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Palladium catalyzed alkynylation of aryl halides (Sonogashira reaction) in water

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Abstract—The palladium catalyzed alkynylation of aryl halides (Sonogashira reaction) has been achieved in pure water without any additives or phase transfer catalysts. The reaction, which requires only 0.5 mol% of $Pd(PPh_3)_4$ catalyst, is remarkably fast (30 min at 70 °C) producing high yields of the aryl alkyne products.

The palladium catalyzed coupling of vinyl or aryl halides with terminal acetylenes (the Sonogashira reaction) is a powerful synthetic tool for the preparation of substituted acetylenes.[1] The reaction which normally requires a co-catalyst such as CuI has found widespread application in natural product synthesis, organic materials science and in the construction of various functional macromolecules including dendrimers and conducting polymers.[2] Several modifications of the original Sonogashira protocol have been developed during the last few years, prominent among which are the phase transfer[3] and copper-free conditions,[4] and the use of more active catalyst systems, including those having *N*-heterocyclic carbene (NHC) ligands for reaction with the less reactive bromo- and chloroarenes.[5] The effect of different solvents has also been probed[6] including aqueous–organic solvent mixtures in the presence of water soluble phosphine ligands[7] and ionic liquids.[8]

Driven by environmental concerns, in recent years, much attention has been paid towards using water as solvent for organic and organometallic reactions.[9] Apart from being cheap, safe and environmentally benign, water has a high dielectric constant and density so that reactions involving water insoluble substrates when carried out in water often benefit from the hydrophobic effect[9a] resulting in faster and cleaner reactions. Contrary to earlier belief, a number of Pd-catalyzed reactions have been successfully carried out in pure water, some of which even showed rate accelerating effects. Although there are a few reports of Sonogashira couplings in aqueous–organic solvent mixtures using Pd-catalysts ligated with water soluble sulfonated phosphines,[7] there are no reports on Sonogashira reactions being carried out in pure water.[10] A recent paper, however, has described the alkynyl coupling and subsequent cyclization of *ortho*-iodophenols to benzofurans in water,[11] perhaps aided by the enhanced solubility of the phenolic substrates in water in the presence of base. In continuation of our interest in aqueous Pd-catalyzed reactions,[12] we now report that Sonogashira reactions of aryl iodides and bromides can indeed be carried out in pure water without the need of any organic co-solvent or additives such as phase transfer catalysts or water soluble phosphine ligands.

Initial screening of the reaction conditions using iodobenzene and phenyl acetylene as the coupling partners revealed that $Pd(PPh_3)_4$ was the best catalyst for this reaction. Only 0.5 mol% of this catalyst was sufficient to induce the coupling reaction. $PdCl_2(PPh_3)_2$ was less effective in this regard whereas $PdCl_2$ did not produce any coupling product at all. Various bases, for example, Et_3N, DIEA or even aqueous ammonia can be used in this reaction. However, the reaction is much cleaner in the presence of the former two organic bases, of which we chose DIEA for its low volatility. The reaction rate was found to be temperature dependent. While it took 2.5 h for completion at room temperature (90% yield

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Keywords: Sonogashira reaction; Palladium; Water; Aryl halides; Alkynylation.

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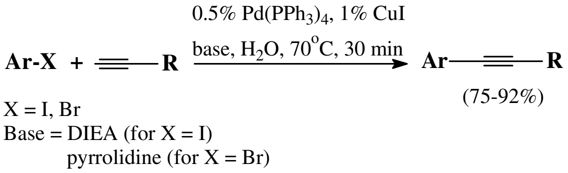


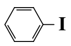
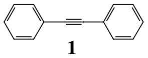
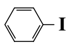
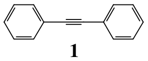
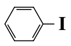
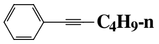
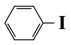
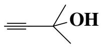
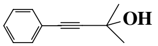
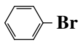
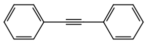
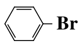
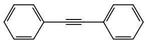
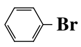
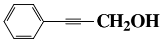
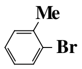
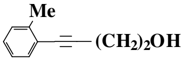
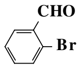
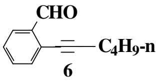
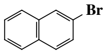
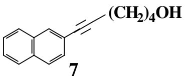
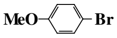
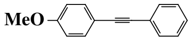
Scheme 1. Sonogashira reaction of aryl halides in water.

of diphenyl acetylene **1**), the reaction time can be shortened (20–30 min) by raising the reaction temperature to 70 °C without any compromise in product yield. At this temperature, the reaction is so facile that it does not even require strict adherence to anaerobic conditions.

The reaction is truly heterogeneous since two distinct layers could be observed throughout the course of the reaction. Hence, hydrophobic effects[9a] appear to be quite pronounced in this reaction and could be the major contributing factor to its facile reaction rate. Notably, the addition of an organic co-solvent such as DMF (DMF/H_2O 9:1) greatly retarded the rate of the reaction and led to the appearance of side products as detected by TLC analysis. Under the optimized conditions [0.5% $Pd(PPh_3)_4$, 1% CuI, DIEA (1.5 equiv), H_2O, 70 °C, 30 min] (Scheme 1), a number of terminal acetylenes reacted with iodobenzene to produce excellent yields of the substituted phenyl acetylene derivatives (Table 1, entries 1, 3 and 4). Interestingly, the coupling reaction between iodobenzene and phenyl acetylene can also be carried out without CuI. However, this resulted in a reduced product yield (entry 2). It is worthy of note that 1-hexyne, a water insoluble and less reactive acetylene, reacted efficiently under these conditions to produce the coupling product **2** in an excellent yield (entry 3).

However, the reaction of bromobenzene with phenyl acetylene under the above conditions was not efficient and afforded only an 18% yield of diphenyl acetylene even after 3 h at 70 °C (Table 1, entry 5). Since bromoarenes are cheaper and more readily available than iodoarenes and hence are synthetically more useful as educts, we explored a variety of reaction conditions in order to induce bromobenzene into this coupling manifold. Increased catalyst loading (up to 5 mol%), higher reaction temperatures (reflux) or the use of excess phenyl acetylene did not lead to any significant improve-

Table 1. Sonogashira reaction of aryl halides in water (Scheme 1)

Entry	ArX	Acetylene	Base[a]	Product	Yield (%)
1		$\equiv$—Ph	A	 **1**	92
2		$\equiv$—Ph	A	 **1**	62[b]
3		$\equiv$—C_4H_9-n	A	 **2**	87
4			A	 **3**	88
5		$\equiv$—Ph	A	 **1**	18[c]
6		$\equiv$—Ph	B	 **1**	82
7		$\equiv$—CH_2OH	B	 **4**	80
8		$\equiv$—$(CH_2)_2OH$	B	 **5**	75
9		$\equiv$—C_4H_9-n	B	 **6**	85
10		$\equiv$—$(CH_2)_4OH$	B	 **7**	80
11		$\equiv$—Ph	B	 **8**	20[c]

[a] A: diisopropylethylamine, B: pyrrolidine.

[b] Without CuI.

[c] At 70 °C for 3 h.

ment in the coupling yield. Addition of a cationic surfactant such as cetyltrimethylammonium bromide (20 mol%) to the reaction mixture did not show any beneficial effect.[10b,c] However, by changing the base to pyrrolidine,[6a] bromobenzene could be smoothly coupled with phenyl acetylene resulting in a high yield of diphenyl acetylene **1** (82%, entry 6). Under these modified conditions, a number of different bromoarenes and terminal acetylenes reacted smoothly to produce the coupling products **4–7** in high yields (entries 7–10). Apparently, there is not much of a steric effect in these reactions since *o*-bromotoluene easily coupled with homopropargylic alcohol to produce the corresponding coupling product **5** in 75% yield (entry 8). The reaction also showed excellent functional group tolerance as evident from the successful coupling of *o*-bromobenzaldehyde with 1-hexyne to give **6** in high yield (entry 9). This particular result is quite significant since aqueous organometallic reactions of aldehyde bearing educts are usually problematic due to the competing Cannizaro reaction of such substrates in water.[10a] However, with a highly electron rich substrate such as *p*-bromoanisole, only a 20% yield of the coupling product **8** could be isolated after 3 h at 70 °C (entry 11). Apart from unreacted starting materials, no other side products (Glaser-type homocoupling products) could be detected in these reactions. Evidently, as observed by others,[13] the strong electron donating effect of the *p*-OMe group greatly retarded the rate of this reaction.

In conclusion, we have shown that Sonogashira reactions of water insoluble aryl iodides and bromides can be carried out in water alone with as low as 0.5 mol% of $Pd(PPh_3)_4$ as the catalyst. The reaction is facile at 70 °C requiring only 30 min for completion and produced high to excellent yields of the coupling products. We have also shown that steric effects are minimum in these reactions and sensitive functionalities like an aldehyde group can be tolerated. The choice of the base is crucial, especially in the case of aryl bromides.

Representative experimental procedure: A round bottom flask fitted with a reflux condenser was charged with the aryl halide (1.0 mmol), terminal acetylene (1.5–2 mmol), DIEA (for aryl iodides) or pyrrolidine (for aryl bromides) (1.5 mmol), $Pd(PPh_3)_4$ (0.5 mol%) and CuI (1 mol%) in water (5 mL). It was then immersed in an oil bath kept at 70 °C. After vigorous stirring for 30 min (the reaction darkened in colour), it was cooled to room temperature and extracted with ether. The combined organic layer was dried and the solvent removed under reduced pressure. Silica-gel chromatography of the residue produced the coupling products.[14]

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14. Physical and spectral data of some selected coupling products—**1**: mp 55–56 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ7.32–7.38 (6H, m), 7.51–7.55 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 89.3 (C_q), 123.2 (C_q), 128.2 (CH), 128.3 (CH), 131.5 (CH). **2**: colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (3H, t, $J = 7.2$ Hz), 1.44–1.63 (4H, m), 2.40 (2H, t, $J = 7$ Hz), 7.25–7.30 (3H, m), 7.37–7.40 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 (CH_3), 19.0 (CH_2), 22.0 (CH_2), 30.8 (CH_2), 80.5 (C_q), 90.3 (C_q), 124.0 (C_q), 127.4 (CH), 128.1 (CH), 131.5 (CH). **5**: colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (3H, s), 2.72 (2H, t, $J = 6$ Hz), 3.81 (2H, t, $J = 6$ Hz), 7.04–7.20 (3H, m), 7.37 (1H, d, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6 (CH_3), 23.8 (CH_2), 61.2 (CH_2), 81.2 (C_q), 90.1 (C_q), 123.0 (C_q), 125.4 (CH), 127.8 (CH), 129.3 (CH), 131.8 (CH), 139.9 (C_q). **6**: colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, t, $J = 7$ Hz), 1.45–1.69 (4H, m), 2.49 (2H, t, $J = 6.9$ Hz), 7.35–7.40 (1H, m), 7.50–7.52 (2H, m), 7.88 (1H, d, $J = 7.8$ Hz), 10.5 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5 (CH_3), 19.2 (CH_2), 22.0 (CH_2), 30.5 (CH_2), 76.2 (C_q), 98.1 (C_q), 126.8 (CH), 127.8 (CH), 127.9 (C_q), 133.2 (CH), 133.6 (CH), 135.9 (C_q), 192.2 (CH). **7**: colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65–1.74 (4H, m), 2.23 (1H, s, O*H*), 2.45 (2H, t, $J = 6.6$ Hz), 3.66 (2H, t, $J = 6$ Hz), 7.37–7.45 (3H, m), 7.69–7.76 (3H, m), 7.89 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1 (CH_3), 24.9 (CH_2), 31.7 (CH_2), 62.1 (CH_2), 81.1 (C_q), 90.2 (C_q), 121.0 (C_q), 126.1 (CH), 126.2 (CH), 127.4 (CH), 127.5 (CH), 127.7 (CH), 128.5 (CH), 130.9 (CH), 132.3 (C_q), 132.9 (C_q).