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Research Article

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Sonogashira Couplings Catalyzed by Fe Nanoparticles Containing ppm Levels of Reusable Pd, under Mild Aqueous Micellar Conditions

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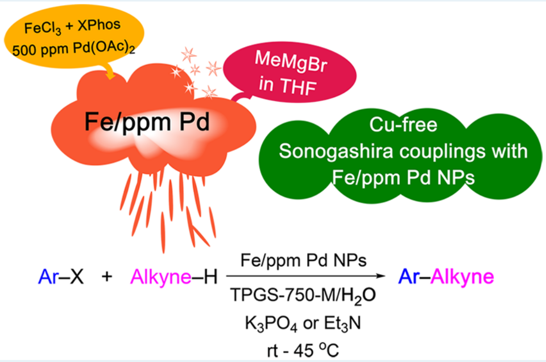
Supporting Information

ABSTRACT: Nanoparticles derived from $FeCl_3$ containing the ligand XPhos and only 500 ppm Pd effect Sonogashira couplings in water between rt and 45 °C. The entire aqueous reaction medium can be easily recycled using an "in-flask" extraction. Several tandem processes in one pot are illustrated, including a sequence involving five steps (10 reactions) in good overall yield.



KEYWORDS: *micellar catalysis, green chemistry, cross-couplings, multistep sequences, chemistry in water*

Notwithstanding the 2010 Nobel Prizes awarded in recognition of the extraordinary value of Pd catalysis in modern organic synthesis, many challenges remain in keeping with the times since the 1970s when the Suzuki, Heck, and Negishi couplings were first reported.[1] Among these challenges, sustainability figures prominently, encouraging evaluation of the impact of such chemistry on the environment. Increased attention is now being paid to issues such as catalyst recovery, cost-effectiveness, status of endangered metals, operational safety and complexity, regulatory requirements, energy consumption, product contamination with residual metals, etc. To begin to address these issues, new Fe-based nanoparticles (NPs) were recently disclosed that effectively catalyze highly useful Suzuki−Miyaura (SM) reactions under very mild aqueous micellar conditions.[2] Strikingly, these NPs were prepared from inexpensive $FeCl_3$ that naturally contained enough palladium (i.e., as an "impurity") for them to function catalytically when prepared in the presence of a ligand. The majority of the chemical makeup of these NPs (>97%) consisted of atoms derived from both the added Grignard reagent (Mg and Cl, from MeMgCl) and the solvent (C, H, and O, from THF) utilized in their formation. The amount of iron present, therefore, was relatively low (<1.5%), while the palladium content was below the detection limit using XPS analysis. And yet, as unequivocally established by control reactions, couplings were indeed mediated by this platinoid, the minimum amount of which required for catalysis was found to be ca. 320 ppm. While the most effective embedded ligand for these SM couplings was found to be SPhos,[3] the likelihood that other Pd-catalyzed C−C bond-forming reactions are amenable to use of these same NPs at the same loading of Pd and/or ligand was not high. Moreover, in altering the NPs to function as catalysts for Sonogashira couplings, new questions arose, including: (i) Are Fe/ppm Pd NPs stable when ligands other than SPhos are used? (ii) With a change of ligand, is the shape and/or size of the resulting NPs impacted such that reactivity is maintained? (iii) Does leaching of Pd become an issue? (iv) Should these Fe/ppm Pd NPs be prepared in the exact same fashion for use in other Pd-catalyzed reactions? We now report on a new, general nanoparticle technology for effecting heterogeneously Pd-catalyzed Sonogashira couplings under environmentally responsible conditions.

The preparation of these modified Fe/ppm Pd NPs is straightforward: $FeCl_3$, $Pd(OAc)_2$, and XPhos are dissolved in

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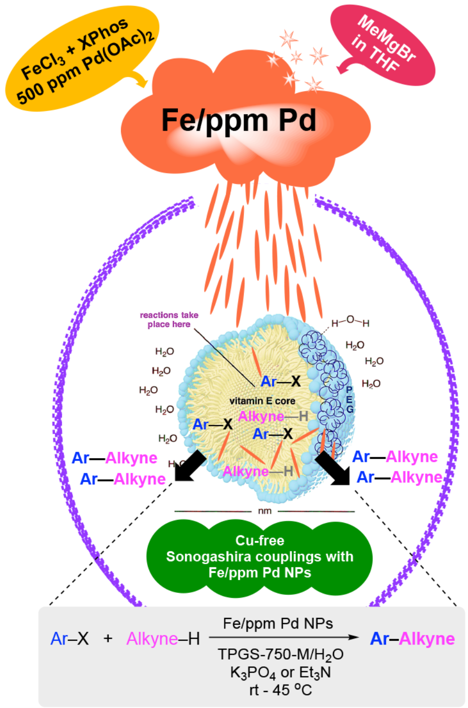


Figure 1. Preparation and application of Fe/ppm Pd nanoparticles (NPs) as a catalyst for Sonogashira couplings.

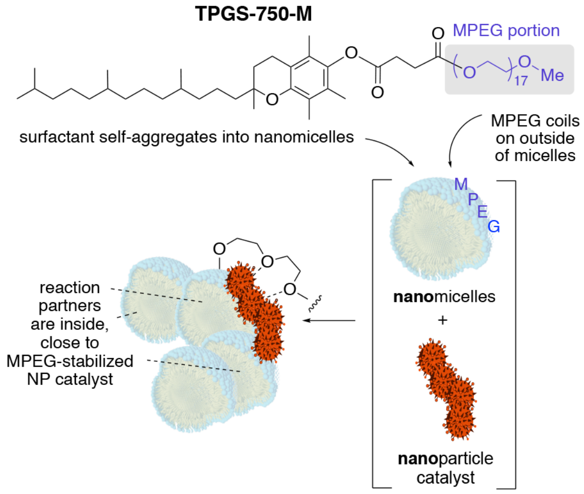


Figure 2. “Nano-to-nano” effect; the MPEG in nanomicelles delivers the reaction partners to the NP catalyst.

dry THF. MeMgBr in THF is then added at rt (Figure 1). After 20 min, quenching with trace amounts of water is followed by evaporation of solvent under reduced pressure, followed by trituration with pentane to give the NPs. These can be used directly in a reaction or isolated via filtration and stored on the shelf at ambient temperatures. NPs containing one of several other ligands (e.g., PPh_3, *t*-BuBrettPhos, SPhos) as well as sources of palladium (e.g., $PdCl_2$) or other metals in place of Pd (e.g., $Ni(OAc)_2$) were all examined, leading to an optimized procedure (see the Supporting Information for details).

Sonogashira reactions catalyzed by these NPs proceeded smoothly in water at temperatures between rt and 45 °C. The presence of the designer surfactant TPGS-750-M[4] (Figure 2; only 2 wt %, or 0.016 mmol/mL water) was instrumental in enabling these heterogeneous couplings to take place under such uncharacteristically mild conditions. That is, the MPEG-terminated nanomicelles housing the reaction partners in high concentrations[5] are delivered to the metal NPs, as the catalyst (containing Fe) is known to be stabilized by the (M)PEG serving as a ligand.[6] This “nano-to-nano” effect,[7] nonexistent in traditional organic solvents and yet seen previously in multiple systems of this type and confirmed by cryo-TEM analyses,[8] leads to product alkynes in very good isolated yields (Table 1).

Several of the examples to be found within Table 1 are worthy of note. For example, heteroaromatics within either the electrophilic or nucleophilic partner appear to be well tolerated (**7**–**9**, **11**, **12**, **17**–**20**). The presence of fluorinated educts, where fluorine is either within a CF_3 residue (**11**, **14**) or present on the ring (**6**, **10**), does not affect the coupling. Enyne derivatives can also be smoothly fashioned (**6**, **9**). Aryl bromides and iodides are the most reactive coupling partners, leaving heteroaryl chlorides intact (**9**). When highly crystalline materials are involved and, hence, solubility issues may arise, use of small percentages of a cosolvent (e.g., THF; see **17**, **20**) may prove beneficial.[9] Notably, a free arylamine residue leading to product **5** did not participate in potentially competitive amination reactions. The presence of both thiophene (**8**) and benzothiophene (**11**) rings also displayed good reactivity without observable polymerization. Coupling partners containing ester functionality were also used with impunity given the mildness of the basic aqueous conditions (**10**, **20**).

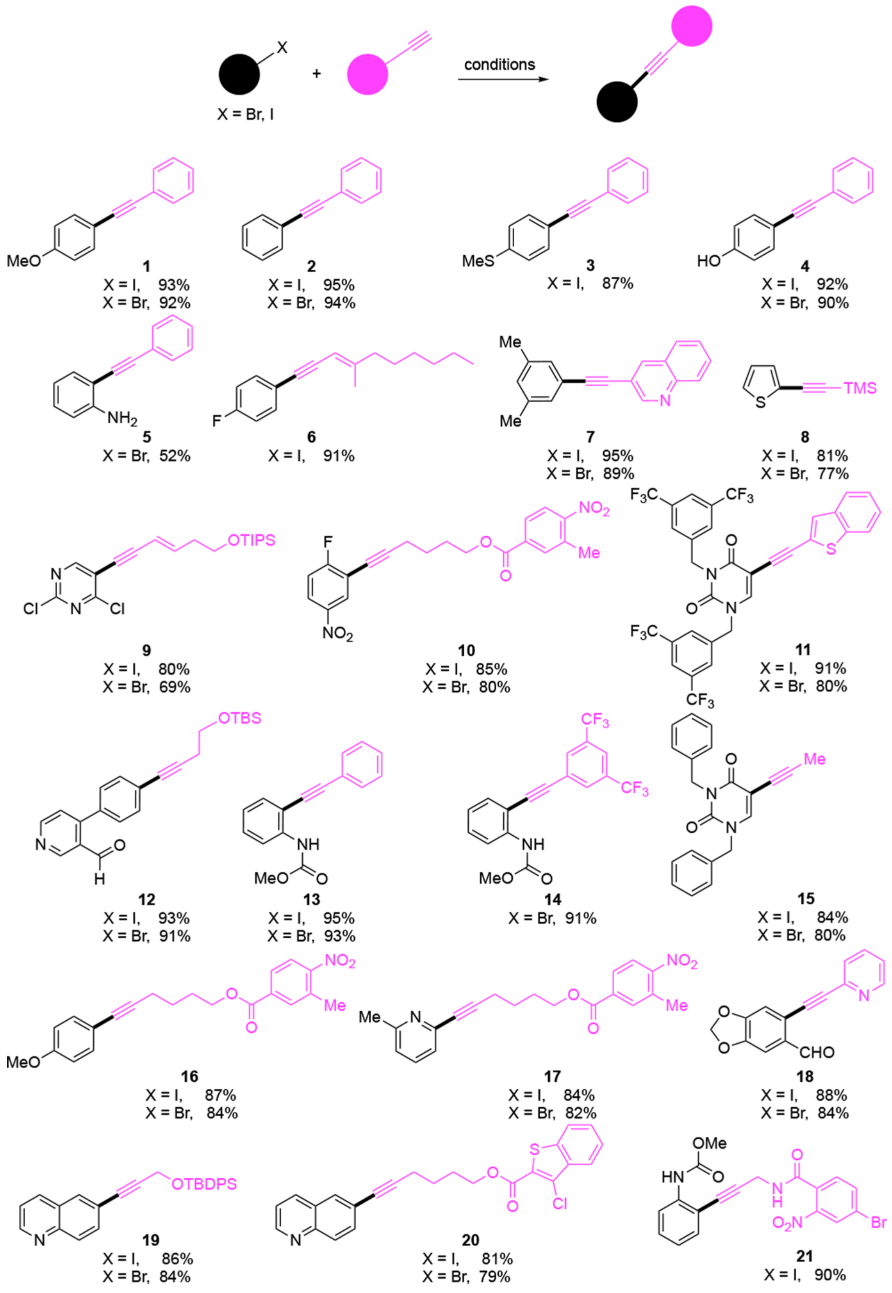
Reactivity differences between aryl iodides and bromides toward this NP catalyst could be used to great advantage. Selective reactions with substrates bearing both iodide and bromide are facile. As illustrated in Scheme 1, highly functionalized acetylenic products **24** and **21** were obtained in excellent yields independent of the original location of the bromide. Notably, for both transformations, aged (2 weeks) NPs were used as catalyst. With freshly prepared NPs, no differences in reaction times and/or yields were observed.

Multiple Sonogashira couplings on a single educt could also be achieved involving suitably halogenated precursors. Three representative examples are shown in Scheme 2, where aryl dihalides **27a** or **27b**, and **30**, each undergo double couplings to afford products **29** and **31**, respectively. 1,3,5-Tribromobenzene reacts with excess TMS-acetylene in a triple Sonogashira reaction to afford an initial product of trisubstitution. This adduct could be treated, without isolation, with added carbonate to afford the all-terminal trialkyne in 88% isolated overall yield from this one-pot process. Product **32** is of considerable general interest in materials chemistry.[10]

To demonstrate an application of this new technology, the disubstituted subsection of the antitumor agent ponatinib was targeted. As illustrated in Scheme 3, coupling between aryl bromide **33** and triethylsilylacetylene catalyzed by these Fe/ppm Pd NPs afforded the adduct **34** in 92% isolated yield. Desilylation led to terminal alkyne **35** (94%), which underwent a second Sonogashira coupling with heteroaromatic iodide **36** to give the desired alkyne **37** (84%).

One particularly noteworthy advantage characteristic of chemistry enabled by aqueous micellar catalysis is the opportunity to effect sequential reactions of the same or different type, in a single flask and without introduction of additional NPs, given that the reaction medium for each

Table 1. Representative Examples of Sonogashira Couplings Catalyzed by Fe/ppm Pd NPs[a]



1 X = I, 93%; X = Br, 92%

2 X = I, 95%; X = Br, 94%

3 X = I, 87%

4 X = I, 92%; X = Br, 90%

5 X = Br, 52%

6 X = I, 91%

7 X = I, 95%; X = Br, 89%

8 X = I, 81%; X = Br, 77%

9 X = I, 80%; X = Br, 69%

10 X = I, 85%; X = Br, 80%

11 X = I, 91%; X = Br, 80%

12 X = I, 93%; X = Br, 91%

13 X = I, 95%; X = Br, 93%

14 X = Br, 91%

15 X = I, 84%; X = Br, 80%

16 X = I, 87%; X = Br, 84%

17 X = I, 84%; X = Br, 82%

18 X = I, 88%; X = Br, 84%

19 X = I, 86%; X = Br, 84%

20 X = I, 81%; X = Br, 79%

21 X = I, 90%

[a] Conditions. (i) $FeCl_3$ (5 mol %), XPhos (3 mol %), $Pd(OAc)_2$ (500 ppm), MeMgBr (10 mol %); (ii) Ar–X (0.5 mmol), alkyne (0.75 mmol), Et_3N (1.0 mmol), 1 mL 2 wt % TPGS-750-M/H_2O, rt −45 °C, Ar.

remains the same. Hence, workup and further processing after each reaction can be minimized, saving time and materials.[11] For example, sequential Sonogashira couplings initially involving *o*-iodoaniline derivative **25** and bromoarene-containing alkyne **26** afford product **21** (Scheme 4). Without isolation, a second Sonogashira coupling could be effected by simply adding alkyne **28** to the reaction vessel. After workup, an 80% isolated yield of diyne **38** was obtained.

The effectiveness of this one-pot strategy is further illustrated in Scheme 5, in this case arriving at a potentially new ligand containing the nonracemic binaphthyl core. Starting with 3,3′-diiodo-BINOL as its *bis*-MOM derivative (**27a**), a double Fe/ppm Pd NP-catalyzed Sonogashira coupling with TMS-acetylene led to the initial adduct **39**. Removal of the TMS moieties, normally done in a separate pot using K_2CO_3 in an aqueous cosolvent medium, now utilizes the water present and the dynamic state of exchange associated with all species in the micellar medium.[5] That is, while charged ions such as carbonate are unlikely to gain entry into the hydrophobic micellar inner core, the exchange processes involving all occupants (i.e., substrates, products, etc.) and the surfactant itself occurring between micelles through the surrounding water allow for double desilylation. The resulting terminal alkynes are then available to participate in a double, region-controlled Cu-catalyzed click

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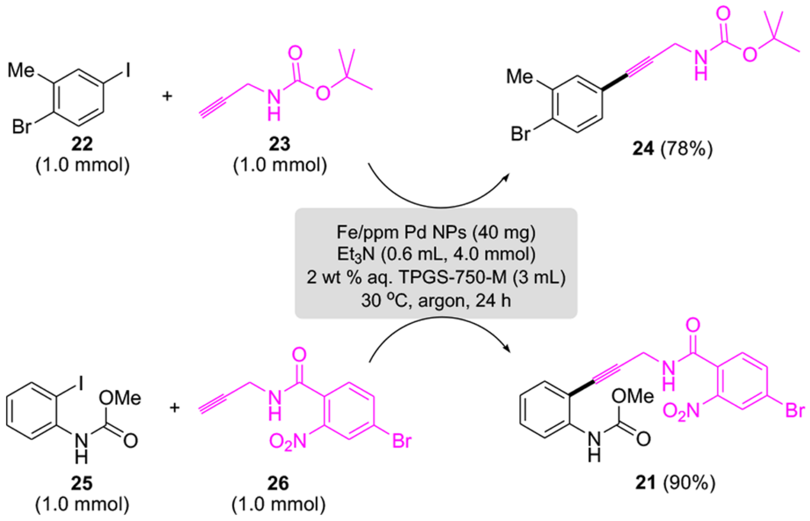
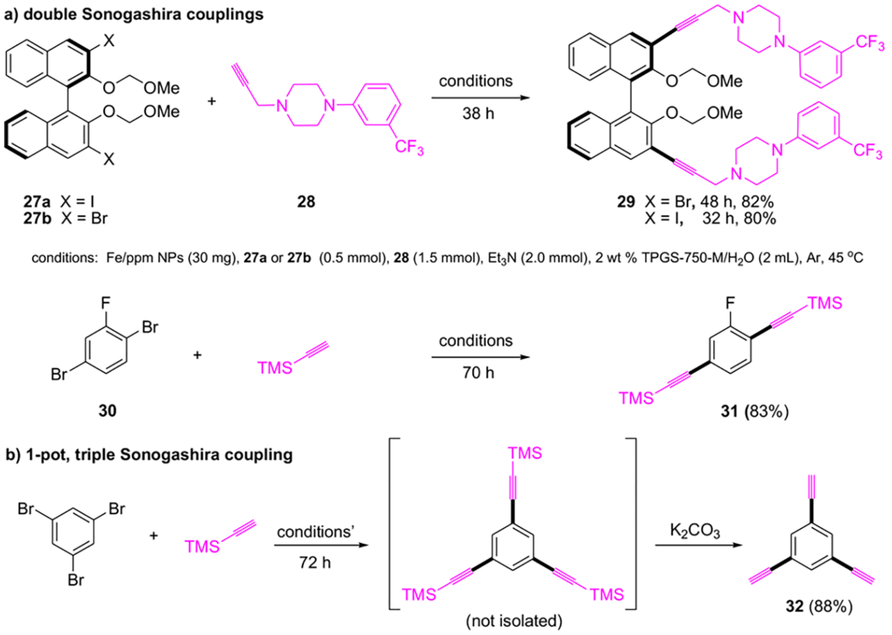
Scheme 1. Representative Examples of Selective Sonogashira Couplings



Scheme 2. Double and Triple Fe/ppm Pd NP-Catalyzed Sonogashira Couplings



conditions: Fe/ppm NPs (30 mg), **27a** or **27b** (0.5 mmol), **28** (1.5 mmol), Et_3N (2.0 mmol), 2 wt % TPGS-750-M/H_2O (2 mL), Ar, 45 °C

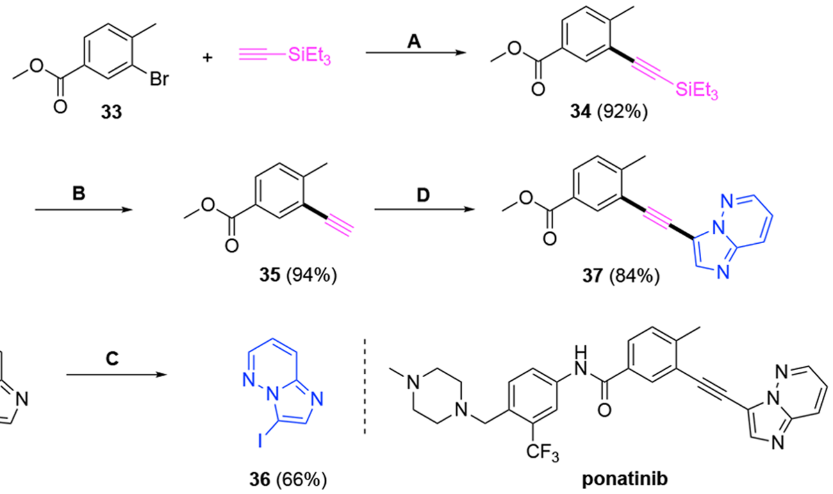
conditions: 1,3,5-triboromobenzene (1 mmol), trimethylsilylacetylene (6.0 mmol), Et_3N (5.0 mmol), Fe/ppm Pd NPs (30 mg), 2 wt % TPGS-750-M/H_2O (2 mL), Ar, 45 °C

reaction[12] to generate the *bis-N*-benzylated triazole **40**. In anticipation of introduction of an alternative group on both nitrogen atoms, debenzylation was achieved by a novel dealkylation upon introduction of inexpensive PMHS. This silane, in the aqueous medium, generates hydrogen gas that can be absorbed by the Pd present on the surface of the Fe/ppm Pd NPs, thereby effecting hydrogenolysis of the two *N*-benzyl groups to afford **41**. Once complete, the desired alkylating agent, a seemingly highly water-sensitive benzylic bromide,[13] can be added to the same flask, ultimately arriving at nonracemic BINOL derivative **42**. This single-pot sequence of five steps involves a total of 10 reactions and affords the product in an overall yield of 75%.

Since the typical workup for reactions run under aqueous micellar conditions is of the "in-flask" nature,[14] here, too, product isolation involves simply adding minimum amounts of a single solvent (e.g., EtOAc) for extraction purposes. After a few minutes of gentle stirring at rt, removal of the organic layer followed by standard processing leads to the purified product. Removal and collection of the organic solvent allows for its recycling in future extractions, while the aqueous reaction mixture left in the reaction vessel is also ready for reuse. A recycling study, as shown in Scheme 6, is suggestive of the options not only for the water containing the surfactant but for the NPs as well. Determination of an *E* factor associated with these couplings, based on the organic solvent used, was 4.1, which is roughly the expected[14] order of magnitude drop in waste generation compared to that typically found from similar reactions run in organic solvents.[15]

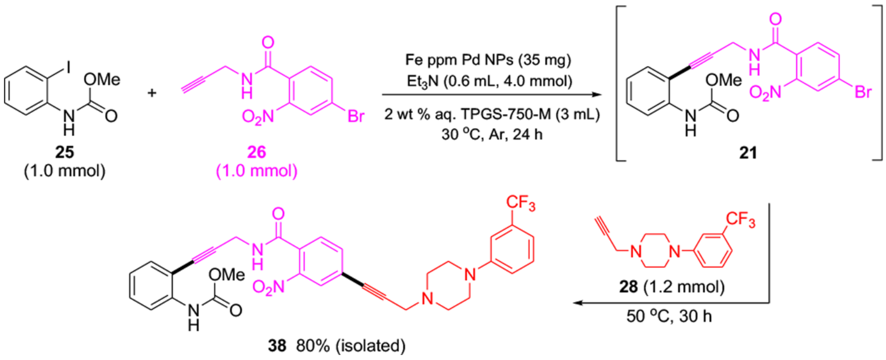
To gain insight regarding the nature of this new catalyst, extensive analytical data was obtained. Cryo-TEM analysis of in situ prepared nanoparticles in the presence of aqueous TPGS-750-M revealed a needle-like shape (Figure 3a). Their

Scheme 3. Use of Fe/ppm Pd NPs for the Synthesis of Ponatinib Intermediate 37[a]

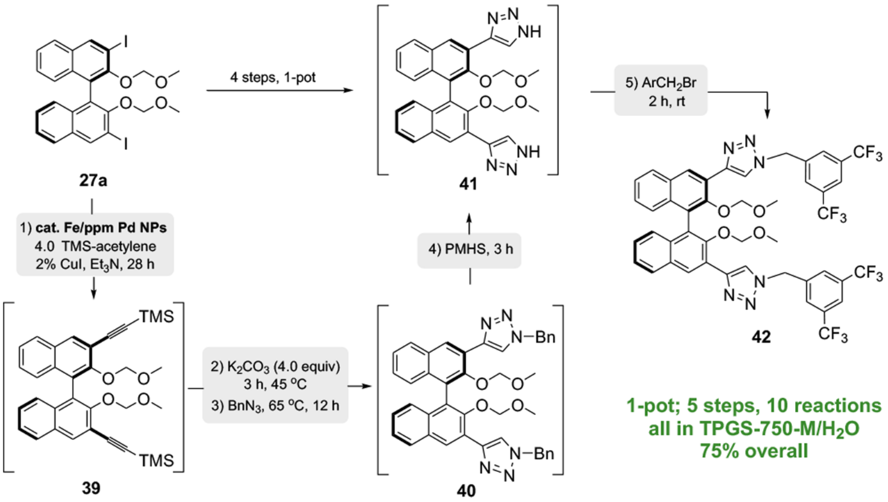


[a]Conditions: Step **A**: **33** (1.0 equiv), (triethylsilyl)acetylene (1.5 equiv), Fe/ppm Pd NPs (500 ppm Pd), Et_3N (3.0 equiv), 0.5 M in 2 wt % TPGS-750-M/H_2O, 50 °C, argon, 14 h. Step **B**: **34** (1.0 equiv), K_2CO_3 (20 mol %), 0.5 M in 1:1 MeOH/THF, 45 °C, 5 h. Step **C**: Imidazo[1,2-*b*]pyridazine (1.0 equiv), *N*-iodosuccinimide (1.2 equiv), 0.53 M in DMF, 80 °C, argon, overnight. Step **D**: **36** (1.0 equiv), **35** (1.2 equiv), Fe/ppm Pd NPs (1000 ppm Pd), Et_3N (3.0 equiv), 0.5 M in 2 wt % TPGS-750-M/H_2O, 50 °C, argon, 43 h.

Scheme 4. Sequential Fe/ppm Pd NP-Catalyzed Sonogashira Couplings in Water

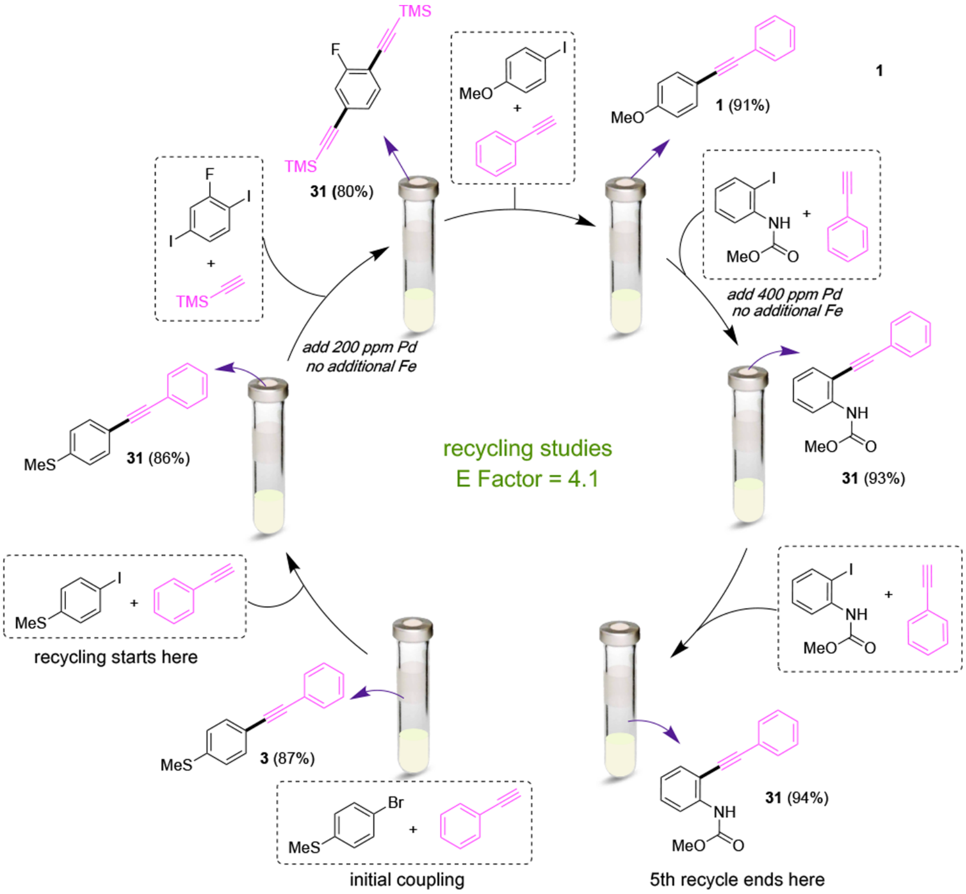


Scheme 5. Multistep, One-Pot Sequence in Aqueous Nanomicelles

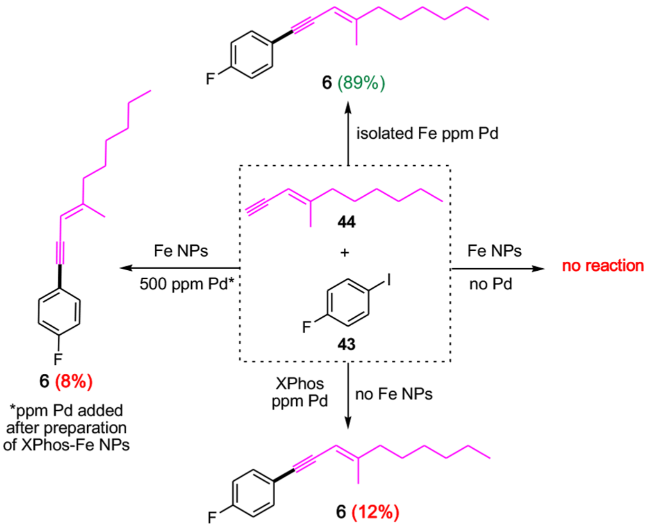


average size is ca. 70 nm, and they were found, as expected,[8] to be surrounded by nanomicelles of surfactant. In control experiments as illustrated in Scheme 7, NPs prepared in the absence of Pd showed no catalytic activity, while adding ppm Pd after their preparation did not provide active catalyst, as only 8% product **6** was obtained. Similarly, reaction in the presence of 1000 ppm of Pd ligated with XPhos (i.e., no NPs), afforded only 12% product even after a prolonged reaction time. This suggests that any leaching of Pd from these NPs, however unlikely given the insolubility of such

Scheme 6. Recycling Study and *E* Factor Determination



Scheme 7. Control Experiments Revealing the Importance of Pd Integrated within the NPs



ligated Pd species in water, does not lead to an active catalyst as compared to Fe/ppm Pd NPs.

Catalyst stability and shelf life were tested as well, including exposing these NPs to thermal gravimetric analysis (TGA). Complete loss of THF bound to the NPs occurs at 154 °C, implying that, at this temperature, NPs lose their integrity and catalytic activity (Figure 3b). Loss of free ligand, however, occurs above 200 °C, while ligand bound to the metal(s) remains intact. Isolated catalyst was highly stable at room temperature (Figure 3c), and aged catalyst was also tested for catalytic activity in many reactions (see Schemes 2b and 4). Analysis of NPs via XPS revealed a binding energy corresponding to Fe^{3+}, with this metal being ligand-bound (Figure 3d). ^{31}P NMR of these NPs also shows that XPhos does not exist as a free ligand. As seen previously,[2] the low levels of Pd present could not be detected by XPS analysis.

The choice of reductant was crucial for bench stability of these nanoparticles. When MeMgCl was added to the mixture of $FeCl_3$, $Pd(OAc)_2$, and XPhos, the resulting isolated NPs, while initially able to mediate the desired coupling, were surprisingly catalytically far less active after 3 days in storage at rt (Scheme 8). Thus, using aged NPs, reaction of aryl bromide **45** with alkyne **46** under typical conditions led to product **18** in only 18% yield after 50 h. However, when MeMgBr was introduced as a reductant, the resulting NPs retained catalytic activity even after 3 weeks, affording the expected product **18** in 82% yield. These observations are in direct contrast to those associated with NPs made previously and applied to SM couplings,[2] where both chloride ions and SPhos are essential for catalytic activity. For Sonogashira reactions, by contrast, the chloride/XPhos combination present within the NP architecture is far less stable, and subject to decomposition over time. Interestingly, when aged material was analyzed by HRTEM (Scheme 8), the initial needle-like shape (see Figure 3a) had completely changed, clumping into far larger, inactive particles.

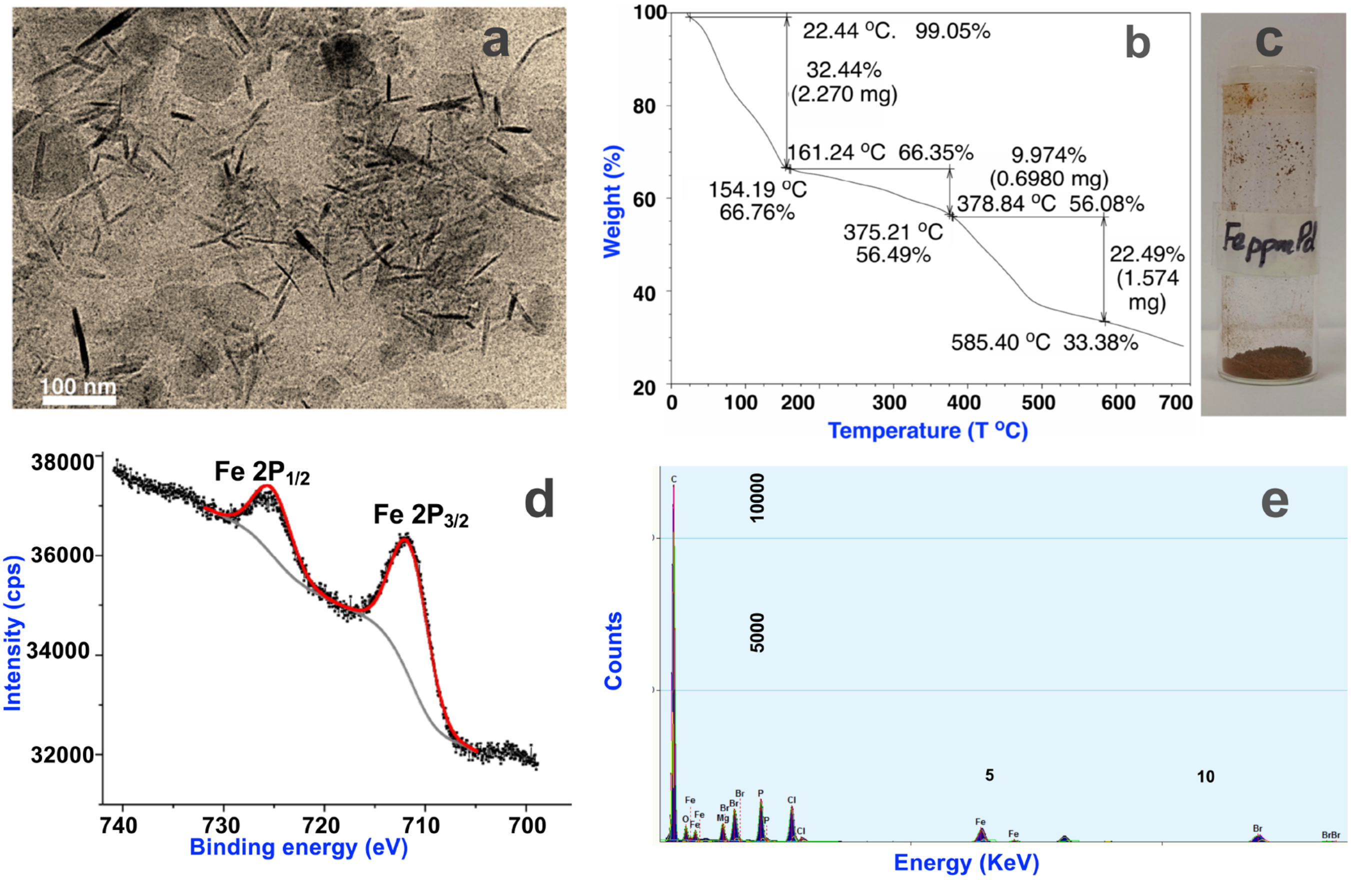
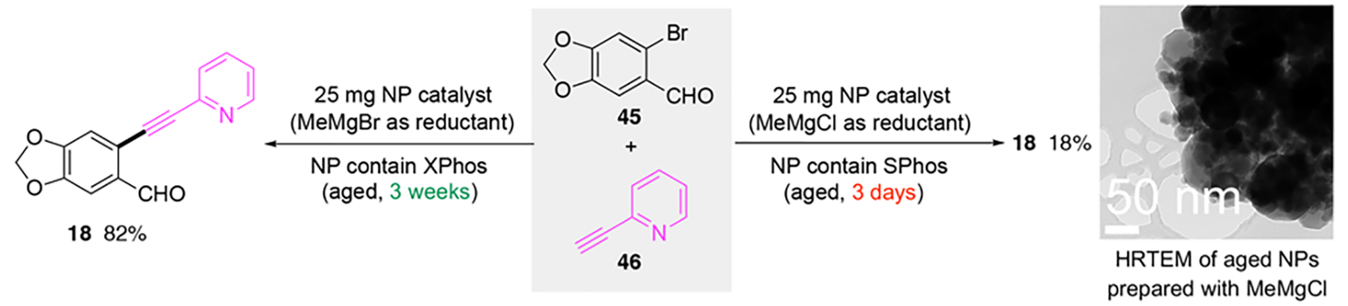


Figure 3. (a) Cryo-TEM analysis of NP; (b) TGA analysis; (c) isolated NP (aged for 4 weeks); (d) XPS analysis; (e) EDX analysis.

Scheme 8. Differences between NPs Formed Using MeMgCl vs MeMgBr



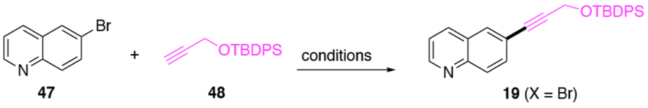
conditions: **45** (0.5 mmol), **46** (0.75 mmol), NPs, Et_3N (1.0 mmol), 2 wt % TPGS-750-M/H_2O (1 mL), Ar, 45 °C, 50 h.

To determine whether NP-bound THF is required for catalysis, control experiments were performed at different temperatures (Scheme 9). Reaction between **47** and **48** proceeded smoothly with aged NPs at 45 °C; after 30 h, **47** was completely consumed and product **19** was obtained in 81% isolated yield. On the other hand, heating the NP catalyst at 80 °C under a vacuum for 6 h led to loss of THF and resulted in a dark brown solid. When tested for activity at the same 45 °C, only 40% of product **19** was obtained, suggesting that most of THF had been lost from the nanostructured catalyst. External addition of THF to the preheated, aged catalyst did not significantly improve the yield, implying that reconstitution of the NPs does not take place. Thus, THF appears to be an essential component of these NPs.

Further testing on the potential loss of THF from these NPs is conducted under aqueous conditions, given its water miscibility. Aged NPs were washed several times with water and dried under air. No change in color was observed. When used as a catalyst for the same Sonogashira coupling between **47** and **48**, no difference in activity was noted, indicative of a strong association of THF within these NPs (Scheme 10).

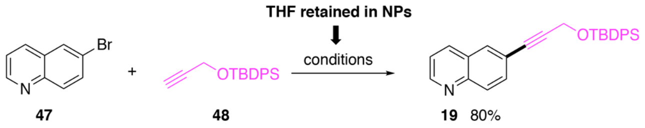
In summary, new nanoparticles are described that function as a highly effective catalyst for especially valuable, copper-free Sonogashira reactions.[1] These reactions take place under mild conditions, in water as the gross reaction medium, and are amenable to recycling as is the entire aqueous system. Given the commonality associated with the reaction conditions that apply to many typical reactions in organic synthesis,[16] a multitude of opportunities for tandem sequences now exist,[11] as exemplified herein. Further

Scheme 9. Control Experiments for Potential Catalyst Decomposition



	yield (%)
NPs used *WITHOUT* pre-heating at 80 °C under vacuum 20 mg NPs **47** (0.5 mmol), **48** (0.75 mmol) Et_3N (1.0 mmol), 2 wt % TPGS-750-M/H_2O (1 mL) 45 °C, 30 h, Ar	81%
NPs used *AFTER* pre-heating at 80 °C under vacuum 20 mg NPs **47** (0.5 mmol), **48** (0.75 mmol) Et_3N (1.0 mmol), 2 wt % TPGS-750-M/H_2O (1 mL) 45 °C, 30 h, Ar	40%
NPs used *AFTER* pre-heating at 80 °C under vacuum followed by addition of THF to the reaction mixture 20 mg NPs **47** (0.5 mmol), **48** (0.75 mmol) Et_3N (1.0 mmol), 2 wt % TPGS-750-M/H_2O (1 mL) 0.2 mL THF, 45 °C, 30 h, Ar	46%

Scheme 10. Strong Association of THF within These NPs as Catalyst



conditions: 20 mg pre-washed NPs, **47** (0.5 mmol), **48** (0.75 mmol) Et_3N (1.0 mmol), 2 wt % TPGS-750-M/H_2O (1 mL), 45 °C, 30 h, Ar

applications of this technology to both stand-alone and one-pot, multistep reactions, applied to targets within the pharmaceutical and agrochemical arenas, are under active investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b00007.

> Detailed reaction optimization, general catalytic procedure, characterization of nanomaterial, and NMR data of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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