Pergamon

Tetrahedron 55 (1999) 14763–14768

TETRAHEDRON

# Palladium-catalyzed Aryl-Aryl Coupling in Water using Molecular Hydrogen: Kinetics and Process Optimization of a Solid-Liquid-Gas system

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Received 26 August 1999; revised 24 September 1999; accepted 7 October 1999

***Abstract:*** Coupling of substituted chlorobenzenes to the respective biphenyls is effected in water, using hydrogen gas and NaOH in the presence of catalytic PEG-400 and Pd/C. The catalyst can be efficiently recycled. The competing reduction process (*e.g.* of chlorobenzene to benzene) can be minimized by altering reaction conditions. The roles of the hydrogen, the hydroxide, the Pd catalyst, and the PEG are discussed. © 1999 Elsevier Science Ltd. All rights reserved.

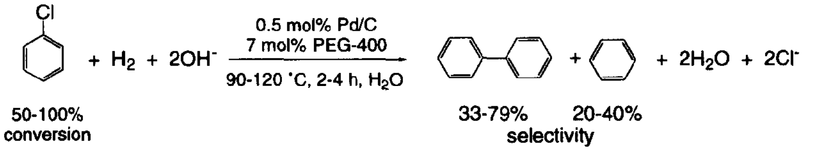
## INTRODUCTION

Aryl-aryl couplings are of interest to many organic chemists and relate to numerous applications, biaryls being key building blocks in the agrochemical and pharmaceutical industries.[1, 2] To meet market needs, diverse synthetic approaches towards biaryls have been developed, from the classic general Ullmann[3] and Suzuki[4] reactions to custom-tailored catalytic transformations. Among the alternatives to the stoichiometric Ullmann reaction with copper there are several palladium-catalyzed processes, based on both homogeneous and heterogeneous systems.[5] The latter benefit from easy catalyst separation and recycling, but still require a reducing reagent such as *i*-propanol,[6] or formate salts,[7] to complete the catalytic cycle.

The advantages of hydrogen gas as a reductant and hydrogen-transfer agent include its low price, easy bulk management, minimal effluents, facile product separation, and longer catalyst life. For these reasons, hydrogen is invariably utilized in all large-scale industrial applications.[8] Despite these advantages, hydrogen gas has not been used as a palladium-regenerator in aryl-aryl coupling, possibly because of reduction side-reactions.[9]

Here we present the results of kinetic investigation and process optimization of the coupling and reduction reactions of haloaryls, catalyzed by heterogeneous palladium on carbon, with molecular hydrogen as the *in situ* catalyst regenerator.

## RESULTS AND DISCUSSION

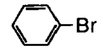
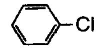
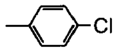
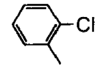
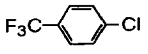
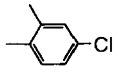
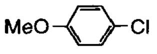


(1)

*PII:* S0040-4020(99)00920-5

In a typical reaction (eq. 1 above), chlorobenzene, water, sodium hydroxide, and catalytic amounts of polyethyleneglycol (PEG) and Pd/C were charged to an autoclave which was then pressurized with 4 atm of hydrogen. After 2-4 h at 90-120 °C, depending on reaction conditions, biphenyl was found to be the major product, together with some hydro-dehalogenation (reduction) product. Good yields for the coupling products were obtained using various substrates, as shown in Table 1. No other products were observed.

**Table 1.** Palladium-catalyzed coupling and reduction of chloroaryls with hydrogen.

| Entry | Substrate | % Conversion | % Yield[a,b], coupling | % Yield[a], reduction |
|---|---|---|---|---|
| 1 |  | 100 | 79 (73) | 20 |
| 2 |  | 100 | 76 (71) | 24 |
| 3 |  | 100 | 56 (51) | 43 |
| 4 |  | 73 | 33 | 40 |
| 5 |  | 100 | 77 (69) | 22 |
| 6 |  | 76 | 39 | 36 |
| 7 |  | 82 | 36 | 46 |

Reaction conditions: 44 mmol substrate, 125 mmol NaOH, 0.5 mol% (relative to substrate) of 10% Pd/C, 7 mol% PEG-400, 4 atm $H_2$, solvent $H_2O$ (total reaction volume 50 ml), 110 °C, autoclave (900 rpm stirring), 150 min. [a] Yield based on GC area, corrected by the presence of an internal standard. [b] Numbers in parenthesis represent isolated yields.

The solid Pd/C catalyst can be recycled simply by filtration and washing with water and methanol. After seven runs, the catalyst retained >99% of its activity (see experimental section).

Chlorobenzene was chosen as a model substrate for the kinetics and process parameter studies. Reaction rates were found to be a function of catalyst loading, hydrogen pressure, and substrate concentration (eq. 2, all three variables exhibit first-order dependence). A pseudo first-order rate law was observed for fixed catalyst loading and hydrogen pressure.

$$\frac{-d[S]}{dt} = k[S]w_{cat}P_{H2} \xrightarrow[\text{constant}]{w_{cat} \text{ and } P_{H2}} \frac{-d[S]}{dt} = k_{obs}[S] \text{ where } k_{obs}=w_{cat}P_{H2} \qquad (2)$$

The partial pressure of hydrogen was also found to influence product selectivity. Generally, a higher pressure of hydrogen increased the reduction reaction, and lowered the yield of biphenyl (Table 2, entries 1-5). Conversely, increasing catalyst loading (entries 6-9) or the addition of sodium hydroxide[10] (entries 10-14) shifted product selectivity towards the coupling product.

The rationale for incorporation of PEG into the reaction mixture stems from the system's multiphase nature.[7] The advantages of PEG as a surfactant and phase-transfer catalyst are availability, low cost, and ease of separation.[11] Presence of PEG affects both conversion and selectivity (table 2, entries 15-18). We assume that PEG does not alter the chemical nature of the intermediates, but rather, that it modifies the physical micro-environment of the catalyst, facilitating the access of $OH^-$ to the catalyst surface.

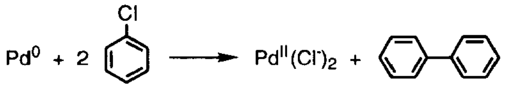
**Table 2.** Effects of $H_2$ pressure, catalyst loading, and NaOH loading on product selectivity.

| Entry | Parameter changed | % Yield[a], coupling | % Yield[a], reduction |
|---|---|---|---|
| 1 | $P_{H2}$ (2 atm) | 79 | 20 |
| 2 | $P_{H2}$ (4 atm) | 76 | 24 |
| 3 | $P_{H2}$ (6 atm) | 70 | 29 |
| 4 | $P_{H2}$ (8 atm) | 67 | 33 |
| 5 | $P_{H2}$ (10 atm) | 55 | 43 |
| 6 | Pd/C (0.12% w/v) | 52 | 48 |
| 7 | Pd/C (0.25% w/v) | 63 | 37 |
| 8 | Pd/C (0.50% w/v) | 74 | 25 |
| 9 | Pd/C (1.00% w/v) | 76 | 23 |
| 10 | NaOH (none)[b] | 16 | 42 |
| 11 | NaOH (2 gr) | 57 | 42 |
| 12 | NaOH (3 gr) | 68 | 32 |
| 13 | NaOH (5 gr) | 76 | 24 |
| 14 | NaOH (8 gr) | 75 | 23 |
| 15 | PEG (none)[c] | 38 | 37 |
| 16 | PEG-400[d] (2 mol%)[e] | 49 | 44 |
| 17 | PEG-400 (4 mol%) | 71 | 29 |
| 18 | PEG-400 (7 mol%)[f] | 76 | 22 |

Standard reaction conditions: 44 mmol $C_6H_5Cl$, 125 mmol NaOH, 0.5 mol% (relative to substrate) of 10% Pd/C, 7 mol% PEG-400, 4 atm $H_2$, solvent $H_2O$ (total reaction volume 50 ml), 110 °C, autoclave (900 rpm stirring), 150 min. [a]100% substrate conversion in all reactions (unless noted otherwise), with yield based on GC area, corrected by the presence of an internal standard. [b]58% conversion. [c]75% conversion. [d]The use of higher Mw PEG resulted in lower conversion and selectivity, perhaps due to low solubility in water. [e]93% conversion. [f]Using larger amounts of PEG-400 did not improve product selectivity.

### *Interdependence between available $Pd^0$ sites, hydrogen pressure, and hydroxide presence*

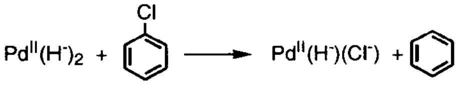
The above findings can be explained if we consider the relationship between catalyst site availability and product selectivity. Previously we suggested a mechanism[12] for coupling of chloroaryls, under similar conditions but using formate salts instead of hydrogen. This consisted of two single-electron-transfer (SET) processes from the catalyst to two substrate molecules,[13] followed by dissociation of the $[Ar\text{-}Cl]^{\bullet -}$ radical anions. Reaction of hydrogen (generated from formate in the presence of palladium[14]) with $PdCl_2$ regenerates the $Pd^0$ catalyst and completes the catalytic cycle. If we postulate a similar simplified representation for the coupling (eq. 3) and catalyst regeneration (eq. 4) reactions in the presence of hydrogen gas we obtain:


(3)

$$Pd^{II}(Cl^-)_2 + H_2 \longrightarrow Pd^0 + 2HCl \qquad (4)$$

However, hydrogen can also adsorb on the reduced palladium catalyst to form palladium hydride (eq. 5), which in turn may reduce chlorobenzene to benzene (eq. 6):

$$Pd^0 + H_2 \rightleftharpoons Pd^{II}(H^-)_2 \qquad (5)$$


(6)

The resulting $Pd^{II}(H^-)(Cl^-)$ may either release HCl (eq. 7), or reduce another chlorobenzene molecule (eq. 8):

$$Pd^{II}(H^-)(Cl^-) \rightleftharpoons Pd^0 + HCl \qquad (7)$$


(8)

Addition of NaOH should enhance eqs 4 and 7, both in which the products are $Pd^0$ and HCl. The significance of this lies in the greater sensitivity of the coupling reaction to the effective concentration of available $Pd^0$ sites. The coordination of a single chlorobenzene molecule to one catalytic site should suffice for reduction, while *coordination of two single chlorobenzene molecules to two available sites may be required for the coupling reaction.*[15] The presence of NaOH will result in a higher effective concentration of vacant $Pd^0$ sites, and in this way may shift the selectivity towards coupling. The fact that higher catalyst loading increases the coupling:reduction ratio supports this argument. Note also that eq 8 is inhibited by the enhancement of eq 7, which may explain part of the shift in product selectivity towards coupling in the presence of NaOH.

Similarly, it may be argued that although hydrogen is necessary for the regeneration of the oxidized palladium catalyst (eq 4), higher hydrogen pressures would cause eq 5 to predominate, favoring the reduction over the coupling.

Performing the reaction at higher temperatures increased the selectivity towards the coupling product, from 52% at 90 °C up to 76% at 110 °C, suggesting that $E_{a,\ coupling} > E_{a,\ reduction}$.[16] The experimental Arrhenius energies of activation were found to be $E_{a,\ coupling}$= 63 KJmol$^{-1}$ (15 Kcalmol$^{-1}$, $r^2$=0.997 for four measurements at 90, 100, 110, and 120 °C) and $E_{a,\ reduction}$= 6 KJmol$^{-1}$ (1.4 Kcalmol$^{-1}$). These findings characterize the reduction as a mass-transfer controlled process,[17a] in contrast with the chemically controlled coupling under these conditions. Indeed, agitation speed[17b] was found to influence both substrate conversion and product selectivity. Thus, performing the reaction at stirring rates of 300, 500, 700, 900, and 1000 rpm led to chlorobenzene conversions of 62%, 78%, 89%, 100%, and 100%, with selectivities to biphenyl of 51%, 59%, 74%, 76%, and 76%, respectively. These results indicate that the reduction is diffusion-controlled below 900 rpm.

## CONCLUSIONS

Hydrogen gas can be directly utilized for the reductive homocoupling of aryl halides in the presence of Pd/C at 90 to 120 °C. The essential characteristics of this system are similar to the corresponding formate-based application. The occurrence of the competing hydro-dehalogenation may depend on the availability of free active catalytic sites. Accordingly, product selectivity can be directed by selection of reaction conditions.

## EXPERIMENTAL SECTION

*Materials and instrumentation.* 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% dimethyl-polysiloxane 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 $^1$H NMR spectra to standard samples, or identified by MS data and comparison of their GC retention times with previously isolated reference samples.[12] Reactions were performed in a 300 ml stainless steel Parr autoclave, equipped with a six-bladed impeller, an external heating mantle and a gas cooling system.

*General procedure for coupling of haloaryls.* Example: biphenyl from $C_6H_5Cl$. In a 300 ml autoclave, were charged 5.0 g (44 mmol) $C_6H_5Cl$, 5.0 g (125 mmol) of NaOH, 1.2 g (7 mol%) PEG-400, 0.25 g 10% w/w Pd/C (0.53 mol% Pd relative to $C_6H_5Cl$), and $H_2O$ (total reaction volume 50 ml). The autoclave was pressurized with 4 atm $H_2$ (>99.99% pure). Reaction progress was monitored by GC. The mixture was stirred (900 rpm) at 110 °C for 150 min, cooled and extracted with 40 ml of $CH_2Cl_2$. Solvent evaporation and recrystallizing afforded 3.55 g (71 mol% based on $C_6H_5Cl$) of biphenyl, mp 69 °C (from cold EtOH) (lit.,[18] 69-71 °C). Found: C, 93.26; H, 6.74. $C_{12}H_{10}$ requires C, 93.46; H, 6.54%. $\delta_H$ ($CDCl_3$; $Me_4Si$) 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.[19]

The substituted biphenyls 4,4'-dimethylbiphenyl and 4,4'-ditrifluoromethylbiphenyl were similarly prepared. 4,4'-dimethylbiphenyl: isolated yield 51% based on 4-chlorotoluene, mp 119 °C (from $CH_2Cl_2$) (lit.,[20] 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 69% based on 4-chloro-1,1,1-trifluorotoluene, mp 80 °C (from EtOH/$H_2O$) (lit.,[21] 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%. $\delta_H$ ($CDCl_3$; $Me_4Si$) 7.69 (8H, m, ArH) (lit.,[22] 7.67).

*Catalyst recycling.* The reaction was performed as above, after which the liquids were filtered and the solid catalyst was washed with $H_2O$ (3×40 ml) and then washed with MeOH (3×10 ml) at 25 °C. The same catalyst batch retained >99% of its activity after 7 runs (100% conversion of $C_6H_5Cl$ with 76% selectivity to biphenyl for the fresh catalyst, and 100% conversion with 76% selectivity for the 7th batch).

*Experimental procedure for kinetic studies.* Example: 44 mmol $C_6H_5Cl$, 125 mmol NaOH, 0.25 g 10% Pd/C (0.5 mol% Pd relative to substrate), and 1.2 g PEG-400 (7 mol% relative to substrate) were mixed in water (50 ml total reaction volume) at 110 °C in an autoclave (*vide supra*) pressurized with 4 atm $H_2$. Reaction progress was monitored by GC.

The following parameters were studied: (i) initial substrate concentration, using toluene as the diluting organic solvent (3 experiments at 1.77 M, $k_{obs} = 2.9\times10^{-2}$, $r^2 = 0.999$ for 4 observations; 2.66 M, $k_{obs} = 3.2\times10^{-2}$, $r^2 = 0.998$ for 4 observations; and 3.55 M, $k_{obs} = 3.5\times10^{-2}$, $r^2 = 0.998$ for 4 observations); (ii) catalyst loading (4 experiments using 0.1% w/v Pd, $k_{obs} = 6\times10^{-3}$ min$^{-1}$, $r^2 = 0.999$ for 6 observations; 0.25% w/v Pd, $k_{obs} = 1.5\times10^{-2}$ min$^{-1}$, $r^2 = 0.999$ for 6 observations; 0.5% w/v mol% Pd, $k_{obs} = 2.9\times10^{-2}$ min$^{-1}$, $r^2 = 0.999$ for 5 observations; and 1.0% w/v Pd, $k_{obs} = 5.2\times10^{-2}$ min$^{-1}$, $r^2 = 0.998$ for 4 observations); (iii) reaction temperature (4 experiments at 90 °C, $k_{obs} = 9\times10^{-3}$ min$^{-1}$, $r^2 = 0.999$ for 5 observations; 100 °C, $k_{obs} = 1.6\times10^{-2}$ min$^{-1}$, $r^2 = 0.999$ for 5 observations; 110 °C, $k_{obs} = 2.9\times10^{-2}$ min$^{-1}$, $r^2 = 0.997$ for 4 observations; and 120 °C, $k_{obs} = 5.3\times10^{-2}$ min$^{-1}$, $r^2 = 0.998$ for 4 observations); and (iv) $H_2$ pressure (5 experiments at 2 atm $H_2$, $k_{obs} = 2.3\times10^{-2}$ min$^{-1}$, $r^2 = 0.999$ for 6 observations; 4 atm $H_2$, $k_{obs} = 2.9\times10^{-2}$ min$^{-1}$, $r^2 = 0.999$ for 6 observations; 6 atm $H_2$, $k_{obs} = 3.6\times10^{-2}$ min$^{-1}$, $r^2 = 0.999$ for 6 observations; 8 atm $H_2$, $k_{obs} = 4.38\times10^{-2}$ min$^{-1}$, $r^2 = 0.996$ for 5 observations; and 10 atm $H_2$, $k_{obs} = 4.4\times10^{-2}$ min$^{-1}$, $r^2 = 0.998$ for 5 observations).

## *Acknowledgment*

We thank Dr. J. Muzart (University of Reims, CNRS) for comments and suggestions.

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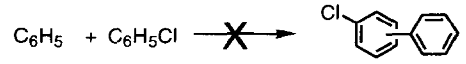
15. Attack of the phenyl radicals on substrate molecules in the bulk (eq 5) is improbable, as no chlorobiphenyls were observed. Nor were analogous products observed in the coupling of the other substrates, so we may conclude that the aryl radicals couple on the catalyst surface, followed by desorption of biphenyl.



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