Polymer bound Pd(0) phosphine catalyst for homogeneous catalysis

Nirmal Koshi*, Shubhangi Naik & Bharat Parab

Galaxy Research Centre, Galaxy Surfactants Ltd., C-49, TTC Ind’l Area, Powai, Navi Mumbai 400 703, India

Received 2 August 2002; accepted (revised) 13 May 2003

Facile synthesis of water-soluble polymer bound Pd(0) phosphine catalyst is described. This recyclable polymeric catalyst is soluble in aqueous or aqueous/organic media and has high activity in nucleophilic allylic substitution, Heck reaction and hydrogenation.

IPC: Int.Cl. C 01 G 55/00

Monomeric as well as polymer bound phosphines have been employed successfully in homogeneous catalysis. Poly(N-isopropyl acrylamide) (PNIPAM) bound phosphines have been used to make efficient and recoverable catalysts by Bergbreiter et al. PNIPAM has lower critical solution temperature (LCST) of 31°C and it phase-separates from its aqueous solution when heated above its lower critical solution temperature. These PNIPAM bound catalysts are soluble in polar solvents like THF, acetonitrile, DMSO and water. And hence, PNIPAM bound catalyst also show similar behaviour which is exploited in recovering and recycling of the polymer bound catalyst. However, due to relatively low LCST, the utility of PNIPAM bound catalyst in aqueous medium is severely restricted to ambient temperature. Nevertheless, in other polar solvents (THF, acetonitrile, DMSO) or solvent water mixed systems these polymeric catalysts have been shown to be extremely efficient for Heck reaction, allylic substitutions, Suzuki coupling, etc. and even for asymmetric hydrogenation using chiral phosphine Rhodium complex. In general, PNIPAM bound catalysts are recovered by either heating aqueous reaction mixture above LCST, addition of the same to brine or by solvent precipitation.

To anchor aryl phosphines on to hydrophilic poly(N-isopropyl acrylamide), Bergbreiter used Whitesides’s strategy of using amino terminated phosphines and Winnik’s copolymer containing N-isopropyl acrylamide and N-acryloxy succinimide. The active ester units of this copolymer are then reacted with the nucleophile to anchor the ligand on the polymer. This strategy of functionalisation of PNIPAM suffers from a major problem of purification because the displaced N-hydroxy succinimide (NHS) remains partly suspended or even solubilised in reaction mixture. Purification by dissolving functionalised polymer in water and reprecipitating by heating the aqueous solution above LCST is the only way of getting rid of displaced NHS. The polymer that precipitates from its aqueous solution has to be completely dried before its actual use. Drying of this wet polymer is another cumbersome step. More importantly, with air-sensitive ligands such as polymer bound phosphines, number of purification steps inevitably lead to oxidation of phosphine to the corresponding oxide.

Results and Discussion

To overcome these difficulties we designed PNIPAM bound phosphines by using copolymers of N-isopropyl acrylamide and 2- vinyl 4,4’-dimethyl-2- oxazoline-5-one commonly referred to as vinyl azlactone (VAL). In this communication, we report poly(N-isopropyl acrylamide) bound phosphine Pd(0) catalyst that can be used in aqueous or in other polar solvents ranging from THF, acetonitrile, N-methyl pyrrolidinone, etc. for effecting a variety of synthetic transformations.

Vinyl azlactone is commercially available and is highly reactive towards all sorts of nucleophiles. Poly(N-isopropyl acrylamide-co-VAL), 1 (Scheme I) was synthesised by co-polymerising both monomers in 8 : 2 mole ratio in t-butanol using AIBN as the initiator.

The IR spectrum of 1 showed a prominent stretch for carbonyl of azlactone at 1814 cm⁻¹ and carbonyl of amide at 1646 cm⁻¹. Molecular weight by viscosity measurement was found to be Mν = 5.1 × 10⁵ using values of 9.59 × 10⁻⁵ and 0.65 for k and a respectively
in THF at 30°C. Unfortunately, due to broad signals, the PMR spectrum was not of any help in ascertaining the mole ratio of 1 vis-à-vis the feed ratio. However, the relative mole ratio of N-isopropyl acrylamide to vinyl azalactone could be easily determined by reacting azalactone units of 1 with excess of benzylamine and after isolation of polymer bound benzylamine, the free amine was estimated by either UV-spectroscopy or HPLC. Alternatively, the monomer ratio in the copolymer can be determined by simple titrimetry after opening the azalactone ring by a diamine like N,N-dimethylaminopropyl diamine (see experimental, synthesis of 1). Based on this analysis the actual mole ratio of the monomers was found to be quite close to the feed ratio.

The copolymer 1 was then reacted with aminopropyl diphenyl phosphine in dry THF and polymer bound phosphine 2 was purified by pouring the reaction mixture into hexane. $^{31}$P spectrum of this polymer 2 showed characteristic signals at δ -17.1 and 34.3 corresponding to phosphine and phosphine oxide (~5.0%) respectively. The polymeric Pd(0) catalyst 3 was made by dissolving 2 in a suitable solvent and then exchanging ligand with Pd(0)(dba)$_2$ using 2 : Pd ≈ 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, $^{31}$P spectrum of yellow coloured 3 showed characteristic signals at δ 19.41 and at δ 32.66 for phosphine bound to Pd and phosphine oxide, respectively.

The purified 3, thus obtained, was used for hydrogenation of N-isopropyl acrylamide in THF. The rate of hydrogen uptake (measured by hydrogen filled burette connected to reaction flask) was found to be same as that observed with nonpolymeric version of homogeneous Wilkinson like Pd(0) catalyst (Chart I).

The catalyst 3 was also employed for allylic substitution of allyl acetate by diethyl amine. In both reactions, the same catalyst was recycled five times by adding fresh substrate at the end of each cycle. Finally, the catalyst was isolated by solvent precipitation and the recovered catalyst was reused for another fresh experiment. The conversions were quantitative and there was no noticeable drop in catalytic activity.

Heck reaction to produce $p$-methoxycinnamic acid was conveniently done in aqueous N-methyl pyrrolidone (NMP) (1 : 1) as medium and an inorganic base. After performing four cycles, the catalyst was recovered by pouring the reaction mixture in warm brine solution (40°C) and reused. In another example of Heck reaction, synthesis of octyl $p$-methoxy cinnamate was carried out in NMP alone. Auration of octyl acrylate was done by iodoanisole using triethylamine. After five successful cycles the isolation of product was accomplished very conveniently by solvent extraction.
(hexane). The catalytic activity of 3 in above mentioned Heck reactions was found to be quite comparable with that of Pd(0)Und, and conversions by HPLC analysis and/or actual isolation of products were found to be quantitative. In addition to chromatographic comparisons with authentic samples, PMR analysis also confirmed the purity of products. Thus, p-methoxycinnamic acid and octyl methoxy cinnamate were found to be exclusively trans stereoisomers.

Currently we are engaged in extending this methodology to synthesise polymer supported palladacycles, chiral phosphines and polymer supported catalyst using other transition metals especially rhodium for homogeneous catalysis.

In summary, we have shown that PNIPAM bound Pd(0) complexes can be recovered by either thermal or solvent precipitation and hence the product can be isolated easily. The catalytic activity in homogeneous system is as good as their low molecular weight analogues. And more importantly, these polymer bound phosphine palladium complexes can be readily synthesised by making use of azalactone ring for functionalisation of polymeric support.

**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 ¹³C NMR spectra were obtained on a Varian Unity p300 spectrometer. TMS was used for internal reference for PMR and 80% phosphoric acid was used as external reference for ³¹P NMR spectra. Infrared spectra were reported as thin films between NaCl plates or as pressed KBr pellets using Perkin-Elmer FT-IR spectrometer. UV-Visible spectra were obtained using Varian Cary 50 spectrometer.
Synthesis of copolymer poly (NIPAM-co-VAL)

1. N-Isopropyl acrylamide (5.0 g, 44.25 mmole) and vinyl azalactone (1.54 g, 11 mmole) were dissolved in t-butanol (80 mL) at 65°C under nitrogen. A solution of AIBN (100 mg) in t-butanol (20 mL) was added to this solution. The reaction mixture was then stirred at 70°C for 20 hours. The reaction mixture was concentrated by removing 50% of the solvent on a rotary evaporator. The concentrated solution thus obtained was poured into stirred hexane (500 mL) to precipitate the copolymer. The precipitated solid polymer was filtered and dried under high vacuum to yield 6.3 g (96%) of copolymer. IR (KBr): 1646, 1814, 3299 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 1.0 to 1.27, 3.13, 3.97 (broad signals for polymer backbone and N-isopropyl groups) and 2.13 (broad tiny signal for dimethyl groups of azalactone unit).

The monomer mole ratio of 8:2 was ascertained by reacting a small portion of copolymer with N,N-dimethylaminopropyl dimine in THF. The polymer was precipitated by adding reaction mixture to hexane. The precipitated polymer was purified by dissolving in water and reprecipitating by heating the aqueous solution to 50°C. The white precipitated polymer was then dried under vacuum. It was found to have amine value of 77 when titrated with standard HCl solution as against amine value of 80 for 8:2 copolymer. The molecular weight (Mv) of this copolymer was determined to be 5.1 × 10⁵ by viscometry.⁷

Synthesis of aminopropyl diphenyl phosphine.

Sodium metal (1.25g, 54 mmole) was washed with hexanes and cut into small pieces into a dry N₂ flushed round bottom flask. The sodium was suspended in dry, degassed THF (20 mL). Chloro diphenyl phosphine (3.0 g, 13.6 mmole) was dissolved in THF (10 mL) and added to the sodium. The red reaction mass was stirred overnight at room temperature. Chloropropyl amine hydrochloride (884 mg, 6.8 mmole) was suspended in dry THF (10 mL) and cooled to -78°C. The red reaction mixture was diluted with dry, degassed THF (10 mL) and transferred via canula to the suspension. This reaction mass was then stirred for 90 minutes and then the cooling bath was removed. The reaction was stirred as the bath was allowed to warm to room temperature. After stirring for 7 hr, the reaction was heated at 50°C for 10 hr. After removal of THF, the reaction was diluted with ether (20 mL) and washed twice with brine solution (10 mL). The organic layer was extracted three times each with 10 mL 1N H₂SO₄. The aqueous layer was neutralised with 5% NaOH and then extracted with ether (3 × 50 mL). The organic extracts were dried over sodium sulphate and rotary evaporated under reduced pressure to afford 1.07 g (67%) of a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.6 (m, 2H), 2.05 (m, 2H), 2.5 (bs, 2H), 2.8 (t, 2H), 7.25 – 7.45 (m, 10H). ³¹P NMR (CDCl₃, 120 MHz): δ -16 (phosphine) and 34 (oxide).

Synthesis of PNIPAM bound phosphine 2. To a stirred solution of poly (NIPAM-co-VAL) 1 (2.6 g) in dry THF (15 mL) under nitrogen, aminopropyl diphenyl phosphine (1.07 g, 4.44 m mole) in dry THF (15 mL) was added under nitrogen. The mixture was stirred at 50°C for 4 hr. The polymer was then precipitated by pouring the reaction mixture into hexane (100 mL). IR spectroscopy showed complete disappearance of carbonyl stretch of azalactone. It was quickly filtered and dried under high vacuum to give 3.2 g of colourless solid. It was stored under nitrogen for subsequent use in preparation of catalysts. IR (KBr) 1646, 3239 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): Broad signals at δ 0.8 to 1.1, 1.75, 1.78 to 2.09, 3.94 and 7.2 to 7.59. ³¹P NMR (CDCl₃, 120 MHz): broad signals at δ -17.1 and 34.3.

Synthesis of [PNIPAM-P(Phh₁,Pd(O)]₃ 3. A solution of 2 (1.0 g) in dry THF (25 mL) was prepared under nitrogen. To this stirred solution, a solution of Pd(0)₅(db₃) (125 mg) in dry THF (25 mL) was added using a double tipped needle under positive nitrogen pressure. Within 5 minutes resulting solution changed from dark purple to golden yellow. The solution was stirred for additional 15 minutes. To this solution, hexane (100 mL) was added and 3 was precipitated as golden solid. The supernatant layer was then removed leaving the polymer bound catalyst 3 ready for use in either water, mixed solvent system or plain organic solvents such as acetonitrile, THF and NMP. ³¹P NMR (CDCl₃, 120 MHz): δ 19.41 and 32.66.

Hydrogenation of N-isopropyl acrylamide.

Preparation of N-isopropyl propylamide. The precipitated catalyst 3 (200 mg) was redissolved in NMP (10 mL) and the reaction flask was evacuated. The reaction flask was filled with hydrogen through a burette that was connected with two two-way valves. After performing evacuation and filling of reaction flask with hydrogen three times, N-isopropyl acrylamide (100 mg, 0.88 mmole) in NMP (10 mL) was added through the septum using a syringe. This was immediately followed by evacuation and filling of hydrogen sequence was performed two times and the reaction was continued to stir at room temperature under hydrogen.
completion of hydrogen uptake, the reaction mass was stirred for additional one hour under hydrogen. A small sample drawn by a syringe was used to do TLC to confirm the completion of reaction. The conversions were ascertained by GC (Capillary column: DB-1; Column temp. prog.: 80°C isothermal; Injector temp.: 250°C; Detector temp.: 300°C). The retention time of N-isopropyl propylamide was checked with authentic material. After ascertaining disappearance of N-isopropyl acrylamide either by TLC or GC a fresh instalment of starting material was added to initiate the next cycle. The reaction mixture was concentrated to remove most of ethanol and poured into hexane to precipitate the polymeric catalyst. The supernatant layer was concentrated to get N-isopropyl propylamide as white needles (extremely hygroscopic). It sublimed at 66°C (0.5 mm Hg).<sup>5</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.07 to 1.31 (one triplet and one doublet overlapping, 9H), 2.11 to 2.18 (q, 2H, J = 7.8 Hz), 3.89 to 3.98 (p, 1H, J = 6.63 Hz).

**Allylic substitution of allyl acetate, preparation of allyl diethylamine.** The precipitated catalyst (3) (200 mg) was redissolved in fresh NMP (10 mL) under nitrogen. Through the septum, a mixture of diethylamine (300 mg, 4.1 mmole) and allyl acetate (200 mg, 2.0 mmole) in dry NMP (10 mL) was introduced into the reaction flask and the stirring was continued at 45°C for 12 hr. Gas chromatography analysis indicated complete consumption of allyl acetate and formation of allyl diethylamine. The same catalyst was used for five more cycles of 2.0 mmole scale of substrate. The catalyst was isolated from the product by solvent (hexane) precipitation. After removal of catalyst, the solvent was rotary evaporated to yield the tertiary amine as colourless liquid, b. p. 110°C (Lit.<sup>6</sup> b, p. 110°C). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.0 (t, 6H, J = 7.2 Hz), 2.53 (q, 4H, J = 6.9 Hz), 5.10 to 5.29 (m, 2H), 5.83 to 5.92 (m, 1H).

**Heck reaction, preparation of 2-ethyl hexyl p-methoxycinnamate.** The PNIPAM supported catalyst 3 (200 mg) was redissolved in NMP (10 mL) under nitrogen. To this stirred solution, a mixture containing iodoanisole (300 mg, 1.28 mmole), triethylamine (518 mg, 5.13 mmole) and 2-ethyl hexyl acetate (236 mg, 1.28 mmole) in dry NMP (10 mL) was added and stirring was continued under nitrogen blanket at 90°C for 12 hr. HPLC analysis (Column: OmniSpher C18; Mobile Phase : 90 : 10 :: Methanol : Water; Flow Rate : 1.0 ml/min.; UV detection at: 280 nm) indicated total disappearance of iodoanisole and formation of 2-ethyl hexyl methoxycinnamate. After every 12 hr the same catalyst was used for additional four cycles and the conversions were complete based on HPLC. At the end of fourth cycle the reaction mixture was extracted with hexane (100 mL). Removal of hexane on rotary evaporator afforded near quantitative recovery of 2-ethyl hexyl methoxycinnamate. Purity by HPLC was found to be > 99.0 %.<sup>7</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 0.88 to 0.94 (two overlapping triplets, 6H), 1.31 to 1.46 (m, 8H), 1.61 to 1.66 (m, 1H), 3.83 (s, 3H), 4.11 (d, 2H, J = 4.2 Hz), 6.30 (d, 1H, J = 15.9 Hz), 6.89 (d, 2H, J = 8.7 Hz, further split due to meta coupling with coupling constants of 2.2 and 3.0 Hz), 7.48 (d, 2H, J = 8.7 Hz, further split due to meta coupling with J = 2.2 Hz), 7.63 (d, 1H, J = 15.9 Hz).

**Heck reaction, preparation of p-methoxycinnamic acid.** To a stirred solution of catalyst 3 (200 mg) in aqueous NMP (1 : 1, 20 mL) under nitrogen, sodium carbonate (544 mg, 5.13 mmole), iodoanisole (300 mg, 1.28 mmole) and acrylic acid (92.3 mg, 1.28 mmole) were added. The reaction system was thoroughly purged with nitrogen and stirring was continued at 90°C for 12 hr. HPLC analysis at this stage indicated complete conversion of iodoanisole to p-methoxyinnamic acid. After five cycles with the same catalyst the product was isolated by phase separating 3 by pouring the reaction mixture into brine and warming it. The alkaline supernatant layer was acidified and the product was isolated as pale yellow solid, m.p. 172°C (Lit.<sup>6</sup> m. p. 172°C). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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).

**Acknowledgement**

Mrs. Nutan Agadi of RSIC, IIT, Mumbai is thanked for the NMR spectra.

**References**