

# On the Mechanism of Palladium-Catalyzed Coupling of Haloaryls to Biaryls in Water with Zinc

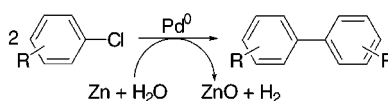
Sudip Mukhopadhyay, Gadi Rothenberg,<sup>†</sup> Diana Gitis, and Yoel Sasson\*

Casali Institute of Applied Chemistry, Hebrew University of Jerusalem, 91904, Israel

ysasson@vms.huji.ac.il

Received November 30, 1999

## ABSTRACT



Kinetics and process parameters of coupling and hydro-dehalogenation reactions of chloroaryls are studied in the presence of zinc, water, and catalytic Pd/C. Good yields are obtained for the coupling of chlorobenzene, 4-chlorotoluene, and 4-chloro-1,1,1-trifluorotoluene. It is shown that water is actually one of the reagents, reacting with zinc in the presence of palladium to give zinc oxide and hydrogen gas, which then regenerates the Pd<sup>0</sup> catalyst for the coupling reaction.

Synthesis of biaryl compounds is of importance for numerous agrochemical and pharmaceutical applications.<sup>1</sup> The classic Ullmann<sup>2</sup> and Suzuki<sup>3</sup> methodologies are well-known in this context. Owing to the versatile chemistry of palladium compounds in carbon–carbon bond formation reactions,<sup>4</sup> several palladium-catalyzed processes have been proposed as eco-friendly replacements for the stoichiometric Ullmann protocol.<sup>5</sup> Essentially based on the Pd<sup>2+</sup> ↔ Pd<sup>0</sup> redox cycle, these processes require in situ regeneration of the active palladium catalyst, which can be achieved using various

reagents; e.g., 2-propanol, hydrogen gas,<sup>6</sup> or aqueous alkali formate salts.<sup>7</sup>

Recently, we showed the feasibility of some of the above transformations and discussed possible reaction mechanisms for aryl–aryl coupling under heterogeneous and homogeneous catalysis conditions.<sup>6,7b</sup> A letter by Venkatraman et al.,<sup>8</sup> describing coupling of iodobenzenes using zinc and palladium in an acetone–water system, prompted us to publish our interesting findings in this field. In that paper, coupling reactions were performed under an air atmosphere, and, while in most cases good selectivity was achieved, the proffered results left much to be explained.

(8) Venkatraman, S.; Li, C.-J. *Org. Lett.* **1999**, *1*, 1133.

(9) **Representative Experimental Procedure for Coupling of Haloaryls.** Instrumentation, experimental apparatus, and product isolation and identification methods have been described in detail previously (refs 6 and 7a). Example: **2a** from **1a**. In a 300 mL autoclave were charged 5.0 g (44 mmol) of **1a**, 3.3 g (50 mmol) of Zn, 5.0 g (125 mmol) of NaOH, 1.5 g (8.4 mol %) of PEG-400, 1.0 g of 5% w/w Pd/C (1.0 mol % Pd relative to **1a**), and H<sub>2</sub>O (total reaction volume 50 mL). The autoclave was heated to 100 °C. Reaction progress was monitored by GC. The mixture was stirred (950 rpm, see ref 11) at 100 °C for 2 h, cooled, and extracted with 40 mL of CH<sub>2</sub>Cl<sub>2</sub>. Solvent evaporation and recrystallizing afforded 2.35 g of **2a** (68 mol % based on **1a**), mp 69 °C (from cold EtOH) [lit. 69–71 °C (Tamura, Y.; Chun, M.-W.; Inoue, K.; Minamikawa, J. *Synthesis* **1978**, 822). Found: C, 93.26; H, 6.74. C<sub>10</sub>H<sub>12</sub> requires C, 93.46; H, 6.54.  $\delta_{\text{H}}$  (CDCl<sub>3</sub>; Me<sub>4</sub>Si) 7.39 (2H, tt, aromatic 4,4'-H), 7.46 (4H, qt, aromatic 3,3',5,5'-H), 7.59 (4H, dq, aromatic 2,2',6,6'-H). Good agreement was found with literature values (Kamewaza, N. J. *Magn. Reson.* **1973**, *11*, 88). Please refer to the Supporting Information for details of the synthesis of compounds **2b** and **2d**.

<sup>†</sup> Current address: York Green Chemistry Group, Clean Technology Centre, Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K. E-mail: gr8@york.ac.uk.

(1) For representative reviews on biaryl preparation methods and applications, see: (a) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (b) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327. See also: (c) Stinson, S. C. *Chem. Eng. News* **1999**, 69.

(2) (a) Ullmann, F. *Ber.* **1903**, *36*, 2389. (b) Fanta, P. E. *Synthesis* **1974**, 9.

(3) (a) Miyamura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. (b) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (c) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346.

(4) For an excellent recent monograph on palladium catalysis see: Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1993.

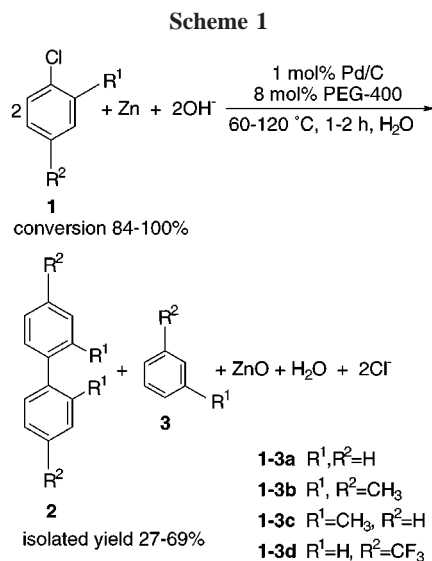
(5) (a) Hennings, D. D.; Iwama T.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 1205. (b) Hassan, J.; Penalva, V.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *54*, 13793.

(6) Mukhopadhyay, S.; Rothenberg, G.; Wiener H.; Sasson, Y. *Tetrahedron* **1999**, *55*, 14763.

(7) (a) Bamfield, P.; Quan, P. M. *Synthesis* **1978**, 537. (b) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Wiener H.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2481.

Here, we present the results of a kinetic investigation and process optimization of the palladium-catalyzed coupling and reduction reactions of haloaryls. The balanced stoichiometric reaction equation presented here provides insight to the nature of the reaction system. In particular, the role of water as the hydrogen source and catalyst regenerator becomes apparent.

In a typical reaction (Scheme 1), chlorobenzene **1a**, zinc,



water, sodium hydroxide, and catalytic amounts of poly(ethylene glycol) (PEG-400) and Pd/C were charged to an autoclave. After 1–2 h of stirring at 60–120 °C, depending on reaction conditions, biphenyl was found to be the major product, together with some hydro-dehalogenation (reduction) product.<sup>9</sup> Good to moderate yields for the coupling products were obtained using various chloroaryls, as shown in Table 1. No other products were observed.

**Table 1.** Coupling of Various Chloroaryls<sup>a</sup>

substrate	% convn	product (% yield) <sup>b</sup>	
<b>1a</b>	100	<b>1b</b> (68) <sup>c</sup>	<b>1c</b> (30)
<b>1b</b>	91	<b>2b</b> (51) <sup>c</sup>	<b>2c</b> (38)
<b>1c</b>	84	<b>3b</b> (27) <sup>c</sup>	<b>3c</b> (45)
<b>1d</b>	100	<b>4b</b> (69) <sup>c</sup>	<b>4c</b> (27)

<sup>a</sup> Reaction conditions: substrate, 45 mmol; Zn, 50 mmol; 5% Pd/C, 1.0 mol % of substrate; PEG-400, 1.5 g (8.4 mol % of substrate); NaOH, 125 mmol; 100 °C; 2 h stirring; 50 mL total reaction volume (water). <sup>b</sup> Yield based on GC area, corrected by the presence of an internal standard. <sup>c</sup> Isolated yield.

Chlorobenzene **1a** was chosen as a model substrate for kinetic and process parameter studies.<sup>10</sup> Reaction rates were found to be a function of substrate concentration, Zn loading, and Pd loading, i.e.,  $-d[1a]/dt = k_{obs}[1a]^{1.05}[Zn]^{0.66}[Pd]^{0.86}$ .

(10) Please refer to the Supporting Information for details of the kinetic studies.

A pseudo-first-order rate law,  $-d[1a]/dt = k_{obs}[1a]$ , was observed for fixed zinc and catalyst loading, with typical  $k_{obs}$  values  $\approx 3.7\text{--}3.8 \times 10^{-2} \text{ min}^{-1}$ .<sup>11</sup>

Performing the reaction at higher temperatures increased selectivity to biphenyl, from 44% at 60 °C up to 74% at 100 °C, suggesting that  $E_{a,coupling} > E_{a,reduction}$ . The Arrhenius energy of activation was found to be  $E_{a,coupling} = 30.0 \text{ kJ mol}^{-1}$  (7.2 kcal mol<sup>-1</sup>,  $r^2 = 0.997$  for four measurements at 60, 80, 100, and 120 °C) and  $E_{a,reduction} = \sim 8 \text{ kJ mol}^{-1}$  (2 kcal mol<sup>-1</sup>). These findings characterize the reduction as a mass-transfer controlled process,<sup>12</sup> in contrast with the chemically controlled coupling under these conditions.

The influence of various reaction parameters on substrate conversion and product selectivity is shown in Table 2. Increasing Zn loading (Table 2, entries 1–5), Pd/C catalyst loading (entries 6–11), or the addition of sodium hydroxide (entries 12–17) shifted product selectivity toward the coupling product.

The advantages resulting from the incorporation of surface-active agents into this multiphase system has been discussed elsewhere.<sup>13</sup> Earlier studies in similar systems have shown that choosing the appropriate surfactant is mostly a matter of trial and error.<sup>7a</sup> Although ammonium salts such as CTAB and PEG-400 displayed similar effects, PEG-400 was chosen due to its low cost, higher solubility in the solvent system, and ease of separation. The presence of PEG-400 increases both conversion and selectivity (Table 2, entries 18–21). We assume that PEG does not alter the chemical nature of the intermediates, but rather, that it modifies the physical microenvironment of the catalyst, facilitating the approach of the organic substrate.

Performing the reaction using less water (Table 2, entries 25–28) increased the selectivity toward the coupling product, although conversion was lower. This tallies with the proposed reaction mechanism (vide infra). Working with less than 1.5 molar equiv of water to substrate proved ineffectual, due to technical mixing and solubilization problems associated with the solid zinc reagent.

Although water does not appear as a reagent in the stoichiometry of the final reaction, it still plays a paramount role. In fact, *without water there would be no reaction*. Indeed, the results of Venkatraman et al. also show this—whenever they excluded water from their reaction using MeCN or pure acetone as solvents—they observed only 7–8% conversion. This conversion was due to the 8 mol % of palladium they put in, which was functioning as a stoichiometric reagent rather than as a catalyst, because it could not be regenerated in the absence of water.

(11) (a) To ensure that reaction rates were not mass transfer controlled, agitation speed was varied from 200 to 950 rpm. Above 800 rpm, no increase in conversion was detected. Thus, all measurements pertain to 950 rpm stirring. (b) For reactions at different chlorobenzene concentrations, xylene was added to make up for the volume of the organic phase.

(12) (a) Cf. Marques, C. A.; Selva, M.; Tundo, P. *J. Org. Chem.* **1994**, *59*, 3830, where hydro-dehalogenation was found to be of zero order in the substrate. (b) Blackmond, D. G.; Rosner, T.; Pfaltz, A. *Org. Proc. Res. Dev.* **1999**, *3*, 275.

(13) (a) Rothenberg, G.; Barak, G.; Sasson, Y. *Tetrahedron* **1999**, *55*, 6301. (b) Ait-Mohand, S.; Hénin, F.; Muzart, J. *Tetrahedron Lett.* **1995**, *36*, 2473. (c) Bouquillon, S.; du Moulinet d'Hardemare, A.; Averbuch-Pouchot, M.; Hénin, F.; J. Muzart, J. *Polyhedron* **1999**, *18*, 3511–3516.

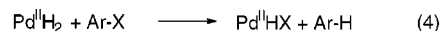
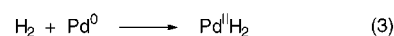
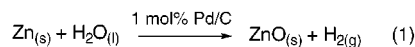
**Table 2.** Coupling of **1a** under Various Conditions<sup>a</sup>

entry	parameter	% convn	% selection <b>2a</b> <sup>b</sup>
Zn/mmol			
1	10.0	21	68
2	20.0	46	74
3	45.3	90	73
4	50.0	97	69
5	60.0	100	57
Pd/C/mol %			
6	none	0	0
7	1.0	18	69
8	2.0	32	70
9	3.0	44	72
10	4.0	90	73
11	6.0	91	75
[NaOH]/mmol			
12	0.0	53	34
13	40.0	90	46
14	60.0	94	57
15	80.0	98	68
16	100.0	100	73
17	120.0	100	74
PEG-400/mol %			
18	2.8	92	58
19	5.6	96	74
20	8.4	100	73
21	11.3	100	61
Zn particle/ $\mu$ m			
22	40–60	100	73
23	60–100	100	70
24	~1000	37	53
<b>1a</b> –water /mol–mol			
25	solvent H <sub>2</sub> O	100	73
26	1:5.0	51	75
27	1:2.5	32	88
28	1:1.5	17	89

<sup>a</sup> Standard reaction conditions: **1a**, 45 mmol; Zn, 50 mmol; 5% Pd/C, 1.0 mol % of **1a**; PEG-400, 1.5 g (8.4 mol % of **1a**); NaOH, 100 mmol; 100 °C; 1 h stirring (2 h for entries 18–28); 50 mL total reaction volume (water, except entries 25–27). <sup>b</sup> Selectivity based on GC area, corrected by the presence of an internal standard.

The key reaction occurs between water and zinc in the presence of a palladium catalyst (eq 1). In a closed vessel, >60% conversion of water to hydrogen gas (based upon mol % consumption of zinc) can be achieved through this reaction. The dihydrogen reacts with the “used catalyst” and regenerates it (eq 2). In fact, as we have shown elsewhere, Pd-catalyzed coupling can be performed efficiently using

hydrogen gas as the catalyst regenerator (in the absence of zinc, using either water or a dry organic solvent).<sup>6</sup> Excess dihydrogen can adsorb on the reduced catalyst surface to form palladium hydride (eq 3), which in turn can reduce the halobenzene substrate (eq 4). Another possible route for the reduction reaction is direct hydrogen-transfer from water, in the presence of zinc, to the organic substrate.<sup>14</sup>



In contrast with the reduction reaction, coupling of aryl halides occurs, in all probability, via two consecutive single electron transfer (SET) processes, from two Pd<sup>0</sup> to two aryl halide molecules. This mechanism has been discussed in detail elsewhere.<sup>7b</sup>

The addition of a base, e.g., NaOH, improves the selectivity toward the coupling product (Table 2, entries 12–17). The significance of this lies in the coupling reaction’s sensitivity to the effective concentration of available Pd<sup>0</sup> sites. While coordination of a single substrate molecule to one catalytic site may suffice for reduction, coordination of two substrate molecules to two available sites would probably be required for the coupling reaction.<sup>15</sup> The presence of NaOH will result in a higher effective concentration of vacant Pd<sup>0</sup> sites, thus shifting the selectivity toward coupling. The fact that higher catalyst loading increases the coupling: reduction ratio also supports this argument.

The reason that Venkatraman et al. needed to use such a large excess (300 mol %) of zinc in their reaction system is also easily explained: the reaction between zinc and water gives ZnO, a solid. However, because zinc itself is insoluble in the reaction medium, a ZnO coating forms on the zinc particles, causing *deactivation of the zinc particles*. Evidence supporting this was obtained from experiments using different sizes of zinc particles (Table 2, entries 22–24), showing a strong correlation between conversion and zinc particle size. Zinc oxide may also coat some of the palladium catalyst surface, which may explain the slight drop in catalytic activity upon recycling (78% conversion was obtained with a recycled batch of palladium).<sup>16</sup>

Zinc-mediated coupling of aryl halides in the presence of water and catalytic Pd/C is therefore the sum of two reactions. One is the coupling of two aryl halide molecules mediated by Pd<sup>0</sup>, which is oxidized in the course of the reaction to Pd<sup>2+</sup>. The other is the reduction of water by zinc to obtain hydrogen gas and zinc oxide, a reaction which is itself catalyzed by Pd<sup>0</sup>/C. The hydrogen generated in situ reacts with Pd<sup>2+</sup> produced from the coupling reaction, to give back the pristine Pd<sup>0</sup> catalyst. Thus, water is not merely a convenient solvent medium but is actually one of the reagents in this remarkable Ullmann-type coupling reaction.

(14) For a detailed discussion of this reaction see: Mukhopadhyay, S.; Rothenberg, G.; Wiener, H.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2*, **1999**, in press. See also ref 6.

(15) No chlorobiphenyls were observed, so we may disregard the possibility of phenyl radicals attacking substrate molecules in this system. Thus, it is probable that the aryl radicals couple on the catalyst surface, followed by desorption of biphenyl.

(16) **Catalyst Recycling.** The reaction mixture was cooled to 25 °C and filtered. The solid residue was washed with H<sub>2</sub>O (3 × 40 mL) and MeOH (3 × 10 mL). The catalyst retained >78% of its activity on a consecutive run with fresh zinc.

**Acknowledgment.** We thank Dr. Dave J. Adams (York Green Chemistry Group, The University of York) for valuable comments, and Dr. Jacques Muzart (University of Reims) for discussions and preprints. G.R. thanks the Royal Society and the Israeli Academy of Sciences and Humanities for an exchange fellowship to visit the York Green Chemistry Group.

**Supporting Information Available:** Synthetic procedures and characterization data for compounds **2b** and **2d**; detailed experimental procedures describing kinetic studies and results; three additional references.

OL9912938