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Letter

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Micelle-Enabled Palladium Catalysis for Convenient sp^2-sp^3 Coupling of Nitroalkanes with Aryl Bromides in Water Under Mild Conditions

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ABSTRACT: The efficacy of custom surfactant FI-750-M, designed to mimic polar solvents such as DMF and 1,4-dioxane, has been demonstrated with the palladium-catalyzed sp2-sp3 coupling of nitroalkanes to aryl bromides using a heteroleptic palladium catalyst under unprecedentedly mild conditions. Optimized reaction conditions mostly provided good yields up to gram scale, with high selectivity and functional group tolerance for a wide scope of aryl bromides. Use of surfactant FI-750-M makes water the gross reaction medium and enables in-flask recycling. The behavior of the surfactant has been elucidated with DLS and cryo-TEM measurements, and mechanistic investigations have revealed the importance of the π-allyl ligand in the catalytic cycle.

KEYWORDS micellar catalysis, green chemistry, cross-couplings, E factor, amphiphiles.

While tracing back the history of the 2010 Nobel Prize in Chemistry, Colacot and Snieckus found palladium catalyzed cross-couplings to be the most heavily used reactions in multiple arenas.[1] Although such reactions can be achieved with other transition-metal catalysts,[2] palladium is still considered as a first choice for synthetic organic chemists.[3] The reasons behind this prevailing preferential approach are ease of handling, broader substrate scope, greater functional group tolerance, mild reaction conditions, high reproducibility at industrial scale, etc.[4] Unfortunately, palladium is an endangered element and its current accessible supply is limited.[5] Options to prolong its supply are to completely move away from pallidum or to use it at a reasonably low level with an opportunity to recycle and re-use without any additional investment of resources. Uozumi and co-workers have demonstrated highly efficient catalysis with very intelligently designed nanocatalysts and amphiphilic palladium species.[6] Very recently, Lipshutz and co-workers have significantly contributed in this area, especially for sustainable and practical Suzuki-Miyaura (SM) cross-couplings, by developing Fe-ppm Pd nanoparticles and a highly potent ligand.[2f, 6] However, these two approaches are only applicable to SM, Sonogashira couplings, and nitro reductions.[7] Along the same lines, Colacot and co-workers have developed very potent phosphine-based π-allylpalladium complexes with versatile activity in cross-coupling chemistry,[8] although these complexes are highly active only under inert atmosphere in organic solvents, mostly at elevated temperature.

Despite the high value of α-arylated/heteroarylated nitroalkanes,[9] among sp^2-sp^3 cross-coupling reactions catalytic but sustainable arylations of nitroalkanes are yet underexplored;[10] there is not a single report focusing on avoidance of organic solvents, use of low palladium loading, in-flask recycling and re-use of catalyst and reaction medium, or reactions under ambient conditions. Typically, these couplings are achieved using up to 10 mol% palladium e.g., (Pd_2dba_3) in toxic organic solvents such as 1,4-dioxane at elevated temperature under very dry conditions. Accordingly, current methods are not sustainable (Figure 1).

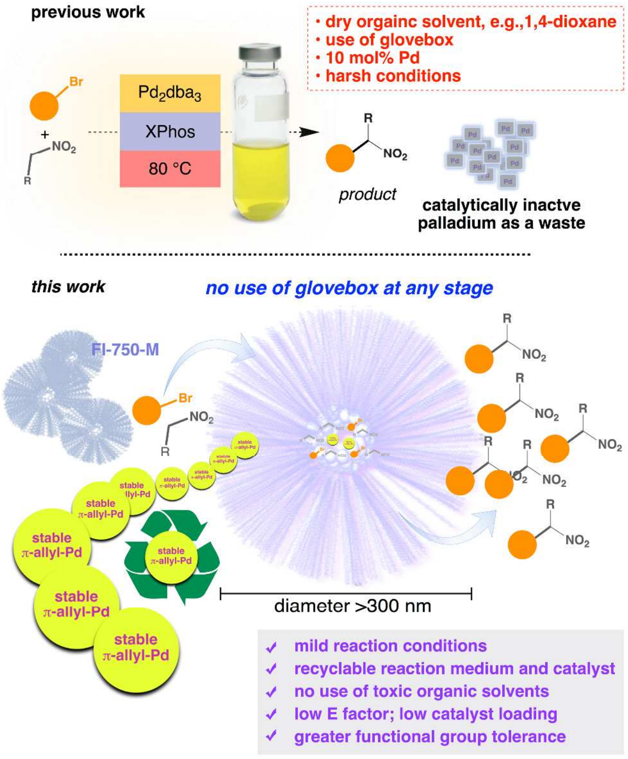
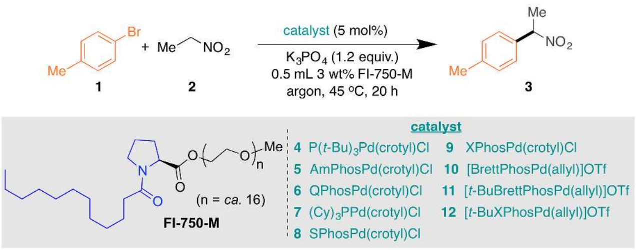


Figure 1. Advances facilitated by a sustainable micellar approach for arylation of nitroalkanes.

To avoid the use of organic solvents and achieve catalysis with low palladium loading, we suspected that micellar catalysis may be the better approach.[11] However, substrates with high to moderate polarity including nitroalkanes, potentially present a challenge, particularly in accommodating these types of molecules in a micellar core—a requisite for the optimal catalytic activity that we had observed in our previous work.[2g] To solve this critical problem, we decided to develop an environmentally benign amphiphile that, when dissolved in water, would form micelles with slightly polar inner micellar cores in order to mimic DMF and 1,4-dioxane, and thus could easily accommodate relatively polar nitroalkanes, as polar as nitroethane. This technology also would enable the chemistry to be conducted in water under ambient conditions without use of toxic organic solvent. The second important consideration was choice of a catalyst demonstrating high compatibility with micellar arrays as well as optimal stereoelectronic properties and potency.[6] A key determinant here is catalyst lipophilicity. In essence, the longer the catalyst spends inside the micelle, the more catalysis that takes place, so more lipophilic catalysts should enable lower catalyst loadings.

Here we disclose the results of this strategy: a general, efficient, mild, and sustainable method for arylation/heteroarylation of nitroalkanes. Our study began with design of FI-750-M, a proline-based environmently benign non-ionic surfactant with a moderately polar inner core, that, when mixed with nitroalakanes, exponentially increases the size of micelles to accomodate reaction components for effective catalysis. During initial catalyst screening for a model reaction between **1** and **2** using K_3PO_4 as a base in a 3 wt% aqueous solution of FI-750-M, various palladium catalysts and ligands that are highly active in routine cross-coupling reactions including HandaPhos,[6] biaryl phosphines,[1,12] and Fe-ppm Pd nanoparticles[2f] were unable to provide fruitful results. Only traces of desired product were identified (for details, see Supporting Information). Finally, to our delight, π-allyl palladium complexes[8] recently developed by the Colacot group, displayed better catalytic acitivity (see SI and Table 1). Further investigation revealed the high bench stability of catalysts from this series. While screening the catalytic activity of such π-allyl palladium complexes over a model reaction, catalysts **11** and **12** were found to demonstrate the desired activity (Table 1). Only 74% conversion was detected with **11** while full conversion was acheived with catalyst **12**. This remarkable difference in catalytic activity fits with expectations of the optimal lipophilicity needed to accomodate a catalyst within the micellar core.

Table 1. Optimizations of micelle-enabled catalytic arylation of nitroalkanes

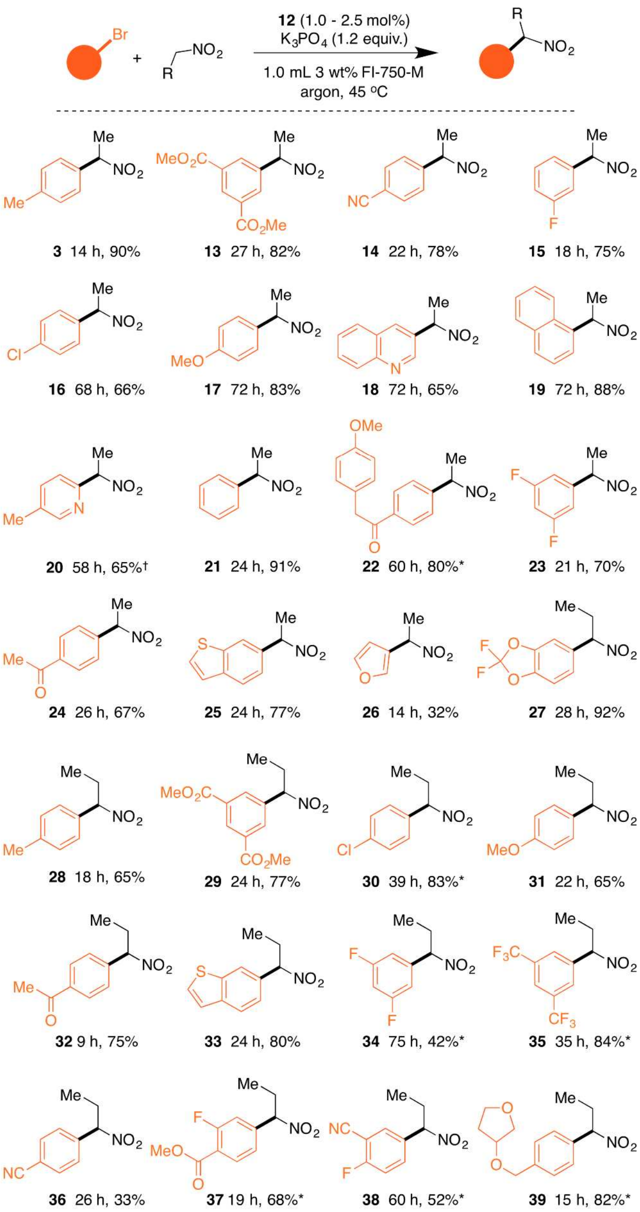


entry	catalyst	base	% yield **3***
1	**4**	K_3PO_4	8
2	**5**	K_3PO_4	0
3	**6**	K_3PO_4	4
4	**7**	K_3PO_4	0
5	**8**	K_3PO_4	3
6	**9**	K_3PO_4	8
7	**10**	K_3PO_4	19
8	**11**	K_3PO_4	74
9	**12**	K_3PO_4	100
10	$Pd(OAc)_2$	K_3PO_4	0
11	**12**	i-$PrNEt_2$	68
12	**12**	NEt_3	60
13	**12**	K_2CO_3	81

Conditions: **1** (0.25 mmol, 43 mg), **2** (2.5 mmol, 180 µL), **12** (5 mol%), base (0.5 mmol, 2.0 equiv.), 0.5 mL 3 wt % FI-750-M, 45 °C, 24 h, argon atmosphere. *Conversions based on GCMS.

Optimization studies revealed a dependence on several variables, most notably the nature of the aryl halide and the palladium source. Compared to aryl bromides and chlorides, poor conversions were observed with aryl iodides. Pre-complexation of *t*-BuXphos with $Pd(OAc)_2$ or Pd_2dba_3 did not show catalytic activity comparable to corresponding π-allyl palladium complex **12**, suggesting that the allyl (η^2 or η^3) component is an active ligand in the catalytic cycle. Other variables for optimal catalytic activity were FI-750-M as surfactant, K_3PO_4 as base, 1–2.5 mol% of catalyst **12**, and 45 °C as reaction temperature (See SI). Low catalyst loading and no use of glovebox at any stage are noteworthy.

Table 2. Substrate scope for catalytic arylation of nitroalkanes



Conditions: unless otherwise noted Ar—Br (0.5 mmol), nitroalkane (2.5 mmol), **12** (1–2.5 mol%), base (0.6 mmol, 1.2 equiv.), 1.0 mL 3 wt% FI-750-M, 45 °C. †Reaction temperature 60 °C; *reaction scale 0.25 mmol. All listed yields are isolated.

After establishing very mild optimal reaction conditions, further substrate scope was explored in order to reveal the generality of the protocol. Special attention was paid to reproducibility, functional group tolerance, and steric and electronic parameters.

Notably, aryl chlorides displayed very sluggish reactivity. Remarkable generality was found with respect to the nature of aryl bromides including excellent functional group tolerance. Electron deficient (Table 2; **13**–**16**, **22**–**24**, **29**, **32**, **34**–**38**) as well as electron-rich (**17**, **18**, **20**, **25**–**28**, **31**, **33**, **39**) aryl residues were very well tolerated with good-to-excellent yields. Ester (**13**, **29**, **37**), nitrile (**14**, **36**), ketone (**22**, **24**), chloro (**16**, **30**), fluoro (**15**, **23**, **27**, **34**, **37**, **38**), trifluoromethyl (**35**), and cyclic ether (**27**, **39**) functionalities all easily survived, and no detrimental effect on outcome of the catalytic process was observed. When a substrate with an acetyl residue was subjected to these conditions, no side product from an Aldol-type reaction was observed (**22**, **24**). Notably, in an aqueous environment and under basic pH, no ester hydrolysis was observed (**13**, **29**, **37**) and good-to-excellent yields were obtained. Both mono- and di-esters were well tolerated (**13**, **29**, **37**). Heteroaromatics quinoline (**18**), pyridine (**20**), benzothiophene (**25**, **33**), and furan (**26**) displayed good to excellent reactivity without formation of any homocoupling side product. No polymerized side product was observed for the benzothiazole moiety. Furthermore, a diarylated nitro product was not observed in any example.

Although micellar media played a crucial role in successful reaction completion (see SI), it was still questionable whether micelles accommodated the moderately polar nitroalkanes or not. Dynamic light scattering (DLS) experiments revealed the existence of nanomicelles composed of FI-750-M with an average diameter of *ca*. 300 nm (Figure 2) which is quite large compared to other non-ionic surfactants.[13] Upon addition of *ca*. 2% of nitroethane to the surfactant solution, particle size exponentially increased and a more diverse population of sizes was observed (Z-average 530 nm). The increase in micelle size along with reduction of peak area around 300 nm supports the formation of larger particles by merging of smaller ones and nitroethane, which occured without any visual turbidity in solution.[13] Size, distribution, and shape of nanomicelles composed of FI-750-M were also confirmed by cryo-TEM imaging and the average size was in agreement with that revealed by DLS.

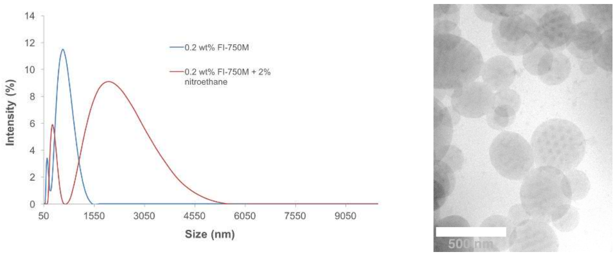
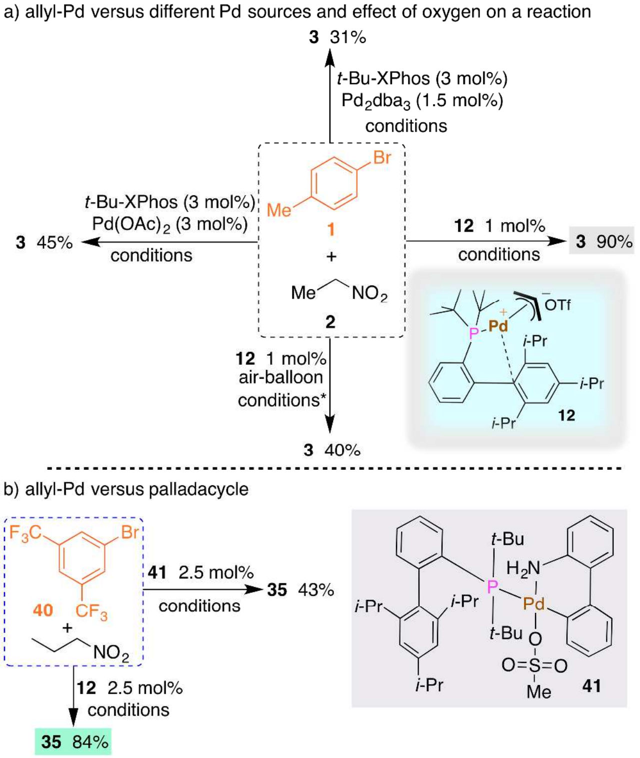


Figure 2. DLS data of FI-750-M in water revealing particle size growth and accommodation of relatively polar reactant nitroethane (left); cryo-TEM of FI-750-M showing large micelles (right).

In order to gain insight into the nature of the catalyst, control experiments were conducted. These revealed that *t*-BuXPhos-bound palladium is not enough for the desired level of catalytic activity (Scheme 1). Using different palladium sources with *t*-BuXPhos as ligand under optimized reaction conditions, less effective catalysis was achieved. Palladium sources Pd(OAc)$_2$ and Pd$_2$dba$_3$ produced only 45% and 31% yield of **3**, respectively. Again, only corresponding π-allyl palladium species **12** was catalytically efficient and highly active. However, use of **12** in the presence of atmospheric oxygen significantly dropped its activity, and only 40% desired product was obtained, which may be due to further oxidation of nitro to ketones or incompatibility of any reaction intermediate with oxygen.

Scheme 1. Control experiments and catalytically active species



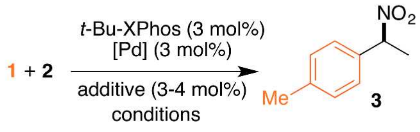
Conditions: unless otherwise noted, Ar—Br (0.5 mmol), nitroethane/nitropropane (2.5 mmol) and catalyst as shown in scheme, base (0.6 mmol, 1.2 equiv.), 1.0 mL 3 wt% FI-750-M, argon atmosphere, 45 °C. *air balloon instead argon atmosphere.

Arguably, such significant differences in catalytic activity between **12** and *t*-BuXPhos bound to different palladium sources may be due to different induction periods for generation of the active palladium(0) species needed for initiation of a catalytic cycle. The induction period could be further lowered by using the corresponding palladacycle. Therefore, by choosing coupling partners **40** and nitropropane, activity of palladacycle **41** was compared with **12**. Compared to 84% isolated yield with standard conditions, relatively poor conversion (43%) was observed for the palladacycle and 50% unreacted **40** was recovered.

Having identified the importance of a π-allyl component in the catalyst, attention was drawn to the mechanistic significance of this system. One suspicion was that the catalytic cycle could involve Pd(I) and Pd(III) intermediates when using π-allyl-Pd as in **12**. However, neither Pd(I) nor Pd(III) were detected in EPR experiments (see SI for details). Because AgOTf was used in the synthesis of **12**, the possibility for synergistic catalysis by residual silver was investigated. Upon control reactions using traces or a catalytic amount of AgOTf and different palladium sources with *t*-ButylXPhos, no synergistic effect was observed (Scheme 2). Finally, it could be inferred that the allyl group is acting as a π-acid ligand and is essential for high catalytic activity. In control experiments using catalytic amounts of propylene or allyl bromide with *t*-ButylXPhos pre-complexed with palladium acetate, efficient catalysis was achieved, revealing the role of the allyl ligand. This result suggests that, unlike in organic solvents, in micelar media *t*-

ButylXPhos may be acting merely as a monodentate ligand without any non-classical metal-arene ligation.[14]

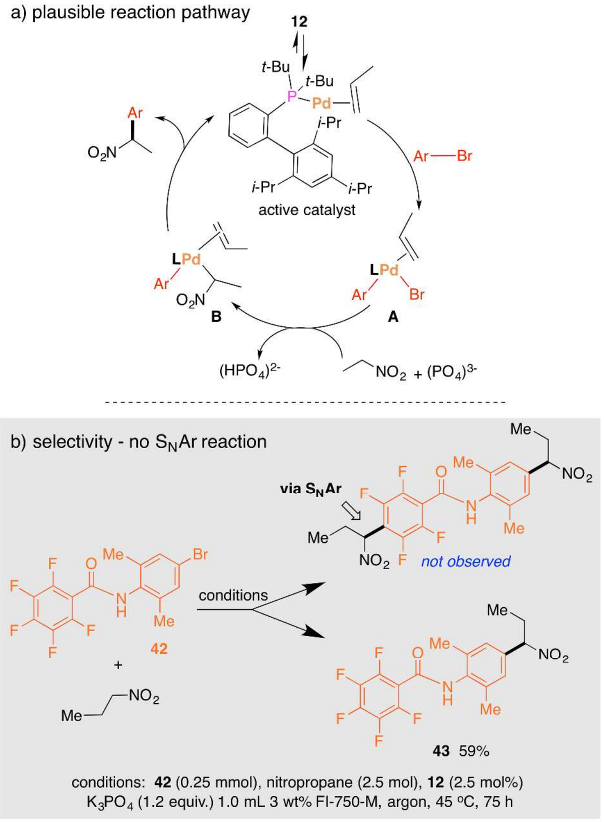
Scheme 2. Effect of silver as a co-catalyst/trace impurity and π-acid ligand



[Pd]	additive	**3** (%)
$Pd(OAc)_2$	AgOTf	42
$Pd(OAc)_2$	*AgOTf	42
**Pd_2dba_3	AgOTf	28
$Pd(OAc)_2$	propylene	90
$Pd(OAc)_2$	allyl bromide	89

Conditions: **1** (0.5 mmol, 85 mg), **2** (2.5 mmol, 180 µL), [Pd] (3 mol%) K_3PO_4 (0.6 mmol, 1.2 equiv.), 1.0 mL 3 wt% FI-750-M, 45 ºC, 24 h, argon atmosphere. Propylene was used as a 0.1 M solution (0.2 mL, 4 mol%) in hexanes. *100 ppm AgOTf was used as a co-catalyst. **Pd_2dba_3 loading was 1.5 mol%.

In light of these revelations, we propose a mechanism that involves *in situ* formation of an η^2 allyl palladium(0) complex that undergoes oxidative addition to form intermediate **A** (Figure 3a). Under basic conditions, the bromide group is slowly replaced by nucleophilic attack from the α-carbon of the nitro coupling partner to form intermediate **B** followed by reductive elimination to generate the product and active catalyst for the next cycle.



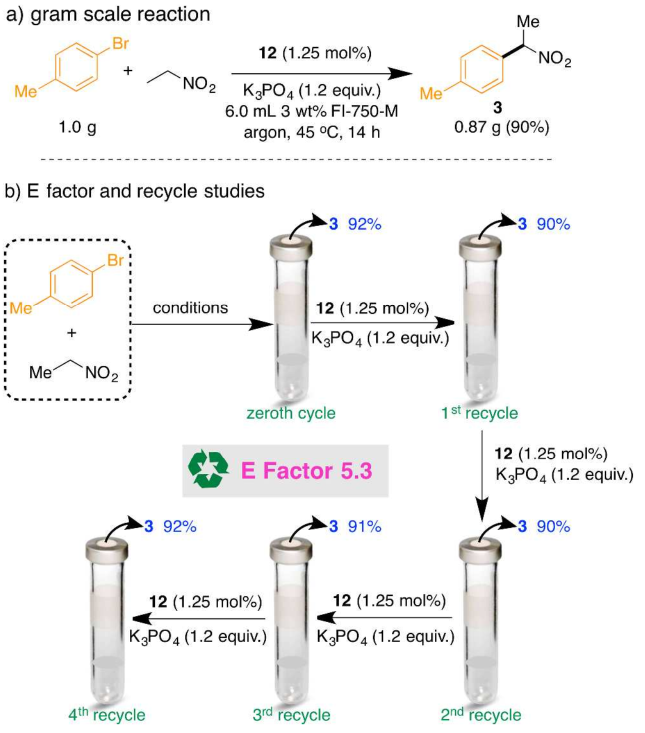
conditions: **42** (0.25 mmol), nitropropane (2.5 mol), **12** (2.5 mol%) K_3PO_4 (1.2 equiv.) 1.0 mL 3 wt% FI-750-M, argon, 45 ºC, 75 h

Figure 3. Plausible mechanism and reaction selectivity.

Next, selectivity of this process was explored by choosing a coupling partner **42** having an activated polyfluoroaryl residue that could easily undergo S_NAr reaction to form a dialkylated product or polymerize (Scheme 3b). However, due to very mild reaction conditions, no such side product was observed and **43** was obtained with 59% isolated yield. Desired reaction was somewhat sluggish and remaining starting material was recovered.

Finally, gram-scale reproducibility and sustainability of this micelle-enabled transformation were assessed (Scheme 3). Using 1.25 mol% catalyst loading, **3** was obtained with 90% isolated yield (Scheme 3a). Attempts at full recycling of the catalyst resulted in slow conversions. A recycling study with partial palladium and full reaction medium recycling resulted in a very low E factor[15] of 5.3 with recovery of solvent used in chromatography and 18.4 without recovery in the last cycle, demonstrating the greenness of this process (Scheme 3b).

Scheme 3. Gram scale reaction and recycle studies



conditions: 12 (2.5 mol%), K_3PO_4 (1.2 equiv.), 1.0 mL 3 wt% FI-750-M, 45 ºC, 24 h

In summary, this work demonstrates the development of an environmentally benign amphiphilic molecule that mimics polar solvents such as DMF and 1,4-dioxane along with a significant advance in the area of palladium catalysis and cross-coupling chemistry, in particular for sp^2-sp^3 couplings. Specifically, it offers the synthetic community a palladium catalyzed arylation of nitroalkanes that is noteworthy for: (1) low palladium loading; (2) general applicability to a broad range of functionalities; (3) very mild conditions; and (4) use of an aqueous reaction medium that avoids organic solvents, requires very little water, and allows for in-flask recycling of the surfactant, water, and catalyst.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at XXX.
Reaction optimization, details of cryo-TEM, DLS, control-experiments, analytical data of compounds, and NMR data.

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Notes

The authors declare competing financial interest for the surfactant FI-750-M and their derivatives.

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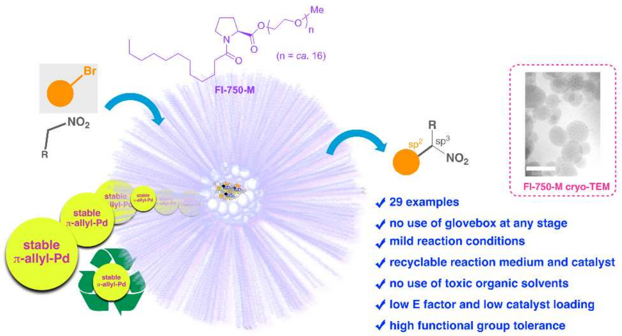
Me
n
(n = ca. 16)
FI-750-M
Br
NO2
R
stable π-allyl-Pd
R
sp2
sp3
NO2
FI-750-M cryo-TEM
✓ 29 examples
✓ no use of glovebox at any stage
✓ mild reaction conditions
✓ recyclable reaction medium and catalyst
✓ no use of toxic organic solvents
✓ low E factor and low catalyst loading
✓ high functional group tolerance