

Carbon-Carbon Bond Formation *via* Palladium-Catalyzed Reductive Coupling of Aryl Halides in Air and Water

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Abstract: Palladium-catalyzed reactions in general are carried out under an inert atmosphere because the palladium intermediates involved in the catalytic cycles are often known to be sensitive to oxygen. In this paper, we report that various palladium-catalyzed reductive couplings proceed smoothly under an air atmosphere and in aqueous medium. Under the air atmosphere reaction conditions, palladium-triphenylphosphine complex was found to be inactive. By using zinc as the reducing reagent, aryl halides were homo-coupled to give symmetrical biaryls either in aqueous acetone or in water in the presence of a catalytic

amount of 18-crown-6 at room temperature. Both aryl iodides and aryl bromides reacted efficiently under the current reaction conditions. The reaction of arylhalosilanes with aryl halides under refluxing conditions in air and water catalyzed by palladium generated unsymmetrical biaryls efficiently in the presence of either KOH or NaF. Such air-stable couplings are also suitable for a Suzuki-type coupling and a Stille-type coupling.

Keywords: aryl halides; biaryls; C–C coupling; cross-coupling; crown compounds; palladium

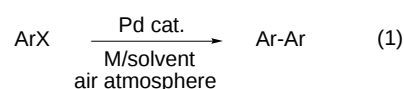
Introduction

Palladium-catalyzed reductive couplings are among the most important carbon-carbon bond forming reactions in modern synthetic organic chemistry.^[1] Such reactions include the π -allyl chemistry (also asymmetric),^[2] the Stille coupling,^[3] the Heck reaction,^[4] the Suzuki reaction,^[5] the Sonogashira coupling,^[6] and many others. While these reactions have also been successful in aqueous media,^[7] they are generally very sensitive towards air and, often, particular care needs to be taken to exclude air from the reaction system. In addition to the requirement of an inert gas atmosphere, these reactions are often carried out in the presence of a phosphine compound (which served as the coordinating ligand to stabilize the reactive palladium intermediate). In the course of our quest for novel methodologies in aqueous media,^[8] we came across this unusual condition wherein the palladium catalyst seemed to be stable in the air.^[9] Subsequently, we found that contrary to general beliefs, palladium-catalyzed reductive couplings in air and water are quite general. Herein, we report the detailed study of using such catalytic reactions to synthesize symmetrical biaryls *via* Ullmann-type homo-coupling of aryl halides and unsymmetrical biaryls *via* cross-coupling of arylhalosilanes with aryl halides.

Results and Discussion

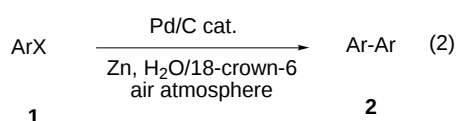
Ullmann-Type Coupling to Generate Symmetrical Biaryls

Conventionally, symmetrical biaryls have been synthesized via the Ullmann reaction^[10] of reductive aryl halide coupling,^[11] where copper is used in stoichiometric quantities.^[12] Generally, the Ullmann coupling is also carried out at a high temperature, typically above 200 °C. Recently, it has been shown that, in the presence of copper(I) thiophene-2-carboxylate, these reactions can be carried out under mild conditions.^[13] Palladium has also been shown to catalyze aryl halide homo-couplings under elevated reaction temperatures in the presence of a reducing reagent.^[14] Ni/C has also been found by Lipshutz to be an effective catalyst for coupling of aryl halides.^[15] As an effort in developing transition metal-catalyzed carbon-carbon bond formation reactions in water, we examined the potential of carrying out such couplings by using palladium-catalyzed couplings in water, Equation (1).



To begin our study, *p*-iodoanisole was stirred with zinc in a mixture of water/acetone (1:1) in the presence of a catalytic amount of palladium acetate (8 mol %) for 12 h (and, accidentally, under an air atmosphere), GC/MS analysis of the reaction mixture revealed the complete disappearance of the starting material and the corresponding homo-coupled product was generated in ca. 48% yield together with the dehalogenated anisole. No reaction was observed with other metals (such as Ni powder or PtO₂) as the catalyst. Subsequently, extensive investigations were made to evaluate the extent of such an air- and water-tolerant reaction. To evaluate conditions for the desired coupling, conversions of starting materials were measured by GC/MS and the results are summarized in Table 1. It appears that the use of a mixture of water/acetone is important. The use of acetone alone resulted in a very low conversion of the starting material, whereas in water alone no reaction was observed. Interestingly, the presence of triphenylphosphine inhibited rather than facilitated the reaction. DMSO, DMF or THF could also serve as the co-solvent but they were much less effective (entries 10, 11, 12). When the catalyst was changed from Pd(OAc)₂ to Pd/C,^[16] the efficiency of the coupling was increased and the dehalogenated product decreased (compare entries 1 and 2). The use of other metals (such as tin and indium) as the reducing agent resulted in a low reactivity (entries 5 and 6).^[17] The ratio of the homo-coupled product can be optimized when the reaction temperature was controlled at 0–10 °C. This might suggest that the coupling reaction is kinetically favored. To validate the air-stable nature of this palladium catalytic system, the reductive coupling was examined and found to be successful even under an oxygen atmosphere. Comparative experiments were carried out (with iodoanisole, zinc, and Pd/C in aqueous acetone) under nitrogen, oxygen, and air atmospheres, virtually identical results were obtained in all cases. However, a relatively low isolated yield of the desired product was obtained for coupling of iodobenzene under the conditions of acetone/water mixture. Subsequently it was found that, in the presence of a catalytic amount of 18-crown-6 (10 mol %),^[18] the zinc (< 10 microns, the use of larger particles sizes reduced the efficiency of the reaction) mediated reductive coupling of aryl halides **1** catalyzed by Pd/C provided improved isolated yields of the Ullmann-type products **2** at ambient temperature, in water alone, and under an atmosphere of air, Equation (2).

As shown in Table 2, various aromatic iodides and bromides were coupled by zinc in water with the



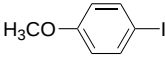
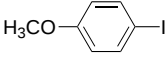
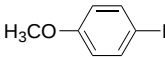
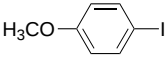
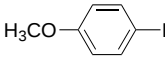
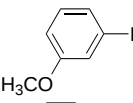
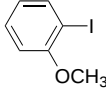
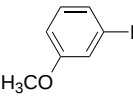
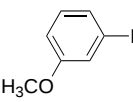
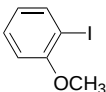
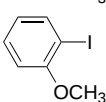
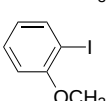
presence of catalytic amounts of Pd/C and 18-crown-6. In the absence of the crown ether, the yield of the desired product diminished considerably (compare entries 1 and 2, 7 and 8). An increase in steric hindrance resulted in a decrease of the yield of the coupled product (compare entries 6, 7, 13 and entries 4, 5, 15). Bromobenzene was similarly coupled in generating the carbon-carbon bond formation product (compare entries 1 and 3). Chloro and fluoro groups were inert under the reaction conditions, which imparts chemoselectivity (entries 9 and 10). On the other hand, only dehalogenation was observed with an electron-deficient aryl halide (entry 14). Subsequent to our initial report, Sasson and co-workers found that under a refluxing temperature, aryl chloride also reacted similarly.^[19]

Coupling of Aryl Halides with Phenylboronic Acid, Phenyl(ethynyl)tributyltin, and Arylsilanes to Generate Unsymmetrical Biaryls and Diphenylacetylene

In order to explore the scope of the air-stable palladium catalytic system, both Suzuki and Stille couplings of iodobenzene were briefly examined with phenylboronic acid (**3**) and phenyl(ethynyl)tributyltin (**5**), Equations (3) and (4), in water. Both reactions generated the desired coupling products **4** and **6** when Pd(OAc)₂ was used as the catalyst in aqueous acetone and under an air atmosphere. However, low conversions of the starting materials were observed at room temperature in both cases. Interestingly, no reaction was observed when Pd/C was used as the catalyst in these cases. Upon refluxing overnight, the reaction of PhI with PhB(OH)₂ and Bu₃SnCCPh in the presence of Pd(OAc)₂ (10 mol %) and Cs₂CO₃ (1 equivalent) provided the desired product **4** (yield: 91%) and **6** (yield: 71%) smoothly. Although both the Suzuki and Stille couplings reactions are successful under the same reaction conditions, a drawback of the Stille coupling is the involvement and generation of relatively toxic tin reagents and by-products. In the boronic acid case, the limitations with regard to synthesis and stability of boron reagents have also been noted.^[20] These limitations led us to investigate other alternative reactions.

Recently, the use of hypervalent silicon reagents for palladium-catalyzed cross couplings has been studied by Hiyama,^[21] DeShong^[22] and others. On the other hand, Denmark and co-workers have developed highly activated silicon reagents for palladium-catalyzed couplings with aryl halides.^[23] A common requirement for these studies has also been performance under anhydrous conditions and in an inert gas atmosphere. Our recent discovery that rhodium-catalyzed conjugated additions of arylhalosilanes proceeded effectively in air and water,^[24] led us to study the coupling of arylhalosilanes with various aryl halides catalyzed by palladium in air

Table 1. Optimization of air-atmosphere reductive coupling of aryl halides under a variety of conditions.^[a]

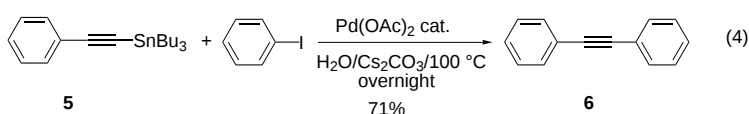
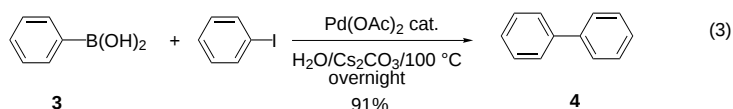
entry	substrate	metal	catalyst	solvent	coupling/dehalogenation ^[b]
1		Zn	Pd(OAc) ₂	acetone/H ₂ O (1:1)	48/50
2		Zn	Pd/C	acetone/H ₂ O (1:1)	80/20
3		Zn	Pd(OAc) ₂	acetone	7/trace
4		Zn	Pd(OAc) ₂	acetone/H ₂ O (9:1)	30/30
5		Sn	Pd(OAc) ₂	acetone/H ₂ O (1:1)	5/trace
6		In	Pd(OAc) ₂	acetone/H ₂ O (1:1)	26/trace
7		Zn	Pd(OAc) ₂	acetonitrile	8/trace
8		Zn	Ni	acetone/H ₂ O (1:1)	no reaction
9		Zn	PtO ₂	acetone/H ₂ O (1:1)	no reaction
10		Zn	Pd(OAc) ₂	DMSO/H ₂ O (1:1)	19/80
11		Zn	Pd(OAc) ₂	DMF/H ₂ O (1:1)	20/40
12		Zn	Pd(OAc) ₂	THF/H ₂ O (1:1)	17/20

^[a] All reactions were carried out at room temperature under an air atmosphere on 100 mg scale of aryl halides with aryl halide/M (1:3) and 8 mmol % of the catalyst.

^[b] Conversion ratios were based on GC/MS analysis of ether extract of the reaction mixtures, the data are only for optimization purpose and may not reflect the actual ratios of the amount of products.

and water. For the reaction of 4-iodoanisole with various organosilanes **7**, a preliminary test indicated the formation of three coupled products **8a**, **8b**, and **8c** under such reaction conditions, Equation (5).

Subsequently, the reaction was evaluated by the overall conversion of starting material, the isolated yield of the desired product **8b**, and the ratio of product/by-products (Table 3). The reaction of phenyltrichloro-



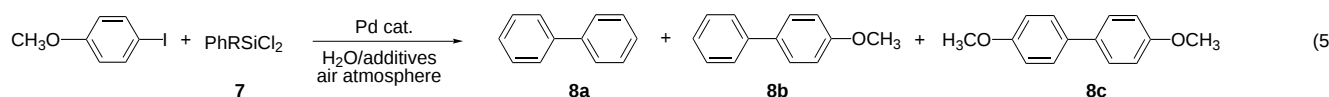


Table 2. Zinc-mediated reductive coupling of aryl halides catalyzed by Pd/C under air atmosphere.^[a]

entry	substrate (1)	product (2)	yield [%]
1			54
2			21 ^[d]
3			44
4			61
5			68
6			57
7			51
8			12 ^[d]
9			60
10			60
11			~40 ^[b]
12			70 ^[c]
13			40
14			dehalogenation only
15			37

[a] Yields were isolated ones after a short chromatography on silica gel.

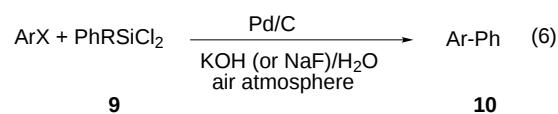
[b] The product was isolated as a mixture of coupling and dehalogenation, with the ratio being estimated by GC/MS.

[c] No coupling product was isolated.

[d] No crown ether was added.

silane with 4-iodoanisole under refluxing conditions overnight [with Pd(OAc)₂ being used as the catalyst] generated the desired product in 20% isolated yield together with a large amount of unreacted 4-iodoanisole. The use of diphenyldichlorosilane in combination with sodium fluoride slightly improved the yield. The yield was further improved by using phenylmethyldichlorosilane as the silicon reagent. The use of KOH instead of NaF provided higher yields for both diphenyldichlorosilane and phenylmethyldichlorosilane reactions. Very similar but slightly better results were observed with Pd/C as the catalyst. In this case, no reaction was observed in the absence of KOH. The relative ratios of the desired product and homo-coupled by-products were quite constant in all cases.

Subsequently, the reaction of methylphenyldichlorosilane (**9**) with a variety of aryl halides was examined under the Pd/C-catalyzed conditions to generate the unsymmetrical biaryls **10**, Equation (6) (Table 4, see page 404). Nearly the same results were obtained with either iodo or bromo derivatives. Iodo- and bromonaphthalenes (entries 1, 2, and 8) reacted similarly. A slightly better yield was obtained with an electron-deficient aryl iodide (entries 3, 9, 10, and 11) than with electron-rich aryl halides. It is worthy of mentioning that 4-bromophenol (bearing a free hydroxy group) reacted smoothly to generate the desired product (entry 6). The use of simple iodobenzene provided the corresponding product quantitatively (part of the product may be due to homo-coupling of the silicon reagent).



Mechanistic Discussions

A tentative mechanism (similar to the one proposed by Jutand^[25]) for the Ullmann-type coupling is proposed involving the oxidative addition of the palladium catalyst to the aryl halides to generate a palladium intermediate (Scheme 1). The intermediate then undergoes reduction by zinc to give an arylpalladium anion. The arylpalladium anion then reacts with another aryl halide to give the diarylpalladium intermediate, which then undergoes reductive elimination to give the homo-

Table 3. Coupling of 4-iodoanisole with arylhalosilanes (**7**) under various conditions.

entry	silicon reagent 7	catalyst	additive ^[a]	conversion [%] ^[b]	8a:8b:8c ^[b]	yield [%] ^[c] of 8b
1	PhSiCl ₃	Pd(OAc) ₂	no	30	15:65:20	20
2	Ph ₂ SiCl ₂	Pd(OAc) ₂	NaF	54	15:75:10	40
3	PhMeSiCl ₂	Pd(OAc) ₂	NaF	70	11:79:10	47
4	Ph ₂ SiCl ₂	Pd(OAc) ₂	KOH	91	12:79:8	70
5	PhMeSiCl ₂	Pd(OAc) ₂	KOH	90	11:81:8	71
6	PhSiCl ₃	Pd/C	KOH	50	5:74:21	36
7	Ph ₂ SiCl ₂	Pd/C	KOH	87	2:88:10	74
8	PhMeSiCl ₂	Pd/C	KOH	97	3:91:6	80
9	PhMeSiCl ₂	Pd/C	no	0	0	0

^[a] 6–8 equivalents of additives were used.^[b] Ratios and conversions were estimated (may not reflect the actual ratios) by GC/MS.^[c] Isolated yields.

coupled product. For the synthesis of unsymmetrical biaryls, the usual mechanism involving the oxidative addition of the palladium catalyst to the aryl halides generates a palladium intermediate.^[26] The intermediate then reacts with phenylboronic acid, phenyl(ethynyl)tributyltin, or the silicate (generated from the arylhalosilane derivative and KOH or NaF) to afford the diarylpalladium species, which undergoes reductive elimination to give the cross-coupling product and to regenerate the active palladium catalyst.

Conclusion

Various palladium-catalyzed reductive couplings were found to proceed smoothly under an air atmosphere and in aqueous media. By using zinc as the reducing reagent, aryl halides were homo-coupled to give symmetrical biaryls catalyzed by Pd/C in air and water in the presence of either acetone or 18-crown-6 at room temperature. Such air-stable couplings were also found to be suitable for Suzuki-type and Stille-type couplings.

In the presence of either KOH or NaF, arylhalosilanes were coupled with aryl halides under refluxing conditions in air and water catalyzed by Pd(OAc)₂ and Pd/C to generate unsymmetrical biaryls efficiently. This air- and water-tolerant palladium catalytic system provides an operational convenience for synthesis.

Experimental Section

General Remarks

Unless otherwise noted, all reagents and solvents were obtained from commercial sources and were used without further purification. Chromatography was carried out using Merck 60 230–400-mesh silica gel. IR spectra of liquid were recorded as thin films on NaCl plates and IR spectra of solids were recorded as KBr pellets. Chemical shift in NMR spectra is expressed in ppm. All NMR spectra were obtained at room temperature in CDCl₃ with TMS as an internal standard. All products for the current studies are known compounds and their characterizations have been compared with authentic samples or literature data.

Typical Experimental Procedure for Ullmann-Type Coupling

To a suspension of 4-iodotoluene (300 mg, 1.3 mmol) in 10 mL of de-ionized water in a 50 mL test-tube were added Pd/C (10%, 291 mg, 0.27 mmol), 18-crown-6 (73 mg, 0.27 mmol) and zinc powder (273 mg, 4.12 mmol). The test tube was capped and the mixture stirred overnight, diluted with 4 mL of 1 N aqueous HCl, filtered through celite and washed with ether. The filtrate was extracted with ether and concentrated. The resulting crude material was passed through a short column of silica gel eluting with hexane to give 4,4'-dimethylbiphenyl; yield: 85 mg (68%).

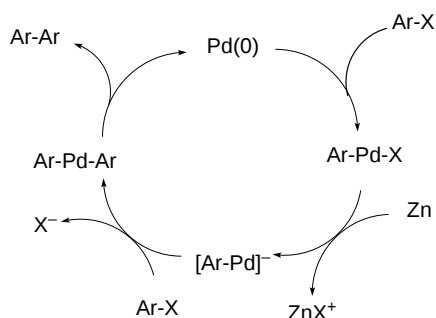
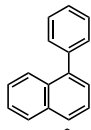
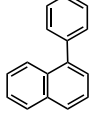
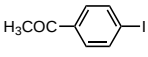
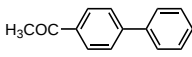
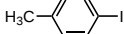
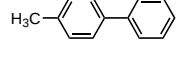
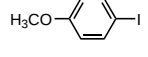
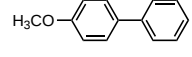
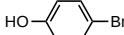
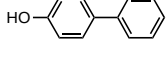
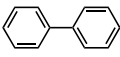
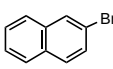
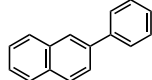
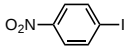
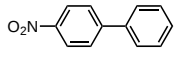
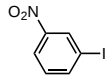
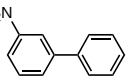
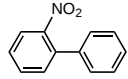
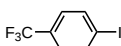
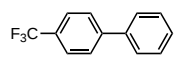
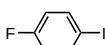
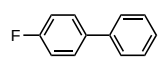
**Scheme 1.** Proposed mechanism for the zinc-mediated Ullmann-type coupling catalyzed by palladium in air and water.

Table 4. Coupling of various aryl halides with methylphenylsilane **9**.^[a]

entry	aryl halide	product 10	yield [%] ^[b]
1			72
2			65 (66%) ^[c]
3			81
4			61
5			80
			59
7			100
8			51
9			100
10			100
11			100
12			71
13			65

^[a] All reactions were carried out with Pd/C, KOH/H₂O, under refluxing conditions for 12–36 h.

^[b] Isolated yields.

^[c] Ph₂SiCl₂ was used.

Coupling of Phenylboronic Acid with Iodobenzene

A suspension of PhB(OH)₂ (146 mg, 1.2 mmol) PhI (204 mg, 1.0 mmol), Pd(OAc)₂ (22 mg, 0.1 mmol), Cs₂CO₃ (326 mg, 1 mmol) in water (5 mL) was stirred at reflux temperature overnight. After the reaction was completed, 15 mL of ethyl acetate were added. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (15 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by a flash chromatography on silica gel to give 140.1 mg (yield 91%) of biphenyl.

Coupling of Phenyl(ethynyl)tributyltin with Iodobenzene

A suspension of phenyl(ethynyl)tributyltin (469 mg, 1.2 mmol) PhI (204 mg, 1.0 mmol), Pd(OAc)₂ (22 mg, 0.1 mmol), Cs₂CO₃ (326 mg, 1 mmol) in water (5 mL) was stirred at reflux temperature overnight. After the reaction was completed, 15 mL of ethyl acetate was added. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (15 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by a flash chromatography on silica gel to give 126 mg (yield 71%) of diphenylacetylene.

Typical Procedure for Arylhalosilanes Coupling with Aryl Halides

A mixture of 4-iodoanisole (234 mg, 1 mmol), dichloromethylphenylsilane (382 mg, 2 mmol), KOH (448 mg, 8 mmol), and Pd/C (5 mol %) in 10 mL of water was stirred at 100 °C (oil bath temperature) for 12 h under an air atmosphere. The reaction mixture was cooled and extracted with ethyl acetate (3 ×). After the combined organic phase was dried and concentrated under vacuum, the residue was separated by silica gel chromatography eluting with hexane to give the desired biaryl product; yield: 140 mg (80%).

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