

Heck reaction using palladium complexed to dendrimers on silica

Howard Alper, Prabhat Arya, S. Christine Bourque, Gary. R. Jefferson, and Leo E. Manzer

Abstract: Polyamidoamine dendrimers, constructed on the surface of silica, were phosphonated using diphenylphosphinomethanol (prepared in situ) and complexed to form a palladium–dimethyl TMEDA complex. This catalyst was found to be effective in the Heck reaction of aryl bromides with both butyl acrylate and styrene, affording coupling products in moderate to good yields. The heterogeneous palladium catalyst can also be recycled and reused with only moderate reduction in activity.

Key words: dendrimer, Heck, palladium, silica.

Résumé : Utilisant du diphenylphosphinométhanol (préparé in situ), on a réalisé la phosphonation de dendrimères de polyamidoamines synthétisés sur une surface de silice et en a fait un complexe de palladium–« TMEDA » de diméthyle. On a trouvé que ce catalyseur est efficace dans la réaction de Heck des bromures d'aryles avec aussi bien l'acrylate de butyle que le styrène et que ces réactions fournissent des produits de couplage avec des rendements allant de modérés à bons. On peut aussi régénérer le catalyseur hétérogène et le réutiliser avec une perte mineure d'activité.

Mots clés : dendrimer, Heck, palladium, silice.

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Introduction

The demand for cleaner, environmentally friendly chemistry is coming from many quarters. Legislative, public, and corporate pressure has led to the rapid development of new innovations in green technology. While the majority of new chemical processes developed in the last 50 years are catalytic, there are still problems associated with catalyst recovery, both in terms of reusing the catalyst or at least recovery of the precious metals often used, with the added advantage of easier purification of products.

Over the past 20 years the Heck reaction, used in the coupling of aryl halides with vinylic substrates, has been shown to be a versatile tool which allows easy access to often complex products from relatively simple substrates (1). Despite

the practical ease of reaction and the reliably good yields, the Heck reaction has not developed past a laboratory method, bar a few examples (2).

The lack of transfer to an industrial scale is primarily due to the expense of the palladium catalyst, as high loadings of palladium (e.g., 10 mol%) (3) and, as with homogeneously catalyzed systems, costly removal of the catalyst residues are required. Only when the reaction products are of high commercial value (e.g., pharmaceutical products) can this catalytic system be used viably because the cost of the catalyst is appreciably a smaller percentage of the final product than in the bulk chemical case. Hence in the large scale synthesis of bulk chemicals, the Heck reaction has made little impact.

Over approximately the last 10 years, in an attempt to extend the Heck reaction to the bulk chemical sector, several groups have worked on developing heterogeneous catalytic systems (4). Such systems could, in principle, reduce the cost and technical problems associated with removal of the catalyst and also increase the lifetime of the palladium catalyst. The use of lower concentrations of palladium might also be a consequence of heterogenizing the catalyst. Many groups have attacked this problem and have made considerable headway in some cases. Of particular note is the work of Ying et al. (5), who have developed a palladium [0] complex on silica which shows very high turnover rates especially for activated bromoarene systems. However it should be noted that the catalyst preparation requires specialized techniques.

Most of the other examples in the literature utilize iodoarenes (6), the most reactive of the haloarene family in the Heck reaction, but unfortunately the most expensive and

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Dedicated to Steve Hanessian – a trailblazer in research; a first class supervisor of some of our leaders of tomorrow; a genuine friend.

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also generally less readily available than its bromo and chloro counterparts. One of the main goals of the Heck reaction in both a heterogeneous and homogenous sense is to utilize the cheaper bromo- and chloroarenes.

Polymer supported metal complexes have attracted considerable interest over the last few years. Terasawa et al. (7) have studied the Heck reaction of styrene with iodobenzene comparing a variety of heterogeneous catalysts. A phosphinated polystyrene complex was compared to palladium with the analogous free palladium complex, palladium salts, Pd/C in terms of catalytic activity and selectivity, and it was found that the polymer supported palladium complex is highly active but noticeable deactivation was observed during repeated use. Zhang et al. reported a polymer supported phenanthroline palladium catalyzed arylation of acrylamide (8); however, when tributylamine was used the catalyst activity declined significantly on recycling, and preparation of the catalyst is complicated. Although there have been several advances in the Heck reaction in terms of increased turnovers and catalyst stability for both heterogeneous and homogenous systems, the catalyst lifetimes and turnovers still preclude industrial use.

We recently developed a dendritic silica supported bidentate phosphine ligand (9). It was postulated that this ligand could be utilized in the Heck reaction with a suitable palladium catalyst. The dendritic support is thought to work with many facets, one of which is to give the reaction a degree of homogenous character, as the dendritic support would be highly solvated in a suitable solvent system. It is also speculated that the ligand increases the stability of the catalytic system.

In recent years, major efforts have been directed toward the development of new catalytic systems that effectively combine the advantages of both heterogeneous and homogeneous catalysis (10). Such a catalyst would ideally be easily recoverable and potentially recyclable while maintaining high catalytic efficiency. Dendrimer-metal complexes are particularly attractive in this regard.

Dendrimers are highly branched macromolecules, which are capable of having multiple sites for metal coordination (11). In 1994, van Koten and coworkers demonstrated that soluble polycarbosilane dendrimer complexes of nickel (II) catalyze the addition of polyhaloalkenes to double bonds (12). Three years later, Reetz and coworkers synthesized a polyaminodiphosphine dendrimer to coordinate to rhodium and palladium catalysts (13). Our research has led to the development of heterogeneous polyaminoamidodiphosphonated dendrimers built on a silica gel core support (PPh₂-PAMAM-SiO₂). This article describes the use of these dendrimers, when complexed to palladium, as effective catalysts for the Heck reaction.

Results and discussion

(a) Preparation of PAMAM-SiO₂ dendrimers

Commercial aminopropyl silica gel was used to prepare generation 0–4 polyaminoamido (PAMAM) dendrimers (9). Propagation of the dendrimers was achieved by standard dendrimer building methods pioneered by Tomalia and coworkers (14). Amino propionate esters were obtained by Michael type addition of the preexisting amino group to methyl

Scheme 1.

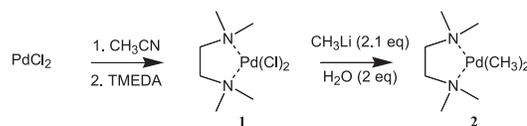


Table 1. Palladium content of the various PPh₂-PAMAM-SiO₂ dendrimers.

Generation	Percentage palladium (%) ^a	g Pd/g Si	μmol Pd/25 mg SiO ₂
G-0	2.93	0.0293	6.91
G-1	1.34	0.0134	3.16
G-2	1.13	0.0113	2.66

^aDetermined by ICP analysis

acrylate. Amidation of the ester units with ethylenediamine completes the generation, with repetition of the two steps affording the desired generation of the dendrimer.

Coordination of the dendrimers to palladium was effected first by phosphonation. Diphenylphosphinomethanol, prepared in situ from paraformaldehyde and diphenylphosphine, was excellent for the double phosphinomethylation of each terminal amine group.

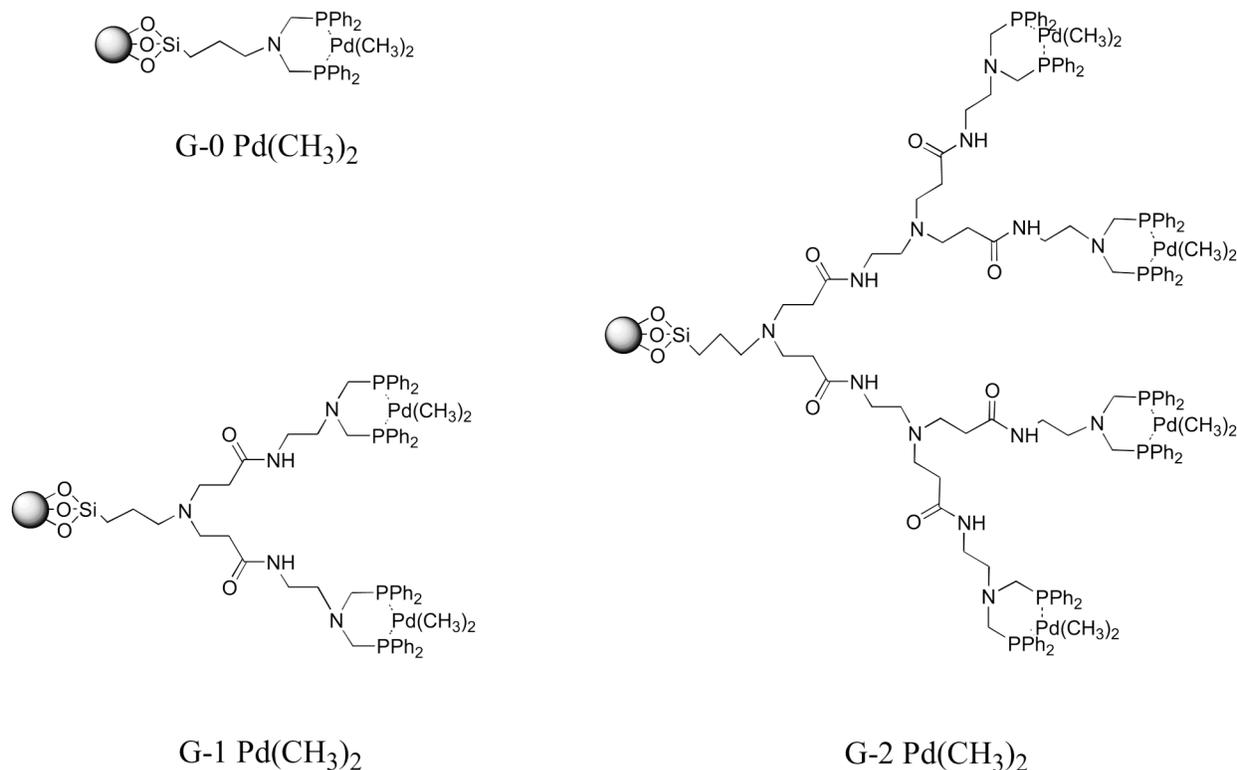
The complex **2** is easily synthesized starting from palladium chloride, in situ formation of the bis(acetonitrile)palladium dichloride (15), followed by displacement of the acetonitrile ligands with TMEDA forming complex **1**. Reaction of complex **1** with methyl lithium gives complex **2** in 65% overall yield (Scheme 1).

The palladium complex is coordinated to the dendrimer on silica by simply stirring the dendrimer in degassed benzene with one equivalent of palladium complex **2**, relative to the theoretical number of end phosphine groups for the respective dendrimer. The dendrimer complexes are easily isolated by microporous membrane filtration. The resulting complexed dendrimers (see Fig. 1) were characterized by ³¹P solid state NMR (complexed δ = 6 ppm, uncomplexed δ = -27 ppm) (13a).

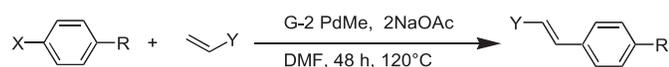
The palladium complexed PPh₂-PAMAM-SiO₂ dendrimers were digested with hydrofluoric acid or aqua regia (nitrohydrochloric acid) by microwave heating and analyzed for Pd content by ICP analysis. The palladium content of the various generations is summarized in Table 1. The degree of complexation decreases significantly with dendrimer generation from G-0 to G-2, and was so low for G-3 and G-4 as to preclude further studies with the latter generations of dendrimers. This is believed to be due to incomplete phosphonation reactions arising from steric crowding and ultimately resulting in the threshold of dendrimer growth being reached.

(b) Catalytic heck reaction of aryl bromides using palladium complexed silica supported dendrimers

As a model reaction for assessing the utility of these Heck catalysts, the reaction of bromobenzene with styrene in DMF at 120°C was investigated in the presence of sodium acetate as base, primarily because these were the conditions

Fig. 1. Dendrimer generations $(\text{CH}_3)_2\text{Pd-PPh}_2\text{-PAMAM-SiO}_2$.

employed by Reetz and co-workers for their dendritic Heck system. The catalytic activity of the palladium complexed $\text{PPh}_2\text{-PAMAM-SiO}_2$ dendrimers was investigated with re-



gards to the Heck reaction (Reaction [1]) and the results are summarized in Table 2. Treatment of styrene and bromobenzene in dimethylformamide, with Pd complexed $\text{PPh}_2\text{-PAMAM-SiO}_2$ dendrimer, and sodium acetate affords *trans* stilbene in good yield and regioselectivity for generations 0, 1, and 2. The yields of stilbene was significantly less when generation 3 and 4 dendrimer complexes are used as catalysts.

The best turnovers in terms of molecules of *trans*-stilbene formed per mol of palladium was achieved with the generation 2 catalyst, as may be expected as this catalyst would have the greatest homogeneity factor (Table 3).

The effect of temperature on the Heck reaction was studied with the generation 2 catalyst and it was found that the best yields were obtained when the temperature was in the 110 to 140°C range (Table 4). At lower temperatures the yields were low due to either poor conversion of the catalyst precursor to the catalyst via reductive elimination of the methyls, or just a factor of low turnovers at low temperatures. At temperatures above 140°C the yield was reduced by catalyst deactivation with noticeable palladium black formation.

The effect of the base on the reaction was studied in terms of yield and recoverability of the catalyst (Table 5). The inorganic bases; potassium carbonate and sodium acetate were

Table 2. Conversions in the Heck reaction of styrene and bromobenzene using the $\text{Pd-PPh}_2\text{-PAMAM-SiO}_2$ catalysts.^a

Time	G-0	G-1	G-2
6 h	67% ^b	10%	17%
24 h	76%	37%	49%
48 h	79%	47%	59%

^a6.0 mmol each of styrene and bromobenzene, 6.6 mmol of NaOAc, and 50 mL of DMF.

^bYields determined by GC and NMR analysis.

Table 3. Turnovers for generations 0, 1, and 2 of the $\text{Pd-PPh}_2\text{-PAMAM-SiO}_2$ dendrimers.^a

Dendrimer generation	Turnovers (h after 6 h)	Turnovers (h after 24 h)
0	72	21
1	31	30
2	81	58

^a6.0 mmol each of styrene and bromobenzene, 6.6 mmol of NaOAc, 50 mL of DMF.

used as well as the organic base, triethylamine. Potassium carbonate and sodium acetate gave the best yields, and low product yield was found using triethylamine (13a). This triethylamine effect was also observed by Reetz and co-workers using their dendritic Heck catalyst system.

As some loss in activity of the catalyst was noticed we examined the possibility of leaching of the catalyst into the reaction mixture. The reaction was carried out with styrene and bromobenzene using the G-2 catalyst, and after 16 h, the reaction was filtered under nitrogen. A further 2 mmol of

Table 4. Conversions in the Heck reaction of styrene and bromobenzene using the Pd-PPh₂-G2-PAMAM-SiO₂ dendrimer at different temperatures.^a

Temperature (°C)	25	50	80	110	140	170
Yield ^b (%)	NR	NR	5	69	44	NR

^a2.0 mmol each of styrene and bromobenzene, 2.2 mmol of NaOAc, and 50 mL of DMF.

^bNR = No reaction, Yields were determined by NMR analysis.

Table 5. Conversions in the Heck reaction of styrene and bromobenzene using the Pd-PPh₂-G2-PAMAM-SiO₂ dendrimer with different bases.^a

Base	Cycle 1 (%)	Cycle 2 (%)
K ₂ CO ₃	53 ^b	43
NEt ₃	5	—
NaOAc	39–69	20–45

^a2.0 mmol each of styrene and bromobenzene, 2.2 mmol of NaOAc, 50 mL of DMF.

^bYields were determined by NMR analysis.

styrene and bromobenzene was added and sample was taken for GC analysis. The reaction was run for a further 48 h and no further reaction of the mixture took place.

The generality of the catalytic system was investigated for a variety of haloarenes, and the results are presented in Table 6. Initially the nature of the halogen used was studied. It was found that the reaction of bromo and iodobenzene gave similar yields with no detectable product using chlorobenzene. We then examined the effect of *para* substituents on the haloarenes. It was surprising to find that electron withdrawing substituents (nitro, ester) gave relatively low yields and conversions, while electron donating groups (methoxy, methyl) gave moderate to good yields of coupled products. This observation suggests that the oxidative addition step of the Heck reaction is relatively facile whereas the alkene insertion or reductive elimination is the rate determining step. This reactivity may be a function of the nitrogen in the ligand donating into the metal center leading to facile oxidative addition. The catalyst system was also found to be active for thiophenes with no catalyst poisoning resulting from the sulfur atom.

Summary

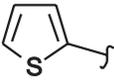
The dendrimer supported complexes, Pd-PPh₂-PAMAM-SiO₂, are new and highly active catalysts for the Heck reaction of a variety of bromoarenes with styrene and butyl acrylate, affording *para* substituted stilbenes and cinnamate esters in good yields. This dendritic system shows comparable activity to the Reetz dendrimer system (13) and can be easily recycled.

Experimental

General

Dimethylformamide (Aldrich) was used in anhydrous form. All the aryl bromides, iodobenzene and alkene substrates were purified before use. Aminopropyl silica gel was purchased from Fluka.

Table 6. Catalytic activity of the G-2 complex catalyst for the reaction of a variety of haloarenes with styrene and butyl acrylate.^a

R group	X group	Y = C(O)O ⁿ Bu	Y = Ph
		Isolated yield ^b (%)	Isolated yield ^b (%)
H	I	—	68
H	Br	85	69
H	Cl	—	0
<i>p</i> -Me	Br	76	81
<i>p</i> -OMe	Br	75	85
<i>p</i> -C(O)OMe	Br	61	59
<i>p</i> -NO ₂	Br	45	31
	Br	67	76

^a2.0 mmol each of styrene and haloarene, 2.2 mmol of NaOAc, 50 mL of DMF.

^bYields were determined by NMR analysis.

General procedure for the complexation of PPh₂-PAMAM-SiO₂ with palladium

The PPh₂-PAMAM-SiO₂ (1.0 mmol with respect to PPh₂) was added to a solution of Pd (Me₂NCH₂CH₂NMe₂)(Me)₂ (0.5 mmol) in freshly distilled benzene (20 mL). The mixture was stirred at room temperature overnight under nitrogen. The product was filtered through a 0.45 mm membrane filter under a stream of nitrogen and washed with ether (50 mL). Residual ether was removed in vacuo.

General procedure for the Heck reaction

The substrates, base, and solvent (dimethylformamide 20 mL) were placed in a 50 mL round bottom-flask equipped with a magnetic stirring bar and condenser connected to a vacuum line. The solution was flushed five times with nitrogen using a vacuum nitrogen cycle. The catalyst was then added. The autoclave was placed in an oil bath and the desired temperature was reached by stirring on a hot plate. After the appropriate reaction time, the reaction was allowed to cool to room temperature. The resulting solution was filtered to remove the catalyst. The filtrate was extracted with diethyl ether (4 × 40 mL), and the ether extracts were washed with brine and distilled water, followed by drying over magnesium sulfate. The product was analyzed by ¹H NMR spectroscopy and (or) gas chromatography, and identified by comparison of spectral results with literature data (6).

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