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Pd-Catalyzed Synthesis of a Tethered Soluble Polymeric Phosphine Ligand

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Abstract: The use of a Pd-catalyzed phosphine-aryl iodide coupling chemistry to prepare soluble polymeric phosphine ligands is described. The lack of sensitivity of the catalyst to the presence of excess phosphine ligand and the fact that the soluble polymeric phosphine ligands are effective ligands for the active catalyst results in a self-replicating ligand synthesis. Ligand or ligand plus catalyst recovery is achieved by solvent precipitation of the polymeric product of this chemistry.

New functionalized polymers for use in catalysis and synthesis are of increasing importance in two major unrelated current foci of chemical attention - Green chemistry and combinatorial chemistry. The success and promise of combinatorial chemistry depends in large part on facile strategies to separate products, reagents or catalysts from one another.[1] Such strategies often use polymeric supports and there is significant interest in extension of solution-state Pd-catalyzed chemistry to such supports.[2-4] Green chemistry emphasizes the design of new processes[5] where polymer supports play a role as recoverable catalyst supports in aqueous, organic, ionic or fluorous phase solvent systems. Here we describe a new strategy for synthesis of polymeric phosphine ligands based on a palladium-catalyzed substitution of an aryl iodide by a phosphine. The product of this synthesis is a catalyst for its own synthesis. Thus, this is a self-replicating polymeric phosphine ligand system. As is true in other polymer-supported syntheses, the solubility properties of the polymeric product are an advantage in product purification.

Various polymers have been chemically modified to serve as supports for catalysts. In many instances, these polymers contain phosphine ligands. Examples of polymeric phosphines include diarylphosphine-terminated poly(ethylene oxide),[6] diarylphosphine-terminated polyethylene,[7] and phosphine-containing derivatives of various addition polymers (polystyrene,[8] poly(*N*-alkylacrylamide)s,[9,10] poly(4-pentenoic acid)[11] and poly(maleic anhydride)-*c*-poly(methyl vinyl ether)[12]. The phosphine-carbon bond in such polymeric supports is typically prepared by some sort of nucleophilic substitution reaction. A nucleophilic carbanionic polymer reacting with $ClPPh_2$ or a nucleophilic phosphide anion reacting with an electrophilic polymer are

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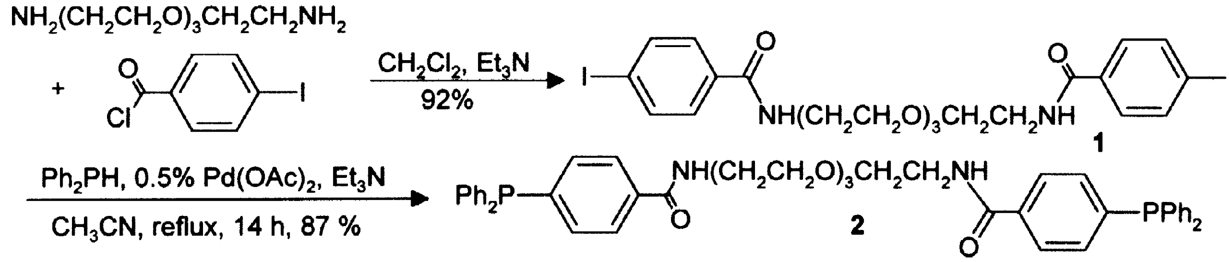
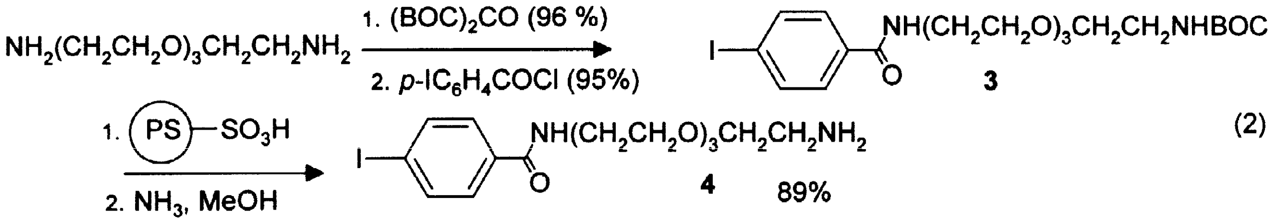
common approaches to effect this synthesis. We have found that the reported reaction of a palladium(0) catalyst, an aryl iodide and diphenylphosphine to form a triarylphosphine[13] can be extended to include polymer bound aryl iodide substrates. The result is a new, simple route to polymeric phosphines that should be broadly useful in synthesis of these common polymer-supported ligand systems and that serves as an example of a self-replicating ligand synthesis.

The chemistry from Stelzer's laboratories shown in eq. 1 is the basis for the chemistry described here.[13] Stelzer showed that aryl iodides containing neutral, electron-withdrawing and electron-donating groups at the 2, 3 or 4 positions give good yields of triarylphosphine in the presence of a base, a Pd-catalyst and $HPPh_2$. We wanted to use this chemistry in synthesis of polymeric phosphine supports. We also wanted to prepare soluble poly(*N*-isopropylacrylamide)-based supports where the ligand was attached via a hydrophilic tether. Our earlier work has shown that groups at the end of a short (e.g. 8-10 atom) tether act more like small molecules when they are attached as side chains to > 500,000 Da PNIPAM polymers. We first tested this chemistry with the low molecular weight PEG-modified aryl iodide **1** which was quantitatively converted to the bisphosphine **2** (the isolated yield of **2** was 87%). A similar amino-functionalized aryl iodide **1** suitable for attachment to a PNIPAM derivative was prepared from an α,ω-diamino derivative of tetra(ethylene glycol) following the procedures outlined in eqs 2 and 3. This synthesis generally involved unexceptional chemistry. Our initial experiments using CF_3CO_2H (TFA) to deprotect the BOC-protected amine intermediate **3** proved surprisingly troublesome (in TFA deprotection of **3** we isolated only 37% of the aryl iodide amine **4**). We found a new procedure using a strong-acid ion exchange resin was simpler.[14] While further optimization might have solved the problem we encountered with the classic TFA deprotection chemistry with this PEG derivative, the combined deprotection/purification afforded by the PS-SO_3H resin more simply solved the problem since ammonia treatment of the resin-bound product yielded an 89% yield of amine **4** that was pure by ^1H NMR spectroscopy (δ ($CDCl_3$) 1.96 (s, 3H), 2.81 (t, 2H), 3.48 (t, 2H), 3.62 (br m, 12 H), 7.6 (d, 2H),

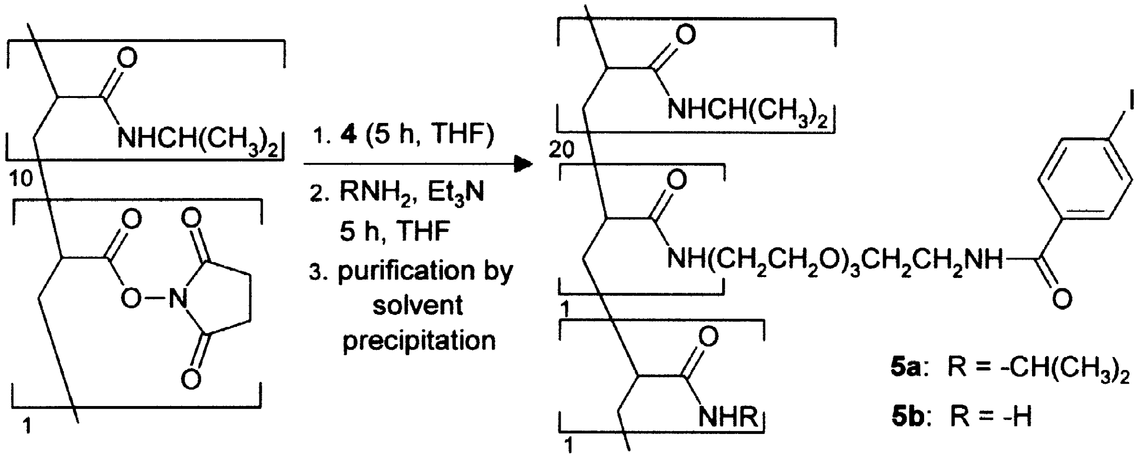


(1)



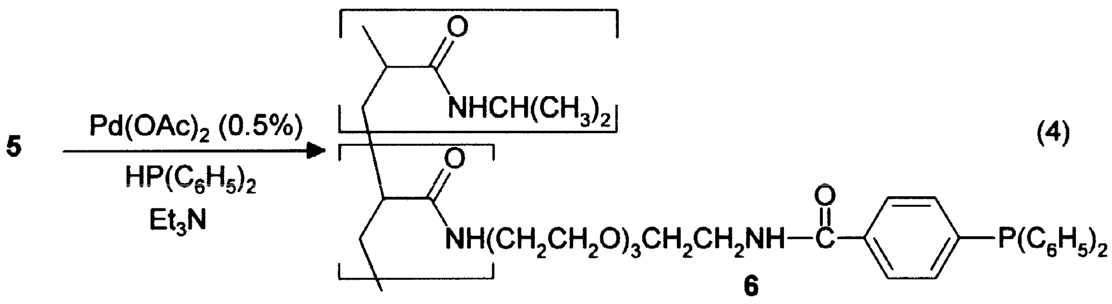
(2)

2.69 (d, 2H)). Coupling of this purified iodoaryl-terminated PEG tether to a 10:1 (N-isopropylacylamide-*c*-N-acryloxysuccinimide) copolymer (eq. 3) used 0.5 equiv of **4**. Quenching unreacted active esters of the co-polymer with $(CH_3)_2CHNH_2$ or NH_3 formed either an organic- or organic/water-soluble polymeric aryl iodide precursor **5a** or **5b** for use in synthesis of polymeric phosphine ligands. In these syntheses, the polymeric iodide suitable for use in phosphine synthesis was isolated by pouring the THF solution of the polymeric iodides **5a** or **5b** into a 5-fold volume excess of hexanes after first removing any *N*-hydroxy succinimide precipitate. The composition of the polymeric products **5a** and **5b** was confirmed by ^1H NMR spectroscopy.



(3)

Exposure of 4 g of **5** to 1.1 equiv of diphenylphosphine and 0.5% $Pd(OAc)_2$ in CH_3CN led to a 98% conversion of the polymeric iodide to the polymer-bound triarylphosphine which could be separated from reactants by precipitation into diethyl ether. Subsequent addition of 0.25 g of this soluble polymer-bound triarylphosphine **6** (which contained <1 mg of Pd), an additional 7 mg of $Pd(OAc)_2$, 0.8 g $HPPh_2$ and 1.5 mL of Et_3N to a solution containing 10 g of **5** then led to an additional 10.3 g of **6**. Thus, this ligand is a self replicating ligand since it ligates the catalyst that makes more ligand from fresh polymer-bound aryl iodide and a small amount of the $Pd(OAc)_2$ catalyst. As is true for other species attached to PNIPAM by tethers, the phosphine **6** resembles its analog **2** in NMR spectroscopy with a sharp single peak at -4.70 δ (line width of 1.1 Hz at 121 MHz) as compared to a similar peak at -4.68 δ for **2** (line width 0.7 Hz at 121 MHz). It is noteworthy that the polymeric triarylphosphine **6** prepared in this way has no phosphine oxide peak – a contaminant seen ubiquitously in our hands in other synthetic routes to similar polymeric phosphine ligands.



(4)

In order to show that **6** promotes formation of itself from **5a**, we carried out two experiments. In the first experiment (A), reaction 4 was allowed to proceed using 2 g of **5a** as starting material. The mixture of polymers present in this reaction were then isolated at 10 min, 40 min and 3 h and the peaks due to the aryl iodide and triarylphosphine in **5a**$_A$ and **6a**$_A$ respectively were integrated relative to the CH of the isopropylamide group. Experment B was similar except that 20 mg of **6a** was added to the starting 2 g of **5a** . In experiment B, the aryl iodide and triarylphosphine contents **5a**$_B$ and **6a**$_B$ were analyzed. The ratios of **5a**$_A$/**5a**$_B$ and the ratios of **6a**$_A$/**6a**$_B$ were 2.2:1 and 1:2.6, respectively. The faster disappearance of **5a** and the faster appearance of **6a** in experiment B are consistent with premise that **6a** acts as a ligand for a catalyst that forms itself. After 40 min, sampling showed that the amounts of triarylphosphine in experiments A and B were essentially equivalent. After 3 h, the reaction was complete (there was no remaining aryl iodide).

In summary, palladium-catalyzed P-C bond formation is an excellent alternative to nucleophilic substitution routes previously used to prepare polymeric triarylphosphine ligands for use in synthesis of soluble polymer-bound catalysts. In the examples here, polymeric phosphines that are suitable for use in either water or organic solvents can be prepared by simply changing the hydrophilicity of the underlying polymer.

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