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Palladium-Catalyzed Reductive Homocoupling of Aromatic Halides and Oxidation of Alcohols

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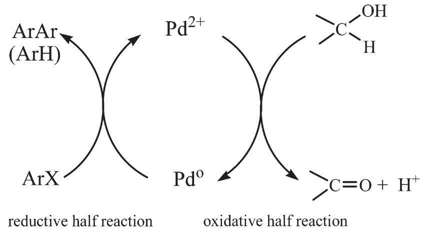
Received January 20, 2010



Palladium-catalyzed reductive homocoupling of aromatic halides can be performed in alcohol solutions without any auxiliary reducing reagents. Pd(dppf)Cl_2 [dppf = 1,1′-bis(diphenylphosphino)ferrocene] has been shown as the most effective catalyst among the palladium catalysts screened for the model reductive homocoupling of iodobenzene in alcoholic solutions. The reduction of iodobenzene is stoichiometrically coupled with the oxidation of solvent alcohol (3-pentanol). The X-ray photoelectron spectroscopic (XPS) studies clearly indicate that the oxidation of solvent alcohol molecules is involved with the *in situ* regeneration of the reductive Pd^0(dppf) active species, indicating that the solvent alcohol also reacts as a reducing reagent for the reductive homocoupling of aromatic halides. Elimination of the external reducing reagents will simplify the product separation and purification. Base is essential for the success of the Pd(dppf)Cl_2-catalyzed redox reaction as 2 molar equiv of base is needed to neutralize the acid byproduct formed. Biaryls are the predominant products for the Pd(dppf)Cl_2-catalyzed reductions of the unsubstituted aromatic halides in 3-pentanol solution, whereas the dehalogenation products are predominant for the Pd(dppf)Cl_2-catalyzed reductions of the substituted aromatic halides. The reaction mechanisms have been discussed for the palladium-mediated concomitant reduction of aromatic halides and oxidation of alcohols without any auxiliary reductants and oxidants.

Introduction

Synthesis of biaryls is an important transformation in synthetic organic chemistry because biaryls are key building blocks for a large number of natural products, biologically significant agrochemicals, and pharmaceuticals.[1] Moreover, biaryls can also be used as chiral ligands, monomers for conductive polymers, and precursors for rigid liquid crystals.[2,3] Traditionally, the symmetrical biaryls are synthesized by the copper-mediated Ullmann reductive homocoupling of aromatic halides.[4] However, the copper-mediated homocoupling Ullmann reaction not only consumes a stoichiometric amount of copper metal and generates a stoichiometric amount of copper halide waste but also has very limited applications for the synthesis of highly functionalized biaryls since the copper-mediated homocoupling reaction can occur only at high reaction temperatures (over 200 °C).[5]

The palladium-catalyzed reductive homocoupling of aromatic halides has been demonstrated as a useful alternative to the traditional copper-mediated Ullmann reaction, primarily

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DOI: 10.1021/jo100089d

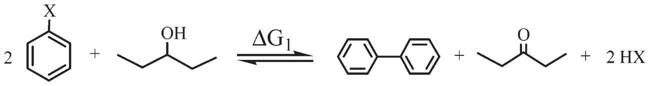
due to the mild reaction conditions and high functional group tolerance of the starting materials.[6−8] However, the palladium-catalyzed reductive homocoupling requires excess external reducing reagents as the hydrogen donor and/or electron source to regenerate the reductive Pd^0 active species from the oxidative Pd^{2+} species to complete the catalytic redox cycle.[9] The active Pd^0 species is usually needed to be *in situ* regenerated because it is prone to agglomerate to form black sediment and lose the catalytic activity. Various auxiliary reducing reagents including hydroquinone,[7a] formate salt,[10] amines,[11] zinc,[12] indium,[13] and triphenylarsine[14] have been used for the palladium-catalyzed reductive homocoupling reactions. The major drawback of these methods is the necessity for the subsequent separation of the excess reducing reagents as well as their oxidized products. Recently, we found that the palladium-catalyzed reductive homocoupling reactions of various aromatic halides could be carried out in dimethyl sulfoxide (DMSO) solution to form the corresponding biaryl products without the need for any external reductants.[15] Although the solvent DMSO molecules were shown to be involved in the *in situ* regeneration of the reductive Pd^0 species, we failed to characterize the oxidation product(s), primarily due to the complicated oxidation of DMSO molecules. This prompted us to search for other potential solvents for the palladium-catalyzed reductive homocoupling of aromatic halides, which could also be used as the reducing reagents.

On the other hand, the Pd^{2+}-mediated oxidation of alcohols has been well documented in the literature.[8,16] The key step for alcohol oxidation is the *in situ* regeneration of the oxidative Pd^{2+} species from the reductive Pd^0 species using various oxidants. Aromatic halides were reported as the oxidant for alcohol oxidation, but the reduction products were not characterized.[17] Thus, we hypothesized that the reductive Pd^0 species generated from the Pd^{2+}-mediated alcohol oxidation could be employed to catalyze the Ullmann-type reductive homocoupling of aromatic halides. In other words, the reductive Pd^0 species could be regenerated *in situ* from the alcohol oxidation by the oxidative Pd^{2+} species. As a result, the reductive homocoupling of aromatic halides and oxidation of alcohols could be concomitantly catalyzed by palladium catalyst without the need for any external reductants and oxidants. Herein, we would like to report our initial results of the $Pd(dppf)Cl_2$-catalyzed reductive homocoupling of aromatic halides in alcohol solutions.

Results and Discussion

Thermodynamic Feasibility for Redox Reactions of Aromatic Halides with Alcohols. A series of theoretical calculations have been performed to examine whether it is thermodynamically feasible for the redox reactions of aromatic halides with alcohols to form biaryls and ketones/aldehydes. The calculated Gibbs free energy differences (ΔG) for the redox reactions of aromatic halides with 3-pentanol are summarized in Scheme 1. The base effects have also been examined on these redox reactions, and the related results are summarized in Scheme 2.

SCHEME 1



X	ΔG_1(kJ/mol)
F	-188.6
Cl	-95.7
Br	-102.3
I	-98.9

Examination of Scheme 1 shows that the calculated Gibbs free energy differences (ΔG_1) are all largely negative, suggesting that the redox reactions of these aromatic halides with 3-pentanol are thermodynamically favorable. Similar conclusions are also reached for the redox reactions of these aromatic halides with other alcohols such as methanol, ethanol, and 2-propanol. Moreover, the calculation results indicate that the Gibbs free energy differences (ΔG_2) are significantly augmented in the presence of base such as cesium fluoride (CsF) and triethylamine (Et_3N). The base neutralization of the acidic byproduct(s) (HX, X = Cl, Br, or I) is expected to shift the redox equilibrium toward the right, i.e., completion. In summary, the redox reactions of aromatic halides with alcohols are thermodynamically allowed, especially in the presence of base.

$Pd(dppf)Cl_2$-Catalyzed Reductive Homocoupling of Iodobenzene in Various Alcoholic Solutions. Palladium catalyst is the catalyst of choice to examine the thermodynamically allowed redox reaction of aromatic halides with alcohols because of its remarkable ability to catalyze a wide variety of organic reactions.[8] In the previous studies, we have demonstrated that $Pd(dppf)Cl_2$ [dppf = 1,1′-bis(diphenylphosphino)ferrocene] is an effective homogeneous catalyst for the reductive homocoupling of aromatic halides in DMSO solution.[15] Thus, $Pd(dppf)Cl_2$ was the first choice to test the model reductive homocoupling of iodobenzene in different alcohol solutions. In addition, a similar protocol was adapted, i.e., 1.0 mmol of iodobenzene, 0.03 mmol of palladium catalyst, 7.5 mmol of cesium fluoride (CsF) in 5.0 mL of solvent alcohol under an atmosphere of argon. The homocoupling biphenyl (**1**) and dehalogenated benzene (**2**) are the only products observed for the palladium-catalyzed reduction of iodobenzene in alcohol solutions as shown

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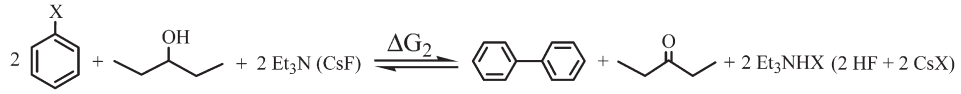
SCHEME 2



X	ΔG$_2$(kJ/mol)	
	Et$_3$N	CsF
F	-197.3	-188.6
Cl	-230.1	-419.1
Br	-253.1	-485.3
I	-240.4	-488.2

in Scheme 3 (X = I, R = H). The reaction progress was monitored by thin layer chromatography (TLC) and/or gas chromatography/mass spectroscopy (GC/MS). Table 1 lists the biphenyl and benzene yields for the model Pd(dppf)Cl$_2$-catalyzed reductive homocoupling of iodobenzene in various alcohol solutions.

SCHEME 3

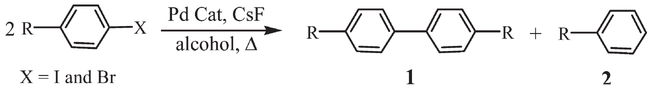
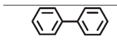
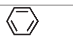


TABLE 1. **Pd(dppf)Cl$_2$-Catalyzed Reductive Homocoupling of Iodobenzene in Various Alcoholic Solutions**[a]

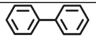
Entry	Solvent	Temperature (°C)	Time (hour)	Yield (%)[b]	
					
1	methanol	50	14	16.9	~0
2	ethanol	50	14	18.3	~0
3	1-butanol	100	5	26.6	52.1
4	1-pentanol	100	5	19.0	81.0
5	1-octanol	100	5	33.2	66.8
6	cyclopentanol	100	4	30.9	69.1
7	cyclohexanol	100	5	45.4	54.6
8	2-butanol	100	5	55.0	45.0
9	2-propanol	75	5	91.3	8.0
10	3-pentanol	100	5	89.3	10.7
11	*tert*-butanol	90	5	~0	~0

[a] Reaction conditions: 1.0 mmol of iodobenzene, 0.03 mmol of Pd(dppf)Cl$_2$ catalyst, and 7.5 mmol of cesium fluoride in 5.0 mL of alcohol solution. [b] Biphenyl and benzene yields, based on the amount of iodobenzene (1.0 mmol), were determined from the GC/MS measurements.

The biphenyl yields are relatively low (17−45%) for the reactions carried out in the primary (entries 1−5) and cyclic (entries 6 and 7) alcohols. In a contrast, the dehalogenation product (benzene) is predominant for most of these reactions (entries 3−7). Most interestingly, the homocoupling biphenyl products are predominant for the reactions carried out in the secondary alcoholic solvents (entries 8−10), especially for the reactions carried out in 2-propanol (entry 9) and 3-pentanol (entry 10) solutions. Nevertheless, the biphenyl product is negligible when carried out in *tert*-butanol solution (entry 11), suggesting that the α-C−H bond cleavage is involved for the palladium-catalyzed reductive homocoupling reaction since *tert*-butanol lacks the α-C−H bond. Although 2-propanol and 3-pentanol are both excellent solvents for the Pd(dppf)Cl$_2$-catalyzed reductive homocoupling of iodobenzene, 3-pentanol was found to be better for other aromatic halide substrates. In order for comparison, the present paper is mainly focused on the studies carried out in 3-pentanol solution.

Catalytic Activities of Different Palladium Compounds. Although catalyst cannot change the thermodynamic properties of a given chemical reaction, an effective catalyst will greatly accelerate the reaction rate by lowering the activation energy required for it to occur. It is well-known that the catalytic activities of the palladium compounds are largely dependent on the reaction conditions, as well as the chemical structure of the ligands.[8] A series of the frequently used palladium compounds have been screened to examine their catalytic activities on the model reductive homocoupling of iodobenzene in 3-pentanol solution. The results of this study are summarized in Table 2.

TABLE 2. **Effects of Palladium Catalysts on Reductive Homocoupling of Iodobenzene in 3-Pentanol Solution**[a]

Entry	Palladium Compound	Biphenyl Yield (%)[d]	
			
1	PdCl$_2$	~0	~0
2	Pd(PPh$_3$)$_4$	~0	97.0
3	Pd(OAc)$_2$	5.1	22.8
4	Pd(dba)$_2$[b]	6.1	17.0
5	Pd(dppf)Cl$_2$[c]	89.3	10.7

[a] Reaction conditions: 1.0 mmol of iodobenzene, 0.03 mmol of palladium catalyst, 7.5 mmol of cesium fluoride in 5.0 mL of 3-pentanol at 100 °C for 5 h. [b] dba: dibenzylideneacetone. [c] dppf: 1,1′-bis-(diphenylphosphino)-ferrocene. [d] Biphenyl and benzene yields, based on the amount of iodobenzene (1.0 mmol), were obtained from the GC/MS measurements.

Examination of Table 2 shows that PdCl$_2$ has no catalytic activity (entry 1) for the reduction of iodobenzene in 3-pentanol solution. Benzene was found to be the exclusive product for the Pd(PPh$_3$)$_4$-catalyzed reduction of iodobenzene (entry 2). A small amount of biphenyl products (5−8%) were obtained when Pd(OAc)$_2$ (entry 3) and Pd(dba)$_2$ (dba = dibenzylideneacetone) (entry 4) were used as the catalysts. These palladium compounds are in a sharp contrast to Pd(dppf)Cl$_2$ (entry 5), which has been shown as an effective catalyst for the reductive homocoupling of iodobenzene in 3-pentanol even without any external reductants. Thus Pd(dppf)Cl$_2$ was chosen as the palladium catalyst for the present studies.

Role of Base for Pd(dppf)Cl$_2$-Catalyzed Reduction of Aromatic Halides and Oxidation of Alcohols. It is well documented in the literature that acidic byproducts are formed from the palladium-catalyzed reduction of aromatic halides[6,8] as well as from the palladium-catalyzed oxidation of alcohols.[16] The catalytic activities of palladium catalysts can be significantly suppressed in a highly acidic medium.[18] The acidic byproduct formation is clearly demonstrated from the reaction medium acidity time course (Figure 1) for the Pd(dppf)-Cl_2-catalyzed homocoupling of iodobenzene in 3-pentanol solution. Examination of Figure 1 shows that the solution pH value gradually decreases with reaction time, indicating that the acidic byproduct is generated during the Pd(dppf)-Cl_2-catalyzed reaction. Much larger acidity increase (or decrease of the pH value) is expected if there is no external base added to the Pd(dppf)Cl_2-catalyzed reaction system since the base (CsF) has a buffer effect by neutralization of the generated acidic byproduct. These results are consistent with the theoretical calculations (Scheme 2).

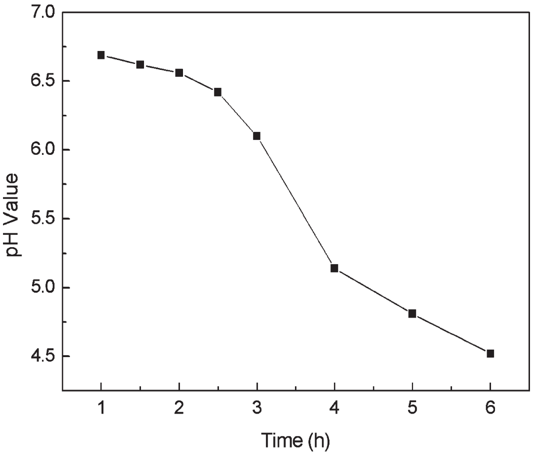
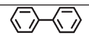


FIGURE 1. Reaction medium acidity time course for the Pd(dppf)-Cl_2-catalyzed reduction of iodobenzene in 3-pentanol solution. Reaction conditions: 10.0 mmol of iodobenzene, 0.3 mmol of Pd-(dppf)Cl_2, and 75.0 mmol of cesium fluoride in 50 mL of 3-pentanol solution at 100 °C.

A series of frequently used inorganic and organic bases have been tested for the model Pd(dppf)Cl_2-catalyzed reductive homocoupling of iodobenzene in 3-pentanol solution, and the results are summarized in Table 3. Examination of entry 1 of Table 3 shows that the biphenyl product is negligible in the absence of base, indicating that base is essential for the Pd(dppf)Cl_2-catalyzed reduction of iodobenzene. Interestingly, fluoride (entries 2 and 3), acetate (entries 4, 5, and 6), hydroxide (entry 7), carbonate (entry 8), ethoxide (entry 9), and triethylamine (entry 10) are all suitable bases for the Pd(dppf)Cl_2-catalyzed reduction of iodobenzene. Obviously, cesium fluoride (CsF) (entry 3) is the most effective base among those screened for the Pd-(dppf)Cl_2-catalyzed reductive homocoupling of iodobenzene in 3-pentanol. Additionally, the cesium salts are more effective than the corresponding sodium and/or potassium salts at promoting the palladium-catalyzed reactions. Similar results were also observed for the palladium-catalyzed reductions in other solvent systems.[15,19] The superior effects of the cesium salts can be attributed to the weaker ion-pairing interactions due to the larger size of the cesium cation (1.66 Å) compared with those of potassium cation (1.33 Å) and sodium cation (0.90 Å),[20] resulting in a relatively higher solubility and basicity.

TABLE 3. Base Effects on the Pd(dppf)Cl_2-Catalyzed Reductive Homocoupling of Iodobenzene in 3-Pentanol Solution[a]

Entry	Base	Yield (%)[b]	
			
1	No base	~0	~0
2	KF	13.3	0.3
3	CsF	89.3	10.7
4	NaOAc	25.1	5.6
5	KOAc	32.4	0.1
6	CsOAc	64.1	0.9
7	KOH	62.8	37.2
8	K_2CO_3	63.8	36.2
9	NaOEt	68.4	7.4
10	Et_3N	37.8	1.0

[a] Reaction conditions: 1.0 mmol of iodobenzene, 0.03 mmol of Pd-(dppf)Cl_2 catalyst, 7.5 mmol of cesium fluoride (CsF) in 5.0 mL of 3-pentanol at 100 °C for 5 h. [b] Biphenyl and benzene yields, based on the amount of iodobenzene (1.0 mmol), were obtained from the GC/MS measurements.

It is noteworthy that cesium fluoride (entry 3) has much better effects than the other bases such as cesium acetate (entry 6). Addition of halide anion has been reported to accelerate the palladium-catalyzed reactions because of coordination of the added halide anion with the palladium metal.[21] Similarly, cesium fluoride was found to have larger effects for the Pd(dppf)Cl_2-catalyzed reductive homocoupling of aromatic halides in DMSO solution.[15] Thus, the superior effects of cesium fluoride for the Pd(dppf)Cl_2-catalyzed reductive homocoupling can be attributed to a combination as a base to neutralize the acidic byproduct(s) and also as a possible ligand to coordinate with the palladium to facilitate the catalytic reactions.

Figure 2 presents the biphenyl yield as a function of molar ratio of the added base (CsF) relative to iodobenzene substrate ([base]/[ArI]) for the Pd(dppf)Cl_2-catalyzed reductive homocoupling of iodobenzene in 3-pentanol solution. Examination of Figure 2 shows that the biphenyl yield increases linearly with the base amount when the base is consumed in less than 2 molar equiv. However, the biphenyl yield levels off when the [base]/[ArI] ratios are over 2 molar equiv, indicating that about 2 molar equiv of base is required to neutralize the acidic byproduct generated from the Pd(dppf)Cl_2-catalyzed reductive homocoupling of iodobenzene in 3-pentanol.

***In Situ* Regeneration of Reductive Pd^0 Species from Oxidative Pd^{2+} Species.** The oxidative addition of the 14-electron Pd^0 active species into aryl halide is the initial step for the palladium-catalyzed reactions, which results in formation of the σ-arylpalladium complex (Pd^{2+}).[21a,22] As a result, the reductive Pd^0 species is oxidized into the oxidative Pd^{2+} species during the catalyzed reaction. The reductive Pd^0

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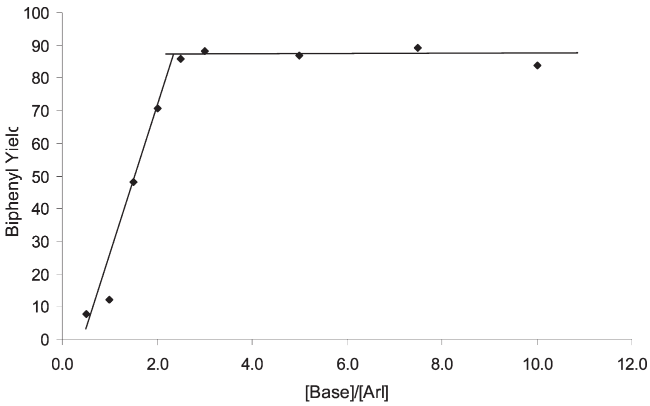


FIGURE 2. Dependence of biphenyl yield on the molar ratios of base (CsF) amount relative to the iodobenzene substrate for the Pd(dppf)Cl_2-catalyzed reductive homocoupling of iodobenzene in 3-pentanol at 100 °C.

species needs to be regenerated; otherwise a stoichiometric amount of Pd^0 is required for the catalyzed reaction. We postulated that the solvent alcohol molecules were involved in the regeneration of the reductive Pd^0 active species from the oxidative Pd^{2+} species since there are no external reducing reagents in the reaction system, and also no oxidation products were detected from the halide anions (X^-) as well as from the catalyst ligands. In order to prove this postulate, we have employed the X-ray photoelectron spectroscopic (XPS) technique to examine the palladium oxidation states through measurement of the electron binding energies because the electron binding energy shift could be correlated with the effective charge change on the atom from which the photoelectron originates.[23]

Figure 3A displays the XPS spectrum of the Pd(dppf)Cl_2 catalyst after being heated in 3-pentanol solution at 100 °C for 3 h. The electron binding energy peaks (338.0 and 343.2 eV) (Figure 3A) can be assigned to the palladium 3d electron of the divalent Pd^{2+} species.[24] Furthermore, the electron binding energies of the heated Pd(dppf)Cl_2 catalyst were found to be exactly identical to those of the fresh Pd(dppf)Cl_2 catalyst. Interestingly, addition of iodobenzene and cesium fluoride base into the 3-pentanol solution of Pd(dppf)Cl_2 at 100 °C resulted in formation of a black precipitate. The XPS spectrum of the resulting precipitate is shown in Figure 3C, which shows that the palladium 3d electron binding energies (334.8 and 340.2 eV) are 3.2 eV lower than those for the divalent Pd^{2+} 3d electron binding energies (Figure 3A). Nonetheless, the electron binding energies of Figure 3C are consistent with the typical metallic palladium (Pd^0) 3d electron binding energies, indicating that the palladium of the resulting black precipitate is primarily in the reductive Pd^0 state.[24,25] In other words, the reductive Pd^0 species has been *in situ* regenerated during the Pd(dppf)Cl_2-catalyzed reductive homocoupling of iodobenzene in 3-pentanol solution.

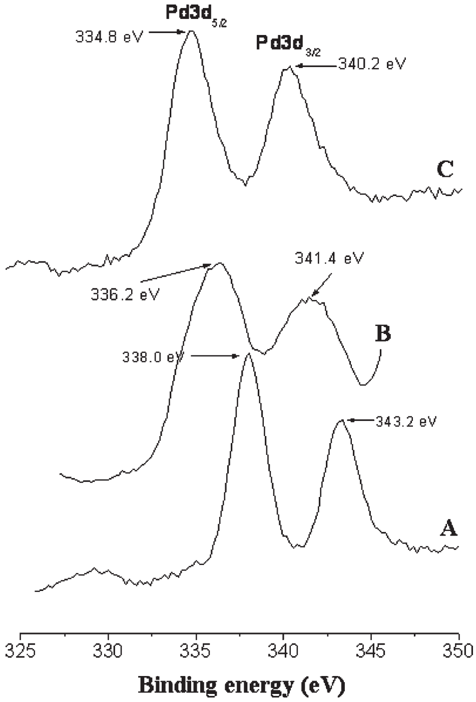
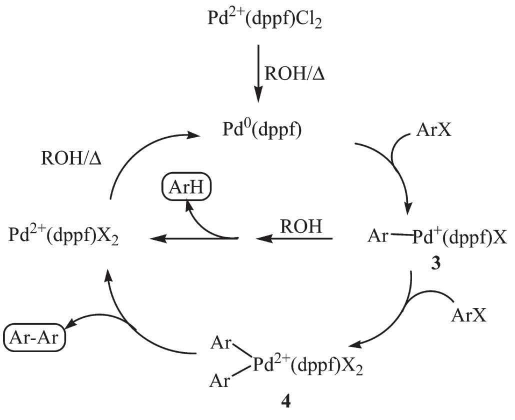


FIGURE 3. X-ray photoelectron spectra of the palladium catalyst samples prepared under different reaction conditions. (A) Pd(dppf)Cl_2 in 3-pentanol at 100 °C for 3 h. (B) Pd(dppf)Cl_2 + CsF in 3-pentanol at 100 °C for 3 h. (C) Pd(dppf)Cl_2 + CsF + iodobenzene in 3-pentanol at 100 °C for 3 h.

Catalytic Mechanism for Reductive Homocoupling of Aromatic Halides. The *in situ* regeneration of the reductive Pd^0 active species from the oxidative Pd^{2+} species in 3-pentanol is similar to that in DMSO solution,[15] suggesting that the Pd(dppf)Cl_2-catalyzed reductive homocoupling of iodobenzene should proceed via the same reaction mechanism in both alcohol and DMSO solutions. The resulting Pd^0 active species undergoes the oxidative insertion to the aromatic halides to form monoarylpalladium intermediate (**3**), which can either react with another aromatic halide to form diarylpalladium intermediate (**4**), followed by elimination of the biaryl product, or react with solvent alcohol molecule to form the dehalogenation product as shown in Scheme 4.

SCHEME 4



The monoarylpalladium (**3**) and diarylpalladium (**4**) intermediates are similar to those proposed by Jutand[9] and Rawal.[7a] The hydrogen atom abstraction of aryl radicals is known to be diffusion-controlled (1 × 10^8 M^{-1} s^{-1}) from the

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solvent DMSO molecules.[26] The hydrogen atom abstraction is expected to be even faster for aryl radicals from alcohol solutions because the α-C−H bond strengths of 2-propanol and 3-pentanol are slightly weaker than the C−H bond strength of DMSO.[27,28] The easier and faster hydrogen atom abstraction from the alcoholic solvents may be responsible for the much higher dehalogenation products for the Pd(dppf)Cl_2-catalyzed reduction of aromatic halides in the alcoholic than DMSO solution.

Alcohol Oxidation by Pd(dppf)Cl_2 in the Presence of Base. Most intriguingly, sole addition of cesium fluoride (base) into the 3-pentanol solution of Pd(dppf)Cl_2 at 100 °C also resulted in the formation of black precipitate. The XPS spectrum of the resulting black precipitate is shown in Figure 3B. The palladium 3d electron binding energies of the black precipitate are 336.2 and 341.4 eV, which are higher than those of the metallic palladium (Pd^0) species (Figure 3C) but lower than those of divalent palladium (Pd^{2+}) species (Figure 3A), suggesting that the resulting black precipitate is a mixture of palladium metal (Pd^0 species) and Pd(dppf)Cl_2 (Pd^{2+} species). These XPS results provide additional evidence to support the conclusion that base is essential for regeneration of the reductive Pd^0 species from the oxidation of 3-pentanol by the divalent Pd^{2+} species. Furthermore, the *in situ* regeneration of the reductive Pd^0 species was found to be accompanied by formation of 3-pentanone from the oxidation of 3-pentanol as shown in Scheme 5.

SCHEME 5

Similarly, 3-pentanone was also obtained and characterized from the Pd(dppf)Cl_2-catalyzed reduction of iodobenzene in 3-pentanol solution, indicating that 3-pentanol plays a dual role, i.e., as the reaction medium (solvent) and also as a reagent to reduce the divalent Pd^{2+} species into the reductive Pd^0 species. Consequently, Pd(dppf)Cl_2 catalyzes the redox reaction of iodobenzene with the solvent 3-pentanol. The cleavage of the α-C−H bond has been suggested as the rate-determining step for the Pd^{2+}-mediated oxidation of alcohols.[29] This may explain why the biphenyl and benzene yields of the Pd(dppf)Cl_2-catalyzed reduction of iodobenzene are greatly dependent upon the chemical structure of alcohol solvents (Table 1) since the α-C−H bond strengths of methanol, primary and secondary alcohols are quite different.[30] Therefore, the higher reactivities of the secondary alcohols for the palladium-catalyzed reductive homocoupling of iodobenzene are associated primarily with the ease of oxidation of the secondary alcohols rather than their solvation effects.

Stoichiometrically Coupling for Reduction of Iodobenzene and Oxidation of 3-Pentanol. Many reagents have been developed to oxidize alcohols, including oxygen gas, stoichiometric Cr(VI) salt, DMSO-coupled reagents, hypervalent iodine, etc.[16] As discussed in the previous sections, iodobenzene can also oxidize 3-pentanol. Figure 4 displays the time courses of the reaction products (3-pentanone, biphenyl, and benzene) for the Pd^0/Pd^{2+}-mediated redox reaction of iodobenzene with 3-pentanol. Examination of Figure 4 clearly shows that formation of the oxidation product (3-pentanone) is stoichiometrically coupled with that of the homocoupling product (biphenyl). Thus, the Pd(dppf)Cl_2-catalyzed redox reaction of iodobenzene with 3-pentanol can be simply described by two concomitant palladium-mediated redox reactions as shown in Scheme 6, i.e., the Pd^0-mediated reduction of iodobenzene and the Pd^{2+}-mediated oxidation of 3-pentanol. Note that no external reductants or oxidants are needed for the palladium-catalyzed redox reaction.

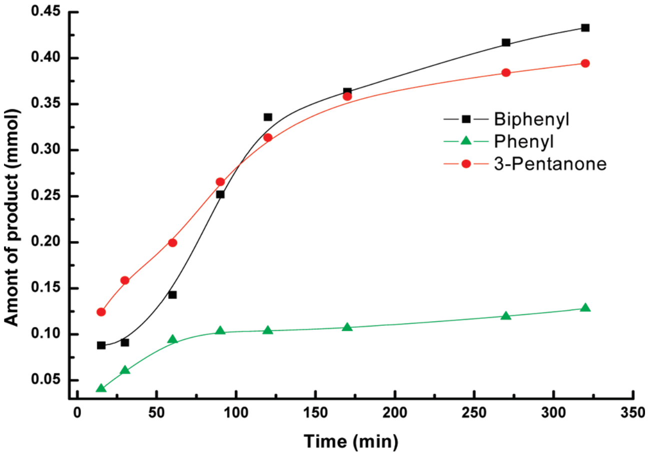
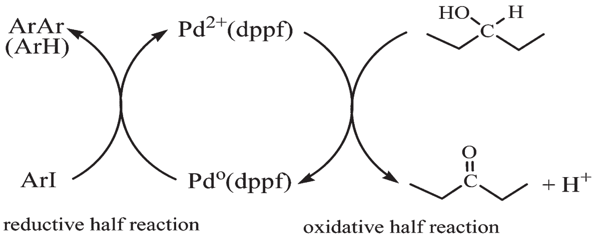


FIGURE 4. Time courses of the reaction products (biphenyl, benzene, and 3-pentanone) for the Pd(dppf)Cl_2-catalyzed reduction of iodobenzene in 3-pentanol solution at 100 °C.

SCHEME 6



Pd(dppf)Cl_2-Catalyzed Reduction of Additional Aromatic Halides in 3-Pentanol Solution. The optimized protocol for the Pd(dppf)Cl_2-catalyzed reduction of iodobenzene in 3-pentanol solution has been extended to a variety of aromatic halides to examine the scope and limitation of this catalytic system as well as the substituent effects. The results of this study are summarized in Table 4.

The palladium-catalyzed reduction is negligible for fluorobenzene (entry 1) and chlorobenzene (entry 2) even though the theoretical calculations show that the reductions of fluorobenzene and chlorobenzene are thermodynamically favorable in 3-pentanol solution (Schemes 1 and 2). The low reactivities of fluorobenzene and chlorobenzene can be attributed to the stronger carbon−fluorine and

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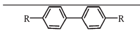
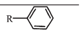
TABLE 4. Pd(dppf)Cl$_2$-Catalyzed Reductive Homocoupling of Various Aromatic Halides in 3-Pentanol Solution[a]

Entry	Substrate	Conversion (%)	Time (h)	Yield (%)[f]	
					
1	C_6H_5F	0	18	0	0
2	C_6H_5Cl	5.65	18	2.5	3.2
3	C_6H_5Br[b]	100	8	88.0±2	11.5±2
4	C_6H_5I[b]	100	5	89.5±2	10.0±2
5	4-FC_6H_4I	100	29	60.3	39.7
6	3-FC_6H_4I	100	29	31.4	68.6
7	4-$CF_3C_6H_4I$	100	30	75.2	24.8
8	2-ClC_6H_4I	100	36	1.6	98.4
9	3-ClC_6H_4I	100	29	7.2	92.8
10	4-ClC_6H_4I	100	20	0.2	99.8
11	4-$NO_2C_6H_4I$	100	6	0	100
12	3-$CH_3OC_6H_4I$	100	36	1.0	98.0
13	4-$CH_3COC_6H_4I$	100	36	0	100
14	2-$CH_3C_6H_4I$	100	12	0	100
15	4-$CH_3C_6H_4I$	100	12	2.9	97.1
16	2-FC_6H_4Br	100	18	4.5	95.5
17	4-FC_6H_4Br	100	47	32.6	57.4
18	4-ClC_6H_4Br	100	57	0.8	99.2
19	2-IC_5H_4N[c]	100	12	83.5	16.5
20	2-BrC_5H_4N[d]	100	18	80.2	19.8
21	2-CH_3-6-BrC_5H_3N[e]	100	18	6.9	93.1

[a] Reaction conditions: 1.0 mmol of aromatic halide, 0.03 mmol of Pd(dppf)Cl$_2$ catalyst, 7.5 mmol of cesium fluoride in 5.0 mL of 3-pentanol solution at 100 °C. [b] Average yields of five separate experiments. [c] 2-Iodopyridine. [d] 2-Bromopyridine. [e] 2-Methyl-6-bromopyridine. [f] Biaryl and arene yields, based on the amount of aromatic halide (1.0 mmol), were determined from the GC/MS measurements.

carbon−chlorine bond strengths. For example, the bond dissociation enthalpies of the C−Cl bond (96 kcal/mol) in chlorobenzene and the C−F (126 kcal/mol) in fluorobenzene are much higher than those of the C−I bond (65 kcal/mol) in iodobenzene and the C−Br bond (81 kcal/mol) in bromobenzene.[31] Consequently, the oxidative addition of the Pd^0 active species into the corresponding carbon−halogen bond, a critical initial step for the palladium-catalyzed reductions, will be extremely slow for fluorobenzene and chlorobenzene.[32]

Examination of entries 3 and 4 of Table 4 shows that the homocoupling yield for bromobenzene is comparable to that for iodobenzene. The reported yields for both bromobenzene and iodobenzene are the average of five separate experiments, indicating that the reactions are highly reproducible. Interestingly, the homocoupling biaryls are also predominant for 2-iodopyridine (entry 19) and 2-bromopyridine (entry 20). However, introduction of either an electron acceptor (entries 11 and 13) or an electron donor (entries 12, 14, 15, and 21) significantly suppressed the homocoupling pathway. As a result, the dehalogenation products are predominant for these substituted aromatic halides, suggesting that the substituents may have the steric and/or electronic effects to prevent formation of the diarylpalladium intermediate (**4**) (Scheme 4) in the alcohol solution. Similarly, the predominant dehalogenation products were obtained for introduction of 2-, 3-, and 4-chlorine groups (entries 8, 9, 10, and 18). On the other hand, introduction of 2-, 3-, and 4-fluorine groups (entries 5, 6, 16, and 17) as well as a 4-trifluoromethyl (entry 7) group seems to have much less suppression effect on the reductive homocoupling pathway. For example, the biaryl yields were found to be 60.3 and 75.2 for 4-fluoroiodobenzene (entry 5) and 4-trifluoromethyliodobenzene (entry 7), respectively. These results may be associated with some interaction of the fluorine substituents with the palladium catalyst, which may facilitate the oxidative addition of the reductive Pd^0 into the carbon−halogen bond.

Experimental Section

Chemicals. Solvents and chemicals were analytical grade or the highest grade commercially available and were used without additional purification. Palladium compounds [PdCl$_2$, Pd(dppf)Cl$_2$, Pd(OAc)$_2$, Pd(PPh$_3$)$_4$, and Pd(dba)$_2$] were purchased from Zhejiang Metallurgical Research Institute.

General Procedures. The quantitative analysis of the reaction products was performed on an GC/MS instrument with a programmable split/splitless injector. The injector-port temperature was set at 270 °C. The oven-temperature program was initially set at 140 °C, then ramped to 270 at 10 °C/min, and maintained for 2 min in each step. Proton NMR spectra were recorded in CDCl$_3$ on an 400 M Hz spectrometer. Proton chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) with the residual solvent peak as the internal reference. Multiplicities are reported as singlet (s), doublet (d), and multiplet (m). Melting points were measured on a Buchi 510 in an open capillary tube and were not calibrated. X-ray photoelectron spectra (XPS) were recorded using a PHI 5000C ESCA spectrometer (PHI Company, USA).

General Procedure for Palladium-Catalyzed Reductive Homocoupling Reactions. In a 20 mL tabular reactor, aromatic halide (1.0 mmol), and palladium catalyst (0.03−0.10 mmol) together with a proper amount of base were dissolved in 5.0 mL of desired alcohol solution under an argon atmosphere. The reaction mixture was allowed to react at the desired reaction temperatures, and the reaction progress was monitored by TLC and/or GC/MS analysis. The reaction mixture was quenched with 10 mL of water when the reaction was complete and then extracted three times with ethyl acetate (3 × 20 mL). The combined organic extract was washed with water and saturated brine and then dried with anhydrous Na$_2$SO$_4$. Solvent was removed under a reduced pressure, and the reaction product was purified by silica gel chromatography with a mixture of petroleum ether and ethyl acetate as eluent.

Biphenyl:[33] mp 70−71.5 °C; ^{1}H NMR δ 7.60 (d, 4 H, J = 7.4 Hz), 7.44 (d, 4 H, J = 7.8 Hz), 7.35 (d, 2 H, J = 7.3); MS (EI) m/z (%) 154 (100) [M$^+$], 76 (7).

4,4′-Dimethylbiphenyl:[34] mp 122−123 °C; ^{1}H NMR δ 7.66 (d, 4 H, J = 8.0 Hz), 7.41 (d, 4 H, J = 8.0 Hz), 2.56 (s, 6 H); MS (EI) m/z (%) 182 (100) [M$^+$], 167 (55), 152 (12), 89 (11), 76 (3).

4,4′-Difluorobiphenyl:[35] mp 87−88 °C; ^{1}H NMR δ 7.48 (m, 4 H), 7.09 (t, 4 H, J = 8.6); MS (EI) m/z (%) 190 (100) [M$^+$], 170 (20).

2,2′-Dichlorobiphenyl:[36] mp 58−59 °C; ^{1}H NMR δ 7.01−7.03(m, 1 H), 7.15−7.22 (m, 1 H), 7.27−7.29 (m, 1 H), 7.30−7.37 (m, 3 H), 7.39−7.42 (m, 1 H), 7.47−7.51 (m, 1 H); MS (EI) m/z (%) 222 (59) [M$^+$], 152 (100), 187 (43), 75 (18).

3,3′-Dichlorobiphenyl:[35] mp 28−29 °C; ^{1}H NMR δ 7.31−7.37 (m, 4 H), 7.40 (t, 1 H, J = 1.8 Hz), 7.42 (t, 1 H, J = 1.6 Hz), 7.52 (s, 2 H); MS (EI) m/z (%) 222 (100) [M$^+$], 152 (57), 93 (9),75 (14).

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3,3′-Difluorobiphenyl:[37] mp 7−8 °C; ^{1}H NMR δ 7.05 (tdd, 2 H, J = 8.0, 2.4, and 0.4 Hz), 7.24 (t, 1 H, J = 2.0 Hz), 7.27 (t, 1 H, J = 2.0 Hz), 7.32 (t, 1 H, J = 1.2 Hz), 7.34 (t, 1 H, J = 1.6 Hz), 7.36−7.42 (m, 2 H); MS (EI) *m*/*z* (%) 190 (100) [M$^+$], 189 (24), 170 (6), 94 (5).

3,3′-Dimethoxybiphenyl:[38] mp 41−42 °C; ^{1}H NMR δ 3.86 (s, 6 H), 6.90 (dd, 2 H, J = 8.2, 2.6 Hz), 7.12 (d, 2 H, J = 1.6 Hz), 7.17 (d, 2 H, J = 7.6 Hz), 7.34 (d, 2 H, J = 8.0 Hz); MS (EI) *m*/*z* (%) 214 (100) [M$^+$], 171 (16), 128 (10).

2,2′-Bipyridinyl:[39] mp 71−72 °C; ^{1}H NMR δ 7.34 (dd, 2 H, J = 7.2, 5.2 Hz), 7.85 (td, 2 H, J = 8.0 and 1.6 Hz), 8.73 (d, 2 H, J = 8.0 Hz), 7.34 (d, 2 H, J = 4.4 Hz); MS (EI) *m*/*z* (%) 156 (100) [M$^+$], 128 (26), 78 (17), 51 (18).

4,4′-Trifluoromethylbiphenyl:[40] mp 82−83 °C; ^{1}H NMR δ 7.72 (q, 8 H, J = 16.0 Hz); MS (EI) *m*/*z* (%) 190 (100) [M$^+$], 172 (50), 85 (10).

Acidity Time Course for Pd(dppf)Cl$_2$-Catalyzed Reductive Homocoupling of Iodobenzene in 3-Pentanol. Iodobenzene (10.0 mmol), palladium catalyst [Pd(dppf)Cl$_2$] (0.30 mmol), and cesium fluoride (75.0 mmol) were charged into a 100 mL three-neck flask containing 50 mL of 3-pentanol under an argon atmosphere at 100 °C. Aliquots (1.0 mL) of the reaction mixture were collected at different time intervals and then diluted with 5 mL of water for pH measurements using a pH Meter (Leizi PHS-3C, electrode E-201-C PH).

Sample Preparation for X-ray Photoelectron Spectroscopic (XPS) Measurements. A 1.5 in. silicon (100) slice with single polishing face was boiled in a solution of sulfuric acid/hydrogen peroxide (v/v, 2/1) for 5 min and rinsed before and after with deionic water. The silicon slice was then dipped in 10% hydrofluoric acid for 30 s with soaking before and after in water for 3 min, and the procedure was repeated twice. The silicon slice was further cleaned by sonication in absolute ethanol and water, respectively, for 5 min. The palladium catalyst samples were applied on the polished surface of the cleaned silicon slice, then dried, and stored for the XPS measurement.

XPS measurements were carried out at room temperature. Relative elemental ratios on the sample surface were determined on an Al/Mg anode with a power of 250 W (14.0 kV). The pressure of the analysis chamber was maintained at $<1 \times 10^{-8}$ Torr. The complete scan diagram of 0−12,000 eV (currency energy 93.9 eV) was obtained by RBD147 data collecting fiche using Auger Scan 3.21 software. The final binding energies were calibrated with C1s of 284.6 eV as the internal reference and the binding energy peaks were secluded using the XPS Peak 4.1 software.

Theoretical Calculations. All of the theoretical calculations were carried out using the Gaussian 03 program.[41] Geometries were optimized at the (U)B3LYP/6-31G(d) level.[42] The B3LYP/SDD method has been used for structure optimizations with high accuracy and moderate computational cost for the Gibbs free energy calculation.[43]

Acknowledgment. This work was generously supported by the Natural Science Foundation of Zhejiang Province (no. Y4080450), People's Republic of China and Shaoxing University. We would like to thank Dr. Z. Fang for his kind help for the XPS measurements and helpful discussions.

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