

# Solid/Liquid Palladium-Catalyzed Coupling of Haloaryls Using Alcohols as Reducing Agents: Kinetics and Process Optimization

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## Abstract:

Heterogeneous Pd-catalyzed coupling reaction of substituted halobenzenes to biphenyls is performed effectively in different organic solvents using an alcohol as the reducing agent in the presence of a base and a catalytic amount of phase-transfer (PT) agent. The alcohol is oxidized to the respective aldehyde or ketone. Kinetic studies show that the reaction rate equation fits to second order in halobenzene. The effects of reaction temperature, catalyst loading, base concentration, PTC concentration, and alcohol concentration and structure are studied and discussed.

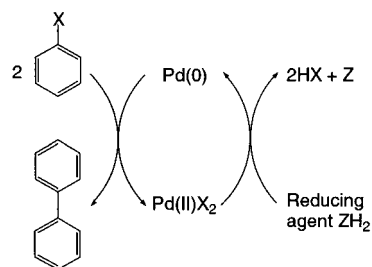
## Introduction

Industrial interest in the synthesis of biaryl compounds reflects their expanding role in natural product synthesis and polymer chemistry, and their usage as key building blocks for many agrochemicals and fine-chemical intermediates.<sup>1</sup> One of the widespread methods in biaryl synthesis is the Ullmann reaction.<sup>2</sup> This method is effective but uses an excess of copper.<sup>3</sup> Several catalytic alternatives exist such as the Suzuki,<sup>4</sup> Stille,<sup>5</sup> Negishi couplings. Aryl–aryl coupling via a radical mechanism under photochemical conditions<sup>6</sup> and intramolecular radical arylations under reductive radical conditions using tributyltin<sup>7</sup> have also been reported. Those reactions are possible due to formation of intermediates such as radical anions of haloaromatic compounds. In several cases these reactions take place in the presence of palladium catalysts.<sup>8</sup>

These palladium-catalyzed reductive coupling reactions involve the interconversion Pd(0)/Pd(II), that is between d<sup>10</sup>

and d<sup>8</sup> electronic configurations. In the case of heterogeneous Pd/C, completion of the catalytic cycle via reduction of the palladium catalyst was achieved using hydrogen gas (Scheme 1),<sup>9</sup> dihydrogen-generating agents (e.g., formate/water<sup>10</sup> or zinc/water<sup>11</sup>), and redox H-transfer agents (e.g., benzene<sup>12</sup> or hydroquinone<sup>13</sup>). Previously we suggested that the catalytic cycle involves two single-electron-transfer (SET) processes from the Pd(0) catalyst to two haloaryl molecules,<sup>14</sup> followed by dissociation of the [Ar–X]<sup>•−</sup> radical anions.<sup>15</sup>

## Scheme 1. Reductive coupling of halobenzenes in the presence of a palladium catalyst



The main drawbacks of these reducing agents are the competitive chemisorption and hydride-forming ability, which lead to the reductive hydrodehalogenation of aryl halides. Accordingly, one might envisage that a mild reducing agent (e.g., an alcohol) would minimize this side reaction.<sup>16</sup> Here we describe studies on the coupling reactions of bromoaryls using alcohols as the reducing agent under basic conditions and discuss some of the elementary processes in this system.

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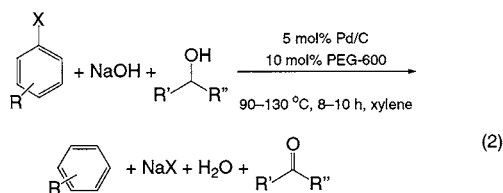
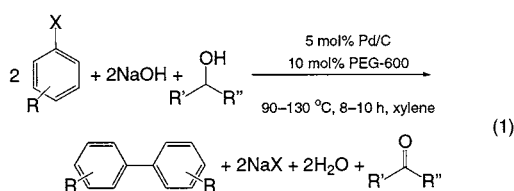
**Table 1.** Coupling of various starting materials<sup>a</sup>

entry	substrate	conversion PhX/% <sup>b</sup>	selectivity to coupling/% <sup>b</sup>
1	bromobenzene	92.0	61.0
2	4-bromotoluene	100.0	65.1
3	4-bromoanisole	91.2	47.8
4	4-chloro-1,1,1-trifluorotoluene	78.6	58.0

<sup>a</sup> Standard reaction conditions: 32 mmol PhBr, 64 mmol NaOH, 35 mmol 2-pentanol, 1.6 mmol 5% Pd/C (5 mol % of Pd relative to PhBr), 3.2 mmol PEG-400, 105 °C, 25 mL of toluene (solvent), 6 h. <sup>b</sup> Based on GC area, corrected by the presence of an internal standard.

## Results and Discussion

In a typical reaction, one molar equivalent of halobenzene was stirred in xylene with 1.1 equiv of alcohol, in the presence of 2 equiv of NaOH and catalytic amounts of Pd/C and (poly)ethyleneglycol (PEG). The reaction yielded mainly biphenyl along with some benzene (eqs 1 and 2), and the



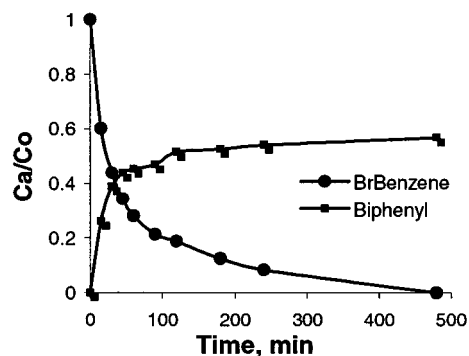
R = H, Me, CF<sub>3</sub>, OMe  
 R' = Me, Et, pentyl, *i*-Pr, Pr, heptyl, Bz, Cy, *t*-Bu, *t*-amyl  
 R'' = H, Me, Ph  
 X = Cl, Br, I

alcohol was oxidized to the corresponding aldehyde/ketone. Good yields of the coupling products were obtained using various substrates as shown in Table 1. No other products were observed by GC and <sup>1</sup>H NMR analysis. No coupling took place in the absence of any one of the sodium hydroxide, alcohol, or catalyst.

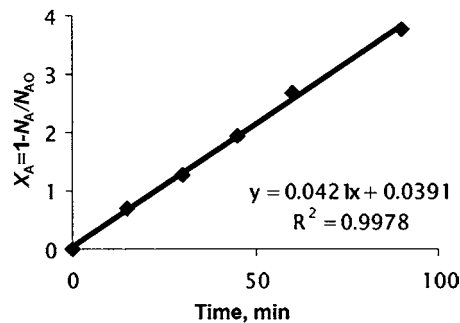
PhBr was chosen as a model substrate for the process parameter studies. A typical profile for the coupling reaction of PhBr is shown in Figure 1. Material balance showed complete conversion of PhBr: 60% to biphenyl and 40% to benzene. The reaction was found to fit a second-order profile (Figure 2).

The reaction temperature was varied from 90 to 125 °C. As expected, higher temperature increased the reaction rate but did not much affect the product selectivity (Table 2, entries 1–4). Reaction rates increased from  $0.9 \times 10^{-4}$  to  $25 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ . The Arrhenius energy of activation was found to be  $E_a = 110 \text{ kJ mol}^{-1}$  (26.3 kcal mol<sup>-1</sup>, with  $r^2 = 0.974$  for four measurements at 90, 105, 115, and 125 °C, see Figure 3). This relatively high  $E_a$  value indicates that the rate-determining step is chemically controlled.

The catalyst loading, expressed as the wt % of catalyst based on substrate concentration, was varied from zero to



**Figure 1.** Coupling reaction profile. Conditions: 32 mmol PhBr, 64 mmol NaOH, 35 mmol 2-pentanol, 1.6 mmol 5% Pd/C, 3.2 mmol PEG-600, 105 °C, 25 g of xylene (solvent).



**Figure 2.** Determination of the reaction order  $X_A =$  fractional conversion of bromobenzene defined as  $X_A = 1 - N_A/N_{A0}$  (conditions are as in Figure 1).

10.0% (Table 2, entries 5–12). At low loadings (<2.5%) relatively little reaction occurred. However, at 2.5% loading the conversion after 6 h increased from 20 to 80% and remained almost constant thereafter.

**Alcohol Type and Concentration.** The mechanism<sup>17</sup> of the catalytic reduction of palladium(II) by alcohols involves the hard base-promoted redox process  $2\text{OH}^- + \text{RH}(\text{OH}) + \text{Pd}^{\text{II}}/\text{C} \rightarrow \text{R}=\text{O} + \text{Pd}^0/\text{C} + 2\text{H}_2\text{O}$ . We examined the effect of alcohol structure on the conversion and the coupling reaction (Table 3). The relative activity was as follows: benzyl alcohol > cyclohexanol > 2-pentanol > 1-pentanol > *tert*-butyl alcohol > *tert*-amyl alcohol. Benzylic alcohols are the best hydrogen donors, probably due to their high affinity for the metal. Conversely, the  $\alpha$ -hydrogen of a primary alcohol is less likely to react as a hydride species because of the smaller electron-releasing inductive effect of the alkyl group.<sup>18</sup> Note that *tert*-butyl alcohol and *tert*-amyl alcohol were also reactive, showing that the presence of  $\alpha$ -hydrogen on the alcohol is not critical (and obviously that the above pathway is not the only one possible). Although the reaction rate was highest with benzyl alcohol ( $k_{\text{obs}} = 8 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ ), the selectivity to biphenyl was not satisfactory. Secondary alcohols were found to be the preferred Ar–Ar coupling reagents.

Changing the alcohol concentration did not influence the reaction rate, but product selectivity proved sensitive to the amount of alcohol (increasing the latter decreased the selectivity to biphenyl due to a higher dehydrohalogenation

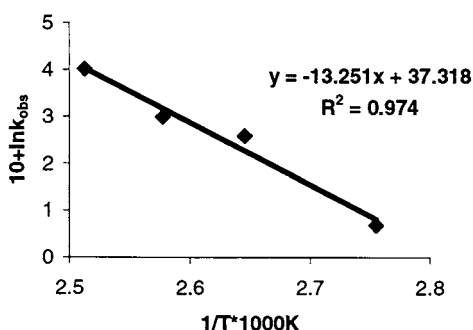
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**Table 2. PhBr coupling under various conditions<sup>a</sup>**

entry	parameter changed	time/h	conversion PhBr/% <sup>b</sup>	selectivity biphenyl/% <sup>b</sup>
	<i>t</i> /°C			
1	90	2	24.0	51.0
2	105	2	72.0	64.0
3	115	2	77.0	54.0
4	125	2	85.0	61.0
	5% Pd/C /mol % relative to PhBr			
5	0.0	6	0.0	0.0
6	0.5	6	17.0	11.0
7	1.0	6	22.8	12.2
8	1.5	6	26.1	19.7
9	2.5	6	75.0	64.0
10	5.0	6	92.0	61.0
11	7.5	6	77.0	59.0
12	10.0	6	82.5	51.2
	KOH /mol % relative to PhBr			
13	0	3	0.0	0.0
14	30	3	14.0	80.0
15	100	3	52.0	68.0
16	200	3	94.0	56.0
17	400	3	88.0	27.0
	PEG-600 /mol % relative to PhBr			
18	0.0	4	5.0	78.0
19	2.5	4	16.0	47.0
20	5.0	4	37.0	63.0
21	10.0	4	81.0	62.0
22	20.0	4	100.0	57.0
	alcohol /mol % relative to PhBr			
23	0	20	0.0	0.0
24	25	20	51.0	70.0
25	50	20	72.0	62.0
26	110	20	100.0	60.0
27	200	20	100.0	48.0

<sup>a</sup> Standard reaction conditions: 32 mmol PhBr, 64 mmol NaOH, 35 mmol 2-pentanol, 1.6 mmol 5% Pd/C (5 mol % Pd relative to PhBr), 3.2 mmol PEG-400, 105 °C, 25 mL of toluene (solvent), 6 h. <sup>b</sup> Based on GC area, corrected by the presence of an internal standard. <sup>c</sup> Cetyl-trimethylammonium bromide (CTAB) was used instead of PEG.



**Figure 3.** Arrhenius plot. Conditions: 32 mmol PhBr, 64 mmol NaOH, 35 mmol 2-pentanol, 1.6 mmol 5% Pd/C, 3.2 mmol PEG-600, 25 g of xylene (solvent).

rate). Note that PEG also acted as the terminal reductant of Pd<sup>II</sup> (Table 2, entries 23–27).

**Type of Base.** The rate of conversion was found to be dependent on concentration of the base (e.g., on [KOH], as shown in Figure 4). In the absence of base, neither reduction nor coupling occurred. Changing the concentration of KOH from 30 to 200 mol % increases the rate 12-fold (from  $0.5 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$  to  $2.3 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ ). This is in agreement with previous studies that showed that reaction velocity and the attainable concentrations of radical anions increased at higher [OH<sup>-</sup>].<sup>19</sup> The role of base compounds is not limited to neutralization of HBr.<sup>20</sup> The base probably promotes both

hydrogen-atom-transfer and the electron-transfer reactions.<sup>21</sup> Adding less than two equivalents of KOH resulted in incomplete conversion. The concentration of base affects the selectivity (Table 2, entries 13–17). A maximum of 80% selectivity occurs with a small 30% concentration of base. Further increase in base concentration decreases the selectivity down from 80 to 30%, and these values were essentially independent of time of reaction. Weaker bases (K<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, and Et<sub>3</sub>N) were also examined, but conversions were <10% (cf. Table 4).

**Changing the Phase-Transfer Catalyst (PTC).** Earlier studies attributed the effects of PTC in similar systems to aiding the “wetting” of the catalyst and facilitating the transport of the alkaline ions to the catalyst surface.<sup>22</sup> A “PTC membrane” surrounding the catalyst may improve the absorption of PhBr or hydrogen species and enhance the “cleaning” of the catalyst surface.<sup>23</sup> We examined three PTC types, viz. quaternary ammonium salts, crown ethers, and the nonionic surfactant, PEG (Table 5). Only 5% conversion

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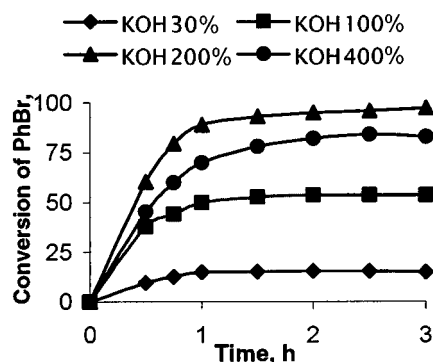
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**Table 3. PhBr coupling using different alcohols as reducing agents<sup>a</sup>**

entry	alcohol	/% <sup>b</sup>	selectivity biphenyl /% <sup>b</sup>	entry	alcohol	/% <sup>b</sup>	selectivity biphenyl /% <sup>b</sup>
1	methanol	67.0	64.1	9	benzyl alcohol	100.0	48.0
2	ethanol	70.0	56.2	10	phenethyl alcohol	79.0	58.0
3	1-pentanol	84.6	43.6	11	2-phenethyl alcohol	66.0	54.0
4	<i>i</i> -propanol	66.6	55.6	12	cyclohexanol	95.7	51.0
5	2-butanol	90.0	58.2	13	<i>tert</i> -amyl alcohol <sup>c</sup>	21.1	72.5
6	2-octanol	82.2	58.1	14	<i>tert</i> -butyl alcohol <sup>c</sup>	36.0	81.3
7	2-pentanol	87.5	59.3	15	2-phenyl-2-propanol	17.0	85.1
8	ethylene glycol	90.0	62.2				

<sup>a</sup> Standard reaction conditions: 32.0 mmol PhBr, 64.0 mmol NaOH, 35.0 mmol alcohol, 1.6 mmol 5% Pd/C (5 mol % Pd relative to PhBr), 3.2 mmol PEG-400, 105 °C, 25 mL of toluene (solvent), 6 h. <sup>b</sup> Based on GC area, corrected by the presence of an internal standard. <sup>c</sup> Cetyl-trimethylammonium bromide (CTAB) was used instead of PEG-400.



**Figure 4. Rates of conversion at different base concentrations. Conditions: 32.0 mmol PhBr, 64.0 mmol KOH, 35 mmol 2-pentanol, 1.6 mmol 5% Pd/C, 3.2 mmol PEG-600, 105 °C, 25 g of xylene (solvent).**

**Table 4. Coupling of PhBr in the presence of various bases<sup>a</sup>**

entry	base	conversion PhBr/% <sup>b</sup>	selectivity biphenyl/% <sup>b</sup>
1	NaOH	74.1	61.9
2	KOH	100.0	51.1
3	K <sub>2</sub> CO <sub>3</sub>	8.0	67.0
4	NaHCO <sub>3</sub>	0.0	0.0
5	triethylamine	4.0	—

<sup>a</sup> Standard reaction conditions: 32.0 mmol PhBr, 64.0 mmol of base, 35.0 mmol 2-pentanol, 1.6 mmol 5% Pd/C (5 mol % Pd relative to PhBr), 3.2 mmol PEG-400, 105 °C, 25 mL of toluene (solvent), 4 h. <sup>b</sup> Based on GC area, corrected by the presence of an internal standard.

was observed in the absence of PTC. The best results were obtained using PEG-400.

The rate constants for conversion of PhBr increased dramatically with increased concentration of PEG-600 going from  $0.1 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$  at 2.5 mol % to  $2.8 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$  at 20 mol % (see Figure 5). However, the selectivity was not affected by increasing the concentration of PEG (Table 2, entries 18–22). The optimal PEG loading was found to be 10 mol %.

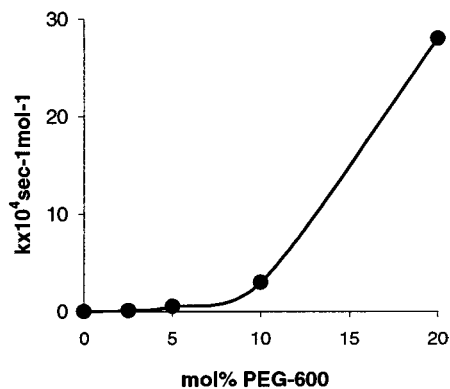
**Effects of Different Supports.** The role of different catalyst supports for Pd was examined (Table 6). Activated carbon supports, which did not contain strong acid centers and had high surface areas,<sup>24</sup> showed optimal results in the coupling reaction. Hydrophobic carbons also had a favorable

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**Table 5. Coupling of PhBr in the presence of different phase-transfer agents<sup>a</sup>**

entry	PTC	conversion PhBr/% <sup>b</sup>	selectivity biphenyl/% <sup>b</sup>
1	none	5.0	78.0
2	18-crown-6	64.3	58.9
3	CTMAB	63.9	59.1
4	PEG-300	67.3	55.2
5	PEG-400	69.5	56.7
6	PEG-600	80.9	61.7
7	PEG-1000	58.7	59.3
8	PEG-1500	52.7	58.5
9	PEG-550 monomethyl ether	53.2	55.5

<sup>a</sup> Standard reaction conditions: 32 mmol PhBr, 64 mmol NaOH, 35 mmol 2-pentanol, 1.6 mmol 5% Pd/C (5 mol % Pd relative to PhBr), 3.2 mmol PTC, 105 °C, 25 mL of xylene (solvent), 4 h. <sup>b</sup> Based on GC area, corrected by the presence of an internal standard.



**Figure 5. Rates of conversion at different PEG-600 concentrations. Conditions: 32 mmol PhBr, 64 mmol NaOH, 35 mmol 2-pentanol, 1.6 mmol 5% Pd/C, 105 °C, 25 g of xylene (solvent).**

effect by facilitating the adsorption of hydrophobic haloarenes.<sup>25</sup> Pd/C (3%) gave the best results with 100% conversion and 58.5% selectivity to biphenyl. Non-carbon supports with strong acidic centers such as alumina or CaCO<sub>3</sub> gave more hydrodehalogenation and lower selectivity to biphenyl (Al/Si supports dissolved in the strong basic reaction medium, and the reaction was stopped).

**Solvent Effects.** The reaction was carried out in various solvents with results shown Table 7. Changing the solvent did not affect conversion, but selectivity to biphenyl de-

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**Table 6.** Effects of different Pd supports on PhBr conversion and product selectivity<sup>a</sup>

entry	Pd supports	conversion PhBr/% <sup>b</sup>	selectivity biphenyl/% <sup>b</sup>
1	Pd/C 3%	100.0	58.5
2	Pd/C 5%	89.5	57.0
3	Pd/C 10%	86.7	54.0
4	Pd/alumina(pellets) 5%	32.5	0.0
5	Pd/CaCO <sub>3</sub> 5%	67.0	13.0
6	Pd/BaSO <sub>4</sub> 5%	81.8	47.5
7	Pd/Graph. 5%	57.5	25.3
8	Pd/Alumina Silicate	41.6	36.8

<sup>a</sup> Standard reaction conditions: 32 mmol PhBr, 64 mmol NaOH, 35 mmol 2-pentanol, 1.6 mmol 5% Pd (5 mol % Pd relative to PhBr), 3.2 mmol PEG-400, 105 °C, 25 mL of xylene (solvent), 7 h. <sup>b</sup> Based on GC area, corrected by the presence of an internal standard.

**Table 7.** Solvent effects on PhBr conversion and product selectivity<sup>a</sup>

entry	solvent	conversion PhBr /% <sup>b</sup>	selectivity biphenyl /% <sup>b</sup>
1	toluene	92.1	60.2
2	xylene	91.2	61.0
3	mesitylene	92.4	59.9
4	DMA	100.0	40.3
5	NMP	95.0	45.3
6	DMSO	78.0	26.6
7	2-pentanol	100.0	46.0

<sup>a</sup> Standard reaction conditions: 32 mmol PhBr, 64 mmol NaOH, 35 mmol 2-pentanol, 1.6 mmol 5% Pd/C (5 mol % Pd relative to PhBr), 3.2 mmol PEG-400, 105 °C, 25 mL of solvent, 8 h. <sup>b</sup> Based on GC area, corrected by the presence of an internal standard.

**Table 8.** Coupling of various halobenzenes<sup>a</sup>

entry	substrate	conversion PhX /% <sup>b</sup>	selectivity biphenyl /% <sup>b</sup>
1	PhI	99.0	12.0
2	PhBr	42.6	49.0
3	PhCl	31.2	32.0
4	PhF	0.0	0.0

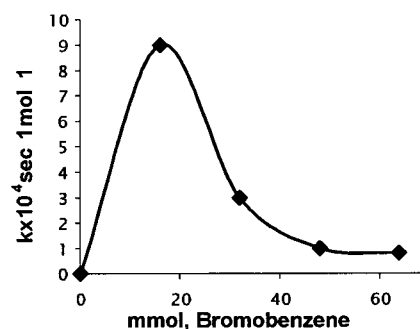
<sup>a</sup> Standard reaction conditions: 32 mmol PhX, 64 mmol NaOH, 35 mmol *i*-PrOH, 0.48 mmol 5% Pd/C (5 mol % Pd relative to substrate), 3.2 mmol PEG-400, 105 °C, 25 mL of toluene (solvent), 22 h. <sup>b</sup> Based on GC area, corrected by the presence of an internal standard.

creased with increasing solvent polarity, possibly because of the high formation rate of hydride species in the more polar solvents. Considering both conversion, selectivity, and ease of temperature control, xylene would be the solvent of choice. Increasing the solvent amount slowed the reaction, probably owing to competition with PhBr at the Pd surface.

**Changing the Halogen Leaving Group.** As shown in Table 8, the leaving halogen significantly affects the product yields. Conversion rates were in the order ArI > ArBr > ArCl.<sup>26</sup> However the selectivity of these reactions to biphenyl does not show the same trend. The initial electron transfer and formation of radical anions from halobenzenes is expected to be a function of the strength of the Ar–X bond.<sup>27</sup> Our results may arise from the combination of two opposite

(26) As expected, no reaction was observed with fluorobenzene.

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**Figure 6.** Effect of different initial concentrations of PhBr on initial reaction rate. Conditions: 64 mmol NaOH, 35 mmol 2-pentanol, 1.6 mmol 5% Pd/C, 3.2 mmol PEG-600, 105 °C, 25 g of xylene (solvent).

factors: (i) the C–X bond energies and (ii) the adsorption strength of the halobenzene on the catalyst. The former decrease in the order  $D_{C-F}$  (453.6 kJ mol<sup>-1</sup>) >  $D_{C-Cl}$  (340.2 kJ mol<sup>-1</sup>) >  $D_{C-Br}$  (281.4 kJ mol<sup>-1</sup>) >  $D_{C-I}$  (222.6 kJ mol<sup>-1</sup>).<sup>18</sup> However, the adsorption strength of aryl halides decreases in the following order: PhI ≫ PhCl ≈ PhBr.<sup>28,29</sup> The high reaction rate and good selectivity observed for PhBr may be therefore due to the combination of moderate adsorption strength and relatively low C–Br bond energy, supporting the suggestion that the rate-determining step in the reaction is the adsorption of the halobenzene on the Pd surface (followed by electron transfer).<sup>30</sup> The low selectivity to biphenyl observed in the case of PhI reflects its high adsorption strength on Pd catalyst.

**Mechanistic Considerations.** When all other reagents are used in excess, the rate of the coupling reaction (eq 1) shows second-order dependence on [PhBr], that is  $r_1 = k_1[ArBr]^2$ . Likewise, we can express the rate of the reduction reaction (eq 2) as  $r_2 = k_2[ArBr]$ , making the overall rate  $r = k_1[ArBr]^2 + k_2[ArBr]$ . When  $k_1 \gg k_2$ , the rate reduces to the second-order, fitting with the experimental observations (Figure 2 above).

Figure 6 shows the influence of different initial concentrations of PhBr on the initial reaction rate. An optimum PhBr concentration is observed, above which the reaction rate decreases. The shape of this curve is consistent with the Langmuir–Hinshelwood model pertaining to adsorption effects on a heterogeneous catalyst when large quantities of starting material cover the Pd surface, so that other reagents are denied access to the surface.<sup>31</sup>

Halobenzenes are known to react with various metals to form radical anions.<sup>32</sup> Diffusion of these radical anions from the surface of the metal into the solution frequently leads to radical coupling/reduction products.<sup>33</sup> In our system, the radical anion formed from PhBr in the presence of Pd/C

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yields a mixture of biphenyl and benzene. The mechanism of the present catalytic reaction seems intriguing as it is different from the well-known coupling reaction in the presence of formate salts. Further studies on the scope and mechanism of this catalytic system are in progress.

## Conclusions

In the absence of water the stoichiometric reductive coupling of halobenzenes was shown to have very low activity. However, this reaction can be achieved using alcohols. Alcohols can be utilized as hydrogen-transfer agents for the coupling of halobenzene in the presence of heterogeneous Pd/C. The reaction was found to be sensitive to the type and concentration of the base. The absorbance strength of ArX on the heterogeneous palladium catalyst and the nature of the support play a key role in the coupling and reduction of halobenzenes.

## Experimental Section

Materials, analytical methods, and instrumentation have been described in detail in a previous publication.<sup>14</sup>

**General Procedure for Haloaryl Coupling.** Example: Biphenyl from PhBr: 5.0 g (32 mmol) of PhBr, 3.1 g (35 mmol) of 2-pentanol, 3.3 g of 5% Pd/C (5 mol % Pd based on PhBr), 2.56 g (64 mmol) of NaOH, 1.92 g of PEG-600 (10 mol % based on PhBr), 0.8 g of naphthalene (internal standard), and xylene (solvent, total reaction volume 40 mL) were charged to a flask that was heated to 105 °C. Reaction progress was monitored by GC. The mixture was stirred for 8 h, after which 91.2% conversion of PhBr was measured. Yields: biphenyl 62% (1.38 g), benzene 38% (0.86 g).

**Kinetic Studies.** The standard reaction conditions were as in the general procedure. The following parameters were studied: (i) initial PhBr concentration, (4 experiments at 16 mmol,  $k_{\text{obs}} = 9 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.983$  for five observations; 32 mmol,  $k_{\text{obs}} = 3 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.990$  for five observations; 48 mmol,  $k_{\text{obs}} = 1 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.981$  for five observations; 64 mmol,  $k_{\text{obs}} = 0.8 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.975$  for 5 observations); (ii) catalyst loading (six experiments using 0.5 mol % of 5% w/w Pd/C,  $k_{\text{obs}} = 0.4 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.979$  for five observations; 1.5

mol %,  $k_{\text{obs}} = 0.5 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.951$  for five observations; 2.5 mol %,  $k_{\text{obs}} = 2 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.993$  for five observations; 5.0 mol %,  $k_{\text{obs}} = 3 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.983$  for five observations; 7.5 mol %,  $k_{\text{obs}} = 2 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.985$  for five observations; and 10.0 mol %,  $k_{\text{obs}} = 1 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.99$  for five observations); (iii) PTC loading (four experiments using 2.5 mol % PEG-600,  $k_{\text{obs}} = 0.1 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.999$  for five observations; 5 mol % PEG-600,  $k_{\text{obs}} = 0.5 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.999$  for five observations; 10 mol % PEG-600,  $k_{\text{obs}} = 3 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.993$  for five observations; and 20 mol % PEG-600,  $k_{\text{obs}} = 28 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.998$  for five observations); (iv) reaction temperature (four experiments at 90 °C,  $k_{\text{obs}} = 0.9 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.993$  for five observations; 105 °C,  $k_{\text{obs}} = 3 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.999$  for five observations; 115 °C,  $k_{\text{obs}} = 9 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.989$  for five observations; 125 °C,  $k_{\text{obs}} = 25 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.998$  for five observations); (v) KOH loading (four experiments using 30 mol % of KOH,  $k_{\text{obs}} = 0.5 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.972$  for five observations; 100 mol % of KOH,  $k_{\text{obs}} = 3 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.956$  for five observations; 200 mol % of KOH,  $k_{\text{obs}} = 2.3 \times 10^{-3} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.994$  for five observations; 400 mol % of KOH,  $k_{\text{obs}} = 5 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.996$  for five observations); (vi) alcohol (2-pentanol) concentration (four experiments using 25 mol % of 2-pentanol,  $k_{\text{obs}} = 1 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.996$  for five observations; 50 mol %,  $k_{\text{obs}} = 2 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.997$  for four observations; 100 mol %,  $k_{\text{obs}} = 3 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.975$  for five observations; and 200 mol %,  $k_{\text{obs}} = 3 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ,  $r^2 = 0.980$  for five observations).

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