

Recyclable polymer bound Pd(0) phosphine catalyst for effecting sp^2 - sp^2 and sp^2 - sp carbon-carbon coupling reactions in aqueous medium

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Aqueous Heck type coupling reactions between aryl iodides and terminal alkenes or alkynes have been effected in good yields using a recyclable catalyst system that consists of poly(*N*-isopropyl acrylamide) bound Pd(0) phosphine and an anionic surfactant, potassium lauryl sulphate.

Keywords: Polymer bound Pd(0) phosphine catalyst, carbon-carbon coupling, aqueous medium, surfactant

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Poly(*N*-isopropyl acrylamide) (PNIPAM) supported catalysts have been successfully employed in effecting C-C bond formation. For example, PNIPAM bound Pd(0) phosphine catalysts have been used for Heck reaction, allylic substitution, Suzuki coupling and hydrogenation^{1,2}. PNIPAM bound Pyrrhos Rhodium(II) catalyst has been used for asymmetric hydrogenation³. These PNIPAM bound catalysts are soluble in polar solvents like NMP, acetonitrile, THF, ethanol, DMF and water. In most cases they are used in either a polar solvent alone or in aqueous polar solvents and are recycled successfully after isolating them from products by solvent precipitation. However, the utility of PNIPAM bound catalyst in aqueous medium alone is restricted to ambient or sub-ambient temperatures due to its lower critical solution temperature (LCST) of 31°C in water. Above its LCST, PNIPAM precipitates out from its aqueous solution. When hydrophobic ligands like phosphines are attached to PNIPAM backbone then the LCST gets further lowered. Hence, reactions involving PNIPAM bound catalysts in aqueous medium have to be necessarily conducted at ambient or sub-ambient temperatures. Bergbreiter *et al.*¹ reported sp^2 - sp coupling of sodium salt of iodobenzoic acid and 2-methyl-3-butyne-2-ol in aqueous medium. In this case despite both reactants being water soluble, the reaction has been conducted at 10°C to ensure that the catalyst and the reactants are in solution for homogeneous catalysis. This results in long reaction

time of 36 hr. Thus, inverse temperature dependent solubility of PNIPAM bound catalyst in aqueous medium severely restricts its utility for reactions at ambient or sub-ambient temperatures resulting in extremely unfavourable reaction kinetics.

In this paper is reported a methodology that overcomes PNIPAM bound Pd (0) catalyst's limitations of being useful only for water soluble substrates and that too at ambient temperatures. Herein, is reported an efficient sp^2 - sp^2 and sp^2 - sp carbon-carbon coupling reaction of aryl iodides with terminal alkenes and alkynes effected by PNIPAM bound Pd (0) phosphine catalyst in completely aqueous medium in the presence of a surfactant.

Results and Discussion

At temperatures below its LCST (31°C), the PNIPAM molecules exist in solution as extended coils surrounded by ordered water molecules. This shell of hydration causes a decrease in entropy of the system. Thus, the free energy of solution is lowered by formation of hydrogen bonds but is raised by loss of entropy. At temperatures above LCST, the entropy term dominates and the polymer precipitates out of the solution. Anionic surfactants like sodium lauryl sulphate (SLS) have been reported to increase the LCST of PNIPAM significantly⁴. SLS at concentrations upto its critical micelle concentration (CMC) causes a gradual increase in LCST of polymers like PNIPAM⁵⁻⁸. This increase in the transition temperature

indicates the formation of surfactant micelles along with polymer chain causing an increase in hydrophilicity and a delayed collapse to the hydrophobic conformation. Formation of small colloidal particles of PNIPAM in the presence of surfactant molecules (SLS) has been observed with small angle neutron scattering by Lee and Cabane⁹. In short, in aqueous medium, the interaction with surfactant molecules prevents PNIPAM's precipitation at elevated temperatures that are significantly above its LCST⁴.

In view of this interesting interaction between PNIPAM and a surfactant it was envisaged that by using a surfactant it would be possible to effect homogeneous catalysis by deploying PNIPAM bound phosphine transition metal catalyst in aqueous medium at elevated temperatures. It was observed that in aqueous medium in the presence of micellar concentrations of SLS, PNIPAM formed complete clear solution at elevated temperature of 80°C whereas PNIPAM bound phosphine Pd(0) **3** catalyst formed a fine colloidal dispersion.

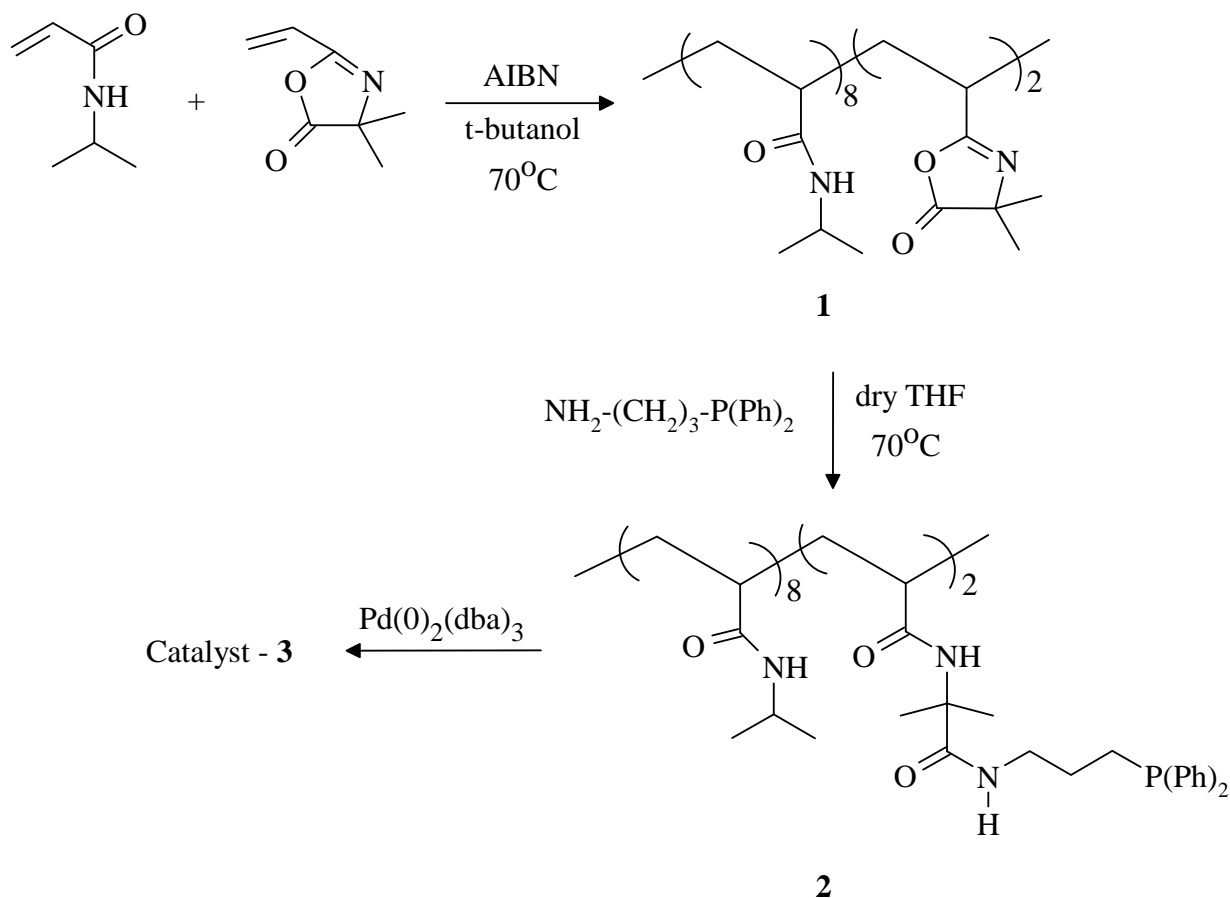
PNIPAM bound Pd(0) Phosphine **3** was formed by ligand exchange between the polymer bound phosphine **2** and Pd(0)₂(dba)₃. PNIPAM bound phosphine **2** in turn was synthesized by opening azalactone ring of copolymer **1** by amino terminated phosphine² (Scheme I). Poly(*N*-isopropyl acrylamide-co-vinyl azalactone) **1** was prepared by radical polymerization of *N*-isopropyl acrylamide and 2-vinyl 4,4-dimethyl 2-oxazoline 5-one commonly referred to as vinyl azalactone (VAL) in the mole ratio of 8 : 2. The copolymer was then reacted with aminopropyl diphenyl phosphine in dry THF and polymer bound phosphine **2** was purified by solvent precipitation effected by pouring the reaction mixture into hexane. ³¹P NMR spectrum of this polymer **2** showed characteristic signals at δ 17.1 and 34.2 corresponding to phosphine and phosphine oxide (~5.0%) respectively.

Polymeric Pd(0) catalyst **3** was prepared by dissolving **2** in NMP and then exchanging ligand with Pd(0)₂(dba)₃ using **2** : Pd in the ratio 4 : 1. The colour change from red to golden yellow indicated the ligand exchange. The catalyst **3** was then isolated by solvent precipitation. On drying ³¹P NMR spectrum of yellow coloured **3** showed characteristic signals at δ 19.41 and 32.66 for phosphine bound to Pd and phosphine oxide respectively.

The catalyst **3** was deployed in a typical aqueous Heck reaction of *p*-iodoanisole and acrylic acid using

SLS as a surfactant and sodium carbonate as a base. The catalyst was finely dispersed by adding it to sodium lauryl sulphate solution (above its critical micelle concentration). The catalyst remained in finely dispersed state even at 80°C, significantly above the LSCT of PNIPAM. HPLC analysis after 8 h showed that the entire *p*-iodoanisole was completely converted into the product, *p*-methoxy cinnamic acid. However, though favorable kinetics was achieved for this aqueous Heck reaction unlike prior art, it turned out to be a difficult task to isolate the catalyst **3** from the reaction mass for subsequent recycling due to the presence of significant quantity of the surfactant, SLS. In view of this practical difficulty it was desired to have a surfactant that would not only allow aqueous Heck reaction at elevated temperature but would also allow the easy separation of the catalyst from the reaction mixture so that the same can be recovered and recycled. Attempts to isolate the catalyst from the reaction mixture by deactivation of anionic SLS with quaternary ammonium type of cationic surfactant proved futile. This clearly indicated that for a catalyst system to be recoverable, a surfactant that is insoluble in water at ambient temperature and that has Krafft point much above the ambient temperature would be the most ideal. A survey of the literature revealed that change in the cation or the alkyl chain of an anionic surfactant results in increase in Krafft temperatures. For example, sodium lauryl sulphate has Krafft point of 16°C whereas potassium lauryl sulphate¹⁰ has Krafft point of 40°C. Similarly, changing from dodecyl alkyl chain to hexadecyl or octadecyl alkyl chain results in significant increase in Krafft points. Both sodium hexadecyl sulphate and sodium octadecyl sulphate have Krafft points¹¹ above 50°C. This is true with higher alkane sulphonates as well as hydroxy alkane sulphonates¹², two different categories of anionic surfactants. For the present catalyst system, potassium lauryl sulphate (KLS) was chosen as a surfactant. Potassium lauryl sulphate (KLS), another anionic surfactant, is practically insoluble in water at ambient temperature and forms micelles at 7.8 mmoles/L at 40°C (Ref. 10).

*sp*²-*sp*² Carbon-carbon coupling of *p*-iodobenzoic acid (1.39×10⁻³ M) and acrylic acid (1.39×10⁻³ M) in aqueous medium by catalyst **3** was best effected in the presence of potassium carbonate as a base and potassium lauryl sulphate as an anionic surfactant (substrate/catalyst 50, Pd 0.27×10⁻⁴ M, surfactant 3×10⁻² M, Pd : phosphine in the ratio 1 : 4). The reaction was conducted at 85°C and was found to be

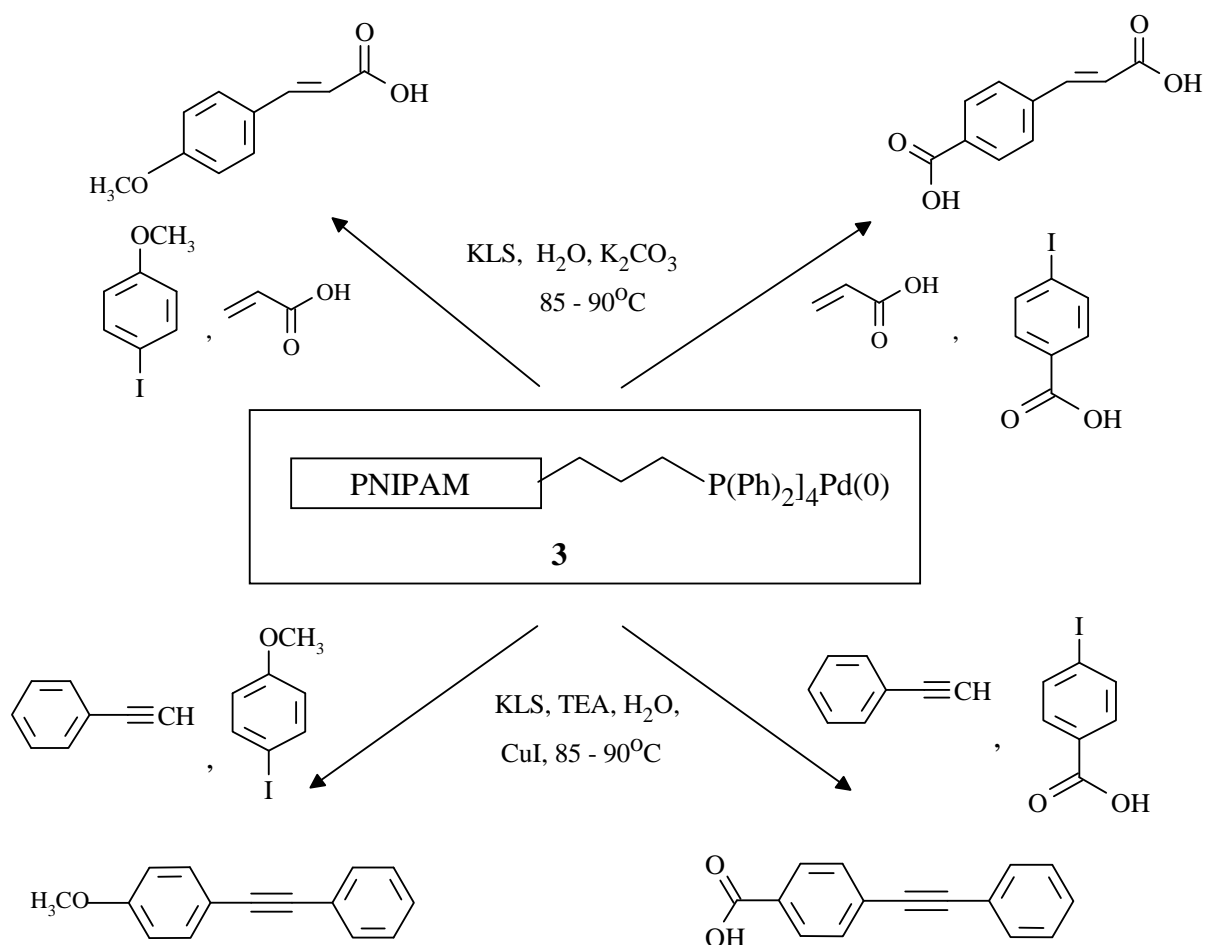


Scheme I

complete after 8 h (HPLC) (**Scheme II**). Addition of small quantity of KCl to the cooled reaction mass (10°C) resulted in complete precipitation of the polymer bound catalyst **3** along with the surfactant quantitatively. At this low temperature of 10°C KLS crystallized out due to its insolubility in aqueous medium and also due to common ion effect exerted by KCl. Polymer bound catalyst **3** precipitated out because KCl disrupted hydrogen bonding between polymer molecules and water. Its ions broke up the ordered structure and promoted hydrophobic polymer-polymer interaction. Also, at 10°C KLS is virtually insoluble in aqueous medium to exert any effect on polymer chains through micellization. Thus, simply by cooling the reaction mass and adding potassium chloride it was possible to precipitate both the catalyst **3** and KLS and to separate them from the reaction mass by filtration. The isolated mixture of the catalyst **3** and the surfactant, KLS was successfully recycled for the next experiment. The product *p*-carboxy cinnamate remained in aqueous medium as its dipotassium salt. It was isolated in 92% yield after the

acidification and extraction. It was found to be quite pure and with exclusively *trans* geometry. Next, this methodology was extended to water insoluble substrate, *p*-methoxy iodo anisole. Surprisingly, the results were as impressive (91% yield) as water soluble substrate *p*-iodo benzoic acid (in its potassium salt form). Clearly, the surfactant KLS played a dual role of solubilising the substrate as well as increasing the LCST of the polymeric catalyst **3**.

Using the same surfactant-polymer supported catalyst system, *sp*²-*sp* carbon-carbon coupling reactions between aryl iodides and phenyl acetylenes (**Scheme II**) were successfully effected. In the first example of this type of aqueous chemistry, *p*-carboxy diphenyl acetylene was synthesized from phenyl acetylene and *p*-iodo benzoic acid, the former being water-insoluble and the later being water-soluble in its salt form. This *sp*²-*sp* carbon-carbon coupling in aqueous medium was demonstrated with triethyl amine in place of potassium carbonate of earlier examples. Cuprous iodide was used as a cocatalyst^{13,14} (promoter) although the coupling reaction did take



Scheme II

place in its absence¹⁵. The detailed study of this promoter's effect on the rate of the reaction has not been done. The catalyst **3** and the surfactant were isolated by adding saturated solution of potassium chloride to the cooled reaction mass at 10°C and recycled. Upon removal of the catalyst-surfactant system the reaction mass was acidified to yield *p*-carboxy diphenyl acetylene in 91% yield. The lowering of temperature of reaction mass and addition of saturated potassium chloride solution are of paramount importance to ensure clean separation and isolation of polymer supported catalyst along with the surfactant. In another example, the utility of aqueous *sp*²-*sp* coupling reaction was demonstrated between both water-insoluble reactants, namely, *p*-iodo anisole and phenyl acetylene. The product of this reaction, *p*-methoxy diphenyl acetylene was isolated by solvent extraction after cooling the reaction mass.

In summary, the PNIPAM bound Pd (0) phosphine catalyst-potassium lauryl sulphate system allows Heck like reactions to be conducted in complete

aqueous medium. The reaction kinetics using this system is comparable to homogeneous catalysis effected by triphenyl phosphine palladium catalyst in a suitable solvent. Moreover, this polymer bound catalyst-surfactant system has been shown to be amenable to both water soluble and water insoluble substrates. Finally, the polymer bound catalyst and the surfactant can be easily isolated and recycled. Thus, the recyclable catalyst system reported herein does not use any organic solvent and hence it has potential application in large scale industrial chemistry. This methodology has already been successfully extended to Pd catalyzed aqueous hydrogenations and Suzuki coupling reactions¹⁶. Currently, the reaction conditions, exact cycle time, substrate to catalyst ratio and number of successful cycles are being optimized with a view to exploit this aqueous Heck chemistry to synthesize commercially important fine chemicals.

Thus, what has been demonstrated here is a recyclable catalyst for aqueous Heck chemistry using a polymer bound phosphine-metal complex and a

surfactant. This can serve as a guideline to design many such simple catalyst systems employing other polymer backbones supporting a variety of ligands and surface active agents. The methodology reported here can be extended to not only Pd catalyzed reactions other than Heck but also to a variety of reactions that are catalyzed by other transition metals.

Experimental Section

All reagents and solvents were obtained from commercial sources and used without purification unless otherwise stated. Dry THF was prepared by distilling the solvent over benzophenone and sodium. Vinyl azalactone was obtained from SNPE Chimie, France. ^1H and ^{13}C NMR spectra were obtained on a Varian Unity 300 spectrometer. TMS was used as internal reference for ^1H NMR and 80% phosphoric acid was used as external reference for ^{31}P NMR spectra. Infrared spectra were reported as thin films between NaCl plates or as pressed KBr pellets using Perkin-Elmer FT-IR spectrometer. UV-Vis spectra were obtained using Varian Cary 50 spectrometer.

Copolymer Poly(NIPAM-co-VAL) **1**, aminopropyl diphenyl phosphine, PNIPAM bound phosphine **2** and [PNIPAM-P(Ph) $_2$] $_4$ Pd(0) **3** (Scheme I) have been synthesized as per the procedures described in a previous paper².

sp^2 - sp^2 Coupling: Synthesis of *p*-carboxy cinnamic acid. Potassium lauryl sulphate (100 mg, 0.32 mmole) was dispersed in water (5 mL) under nitrogen and heated to 40°C. To this solution, PNIPAM supported catalyst **3** (100 mg) was added. This was followed by a mixture containing iodobenzoic acid (344 mg, 1.39 mmole), potassium carbonate (960 mg, 6.95 mmole) and acrylic acid (100 mg, 1.39 mmole) in water (5 mL) and stirring was continued at 90°C for 8 hr. HPLC analysis (Column : OmniSpher C18; Mobile Phase 60 : 40 Methanol : Water; Flow Rate : 1.0 ml/min.; UV detection at 280 nm) indicated total disappearance of iodobenzoic acid and formation of dipotassium *p*-carboxylate cinnamate. The reaction mass was cooled in an ice bath. To this, a saturated solution of potassium chloride (5 mL) was added to precipitate out the polymer-Pd complex along with KLS. The solution was filtered and the precipitated polymer along with KLS was recycled for next reaction.

The product was isolated by acidifying the filtrate and filtering the precipitate. It was washed with water and dried to yield (245 mg, 92%) buff colored solid, m.p. 255°C (Lit.¹⁷ m.p. 250-55°C). Its purity was ascertained by HPLC which was found to be 99.0%.

^1H NMR (CDCl $_3$, 300 MHz): δ 6.55 (d, 1H, J = 16Hz), 7.75 (d, 1H, J = 16.0 Hz), 7.76 (d, 2H, J = 8.4 Hz), 8.05 (d, 2H, J = 8.4 Hz).

sp^2 - sp^2 Coupling : Synthesis of *p*-methoxy-cinnamic acid. *p*-Methoxy cinnamic acid was prepared according to the methodology described above using PNIPAM supported catalyst **3** (100 mg), potassium lauryl sulphate (100 mg, 0.32 mmole), *p*-iodoanisole (325 mg, 1.39 mmole), potassium carbonate (384 mg, 2.78 mmole), acrylic acid (100 mg, 1.39 mmole) and water (10 mL). The usual work up yielded *p*-methoxy cinnamic acid as pale yellow solid (225 mg, 91%), m.p. 172°C (Lit.¹⁷ m. p. 172°C). ^1H NMR (CDCl $_3$, 300 MHz): δ 3.84 (s, 3H), 6.30 (d, 1H, J = 16.0 Hz), 6.93 (d, 2H, J = 9.0 Hz), 7.50 (d, 2H, J = 9.0 Hz), 7.75 (d, 1H, J = 16.0 Hz).

sp^2 - sp Coupling : Synthesis of *p*-methoxy diphenyl acetylene.

Potassium lauryl sulphate (100 mg, 0.32 mmole) was dispersed in water (5 mL) under nitrogen and heated to 40°C. To this solution, PNIPAM supported catalyst **3** (100 mg) was added. This was followed by *p*-iodoanisole (300 mg, 1.28 mmole), cuprous iodide (5 mg, 0.02 mmole), phenyl acetylene (132 mg, 1.28 mmole) and triethyl amine (130 mg, 1.29 mmole) in water (5 mL) and stirring was continued at 90°C for 8 hr HPLC analysis at this stage (Column: OmniSpher C18; Mobile Phase 70 : 30 Methanol : Water; Flow Rate : 1.0 mL/min.; UV detection at 280 nm) indicated total disappearance of iodo anisole and formation of *p*-methoxy diphenyl acetylene. The reaction mass was cooled to 10°C in an ice bath. To this, a saturated solution of potassium chloride (5 mL) was added and the product was extracted by petroleum ether (2×10 mL). The precipitated polymer-Pd complex was isolated along with KLS and cuprous iodide by filtration for recycling in the next reaction.

The solvent removal on rotary evaporator yielded *p*-methoxy diphenyl acetylene as pale yellow solid (245 mg, 91.76%), m.p. 56°C (Lit.¹⁸ m.p. 58-59°C). ^1H NMR (CDCl $_3$, 300 MHz) : δ 3.9 (s, 3H), 6.9 (d, 2H, J = 9.0 Hz), 7.43 (d, 2H, J = 9.3 Hz), 7.35 to 7.65 (m, 5H).

sp^2 - sp Coupling : Synthesis of *p*-carboxy diphenyl acetylene.

p-Carboxy biphenyl acetylene was prepared according to the methodology described above using PNIPAM supported catalyst **3** (100 mg), potassium

lauryl sulphate (100 mg, 0.32 mmol), *p*-iodobenzoic acid (300 mg, 1.20 mmole), triethyl amine (122 mg, 1.20 mmole), cuprous iodide (5 mg, 0.02 mmole), phenyl acetylene (132 mg, 1.28 mmole) and water (10 mL). The usual work up as described above yielded *p*-carboxy diphenyl acetylene as pale yellow solid (245 mg, 91%), m.p. 192°C (Lit.¹⁸ m.p. 221-22°C). ¹H NMR (CDCl₃, 300 MHz) : δ 7.62 (d, 2H, *J* = 8.7 Hz), 8.03 (d, 2H, *J* = 8.7 Hz), 7.35 to 7.65 (m, 5H).

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