ORGANIC
LETTERS

2013
Vol. 15, No. 17
4342–4345

Flow Heck Reactions Using Extremely Low Loadings of Phosphine-Free Palladium Acetate

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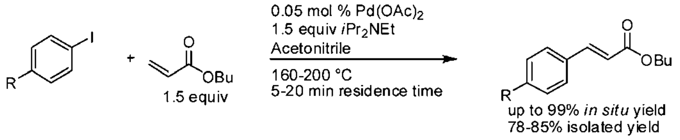
Received June 27, 2013

ABSTRACT



High-yielding Heck reactions are demonstrated using 0.05 mol % $Pd(OAc)_2$ without phosphine ligands. These reactions are run in a mesoscale flow reactor which allows precise control of reaction times and temperatures. Profiling yield and selectivity versus Pd loading shows 500 ppm to be optimal for aryl iodides; higher loadings favor side reactions caused by Pd(II) species. Aryl halides are examined via concise Design of Experiment to expand the scope and optimize conditions.

The Heck reaction is a versatile method for the formation of C–C bonds between alkenes and aryl or alkyl halides.[1] Typically catalyzed by palladium–phosphine complexes, this reaction has seen use across a wide variety of substrates and has been employed on large scale for the synthesis of pharmaceutical intermediates.[2,3] More widespread adoption of Heck chemistry on industrial scale is challenged by the need for high catalyst loadings (1–5 mol %). This adds cost, especially as the cost of palladium increases. High catalyst loadings also increase the difficulty of purging palladium and ligands to prevent poisoning downstream chemistry or contamination of active pharmaceutical ingredients.[3,4] Consequently, there remains a significant need to develop new techniques for Heck reactions with reduced palladium loading and little or no phosphine ligand.

The ligand-free Heck reaction is not new; Heck and Mizoroki both introduced the reaction between aryl iodides and activated alkenes in the early 1970s with ligand-free $PdCl_2$ or $Pd(OAc)_2$.[5] The addition of tetraalkylammonium salts improved the ligand-free Heck reaction, and subsequent work has broadened the scope further to include aryl bromides and chlorides.[6,7] This reaction remains limited by the requirement for high temperatures and, in some cases, extended reaction times.[8]

Flow reactors directly address these challenges by providing straightforward access to the high temperatures

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(3) (a) Ripin, D. H. B.; Bourassa, D. E.; Brandt, T.; Castaldi, M. J.; Frost, H. N.; Hawkins, J.; Johnson, P. H.; Massett, S. S.; Neumann, K.; Phillips, J.; Raggon, J. W.; Rose, P. R.; Rutherford, J. L.; Sitter, B.; Stewart, A. M., III; Vetelino, M. G.; Wei, L. *Org. Process Res. Dev.* **2005**, *9*, 440–450. (b) Jiang, X.; Lee, G. T.; Prasad, K.; Repic, O. *Org. Process Res. Dev.* **2008**, *12*, 1137–1141. (c) Caron, S.; Vazquez, E.; Stevens, R. W.; Nakao, K.; Koike, H.; Murata, Y. *J. Org. Chem.* **2003**, *68*, 4104–4107. (d) Chekal, B. P.; Guinness, S. M.; Lillie, B. M.; McLaughlin, R. W.; Palmer, C. W.; Post, R. J.; Sieser, J. E.; Singer, R. A.; Sluggett, G. W.; Vaidyanathan, R.; Withbroe, G. J. *Org. Process Res. Dev.* **2013**, ASAP; DOI: 10.1021/op400088k. (e) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177–2250.

(4) Konigsberger, K.; Chen, G. P.; Wu, R. R.; Girgis, M. J.; Prasad, K.; Repic, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2003**, *7*, 733–742.

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(8) To reach the high temperatures, high boiling point solvents are needed and some, including DMAc and DMF, are strongly regulated in Europe due to their toxicity, limiting their use on scale.

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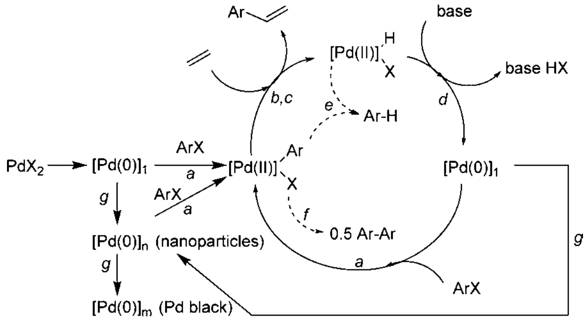
10.1021/ol4018134

needed for the ligand-free Heck reaction without the extended heating and cooling ramps required in batch reactors.[9] Because of their relatively low volumes, flow reactors can be run at temperatures and pressures far beyond those obtainable using standard glass equipment, obviating the need for high boiling solvents which are difficult to remove during workup. High temperatures accelerate the reaction; thus the catalyst only needs to be stable for 5−20 min, allowing elimination of ligands and potentially reduced loadings. Flow Heck reactions have been demonstrated with both hetero- and homogeneous catalysts,[10] and Kappe recently reported an example with $Pd(OAc)_2$.[11] Here, we describe the optimization of fast ligand-free flow Heck reactions with $Pd(OAc)_2$ and show that very low catalyst loadings are essential to minimize byproducts.

Scheme 1. Heck Catalyst Cycle and Palladium Aggregation Pathway



The primary challenge in running Heck chemistry is to facilitate the desired coupling reaction while minimizing byproduct formation and catalyst deactivation. The main catalytic cycle for the Heck reaction is unimolecular in Pd, and its rate increases with increased Pd concentration (Scheme 1, steps *a*−*d*).[1c] The undesired reduction product (Ar−H) and biaryl product (Ar−Ar) are formed via bimolecular pathways through reactions between [Pd−Ar] species and [Pd−H] species (step *e*) or [Pd−Ar] species (step *f*). Catalytically active Pd(0) species also convert to nonactive palladium black via agglomeration in a pathway which is also higher-order in Pd (step *g*).[7a] Since the Pd loading will affect the rate of the main catalytic cycle, which is unimolecular in Pd, and the rate of undesired processes, which are higher order in Pd, differently, we focused first on optimizing the catalyst loading.

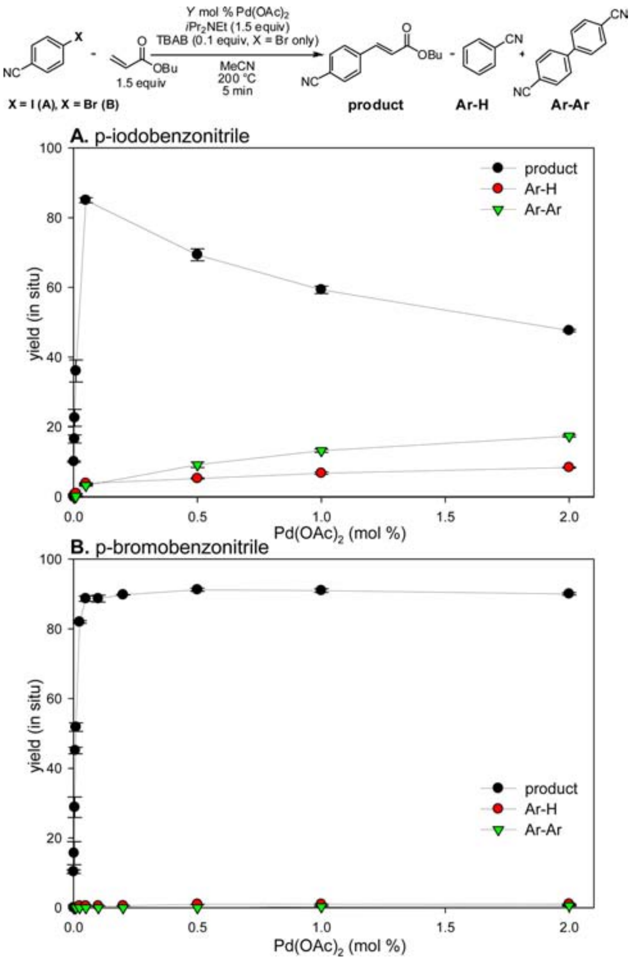


Figure 1. Yield of the Heck product, the reduction product (Ar−H), and the biaryl product (Ar−Ar) calibrated against an internal standard as a function of $Pd(OAc)_2$ loading.[12,13] (A) Reactions of *p*-iodobenzonitrile with *n*-butylacrylate (1.5 equiv of olefin, 1.5 equiv of $i Pr_2NEt$, acetonitrile, 200 °C, 5 min). (B) Reactions of *p*-bromobenzonitrile with *n*-butylacrylate (1.5 equiv of olefin, 1.5 equiv of $i Pr_2NEt$, 0.1 equiv of Bu_4NBr, acetonitrile, 200 °C, 5 min).[14] The very narrow error bars illustrate the reproducibility between runs.

We initially used a fixed residence time (5 min) and temperature (200 °C) to profile the reaction between *p*-iodobenzonitrile and *n*-butyl acrylate (Figure 1A). In this study, the palladium acetate loading was varied from 0.002 to 2 mol %. The data are presented as the *in situ* yields of the Heck product, reduction product (Ar−H), and biaryl product (Ar−Ar) as a function of Pd loading.[15] This differs from the more traditional graph of yield as a function of time; here the reaction time is fixed at 5 min.[16] The use of an automated flow reactor simplified the collection of these data, and replicates at each Pd concentration showed excellent reproducibility.[12,17] Notably, product

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(10) Noel, T.; Buchwald, S. L. *Chem. Soc. Rev.* **2011**, *40*, 5010–5029.

(11) Glasnov, T. N.; Findenig, S.; Kappe, C. O. *Chem.—Eur. J.* **2009**, *15*, 1001–1010. In this paper, all optimization is carried out in microwave batch and then executed in flow.

(12) Expanded views of Figure 1 and data are provided in the Supporting Information (SI).

(13) Points are connected by lines (for visualization) not fitted to curves.

(14) Multiple cleaning segments were executed between each reaction segment to prevent Pd buildup in the reactor and to ensure that any catalysis occurs with the indicated loading. See SI for more details.

(15) All *in situ* yields determined against an internal standard, biphenyl, included in the reaction.

(16) de Vries uses this type of graph to illustrate the impact of Pd loading on batch Heck reactions; see refs 7 and 17a.

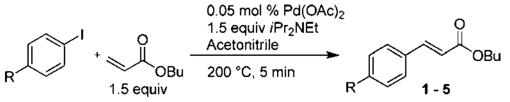
yield dramatically peaks at the low loading of 0.05 mol % $Pd(OAc)_2$.[12] At lower Pd loadings (20−500 ppm), the product yield increases with Pd concentration. At 500 ppm, the aryl iodide is virtually consumed (product distribution: 85% product, 4% Ar−H, and 3% Ar−Ar, accounting for 95% of the reaction mass). As the loading is further increased from 500 to 2000 ppm Pd, the amount of reduction product, Ar−H, and biaryl product, Ar−Ar, increase, attenuating the yield of the desired product.

Palladium loading has a different impact on the reaction of *p*-bromobenzonitrile with *n*-butylacrylate (Figure 1B). Quaternary ammonium salts are typically included in ligand-free reactions with aryl bromides, and here tetrabutylammonium bromide was used.[11,18,19] The Pd loading was varied from 0.001 mol % (10 ppm) to 2 mol % in reactions run at 200 °C for 5 min. At low Pd loadings (0.001 to 0.05 mol %), the yield of product increases from a 10% to 88% yield as the Pd loading increases. This part of the graph is very similar to the aryl iodide case. Interestingly, as the catalyst loading was further increased from 0.05 to 2 mol %, the yield increased slightly and then leveled off. Also, the biaryl product (Ar−Ar) and reduction product (Ar−H) are observed in very low amounts ($<1\%$) in all aryl bromide reactions, in contrast to the aryl iodide case.

The differing effect of catalyst loading on product distribution in the *p*-iodobenzonitrile and *p*-bromobenzonitrile reactions in Figure 1 is consistent with a change in the catalyst resting state due to changes in the oxidizing power of the aryl halide and thus relative rates in the catalytic cycle.[20]

The increased formation of byproducts (Ar−Ar and Ar−H) observed in reactions of *p*-iodobenzonitrile imply an increasing concentration of Pd(II) [Pd−Ar] species and thus a Pd(II) resting state. This is consistent with literature findings that the oxidative insertion is facile with aryl iodide substrates, and the palladium will be observed as Pd(II) rather than Pd(0).[6,21] In the aryl bromide case, the insertion of Pd(0) into the Ar−Br bond is slow, resulting in a Pd(0) resting state. The Pd(0) concentration will increase as the loading of $Pd(OAc)_2$ increases, and the concentration of Pd(II) species will remain small. Consequently, Ar−Ar and Ar−H formation will be slow even at higher catalyst concentrations. Also, because the Pd is largely in the Pd(0) oxidation state, stabilizing salts such as Bu_4NBr have a beneficial effect on the yield, as has been observed previously.[18]

Table 1. Isolated Yields from Aryl Iodide Reactions



product	R	isolated yield[a]
1	H	83%
2	CN	81%
3	Cl	85%
4	Me	81%[b]
5	OMe	78%[c]

[a] Chromatographed yield, ~1 g scale. [b] 200 °C, 9 min residence time. [c] 160 °C, 20 min residence time.

These conditions were then verified using larger scale reactions. A variety of aryl iodide substrates provided 78%−85% isolated yields after chromatography (Table 1). Additional investigations focused on delineating the influence of residence time and temperature on the reaction of each substrate. To optimize time and temperature simultaneously, a DoE (Design of Experiment) optimization sequence was executed for each aryl iodide. In the automated flow system, the DoE requires <400 mg of aryl iodide and <1 h of experiment setup time.[22,23] Visualization of a selection of these experiments[24] illustrates the impact of substrate electronics on the reaction with unique response surfaces and optimal conditions for each aryl iodide (Figure 2).

Because of the substrate dependence observed with the aryl iodides, a similar DoE was applied to the aryl bromides (Figure 2, Table 2).[25] These experiments served to define the method scope rapidly and to illustrate the extremely divergent impact of time and temperature on each substrate's reactivity.

Thus Heck reactions with a range of aryl iodides and electron-poor aryl bromides can be run with very low loadings of a simple palladium catalyst, 0.05 mol % $Pd(OAc)_2$ without any phosphine ligands, by a 5−20 min exposure to 160−200 °C. Stabilizing ligands are not required because the catalyst only needs to be active for these short residence times. Flow reactors provide easy access to

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(17) (a) Conjure and Propel flow systems were used for these experiments (www.accendocorporation.com). (b) Bogdan, A. R.; Sach, N. W. *Adv. Synth. Catal.* **2009**, *351*, 849–854.

(18) (a) (NMP/NaOAc) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; deVries, J. G. *Org. Lett.* **2003**, *5*, 3285–3288. (b) (NMP/DMG/NaOAc) Reetz, M. T.; Westermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, *39*, 8449–8452. (c) (Et_4NCl, Cy_2NMe) Gurtler, C.; Buchwald, S. L. *Chem.—Eur. J.* **1999**, *5*, 3107–3112.

(19) The reaction of 4-bromobenzonitrile and butyl acrylate with iPr_2NEt in acetonitrile (0.6 M) was compared in the presence and absence of 0.1 equiv of Bu_4NBr. There was a 10−20% increase in conversion (relative to an internal standard) when the reaction was run in the presence of Bu_4NBr. Addition of Bu_4NI provided comparable results to Bu_4NBr. The addition of Bu_4NBr had no impact on the yield in the reaction of *p*-iodobenzonitrile (see SI).

(20) For more information on resting states: Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000.

(21) Evans, J.; O'Neill, L.; Kambhampati, V. L.; Rayner, G.; Turin, S.; Genge, A.; Dent, A. J.; Neisius, T. *J. Chem. Soc., Dalton Trans.* **2002**, 2207–2212.

(22) Optimization experiments on the Conjure varied the temperature between 160 and 200 °C and the time between 5 and 20 min (see SI). Reactions were 0.6 M in aryl halide.

(23) Design Expert Version 7.1.5 (Stat-Ease Inc.) was used to generate the contour plots captured in Figure 2. The data can be found in the SI.

(24) Figure 2 is a small multiple graph. For more information on small multiples, see: Tufte, E. R. *The Visual Display of Quantitative Information*, 2nd ed.; Graphics Press LLC: Cheshire, CT, 2001; p 42.

(25) The catalyst loading has not yet been further evaluated for the electron-rich aryl bromide substrates.

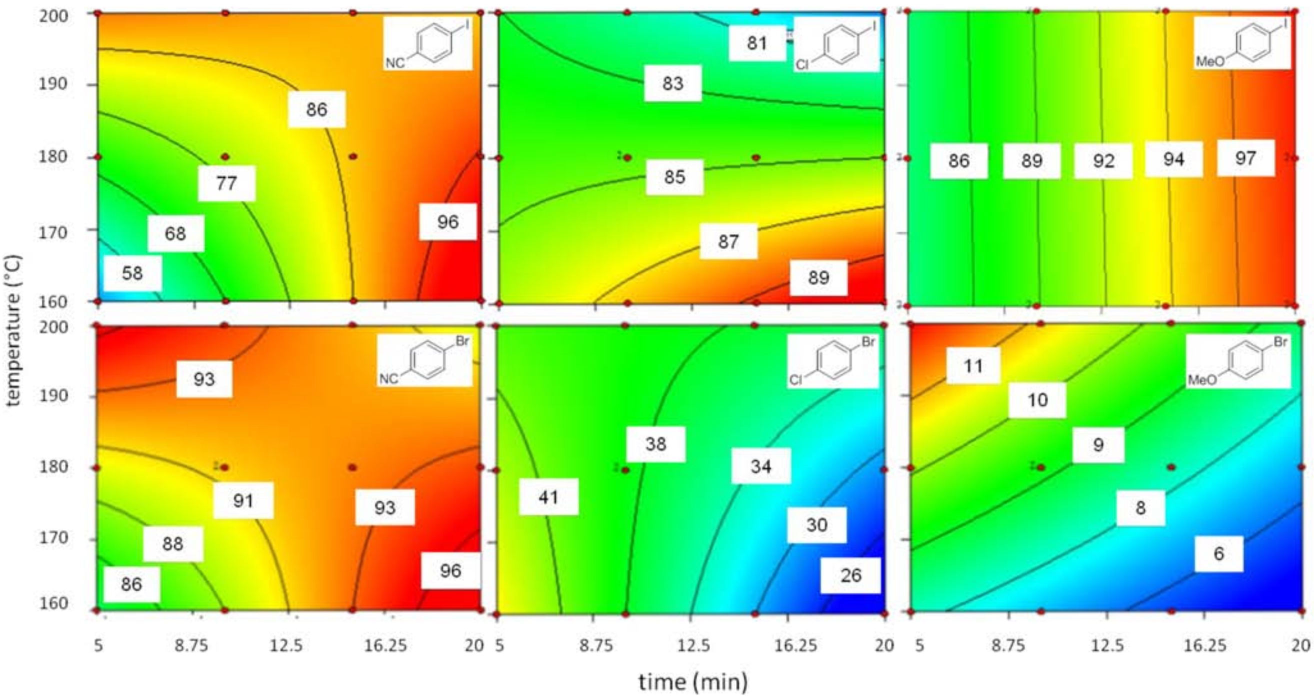
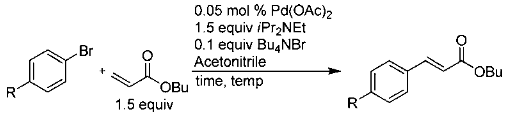


Figure 2. Effect of residence time and temperature on the yield of reactions between aryl iodides and aryl bromides with *n*-butyl acrylate. All reactions run with 1.5 equiv of $i\text{Pr}_2\text{NEt}$ and 0.05 mol % Pd(OAc)_2 in acetonitrile. The aryl bromide reactions included 0.1 equiv of Bu_4NBr. Contour lines represent reaction predicted yields. Red circles represent data points.

Table 2. *In situ* Yield from Optimized Aryl Bromide Reactions



R	*in situ* yield	temp	time
H	8%	200 °C	5 min
CN	>99%[a]	180 °C	5 min
Cl	52%	160 °C	5 min
Me	12%	200 °C	5 min
OMe	12%	200 °C	5 min
CF_3	90%[b]	160 °C	5 min

[a] Isolated yield is 71% at 200 °C, 5 min. [b] Conversion.

high reaction temperatures even with low boiling solvents such as acetonitrile. Automated flow reactors offer the further advantage of easily profiling continuous variables such as the catalyst loading, reaction temperature, and residence time. Profiling the Heck reactions against the catalyst loading showed a distinct peak in yield and selectivity at 0.05 mol % Pd(OAc)_2 for aryl iodides which minimized byproducts seen at higher loadings.[26] Profiling reactions vs time and temperature provided a unique response surface for each substrate, allowing high yielding conditions to be identified with rapid experiment setup and < 400 mg of substrate. The ability to study continuous variables easily in an automated fashion complements traditional batch reaction catalyst screening that focuses on categorical variables and often uses higher catalyst loadings.

Acknowledgment. The authors thank the following Pfizer colleagues: John Lucas for assistance with the Accendo Propel flow system, David Pattavina for assistance with reaction analysis, and Neal Sach and Marty Berliner for helpful discussions. The authors also thank Terry Long and Jan Hughes from Accendo Inc. for assistance with the Conjure and Propel systems. The authors thank Prof. David Collum, Cornell University, and Prof. Steven Ley, University of Cambridge, for helpful discussions.

Supporting Information Available. Experimental procedures, expanded figures, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[26] This is consistent with earlier findings in ligand-free Heck reactions; see refs 7a and 11.

The authors declare no competing financial interest.