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Surfactant-free synthesis of palladium nanoclusters for their use in catalytic cross-coupling reactions[†]

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Surfactant-free Pd nanoclusters (Pd NCs) (size: 1–1.5 nm) showed high catalytic activity in the Suzuki–Miyaura cross-coupling and Mizoroki–Heck reactions. The Pd NCs had a high turnover number, up to 6.0×10^8 , which can be recycled at least five times without loss of catalytic activity.

Small colloidal metal nanoclusters (NCs) (<2 nm) have attracted much interest in catalytic applications because of their high surface-to-volume ratio and their high surface energy that makes their surface atoms very active,1 which have different properties from metal nanoparticles with larger sizes (3-100 nm). To date, various methods for the preparation of colloidal metal nanoparticles (NPs) have been reported,² but they additionally suffer from significant corrosion and stability problems. Metal NPs are prone to loss of reactivity because they precipitate or aggregate as bulk metals, so stabilizers such as functionalized polymers,³ dendrimers,⁴ inorganic solids⁵ (e.g., carbon, metal oxides, sol-gel clays, and zeolites), ligands⁶ (e.g., pincer ligands), or ionic surfactants⁷ are generally used in their preparation, and utilized as catalysts in cross-coupling reactions.^{3,4a-d,5b,6,7a,8} Therefore, we need to develop an innovative preparation method for surfactant-free and stable metal nanoclusters with minimum surface deactivation for the highly active catalyst. Here, we report the first example of a solution synthesis of DMF-protected Pd NCs with sizes of 1-1.5 nm using a surfactant-free DMF reduction method.⁹ We found substantially enhanced catalytic activity of the Pd NCs in Suzuki-Miyaura, and Mizoroki-Heck cross-coupling reactions, and the Pd NCs had a high turnover number, up to 4.5×10^5 and 6.0×10^8 , respectively. The Pd NCs catalysts can be recycled at least five times without loss of catalytic activity in the Suzuki-Miyaura cross-coupling reaction.

The preparation of Pd NCs is as follows. A solution of 150 μ L of 0.1 M aqueous PdCl₂ was added to 15 mL of DMF at 140 °C; the DMF solution was heated under reflux at 140 °C for 6 h. The resulting yellow solution contained photoluminescent Pd

NCs; the maximum emission wavelengths were around 460 nm at a UV excitation of 350 nm (Fig. 1, right). This photoluminescence may have originated from the size-dependent effect of the metal clusters when the free electrons are confined to the Fermi wavelength in the cluster conduction band.¹⁰ The high-resolution transmission electron microscope (HRTEM) image of the Pd NCs shows numerous nanoparticles of size approximately 1–1.5 nm (Fig. 1, left), and these small nanoparticles were confirmed to be Pd species by transmission electron microscopy-energy dispersive X-ray (TEM-EDX) analysis (Fig. S2, ESI†).

The Pd NCs prepared above were evaluated as catalysts for Suzuki-Miyaura¹¹ and Mizoroki-Heck cross-coupling reactions,¹² which are versatile methods for carbon-carbon bond formation in organic synthesis. The results for the Suzuki-Miyaura crosscoupling reaction are shown in Table 1. For instance, the reaction of iodotoluene (1a: 0.5 mmol) with phenylboronic acid (2a: 0.75 mmol) was performed in the presence of a Pd NCs catalyst (0.2 mol% based on 1a used) and K₂CO₃ (0.5 mmol) in NMP/H₂O (1 : 1, 2 mL) at 100 °C for 5 h, giving 3a in 86% yield (entry 1, Table 1). When the catalyst loading was further decreased to 0.002 mol%, the reaction proceeded efficiently with 81% yield (entry 2, Table 1). Next, the solvent was evaporated under vacuum from Pd NCs (1 mM) synthesized in DMF, and the residue was redissolved in selected solvents such as N-methylpyrrolidone (NMP), methanol (MeOH), and tetrahydrofuran (THF). When Pd NCs using NMP as the solvent were used, the reaction was promoted to give 3a in quantitative vield and 95% isolated vield (entry 3, Table 1). The reaction using MeOH was also efficient, giving 92% yield (entry 4, Table 1). In contrast, THF was less effective in this reaction,



Fig. 1 Left: HRTEM image of DMF-protected Pd NCs. Bar length: 2 nm (\times 4500000); right: a photograph of colloidal Pd NCs (1 mM in DMF) under UV light.

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[†] Electronic supplementary information (ESI) available: TEM image, UV-visible absorption spectra and photoluminescence emission spectra; experimental and characterization data and original ¹H and ¹³C NMR spectra for products **3a–3i** and **5a–5h**. See DOI: 10.1039/c1cc11487e

Table 1Pd-NCs-catalyzed Suzuki-Miyaura cross-coupling reactionof iodotoluene (1a) with phenylboronic acid $(2a)^{\alpha}$

-() +) 1a 2a	$B(OH)_2 \frac{\text{cat. Po}}{\text{K}_2 \text{CO}_3,}$	Solvent C, 5 h	J-C) 3a
Entry	Pd NCs (mol%)	Solvent	Yield $3a^{b}$ (%)	TON ^c
1	2×10^{-1}	DMF/H ₂ O	86	4.3×10^{2}
2	2×10^{-3}	DMF/H ₂ O	81	4.1×10^{4}
3	2×10^{-3}	NMP/H ₂ O	>99 (95)	$> 5.0 \times 10^4$
4	2×10^{-3}	MeOH/H ₂ O	92	4.6×10^{4}
5	2×10^{-3}	THF/H ₂ O	56	2.8×10^{4}
6	2×10^{-4}	NMP/H ₂ O	89	4.5×10^{5}
7^d	2×10^{-3}	NMP/H_2O	86	4.9×10^{4}

^{*a*} Conditions: **1a** (0.5 mmol) was allowed to react with **2a** (0.75 mmol) in the presence of 1 mL of Pd NCs catalyst solution (1 mM–1 μ M) and K₂CO₃ (0.5 mmol) in solvent (1 mL)/H₂O (1 mL) at 100 °C for 5 h. ^{*b*} GC yields based on **1a** used. The number in parenthesis shows the isolated yield. ^{*c*} TON = **3a** (mol)/Pd NCs (mol). ^{*d*} Bromotoluene was used instead of iodotoluene.

and a 56% yield was obtained (entry 5, Table 1). The Pd NCs showed efficient catalytic activity, and the highest turnover number (TON, 4.5×10^5) was achieved in the presence of 2×10^{-4} mol% of the Pd NCs catalyst (entry 6, Table 1). When bromotoluene was used instead of iodotoluene, the reaction generated **3a** in 86% yield and the TON was 4.9×10^4 (entry 7, Table 1).

When the reaction time course was examined, the reaction rate for Pd NCs in NMP was faster than that for Pd NCs in DMF. The highest turnover frequency achieved was 1.7×10^5 for 1 h.

To expand the scope of the reaction substrate, various aryl iodides and different arylboronic acids were used in the Suzuki–Miyaura cross-coupling reaction, under the same conditions as for entry 3 in Table 1, as shown in Table 2. The reactions of aryl iodides bearing both electron-donating and electron-withdrawing substituents, such as -OMe, $-CF_3$ and $-NH_2$, with phenylboronic acid gave rise to the corresponding biphenyls, **3b–3d**, in excellent yields (entries 1–3, Table 2). 1-Iodonaphthalene and 2-iodothiophene also reacted with **2a** to produce the aryl derivatives **3e** and **3f** in good yields (entries 4 and 5, Table 2). The Suzuki–Miyaura cross-coupling reaction of **1a** with various substituted phenylboronic acids proceeded efficiently (entries 6–8).

To investigate the economy of the reaction, we performed recycling experiments for the Pd NCs catalyst in the Suzuki–Miyaura cross-coupling reaction. In the first cycle, the coupling product **3a** was obtained in 92% yield under the conditions given in entry 4, Table 1 (Step 1 to Step 2, Fig. 2).

After performing the reaction under the conditions given in entry 4, Table 1 (Step 2), the reaction mixture was extracted with hexane (8 mL \times four times) (Step 3), and the organic layer containing **3a** and unreacted **1a** was separated (Step 4). The resulting aqueous layer containing Pd NCs can be used for the next catalytic sequence (see the ESI† for the detailed experimental procedure). The catalyst-recycling methodology was successfully applied to a second reaction cycle and afforded **3a** in 90% yield. The Pd NCs catalyst could be recycled at least five times without loss of catalytic activity to afford **3a** in high yields (Fig. 3).

Table 2 Pd-NCs-catalyzed Suzuki–Miyaura cross-coupling reaction of aryl iodides (1) with various arylboronic acids $(2)^a$

R ¹	-1 + R ²	\supset	►B(OH) ₂ — ⊮ 2	^{cat.} (₂ CO ₃ 100	<u>Pd NCs</u> ,, NMP/H₂O F) ℃, 5 h	,1×	
Entry	$1 (R^1 =)$		2 ($\mathbf{R}^2 =$)		$\operatorname{Yield}^{b}(\%)$		TON^c (×10 ⁴)
1 2 3	p-CH ₃ O p-CF ₃ p-NH ₂	1b 1c 1d	H H H	2a 2a 2a	> 99 (93) 97 (94) > 99 (87)	3b 3c 3d	> 5.0 4.8 > 5.0
4	\bigcirc	1e	Н	2a	87 (75)	3e	4.6
5	(^s)	1f	Н	2a	82 (69)	3f	4.7
6 7 8	<i>p</i> -CH ₃ <i>p</i> -CH ₃ <i>p</i> -CH ₃	1a 1a 1a	p-Cl p-CH ₃ O m-NO ₂	2b 2c 2d	87 (79) > 99 (88) 75 (73)	3g 3h 3i	4.5 > 5.0 3.8

^{*a*} Conditions: same as given in entry 3, Table 1. ^{*b*} GC yields based on **1** used. The numbers in parentheses show the isolated yields. ^{*c*} TON = **3** (mol)/Pd NCs (mol).



Fig. 2 Depiction of the catalyst-recycling sequence in the Suzuki-Miyaura cross-coupling reaction under the reaction conditions given in entry 4, Table 1. Step 1: reaction mixture containing **1a**, **2a**, Pd NCs, methanol, and water before the Suzuki-Miyaura cross-coupling reaction began; Step 2: reaction mixture when the reaction was finished (first time); Step 3: reaction mixture when *n*-hexane (8 mL) was added and stirred (upper: organic layer containing **3a**, bottom: aqueous layer containing Pd NCs); Step 4: aqueous layer containing Pd NCs after removal of the organic layer; this layer can be used for the next catalytic sequence.

To further examine the efficacy of the Pd NCs catalyst, the Mizoroki–Heck reaction of iodobenzene (1g) with ethyl acrylate (4a) was chosen as a model reaction, and carried out under various conditions (Table 3). For example, the reaction of 1g (1 mmol) with 4a (1.2 mmol) was performed in the presence of the Pd NCs catalyst (0.1 mol% based on 1g used) and NEt₃ (1 mmol) in DMF (2 mL) at 140 °C for 15 h, giving 5a in quantitative yield (entry 1, Table 3). A TON of over 10^3 was achieved. When the catalyst loading was further decreased to 10^{-3} mol% and 10^{-5} mol%, the reaction proceeded efficiently with 97% and quantitative yields, respectively (entries 2 and 3, Table 3).

Next, a DMF solution of Pd NCs was evaporated and the residue was redissolved in selected solvents such as NMP and THF. The reaction using NMP as a solvent was not effective and gave 5a in 30% yield (entry 4, Table 3). In the reaction using THF, no 5a was produced (Table 3, entry 5).

It is noteworthy that the Pd NCs showed efficient catalytic activity and that the highest TON (6.0×10^8) was achieved in the presence of 10^{-7} mol% of the Pd NCs catalyst (entry 6, Table 3). The catalytic activity of surfactant-free Pd NCs is better than that of Pd NCs stabilized with polymer micelles



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Fig. 3 Multiple catalyst-recycling in the Suzuki–Miyaura crosscoupling reaction. Conditions: as given in entry 4, Table 1.

Table 3Pd-NCs-catalyzed Mizoroki–Heck reaction of iodobenzene(1g) with ethyl acrylate (4a) under various conditions^a

	$ + CO_2E $ $ Ig 4a $	Et <u>Cat.</u> Pd NEt ₃ , D 140 °C,	NCs DMF 15 h	CO ₂ Et
Entry	Pd NCs (mol%)	Solvent	Yield $5a^{b}$ (%)	TON ^c
1	10^{-1}	DMF	> 99	$> 1.0 \times 10^{3}$
2	10^{-3}	DMF	97	$> 1.0 \times 10^{5}$
3	10^{-5}	DMF	>99 (85)	$> 1.0 \times 10^{7}$
4	10^{-5}	NMP	30	3.0×10^{6}
5	10^{-5}	THF	n.d.	_
6	10^{-7}	DMF	60	6.0×10^{8}
7^d	10^{-1}	DMF	23	2.3×10^{2}

^{*a*} Conditions: **1g** (1 mmol) was allowed to react with **4a** (1.2 mmol) in the presence of 1 mL of Pd NCs catalyst solution (1 mM–1 nM) and NEt₃ (1 mmol) in DMF (1 mL) at 140 °C for 15 h. ^{*b*} GC yields based on **1g** used. The number in parenthesis shows the isolated yield. ^{*c*} TON = **5a** (mol)/Pd NCs (mol). ^{*d*} Bromobenzene was used instead of iodobenzene.

Table 4Pd-NCs-catalyzed Mizoroki–Heck reaction of aryl iodides(1) with olefins $(4)^a$

$R^{1} \underbrace{\bigcap_{R}^{1}}_{1} + \underbrace{R^{2}}_{4} \underbrace{\frac{\text{cat. Pd NCs}}{\text{NEt}_{3}, \text{ DMF}}}_{140 \text{ °C}, 15 \text{ h}} R^{1} \underbrace{\int_{5}^{7}}_{5}$	\sim R ²
Entry 1 4 ($\mathbf{R}^2 =$) Yield 5 ^{<i>b</i>} (%)	TON^c
1 1a CO_2Et 4a > 99 (83) 5b	$> 1.0 \times 10^{5}$
2 1b CO_2Et 4a 97 (94) 5c	9.7×10^4
3 1c CO_2Et 4a > 99 (95) 5d	$> 1.0 \times 10^{5}$
4^d 1e CO ₂ Et 4a 82 (80) 5e	8.3×10^{4}
5^d 1f CO ₂ Et 4a 51 (50) 5f	5.1×10^{4}
6 1g $CO_2^{t}Bu$ 4b 72 (57) 5g	7.7×10^{4}
7 1g CO_2Cy 4c > 99 (92) 5h	$> 1.0 \times 10^{5}$
8^e 1g Ph 4d 87 (70) 5i	9.7×10^{4}

^{*a*} Conditions: same as given in entry 2, Table 3. ^{*b*} GC yields based on **1** used. The numbers in parentheses show the isolated yields. ^{*c*} TON = **5** (mol)/Pd NCs (mol). ^{*d*} NEt₃ (2 mmol) was used. ^{*e*} A 9 : 1 mixture of **5i** and 1,1-diphenylethylene.

reported by Kobayashi and co-workers, which showed highest TON up to 2.8×10^5 in the reaction of **1g** and **4a**.^{3a} When bromotoluene was used instead of iodotoluene, the reaction proceeded and **5a** was obtained in 23% yield (entry 7, Table 3).

Table 4 shows data for the Mizoroki–Heck reactions of various aryl iodides (1) with olefins (4) under the same conditions given in entry 2, Table 3. As in the Suzuki–Miyaura cross-coupling reaction, various aryl iodides and olefins underwent coupling and afforded the corresponding product in excellent yields in the presence of a Pd NCs catalyst.

In conclusion, we have demonstrated a method for solution synthesis of Pd NCs by DMF reduction. The photoluminescent Pd NCs can be prepared by a simple, non-supported, and surfactant-free method, which showed high catalytic activity for two important carbon–carbon bond forming reactions, namely the Suzuki–Miyaura and the Mizoroki–Heck crosscoupling reaction, and excellent TONs were achieved (TONs up to 4.5×10^5 and 6.0×10^8 , respectively). We have developed a method for recycling the catalyst at least five times in the Suzuki–Miyaura cross-coupling reaction.

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