Highly Selective Pd-Catalyzed Reductive Coupling of Substituted Haloarenes with Supported Phase-Transfer Catalyst using Zn as the Reducing Agent

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Abstract: Highly selective reductive coupling of substituted haloarenes to biaryls is accomplished by Zn in *N,N*-dimethylformamide (DMF) and in the presence of a catalytic amount of $PdCl_2$, PPh_3, and a carbon-supported phase-transfer catalyst (PTC). Selectivity as high as 100% is achieved with chlorotoluenes. It is realized that the supported PTC has a predominant role in minimizing the rate of the hydrodehalogenation reaction. The reaction is found to be selective only when homogeneous $PdCl_2$ is applied as the catalyst, whereas heterogeneous Pd/C-catalyst selectively reduces chloroarenes to arenes under similar conditions. The role of PPh_3 is discussed and the effects of different process parameters such as temperature, $PdCl_2$ loading, PPh_3 to $PdCl_2$ ratio, amount of supported PTC, and solvents have been examined. A mechanism is proposed which is in good agreement with the experimental results obtained.

Keywords: biaryls; C–C coupling; haloarenes; Pd; reduction; Zn

Introduction

The syntheses and utilization of biaryl compounds is a subject of considerable contemporary interest as they represent important building blocks[1] for numerous agrochemicals, pharmaceuticals, and for a large number of natural products of varied structure, biological activity, and biosynthetic origins.[2] Also, biaryls are the structural units of the chiral skeleton of many of the asymmetric catalysts.[3] Besides stoichiometric classic general Ullmann,[4a, b] Suzuki,[4c–f] and Stille[4g] coupling reactions, Pd-catalyzed reductive coupling of haloarenes[5] has attracted the attention of many researchers. The reductive coupling of haloarenes benefits from simple reactor design, easy catalyst separation, and recycling. Unfortunately, the product selectivity is often low due to the competing reduction reaction.[6] We successfully explored[7a–c] the reductive coupling of haloarenes; however, the goal to diminish side reactions, namely, reduction of haloarenes to arenes, and to utilize substrates of industrial importance *viz.*, 4-chlorotoluene and 4-chlorobenzaldehyde was still unattained. Moreover, the role of a phase-transfer catalyst (PTC) in these reactions is not understood. However, the strong impact of a PTC on the coupling product selectivity was realized. Recently, we reported[8] the effectiveness of carbon-supported PTC on the coupling selectivity in heterogeneous Pd-catalyzed reductive couplings of haloarenes using formate salts as the reducing agents. High selectivity to the respective biphenyls was achieved with unsubstituted halobenzenes; however, the same process scheme failed to achieve the desired selectivity with 4-chlorotoluene and 4-chlorobenzaldehyde as the substrate.

In this communication, we show that the $PdCl_2$-catalyzed reductive coupling method can be employed to selectively synthesize biphenyls from haloarenes, namely, 4-chlorotoluene in the presence of an activated carbon-supported phase-transfer catalyst, a ligand (PPh_3), and a reducing agent such as zinc in anhydrous *N,N*-dimethylformamide (DMF). Similar attempts have been made before to utilize $PdCl_2$ as the catalyst. However, only low reactivity was observed with chloroarenes, whereas bromo- and iodoarenes have reacted to give coupling products.[9] In fact, $NiCl_2$ has been employed[10] successfully as a catalyst in similar coupling reactions; however, the need for extremely toxic solvents[10] such as pyridine or quinoline invalidates the utility of such processes. Also, Jutand and Mosleh[11] have been reported Pd- and Ni-catalyzed synthesis of biaryls from aryl triflates in the presence of Zn powder. Thus, in this work, for the first time, we will show that 4-chlorotoluene is coupled with almost 100% selectivity by $PdCl_2$ catalyst under mild conditions using carbon-supported PTC in DMF.
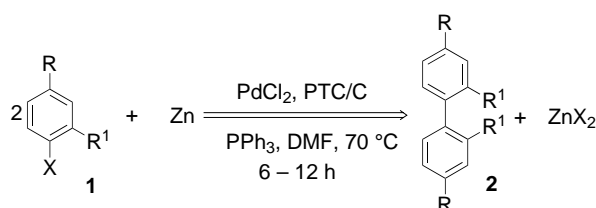
1a, 2a: R = CH₃, R¹ = H, where X= Cl
1b, 2b: R = H, R¹ = CH₃, where X= Cl
1c, 2c: R = CF₃, R¹ = H, where X= Cl
1d, 2d: R = CHO, R¹ = H, where X= Cl
1e, 2e: R = H, R¹ = H, where X= Cl
1f, 2f: R = H, R¹ = H, where X= Br

Scheme 1. Pd-catalyzed reductive coupling.

Carbon was selected as the support for PTC over other common supporting materials[12a–c] such as polymers[12a, b], alumina, or silica gel[12c], because of its high surface area, insolubility in acidic or basic solution, high porosity, as well as its high selectivity as a support towards our previously studied heterogeneous Pd-catalyzed reductive coupling reactions.[7]

Results and Discussion

In a typical reaction (see Experimental Section), **1** was coupled to form **2** with Zn as the reducing agent in the presence of a catalytic amount of PdCl₂, PPh₃, and the carbon-supported PTC in anhydrous DMF at 70 °C (Scheme 1). Excellent selectivity (> 91%) was achieved with each one of the substrates, **1a – f** as shown in Table 1. With 4-chlorotoluene (**1a**), 96% selectivity was achieved to the corresponding biaryl. Bromobenzene (**1f**) appeared to be the most reactive among the substrates under these conditions, whereas 2-chlorotoluene had reacted minimally. Also, with 4-chlorobenzaldehyde (**1d**), 97% selectivity to the coupling product was achieved.

Table 1. Reductive coupling of different substrates.[a]

Entry	Halo-arene	t [h]	% Conversion	% Selectivity, Ar-Ar
1	**1a**	10	73	96
2	**1b**	6	33	100
3	**1c**	10	65	98
4	**1d**	6	36	97
5	**1e**	12	81	91
6	**1f**	12	84	98

[a] Reaction conditions: substrate, 7.9 mmol; PdCl₂, 1.4 mmol; Zn, 19 mmol; PPh₃, 1.9 mmol; carbon-supported TBAB, 0.5 g; solvent, 20 mL of anhydrous DMF, temperature 70 °C.

Nevertheless, a 100% selectivity to the coupling product was obtained with 2-chlorotoluene as the starting material. 4-Chlorotoluene was used as a model compound for process parameters and kinetic studies. With each one of the substrates in Table 1, the reactions were found to be 100% selective within the reaction time period of 4 – 5 h. Unfortunately, the rate of reaction was very low. Thus, the reaction time was optimized at 10 h with 4-chlorotoluene as the substrate. It was observed that the reaction followed first-order kinetics.

The reaction temperature proved to be one of the key process parameters to control selective homocoupling.[7b] Initially, with an increase in temperature from 60 to 70 °C, the reaction rate and selectivity were increased, however, a further increase in temperature above 70 °C was deleterious to the product selectivity (Table 2, entries 1 – 6).

A set of experiments was performed with various amounts of PdCl₂. The conversion and selectivity both increased marginally when the amount of PdCl₂ was raised to 2.0 mmol (Table 2, entries 7 – 10). However, the coupling of 4-chlorotoluene was optimized at a 1.4 mmol PdCl₂ catalyst loading.

Table 2. Effect of different process parameters on the coupling reaction.[a]

Entry	Parameters	% Conversion	% Coupling, Ar-Ar	% Reduction, ArH
1	temp, 60 °C	42	92	8
2	70 °C	26[b]	100	0
3	70 °C	73	96	4
4	70 °C	92[c]	82	18
5	80 °C	79	92	8
6	90 °C	93	83	17
7	PdCl₂, 0 mmol	0	0	0
8	0.7 mmol	41	83	17
9	1.4 mmol	73	96	4
10	2.0 mmol	78	98	2
11	Zn, 0 mmol	0	0	0
12	15 mmol	43	99	1
13	19 mmol	56[d]	98	2
14	19 mmol	73	96	4
15	23 mmol	79	84	10
16	PTC[e], 0 g	43	58	42
17	0.5 g	73	96	4
18	0.8 g	78	76	24
19	1.0 g	83	65	35
20	PPh₃/PdCl₂ = 1.35	73	96	4
21	PPh₃/PdCl₂ = 1.8	84	96	4
22	PPh₃/PdCl₂ = 2.1	96	97	3

[a] Reaction conditions: 4-chlorotoluene, 7.9 mmol; PPh₃, 1.9 mmol; solvent, anhydrous DMF (total volume 20 mL); reaction time, 10 h.
[b] Reaction time: 5 h.
[c] Reaction time: 20 h.
[d] Reaction time: 8 h.
[e] The amount of carbon-supported PTC used.

Primarily, Zn was used as the reducing agent.[13] The rate of reaction was found to be a function of Zn loading (Table 2, entries 11 – 15). When the Zn loading was increased up to 19 mmol, the conversion of halobenzene increased up to 73% and selectivity increased up to 96%. However, when Zn loading was increased above 19 mmol, the coupling selectivity decreased.

Also, a different set of reactions was performed to study the effect of the amount of carbon-supported PTC on the rate and selectivity. The reaction rate and selectivity were found to be functions of the amount of carbon-supported PTC (see Experimental Section) used in these reactions (Table 2, entries 16 – 19). It was observed that the reaction rate varied in direct proportion to the amount of supported PTC above a 0.5 g loading, whereas, the selectivity to 4,4′-dimethylbiphenyl varied in inverse proportion to the amount of carbon-supported PTC. Attempts to replace carbon by Al_2O_3, $BaSO_4$, or fused silica did not pay off. The ratio of $PdCl_2$ to PPh_3 was also studied and the reaction was optimized at a ratio of 1:2.1 (Table 2, entries 20 – 22).

To examine the effect of different types of PTC such as tetrabutylammonium bromide (TBAB), cetyltrimethylammonium bromide, and PEG-400, a set of reactions was performed. TBAB was found to be the best PTC under these reaction conditions. With cetyltrimethylammonium bromide, the rate obtained was similar to that of TBAB, but the coupling selectivity was 78% and with PEG-400, the selectivity obtained was only 69%. Thus, in subsequent reactions carbon-supported TBAB was used as the PTC. While preparing the supported PTC, the weight ratio of TBAB to the activated carbon was kept at 1:5. In fact, upon increasing this ratio to 2:5, a decrease in selectivity to the coupling product was observed. Needless to say that the conversion increased minimally.

Table 3 shows the effect of different solvents such as DMSO, dioxane, toluene, DMF, and water on the rate and product selectivity. Toluene was found to be completely inactive and dioxane and water were found to be significantly less effective. DMSO was moderately effective, and DMF was found to be the most effective solvent medium with respect to the conversion and selectivity to the coupling products.

The experimental results can be interpreted in terms of the mechanism previously proposed by Amatore and Jutand.[14] Thus, the reaction proceeds *via* (1) formation of the $PdCl_2(PPh_3)_2$ complex by the reaction of $PdCl_2$ and PPh_3, (2) reduction of $PdCl_2(PPh_3)_2$ to the $Pd^0(PPh_3)_2Cl^-$ species, (3) oxidative addition of ArCl to an anionic $Pd^0(PPh_3)_2Cl^-$ species to form an Ar-$Pd^{II}Cl$-$(PPh_3)_2Cl^-$ species, (4) reduction of the later complex by Zn to form an anionic Ar-$Pd^0(PPh_3)_2Cl^-$ species, (5) a second oxidative addition of ArCl to the resulting species followed by reductive elimination of the biaryl.

However, the Ar-$Pd^0(PPh_3)_2Cl^-$ species can react with an electrophile such as water to form ArH as reported by

Table 3. Effect of solvent on the homocoupling of 4-chlorotoluene.[a]

Entry	Solvent	t [h]	% Conversion	% Selectivity, coupling
1	DMF	10	73	96
2	Dioxane	48	80	10
3	DMSO	8	23	100
4	Toluene	8	0	0
5	Water	2	100	10

[a] Reaction conditions: 4-chlorotoluene, 7.9 mmol; $PdCl_2$, 1.4 mmol; Zn, 19 mmol; PPh_3, 1.9 mmol; carbon-supported TBAB, 0.5 g, temperature, 70 °C.

Amatore and coworkers.[15] Also, it has been shown elsewhere[16] that Zn can reduce water to H_2 in the presence of a catalytic amount of Pd^0 or Pd^{2+}. Thus, reactions were executed in anhydrous DMF (0.02 wt. % water) to achieve higher coupling selectivity. Interestingly, the product selectivity gradually decreased with time of reaction progress, while performing the reaction in an open glass reactor. This problem was solved when the reaction was performed in a closed vessel. In fact, when the reaction was performed in a 300-mL Parr autoclave[17], 100% conversion and 97% selectivity to 4,4′-dimethylbipenyl were achieved in 48 h. Even after standard drying of DMF (see Experimental Section), 0.02% water (analyzed by Karl–Fischer titration) still remained in the solvent. This may be the reason (steps 3 – 5) for getting 3 – 4% dehydrohalogenation products even under the best reaction conditions in a closed vessel with 4-chlorotoluene as the substrate.

With an increase in $PdCl_2$ loading, the active concentration of anionic Pd^0 species is increasing; thus, we observe an increase in the rate of coupling reaction.

The role of the PTC could be explained if we consider the solution stability of the anionic species,[14] $Pd^0Cl(PPh_3)_2Cl^-$, in the presence of a PTC. Here, the PTC (except PEG-400) is nothing but Q^+X^-. Thus, the stability of the anionic Pd(0) species should be increased due to the counter ion stabilization by Q^+. In the case of PEG-400, the lone pair of oxygen might be providing the same stabilization. However, the role of the carbon support is not understood. While performing a reaction without the carbon support, only 69% selectivity to biphenyl was obtained.

On the other hand, it is understood that the presence of PPh_3[18,19] is very essential to form the $Pd^0Cl(PPh_3)_2Cl^-$. Certainly, the active species might not be stabilized in a ligand-free atmosphere. In fact, in the absence of PPh_3, a very slow rate and low coupling selectivity were achieved.[20] Clearly, this reaction is built upon homogeneous liquid phase chemistry, thus when homogeneous $PdCl_2$ was replaced by a heterogeneous Pd/C, only 3% coupling selectivity was achieved after 10 h at a bromobenzene conversion of 42%. The major

product was benzene. PPh$_3$ is an effective ligand and has been employed by many researchers[18,19] in similar types of coupling reactions. However, considering its toxicity and the hazards associated with handling PPh$_3$ from large-scale manufacturing perspectives, we performed a set of reactions with various ligands such as acetylacetone, 2,6-pyridinedicarboxylate, and pyridine in place of PPh$_3$. However, the reaction was found to be selective only when PPh$_3$ is used as the ligand. The ratio of PPh$_3$ to PdCl$_2$ is another essential parameter in terms of selectivity. We observed that a ratio higher than 2.1 is good for higher conversion and selectivity.

Conclusions

In conclusion, a new method for the selective biphenyl synthesis is developed. Use of the carbon-supported PTC, and a ligand such as PPh$_3$, can minimize the occurrence of hydrodehalogenation, thus, making this PdCl$_2$-catalyzed reductive coupling process attractive from the selectivity point of view. The isolation of products from the reaction mixture is also straightforward.

Experimental Section

Melting points were measured in glass capillaries using an Electrothermal 9100 instrument. ^{1}H NMR spectra were measured on a Bruker AMX 300 instrument at 300.13 MHz. GC and GCMS analyses were performed using an HP-5890 gas chromatograph with a 50% diphenyl-50% dimethylpolysiloxane packed column (25 m/0.53 mm). Chemicals were purchased from commercial sources (>99% pure) and used without further purification. Products were either isolated and identified by comparison of their ^{1}H NMR spectra to standard samples, or identified by MS data and comparison of their GC retention times with previously isolated reference samples in our laboratory.

General Procedure for Coupling of Haloarenes:

In a 100-mL glass reactor equipped with a reflux condenser, 1 g of 4-chlorotoluene (7.9 mmol), 1.25 g of zinc (19 mmol), 0.5 g PPh$_3$ (1.9 mmol), 0.25 g of PdCl$_2$ (1.4 mmol), 0.5 g of the supported TBAB on carbon, and 20 mL of DMF were mixed together. The reaction mixture was then heated to 70 °C and kept at that temperature for 10 – 16 h under vigorous (900 rpm) stirring. The reaction progress was monitored by GC. After the stipulated period of time the solids were filtered off and then the filtrate was distilled under vacuum to remove DMF completely. To the resulted residue, 10 mL of water were added and the mixture was stirred for 1 h at 60 °C. The mixture was cooled to 25 °C, and 15 mL of dichloromethane were added and stirred for 30 min to extract the organic compounds completely in to the organic layer. The mixture was then filtered and the layers were separated. Crude biaryl com-

pounds were then recovered by distilling off the dichloromethane and subsequent crystallization in ethanol.

Preparation of Carbon-Supported Phase Transfer Catalyst

3 mmol of a phase transfer catalyst (any one of TBAB, cetyltrimethylammonium bromide, or polyethylene glycol-400) were mixed with 5 g of activated charcoal and then added in to 50 mL H$_2$O. The mixture was then stirred for 2 h. The water was then evaporated in a rota-vapor to complete dryness under 60 torr vacuum at 60 °C bath temperature. The residual solid was then again dried in the oven at 60 °C for 72 h, then ultimately cooled and ground to give a finely divided powder. Portions of this were then taken for the reactions.

Drying Procedure of DMF

DMF with a 1.02 wt. % water content (analyzed by Karl–Fischer method) was distilled and dried over molecular sieves (500 g/L) over a three-day time period. After this period of time, the water content was lowered to 0.02%. The DMF thus obtained was stored under N$_2$ gas and used subsequently in the reactions.

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