

## Ligand-Free Heck Reaction: Pd(OAc)<sub>2</sub> as an Active Catalyst Revisited

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Received May 14, 2003

**Abstract:** Palladium acetate was shown to be an extremely active catalyst for the Heck reaction of aryl bromides. Both the base and the solvent were found to have a fundamental influence on the efficiency of the reaction, with K<sub>3</sub>PO<sub>4</sub> and *N,N*-dimethylacetamide being the optimal base and solvent, respectively.

Palladium-catalyzed coupling of olefins with aryl and vinyl halides, known as the Heck reaction,<sup>1,2</sup> is one of the prime tools for carbon–carbon bond formation in organic synthesis. This powerful reaction can lead to the construction of a C–C bond at an unfunctionalized olefinic carbon in a single transformation employing a wide variety of aryl and vinyl halide substrates. Unlike other C–C bond-forming reactions that involve a polar addition, the Heck reaction tolerates almost any sensitive functionality such as unprotected amino, hydroxyl, aldehyde, ketone, carboxy, ester, cyano, and nitro groups.<sup>1</sup> However, the traditional Heck reaction is typically performed with 1–5 mol % of a palladium catalyst along with a phosphine ligand in the presence of a suitable base. Under these conditions, the maximum turnover numbers (TON) are only 20–100 and large-scale industrial application is not practical.<sup>21</sup> In recent years, numerous efforts have been made to develop more efficient catalyst systems. A major challenge in this area has been the development of new Heck reaction catalysts with higher TON and with enhanced reactivity toward deactivated aryl bromides and, ultimately, toward the more readily available aryl chlorides. Significant advances have been made in the past several years in meeting these goals. These include the use of sterically bulky and

electron-rich phosphines,<sup>3</sup> phosphorus,<sup>4</sup> nitrogen,<sup>5</sup> and sulfur<sup>6</sup>-based palladacycles, and very recently, nucleophilic carbene ligands.<sup>7,8</sup> All of these catalyst systems suffer from drawbacks of one kind or another, such as the high ligand sensitivity toward air and moisture, the tedious multistep synthesis, hence the high cost of the ligands, and the use of various additives. On the other hand, the operationally and economically more advantageous ligand-free Heck reaction catalyst systems remain extremely rare.<sup>9,10</sup> Pd(OAc)<sub>2</sub> has been traditionally used only as a

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**TABLE 1.** Effect of the Base on the Pd(OAc)<sub>2</sub>-Catalyzed Reaction of Bromobenzene and Styrene<sup>a</sup>

$$\text{Ph-Br} + \text{Ph-CH=CH}_2 \xrightarrow[\text{DMA, 140 }^\circ\text{C}]{\text{Pd(OAc)}_2, \text{ base (1.4 equiv.)}} \text{Ph-CH=CH-Ph}$$

(1.2 equiv.)

entry	base	mol % of Pd(OAc) <sub>2</sub>	time (h)	yield <sup>b</sup> (%)	TON
1	Et <sub>3</sub> N	0.1	21		
2	Na <sub>2</sub> CO <sub>3</sub>	0.1	21	56	560
3	NaOAc	0.1	21	72	720
4	K <sub>3</sub> PO <sub>4</sub>	0.1	19	93	930
5	K <sub>3</sub> PO <sub>4</sub>	0.01	19	82	8200
6 <sup>c</sup>	K <sub>3</sub> PO <sub>4</sub>	0.00247	44	95	38500

<sup>a</sup> Unless otherwise noted, all reactions were performed with 1.0 mmol of PhBr in DMA (1–2 mL) at 140 °C. <sup>b</sup> Isolated yield after chromatography on silica gel. <sup>c</sup> 2.0 mmol of PhBr was used.

convenient and inexpensive source of palladium and its role as an active catalytic species has not been fully appreciated, except when the more reactive aryl iodides are used as the substrates. Herein, we wish to report our finding that Pd(OAc)<sub>2</sub>, in combination with K<sub>3</sub>PO<sub>4</sub> as the base, is an extremely effective catalyst for the coupling of aryl bromides with terminal olefins.

Heck's original recommendation for the catalyst cocktail involved the combination of Pd(OAc)<sub>2</sub>, a triaryl phosphine ligand, and a tertiary amine such as Et<sub>3</sub>N as the scavenger base. It is commonly believed that one role of the phosphine ligand is the reduction of Pd(II) to a catalytically active Pd(0) species, for which a stabilizing ligand is required to prevent the formation of palladium black.<sup>1,2a,h,11</sup> The base Et<sub>3</sub>N has also been implicated as a reducing agent for the generation of the Pd(0) species.<sup>2h</sup> Since many catalytic systems such as these involving palladacycles have been proposed to be operative by the [Pd(II)–Pd(IV)] catalytic cycle,<sup>4c,g,12</sup> the capability of Pd(OAc)<sub>2</sub> to participate in productive catalytic turnovers under appropriate conditions seems plausible.

Our initial attempt was to examine the efficiency of Pd(OAc)<sub>2</sub> in the coupling of bromobenzene with styrene *in the absence of any phosphine ligand*. Not surprisingly, no detectable conversion was observed when Et<sub>3</sub>N was used as the base (Table 1, entry 1). However, when several heterogeneous inorganic bases were substituted for Et<sub>3</sub>N, all the reactions examined led to some conversion, albeit with quite different efficiency (Table 1, entries 2–4), with K<sub>3</sub>PO<sub>4</sub> giving the best result. Thus, the coupling of bromobenzene with styrene in the presence of only 0.1 mol % of Pd(OAc)<sub>2</sub> with *N,N*-dimethylacetamide (DMA) as the solvent gave *trans*-stilbene in 93% isolated yield after 19 h at 140 °C. Decreasing the catalyst loading to 0.01 mol % still gave a respectable 82% yield of the product (Table 1, entry 5). When the reaction was performed for an extended period of time, 0.0025 mol % of Pd(OAc)<sub>2</sub> was found to be sufficient to give a high conversion with 95% isolated yield of the product, corresponding to a TON of 38 000 (Table 1, entry 6). Several other solvents including DMF, NMP, and 1,4-dioxane were also tested under similar conditions but all gave inferior results compared to DMA (Table 2).

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**TABLE 2.** Effect of the Solvent on the Pd(OAc)<sub>2</sub>-Catalyzed Reaction of Bromobenzene and Styrene<sup>a</sup>

$$\text{Ph-Br} + \text{Ph-CH=CH}_2 \xrightarrow[\text{solvent, 140 }^\circ\text{C}]{\text{Pd(OAc)}_2, \text{ K}_3\text{PO}_4 (1.4 \text{ equiv.})} \text{Ph-CH=CH-Ph}$$

(0.1 mol%), (1.2 equiv.)

entry	solvent	yield <sup>b</sup> (%)
1	DMA	95
2	DMF	74
3	NMP	54
4 <sup>c</sup>	dioxane	<2

<sup>a</sup> Unless otherwise noted, all reactions were performed with 1.0 mmol of PhBr in 1.6 mL of the solvent at 140 °C for 19 h. <sup>b</sup> Isolated yield after chromatography on silica gel. <sup>c</sup> This reaction was performed at 100 °C.

Having established that the combination of Pd(OAc)<sub>2</sub> and K<sub>3</sub>PO<sub>4</sub> constitutes a highly active catalyst system for the Heck reaction, we next examined the coupling of several other representative aryl bromides with different olefin substrates with the results listed in Table 3. As expected, the more reactive 4-bromobenzaldehyde underwent clean coupling with styrene, giving essentially a quantitative yield of the product (entry 1). Reactions involving deactivated aryl bromides bearing a methyl or a methoxy group also gave high yields of the coupling products with either styrene or 4-*tert*-butylstyrene (entries 2–5), although the sterically hindered 2-bromotoluene gave a diminished yield (entry 6). Furthermore, it was found that the reaction also proceeded nicely with the aliphatic olefin vinylcyclohexane. In all cases tested, high yields of the *trans* products were obtained by using 0.05–0.1 mol % of Pd(OAc)<sub>2</sub> regardless of the electronic or sterical variation on the aryl bromides (entries 7–10). Surprisingly, however, with activated terminal olefins such as *n*-butyl acrylate the reaction gave low yields except for the coupling with the more active 4-bromobenzaldehyde (entries 11–13). Cyclic olefins such as norbornene and 3,4-dihydropyran did not participate in the Heck reaction under these conditions. The reactivity of aryl triflates and chlorides was also examined. The catalyst system appeared to be completely ineffective for the Heck coupling of phenyl triflate<sup>17</sup> and chlorobenzene with styrene.

The data presented in Table 4 show that the efficiency of this new catalyst system toward the Heck coupling of aryl bromides and terminal olefins compares<sup>18</sup> very favorably with some of the most active catalyst systems that utilize expensive ligands and/or require the presence of various additives. The high activity of Pd(OAc)<sub>2</sub> toward

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(17) The reaction with phenyl triflate led to complete consumption and self-coupling of the triflate starting material, and resulted in the isolation of diphenyl ether in high yield (83%). Although the formation of diphenyl ether under these conditions points to a process involving the coupling between the phenyl triflate and a phenoxide nucleophile, the exact nature of the facile formation of the aryl ether is not clear at this time.

**TABLE 3. Pd(OAc)<sub>2</sub>-Catalyzed Heck Reactions of Aryl Bromides with Terminal Olefins, Using K<sub>3</sub>PO<sub>4</sub> as the Base<sup>a</sup>**

entry	Ar-Br (1)	R <sup>2</sup> (2)	product (3)	mol % Pd(OAc) <sub>2</sub>	time (h)	yield <sup>b</sup>	TON	
1				3a <sup>6a</sup>	0.05	25.5	98%	1960
2				3b <sup>6b</sup>	0.05	24.5	92%	1840
3				3c <sup>13</sup>	0.05	24.5	97%	1940
4				3d <sup>3a</sup>	0.05	17	71% <sup>c</sup>	1420
5				3e	0.05	17	93%	1860
6 <sup>d</sup>				3f <sup>3a</sup>	0.10	20	63%	630
7				3g <sup>14</sup>	0.05	21	89%	1780
8 <sup>d</sup>				3h <sup>15</sup>	0.10	22.5	86%	860
9 <sup>d</sup>				3i	0.10	22.5	77%	770
10 <sup>d</sup>				3j <sup>16</sup>	0.10	21	82%	820
11 <sup>e</sup>				3k <sup>5e</sup>	0.05	22	36%	720
12				3l <sup>8</sup>	0.10	22	91%	910
13				3m <sup>8</sup>	0.10	22	9%	90

<sup>a</sup> Unless otherwise noted, all reactions were performed with 1.0 mmol of the aryl bromide, 1.2 mmol of the alkene, and 1.4 mmol of K<sub>3</sub>PO<sub>4</sub> at 140 °C. <sup>b</sup> Isolated yield after chromatography. Only the trans isomers were isolated in all cases. <sup>c</sup> When this reaction was repeated and run for a longer time (42 h), the product was isolated in quantitative yield. <sup>d</sup> 0.5 mmol of the aryl bromide was used. <sup>e</sup> 2.0 mmol of PhBr was used.

the reaction of aryl bromides, regardless of the nature of the substituent groups, is unprecedented. In light of the low reactivity observed with *n*-butyl acrylate, which is normally more reactive than styrene for most of the existing Heck reaction catalysts, the classical Pd(0)–Pd(II) catalytic cycle seems highly unlikely.<sup>19</sup> Although several Heck reaction mechanisms involving a Pd(II)–

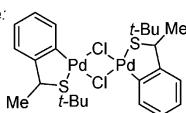
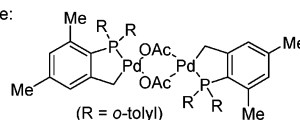
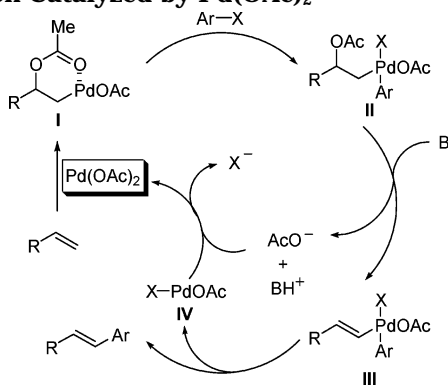
Pd(IV) catalytic cycle have been advanced previously,<sup>4c,g,12</sup> the lack of precedent for a direct oxidative addition of the aryl bromide to Pd(OAc)<sub>2</sub> precludes an underligated Pd(II)–Pd(IV) catalytic cycle. A new mechanism that reconciles most of our experimental results was proposed in Scheme 1. This involves first the formation of a transient palladacycle **I**<sup>20</sup> by the reaction of Pd(OAc)<sub>2</sub> with

(18) Gruber, A. S.; Pozebon, D.; Montero, A. L.; Dupont, J. *Tetrahedron Lett.* **2001**, *42*, 7345–7348. The literature data compiled in Table 4 were based on reactions that were performed under comparable conditions including the reaction temperature and reaction time.

(19) Although we could not rule out the possibility of the involvement of a Pd(0) species in the catalytic cycle, the formation of palladium black, which could otherwise be expected at the reaction temperature and in the absence of a stabilizing ligand, was not observed throughout the reaction except when the acrylate was used as the terminal olefin.

**TABLE 4. Pd(OAc)<sub>2</sub>/K<sub>3</sub>PO<sub>4</sub> in DMA as an Active Catalyst System for the Heck Reaction: Comparison with Other Catalyst Systems<sup>18</sup>**

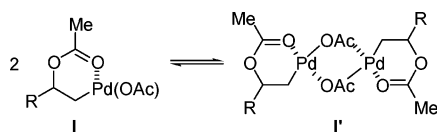
entry	Ar-Br	[Pd] (mol %)	base	solvent	Additive (amount)	conditions	yield	TON	Ref
1	PhBr	Pd(OAc) <sub>2</sub> (0.01)	K <sub>3</sub> PO <sub>4</sub>	DMA	none	140 °C, 19 h	82%	8,200	This work
2	PhBr	Pd(OAc) <sub>2</sub> (0.00247)	K <sub>3</sub> PO <sub>4</sub>	DMA	none	140 °C, 44 h	95%	38,500	This work
3	4-MePhBr	Pd(OAc) <sub>2</sub> (0.05)	K <sub>3</sub> PO <sub>4</sub>	DMA	none	140 °C, 24.5 h	92%	1,840	This work
4	4-MeOPhBr	Pd(OAc) <sub>2</sub> (0.05)	K <sub>3</sub> PO <sub>4</sub>	DMA	none	140 °C, 17 h	71%	1,420	This work
5	PhBr	Pd(OAc) <sub>2</sub> (1.5)	NaOAc	NMP	Bu <sub>4</sub> NBr (20 mol %)	150 °C, 30 h	70%	47	9g
6	PhBr	PdCl <sub>2</sub> (SEt <sub>2</sub> ) <sub>2</sub> (0.1)	NaOAc	DMA	Bu <sub>4</sub> NBr (20 mol %)	150 °C, 24 h	76%	760	18
7	4-MeOPhBr	PdCl <sub>2</sub> (SEt <sub>2</sub> ) <sub>2</sub> (0.1)	NaOAc	DMA	Bu <sub>4</sub> NBr (20 mol %)	140 °C, 24 h	38%	380	18
8 <sup>a</sup>	PhBr	Dupont's Pd-cycle (0.002)	NaOAc	DMA	Bu <sub>4</sub> NBr (100 mol %)	140 °C, 28 h	56%	28,000	6a
9 <sup>a</sup>	4-MeOPhBr	Dupont's Pd-cycle (0.002)	Et <sub>3</sub> N	DMA	Bu <sub>4</sub> NBr (20 mol %)	140 °C, 90 h	10%	5,000	6a
10 <sup>b</sup>	PhBr	Hermann's Pd-cycle (0.1)	NaOAc	DMA	none	140 °C, 26 h	77%	770	4b
11 <sup>b</sup>	4-MeOPhBr	Hermann's Pd-cycle (0.1)	NaOAc	DMA	none	140 °C, 30 h	69%	690	4b

<sup>a</sup> Dupont's Pd-cycle:<sup>b</sup> Hermann's Pd-cycle:**SCHEME 1. Proposed Mechanism for the Heck Reaction Catalyzed by Pd(OAc)<sub>2</sub>**

the olefin.<sup>21</sup> The palladacycle **I** is expected to be able to undergo oxidative addition by the aryl bromide, generating the Pd(IV) species **II**. Base-promoted elimination of the acetate ion gives intermediate **III**, which subsequently collapses to the Pd(II) species **IV** and releases the coupling product. Equilibration of **IV** with the acetate ion then regenerates Pd(OAc)<sub>2</sub>. Additionally, **IV** itself could participate in the catalytic cycle in a similar way to that of the first turnover.

In summary, we have shown that Pd(OAc)<sub>2</sub>, in combination with K<sub>3</sub>PO<sub>4</sub> as the base and DMA as the solvent, can be used as a highly reactive catalyst for the Heck

(20) By analogy to other palladacycles, **I** may exist in equilibration with its dimeric form:



(21) Electrophilic oxypalladation, including the acetoxylation of alkenes with Pd(OAc)<sub>2</sub>, is a well-documented process and is involved in many alkene functionalization reactions such as the Pd(OAc)<sub>2</sub>-mediated Wacker-type oxidation, see: Tsuji, J. *Transition Metal Reagents and Catalysts*; John Wiley: Chichester, UK, 2000; Chapter 11.

reaction of both activated and deactivated aryl bromides in the absence of any stabilizing ligands or special additives. Although the reactivity of Pd(OAc)<sub>2</sub> under these conditions is limited only to the coupling of aryl bromides and unactivated terminal olefins, this limitation is more than offset by the benefit of using a ligand-free, inexpensive catalyst, as well as by the low cost of the base used.<sup>22</sup>

**Experimental Section**

**General Procedure for the Heck Reaction of Aryl Bromides with Pd(OAc)<sub>2</sub> as the Catalyst (Table 1, entry 4).** An oven-dried 10-mL Schlenk flask was charged under Ar with K<sub>3</sub>PO<sub>4</sub> (298 mg, 1.40 mmol) and DMA (1.0 mL). Bromobenzene (105 μL, 157 mg, 1.00 mmol) and styrene (140 μL, 127 mg, 1.20 mmol) were added via syringes. A solution of Pd(OAc)<sub>2</sub> in DMA (1.8 × 10<sup>-3</sup> M, 560 μL, 0.0010 mmol) was then added via syringe. The Schlenk tube was sealed under Ar and placed in an oil bath preheated to 140 °C (controlled by a J-KEM temperature controller) and the reaction mixture was stirred for 19 h at this temperature. After being cooled to room temperature, the reaction mixture was poured into water (25 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to dryness under vacuum. The crude product was purified by flash chromatography on silica (hexane) to give 168 mg (93%) of pure *trans*-stilbene.

**Acknowledgment.** This work was supported in part by the Petroleum Research Fund, administered by the American Chemical Society (36466-G1).

**Supporting Information Available:** General experimental conditions and characterization of **3e** and **3i**. This material is available free of charge via the Internet at <http://pubs.acs.org>. JO034646W

(22) Although the reactions reported in Tables 1–3 were run on 0.5–2 mmol scales, this protocol is readily scalable as exemplified by the following reactions performed on a 10 mmol scale:

