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Palladium–phosphinous acid-catalyzed Sonogashira cross-coupling reactions in water†

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A palladium–phosphinous acid-catalyzed Sonogashira cross-coupling reaction that proceeds in water under air atmosphere in the absence of organic co-solvents has been developed. Disubstituted alkynes have been prepared in up to 91% yield by POPd-catalyzed coupling of various aryl halides including chlorides in the presence of tetrabutylammonium bromide and pyrrolidine or NaOH.

Palladium-catalyzed Suzuki, Stille, Hiyama, Negishi, Buchwald–Hartwig, Kumada and Heck coupling reactions are among the most powerful carbon–carbon bond forming reactions.[1] The recent development of highly active palladium complexes bearing bulky, electron-rich phosphane ligands has allowed chemists to extend these methods from reactive substrates such as aryl iodides, bromides, and triflates, to less reactive but inexpensive and readily available chlorides.[2] Because of the instability of most catalysts and coupling reagents, cross-coupling reactions are usually carried out in polar organic solvents under inert and anhydrous conditions. However, from an environmental and economic standpoint, it is desirable to avoid any use of hazardous and expensive organic solvents. Water or aqueous solutions have been recognized as a very attractive medium for organic reactions because solvents do not have to be dried prior to use, and products can easily be isolated after completion of the reaction by extraction which greatly facilitates operation.[3] Recent efforts to introduce water into cross-coupling reactions have resulted in aqueous Suzuki,[4] Buchwald–Hartwig,[5] Stille,[6] Hiyama-like,[7] and Heck[8] reactions.[9] Leadbeater recently described a microwave-assisted Suzuki coupling method using palladium acetate in water.[10]

Sonogashira cross-coupling of terminal alkynes with aryl and vinyl halides has attracted increasing attention. A variety of aryl halides including electron-deficient heteroaryl chlorides has been employed in palladium-catalyzed coupling reactions with terminal alkynes to afford versatile precursors for the formation of fused aromatic heterocycles, whereas the coupling of less reactive electron-rich aryl chlorides remains challenging.[11] Typically, the Sonogashira reaction requires inert and anhydrous reaction conditions and only a few studies using water as an additive or co-solvent have been reported. Sub-stoichiometric amounts of water have been found to promote the formation of symmetrical and unsymmetrical bisarylethynylenes in a modified Sonogashira-type coupling reaction.[12] The heterogeneous cross-coupling of aryl iodides and alkynes using Pd-catalysts immobilized on mesoporous silica under aqueous conditions has been reported to suffer from significant leaching.[13] Kotschy and co-workers observed that catalyst leaching can be limited to less than 2% using Pd(0) immobilized on charcoal in CuI-promoted Sonogashira couplings of aryl halides in aqueous dimethyl acetamide.[14] Palladium on carbon has successfully been used to catalyze the arylation of *N*-propargylated amino acids at terminal and nonterminal peptide positions in aqueous DMA.[15] The employment of water-soluble palladium(II) acetate and sulfonated triphenylphosphine in a water–acetonitrile solution enabled Amatore and co-workers to conduct Sonogashira couplings of aryl iodides under homogeneous conditions.[16] It is noteworthy that the presence of water has been found to be essential to the coupling reaction of aryl iodides and various alkynoates when using an amphiphilic polystyrene–poly(ethylene glycol) resin-supported palladium–phosphine complex.[17] Dibowski and co-workers utilized palladium–guanidinophosphane catalysts for the coupling of water-soluble aryl iodides and terminal alkynes under mild and biocompatible aqueous conditions.[18] Their procedure allowed the bioconjugation of peptide derivatives without compromising their native structure and biological activity. A similar strategy has recently been employed in the chemoselective coupling of aryl iodide-functionalized peptides to a trialkyne nucleus under both acidic and basic aqueous conditions.[19]

Recently, palladium–phosphinous acid complexes have been introduced to a variety of C–C bond forming reactions by us and others.[20] We have reported the use of these electron-rich Pd-complexes in Heck, Stille, and Hiyama couplings and also in amination and thiation reactions of aryl chlorides and bromides.[21] We also found that palladium–phosphinous acid complexes exhibit high stability to air and water and afford high yields in Stille coupling reactions in water.[22] Herein, we describe the usefulness of palladium–phosphinous acid complexes $[(t\text{-Bu})_2P(OH)]_2PdCl_2$ (POPd), $[[(t\text{-Bu})_2P(OH)(t\text{-Bu})_2PO)]PdCl]_2$ (POPd1) and $[(t\text{-Bu})_2P(OH)PdCl_2]_2$ (POPd2) in Sonogashira cross-coupling reactions of aryl halides in water (Fig. 1).

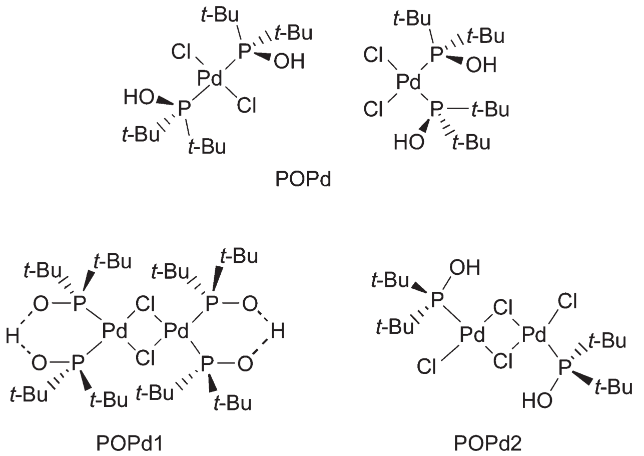

Fig. 1 Structures of POPd, POPd1 and POPd2.

To investigate the feasibility of aqueous Sonogashira coupling, we screened the catalytic performance of POPd, POPd1, and POPd2 in the cross-coupling reaction of 3-bromopyridine, **1**, and phenylacetylene, **2**, in the presence of pyrrolidine and tetrabutylammonium bromide, TBAB, in water under air without any organic co-solvents or surfactant additives (Scheme 1). We did not observe product formation using POPd1 and POPd2 but obtained alkyne **3** in 80% yield with POPd as the catalyst (Table 1,

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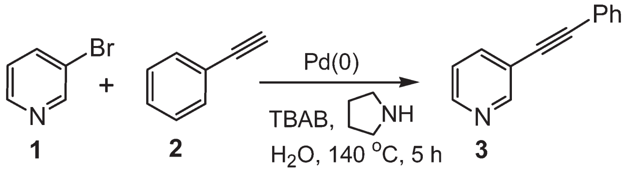
† Electronic supplementary information (ESI) available: Experimental procedures and characterization of Sonogashira coupling products. See http://www.rsc.org/suppdata/ob/b4/b407773c/

DOI: 10.1039/b407773c



Scheme 1 Aqueous Sonogashira coupling of 3-bromopyridine, **1**, and phenylacetylene, **2**.

Table 1 Optimization of the Sonogashira coupling of **1** and **2**

Entry	Catalyst	Base	Additives	Yield (%)^a
1	POPd	pyrrolidine	TBAB	80
2	POPd1	pyrrolidine	TBAB	—^{b}
3	POPd2	pyrrolidine	TBAB	—^{b}
4	POPd	pyrrolidine	TBAB	60^c
5	POPd	pyrrolidine	TBAB	—^{d}
6	POPd	pyrrolidine	none	—^{b}
7	POPd	Cy$_2$NMe	TBAB	10
8	POPd	2,2,6,6-TMP	TBAB	10
9	POPd	NaOAc	TBAB	44
10	POPd	Cs$_2$CO$_3$	TBAB	10
11	POPd	pyrrolidine	TBAB/CuI	90
12	POPd	NaOH	TBAB/CuI	81

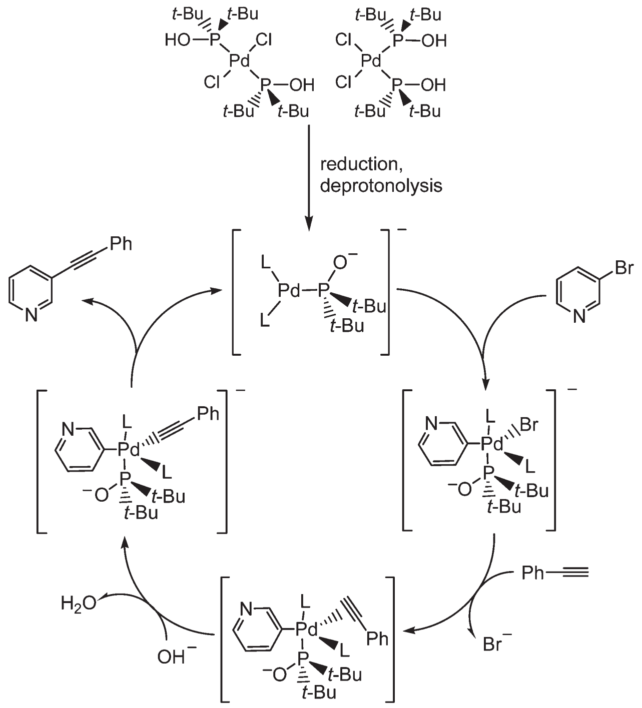
^{a} General reaction conditions: 100 mg of **1**, 2 equivalents of **2**, 10 mol% Pd catalyst, 1.0 equivalent of TBAB in 5 mL of deionized water at 135–140 °C for 5 h in a closed vessel. ^{b} No product formation was observed. ^{c} 1.5 equivalents of **2**. ^{d} Reaction temperature was 100 °C.

entries 1–3). Optimization studies revealed that the coupling reaction requires two equivalents of the terminal alkyne and does not proceed in the absence of TBAB or at lower temperature (Table 1, entries 4–6).

We then decided to screen various organic and inorganic bases. In general, we obtained superior results with pyrrolidine. Replacement of pyrrolidine by *N*-methyldicyclohexylamine (Cy$_2$NMe), 2,2,6,6-tetramethylpiperidine (TMP), sodium acetate or caesium carbonate resulted in significantly decreased yields of **3** (entries 7–10). Employing other additives than TBAB in the reaction mixture is not necessary albeit the yield of **3** further increased to 90% in the presence of 10 mol% of CuI (entry 11). Interestingly, the CuI-promoted POPd-catalyzed Sonogashira coupling of **1** and **2** affords **3** in remarkable 81% yield in 0.5 M sodium hydroxide solution (entry 12).

It is assumed that reduction and deprotonolysis of the palladium phosphinous acid complex results in the formation of a highly active anionic Pd(0) complex that undergoes oxidative addition with aryl halides in water (Scheme 2). Complexation by the terminal acetylene and subsequent deprotonation gives an intermediate complex that generates disubstituted alkynes *via* reductive elimination. Thus, sodium hydroxide or pyrrolidine fulfil two fundamental functions, *i.e.*, activation of the catalyst for oxidative addition and alkyne deprotonation during catalysis.

We applied our optimized coupling procedure to a variety of aryl halides and alkynes to determine the scope of the POPd-catalyzed Sonogashira reaction in water (Table 2). Aryl iodides and bromides were converted to the corresponding alkynes in 70–91% yield (entries 1–5, 9–11). It is noteworthy that nitrile and carbonyl functions are tolerated under the reaction conditions employed in this study. We obtained alkynes **9** and **20** from 2-bromobenzonitrile, **8**, and 3-bromoacetophenone, **19**, in 81% and 70% yield, respectively (entries 4 and 10). As expected, 3-chloropyridine, **16**, affords lower yields than its bromo derivative **1** (entries 1 and 8). Introduction of *ortho*-substituents to phenylacetylene does not result in lower yields and we obtained alkyne **18** from 2-methylphenylacetylene, **17**, and **1** in 90% (entry 9). As we had experienced with 3-bromopyridine, **1**, replacement of pyrrolidine by NaOH slightly decreases the results of the Sonogashira coupling between phenylacetylene and bromonaphthalenes **4** and **6** (entries 2 and 3). The pyrrolidine-promoted Sonogashira coupling reaction procedure did not result in any alkyne formation with chloroquinolines **12** and **14**. Instead, we found that the amine undergoes nucleophilic aromatic substitution to form the corresponding 4-pyrrolidinoquinolines.[23] However, the quinoline-derived alkynes **13** and **15** can be obtained in 71% and 73% yields, respectively, using aqueous 0.5 M NaOH (entries 6 and 7).



Scheme 2 Proposed catalytic cycle of the POPd-catalyzed Sonogashira coupling.

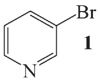
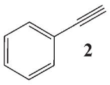
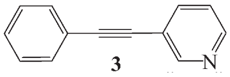
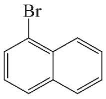
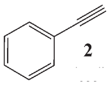
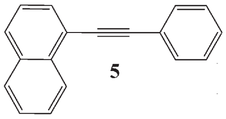
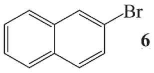
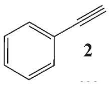
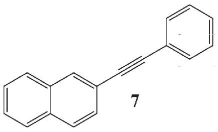
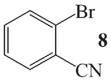
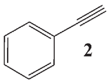
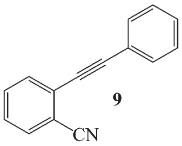
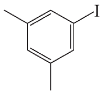
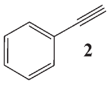
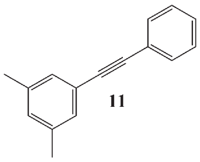
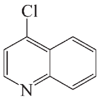
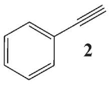
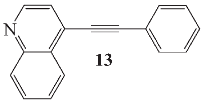
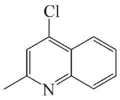
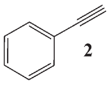
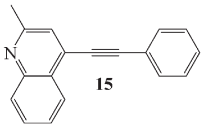
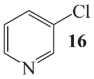
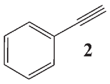
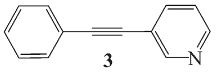
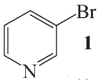
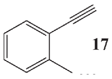
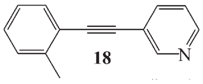
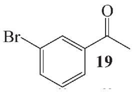
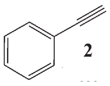
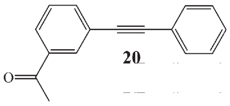
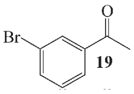
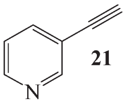
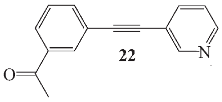
Formation of 5–10% butadiynes derived from terminal alkynes **2** and **17** was observed when CuI was used as a co-catalyst. This may be attributed to oxidative Glaser coupling, which is a well known side reaction of Cu(I)-promoted coupling reactions in the presence of air. Recently, copper-free Sonogashira coupling methods using aryl bromides and iodides have been introduced.[24] We observed that POPd-catalyzed Sonogashira coupling also proceeds with aryl chlorides in the absence of CuI albeit with slightly decreased yields (entries 1 and 8).

In summary, we have developed a Sonogashira coupling method that utilizes a palladium–phosphinous acid catalyst in water and avoids the use of hazardous organic co-solvents. Disubstituted alkynes have been prepared in good to high yields from aryl chlorides, bromides and iodides with POPd in the presence of TBAB. Pyrrolidine was found to afford superior results over other organic and inorganic bases but its use is limited to aryl halides that are not susceptible to nucleophilic aromatic substitution. Replacement of pyrrolidine by NaOH avoids amination of chloroquinolines and thus allows conversion of these electron-deficient aryl chlorides to alkynes in high yields. The present and previously reported studies from our laboratories show that POPd combines high catalytic activity for Stille and Sonogashira cross-coupling reactions with remarkable stability to air and water. We believe that this catalyst is also a very promising candidate for developing other C–C bond forming reactions that proceed in water and thus minimize waste production and environmental pollution.

Acknowledgements

We thank Combiphos Catalysts, Inc., New Jersey (www.combiphos.com) for POPd, POPd1 and POPd2.

Table 2 Aqueous Sonogashira cross-coupling reactions

Entry	Aryl halide	Alkyne	Product	Yield (%)[a]
1	 **1**	 **2**	 **3**	90 (80[c])
2	 **4**	 **2**	 **5**	91(82[b])
3	 **6**	 **2**	 **7**	73(64[b])
4	 **8**	 **2**	 **9**	81
5	 **10**	 **2**	 **11**	90(90[b])
6	 **12**	 **2**	 **13**	71[b]
7	 **14**	 **2**	 **15**	73[b]
8	 **16**	 **2**	 **3**	65[b](51[c])
9	 **1**	 **17**	 **18**	90
10	 **19**	 **2**	 **20**	70
11	 **19**	 **21**	 **22**	81

[a] General conditions: 100 mg of **1**, 2 equivalents of the terminal alkyne, 10 mol% POPd, 1.0 equivalent of TBAB, 2 equivalents of pyrrolidine, 10 mol% of CuI in 5 mL of deionized water at 135–140 °C for 5 h in a closed vessel. [b] Pyrrolidine was replaced by 0.5 M NaOH. [c] No CuI was added.

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