

Remarkably facile Heck and Suzuki reactions in water using a simple cationic surfactant and ligand-free palladium catalysts

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Abstract—A facile surfactant mediated Heck and Suzuki coupling procedure in water has been developed using ligand-free Pd-catalysts. The procedure which involves nanometric palladium colloids, is operationally simple, environmentally benign and synthetically as efficient as conventional procedures using organic solvents.

Palladium catalyzed arylation of olefins, the Heck reaction, is a powerful tool in organic synthesis.¹ It has found widespread use in the synthesis of natural products, polymers, dendrimers and various conjugated architectures of materials science interest. The Heck reaction also holds much promise in many industrial processes, especially in the synthesis of fine chemicals and active pharmaceutical intermediates.² In view of these, much attention has been paid in recent years to develop milder and operationally simpler procedures for the Heck reaction. Some important developments include the use of ligand-free Pd-catalysts in combination with tetraalkylammonium salts (Jeffery conditions), the use of palladacycles, pincer and supported palladium catalysts and more recently, the bulky electron rich phosphine and the *N*-heterocyclic carbene (NHC) ligands for palladium.³ Additives such as tetrabutylammonium bromide have led to remarkable rate enhancements in the Heck reactions of aryl iodides in organic solvents^{3a} whereas by using the pincer catalysts or electron rich phosphine or NHC ligands, the Heck reaction can now be carried out with the cheap, but otherwise unreactive, chloroarenes.^{3f–j} Recently, Reetz et al. have shown that Pd(OAc)₂ in combination with tetrabutylammonium bromide gives rise to nanometric Pd-colloids which are the actual catalysts under the so-called Jeffery conditions.⁴ Pd-nanoparticles were also shown to be involved in Heck reactions with palladacy-

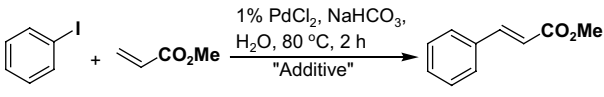
cles, pincers and NHC ligated catalysts and are thought to be responsible for their superior reactivity.⁵

However, despite all these developments on catalyst design, polar aprotic solvents (CH₃CN, DMF, DMA, NMP) still remain the preferred medium for carrying out Heck reactions. Driven by environmental concerns, recently, much effort has been directed towards using water as solvent for organic and organometallic reactions.⁶ Although there are some reports on the Heck reaction in mixed aqueous organic solvents in the presence of PTCs or Pd-catalysts having water soluble phosphine ligands,^{6d} studies directed towards the Heck reaction in water alone are less common.⁷ The latter are mostly confined to reactions with water soluble substrates using special additives and hence, lack a general synthetic appeal. We now report a facile surfactant-mediated Heck reaction in water catalyzed by ligand-free palladium catalysts which, while being environmentally benign, rival conventional Heck reaction procedures in synthetic efficacy and operational simplicity.

As a model, the Heck reaction of PhI with methyl acrylate (MA) in water (1% PdCl₂, NaHCO₃) at 80 °C was examined under a variety of conditions (Table 1). In the absence of any surfactant, only 30% conversion was obtained after 2 h (entry 1). Addition of cetyltrimethylammonium bromide (CTAB) led to a gradual increase in the conversion rate reaching a maximum of 95% after 2 h when 50 mol % of CTAB was used (entries 2–4). On the other hand, the use of SDS, Brij 56 or

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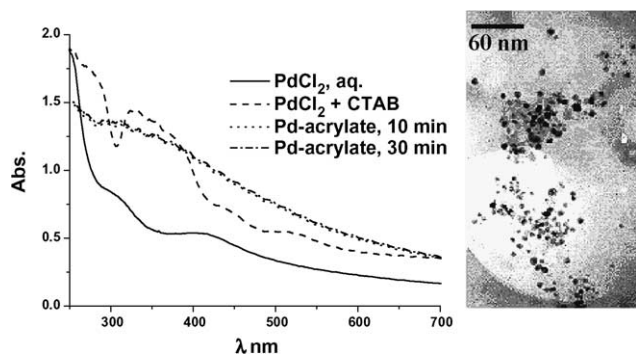
Table 1. Effect of additives on the Heck reaction of PhI in water



Entry	Additive (mol %)	Yield (%)
1	CTAB (0)	30
2	CTAB (7)	50
3	CTAB (25)	80
4	CTAB (50)	95
5	SDS (50)	40
6	Brij 56 (50)	30
7	Bu ₄ NBr (50)	50

Bu₄NBr (50 mol % each) gave only marginal increases in conversion rates over those obtained in water alone (entries 5–7). It appears from these results that only cationic surfactants are capable of enhancing the rate of the Heck reaction through micellar effects. That CTAB is more efficient than Bu₄NBr is also noteworthy since the latter has been shown to greatly enhance the rate of Heck reactions in conventional organic solvents.^{3a}

In order to understand the superiority of CTAB over other surfactant types in this aqueous Heck reaction, further physical studies were undertaken. The UV–Vis spectra of PdCl₂ in water and that of a mixture of PdCl₂ and CTAB in water at room temperature are shown in Figure 1a. The marked difference in their spectra indicates a strong interaction between PdCl₂ and CTAB in water. Addition of MA to this mixture and heating to 80 °C led to a color change from golden yellow to chocolate brown. The fine structures in the spectra disappeared and a new structureless band with increased intensity in the visible region appeared, indicating that Pd-nanoparticles had been formed.⁸ Pd-nanoparticles prepared authentically via EtOH reduction^{8c} of PdCl₂ showed an identical structureless UV–Vis band (Fig. 1a). Notably, addition of PhI to the mixture of PdCl₂ and CTAB in water and heating to 80 °C did not lead to any color change or any difference in the UV–Vis spectra (not shown). These results clearly showed that MA acted as the reducing agent for PdCl₂ to produce the CTAB-stabilized Pd-nanoparticles. A transmission electron microscopic (TEM) image clearly indicated

**Figure 1.** (a) UV–Vis changes during Pd-nanoparticle formation in water with MA and CTAB; (b) TEM image of the Pd-nanoparticles formed.

the formation of Pd-nanoparticles having an average diameter of 5 nm (Fig. 1b).

In a control experiment, the reaction components without CTAB were heated in water at 80 °C for 2 h which gave a nearly clear solution with some Pd-black formation (30% conversion, cf. entry 1, Table 1). Addition of CTAB (50 mol %) immediately led to the formation of a brown black emulsion attesting to the stabilizing role of CTAB towards Pd-nanocluster formation. Further heating at 80 °C for 2 h produced methyl cinnamate in 67% yield. Thus, CTAB performs a dual role in these aqueous Heck reactions. First, it provides a strong micellar effect and second, it acts as a stabilizer for Pd-nanocluster formation.⁹ Perhaps, SDS and Brij 56 are not capable of stabilizing Pd-nanoclusters under the above conditions and Bu₄NBr, while being able to stabilize Pd-nanoparticles,^{4c,9} cannot provide a micellar effect to the extent CTAB is capable of, thus explaining the decisive advantage of using CTAB over the other additives in these aqueous Heck reactions. Organic reactants are usually partitioned into micelles by hydrophobic interactions. CTAB with its C₁₆-hydrocarbon chain provides a strong hydrophobic force that can solubilize the organic reactants much more efficiently than Bu₄NBr can do with its shorter C₄-chains. The rate enhancing micellar effect may be due to the increased localization of the reactants in micelles together with the typical physicochemical properties of its environment which are significantly different from those of the bulk solvents.¹⁰

The synthetic efficacy of this surfactant mediated aqueous Heck reaction was then studied with a number of different aryl halides and olefins (Scheme 1) and the results shown in Table 2. Heck reaction of iodobenzene (**1a**) with MA, styrene and acrylonitrile gave good yields of the corresponding products **2a–c** within 2–3 h at 80 °C (entries 1–3). Pd(OAc)₂ can also be used as a catalyst in these reactions with equal efficacy. A lower catalytic loading (0.1% PdCl₂) can be used with no loss in product yield (entry 2). As expected, iodoarenes with an *ortho*-substituent (**1b**) or an electron donating substituent (**1c**) considerably lowered the reaction rate. In these cases, a full equivalent of CTAB, a higher temperature (100 °C) and prolonged reaction times were required to obtain good yields of the products **2d–f** (entries 4–6). NaOAc was found to be a superior base over NaHCO₃ for these latter reactions. Nevertheless, the reaction times and product yields are comparable, if not better, than those reported in organic solvents under conventional Heck reaction conditions. Less reactive bromoarenes such as **1d** required an even higher reac-

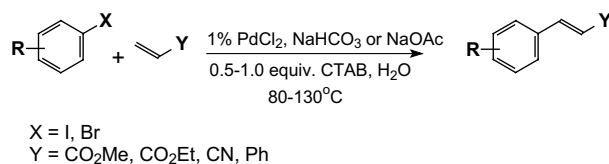

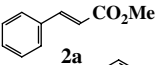
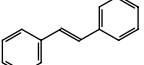
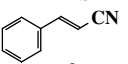

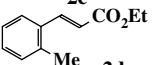
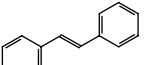
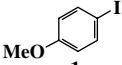
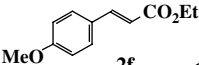
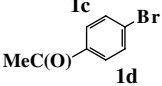
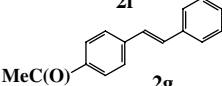
**Scheme 1.**

Table 2. CTAB-mediated Heck Reaction in water^a

Entry	ArX	Olefin	T (°C/h)	Product	Yield (%)
1		MA	80/2		95
2	1a	S	80/3		89
3	1a	AN	80/2		83
4		EA	100/13		87 ^b
5	1b	S	100/20		80 ^b
6		EA	100/10		82 ^b
7		S	130/12		80 ^b

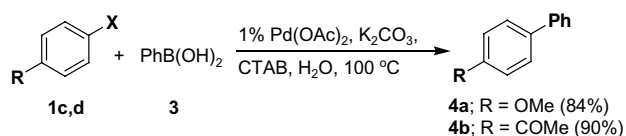
^a 1 mmol ArX, 2 mmol olefin, 0.5 mmol CTAB, 2 mmol NaHCO₃ and 0.01 mmol of PdCl₂ in water (3 mL).

^b 1 equiv CTAB and 2 equiv NaOAc were used. MA = methyl acrylate, S = styrene, AN = acrylonitrile, EA = ethyl acrylate.

tion temperature (130 °C), the corresponding Heck product **2g** being obtained in 80% yield after 12 h (entry 7). It may be noted that even in traditional organic solvents, the Heck reactions of bromoarenes usually require higher reaction temperatures (ca. 130–140 °C)^{4d,5c} and hence, our aqueous Heck reaction protocol compares favorably with conventional conditions. Notably, in contrast to the findings of Reetz and de Vries,^{4d} lowering of the Pd-loading (0.1% PdCl₂ or Pd(OAc)₂) did not improve the Heck reaction profile of the bromoarene **1d**.

The Suzuki cross coupling reaction is a powerful Pd-catalyzed regime for the synthesis of unsymmetrical biaryls from aryl boronic acids and haloarenes.¹¹ Pd-nanoparticle catalyzed Suzuki coupling in organic solvents has also been described.^{4a,d,12} However, there are no reports on Suzuki coupling reactions with ligand-free Pd-catalysts in water alone, except for one example that involved high reaction temperatures (>150 °C) under microwave irradiation.¹³ The above success with the Heck reaction in water prompted us to explore such a possibility. In the event, PhB(OH)₂ **3** was smoothly coupled with haloarenes **1c,d** in water in the presence of CTAB and 1% Pd(OAc)₂ at 100 °C to give the biaryls **4a,b** in excellent yields (Scheme 2). The reactions are remarkably fast (1–3 h) with high turnover frequencies.

In conclusion, a CTAB-mediated aqueous Heck and Suzuki coupling procedure has been developed using

**Scheme 2.**

ligand-free Pd-catalysts.¹⁴ The procedure is operationally simple, environmentally benign and is comparable, if not better, in synthetic efficacy to conventional Pd-catalyzed coupling protocols in organic solvents. The use of an aqueous reaction medium and colloidal Pd-catalysts promise further opportunities in batch processing and catalyst recycling.¹⁵

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References and notes

- (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985; (b) de Meijere, A.; Meier, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379; (c) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998, p 99; (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009; (e) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449; (f) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553.
- (a) de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086; (b) Blaser, H.-U.; Indolese, A.; Schnyder, A.; Steiner, H.; Studer, M. *J. Mol. Catal. A: Chem.* **2001**, *173*, 3; (c) Tucker, C. E.; de Vries, J. G. *Topics in Catalysis* **2002**, *19*, 111; (d) de Vries, J. G.; de Vries, A. H. M. *Eur. J. Org. Chem.* **2003**, 799; (e) Blaser, H.-U.; Indolese, A.; Naud, F.; Nettekoven, U.; Schnyder, A. *Adv. Synth. Catal.* **2004**, *346*, 1583.
- (a) Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, 1996; Vol. 5, p 153; (b) Böhm, V. P. W.; Herrmann, W. A. *Chem. Eur.*

- J. Am. Chem. Soc.* **2002**, *124*, 4540; (c) Scott, R. W. J.; Ye, H.; Henriquez, R. R.; Crooks, R. M. *Chem. Mater.* **2003**, *15*, 3873.
- (a) Tetraalkylammonium salts are known to stabilize Pd-nanoclusters: Reetz, M. T.; Maase, M. *Adv. Mater.* **1999**, *11*, 773; (b) Reetz, M. T.; Winter, M.; Breinbauer, R.; Thurn-Albrecht, T.; Vogel, W. *Chem. Eur. J.* **2001**, *7*, 1084.
 - Bhattacharya, S.; Praveen Kumar, V. *J. Org. Chem.* **2004**, *69*, 559.
 - (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998, p 49; (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359; (d) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.
 - (a) Kogan, V.; Aizenshtat, Z.; Popovitz-Biro, R.; Neumann, R. *Org. Lett.* **2002**, *4*, 3529; (b) Mori, K.; Yamaguchi, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2002**, *124*, 11572; (c) Narayanan, R.; El-Sayed, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 8340.
 - Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973.
 - General procedure for the CTAB-mediated Heck reaction in water: A hard glass pressure tube (25 mL) with a Teflon screw cap was charged with the aryl halide **1a-d** (1.0 mmol), olefin (2.0 mmol), CTAB (0.5 mmol for **1a**; 1.0 mmol for **1b-d**), PdCl₂ (0.01 mmol), NaHCO₃ (2.0 mmol for **1a**) or NaOAc (2.0 mmol for **1b-d**) in water (3 mL). The mixture was then heated with vigorous stirring at the temperature and for the time shown in Table 2. It was then cooled, diluted with water and extracted with ethyl acetate. The products **2a-g** were purified by column chromatography over silica gel.
 - (a) de Vries, A. H. M.; Parlevliet, F. J.; Schmieder-van de Vondervoot, L.; Mommers, J. H. M.; Henderickx, H. J. W.; Walet, M. A. M.; de Vries, J. G. *Adv. Synth. Catal.* **2002**, *344*, 996; (b) Chandrasekhar, S.; Narsihmulu, Ch.; Sultana, S. S.; Reddy, N. R. *Org. Lett.* **2002**, *4*, 4399; (c) Liu, S.; Fukuyama, T.; Sato, M.; Ryu, I. *Org. Process Res. Dev.* **2004**, *8*, 477; (d) Nobre, S. M.; Wolke, S. I.; da Rosa, R. G.; Monteiro, A. L. *Tetrahedron Lett.* **2004**, *45*, 6527.
 - (a) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917; (d) Biffis, A.; Zecca, M.; Basato, M. *J. Mol. Catal. A: Chem.* **2001**, *173*, 249; (e) Köhler, K.; Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J. *Chem. Eur. J.* **2002**, *8*, 622; (f) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290; (g) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176; (h) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759; (i) Bedford, R. B. *Chem. Commun.* **2003**, 1787; (j) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055; (k) Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239; (l) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366.
 - (a) Reetz, M. T.; Breinbauer, R.; Wanninger, K. *Tetrahedron Lett.* **1996**, *37*, 4499; (b) Beller, M.; Fischer, H.; Kühlein, K.; Reisinger, C.-P.; Herrmann, W. A. *J. Organomet. Chem.* **1996**, *520*, 257; (c) Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165; (d) Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559.
 - (a) Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V. *Chem. Commun.* **2001**, 1544; (b) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285; (c) Eberhard, M. R. *Org. Lett.* **2004**, *6*, 2125.
 - (a) Li, C.-H.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997; (b) Cornils, B.; Herrmann, W. A. *Aqueous Phase Organometallic Chemistry: Concepts and Applications*; Wiley-VCH: Weinheim, 1998; (c) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998; (d) Genet, J.-P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305; (e) Joo, F. *Aqueous Organometallic Catalysis*; Kluwer: Dordrecht, 2001.
 - (a) Bumagin, N. A.; More, P. G.; Beletskaya, I. P. *J. Organomet. Chem.* **1989**, *364*, 231; (b) Bumagin, N. A.; Bykov, V. V.; Sukhomlinova, L. I.; Tolstaya, T. P.; Beletskaya, I. P. *J. Organomet. Chem.* **1995**, *486*, 259; (c) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113; (d) Mukhopadhyay, S.; Rothenburg, G.; Joshi, A.; Baidossi, M.; Sasson, Y. *Adv. Synth. Catal.* **2002**, *344*, 348; (e) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2004**, *60*, 4059.
 - (a) Teranishi, T.; Miyake, M. *Chem. Mater.* **1998**, *10*, 594; (b) Ohde, H.; Wai, C. M.; Kim, H.; Kim, J.; Odhe, M.