

Articles

Highly Chemoselective Heterogeneous Pd-Catalyzed Biaryl Synthesis from Haloarenes: Reaction in an Oil-in-Water Microemulsion

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Abstract:

Heterogeneous Pd/C-catalyzed reductive coupling of substituted haloarenes to the respective biaryls is effected with very high chemoselectivity in an oil-in-water microemulsion, using a reducing agent such as formate and a base, NaOH, in the presence of a catalytic amount of tetrabutylammonium bromide (TBAB) at 75 °C. Almost 100% biphenyl selectivity is obtained with iodobenzene. High coupling yields are achieved with 4-chlorotoluene and 4-chlorobenzaldehyde as the substrate. The competitive reduction reaction becomes predominant when the water-in-oil microemulsion is used as the solvent medium.

Introduction

Besides stoichiometric classic Ullman,^{1a,b} Suzuki,^{1c–e} and Stille^{1f} coupling reactions, the selective Pd-catalyzed reductive coupling reaction² of haloarenes to biaryls has attracted the attention of process chemists, as it is a precursor of

numerous agrochemicals and pharmaceuticals.³ The selectivity is usually low due to the parallel reduction⁴ reaction. However, the reductive coupling of haloarenes benefits from simple reactor design, easy catalyst separation, and recycling. The reaction has been carried out in different solvent media⁵ such as water,^{5a–d} DMF,^{5e} methanol,^{5f} and acetic acid^{5g} in the presence of formate salts,^{5a} hydrogen gas,^{5b} or zinc^{5c,h,i} as the reducing agent, a base, and catalytic amount of phase transfer catalyst (PTC). Regardless, water is the best solvent for this process scheme. The PTC has a remarkable effect on the selectivity of these processes.

It has recently been shown that the coupling selectivity can be improved by administering the PTC on a carbon support,⁶ which is presumed to be modifying the micro-environment around the catalyst surface and, thus, increasing the rate of reaction and biaryl selectivity. However, we considered it useful to modulate the system using micro-emulsions⁷ as the reaction media. This turned out to be an exciting finding in terms of chemoselectivity.

Here, we present the results and discuss how the micro-structure in a microemulsion could turn the reaction chemoselectively towards the coupling side. One-phase isotropic microstructured systems have been used before as micro-reactors in chemical as well as enzymatic reactions.^{7a–e} Noteworthy, Davydov and Beletskaya have reported the use

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Table 1. Coupling reaction of haloaryls in microemulsion^a

entry	microemulsion	haloaryl	t, h	conv. %	sel.% Ar–Ar	sel.% ArH
1	O/W	ArCl	5.5	100	92	8
2	O/W	ArBr	3.5	100	94	6
3	O/W	ArI	3.5	100	98	2
4	O/W	CT ^b	6	83	89	11 ^c
5	O/W	CB ^d	5	92	92	8
6 ^e	O/W	ArCl	22	92	53	47
7	W/O	ArCl	5.5	100	31	69
8	none ^f	ArCl	4	100	54	46

^a Reaction conditions: haloaryls, 0.013 mol; 5% Pd/C, 1 g; TBAB, 1 g.; sodium formate, 1.5 g; NaOH, 1.5 g; temperature, 75 °C. ^b CT is 4-chlorotoluene. ^c Toluene. ^d CB is 4-chlorobenzaldehyde. ^e No TBAB is used. ^f Water is used as the solvent.

of a basic water–butanol emulsion^{7f,g} in the presence of sodium dodecyl sulfate as an emulsifier and a homogeneous Pd complex as the catalyst, for the low-yield (30–50%) homocoupling of aryl iodides and bromides.^{7f} However, to the best of our knowledge, this is the first example of a chemoselective reductive coupling reaction of haloaryls in a solid (Pd/C catalyst) and microemulsion^{7h} two-phase system, where the two competitive reactions, reduction and coupling, become entirely one way, depending on the microstructure (W/O or O/W).

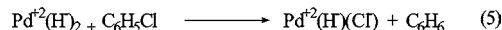
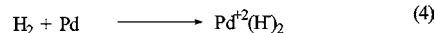
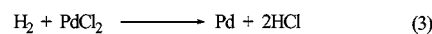
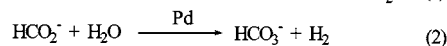
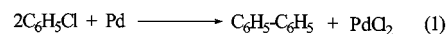
Results and Discussion

In a typical reaction, 1 g of 5% Pd/C was mixed with the oil-in water (O/W) microemulsion in a 100 mL glass reactor (see Experimental Section). The mixture was heated to 75 °C. The reaction mixture was stirred for 5–7 h, depending on the reaction conditions at that temperature. Following the reaction, the reactor was cooled to room temperature, and the solution was analyzed by GC.

Exceptional yields for the coupling products were obtained using various substrates, as shown in Table 1, entries 1–5. For iodobenzene, the selectivity was almost 98%. With bromobenzene as the substrate, 94% selectivity to biphenyl was achieved. Excellent coupling selectivity (89%) was achieved with 4-chlorotoluene, whilst 92% selectivity to the coupling products was obtained with both 4-chlorobenzaldehyde and chlorobenzene as the substrate. This is the best selectivity ever reported on these substrates in a liquid-phase heterogeneous Pd-catalyzed reductive coupling reaction. In all cases, except for a few percent reduction product, no other byproducts were observed. Chlorobenzene (ArCl) was chosen as the model compound for further process studies.

When the reaction was executed in an O/W microemulsion (see Experimental Section) with varied Pd amounts, the

Scheme 1. Proposed mechanism for the coupling



selectivity to biphenyl was increased from 73 to 92%, with an increase in 5% Pd/C amount from 0.75 to 1.0 g. A further increase to 2.6 g was not advantageous for this reaction.

The temperature also has a governing role on both rate of reaction and on the biphenyl selectivity. Generally, the rate increased with an increase in temperature from 65 to 75 °C as well as the selectivity from 83 to 92%. A further increase in temperature to 85 °C did not help in terms of selectivity. Therefore, all subsequent reactions were performed at 75 °C.

Performing the reaction in an O/W microemulsion without adding PTC (tetrabutylammonium bromide, TBAB), only 53% selectivity to the coupling product at 92% chlorobenzene conversion was achieved in 22 h (Table 1, entry 6). When the amount of PTC was increased from 0 to 1 g, the selectivity to biphenyl increased from 53 to 92%.

Conversely, changing the microstructure from O/W to W/O or using no microemulsion changes the path of the reaction selectively to the reduction side (Table 1, entries 1, 7–8). It is surprising that the W/O microemulsion is not helpful for biphenyl selectivity and in fact leads to a higher benzene selectivity.

However, it is realized that when NaOH, PTC, and Pd catalyst are all together present in the O/W microemulsion media, the rate and selectivity accomplished are the highest under the reaction conditions. The solid Pd/C catalyst can be recycled without losing any catalytic activity. Also, the microemulsion once formed is stable for at least two months at room temperature.

Unlike homogeneous Pd-catalyzed coupling reactions,^{2q–s} the mechanism of the heterogeneous Pd-catalyzed reactions is not yet understood. In fact, we previously proposed a mechanism^{5a,8} for the reductive coupling of halobenzenes to biphenyls. The basic reactions are depicted by eqs 1–5 in Scheme 1. The basic difference between the reductive coupling and the reduction is that the homocoupling requires only electrons, whilst reduction requires hydrogen atoms. As has been proposed before,^{5a} the selectivity to the coupling products depends on the number of vacant active Pd⁰ sites, which in turn reflects the balance between the reduction of Pd²⁺ (eq 3), and the formation of Pd²⁺(H⁻)₂ via eq 4. The latter reaction is a function of the available dihydrogen concentration on the active site. Obviously, with an increase in the amount of Pd the number of Pd⁰ active sites is increasing, and thus, an enhanced selectivity is attained.

The other experimental results obtained could be explained if we realize how the reactions shown in eqs 4 and

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5 were suppressed to give a higher selectivity to biphenyl. This could apparently be due to lower hydride formation rate on the Pd surface. The phenomenon of enhanced selectivity obtained in an oil-in-water microemulsion could be due to the following: (a) PTC microencapsulation^{6,9} of the Pd surface prior to the contact of the oil phase with the solid Pd surface in case of an oil-in-water microemulsion and (b) or the lower rate of formate adsorption on the Pd surface which is essentially the source of H₂.

The low selectivity obtained in water-in-oil microemulsion is not understood; however, it is realized that under these conditions the rate of reactions written in eqs 4 and 5 are increased. Solubility or distribution of PTC in this system, though not clear, might have influenced the observed selectivity.

Conclusions

In summary, biaryls are chemoselectively synthesized for the first time in very high yield by the heterogeneous Pd-catalyzed reductive homocoupling of aryl halides in the presence of TBAB, formate salt, and NaOH at 75 °C in an O/W microemulsion. In the case of a reverse microstructure, the reduction reaction of haloaryls to arenes becomes predominant. The chemoselectivity has thus shifted to the reduction side. This work shows that many industrially important substituted biaryls may be amenable to synthesis in very high yields by simply modifying the solvent assemblage.

Experimental Section

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 (>99% 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 those of previously isolated reference samples in our laboratory.

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Preparation of Oil-in-Water Microemulsion(O/W). In a round-bottom flask 1.5 g (0.013 mol) of chlorobenzene, 3.125 g of dodecane, and 3.125 g of ethyl alcohol were mixed and stirred for 15 min to make the oil phase. In another round-bottom flask 18.75 g of water, 1.5 g of sodium formate, 1.5 g of NaOH, 1 g of TBAB, 18.75 g of propylene glycol, and 6.25 g of surfactant (Brij 96V) were mixed, and the contents were stirred for 30 min at room temperature. The contents of the first round-bottom flask were then poured into the second flask and stirred for another 30 min. Thus, a clear and transparent O/W microemulsion was obtained, which was then transferred to the reactor for the coupling reaction.

Preparation of Water-in-Oil Microemulsion(W/O). The procedure for W/O microemulsion preparation was the same as described above; however, the composition of the phases was different. Thus, the water phase contained 8.75 g of deionized water, 1.5 g of NaOH, 1.5 g of sodium formate, 1 g of TBAB (phase-transfer catalyst), 8.75 g of propylene glycol, and 18.75 g of Brij 96V (the surfactant). The oil phase contained 9.375 g of dodecane, 9.375 g of ethyl alcohol, and 1.5 g of chlorobenzene.

General Procedure for Coupling of Haloarenes. In a 100 mL glass reactor equipped with a reflux condenser, the oil-in-water microemulsion and 1.0 g of 5% Pd/C (3.6 mol %) were added, and the mixture was then heated to 75 °C. The reaction mixture was stirred for 5–7 h, depending on the reaction conditions at that temperature. Following the reaction, the reactor was cooled to room temperature, and the solution was analyzed by GC, and the products were identified by MS and ¹H NMR.

Scale-Up Reaction. A 10 times larger batch size was tried using the best conditions described above. A 100% conversion of chlorobenzene with 87% selectivity to biphenyl was obtained after 7 h of reaction. The isolated yield of biphenyl was 81%.

Acknowledgment

We thank Mr. Larry Chan and Dr. Frank Ling of UC Berkeley for their critical comments on this manuscript.

Received for review November 15, 2002.

OP020094S