# Glucose as a Clean and Renewable Reductant in the Pd-Nanoparticle-Catalyzed Reductive Homocoupling of Bromo- and Chloroarenes in Water

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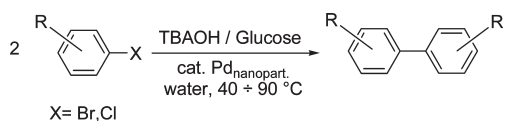
An efficient and highly sustainable Ullmann-type homocoupling of bromo- and chloroarenes, including the more challenging electron-rich chloroarenes (e.g., 4-chloroanisole), catalyzed by in situ generated Pd colloids, is carried out in aqueous medium under relatively mild conditions (temperatures ranging from 40 to 90 °C). Glucose is used as a clean and renewable reductant, while tetrabutylammonium hydroxide (TBAOH) acts as base, surfactant, and phase-transfer agent, creating a favorable environment for the catalyst. Pd nanoparticle sizes, morphology, and chemical composition are ascertained by TEM and XPS analyses.

In the past decade, the biaryl scaffold has received increased attention as a privileged structure by the agrochemical and pharmaceutical industries.[1] The core of many types of natural products,[2] advanced materials,[3] polymers,[4] sensors,[5] and ligands for asymmetric catalysis[6] contains the biaryl moiety. Consequently, the development of new and efficient methods of synthesizing these structures is crucial to the work of a broad area of organic chemistry.

Besides the classic general Ullmann,[7] Suzuki,[8] and Stille[9] coupling reactions, the Pd-catalyzed reductive coupling of haloarenes has gained great attention as a useful route to the formation of aryl—aryl bonds. This simple method for preparing symmetrical biaryls is of ongoing interest, as it prevents the use of stoichiometric amounts of expensive or moisture-sensitive organometallic compounds (i.e., boronic acids, stannanes, Grignard reagents, etc.).

This approach may be particularly attractive for industrial applications provided that it can be carried out in eco-friendly solvents, employing cheap and renewable raw materials. From this standpoint, of special interest is the use of chloroarenes as substrates, safe and clean reducing agents, and water as the most desirable green solvent. In addition to that, the use of metal nanoparticles as catalyst is gaining interest due to the enhanced ability of colloids to transfer electrons because of the large surface area-to-volume ratio.[10]

As part of our ongoing program aimed at finding new eco-efficient synthetic solutions,[10a,11] we were attempting to develop a highly sustainable catalyst system to perform the reductive coupling of aryl chlorides in water by replacing the most commonly used reductants, Zn powder, formate salts, and hydrogen gas, with safer and cleaner reducing agents. Among these, sugars were thought to be suitable candidates because they are cheap, inexhaustible base chemicals and highly soluble in water.

Although several reductive aryl—aryl coupling protocols have been studied in water,[10b,12] no examples have been reported on the use of sugars as stoichiometric reductants. Among several monosaccharides, we focused our attention particularly on glucose, which is known to reduce many metals in colloidal form smoothly.[13]

Our investigations started by checking the ability of glucose to generate catalytically active Pd nanoparticles (Pd-NPs) in situ. To this end, a series of model reductive

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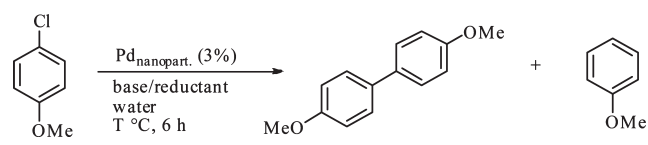
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TABLE 1. Optimization of the Reaction Conditions in the Pd Colloid-Catalyzed Reductive Homocoupling of 4-Chloroanisole in Water[a]

run	reductant	base	T [°C]	conv[b] (%)	selectivity[c]
1	glucose	TBAOH	40	35	88
2	glucose	TBAOH	60	45	89
3	glucose	TBAOH	90	92	93
4	glucose	TBAOH	110	91	90
5	glucose[d]	TBAOH	90	93	96
6	glucose[e]	TBAOH	90	93	50
7	glucose	KOH	90	< 1	
8	glucose	KOH[f]	90	16	62
9	glucose	K$_2$CO$_3$[f]	90	15	66
10	glucose	NaHCO$_3$[f]	90	32	75
11	glucose	Et$_4$NHCO$_3$	90	15	80
12	glucose	TBAOH[g]	90	20	90
13	fructose	TBAOH	90	56	68
14	HCOONa	TBAOH	90	> 99	27
15	propanal	TBAOH	90	13	23
16	hydroquinone	TBAOH	90	7	30
17	Zn powder	TBAOH	90	33	39
18	NaBH$_4$	TBAOH	90	39	5
19	glyceraldehyde	TBAOH	90	66	83
20	ascorbic acid	TBAOH	90	96	95

[a]Reaction conditions: 4-chloroanisole (0.5 mmol), reductant (0.5 mmol), base (1.5 mmol), and Pd acetate (3 mol %) in 1 mL of H$_2$O, heated under stirring for 6 h. [b]Conversions based on GLC areas by using biphenyl as external standard. [c]Percentage of the coupling with respect to the reduction product. In some cases, small percentages (< 2%) of the regioisomeric homocoupling product 3,4′ were also observed. [d]With 0.25 mmol of glucose. [e]With 1 mmol of glucose. [f]In the presence of 1.5 mmol of di-Bu$_4$NBr as PTC. [g]In the presence of 1.5 mmol of KBr.
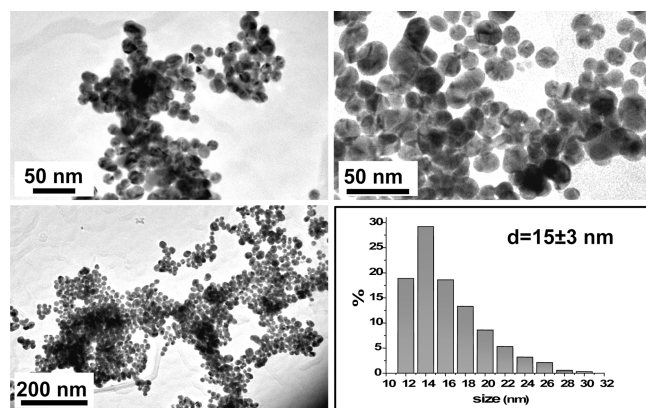
FIGURE 1. TEM pictures and core diameter distribution of Pd-NPs chemically synthesized in aqueous solution in the presence of glucose and tetrabutylammonium hydroxide.

couplings of 4-chloroanisole were carried out under varied conditions in terms of temperature, base, and additive (Table 1). At the same time, the reaction mixture was analyzed by the transmission electron microscopy technique to ascertain both NP core morphology and size dispersion. Colloidal Pd-NPs shape was almost spherical, and nanoparticles showed an appreciable dimensional homogeneity with a mean core diameter of 15 ± 3 nm and a slightly tailed size distribution (see Figure 1 for typical TEM pictures and quantitative core size information).
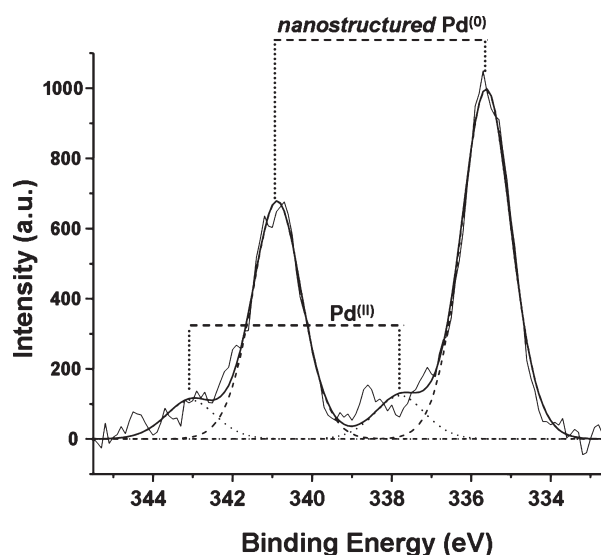
FIGURE 2. Pd 3d XP spectrum of Pd-NPs chemically synthesized in aqueous solution in the presence of glucose and tetrabutylammonium hydroxide. Before XPS analysis, the colloidal suspension was deposited on an inert Pt substrate. BE(Pd3d$_{5/2}$) values for nano-Pd(0) and Pd(II) were obtained via curve fitting and were, respectively, equal to 335.6 ± 0.2 and 337.8 ± 0.2 eV.

The surface chemical composition of Pd nanocolloids was assessed by means of X-ray photoelectron spectroscopy (XPS). The main palladium XP signal, the Pd3d high resolution region, is reported in Figure 2. Two doublets, corresponding to two chemical states, were detected on the NP surface, namely nanostructured Pd(0)[14] and Pd(II) oxide and/or hydroxides.[15]

The oxidized palladium species always showed a low relative abundance (10 ± 4% in the case reported in Figure 2). The presence of this chemical environment can probably be interpreted in terms of air-oxidation induced by the ex situ characterization of Pd-NPs, although we cannot exclude that residual Pd(II) ions derived from the NPs precursors have formed traces of oxide/hydroxide species in the basic colloidal suspension.

To avoid use of organic cosolvents, a phase-transfer agent (PTC) was exploited to facilitate solvation of the aryl halide in neat water. In line with our previous findings,[11a] the PTC was properly chosen among the quaternary ammonium salts by virtue of their ability to stabilize colloids. Because a base was necessary, we decided to use tetrabutylammonium hydroxide (TBAOH).

Preliminary experiments showed that conversions of the chloroarene increased with temperature until a plateau was reached at 90 °C, while selectivity remained roughly constant throughout the reaction (Table 1, runs 1−4).

Interestingly, due to the capacity of glucose to release many reducing equivalents, the coupling was found to be complete with a half-equimolar amount of reductant (0.25 mmol), obtaining simultaneously almost complete

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selectivity (Table 1, run 5). On the contrary, with an excess of glucose (twice the equimolar amount with respect to the chloroarene), selectivity toward the homocoupling product was lowered drastically (Table 1, run 6).

To date, the reduction mechanism of palladium with glucose has not been thoroughly investigated. It is known that under alkaline conditions the initial step should be the formation of gluconic acid and then, the gluconate.[13a]

However, it is known also that under heating at 100 °C a complete alkaline degradation of glucose can occur in only 30 min, leading, via the enediol intermediate, to a number of byproducts with shorter chains.[16] Among them, formic acid, lactic acid, and glyconic acid are the most abundant, some of which can act as reducing agents for palladium. This is the rationale for using less than equimolar amounts of glucose.

Next, the effect of other bases and the role of TBAOH were examined more deeply. To this end, both inorganic carbonates and hydroxides were used in place of TBAOH, adding to the reaction mixture Bu₄NBr as phase-transfer agent. All of them gave disappointing results (Table 1, runs 7−10).

At the same time, low conversions were also observed when other tetraalkylammonium bases (Table 1, run 11) were employed or when the same TBAOH was used but in the presence of KBr as an additive (Table 1, run 12).

These results clearly demonstrate that TBAOH plays a special role in creating a favorable environment for the catalyst. Indeed, into the emulsioned mixture generated by the surfactant, reactions presumably occur into the special layer surrounding the nanoparticles surface, which contains the organic species, Bu₄N⁺ cations, and the anionic counterpart. Under these conditions, in the presence of TBAOH as the sole surfactant, a high concentration of the base OH⁻ should be reached on the colloidal surface, with a corresponding increase of the reaction rate. Otherwise, the presence of other anions, such as, for example, the Br⁻ ions arising from additives or other PTCs, should decrease the [OH⁻] in close proximity to the active catalyst sites, lowering the catalyst performances. Moreover, besides the role of base, OH⁻ chemisorbed[13a] on the nanoparticles surface is expected to increase the electron density on palladium in so much that the less reactive electron-rich chloroarenes can also be coupled.[17] Preliminary investigations were completed by comparing, under the same reaction conditions, the performances of glucose with those of the most common reductants used in this process (Table 1, runs 13−20): ascorbic acid was the sole reagent capable of providing yields and selectivity comparable with those of glucose (Table 1, run 20).[12d]

Having established the optimal reaction conditions (glucose/chloroarene 1:2 molar ratio, Pd source 3 mol % and TBAOH 3 equiv with respect to chloroarene), the protocol was extended to other aryl chlorides and bromides to verify scope and limitations of the method (Table 2).

Notably, the results showed that this catalyst system proved to be so active that bromoarenes, such as bromobenzene, 4-bromotoluene, 4-bromoanisole, and the heteroaryl 3-bromothiophene, were coupled in excellent yields under

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TABLE 2. Pd-Catalyzed Homocoupling of Aryl Halides Promoted by Glucose in Water[a]

Run	Aryl halide	T (°C)	Product	Yields (%)[b]
1	Ph−Br	40	biphenyl	85
2	Me−C₆H₄−Br	40	Me−biphenyl−Me	83
3	MeO−C₆H₄−Br	40	MeO−biphenyl−OMe	82
4	thiophene−Br	40	bithiophene	86
5	2-Me−C₆H₄−Br	60	2,2′-dimethylbiphenyl	73
6	F₃C−C₆H₄−Cl	60	F₃C−biphenyl−CF₃	94
7[c]	NC−C₆H₄−Cl	60	NC−biphenyl−CN	80[d]
8	Ph−Cl	60	biphenyl	95
9	F−C₆H₄−Cl	60	F−biphenyl−F	95
10	naphthyl−Cl	60	binaphthyl	80
11[c]	Ac−C₆H₄−Cl	90	Ac−biphenyl−Ac	88[e]
12	Me−C₆H₄−Cl	90	Me−biphenyl−Me	79
13	MeO−C₆H₄−Cl	90	MeO−biphenyl−OMe	83

[a]Reaction conditions: haloarene (0.5 mmol), glucose (0.25 mmol), TBAOH (1.5 mmol), and Pd acetate (3 mol %) in 1 mL of H₂O, heated under stirring for 6 h. [b]Isolated yields. Selectivity of the coupling vs the reduction product is higher than 95%. [c]Tetrabutylammonium acetate in 0.1 mL of water was used as base instead of the TBAOH aqueous solution. [d]A GLC 15% of benzonitrile was detected. [e]A GLC 13% of acetophenone was detected.

extremely mild conditions (*T* = 40 °C, Table 2, runs 1−4), with the exception of 2-bromotoluene which required the slightly higher temperature of 60 °C (Table 2, run 5).

Instead, the reaction conditions suitable to couple chloroarenes were found to be dependent on the nature of the substituent on the aromatic ring. In particular, neutral and electron-poor chloroarenes were reacted smoothly at 60 °C (Table 2, runs 6−10) and the electron-rich chloroarenes required the minimum temperature of 90 °C (Table 2, runs

12−13), while for substrates bearing functional groups susceptible to the extreme basic conditions, such as 4-chlorobenzonitrile and 4-chloroacetophenone, the replacement of TBAOH with a weaker base such as tetrabutylammonium acetate (TBAA) was necessary (Table 2, runs 7, 11).

It is worth mentioning that all of the reactions in Table 2 occurred, with few exceptions (Table 2, runs 7 and 11), with a selectivity higher than 95% toward the coupling product with respect to the reduction product.

To further verify the sustainability of our method, we checked the feasibility of the catalyst recycling. To this end, we decided to work on a larger scale by processing 10 mmol of aryl halide (chlorobenzene). After completion of the reaction, the coupling product was extracted with cyclohexane, and fresh reagents were added to the reaction mixture for the next run. Results[18] showed that the aqueous catalyst solution was active for 3 runs, after which yields dropped drastically. This clearly indicates that during the workup operations nanoparticles undergo a rapid aggregation that causes the loss of activity. Work aimed at anchoring colloids on a solid support to improve the catalyst robustness is in progress.

In conclusion, homocoupling of bromo- and chloroarenes under moderate conditions can be achieved in water in the presence of Pd colloids generated in situ by glucose as reductant. This method proved to be highly efficient and green for the following reasons: (i) the use of a green a renewable reagent such as glucose provides a great advantage in terms of safety, economy, and sustainability, (ii) more challenging substrates, including the less reactive electron-rich chloroarenes (e.g., 4-chloroanisole), are activated without use of special additives or ligands under relatively mild conditions (reaction temperatures ranging from 40 to 90 °C), and (iii)

the combined activating and stabilizing effects of both glucose and TBAOH provide a favorable environment for the catalyst.

To the best of our knowledge, this is the first example of using glucose as reagent in the biaryl homocoupling of aryl halides. A comparison with the literature data on the reductive coupling in water[12] shows how this method can compete with the most efficient known protocols, and we anticipate that it will find wide applicability due to its simple operating procedure.

Experimental Section

General Procedure for the Reductive Homocoupling in Water. In a 1 mL gastight vial, equipped with a screw cap and a magnetic bar, were placed chloroarene (0.5 mmol), glucose (0.25 mmol), TBAOH (1.5 mmol), and Pd acetate (3 mol %). For a better reproducibility of experiments, the use of a gastight vial having a proper capacity (leaving a very small head space) to avoid the formation of droplets of the reaction mixture on the walls of vial is recommended. The flask was heated under air and under stirring at the reaction temperature for a maximum of 6 h (see Tables 1 and 2). The reaction mixture was washed with HCl 5% and extracted with dichloromethane. To the organic phase was added a known amount of an external standard (in almost all cases biphenyl), and the mixture was examined by GLC and GC−MS, providing both conversion and product identification by comparison with spectral data reported in the literature. Isolated yields in Table 2 were determined by purification of the extracted dichloromethane solutions after evaporation of the solvent in vacuo with a short pad of silica gel (eluent: petroleum ether).

Supporting Information Available: Experimental details and spectroscopic XPS and NMR data for colloids and the coupling products, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Results on the recycling experiments of the aqueous catalyst solution in the honocoupling of chlorobenzene(10 mmol) are summarized below. Experimental details on the recycling tests are given in the Supporting Information.

run	first recycle	second recycle	third recycle	fourth recycle
yield (%)	94	91	62	21