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## Water-Sculpting of a Heterogeneous Nanoparticle Precatalyst for Mizoroki—Heck Couplings under Aqueous Micellar Catalysis Conditions

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ABSTRACT: Por	wdery, spherical nanoparticles	(NPs) containing ppm	Mizoroki-Heck couplings

Abstract P Powdery, spherical haloparticles (NPS) containing ppin levels of palladium ligated by t-Bu<sub>3</sub>P, derived from FeCl<sub>3</sub>, upon simple exposure to water undergo a remarkable alteration in their morphology leading to nanorods that catalyze Mizoroki–Heck (MH) couplings. Such NP alteration is general, shown to occur with three unrelated phosphine ligand-containing NPs. Each catalyst has been studied using X-ray photoelectron spectroscopy (XPS), energy-dispersive X-ray spectroscopy (EDX), transmission electron microscopy (TEM), and cryogenic transmission electron microscopy (cryo-TEM) analyses. Couplings that rely specifically on NPs containing t-Bu<sub>3</sub>P-ligated Pd occur under aqueous micellar catalysis conditions between room temperature and 45 °C, and show broad substrate scope. Other key features associated with this new technology include low residual Pd in



the product, recycling of the aqueous reaction medium, and an associated low E Factor. Synthesis of the precursor to galipinine, a member of the Hancock family of alkaloids, is suggestive of potential industrial applications.

## INTRODUCTION

Transition-metal-containing nanoparticles (NPs) offer timely opportunities for development of new heterogeneous catalysts and their applications to a broad range of synthetic processes. Given the endangered status of the platinoids, and Pd in particular,<sup>2</sup> reducing the common use of  $1-10 \mod \%$  of Pd catalysts<sup>3</sup> by an order of magnitude provides one solution to this problem. While numerous types of Pd NPs have been described over the past two decades,<sup>4</sup> few have found their way into the toolbox of general reagents for effecting C-C bond formation,<sup>5-7</sup> with most of the interest focused on their physical characteristics and properties. Oftentimes, Pdcontaining NPs, whether composed of pure atoms or metal on the surface of solid supports (such as  $Al_2O_3$ ), require exposure to gases at elevated temperatures to arrive at the active form(s), which can be reversible both during reactions and once reactions are completed.8 These conditions are associated with distinct changes in NP shape and size that can dramatically alter, and thereby decrease, catalyst activity.

In 2015,<sup>9</sup> we described new NPs that could be easily fashioned upon simple treatment of inexpensive FeCl<sub>3</sub> with MeMgCl in THF solution containing SPhos as ligand, performed at room temperature (Scheme 1). Catalyst loading at the ppm level of Pd, whether found naturally as an "impurity" in this iron salt, or as added Pd(OAc)<sub>2</sub> ( $\geq$ 320 ppm) to pure FeCl<sub>3</sub>, was sufficient en route to these NPs that mediate Suzuki–Miyaura cross-couplings, reactions that could

# Scheme 1. Reactions Catalyzed by Ligand-Dependent, ppm Pd-Containing NPs





## Scheme 2. Optimization Requiring a Modified Preparation of Fe/ppm Pd NPs

Various combinations of reagents to arrive at optimized NPs for Mizoroki-Heck (MH) couplings:

Method A:	FeCl <sub>3</sub> + Pd co	mplex + L	igand <u>MeMgCl</u> THF	Fe/ppm Pd NPs	[ original pre	eparation; Ligan	d = SPhos] <sup>9</sup>	
Method B:	FeCl <sub>3</sub> + Liga	nd	MeMgCI THF	Fe NP core with L	igand	+ Pd complex	+ MeMgCl THF	Fe/ppm Pd NPs
Method C:	FeCl <sub>3</sub> + Pd co	mplex	MeMgCl	Fe NP core with P	d complex	+ Ligand	+ MeMgCl	Fe/ppm Pd NPs
Method D:	FeCl <sub>3</sub>		MeMgCl THF	Fe NP core		+ Pd complex + Ligand	+ MeMgCl	Fe/ppm Pd NPs
	0	+ P Pł	$ \begin{array}{ccc} 0 & Fe \\ \hline 0 & E \\ \hline 0 & FBu & He \\ \hline 0 & FBu & Fe \\ \hline 0 & Fe \\ \hline \hline \hline \hline 0 & Fe \\ \hline \hline \hline \hline \hline \hline 0 & Fe \\ \hline \hline \hline \hline \hline \hline \hline \hline \hline $	2/ppm Pd NPs (t <sub>3</sub> N (3 equiv)) ICl (6 equiv), rt 6 PTS/H <sub>2</sub> O, 0.5 M P2P ← PPh <sub>2</sub>		N-Ph	Bu	
			L1	L2	F	ν(t-Bu) <sub>2</sub> L <b>3</b>		
	Entry <sup>a</sup>	Method	Pd complex / mol %	L / mol %	MeMgCl (e	equiv) <sup>b</sup> Yield	(%) <sup>c</sup>	
	1	А	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> / 0.50	<i>t</i> -Bu <sub>3</sub> P / 2	1.5	NF	2	
	2	А	Pd(t-Bu <sub>3</sub> P) <sub>2</sub> / 0.50	<i>t</i> -Bu <sub>3</sub> P / 2	2.5	NF	R	
	3	А	Pd(t-Bu <sub>3</sub> P) <sub>2</sub> / 0.50	<i>t</i> -Bu <sub>3</sub> P / 2	3.5	<	i	
	4	В	Pd(t-Bu <sub>3</sub> P) <sub>2</sub> / 0.50	<i>t</i> -Bu <sub>3</sub> P / 2	1+2.5	5 NF	8	
	5	С	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> / 0.50	<i>t</i> -Bu <sub>3</sub> P / 2	1+2.5	5 <5	i	
	6	D	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> / 0.50	<i>t</i> -Bu <sub>3</sub> P / 2	1+2.5	5 89	)	
	7	D	Pd(t-Bu <sub>3</sub> P) <sub>2</sub> / 0.25	<i>t</i> -Bu <sub>3</sub> P / 2	1+2.5	5 31		
	8	D	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> / 0.25	<i>t</i> -Bu <sub>3</sub> P / 2	2+1.5	5 80	)	
	9	D	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> / 0.25	<i>t</i> -Bu <sub>3</sub> P / 6	2+1.5	5 90	)	
	10	D	Pd(OAc) <sub>2</sub> / 0.25	<i>t</i> -Bu <sub>3</sub> P / 6	2+1.5	5 15	i	
	11	D	[Pd(allyl)Cl] <sub>2</sub> / 0.25	<i>t</i> -Bu <sub>3</sub> P / 6	2+1.5	5 17	,	
	12	D	Pd(OAc) <sub>2</sub> / 0.25	<b>L1</b> /6	2+1.5	5 NF	R	
	13	D	Pd(OAc) <sub>2</sub> / 0.25	<b>L2</b> /6	2+1.5	5 <5	;	
	14	D	Pd(OAc) <sub>2</sub> / 0.25	<b>L3</b> / 6	2+1.5	5 8		

<sup>*a*</sup>Conditions: 1-Iodo-4-methoxybenzene (0.2 mmol), *tert*-butyl acrylate (0.4 mmol), Fe/ppm Pd NPs (13 mg, containing 0.50 mol % or 0.25 mol % Pd), Et<sub>3</sub>N (0.6 mmol), NaCl (1.2 mmol), 5 wt % PTS/H<sub>2</sub>O (0.4 mL), rt, 16 h. <sup>*b*</sup>Amount relative to FeCl<sub>3</sub>. <sup>*c*</sup>Yield determined by GC-MS; naphthalene as standard, NR = no reaction.

be run in aqueous micellar media under very mild conditions (20-45 °C). NP characterization was performed using several techniques, including their cryo-TEM analyses as used in their aqueous reaction medium that revealed their size and raft-like shape. Switching ligands to XPhos, as well as the Grignard reagent to MeMgBr, resulted in NPs of similar shape and size that are also very effective for catalyzing Sonogashira couplings under the same aqueous conditions (Scheme 1).<sup>10</sup> As our interests turned toward developing related NPs that catalyze Mizoroki-Heck (MH) couplings in water, not only was a different ligand required, but modification in the mode of preparation was also needed to arrive, ostensibly, at the same type of NPs. These changes necessitated a more complete analyses of these initially formed NPs (in THF). These new data have led to the discovery of a remarkable room temperature transformation that converts these initially constructed NPs into their active state upon simple exposure to the aqueous conditions under which they would normally be used. In this report, we disclose this unexpected and rare water-mediated conversion, the generality of this catalyst sculpting in water, and the application of these new ppm Pd-containing NPs as a

new heterogeneous catalyst for MH reactions that take place in recyclable water under environmentally responsible conditions.

Fe/ppm Pd NPs as Catalyst: Preparation. After an extensive ligand screening indicating that t-Bu<sub>3</sub>P was, by far, the best ligand for the intended Mizoroki-Heck reactions (see Table S1), the corresponding Fe/ppm Pd NPs were formed using  $FeCl_3$ ,  $Pd(t-Bu_3P)_2$ , and  $t-Bu_3P$ , following our earlier procedure.9 Using 1-iodo-4-methoxybenzene and tert-butyl acrylate as partners for this model reaction, NPs with different equivalents of MeMgCl were tested in 2 wt %  $PTS^{11}/H_2O$  at room temperature, but none led to significant product formation (Scheme 2, entries 1 to 3). Modified sequences for reagent formation (Methods B-D) were investigated to enhance the level of activation of the resulting NPs in this same coupling (entries 4 to 6). From the GC results obtained, Method D afforded the best coupling yields. Further optimization based on equivalents of MeMgCl, both prior to and after addition of Pd and ligand (entries 7 to 9), arrived at the best combination: initial addition of 2.0 equiv of MeMgCl followed by another 1.5 equiv (relative to FeCl<sub>3</sub>), together with a Pd loading of 0.25 mol % (entry 8). Refinement of the amount of ligand afforded a further improved yield (90%; entry 9). Other palladium salts, such as  $Pd(OAc)_2$  or  $[Pd(allyl)Cl]_2$ , or ligands (L1: Cy-cBRIDP;<sup>12</sup> L2: dppp; L3: N-Ph-2- $(t-Bu)_2P$ -pyrrole; see also Table S1 for ligand screening) clearly showed that the combination of  $Pd(t-Bu_3P)_2$  and  $t-Bu_3P$  afforded much better yields in the aqueous PTS medium than did other sources of palladium or ligands (entries 10 to 14).

To arrive at finalized reaction conditions for use of these NPs, an evaluation of the base and surfactant was undertaken (reactions 1 and 2; Scheme 3). Switching to  $K_3PO_4$  from  $Et_3N$ 



Optimized method for Fe/ppm Pd NPs



<sup>a</sup>1-Iodo-4-methoxybenzene (0.2 mmol), *tert*-butyl acrylate (0.4 mmol), Fe/ppm Pd NPs (12.5 mg, 0.25 mol % or 5 mg, 0.10 mol % Pd), base (0.6 mmol), NaCl (1.2 mmol), surfactant/H<sub>2</sub>O (0.4 mL), rt, 16 h. <sup>b</sup>Yield determined by GC-MS; naphthalene as standard. <sup>c</sup>Isolated yield in parentheses. <sup>d</sup>1-Iodo-4-methoxybenzene (0.2 mmol), styrene (0.4 mmol), Fe/ppm Pd NPs (12.5 mg, 0.25 mol % Pd), K<sub>3</sub>PO<sub>4</sub> (0.6 mmol), NaCl (1.2 mmol), 2 wt % TPGS-750-M/H<sub>2</sub>O (0.4 mL), and cosolvent (0.04 mL) at 45 °C, 16 h. <sup>e</sup>40 h.

gave similar results in aqueous micellar media derived from designer surfactant PTS<sup>11</sup> and, remarkably, was equally effective when the loading of Pd was reduced from 2500 to 1000 ppm (i.e., 0.1 mol %; entry 4). Other surfactants,<sup>13</sup> as well as different amounts (i.e., weight percent) of surfactant, in water as the reaction medium (entries 5 to 12) indicated that 2 wt % TPGS-750-M<sup>13b</sup> afforded the best outcome (entry 6). Using the same educts, the potential beneficial role of a cosolvent (reaction 2, entries 13 to 18; also see Table S3) led to the finding that, if needed, DMF was the cosolvent of choice (entry 18). Varying percentages of cosolvent were reported to

increase the size of nanomicelle by DLS (dynamic light scattering).<sup>14</sup> Under otherwise identical conditions, use of pure THF as the reaction medium together with these same NPs (albeit at the higher loading: 0.25 mol % Pd) led to the expected product in only 9% yield (Table 2, entry 2). Running this reaction in micellar media in the presence of the same amounts of Pd(*t*-Bu<sub>3</sub>P)<sub>2</sub> and *t*-Bu<sub>3</sub>P but *without prior NP formation* gave a significant reduction in yield (19% with FeCl<sub>3</sub>; 8% in the absence of FeCl<sub>3</sub>; see Table S4), indicative of the importance of prior nanoparticle formation.

**Characterization of the NPs.** We next turned our attention to investigating the nature of the NPs that catalyze these MH couplings. As previously pursued,<sup>9,10</sup> a variety of techniques were applied to establishing the makeup of the surface of this catalyst. Most informative, however, was determination via STEM analyses of their morphology as made initially in THF, and then again when present within an aqueous reaction mixture. Analyses of NPs containing either SPhos or XPhos prior to their use under aqueous micellar catalysis conditions had never been carried out. We were certainly not anticipating the astonishing changes in NP morphology that would be uncovered from these STEM studies.

Examination of these new NPs (prepared following Method D, L = t-Bu<sub>3</sub>P) under typical aqueous reaction conditions (i.e., in 2 wt % TPGS-750-M/H<sub>2</sub>O) indicated that, as seen previously in both cases of NPs containing SPhos-ligated Pd used for Suzuki–Miyaura couplings<sup>9</sup> and NPs composed of XPhos-ligated Pd for Sonogashira couplings,<sup>10</sup> nanorods measuring 30 to 100 nm in length were present (Figure 1C).



**Figure 1.** High angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) image of (A) dry Fe/ppm Pd nanoparticles; (B) Fe/ppm Pd nanomaterial in pure degassed water; (C) Fe/ppm Pd nanorods in 2 wt % TPGS-750-M/H<sub>2</sub>O.

However, the corresponding analyses of the initially formed NPs prepared in THF revealed a completely different morphology: these (as a dry powder) are spherical, measuring 2-5 nm (Figure 1A). Exposure of the initial spherical NPs to just water begins the "sculpting" process (Figure 1A to 1B). Upon addition of an aqueous solution of TPGS-750-M the conversion to nanorods is complete (Figure 1B to 1C). Hence, the original NPs formed, in fact, are not the actual catalyst being used for these couplings; rather, their exposure to the aqueous surfactant had transformed them entirely into the active form capable of catalyzing MH couplings at the ppm level of Pd.

As revealed by elemental mapping images of spherical NPs, O, P, Cl, Mg, and Fe are homogeneously distributed throughout these nanoclusters, while the presence of Pd is too low to be detected (Figure 2). The corresponding EDX spectrum confirmed the existence of O, P, Cl, Mg, and Fe (also with low atomic percentage of Pd; see SI). Elemental mappings on the derived nanorods also showed the distribution of O, Cl, Mg, and Fe; however, by contrast, phosphorus was noticeably absent.

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Figure 2. HAADF-STEM elemental mapping of dry Fe/ppm Pd nanoparticles vs Fe/ppm Pd nanorods in 2 wt % TPGS-750-M/H<sub>2</sub>O.

To determine if this water-induced change in morphology of t-Bu<sub>3</sub>P-containing NPs is independent of the associated ligand, two additional sets of NPs were made using the same approach (i.e., Scheme 2, Method D). In these cases, however, t-Bu<sub>3</sub>P was replaced with SPhos, and by Cy-cBRIDP. The Fe/ppm Pd NPs for each consisted of very similar looking dry powders, likewise made in THF. Their analyses by STEM showed related nanospheres (2 to 5 nm; Figures 3A and 3D), as seen



**Figure 3.** HAADF-STEM image of (A) dry Fe/ppm Pd nanoparticles with SPhos as ligand; (B) Fe/ppm Pd nanocatalyst with SPhos as ligand in pure water; (C) Fe/ppm Pd nanocatalyst with SPhos as ligand in aqueous TPGS-750-M; (D) dry Fe/ppm Pd nanoparticles with Cy-cBRIDP as ligand; (E) Fe/ppm Pd nanocatalyst with Cy-cBRIDP as ligand in aqueous TPGS-750-M.

previously when made in the presence of t-Bu<sub>3</sub>P (see Figure 1A). After stirring each in pure degassed water, both formed nanorods to varying extents (see Figure 3B and 3E). However, upon addition of 2 wt % TPGS-750-M/H<sub>2</sub>O, which is the usual reaction medium, further stirring for 1 h led to complete conversion to nanorods (50 to 130 nm; Figure 3C and 3F). Thus, a change in morphology, independent of ligand, results

upon exposure of the NPs to water to varying extents. Subsequent addition of aqueous TPGS-750-M (or, addition of this aqueous solution to the spherical NPs directly) leads to complete conversion from small spherical NPs to far larger nanorods.

Analyses via XPS was also applied to both the initially prepared powders and the catalytically active NPs used for Mizoroki-Heck couplings. These full scans reveal the surface of the prenanocatalyst (i.e., the powder form) consists of oxygen (13.15%), carbon (55.56%), iron (0.21%), chlorine (16.24%), phosphorus (3.23%), magnesium (11.48%), and palladium (0.13%; see p S27 in the Supporting Information (SI)). However, after stirring in water for the same 1 h period, over 85% of their mass had dissolved in water, with XPS analysis now showing the surface of the newly formed nanorods to contain oxygen (30.58%), carbon (48.65%), iron (5.02%), chlorine (4.60%), phosphorus (2.65%), magnesium (7.63%), and palladium (0.88%; see p S31 in the SI). Hence, these comparisons between precatalyst spheres and water-sculpted nanorods indicate that the proportions of oxygen, iron, and palladium have increased, while the levels of phosphorus, chlorine, and magnesium have decreased, which is consistent with observations from elemental mapping (vide supra). The percentage changes in metal content in the NPs before and after rinsing with water could be determined by ICP-MS (Table 1, and p S25 in the SI). Thus, in 10 mg of dry NP powder, there was found to be present 0.983 mg of Mg, 0.627 mg of Fe, and 0.039 mg of Pd. After stirring in pure water for 1 h, ca. 90% of the Mg had dissolved. By contrast, over 90% of both Fe and Pd remained associated with the nanorods. Overall, close to 90% of the mass of the original nanoparticles had been dispersed into the aqueous medium (i.e., the supernatant) during this 1 h process.

Table 1. ICP-MS Analyses of Dry Powder, Remaining Material, and Supernatant

	Dry powder (10 mg)	Leftover (1.2 mg)	Supernatant (1.7 mL)
Mg (mg)	0.983	0.089	0.894
Fe (mg)	0.627	0.587	0.051
Pd (mg)	0.039	0.033	0.0018

High resolution XPS measurements further disclosed the oxidation states and variation of content of different elements in the nanomaterial before and after exposure to water (see SI). The P 2p spectrum reveals that the proportion of P(V) is much higher than that of P(III) on the surface of the dry powder spheres. And the Pd 3d spectrum indicated that the oxidation state of Pd in the nanomaterial is Pd(II), rather than Pd(0).

Control experiments, the results from which are shown in Table 2, correlated NP catalyst changes and resulting activity with changes in reaction conditions used for MH couplings. First, and as expected, neither nanomicelles nor nanorods were formed (i.e., the NPs remained as spheres) when an organic solvent such as THF (entry 2) or DMF (entry 3) was used as the reaction medium, leading to only 9% and 41% yields, respectively. Reaction in pure, degassed water, in which the nanorod structure could form but in the absence of nanomicelles (entry 4), led to a 68% yield of cinnamate coupling product. The reaction containing both nanomicelles and nanorod catalyst in surfactant/water, but in the absence of the majority of ligand  $(t-Bu_3P)$  upon removal of the aqueous medium and replacement with fresh TPGS-750-M/water (entry 5), gave only a 78% yield. However, replenishing this newly introduced aqueous reaction mixture by addition of fresh ligand (entry 6) resulted in the expected yield increase. Utilizing the initially removed aqueous supernatant (entry 7) as reaction medium and adding fresh reaction partners (along with base and NaCl), likewise, gave a yield quite similar to levels observed previously (entries 1 and 6) which contained the same amount of t-Bu<sub>3</sub>P in the pot. These last two entries provide strong evidence that all reaction components, although most notably, the required levels of phosphine, which under the reaction conditions are distributed between the surface of the NPs and, mainly, best accommodated within the nanomicelles in the water, must be present for a highly successful reaction outcome.

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Cryo-TEM analyses also provided insight as to the special role played by (10%, v/v) DMF as cosolvent, which facilitates these MH reactions in water. Other potential solvents (DMSO, MeOH, etc.) that could, in principle, function similarly (e.g., if only for substrate dissolution purposes) were totally ineffective (Figure 4). The images reveal that the size of the typically



**Figure 4.** (A) Cryo-TEM analyses of NP catalyst among nanomicelles of TPGS-750-M. (B) Cryo-TEM of NP catalyst in the same micellar media, but after adding DMF as cosolvent.

spherical nanomicelle derived from TPGS-750-M (40–60 nm; see A)<sup>13b</sup> is expanded upon addition of DMF to 100 nm (as seen in B). Moreover, the nanorod NPs present in water alone are distinctly separated from the nanomicelles; there is no interaction between them (as in A). However, upon addition of DMF, and in addition to nanomicelle swelling,<sup>14</sup> the crucial "nano-to-nano" effect<sup>15</sup> is now operating, leading to substrate (within the micelles) delivery to the NP catalyst with the resulting reactivity enhancement manifested by much higher levels of conversion and associated isolated yields being obtained under mild conditions.

Application to Mizoroki–Heck (MH) Couplings. With considerable insight as to the nature of the active NP catalyst involved (i.e., its optimized preparation, its interactions with nanomicelles present in the aqueous medium, and the role of added DMF), the scope of this ppm level Pd catalysis (1000–2500 ppm or 0.10-0.25 mol %) for MH couplings was evaluated (Table 3). Several aryl and heteroaryl iodides, together with various alkenyl partners, were examined. Most reactions took place quite smoothly and afforded excellent yields of coupled products. Numerous functional groups are tolerated, including methoxy- (1, 3, 6), ester (1, 2, 4, 5, 7, 8), ketone (2), chloride- (5), nitrile- (7, 9), trifluoromethyl- (10, 11, 12, 14), thio- (10), nitro- (11, 14), a Boc-protected amine (12), fluoride- (17, 24), isolated olefins (19), aldehyde (20,

#### Table 2. Control Experiments



Entry	Conditions	Nanorod structure	Aquecus micelles	Excess ligand	Yield
1	2 wt % TPGS-750-M/H <sub>2</sub> O as reaction medium				99%
2	THF as reaction medium	no	no		9%
3	DMF as reaction medium	no	no		41%
4	Degassed H <sub>2</sub> O as reaction medium		no		68%
5	Fe/ppm Pd NPs stirred in degassed H <sub>2</sub> O for 1 h; remove H <sub>2</sub> O; add starting materials, K <sub>3</sub> PO <sub>4</sub> , and NaCI; add fresh 2 wt % TPGS-750-M/H <sub>2</sub> O as reaction medium ( <b>no phosphine</b> )			no	78%
6	Fe/ppm Pd NPs stirred In degassed H <sub>2</sub> O for 1 h; remove H <sub>2</sub> O; add <i>t</i> -Bu <sub>3</sub> P, starting materials, K <sub>3</sub> PO <sub>4</sub> , and NaCI; add fresh 2 wt % TPGS-750-M/H <sub>2</sub> O as reaction medium				95%
7	Fe/ppm Pd NPs stirred in 2 wt % TPGS-750-M/H <sub>2</sub> O for 1 h; remove aq. surfactant solution; add fresh starting materials, K <sub>3</sub> PO <sub>4</sub> , and NaCl; add back the previously removed aq. surfactant solution as the reaction medium				92%

Table 3. Substrate  $Scope^{a,b}$ 



<sup>*a*</sup>Iodide (0.2 mmol), alkene (0.4 mmol), NaCl (1.2 mmol), K<sub>3</sub>PO<sub>4</sub> (0.6 mmol) and Fe/ppm Pd (12.5 mg, 0.25 mol % Pd), 2 wt % TPGS-750-M/ H<sub>2</sub>O (0.4 mL), DMF (0.04 mL), 45 °C, 16 h. <sup>*b*</sup>Isolated yield. <sup>*c*</sup>Fe/ppm Pd NPs (5 mg, 0.10 mol % Pd). <sup>*d*</sup>No DMF. <sup>*e*</sup>At rt. <sup>*f*</sup>40 h. <sup>*g*</sup>72 h.

25), alkyne (23), and a TIPS-protected phenol (24). Moreover, various heterocyclic rings, such as pyridine (3, 15), pyrazole (8), pyrrole (9), piperazine (10), dihydrobenzofuran (11), benzodioxol (13), thiophene (14), a THPprotected indazole (15), morpholine (16, 22), pyrimidine (16, 21, 26), indole (17, 22), pyrrolindine (18), tetrahydrofuran (20, 23), and benzo[d]oxazol (26) all led to good yields of the anticipated products. Many of these have extensive applications to targets in the agricultural and pharmaceutical industries.<sup>16</sup>

A direct comparison between heterogeneous catalysts described in the literature for Mizoroki–Heck couplings, in this case leading to *tert*-butyl (E)-3-(4-methoxyphenyl)-acrylate, is illustrated in Table 4. The results suggest that

this NP technology leads to the cinnamate product in comparable or better yields, can be accomplished using lower catalyst loadings and temperatures, and does so in an aqueous reaction medium that is much more environmentally friendly than all others used in organic solvents, especially those run in dipolar aprotic media.

As is characteristic of designer surfactant technology in water, recycling of the aqueous reaction mixture is straightforward and routine, thereby decreasing wastewater streams (Scheme 4).<sup>17</sup> In order to introduce fresh NPs, the typical "inflask" extraction of the reaction mixture using methyl *tert*-butyl ether (MTBE) was followed by its transfer to a vessel containing premeasured Fe/ppm Pd NPs and K<sub>3</sub>PO<sub>4</sub>. The E Factor,<sup>18</sup> introduced by Sheldon and co-workers as a measure

H<sub>2</sub>O/DMF

 $H_2O$ 

H<sub>2</sub>O

5a

5h

19

1h

			O catalyst	o o r-Bu	
Entry	Catalyst	Pd (%)	Temp (°C)	Solvent	Yield (%)
1	Fe/ppm Pd NPs	0.1	rt	2 wt % TPGS-750-M/H <sub>2</sub> O	99
2	SiO <sub>2</sub> @Fe <sub>3</sub> O <sub>4</sub> -Pd	1	100	DMF	96
3	$K-Pd-Me_{10}CB[5]$	1	140	DMF	88
4	NO <sub>2</sub> -NHC-Pd@Fe <sub>3</sub> O,	1	80	$EtOH/H_2O$ (1:1)	90
5	Pd-pyridinophane unit	5	100	DMF	94
6	Pd(OAc) <sub>2</sub> /DABCO	2	120	DMF	100
7	Pd/CuFe <sub>2</sub> O <sub>4</sub>	4	120	DMSO	95
8	Pd-Fe <sub>3</sub> O <sub>4</sub>	1	110	DMF	82
9	tetraimine Pd(0) complex	0.4	90	H <sub>2</sub> O	88 <sup>a</sup>

#### Table 4. Comparisons between Heterogeneous Catalysts

100 <sup>a</sup>Different alkenes were used in the couplings: styrene and <sup>b</sup>1-octene. <sup>c</sup>Bromobenzene and styrene were used as coupling partners.

rt

0.5

0.05

0.8

90 - 100

#### Scheme 4. Recycle, E Factor, Gram-Scale Reaction, and Residual Pd in Products from MH Reactions

CPS-MNPs-NNN-Pd

PEDOT-NFs@Pd

PdTSPc@KP-GO



10

11

12



residual Pd in products from MH couplings

			palladium [mg/g]	
products	Pd loading for HM reaction	weight of sample used (mg)	average <sup>b</sup>	Std. dev.
F <sub>3</sub> C	2500 ppm (0.25 mol %)	9.15	ND <sup>c</sup>	ND <sup>c</sup>
	1000 ppm (0.10 mol %)	9.41	ND <sup>c</sup>	ND <sup>c</sup>

<sup>a</sup>ICP-MS data were obtained from the UC Center for Environmental Implications of Nanotechnology at UCLA. <sup>b</sup>Each sample was done in triplicate with background correction. <sup>c</sup>ND = not detected.

of greenness (on the basis of "solvents" used), is even lower when the product of interest is a solid that precipitates out from the reaction and is simply filtered. As a representative example, using tert-butyl 5-iodo-1H-indole-1-carboxylate and 4-nitrostryene as starting materials, product 27 was thus obtained in 97% isolated yield. The crude product was washed with small amounts of DI water and then purified by filtration through a column. The E Factor associated with this process based on solvent usage is only 0.62, while that including water is only 6.3. A gram-scale reaction run as a measure of the

potential for industrial application scale up using the same educts (albeit with fewer equivalents of alkene), under otherwise identical conditions, afforded the desired product in 87% isolated yield (Scheme 4, middle).

72<sup>b</sup>

89

87

Another noteworthy feature associated with ppm level Pdcatalyzed MH couplings focuses on the amount of residual metal found in the product after filtration or standard extraction/purification. According to FDA-approved guidelines,<sup>19</sup> residual Pd residue must be below 10 ppm per dose per day. Exceeding these limits, which is routine when using traditional levels of Pd catalysts (i.e., 1-10 mol %), requires additional time and cost. Hence, two isolated products (Scheme 4, bottom) were chosen randomly and analyzed independently by ICP-MS. The results obtained indicated undetectable levels of Pd in each sample. One application leading to a precursor to galipinine (28) was prepared using these NPs, indicative of the potential for additional applications to targets in the pharmaceutical industry (Scheme 5).<sup>2</sup>



The option for sequential reactions in one pot represents one of the hallmarks of this chemistry in recyclable water, given the variety of reactions that can now be run under aqueous micellar conditions. By "telescoping" such consecutive reactions, there is typically a dramatic decrease in both newly created organic waste and the effort normally devoted to purification associated with each step. In the first example shown (Scheme 6), MH coupling led to product 27, that, without isolation, was followed by nitro group reduction using added Fe/ppm (Ni + Pd) NPs described previously.<sup>28</sup> In this second step, it was important to form ligandless NPs in 2 wt % Coolade/ $H_2O_1^{29}$  since the addition of NaBH<sub>4</sub> leads to frothing from hydrogen generation that is eliminated using this designer surfactant. This reagent is then transferred to the same vial used for the initial MH reaction (run in TPGS-750-M/ $H_2O$ ).

## Scheme 6. Tandem Reactions in Water

1<sup>st</sup> Sequence: 3 steps, 1-pot



The resulting aniline **29** was then treated directly with 2,4,5trichloropyrimidine leading to an  $S_NAr$  reaction, ultimately affording final product **30** in 86% overall isolated yield. As a second example (Scheme 6, bottom), by taking advantage of inherent differences in activity between an aryl iodide and bromide, an initial MH reaction with **31** led to bromide **32**, which (without isolation) participated in a Suzuki–Miyaura cross-coupling to give biaryl product **33** in 82% overall yield.

## SUMMARY AND CONCLUSIONS

In summary, new nanoparticles (NPs) derived from FeCl<sub>3</sub> have been formulated that effectively catalyze Mizoroki-Heck couplings with considerable generality, used under uncharacteristically mild and environmentally responsible conditions. Unlike those previously prepared from similar precursors, these NPs require both a modified protocol as well as a significant change in ligand for optimal catalyst activity. Notwithstanding their differences that enable heterogeneous MH couplings to now occur in water under such mild conditions, the initially generated ca. 5 nm spherical NPs have been found to be, in fact, a precatalyst to those 100-200 nm rod-shaped NPs that catalyze these couplings. Using several methods of analyses, the actual active catalytic species results only upon exposure to (usually surfactant-containing) water, which is responsible for their significant alteration, or sculpting, from small, inactive spherical NPs into much larger, reactive nanorod-shaped materials. Documentation is provided as to the extent of greenness in the form of E Factor determination, and well as the facility with which an aqueous reaction mixture can be recycled. Notably, in situations where residual levels of metal must meet rigorously prescribed (FDA) standards, ICP-MS analyses reveal that products resulting from these couplings contain undetectable amounts of palladium. The advances discussed in this contribution therefore include the following: (1) unprecedented use of water to completely alter the morphology of initially formed, and inactive, NPs into an active catalyst; (2) using various techniques common to material science to document these changes along the pathway

to an active catalyst; (3) new NPs that contain a ligand that leads to a catalyst that, in water, effects ppm level Pd catalysis of Mizoroki–Heck reactions.

The prognosis for applications to industrial targets is further strengthened by (1) a gram-scale experiment that affords the intended product without variation in yield, (2) an application to a known target in folk medicine, and (3) opportunities for tandem reactions to be carried out in a one-pot sequence in water, thereby eliminating individual step handling, processing, and waste generation.

## ASSOCIATED CONTENT

## **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11484.

Full experimental details and procedures for optimizations and couplings, analyses, full spectral data, recycling, and E Factor determination (PDF)

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## Notes

The authors declare no competing financial interest.

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