Tetrahedron xxx (2018) 1–4

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Palladium nanoparticles: Chemoselective control for reductive Heck with aryl triflates and 2,3-dihydrofuran

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ARTICLE INFO

*Article history:*
Received 13 February 2018
Received in revised form
13 April 2018
Accepted 17 April 2018
Available online xxx

*Keywords:*
Palladium catalysis
Reductive Heck
Nanoparticles

ABSTRACT

The reductive-Heck reaction offers a unique entry to formal $Csp^2$-$Csp^3$ cross-coupling reactions that proceed in the absence of a main group organometallic coupling partner. Consequently, further development of new variants would be transformative. Unfortunately, controlling the relative rates of the organopalladium intermediates has proven difficult with homogenous, single-site Pd catalysts. This work describes a selective reductive Heck reaction catalyzed by Pd-nanoparticles. The reaction works well with electron-deficient aryl triflates at room temperature in the absence of ligands. This work addresses some of the challenges found in the reductive-Heck literature.



## 1. Introduction

The Mizoroki-Heck reaction maintains a privileged status in synthesis due to its broad use in organic chemistry. Since the first reports by Mizoroki and Heck, the ability to combine an aryl/vinyl halide and an olefin to create a carbon-carbon bond has empowered legions of chemists.[1,2] The impact of this work culminated in a share of the 2010 Nobel Prize award for Richard F. Heck. While originally investigated as an intermolecular variant,[3–9] the intramolecular Mizoroki-Heck enabled the construction of highly hindered carbon atoms.[10]

In 1984, Jeffery reported unique conditions for the Heck reaction that included tetrabutylammonium chloride (TBAC), $Pd(OAc)_2$, and $NaHCO_3$ but notably lacked any ligands.[11,12] Through the use of 'solid-liquid phase transfer conditions' Jeffery could lower Pd loading and use milder conditions with several unstable vinylic substrates as well as allylic alcohols. Since these early reports, further investigations have implicated Pd nanoparticles as the active catalysts that are responsible for the surprising differences in reactivity relative to typical homogenous Pd-catalyzed Heck reactions.[13–19] For example, stabilized Pd nanoclusters led to improved reactivity of chloro- and bromobenzene in Heck reactions before modern ligands enabled the similar reactivity with single-site homogenous palladium.[14]

Our interest in Pd nanoparticles began with our work on an intramolecular reductive-Heck reaction en route to englerin A.[20] Initial evaluation of reaction tactics revealed that Jeffery-type conditions provided optimal selectivity for the reductive-Heck product over the Heck product. Preliminary mechanistic investigations suggested that these conditions support the formation of Pd nanoparticles in situ with $Pd(OAc)_2$ and TBAC. While there have been several reports of intramolecular reductive-Heck reactions and applications in total synthesis,[19,21–32] our reaction was unusual in that it provided an intramolecular reductive-Heck reaction in the presence of β hydrogens.[20] In spite of these advances, intermolecular reductive-Heck variants remain a challenge in cross coupling chemistry.

Learning from our work on the intramolecular reductive-Heck reaction, we sought to employ Pd-nanoparticle conditions to create a viable intermolecular variant. During the course of this research, Sekar and coworkers reported a Pd-nanoparticle reductive-Heck reaction between aryl iodides and enones.[33] Notably, the conditions required ligand-stabilized nanoparticles and heat but did not investigate alternate electrophiles or olefin substrates beyond enones. We were interested in the potential advantages of Jeffery-type Pd nanoparticles for an intermolecular reductive-Heck beyond conjugate-type addition reactions (Scheme 1). We postulated that in the presence of a Pd precatalyst and alkyl ammonium salts, a Pd nanoparticle pool will form,[34] thereby allowing Pd to undergo oxidative addition with an aryl pseudohalide followed by *syn* migratory insertion of an alkene (Scheme 2). The resulting alkylpalladium species undergoes a hydride transmetallation,

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https://doi.org/10.1016/j.tet.2018.04.052
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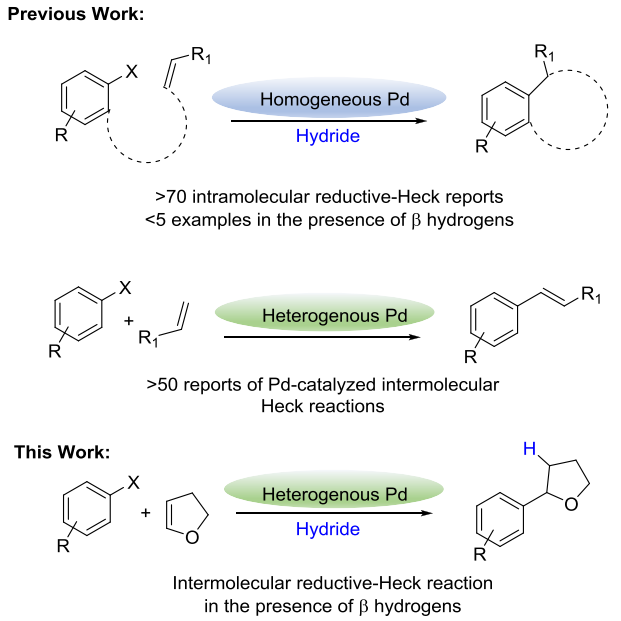



**Scheme 1.** Pd-nanoparticle reductive-Heck reaction.

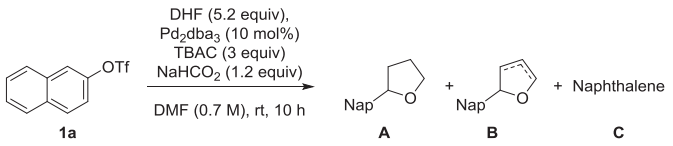
outcompeting the traditional *syn* β-H elimination, to provide a hydridopalladium species. Then, reductive elimination provides the reductive-Heck product to regenerate the Pd nanoparticles (Scheme 2). Here, we describe ligand- and base-free conditions to produce competent Pd nanoparticles that function in an intermolecular reductive-Heck reaction.

## 2. Results and discussion

### 2.1. The reductive-Heck reaction

We began by testing our previously reported Pd conditions with naphthyl triflate **1a,** 2,3-dihydrofuran (DHF) and sodium formate ($NaHCO_2$) as the hydride source (Table 1, entry 2).[20] The major challenge with the intermolecular reductive-Heck reaction lies in controlling the relative rates of migratory insertion, reductive

**Table 1**
Optimization of the reductive-Heck reaction.

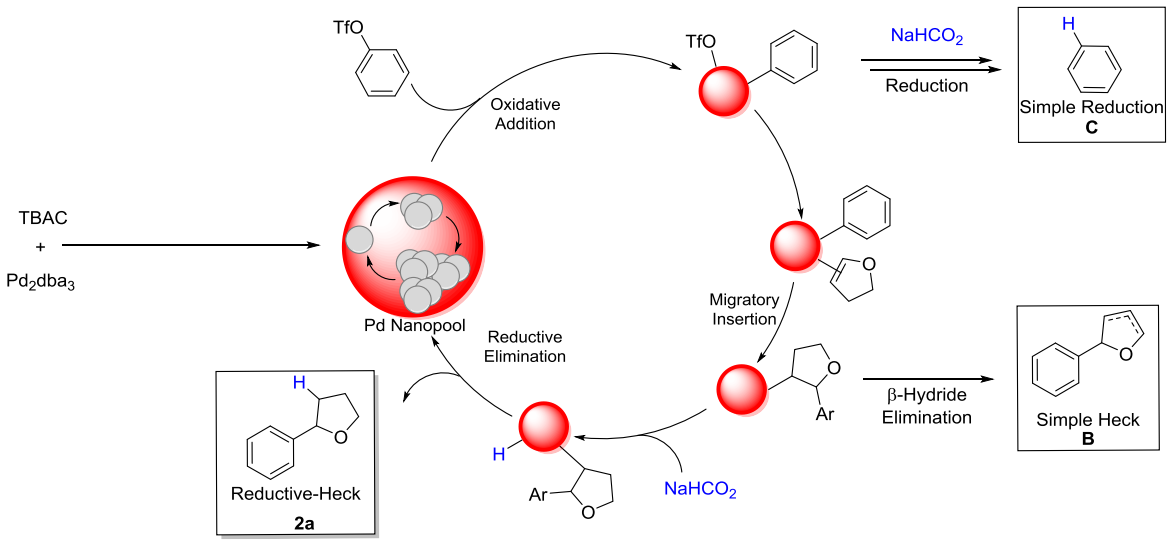



| Entry | Deviation from above | % yield:[a] | | |
|---|---|---|---|---|
| | | A | B[b] | C |
| 1 | no Pd | 0 | 0 | 0 |
| 2 | as above | 36 | 20 | 38 |
| 3 | **TBAC (1.5 equiv)** | **58** | **18** | **<15** |
| 4 | $Pd_2dba_3$ (1 mol%) | 22 | 36 | <40 |
| 5 | Pd(OAc)2 (10 mol%) instead of Pd2dba$_3$ | 13 | 37 | 50 |
| 6 | (*rac*)-BINAP (20 mol%) added | <5 | 0 | 0 |
| 7 | $KHCO_2$ instead of $NaHCO_2$ | <5 | 19 | 60 |

[a] Yield based on $^1$H NMR using trimethoxybenzene as internal standard.
[b] Major alkene isomer. TBAC = tetrabutylammonium chloride.

elimination, and β-hydride elimination (Scheme 2). Consequently, preventing the formation of the side products from Heck (product **B)** and reduction (product **C)** became paramount. Other hydride sources, such as different formate salts or proton sponge,[35] did not improve the selectivity (see Supporting Information). Addition of a ligand used previously in intermolecular Heck reactions,[8,36,37] (*rac*)-BINAP inhibited the reaction (Table 1, entry 6). While phosphines have been used under special circumstances to prepare Pd nanoparticles,[13] they often adversely affect the formation of Pd nanoparticles under similar conditions.[17–19] Elevated temperatures are detrimental to the target reaction (see SI). $Pd_2dba_3$ proved superior than $Pd(OAc)_2$ in the reaction, as it increased the reductive-Heck yield and significantly decreased reduction product **C** (Table 1, entry 5). Next, investigation of the alkyl chain length and counterion demonstrated that tetrabutylammonium salts provide higher yields and selectivity (see SI).

Furthermore, the chloride ion proved critical to reductive-Heck formation within each alkyl ammonium group, thereby suggesting an important role of chloride to stabilize the Pd nanoparticle pools irrespective of the ammonium alkyl chain length.[38] For example, long alkyl chain ammonium salts like cetyl trimethylammonium




**Scheme 2.** Catalytic cycle of Pd-nanoparticle reductive-Heck reaction.

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bromide showed modest improvement in reductive-Heck formation relative to entry 2 (see SI). However, if the chloride is replaced with a bulkier anion, such as an acetate, the reactivity shifts toward Heck product **B** (See SI). We made tetrabutylammonium formate in an attempt to simplify the system, but it proved inferior (see SI). Decreasing the amount of TBAC increased the yield of the reaction (Table 1, entry 3), which may be a result of the nanoparticle environment dependent on the ammonium salt. Finally, the use of a homogenous Pd system employing TBAC led to low conversion and no reductive Heck formation (see SI).[39] Lowering the Pd loading decreased the reductive-Heck product and increased the Heck product **B** (Table 1, entry 4). It is unknown whether the loading of Pd affects nanoparticle formation or stability under these conditions. To probe the existence of Pd nanoparticles in the reaction, we added (*rac*)-BINAP and observed complete inhibition of the reductive-Heck and Heck product **B** (Table 1, entry 6). This result is consistent with several reports of the detrimental effects of phosphine ligands to the formation of certain pools of Pd nanoparticles.[11,12,16–18]

With the optimized conditions, we evaluated the substrate scope of the reductive-Heck reaction (Table 2). The DHF reacted with several aryl triflates to afford the corresponding reductive-Heck product (39–67%). Electron-deficient aryl triflates provided moderate yields and afforded little-to-no reduction of the aryl triflates (Table 2, **2b-2f**). Electron-rich aryl triflates did not provide the reductive-Heck product (Table 2 and **2i**). The lower yields observed with electron-rich aryl triflates are consistent with a slow oxidative addition that leaves significant quantities of unreacted aryl triflate. The sterically hindered aryl triflate **1h** was not an effective substrate and led only to side product formation. The reaction tolerated quinoline in the substrate to produce product **2g** in reasonable yield.

No one individual experiment or analytical technique can establish the presence of nanoparticles in a catalytic reaction.[40] To probe the reaction for Pd nanoparticles, we used several experiments and analytical methods. The addition of a drop of Hg at the beginning of the reaction inhibited the reaction.[41] Addition of a phosphine ligand (Table 1, entry 6) or $CS_2$ (0.10 equiv) inhibited the reaction. The lack of Pd nanoparticles under these conditions were also confirmed by TEM (see SI).

Next, we turned to transmission electron microscopy (TEM) to directly observe the presence of Pd nanoparticles under our reaction conditions. Interestingly, TEM revealed nanoparticles in the range of 4–8 nm with clusters about 12–70 nm in size (Fig. 1). In the absence of TBAC in the reaction conditions, Pd nanoparticles were not observed (Fig. 1). Taken together, these experiments provide strong evidence that our intermolecular reductive-Heck reaction is catalyzed by Pd nanoparticles. Whether this is accomplished through Pd leaching or "on-surface" remains an open question worthy of further exploration.

## 3. Conclusion

In conclusion, we developed a mild Pd-nanoparticle reductive-Heck reaction devoid of costly ligands. The methodology works

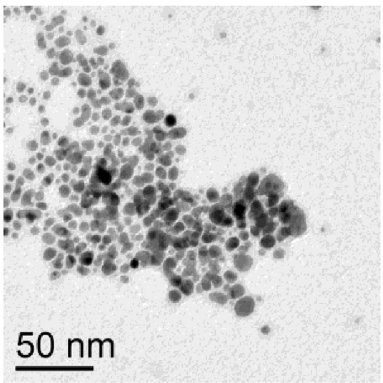
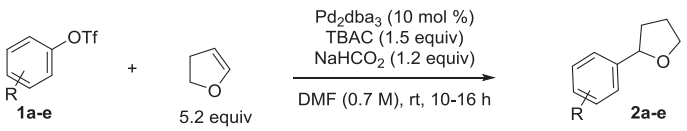
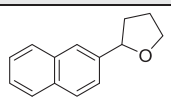
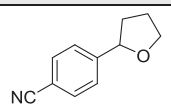
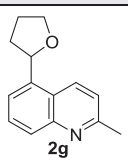
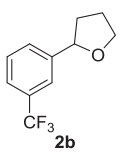
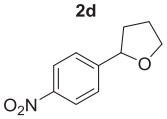
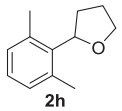
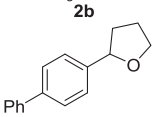
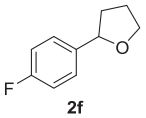
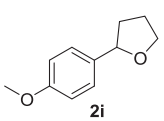



**Fig. 1.** TEM image of Pd-nanoparticles after reaction under standard conditions.

**Table 2**
Substrate scope.




| Aryl-OTf | Product | Yield[a] | Aryl-OTf | Product | Yield[a] | Aryl-OTf | Product | Yield[a] |
|---|---|---|---|---|---|---|---|---|
| 1a |  2a | 55% | 1d |  2d | 67% | 1g |  2g | 39% |
| 1b |  2b | 60% | 1e |  2e | 65% | 1h |  2h | 0% |
| 1c |  2c | 58% | 1f |  2f | 36% | 1i |  2i | <10% |

a Isolated yield.

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well with electron-deficient aryl triflates and is selective for reductive-Heck relative to the Heck or simple aryl triflate reduction. Preliminary investigations suggest the process is catalyzed by Pd nanoparticles. While the possibility of homogenous, unligated Pd as the catalytic agent remains, current evidence points toward a nanoparticle-mediated process. Mechanistic and kinetic studies with regards to nanoparticle formation for this reductive-Heck reaction remain an active area of pursuit.

## 4. Experimental

### 4.1. 2-(Naphthalen-2-yl)tetrahydrofuran (**2a**)

To a flame-dried, 0.5-dram vial fitted with a rubber septum and equipped with a magnetic stir bar was added 2-naphthalen-2-yl trifluoromethanesulfonate **1a** (0.4 mmol, 1.0 equiv), $Pd_2dba_3$ (10 mol %), TBAC (1.5 equiv) and $NaHCO_2$ (1.2 equiv). The contents were evacuated and backfilled three times with argon. 2,3-Dihydrofuran (DHF) (5.2 equiv) and DMF (0.7 M) was added via syringe and the reaction vial was sealed with a screw-top cap. The reaction mixture was stirred at room temperature for 14 h. The reaction was diluted with $Et_2O$ (3 mL) and filtered through a 3 cm pad of silica, flushing with 35 mL of $Et_2O$. The solution was concentrated via rotary evaporation. The reductive-Heck product was isolated by flash chromatography (gradient 2–20% EtOAc/hexanes over 400 mL), to give desired product *2-(naphthalen-2-yl) tetrahydrofuran* **2a** (44 mg, 56% yield) as a colorless oil. $^1$H NMR: (400 MHz, chloroform-*d*) δ 7.85–7.78 (m, 4H), 7.49–7.41 (m, 3H), 5.07 (t, $J = 7.2$ Hz, 1H), 4.22–4.12 (m, 1H), 4.06–3.95 (m, 1H), 2.47–2.32 (m, 1H), 2.12–1.99 (m, 2H), 1.96–1.82 (m, 1H). $^{13}$C NMR: (126 MHz, chloroform-*d*): δ 141.05, 133.45, 132.93, 129.10, 128.22, 128.04, 127.79, 126.15, 125.72, 124.18, 80.93, 68.98, 34.76, 26.23. TLC: $R_f = 0.22$ (10% $Et_2O$ in hexanes).

## Acknowledgments

We acknowledge funds from Indiana University in partial support of this work. We also gratefully acknowledge the NSF CAREER Award (CHE-1254783) and an AGEP supplement for DRV. Eli Lilly & Co. and Amgen supported this work through the Lilly Grantee Award and the Amgen Young Investigator Award. Finally, this project was partially funded by the Vice Provost for Research through the Research Equipment Fund. Jocelyn T.L. Gamler is acknowledged for help with the TEM images in Fig. 1.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.04.052.

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