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Technical Notes

Heterogeneous Pd-Catalyzed Biphenyl Synthesis under Moderate Conditions in a Solid−Liquid Two-Phase System

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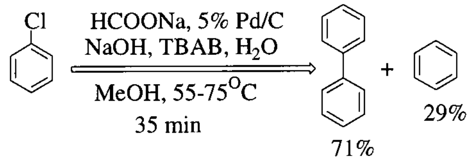
Abstract:
The coupling of substituted halobenzenes to form biphenyls is effected at moderate temperature (65 °C) using a reducing agent such as a formate salt and a base (NaOH) in the presence of a catalytic amount of phase-transfer catalyst and 5% Pd/C catalyst. The reaction conditions can be optimized to give reasonable selectivity, and the competing reduction process is minimized. The roles of temperature, catalyst loading, reducing agents, the base, and the phase-transfer catalyst are discussed. The catalyst can be efficiently recycled. However, an entirely different course of reaction occurs when a mixture of halobenzenes is utilized.

Introduction

Halobenzene can be reduced to benzene by using Pd catalyst and a reducing agent[1a,b] such as hydrogen gas or formate salts. The selectivity is generally very high. Under similar conditions, the addition of a surface active agent and base can shift the selectivity to the coupling product,[2] biphenyl, the building blocks for numerous agrochemicals and pharmaceuticals.[3] To meet market needs, several synthetic approaches towards biphenyl coupling have been developed,[4a−f] from the classic general Ullmann,[4a,b] Suzuki,[4c−e] and Stille[4f] reactions to custom-tailored catalytic transformations aimed at specific molecules. Amongst the variety of developed methods the most attractive one is the Pd-catalyzed reductive coupling of haloaryls as it benefits from simple reactor design, easy catalyst separation, and recycling. We recently demonstrated the reductive coupling[5a−d] of haloaryls in water using formate salts,[5a] hydrogen gas,[5b] or zinc[5c−e] as reducing agents. However, the major drawbacks of these processes are the formation of 25−35% reduction product derived from the parallel hydrodehalogenation reaction[1a] of haloaryls to arenes and the use of high temperature.

Scheme 1



A tandem one-pot biphenyl production process,[6] combining the reductive coupling[5] of chlorobenzene to biphenyl and the oxidative coupling[7] of benzene to biphenyl was explored, to minimize the reduction side reactions. The effort was partly successful in avoiding the use of any oxidant or reductant; however, this process[6] requires further investigations regarding catalyst deactivation and separation of the close boiling products before becoming an industrial process.

Unfortunately, in most of the cases a very high temperature, 100−120 °C, is needed to achieve 60−70% selectivity to biphenyl. Thus, in this report, we present the results of process parameter studies of the highly selective and rapid reductive coupling of haloaryls to biphenyls, catalyzed by Pd/C at only 55 to 60 °C in methanol, with any one of formate, hydrogen gas, or Zn[8] as the in situ catalyst regenerator.

Results and Discussion

Chlorobenzene was chosen as a model substrate for the process parameter studies (Scheme 1); however, good yields for the coupling products were obtained using various substrates, as shown in Table 1. No other products were observed.

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Table 1. **Pd-catalyzed reductive coupling reaction with various starting materials**[a]

substrate	*t*, min	% conv.	% selec., coupling	%selec., reduction
chlorobenzene	35	100	71	29
bromobenzene	20	100	73	27
4-chlorotoluene	100	100	64	36
2-chlorotoluene	120	100	32	68
4-chloro-1,1,1,-trifluorotoluene	55	100	70	30

[a] *Reaction conditions*: substrate, 22 mmol; NaOH, 62.5 mmol; HCOONa, 26.4 mmol; catalyst, Pd/C, 0.53 mol % of substrate on Pd basis; TBAB, 4.9 mol % of the substrate; H_2O, 3.5 g; temperature, 65 °C; agitation speed, 900 rpm; solvent, MeOH (total volume) 25 mL.

Table 2. **Effect of different process parameters on the rate and product selectivity**[a]

entry	parameter	*t*, min	% conv.	% selec., biphenyl	% selec., benzene
1	temp., 45 °C	35	43	48	52
2	55 °C	35	89	62	38
3	65 °C	35	100	71	29
4	75 °C	25	100	72	28
5	Pd/C, 0.266 mol %	35	69	49	51
6	0.53 mol %	35	100	71	29
7	0.79 mol %	30	100	75	25
8	1.0 mol %	20	100	77	23
9	NaOH, 0 mmol	35	53	39	59
10	40 mmol	35	71	53	47
11	50 mmol	35	83	59	41
12	62 mmol	35	100	71	29
13	75 mmol	35	100	69	31
14	TBAB, 0 g	35	61	27	73
15	3.5 mol %	35	91	53	47
16	4.9 mol %	35	100	71	29
17	7.0 mol %	35	100	69	31
18	10 mol %	35	100	59	41
19	H_2O, 0 g	35	7	-	-
20	2.0 g	35	79	68	42
21	3.5 g	35	100	71	29
22	solvent, MeOH	35	100	71	29
23	EtOH	30	100	70	30
24	H_2O	90	100	46	54
25	Reductant, HCOONa	35	100	71	29
26	H_2 (5 atm)	20	100	49	51
27	Zn	35	43	67	43
28	HCOONa[b]	105	100	23	77

[a] *Reaction conditions:* chlorobenzene, 22 mmol; HCOONa, 26.4 mmol; catalyst, 5% Pd/C; speed of agitation, 900 rpm; solvent (total volume), 25 mL. [b] Reaction was performed in the absence of TBAB and NaOH.

Table 3. **Pd-catalyst reusability**[a]

entry	catalyst	*t*, min	% conv.	% selec., biphenyl	% selec., benzene
1	fresh	35	100	71	29
2	1st reuse	35	100	70	30
3	2nd reuse	35	100	72	28
4	3rd reuse	35	100	71	29
5	4th reuse	35	96	71	29

[a] *Reaction conditions:* chlorobenzene, 22 mmol; NaOH, 62 mmol; HCOONa, 26.4 mmol; 5% Pd/C catalyst, 0.53 mol % of substrate; TBAB, 4.9 mol % of substrate; temperature, 65 °C; H_2O, 3.5 g; agitation speed, 900 rpm; solvent, MeOH (total volume) 25 mL.

The reaction temperature affects both rate and product selectivity. With an increase in temperature the reaction shifted favorably to the coupling product (Table 2, entries 1−4). This was probably because of $E_{\mathrm{a,coupling}} > E_{\mathrm{a,reduction}}$.[5b,9] Generally, at higher Pd-catalyst loading the rate of the reaction increased linearly. It was observed initially that an increase in catalyst loading increased the selectivity; however, the selectivity remained unchanged with a further increase in catalyst loading above 0.53 mol % (Table 2, entries 5−8). Also, addition of sodium hydroxide[5a,10] (Table 2, entries 9−13) or a phase-transfer catalyst,[2,5a] namely, tetrabytylammonium bromide (TBAB), shifted product selectivity towards the coupling product (Table 2, entries 14−18). The use of TBAB does not alter the chemical nature of the intermediates; rather it modifies the physical microenvironment in the proximity of the catalyst surface.[11] The amount of water has a strong impact on the rate of reaction. It has been described elsewhere[1a] that water molecules should also be adsorbed on the Pd surface to generate hydrogen from formate salt. Thus, in all subsequent runs, 3.5 g of water was added to obtain a faster rate and maximum selectivity to biphenyl (Table 2, entries 19−21).

In terms of rate and selectivity almost identical results were obtained when the reaction was performed in either methanol or ethanol (Table 2, entries 22−24). Unlikely, the reduction of chloroaryls to arenes was scarcely commenced when methanol was used as the solvent.[1a] Also, while carrying out the reactions in water; low biphenyl selectivity was achieved.

To investigate the effects of utilizing different reducing agents, Zn and H_2 gas were also examined in place of formate salts (Table 2, entries 25−27). When formate salt was replaced by H_2 gas, the reduction reaction became dominant; however, similar rate and selectivity were accomplished when Zn replaced it.

Chlorobenzene was selectively reduced to benzene (77%) in the absence of TBAB and NaOH. The rest was biphenyl (Table 2, entry 28). This is mainly due to formate salt, which was dissociated on the Pd surface in the presence of water to form H_2 and bicarbonates. Thus, the basicity provided by the in situ generated bicarbonates in the system that was sufficient to yield 23% coupling product. Particularly, when chlorobenzene was reduced with molecular H_2 under similar conditions, 98% benzene selectivity was achieved.

An entirely different course of reaction occurred when a mixture of chlorobenzene and bromobenzene was employed for the coupling reaction. Initially, chlorobenzene did not start to react until 86% of the bromobenzene had reacted. This could be due to the differences in the relative rates of adsorption of the two haloaryls on the Pd surface when they were introduced in a mixture.

Also, the solid Pd/C catalyst was recycled without losing its catalytic activity (Table 3) simply by filtration and washing with methanol at room temperature (see also Experimental Section).

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Scheme 2

$$2C_6H_5Cl + Pd \longrightarrow C_6H_5\text{-}C_6H_5 + PdCl_2 \quad (1)$$

$$HCO_2^- + H_2O \xrightarrow{Pd} HCO_3^- + H_2 \quad (2)$$

$$H_2 + PdCl_2 \longrightarrow Pd + 2HCl \quad (3)$$

$$H_2 + Pd \longrightarrow Pd^{+2}(H^-)_2 \quad (4)$$

$$Pd^{+2}(H^-)_2 + C_6H_5Cl \longrightarrow Pd^{+2}(H^-)(Cl^-) + C_6H_6 \quad (5)$$

The experimental results can be elucidated in terms of the mechanism represented by eqs 1−5 as displayed in Scheme 2. Earlier, we suggested a mechanism[5a] for the coupling of chloroaryls, consisting of two single-electron-transfer (SET) processes from the Pd to two chlorobenzene molecules,[12] followed by dissociation of $[Ar{-}Cl]^{\bullet -}$ radical anions. Consequently, the coupling of haloaryls can be shown as depicted in eq 1. The hydrogen thus generated from formate salt (eq 2) in the presence of palladium[1a,13] can reduce $PdCl_2$ to Pd and complete the catalytic cycle (eq 3). Notwithstanding, hydrogen can also adsorb on the reduced palladium species to form palladium hydride (eq 4), which in turn may reduce chlorobenzene to benzene (eq 5). The sequential $Pd^{II}(H^-)(Cl^-)$ species may then liberate HCl. Clearly, the main difference between the reductive coupling (eq 1) and the reduction (eq 5) is that the coupling requires electrons, while mainly H_2 atoms initiate the reduction. To achieve better understanding of the mechanism, a reaction was executed with a stoichiometric amount of Pd/C and chlorobenzene in the presence of a base and TBAB (eq 1). No reducing agent was introduced, yet a quantitative yield of biphenyl was accomplished relative to the Pd amount. A fresh batch of chlorobenzene addition could not produce further reaction; however, addition of a stoichiometric amount of formate salt (recycling of $PdCl_2$ to Pd, eqs 2 and 3) could carry the reaction further. These observations are in good agreement with our mechanistic postulation.

Moreover, with an increase in Pd/C loading the number of active Pd sites is increasing, which further results in an increase in the rate of coupling reaction (according to eq 1). The presence of water is crucial for the hydrogen generation from formate salt (eq 2) which in turn reacts with Pd to form PdH_2 (eq 4). Of course, when the reaction was performed in water as a solvent, the selectivity to coupling decreased due to the higher rate of hydrodehalogenation reaction (eq 5). The purpose of adding base in this reaction is to drag forward the reaction in eq 3 (reversible reaction) by neutralizing the HCl formed thereupon. It can also react with the HCl generated by the dissociation of $Pd^{II}(H^-)(Cl^-)$ species. On the contrary, the role of PTC is not fully understood. However, it is realized that in the presence of a PTC, the rate of reactions written in eqs 4 and 5 decreases by certain factors. This may be bacause of the PTC encapsulation around the Pd(0) species as postulated before.[11]

Conclusions

Biphenyls can be readily synthesized by the Pd-catalyzed reductive homocoupling of aryl halides in the presence of TBAB, NaOH, and H_2O at 65 °C in methanol. Altering the process variables minimizes the occurrence of the competing hydrodehalogenation reaction. The highest selectivity obtained to biphenyl was 71%.

Experimental Section

Materials and Instrumentation. Melting points were measured in glass capillaries using an Electrothermal 9100 instrument. ^1H NMR spectra were measured on a Bruker AMX 300 instrument at 300.13 MHz. GC and GC/MS 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 firms (>98% pure) and used without further purification. Products were either isolated and identified by comparison of their ^1H NMR spectra to standard samples or identified by MS data and comparison of their GC retention times with previously isolated reference samples.[5a] Reactions were performed in a 100-mL glass reactor fitted with a six-bladed impeller and a condenser.

General Procedure for Coupling of Haloaryls. Example: Biphenyl from C_6H_5Cl. A 100 mL glass reactor was charged with 2.5 g (22 mmol) of C_6H_5Cl, 1.8 g (26.4 mmol) of HCOONa, 2.5 g (62.5 mmol) of NaOH, 0.35 g (4.9 mol %) of TBAB, 0.5 g of 5% w/w Pd/C (50% water, 0.53 mol % Pd relative to C_6H_5Cl), 3.5 g of water, and MeOH, 25 mL (total reaction volume). The reactor was then heated to 65 °C. Reaction progress was monitored by GC. The mixture was stirred (900 rpm) at 65 °C for 35 min, cooled, and diluted with water. The organic compounds were extracted with 40 mL of CH_2Cl_2. Solvent evaporation and recrystallization afforded 2.3 g (68 mol % based on C_6H_5Cl) of biphenyl, mp 69 °C (from cold EtOH) (lit.[14a,b] 69−71 °C). Found: C, 93.26; H, 6.74. $C_{12}H_{10}$ requires C, 93.46; H, 6.54. ^1H ($CDCl_3$, Me_4Si) 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.[14c]

The substituted biphenyls 4,4′-dimethylbiphenyl and 4,4′-ditrifluoromethylbiphenyl were similarly prepared. 4,4′-Dimethylbiphenyl: isolated yield 55% based on 4-chlorotoluene, mp 119 °C (from CH_2Cl_2) (lit.[14d] 120.7−121.5 °C). Found: C, 91.60; H, 7.63. $C_{14}H_{14}$ requires C, 92.30; H, 7.69. 4,4′-Ditrifluoromethylbiphenyl: isolated yield 65% based on 4-chloro-1,1,1-trifluorotoluene, mp 80 °C (from EtOH/H_2O) (lit.[14e] 93−94.5 °C). Found: C, 57.82; H, 2.90; F, 39.28. $C_{14}H_8F_6$ requires C, 57.93; H, 2.75; F, 39.31. ^1H ($CDCl_3$, Me_4Si) 7.69 (8H, m, ArH) (lit.[14f] 7.67).

Scale-Up Batch. A batch size of 15 times the usual reaction has been carried out for the scale-up reaction, and

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in 45 min, 100% conversion and 70% selectivity was obtained. The isolated yield of biphenyl was 66 mol % on chlorobenzene basis.

Pd Catalyst Recycling. The reaction was performed as above, after which the liquids were filtered, and the solid catalyst was washed with methanol (3 × 20 mL) and then dried under vacuum. The same batch, when utilized in the subsequent reactions, retained >99% of its initial activity.

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