Tuning the Selectivity of Heterogeneous Catalysts: A Trimetallic Approach to Reductive Coupling of Chloroarenes in Water

Sudip Mukhopadhyay,[a] Gadi Rothenberg,[b] Yoel Sasson[c,*]

[a] Chemical Engineering Department, University of California at Berkeley, Berkeley, CA 94720, U.S.A
E-mail: sudip@uclink2.berkeley.edu
[b] York Green Chemistry Group, Chemistry Department, The University of York, Heslington, York YO10 5DD, U.K.
E-mail: gr8@york.ac.uk
[c] Casali Institute of Applied Chemistry, Hebrew University of Jerusalem, Jerusalem 91904, Israel
Fax (+972) 2 6528 250, E-mail: ysasson@vms.huji.ac.il

Received November 19, 2000; Accepted January 2, 2001

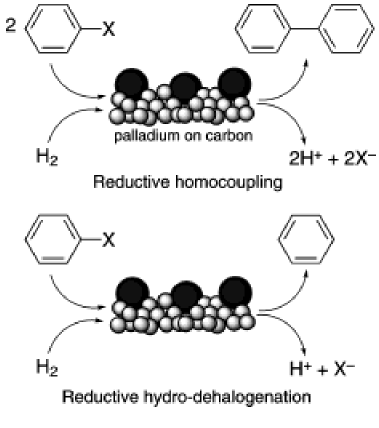
Abstract: Reductive homocoupling of chlorobenzenes to the respective biphenyls affords high yields (93–95%), in the presence of catalytic PEG-400 and 0.4 mol % of a recycleable, heterogeneous trimetallic catalyst (4% Pd, 1% Pt, and 5% Bi on carbon). The competing reduction process is minimized. The catalytic cycle is completed using hydrogen gas, or formate + water or zinc + water mixtures, which generate dihydrogen *in situ*. Primary kinetic data and some process parameters are studied. The roles of the Pd, Pt, and Bi, different reducing agents, and the phase-transfer agent are discussed. The reaction mechanism is proposed to depend on the relative concentration of hydride species in the immediate vicinity of the palladium metal.

Keywords: bismuth; C–C coupling; chloroarenes; heterogeneous catalysis; palladium; trimetallic catalysis

Introduction

Heterogeneous catalysis, which until recently has been utilized chiefly in large-scale applications such as cracking and reforming of petrochemicals, is increasing in importance for new liquid phase processes in the production of various fine chemicals.[1] This trend reflects global efforts towards eco-efficient synthetic solutions.[2]

One practicable application of such a catalytic system can be the production of biaryl compounds, which are valuable industrial building blocks for many agrochemicals and pharmaceuticals.[3] However, although several aryl-aryl coupling protocols have been studied, the Ullmann synthesis,[4] which uses stoichiometric copper powder and is over a century old,[5] is still being employed. Alternatives include various reductive and oxidative pathways, that utilize both homogeneous and heterogeneous transition-metal catalysts.[6] Of these, the heterogeneous reductive coupling of ArX to Ar–Ar (Scheme 1, top) incorporates three important process advantages, viz. simplistic reactor design, facile product separation, and effective catalyst recycling.



Scheme 1.

Results and Discussion

As we have demonstrated recently,[7] completion of the catalytic cycle can be accomplished using diverse reducing agents such as hydrogen gas,[7a] formate + water,[7b] or zinc + water.[7c–e] However, the compet-

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/asc/ or from the author.

ing reduction reaction (i. e., the hydro-dehalogenation of ArX to ArH, Scheme 1, bottom) prevents the exclusive formation of the coupling product. Thus, regardless of the reagents used, 20–35% of the reduction product is formed at high (>80%) conversions, encumbering possible industrial applications.[8] Whilst any industrial process would be judged by the final cost of materials vs. products, the combination of high selectivity and using formate salts instead of stoichiometric copper metal makes this process an environmentally friendly alternative.

The fundamental reactions in this reductive coupling system are given by Equations 1–5, wherein the reduction of Pd(II) to Pd(0) occurs via reaction with dihydrogen. This dihydrogen can be produced either from the *in situ* reaction of water with zinc (Equation 3) or formate (Equation 4), or generated *ex situ* and supplied as a gas.

The main difference between the two processes depicted in Scheme 1 is that the homocoupling (top) requires only electrons, while the reduction (bottom) requires only hydrogen atoms. As we have shown before, the selectivity to the coupling products depends on the number of vacant Pd(0) sites, which in turn reflects the balance between the reduction of Pd(II) (Equation 2), and the formation of Pd(II)(H⁻)$_2$ via Equation 5. The latter reaction is a function of the available dihydrogen concentration close to the catalyst surface.[9]

$$2PhCl + Pd^0 \longrightarrow Ph{-}Ph + Pd(II)(Cl^-)_2 \qquad (1)$$

$$H_2 + Pd(II)(Cl^-)_2 \xrightarrow{k_2} Pd(0) + 2HCl \qquad (2)$$

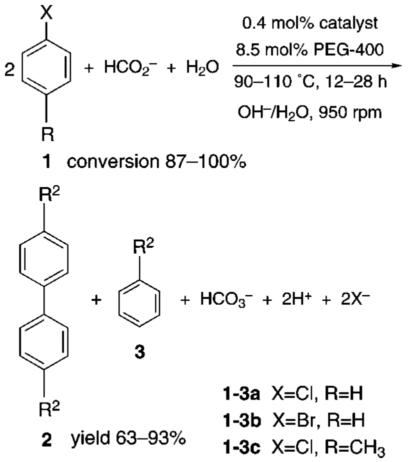
$$Zn_{(s)} + H_2O_{(l)} \xrightarrow{Pd^0/C} ZnO_{(s)} + H_{2(g)} \qquad (3)$$

$$HCO_2^-Na^+ + H_2O \xrightarrow{Pd^0/C} HCO_3^-Na^+ + H_2 \qquad (4)$$

$$H_2 + Pd(0) \xrightarrow{k_5} Pd(II)(H^-)_2 \qquad (5)$$

A desired system, therefore, is one which would enhance Equation 2 and retard Equation 5, thus increasing the number of available Pd(0) sites for the coupling reaction, *and decreasing the number of palladium-hydride sites*, at which the unwanted reduction process occurs. It is known that certain group VII and group IV metals influence the outcome of hydrogenation and hydrogenolysis reactions when employed as surface modifiers together with palladium or platinum on various supports.[10] On this basis we initiated an experimental search for a heterogeneous catalyst with "tunable" parameters, which would perhaps enable the selective formation of the desired coupling product.

In a typical reaction (Scheme 2), the haloaryl **1**, NaOH, sodium formate, water, and catalytic amounts of polyethyleneglycol (PEG-400) and metal/C catalyst were charged to an autoclave. After stirring for 12–28 h at 90–110 °C (depending on reaction conditions), biphenyl **2** was isolated as the major product, together with small amounts of benzene **3** (hydro-dehalogenation product). No other products were discernable by GC and ^{1}H NMR analysis. Table 1 shows PhCl conversion and biphenyl selectivity that was obtained using different metal/C combinations. Control experiments confirmed that no reaction took place in the absence of either formate, haloaryl, water, or catalyst.



Scheme 2.

The rationale for incorporating platinum and/or nickel is based on the known catalytic activity of these metals in the oxidation of dihydrogen, *i. e.* $H_2 \Rightarrow$

Table 1. PhCl coupling with different catalysts

Entry	Catalyst (wt %)[b]	Time (h)	% Conversion	% Selectivity[c]
1	Pd (3)	1.5	100	73
2	Pd (1.5); Pt (2.5)	2	100	67
3	Pd (3); Bi (3)	23	34	91
4	Pd (3); Cu (3)	25	41	67
5	Pd (5); Bi (6)	17	27	84
6	Pd (5); Ni (5);[d] Bi (6)	24	73	84
7	Pd (4); Pt (1); Bi (5)	17	100	93[e]

[a] Standard reaction conditions: PhCl, 45 mmol; HCOONa, 50 mmol; catalyst, 0.4 mol % of substrate (based on Pd content, e. g., if the catalyst contains 1 mol Pd then 250 mol substrate was used); PEG-400, 1.5 g (8.5 mol % of substrate); NaOH, 125 mmol; 950 rpm mechanical stirring; 110 °C.

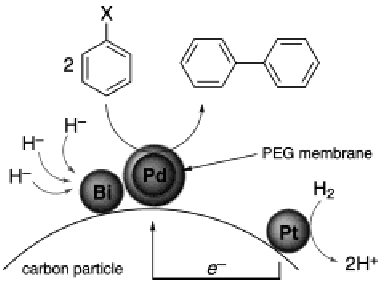
[b] The various catalysts were prepared by mixing predetermined quantities of commercial Pd/C and/or Pt/C (Aldrich). Bismuth powder (Aldrich, 100 mesh size) was added as needed and mixed in water under 5 atm H_2 pressure before filtration, washing with acetone and drying under vacuum for 3 h.

[c] Selectivity to the coupling product **2a** based on GC area, corrected by the presence of an internal standard.

[d] A mixture of the catalyst with Raney Nickel was used.

[e] Yield of isolated product.

$2H^+ + 2e^-$. Bismuth, on the other hand, is known to suppress hydro-dehalogenation reactions. We therefore expected that a combination of platinum, palladium, and bismuth in the right ratio would enhance k_2 by "supplying" electrons for the coupling process from the Pt to the Pd sites, and to retard k_5 by trapping surplus hydrides on the Bi sites (bismuth can also form an intermetallic complex with palladium, which could also facilitate the withdrawing of the hydrides from the palladium towards the bismuth atoms).[11] Thus, the palladium may serve as an "electron shuttle".[12] A cartoon of this process is shown in Scheme 3. This transfer of electrons would not be expected to work on a non-conductive support. Indeed, we have found that using identical trimetallic combinations on SiO_2 or Al_2O_3 supports was ineffective.



Scheme 3.

Under the same conditions, PhCl **1a** was totally consumed after 17 h, the selectivity to **2** being 93–95%. With PhBr **1b**, 100% conversion was reached after 12 h, but selectivity to **2** was lower (86%), while *p*-chlorotoluene **1c** reached a conversion of 87% after 28 h, with selectivity to **2** at only 63%. Chlorobenzene **1a** was chosen as a model substrate for kinetic and process parameter studies.

Performing the reaction at higher temperatures increased selectivity to biphenyl, from 79% at 90 °C up to 93% at 110 °C, suggesting that $E_{a,\ coupling} > E_{a,\ reduction}$.[13] The calculated Arrhenius energy of activation was found to be $E_{a,\ coupling} = 33.0\ \mathrm{KJ\ mol^{-1}}$ (8.3 $\mathrm{Kcal\ mol^{-1}}$, $r^2 = 0.996$ for four measurements at 90, 100, 110, and 120 °C). These findings are in agreement with our previous kinetic studies of similar systems.[7a,7b,7c]

Reaction duration (for 100% PhCl conversion) and selectivity to **2a** are given in Table 2. Rates were found to be a function of substrate concentration, formate concentration, and catalyst loading, i. e., $-d[\mathbf{1a}]/dt = k_{obs}[\mathbf{1a}][HCO_2^-][Cat]$. A pseudo first-order rate law, $-d[\mathbf{1a}]/dt = k_{obs}[\mathbf{1a}]$, was observed for fixed formate and catalyst loading, with typical $k_{obs} \sim 4.8$–$6.2 \times 10^{-3}\ \mathrm{min^{-1}}$.[14]

Table 2. Trimetallic catalyst application with PhCl.[a]

Entry	Parameter	Time (h)	% Selectivity **2a**[b]
	Cat. (mol %)		
1	0.2	17[c]	89
2	0.4	17	93
3	0.6	12	90
4	0.8	10	89
	[NaOH] (mol %)		
5	110	26	73
6	220	21	81
7	275	17	93
8	330	16	91
9	385	15	92
	PEG-400 (mol %)		
10	2.8	21	70
11	5.6	19	95
12	8.5	17	85
13	11.3	16	83
14	14.1	16	93
	Reducing agent		
15	Formate + water	17	93[d]
16	Zinc + water	20	94[d]
17	Hydrogen gas	8	82

[a] Standard reaction conditions: PhCl, 45 mmol; HCOONa, 50 mmol; catalyst [(4% Pd, 1% Pt, 5% Bi)/C], 0.4 mol % of substrate (based on Pd content, e. g., if the catalyst contains 1 mol Pd then 250 mol substrate was used); PEG-400, 1.5 g (8.5 mol % of substrate); NaOH, 125 mmol; 950 rpm mechanical stirring; 110 °C; 100% substrate conversion.
[b] Selectivity based on GC area, corrected by the presence of an internal standard.
[c] 93% conversion.
[d] Yield of isolated product.

The solid catalyst can be easily recycled. We have re-used the same batch of catalyst three times, with unchanging activities, which showed that turnover numbers (TONs) were in the thousands at least. Catalyst losses were negligible, and the recycling procedure is simple.

Catalytic amounts (5–8 mol %) of phase-transfer agent increased the selectivity towards the coupling products (Table 2, entries 10–14). This has been observed before,[15] but the fact that an inexpensive PTC such as PEG-400 can be effectively used is significant. We suggest that the PEG coats the palladium with a membranal layer which is not permeable to hydrogens but allows the passage of electrons[16] (see Scheme 3). Indeed, separate experiments showed that PEG easily adsorbs on the carbon surface.[17] The base (entries 5–9) is thought necessary to maintain a high percentage of active Pd(0) sites, at which the coupling reaction occurs, by neutralizing the HCl formed.[7a] That the results obtained using formate + water and zinc + water were practically identical (entries 15–16) supports our stand that these systems operate via similar mechanisms.

Conclusion

We have demonstrated here the tuning of a heterogeneous catalyst to obtain high yields of carbon-carbon coupling in a reductive medium. This catalyst features high turnover numbers and is fully recyclable.

Experimental Section

General Remarks

Melting points were measured in glass capillaries using an Electrothermal 9100 instrument and are uncorrected. ^{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). Unless stated otherwise, 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 standard samples. Reactions below 100 °C were carried out in glass apparatus, and reactions at 100 °C and above were performed in a stainless steel Parr autoclave.

Catalyst Preparation

Predetermined quantities of commercial 5% Pd/C, 5% Pt/C, Bi powder (Aldrich, 100 mesh size), activated carbon as a make up (when required) and 50 mL water were charged to a 300 mL autoclave. This was then pressurized with 5 atm H_2 and stirred vigorously for 3 h. The mixture was then filtered and washed, first with water (3 × 25 mL) and then with acetone (4 × 20 mL). The solid cake was then dried under vacuum (10 torr) at 36 °C for 3–7 h, after which the catalyst flakes were ground using a mortar and pestle. For Raney Ni, the same procedure was applied except the vacuum drying step which was performed at 25 °C.

Biphenyl (2a) from PhCl (1a)

44 mmol C_6H_5Cl, 50 mmol $NaHCO_2$, 125 mmol NaOH, 0.5 g of catalyst [(4% Pd, 1% Pt, 5% Bi)/C, which corresponds to 0.4 mol % of Pd relative to substrate], and 1.5 g PEG-400 (8.5 mol % relative to substrate) were mixed in water (50 mL total reaction volume) at 110 °C in an autoclave. Reaction progress was monitored by GC. The mixture was stirred (950 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 of biphenyl (93 mol % based on C_6H_5Cl), mp 69 °C (from EtOH, at 40 °C and going down to 10 °C) [cf. 69–71 °C (Y. Tamura, M. -W. Chun, K. Inoue, J. Minamikawa, *Synthesis,* **1978**, 822)]; anal.: found: C, 93.26; H, 6.74; $C_{12}H_{10}$ requires: C, 93.46; H, 6.54%; ^{1}H NMR ($CDCl_3$; Me_4Si, cf. N. Kamewaza, *J. Magn. Reson.,* **1973**, *11,* 88): $\delta = 7.39$ (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).

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 heated at reflux in methanol under 0.5 MPa hydrogen pressure at 100 °C for 3 h. The pretreated catalyst retained >99% of its activity in four such subsequent runs. PEG was not recycled.

Supporting information available: Procedures and characterization data for synthesis of 4,4'-dimethylbiphenyl; details of kinetic studies (11 experiments; 3 graphs).

Acknowledgements

We thank Professor C. Amatore (Ecole Normale Supérieure, Paris, France) for valuable comments, and the European Commission for a Marie Curie Individual Research Fellowship (to GR).

References and Notes

[1] For a review, see J. H. Clark, D. J. Macquarrie, *Org. Process Res. Dev.* **1997**, *1*, 149.

[2] (a) R. A. Sheldon, *Chem. Ind.* **1997**, 12; (b) R. A. Sheldon, *J. Chem. Tech. Biotechnol.* **1997**, *68*, 381.

[3] For reviews on biaryl preparation methods and applications, see: (a) G. Bringmann, R. Walter, R. Weirich, *Angew. Chem., Int. Ed. Engl.* **1990**, *29,* 977; (b) M. Sainsbury, *Tetrahedron* **1980**, *36,* 3327.

[4] For a review, see: P. E. Fanta, *Synthesis* **1974**, 9.

[5] F. Ullmann, *Ber. dtsch. chem. Ges.* **1903**, *36,* 2389.

[6] (a) D. D. Hennings, T. Iwama, V. H. Rawal, *Org. Lett.* **1999**, *1,* 1205; (b) J. Hassan, V. Penalva, L. Lavenot, C. Gozzi, M. Lemaire, *Tetrahedron* **1998**, *54,* 13793; (c) for a combined homogeneous-heterogeneous approach, see: S. Mukhopadhyay, G. Rothenberg, D. Gitis, Y. Sasson, *J. Org. Chem.* **2000**, *65*, 3107.

[7] (a) S. Mukhopadhyay, G. Rothenberg, H. Wiener, Y. Sasson, *Tetrahedron* **1999**, *55,* 14763; (b) S. Mukhopadhyay, G. Rothenberg, D. Gitis, H. Wiener, Y. Sasson, *J. Chem. Soc., Perkin Trans. 2* **1999**, 2481; (c) S. Mukhopadhyay, G. Rothenberg, H. Wiener, Y. Sasson, *New J. Chem.* **2000**, *24*, 305; (d) S. Mukhopadhyay, G. Rothenberg, D. Gitis, Y. Sasson, *Org. Lett.* **2000**, *2*, 211; (e) for a critical discussion of this system, see also: J. A. Marshall, *Chemtracts: Org. Chem.* **2000**, 265.

[8] We achieved quantitative conversion of PhCl to biphenyl when *stoichiometric* palladium was employed in the reaction $2PhCl + Pd(0) \Rightarrow Ph–Ph + PdCl_2$ (cf. ref.[7b]); similarly, we have obtained better than 90% yield of biphenyl using stoichiometric equivalents of water and zinc powder in the presence of a Pd/C catalyst (cf. ref.[7d]). Both of these options, however, were impractical for large-scale synthesis.

[9] S. Mukhopadhyay, G. Rothenberg, D. Gitis, M. Baidossi, D. E. Ponde, Y. Sasson, *J. Chem. Soc., Perkin Trans. 2* **2000**, 1809.

[10] (a) R. Ohnishi, W.-L. Wang, M. Ichikawa, *Appl. Catal. (A)* **1994**, *113*, 29; (b) for a review, see: H. Van Bekkum, H. Roeper, F. Voragen, *Carbohydr. Org. Raw Ma-*

ter. III Workshop, Verlag Chemie: Weinheim, 1996, pp. 37–65.

[11] In fact, this same combination of Pd, Pt and Bi on activated carbon was employed also for the elective oxidation of glucose to gluconic acid, cf. K. Deller, B. Despeyroux, in *Catalysis of Organic Reactions* (W.E. Pascoe, Ed.), Marcel Dekker: New York, NY, 1992; pp. 261–265; see also K. Deller, H. Krause, E. Peldszus, B. Despeyroux, *German Patent* DE 3823301, 1989 (to Degussa AG).

[12] N. Korte, L. Liang, R. Muftikian, C. Grittini, Q. Fernando, *Platinum Metals Rev.* **1997**, *41*, 2.

[13] O. Levenspiel, *Chemical Reaction Engineering;* 2nd. edn., Wiley: New York, NY, 1972; pp. 238–239.

[14] (a) To ensure that reaction rates were not mass transfer controlled, agitation speed was varied from 400 to 1000 rpm. Above 900 rpm, no increase in conversion was detected. All measurements hence pertain to 950 rpm stirring; (b) for reactions at different PhCl concentrations, xylene was added to make up the volume of the organic phase.

[15] P. Bamfield, P. M. Quan, *Synthesis* **1978**, 537; see also ref.[7].

[16] K. K. Park, C. H. Oh, W.-J. Sim, *J. Org. Chem.* **1995**, *60*, 6202.

[17] Cf. M. Selva, C. A. Marques, P. Tundo, *J. Org. Chem.* **1994**, *59*, 3830.