 82% with 0.001 mol % loading. The key point to note is that with this combination of reagents, only a few percent of the hydrodehalogenated side product was observed in any case.

In conclusion, Pd(OAc)$_2$ is an efficient catalyst for Negishi coupling. Secondary and primary alkylzinc reagents with β-H were suitable nucleophiles to react with aryl iodides, and the yields of the $\mathrm{Csp^2}$−$\mathrm{Csp^3}$ coupling were moderate to excellent. In addition, the protocol has also been successfully applied in $\mathrm{Csp^2}$−$\mathrm{Csp^2}$ and Csp−$\mathrm{Csp^2}$ couplings. Preliminary kinetic results indicated that the process involved PdNPs as the active catalytic species, and the reaction was very efficient even with only 0.05 mol % of Pd(OAc)$_2$ in the presence of Bu$_4$NBr or 0.01 mol % of Pd(OAc)$_2$ in the absence of Bu$_4$NBr at room temperature.

Supporting Information Available: General procedure for the Negishi couplings, in situ IR, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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