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Microwave-Promoted Heck Coupling Using Ultralow Metal Catalyst Concentrations

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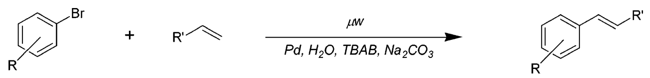

We show that Heck couplings can be performed in water using microwave heating and Pd catalyst concentrations as low as 500 ppb. The methodology is simple; all that is required as the catalyst is a stock solution of palladium.

Introduction

Palladium-catalyzed Heck reactions between aryl halides and alkenes continue to attract attention within the chemistry community because of the versatility of the reaction and the use of the products formed.[1] Of all the work undertaken, the area that has perhaps received most research effort is the development of new catalysts and ligands for Heck coupling reactions and then chemists using these catalyst systems in, for example, natural product synthesis. Recently, there has been increasing interest in the use of "ligand-free" palladium catalysis of the Heck reaction, either using simple palladium salts, metallic palladium, or palladium nanoclusters immobilized on inorganic supports. In addition, there have been several reports that have recently appeared in the literature that suggest that Heck coupling reactions can be catalyzed by trace quantities of ligand-free palladium sources. This is an area of considerable current interest and discussion in the literature and here we want to present findings from our laboratory.

Reetz and co-workers and also De Vries and co-workers have shown that the reaction between aryl iodides or bromides and alkenes can be run with the addition of what they term "homeopathic" quantities of palladium acetate using NMP as a solvent.[2−5] They suggest that the reaction proceeds via the formation of palladium colloids and that there is an equilibrium between these and a lower-order species such a monomeric or dimeric moiety that is the actual catalytically active species.[6] They, and others, have suggested that many of the palladacyclic complexes reported as catalysts for the Heck reaction are, in essence, sources of palladium nanoparticles or clusters which are the real catalyst precursors, these again being in equilibrium with lower-order palladium species.[7]

Choudary[8] and co-workers have obtained high turnover numbers in Heck couplings with aryl chlorides when using layered double hydroxide supported nanopalladium catalysts. They suggest that the reaction occurs at the surface of the nanoparticles. Köhler and co-workers have recently studied the Heck reaction using a range of solid catalysts.[9] Their results point toward the fact that there is in-situ generation of highly active dissolved palladium species and thus that the catalysis is in effect homogeneous with palladium dissolution, reprecipitation being a crucial and inherent part of the catalytic cycle. Similar observations have been reported for Suzuki coupling reactions.[8,10,11] One drawback with using these ultralow

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(2) For a recent review of the area see: Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559−1563.

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(6) For a recent review of C−C bond formation using transition-metal nanoparticles as catalysts see: Moreno-Manas, M.; Pleixats, R. *Acc. Chem. Res.* **2003**, *36*, 638−643.

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(8) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127−14136.

(9) Prockl, S. S.; Kleist, W.; Gruber, M. A.; Kohler, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1881−1182.

(10) Smith, M. D.; Stepan, A. F.; Ramarao, C.; Brennan, P. E.; Ley, S. V. *Chem. Commun.* **2003**, 2652−2653.

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catalyst loadings can be the rate of reaction when using conventional heating. For example, De-Vries and co-workers in their work showed that palladium acetate catalyzed Heck reactions of aryl bromides work well if the palladium concentration is kept between 0.01 and 0.1 mol %. At lower palladium concentrations, the reaction is too slow to be practical.[4]

In our group, we have an interest in using water as a solvent in conjunction with microwave heating. The concept of efficient and selective synthesis in water has been exemplified as the rates, yields, and selectivity observed for many reactions in water have begun to match, or in many cases, surpass those in organic solvents.[12] Water also offers practical advantages over organic solvents. It is cheap, readily available, nontoxic, and nonflammable. There have been several reports of Heck couplings using water or water/organic solvent mixtures as solvent.[13,14] Simple palladium salts have been used as catalysts for the reaction.[15] Beletskaya and co-workers have shown that the coupling of acrylic acid and acrylonitrile with aryl halides can be effected in neat water or in DMF−water or HMPA−water mixtures at 70−100 °C with good yields.[16] The reaction can be performed under milder conditions using potassium acetate. Jeffery and co-workers have shown that reactions involving water-insoluble substrates can be efficiently performed in water, in the presence of a combination of an alkali metal carbonate and a quaternary ammonium salt.[17]

Microwave-promoted synthesis is an area of increasing research interest as evidenced by the number of papers and recent reviews appearing in the literature.[18,19] As well as being energy efficient, microwaves can also enhance the rate of reactions and in many cases improve product yields. Microwave heating has been used for the Heck reaction before, a range of solvents and catalysts being utilized.[20] The use of water in conjunction with microwave heating for Heck couplings has been reported.[21] The phosphine-ligated palladium complex $PdCl_2(PPh_3)_2$ (5 mol %) is used as the catalyst and tetrabutylammonium bromide (TBAB) as a phase-transfer agent. Our interest in studying the Heck reaction sprang from a knowledge that the Suzuki reaction can be greatly accelerated by running the reaction using water as solvent and, in some cases, by using microwave heating as opposed to conventional heating. The total reaction time is between 5 and 10 min and low palladium loadings are used. The reactions can be performed on small (1 mmol) scales using sealed tubes or larger scales (20−50 mmol) using open reaction vessels.[22,23] We subsequently reported that it is possible to perform the coupling without the need for addition of a transition-metal catalyst.[24,25] We now believe that, although the reaction can be run without the need for addition of a metal catalyst, palladium contaminants down to a level of 50 ppb found in commercially available sodium carbonate are responsible for the generation of the biaryl rather than, as previously suggested, an alternative nonpalladium-mediated pathway.[26] We wanted to see if it was possible to accelerate the Heck reaction using similar reaction conditions to our palladium-mediated Suzuki couplings, with particular focus on the use of ultralow catalyst concentrations.

Results and Discussion

In our initial experiments, we chose to study the coupling of 4-bromoanisole with styrene. Our data are summarized in Table 1. Since we wanted to work with very low catalyst loadings, we needed a reliable source of palladium, the concentration of which could be guaranteed. When working in water, a major problem can be precipitation of palladium from a stock solution, particularly when working with a salt such as palladium acetate. This is, however, avoided by using an acid-stabilized stock solution. We therefore used a commercially available 1000 ppm palladium solution stabilized with 20% HCl as our catalyst source. This was diluted accordingly to give solutions of the desired concentrations. For low concentrations, a couple of drops of HCl were added to avoid precipitation of the palladium from solution. In addition, the solutions were prepared freshly each day from the 1000 ppm stock. Working on a 1 mmol scale of 4-bromoanisole, 2 mmol of styrene, and using a palladium loading of 0.38 mol %, 6.0 mmol K_2CO_3 as base, 2 mL water, and 1 mmol of TBAB as a phase-transfer agent,

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(15) For a recent discussion of ligand-free Heck couplings, albeit not in water, see: Yao, Q.; Kinney, E. P.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 7528−7531.

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(19) For a review on the concepts see: Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213−223.

(20) For selected reports see: (a) Bergbreiter, D. E.; Furyk, S. *Green Chem.* **2004**, *6*, 280−285. (b) Xie, X. G.; Lu, J. P.; Chen, B.; Han, J. J.; She, X. G.; Pan, X. F. *Tetrahedron Lett.* **2004**, *45*, 809−811. (c) Stadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; Van der Eycken, E.; Kaval, N.; Kappe, C. O. *Org. Proc. Res. Dev.* **2003**, *7*, 707−716. (d) Vallin, K. S. A.; Emilsson, P.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6243−6246. (e) Villemin, D.; Caillot, F. *Tetrahedron Lett.* **2001**, *42*, 639−642. (f) Diaz Ortiz, A.; Prieto, P.; Vazquez, E. *Synlett.* **1997**, 269−270. (g) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582−9584.

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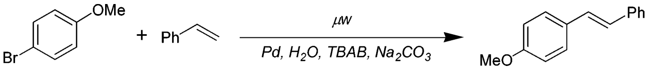
TABLE 1. Effects of Palladium Concentration on Product Yield in the Heck Coupling of 4-Bromoanisole and Styrene in Water Using Microwave Heating[a]



entry	palladium concentration (ppm)	catalyst loading (mol %)	yield/%
1[b]	200	0.3773	90
2[c]	200	0.3773	92
3[c]	10	0.0188	90
4[c]	2.5	0.0047	83
5[c]	1	0.0019	59
6[c]	0.5	0.0009	55
7[c,d]	0.5	0.0009	80

[a] Initial microwave irradiation of 70−100 W was used, the temperature being ramped from r.t. to 170 °C where it was then held for 10 min. Reactions were run using 1 mmol 4-bromoanisole and 2 mmol styrene. A total water volume of 2 mL was used. [b] Using 6.0 equiv K_2CO_3. [c] Using 3.7 equiv K_2CO_3. [d] The temperature was ramped from r.t. to 170 °C where it was then held for 20 min.

it was possible to obtain a yield of 4-methoxystilbene of 90% after 10-min microwave irradiation (Table 1, entry 1). Using an inital microwave power of 70−100 W, we ramped the temperature from room temperature (r.t.) to 170 °C, this taking 80−100 s, and then held the reaction mixture at this temperature for 10 min. [**CAUTION**: The water is heated well above its boiling point so all necessary precautions should be taken when performing such experiments. Vessels designed to withhold elevated pressures must be used. The microwave apparatus used here incorporates a protective metal cage around the microwave vessel in case of explosion. After completion of an experiment, the vessel must be allowed to cool to a temperature below the boiling point of the solvent before removal from the microwave cavity and opening to the atmosphere.] Our motivation for using such a large quantity of base was that we thought it would be necessary to neutralize the acid from the stock solution and have enough base left for the reaction. However, if we decrease the base to 3.7 equivalents, we obtain a comparable yield of the desired product (Table 1, entry 2). Smaller quantities of base are deleterous to product yield. A quick screen of other mineral bases (sodium carbonate, sodium hydroxide, and potassium acetate) showed us that potassium carbonate was the best. We also investigated the effect of decreasing the reaction time but found that this has a deleterious effect on the product yield. Our primary objective was to see how low we could take the catalyst concentration without a significant drop in product yield. Our data are summarized in Table 1. Dropping the catalyst loading from 0.38 mol % to 0.0188 mol % has no effect on product yield (Table 1 entry 3). Below this limit, product yield does begin to drop. Catalyst loadings of 0.0047 mol %, 0.0019 mol %, and 0.0009 mol % lead to product yields of 83%, 59%, and 55%, respectively (Table 1, entries 4−6). Running the reaction with a catalyst loading of 0.0009 mol % for 20 min as opposed to 10 min does lead to an increase of yield from 55% to a very respectable 80% (Table 1 entry 7). This corresponds to a catalyst concentration of 500 ppb Pd and shows that, using microwave heating, ultralow palladium concentrations can be used for C−C bond-forming reactions, the problem of slow reaction rate encountered using conventional heating being overcome.

For dilution of our 1000 ppm Pd stock solution, we needed to use water. Both this and the reagents we use in the reaction could be sources of additional palladium, thereby making our results inaccurate. To address this, we used ultrapure water, purified to a specific resistance of >16 mΩ·cm in all of our dilutions. We analyzed this for palladium and found levels in the region of 0.24 ppb which we believe does not affect our results. The organic reagents used in the reactions we believe to be palladium free. The only reagent we believe could have contained traces of palladium is the potassium carbonate. However, analysis of a solution of our potassium carbonate in ultrapure water showed levels of palladium corresponding to <1 ppb in the concentrations used in our experiments.

In all the reactions, yields are significantly higher when the reaction mixture is NOT stirred. We attribute this to problems associated with competitive decomposition of the starting aryl halide and styrene during the reaction. In the absence of stirring, the reaction mixture forms two distinct phases: a lower aqueous layer containing the base and an upper organic layer containing the organic substrates. We believe that one of the key roles of the water is simply to dissolve the base and that the coupling reaction takes place either at the aqueous/organic interface or else the palladium migrates to the organic phase where it could feasibly be stabilized as a cluster or lower-order species by the TBAB. When the reaction mixture is stirred, the aryl halide is more exposed to the basic aqueous medium and this could accelerate the competitive decomposition process. The reason we do not observe similar decomposition in our palladium-mediated Suzuki coupling protocol is, we believe, because the Suzuki coupling is significantly faster than the Heck coupling, and thus the aryl halide is consumed at a greater rate and hence any competitive decomposition pathway is not so much of a problem.

To probe more fully the role of water in the reaction, we ran the coupling of 4-bromoanisole and styrene in the absence of water. Since it is not possible to prepare accurately ultralow concentrations of Pd without the use of a stock solution of metal in a suitable solvent, we had to run the solvent-free reaction at the higher catalyst loading of 0.4 mol % $Pd(OAc)_2$ to obtain reliable data. We obtained a 53% yield of the desired product. This therefore suggests that water is not essential to the success of the reaction, although higher yields are obtained if water is used.[27] We believe that one of the key roles of the water is simply to dissolve the base and that the reaction takes place at the aqueous/organic interface. Using water does offer a convenient way to use very low catalyst loadings and also makes workup very easy. Running the reaction in organic solvents such as DMF, NMP, and DMSO did not meet with success at low catalyst loadings (<0.05 mol %). We obtained significant decomposition in all of these solvents.

We next wanted to probe the substrate scope of the reaction (Table 2). We find that the coupling using 0.0019

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(27) This agrees with other reports of Heck reaction run using solvent-free conditions but in the presence of tetra-alkylammonium salts. See: Bouquillon, S.; Ganchegui, B.; Estrine, B.; Henin, F.; Muzart, J. *J. Organomet. Chem.* **2001**, *634*, 153−156.

TABLE 2. Heck Coupling in Water Using Microwave Heating[a]

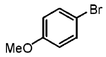
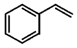
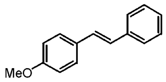
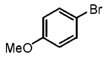
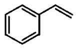
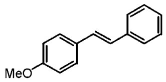
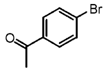
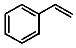
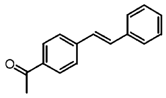
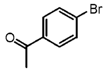
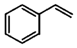
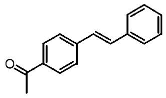
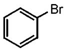
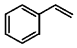
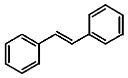
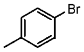
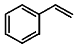
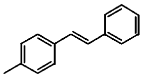
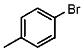
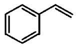
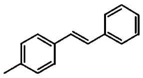
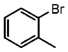
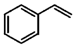
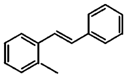
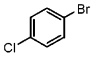
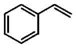
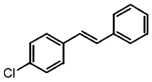
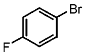
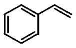
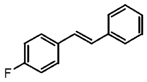
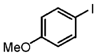
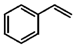
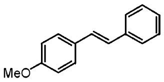
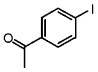
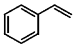
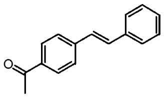
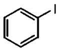
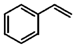
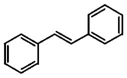
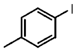
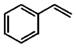
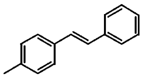
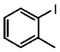
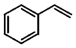
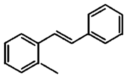
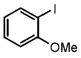
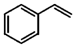
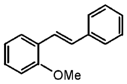
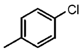
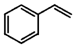
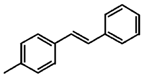
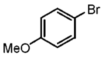
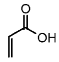
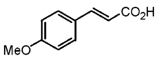
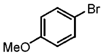
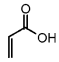
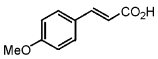
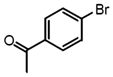
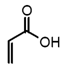
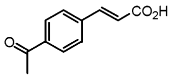
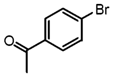
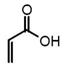
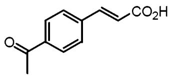
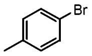
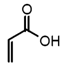
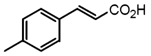
entry	aryl halide	alkene	product	catalyst loading (mol %)	product yield / %
1				0.0019	59
2[b]				0.0009	80
3				0.0019	83
4				0.0009	27
5				0.0019	76
6				0.0019	75
7[b]				0.0009	48
8				0.0019	82
9				0.0019	30
10				0.0019	62
11				0.0019	64
12				0.0019	3[c]
13				0.0019	51
14				0.0019	52
15				0.0019	69
16				0.0019	45
17				0.0019	13[c]
18				0.0019	52
19[b]				0.0009	25

Table 2. (Continued)

entry	aryl halide	alkene	product	catalyst loading (mol %)	product yield / %
20				0.0019	65
21[b]				0.0009	66
22				0.0019	47

[a] Initial microwave irradiation of 70−100 W was used, the temperature being ramped from r.t. to 170 °C where it was then held for 10 min. Reactions were run using 1 mmol aryl halide and 2 mmol alkene. A total water volume of 2 mL was used. [b] Ramped from r.t. to 170 °C where it was then held for 20 min. [c] Loss of material noted.

mol % and 0.0009 mol % Pd is unfortunately currently limited to aryl halide substrates bearing certain functional groups. Bromotoluene (both 2- and 4-), 4-bromoacetophenone, and bromobenzene all couple with styrene in respectable yields (Table 2, entries 2−8). To put our results in context, however, a review of the literature shows that the majority of reports of Heck couplings at high temperatures in aqueous media and ionic liquids tend to focus on simple substrates. The same is also true of some studies in organic solvents at elevated temperature. We believe that the main problem, certainly in our case, is again competitive decomposition of the starting aryl/heteroaromatic halide. In an additional series of experiments, we screened the coupling of 4-bromoacetophenone, 4-bromotoluene, and 4-bromoanisole with acrylic acid. We find that yields are not as high as those obtained in analogous experiments using styrene, the desired cinnamic acids being obtained between 25 and 67% yields (Table 2, entries 18−22). Representative aryl iodides were also screened in the coupling reaction using our methodology (Table 2, entries 11−16) but product yields were lower than their bromo- counterparts, as was observed previously in both Heck and Suzuki couplings using water as a solvent. Aryl chlorides could be coupled only in very low yields using the current methodology (Table 2, entry 17).

Conclusions

In summary, we have presented here our observations that Heck couplings can be performed in water using microwave heating and Pd catalyst concentrations as low as 500 ppb. The methodology is simple; all that is required is a stock solution of palladium, but admittedly the substrate scope is currently somewhat limited. We are continuing our studies in the area and our results will be reported in due course.

Experimental Section

Representative Example of a Heck Coupling Using Styrene as the Alkene Coupling Partner. Reaction between 4-Bromoanisole and Styrene. In a 10-mL glass tube was placed 4-bromoanisole (187 mg, 0.125 mL, 1.0 mmol), styrene (208 mg, 0.230 mL, 2.0 mmol), K_2CO_3 (511 mg, 3.7 mmol), tetrabutylammonium bromide (322 mg, 1.0 mmol), palladium stock solution (0.4 mL of a 1000 ppm solution in water), and water (1.6 mL) to give a total volume of water of 2 mL and a total palladium concentration of 200 ppm. The vessel was sealed with a septum, shaken, and placed into the microwave cavity. Initial microwave irradiation of 70 W was used, the temperature being ramped from r.t. to the desired temperature of 170 °C. Once this was reached, the reaction mixture was held at this temperature for 10 min. After allowing the mixture to cool to room temperature, the reaction vessel was opened and the contents poured into a separating funnel. Water (30 mL) and ethyl acetate (30 mL) were added and the organic material was extracted and removed. After further extraction of the aqueous layer with ethyl acetate, combining the organic washings and drying them over $MgSO_4$, the ethyl acetate was removed in vacuuo leaving the crude product. Product was characterized by comparison of NMR data with that in the literature.[28] ^{1}H NMR ($CDCl_3$) δ 7.46−7.53 (m, 4H), 7.37 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.10 (d, J = 16.3 Hz, 1H), 7.00 (d, J = 16.3 Hz, 1H), 6.93 (dd, J = 8.8 Hz, J = 1.9 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.4, 137.7, 130.2, 128.7, 128.3, 127.8, 127.2, 126.7, 126.3, 114.2, 55.3.

Representative Example of a Heck Coupling Using Acrylic Acid as the Alkene Coupling Partner. Reaction between 4-Bromoanisole and Acrylic Acid. The reaction mixture was prepared and run as with the reaction using styrene as a coupling partner but replacing the styrene with acrylic acid (144 mg, 0.137 mL, 2 mmol) and using an increased quantity of K_2CO_3 (600 mg, 4.7 mmol). After allowing the mixture to cool to room temperature, the reaction vessel was opened and the contents were poured into a separating funnel. Water (30 mL) and ethyl acetate (30 mL) were added and the aqueous layer was acidified using HCl. The organic material was then extracted and removed. After further extraction of the aqueous layer with ethyl acetate, combining the organic washings and drying them over $MgSO_4$, the ethyl acetate was removed in vacuuo leaving the crude product. Product was characterized by comparison of NMR data with that in the literature. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 15.9 Hz, 1H), 7.51 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.32 (d, J = 15.9 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl^3$) δ 172.3, 161.8, 146.7, 130.1, 126.8, 114.6, 114.4, 55.4.

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Supporting Information Available: General experimental and spectral data for the coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; de Vicente, J. *J. Am. Chem. Soc.* **2003**, *125*, 6034−6035.