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Soluble polymer-supported hindered phosphine ligands for palladium-catalyzed aryl amination†

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Strategies for synthesis of more effective soluble supported ligands for phosphine-ligated Pd(0) cross coupling catalysts have been explored. Reversible addition-fragmentation chain transfer (RAFT) polymerization has been used to prepare alkane-soluble poly(4-alkylstyrene)-bound phosphine ligands. 4-*tert*-Butylstyrene and 4-dodecylstyrene were copolymerized with *ca.* 7 mol% of 4-chloromethylstyrene or a 4-diphenylphosphinestyrene monomer using RAFT chemistry to afford poly(*tert*-butylstyrene-*co*-4-dodecylstyrene) copolymers. Polymers with chloromethyl groups were allowed to react with the phenolic group of a hindered dicyclohexylbiarylphosphine ligand. This hindered polymer-bound phosphine formed reactive Pd complexes useful in haloarene amine couplings. All aryl halide amination reactions had Pd leaching that was typically <0.1% of the charged Pd with one example having only 0.02% Pd leaching. These Pd complexes of poly(4-alkylstyrene)-bound phosphines were also compared to similar hindered phosphine complexes formed with a polyisobutylene (PIB), whose terminus was also converted into a dicyclohexylbiarylphosphine ligand. Palladium catalysts ligated by these hindered biarylphosphines on poly(4-alkylstyrene) and PIB-bound both were recyclable in the absence of oxygen, had similar activity, and very low Pd leaching.

Introduction

Palladium-catalyzed cross-coupling is widely recognized as a powerful synthetic tool.[1] In addition to Pd-catalyzed Heck and Suzuki reactions, the Buchwald–Hartwig amination has become an important route to aromatic amines.[2–5] These amination reactions also tend to be more sensitive tests of Pd cross-coupling catalyst activity. They typically require the presence of phosphine ligands although there are examples of such chemistry with nanoparticle or 'ligand-free' Pd catalysts.[6–9] The use of hindered phosphine ligands has been demonstrated to be especially important and reactions using such ligands and Pd catalysts afford good product yields even with relatively unreactive aryl chlorides.

The recovery and recycling of the Pd catalysts used in cross-coupling chemistry is also important. Many papers have detailed recycling/recovery strategies for Pd cross-coupling catalysts.[10] Most commonly insoluble polymeric or insoluble inorganic supports have been used in recovery and recycling of such catalysts. Such supports also recycle and recover phosphine ligands.[11,12] This paper focuses on recovery and recycling of reactive Pd catalysts that employ a typical hindered biaryldicyclohexylphosphine ligand using alternative soluble poly(4-alkylstryene) and polybutyrene supports.

Extensive work by various groups has examined soluble polymer-supported conventional phosphines both as ligands for transition metal catalysts or as catalysts themselves.[12–15] This work extends those studies to include designing polymer supports that we expected to have heightened phase selective solubility using as examples supports that could be easily modified to include hindered biaryldicyclohexyl-phosphine ligands. The results below show that soluble supported polymer-bound versions of these hindered ligands are readily accessible and that the Pd complexes formed using these ligands are highly reactive and recyclable in Pd-catalyzed haloarene-amine coupling reactions.

The general approach our lab has favored in immobilizing catalysts which we have applied here to hindered phosphine ligated Pd catalysts has been to use soluble polymers as supports for the phosphine ligands. This is an approach with considerable precedent at least for conventional phosphine ligands. Our work has emphasized using soluble polyolefin supports where a liquid/liquid or liquid/solid phase separation is used to effect recycling of the phosphine ligand and/or its associated catalyst from products.[16] Alternative

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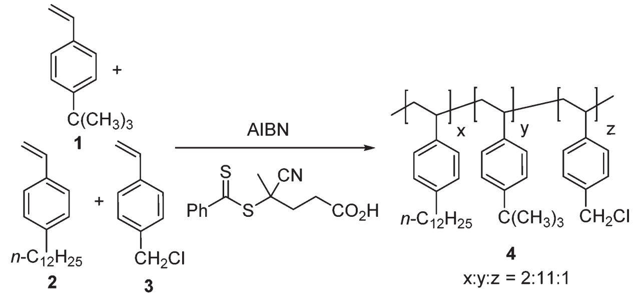
strategies have also been used. For example, soluble supports studied by other groups that incorporate polymer-bound phosphine ligands for Pd catalysis include using polymers like poly(ethylene glycol) that are separated from products by solvent precipitation,[12] poly(alkene oxide) copolymers that are separable in thermoregulated systems[17] or poly(4-methylstyrene)s that are separable from products by solvent precipitation or a thermomorphic separation.[18] Recent work also suggests that poly(4-alkylstyrene)-bound phosphines prepared using a reversible addition-fragmentation chain transfer (RAFT) polymerization are still another alternative.[19,20]

Results and discussion

The studies described here use two sorts of linear lipophilic polymer supports – poly(4-alkylstyrene) and polyisobutylene.[19–21] The first 4-alkyl-substituted polystyrene support is an alternative to unsubstituted polystyrene. Such a poly(4-alkylstyrene) can be separated using a liquid/liquid separation avoiding the need for excess solvent needed for solvent precipitation as a catalyst/product separation step. By preparing poly(4-alkylstyrene)s with hydrophobic 4-alkyl substituents, we can prepare supports that are highly heptane phase selectively soluble (Scheme 1). The quantitative phase selective solubility of these poly(4-alkylstyrene) copolymers had been previously studied using fluorescent labels.[20] Those studies showed that polymers prepared as in Scheme 1 are quantitatively separable as heptane solutions from a polar solvent phase with <0.1% of leaching of a dansyl labeled polymer into the CH_3CN phase of an always biphasic heptane/CH_3CN mixture or into the polar DMF phase of a equivolume thermomorphic heptane/DMF solvent mixture.

The synthesis in Scheme 1 led to a copolymer of 4-*tert*-butylstyrene and 4-dodecylstyrene (**4**) as the support and incorporated 7 mol% of a third 4-chloromethylstyrene monomer. The benzyl chloride groups in this group served as a handle for subsequent incorporation of nucleophiles that are spectroscopic probes for estimating phase selective solubility or that are ligands for catalysis. While we could have prepared homopolymers of 4-dodecylstyrene, using homopolymers would require more substantial quantities of the monomer 4-dodecylstyrene which is not commercially available. Our prior work with dansyl labeled copolymers showed that copolymers prepared with the commercially available monomer 4-*tert*-butylstyrene with modest mole fractions of dodecyl groups have most of the desired phase selective solubility of a 4-dodecylstyrene homopolymer. Thus, we chose to use copolymers with a *ca.* 10 : 1 ratio of 4-*tert*-butyl/4-dodecyl groups to minimize the need to synthesize monomers. Such poly(4-alkylstyrene)s have previously been shown to afford highly phase selective supports for organocatalysts.[19]



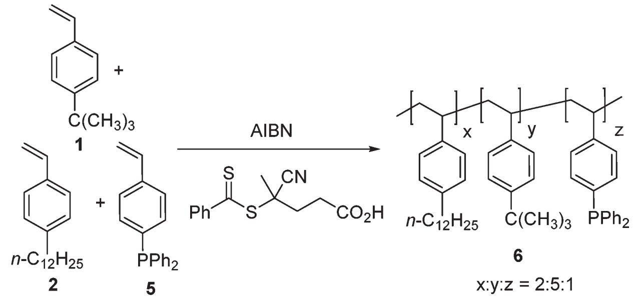
Scheme 1 Synthesis of chloromethylated poly(4-alkylstyrene) terpolymers suitable for conversion into a heptane phase-selectively soluble supports.

A further consideration in our design of phase selectively soluble poly(4-alkylstyrene) supports for relatively lipophilic hindered phosphine ligands related to the fact that we have observed that the leaching of metals from soluble polymer supported catalysts is often higher in the first few cycles of a recycling study, especially when the mass of the catalyst or ligand is large relative to the mass of the support.[22] We have previously ascribed this leaching in part to the presence of a small fraction of lower molecular weight polymer chains that have less phase selective solubility. The synthesis in Scheme 1 takes advantage of more modern controlled radical polymerization techniques using a RAFT polymerization to prepare the product polymers with M_n values of *ca.* 20 kDa and PDIs of *ca.* 1.2 – PDIs that are substantially lower than what can be obtained in a conventional radical polymerization of these same monomers. As shown below, the polymers prepared by this RAFT chemistry are as effective as supports as polymers prepared by a conventional radical polymerization.[20]

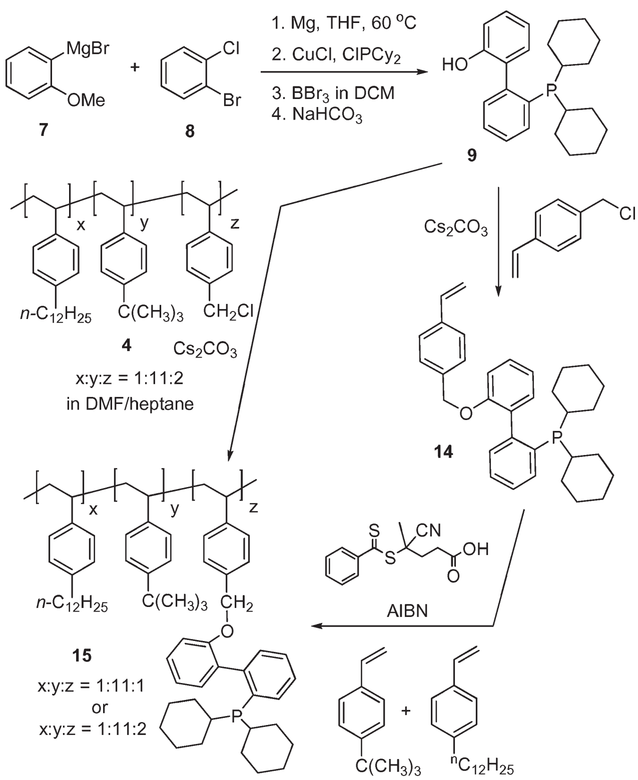
The terpolymer **4** was characterized by GPC and ^1H NMR spectroscopy and contained 7 mol% –CH_2Cl groups based on ^1H NMR spectroscopy analysis of the relative peaks at 2.47 δ for the benzylic protons of the 4-dodecylstyrene groups and at 4.45 δ for the –CH_2Cl protons of the chloromethyl group. The molecular weight of the terpolymer **4** varied, ranging from 9–25 kDa with PDI of *ca.* 1.2.

In initial experiments, we prepared an analog of **4** that used a 4-diphenylphosphinylstyrene in place of the chloromethyl group to prepare a heptane soluble poly(4-alkylpolystyrene)-bound phosphine ligand directly without a post polymerization modification step. However, while this heptane soluble polymeric phosphine formed a Pd catalyst on reaction with $Pd(dba)_2$ that was active and recyclable in Suzuki coupling reactions,[20] the Pd catalyst formed using this relatively simple phosphine ligand was not active in haloarene amine cross coupling affording only traces of *N*-phenylmorpholine in a reaction of morpholine and bromobenzene (Scheme 2).

To prepare a more active catalyst, we incorporated a more electron-rich hindered phosphine onto the poly(4-*tert*-butyl-*c*-4-dodecyl)styrene copolymer. As noted above, Buchwald has shown that similar phosphine ligands lead to formation of more active catalysts for Pd-catalyzed aminations.[22] We explored two approaches to anchor a Buchwald-like hindered biaryldicyclohexylphosphine onto a heptane phase-selectively soluble polystyrene support (Scheme 3). The first of these approaches was modeled after the approach Buchwald's



Scheme 2 Synthesis of chloromethylated poly(4-alkylstyrene) supported triarylphosphine from hydrophobic 4-alkylstyrene monomers and 4-diphenylphosphinylstyrene.

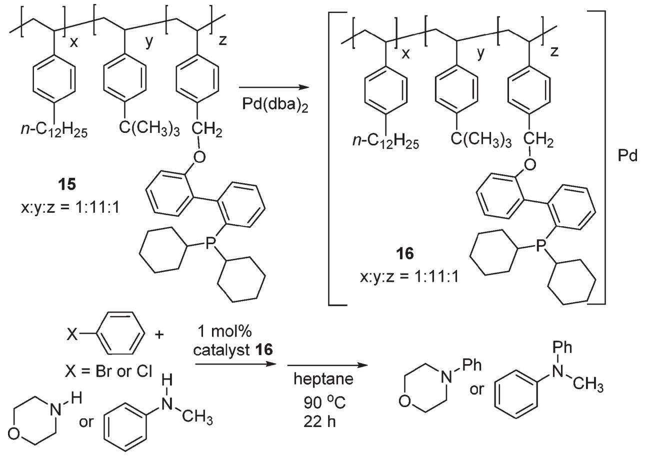


Scheme 3 Syntheses of poly(4-alkylstyrene) copolymer bound dicyclohexylbiarylphosphine.

group used to attach similar phosphines to insoluble divinylbenzene-crosslinked polystyrene supports[11] and involved a post-polymerization modification of the benzyl chloride groups of **4**. This approach began by using the reaction of an *ortho*-methoxyphenylmagnesium bromide with benzyne that was formed *in situ*. The 2′-methoxybiaryl-2-magnesium bromide formed *in situ* by this chemistry was then allowed to react with dicyclohexylchlorophosphine to form a 2′-methoxy-2-dicyclohexylphosphinylbiphenyl phosphine. Removal of the methoxy group followed by dimethylation formed a phenolic group that could then be converted into a nucleophilic phenolate group by reaction with $CsCO_3$ in a monophasic equivolume mixture of heptane and DMF at 100 °C. The resulting nucleophile then formed the desired lipophilic linear poly(4-alkylstyrene) polymer-bound phosphine **15** in a Williamson ether synthesis.

The second approach to coupling a hindered dicyclohexylbiarylphosphine ligand to a soluble poly(4-alkylstyrene) used a nucleophilic substitution reaction of the phenolic phosphine ligand with vinylbenzyl chloride to form a phosphine-containing monomer (Scheme 3). Copolymerization of this monomer **14** with a mixture of 4-*tert*-butylstyrene and 4-dodecylstyrene following the approach we had successfully used earlier to prepare poly(4-alkylstyrene-*c*-4-diphenylphosphine)-bound Pd catalysts for Suzuki catalysis led to **15**. These two approaches that were equally successful in preparing the polymer-bound benzyloxy-substituted dicyclohexyl phosphine ligand **15** are shown in Scheme 3.

The polystyrene-supported dicyclohexylbiaryl phosphine **15** prepared by either of the routes in Scheme 3 was an effective phase separable ligand for *in situ* formation of a Pd catalyst for arylhalide amination (Scheme 4). While the loading of phosphine on the soluble polystyrene differed in the two approaches, experiments showed that Pd catalysts formed with each polymer using the same Pd/phosphine ratio at 1 mol% loading of Pd had similar activity in reactions of bromobenzene with morpholine. In using the phosphine **15** to prepare a Pd catalyst, the linear polystyrene-bound phosphine **15** was converted into a Pd catalyst by stirring a heptane solution of this phosphine with $Pd(dba)_2$ at *ca.* 90 °C for 30 min. During this process, the initial clear solution changed to a clear yellowish solution. The polymer-bound Pd(0) complex so formed was not isolated but was used and recycled as a solution in heptane. ICP-MS analysis of a solution of the recycled catalyst in cycle 3 showed that the Pd content of the heptane solution was equivalent to that in the initial solution (*i.e.* a Pd content of *ca.* 520 ppm that was unchanged from the initial Pd loading). Separate experiments showed that $Pd(dba)_2$ alone cannot be recycled as a heptane



Scheme 4 Synthesis and use of a Pd(0) aryl amination catalyst prepared using a phase-separable poly(4-alkylstyrene)-bound dicyclohexylbiarylphosphine.

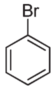
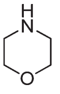
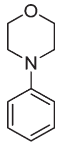
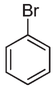
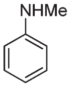
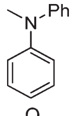
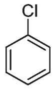
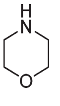
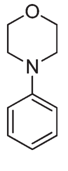
solution and that Pd(dba)$_2$ is not competent as a catalyst in aryl aminations.

To effect catalysis, the heptane solution of the Pd catalyst **16** formed *in situ* was mixed with bromobenzene or chlorobenzene along with a secondary aliphatic or benzylic amine and KO-*tert*-Bu was added. These reactions were carried out on a 1 mmol scale in 3 mL of heptane in a sealed 10 mL vial. The resulting mixture was stirred for *ca.* 20 h at 90 °C. After cooling to room temperature, 2 mL of degassed methanol solution saturated with heptane was added to the reaction vial by forced siphon *via* a cannula. After brief stirring, this biphasic mixture was centrifuged to separate the heptane containing catalyst phase from the product containing methanol rich phase. After the colorless methanol phase was physically separated from the yellowish heptane phase containing the Pd catalyst, the catalyst containing heptane phase was transferred to another sealed test tube containing fresh substrates and base. In this way, the catalyst was recycled five times without any observed loss of catalytic activity. The conversions in each cycle were >98% by ^{1}H NMR spectroscopic analysis. In cycles 1 and 2, the reaction mixture was analyzed by ^{1}H NMR spectroscopy every 6–8 h. These analyses showed that the reactions were complete (*i.e.* >98% conversion) after 20 h. Cycles 3–5 were then analyzed at 20 h and in each case the conversion of starting aryl bromide was complete. These reaction times are similar to the 15–20 h reaction times reported by Parrish and Buchwald for a similar Pd(0) catalyst formed *in situ* by a DVB-crosslinked polystyrene supported ligand analogous to **15**. The five methanol product phases were combined and the product arylamine from these five cycles was isolated after column chromatography with an average yield of product for five cycles that varied from 82–95% (Table 1). While the yellow catalyst phase did not discolour and while the product phases were colorless, inductively coupled plasma mass spectroscopy (ICP-MS) analyses were used in cycle 3 to provide a quantitative analysis of leaching. These ICP-MS analyses of the product isolated from the polar methanol phase showed 0.08, 0.04, or 0.04% Pd leaching in cycle 3 for experiments that used 1 mol% of the Pd catalyst **16** in reactions of bromobenzene with morpholine, bromobenzene with *N*-methylaniline, or chlorobenzene with morpholine, respectively. These leaching levels correspond to 1–10 ppm Pd in the product arylamine when catalyst loadings of *ca.* 1–2 mol% are used.

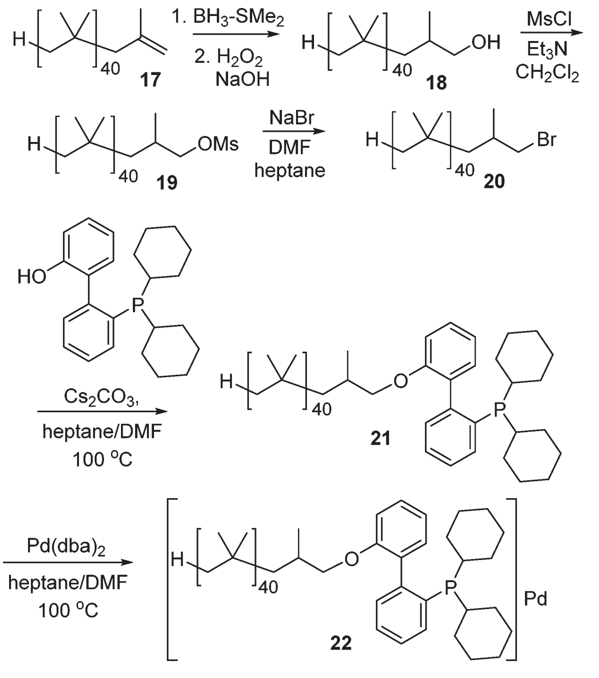
Polyisobutylene (PIB) is an alternative heptane-soluble support that our group has studied extensively.[21] We therefore also examined syntheses of PIB-bound hindered phosphines. While our initial efforts to prepare PIB-bound dicyclohexyl or di-*tert*-butylphosphine were unsuccessful or formed phosphines that were easily contaminated by phosphine oxide, the use of hydroxyl-substituted dicyclohexylbiaryl phosphine as a nucleophile was more successful and led to the relatively stable PIB-bound dicyclohexylbiarylphosphine **21** (Scheme 5). This phosphine is formed as a mixture of diastereomers because of the presence of two elements of chirality in this soluble polymer bound phosphine ligand – a chiral tetrahedral carbon on the PIB group due to the carbon containing a single methyl group and an axially chiral biarylphosphine ligand. No attempt was made to separate these diastereomers.

The catalytic activity of Pd catalyst formed *in situ* from the PIB-supported phosphine ligand **21** with Pd(dba)$_2$ was equivalent to that of the Pd complexes prepared from a poly(4-alkylstyrene) supported ligand. The conversions in each cycle

Table 1 Aryl halide amination using soluble Pd catalysts ligated by heptane soluble polymer-bound biaryldicyclohexylphosphine ligands[a]

Aryl halide	Amine	Product	Cycles	Average yield (%)
			5	82(82)[b]
			5	85(84)[b]
			4	95(94)[b]

[a] Reactions carried out on a 1 mmol scale with 1 mol% of 16 (or 1.5 mol% of 22) at *ca.* 90 °C for *ca.* 20 h. [b] Yields in parentheses refer to average yields for reactions using catalyst 22 for 8, 8, or 6 cycles in reactions with morpholine, *N*-methylaniline, or morpholine respectively isolating the product using either MeOH extraction of PS–SO$_3$H sequestration.



Scheme 5 Synthesis of a PIB-bound hindered phosphine **21** and its reaction to form a Pd catalyst **22**.

were >98% by ^{1}H NMR spectroscopic analysis. These reaction times are similar to the 15–20 h reaction times reported by Parrish and Buchwald for a similar Pd(0) catalyst formed *in situ* by a similar DVB-crosslinked polystyrene supported ligand and by the soluble polystyrene ligand described above. Isolated yields of products from are listed in Table 1. These isolated yields like those reported above are an average yield for 5 cycles since the five 1 mmol scale reactions were combined prior to workup.

Recycling of the PIB catalyst **21** was effected with product separation in methanol and catalyst recycling in heptane. This separation was effective as was the case with poly(4-alkylstyrene) supported Pd ligated by the phosphine **15** with Pd leaching of 0.1% Pd leaching or 0.02% in reactions that used 1.5 mol% of the Pd catalyst **22** in coupling of bromobenzene with *N*-methylaniline or morpholine, respectively. The product phases were colorless.

We did not examine the polar phase that contained *ca.* 0.1% of leached Pd for catalytic activity in any of these reactions. The concentration of Pd in that phase was *ca.* 1000-fold lower that the concentration of Pd in the heptane phase and at these Pd concentrations, catalyst activity would not be significant.

Both the poly(4-alkylstyrene) terpolymer support above and the commercial PIB used below have low PDI values (the PIB reportedly has a PDI of *ca.* 1.3).[23] While the narrow PDI may affect leaching of catalyst in the first or second cycle, the high heptane phase solubility of these polymers is likely the most important feature in achieving low Pd leaching. For example, a simple diphenylphosphine-ligated Pd catalysts attached to a similar poly(4-alkylstyrene) terpolymer prepared by conventional AIBN polymerization had Pd leaching that is only slightly higher than that for Pd ligated by **15**.[20]

We also explored an alternative product isolation scheme with the PIB-bound catalyst **22**. This scheme used Amberlyst 15 as an *in situ* sequestrant following a protocol we had previously described.[24]

This approach afforded yields of arylamine product that were essentially identical to those obtained using methanol as an extracting solvent in the initial reaction. However, recycling was less effective when this product isolation strategy was used. Separate studies showed that the –SO_3H groups of the Amberlyst were sufficiently acidic in heptane such that they removed significant (20% or more) of phosphine **21** per cycle.

Conclusions

In summary, we have prepared two versions of a soluble polymer supported hindered dicyclohexylbiarylphosphine ligand. RAFT chemistry afforded highly phase selectively soluble poly(4-alkylstyrene)supports that incorporate such ligands by post-polymerization phosphinylation or directly using a phosphine-containing monomer. Polyisobutylene with terminal dicyclohexylbiarylphosphine groups can be prepared from a bromo-terminated polyisobutylene by a Williamson ether synthesis. Either of these polymers form Pd catalysts that show excellent catalytic activity in Buchwald–Hartwig amination reactions affording good isolated yields of arylamines from secondary alkyl or benzylic amines and bromobenzene or chlorobenzene. Successful catalyst recycling was effective and using biphasic liquid/liquid separation. Pd leaching was analyzed by ICP-MS analysis and was uniformly very low with typical values for Pd leaching consistently <0.1% for reactions that used 1.5 or 1 mol% of the Pd catalyst.

Acknowledgements

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