Catalysis Today 227 (2014) 207–214

Contents lists available at ScienceDirect

Catalysis Today

journal homepage: www.elsevier.com/locate/cattod

Synthesis and catalytic evaluation in the Heck reaction of deposited palladium catalysts immobilized via amide linkers and their molecular analogues

Miloslav Semler[a,b], Jiří Čejka[b], Petr Štěpnička[a,*]

[a] Department of Inorganic Chemistry, Faculty of Science, Charles University in Prague, Hlavova 2030, 128 40 Prague, Czech Republic
[b] J. Heyrovský Institute of Physical Chemistry, Academy of Sciences of the Czech Republic, v.v.i., Dolejškova 3, 182 23 Prague, Czech Republic

ARTICLE INFO

Article history:
Received 21 June 2013
Received in revised form
11 September 2013
Accepted 17 September 2013
Available online 12 October 2013

Keywords:
Deposited catalysts
Palladium
Amide linkers
Heck reaction
Poisoning tests

ABSTRACT

A series of deposited palladium catalysts was prepared by amidation of 3-aminopropylated silica gel with donor-functionalized acetic acids followed by treatment with palladium(II) acetate. The resulting materials containing $YCH_2CONH(CH_2)_3Si\equiv$ groups at the surface, where Y = SMe, NMe_2, and PPh_2, as well as the corresponding catalysts generated in situ from the analogous molecular donors $YCH_2CONH(CH_2)_2Me$ and palladium(II) acetate were evaluated in the Heck reaction of *n*-butyl acrylate with bromobenzene to give *n*-butyl cinnamate. The heterogenized catalysts afforded consistently better yields of the coupling product than their respective molecular counterparts with the best results being achieved with the catalyst obtained from the amidoamine-functionalized support ($Y = NMe_2$). Additional tests revealed that the deposited catalysts serve as a source of active metal for the reaction occurring in the liquid phase and that the yield of the coupling product is controlled by the amount of the leached-out metal.

1. Introduction

Catalysis nowadays plays a vital role in the synthesis of many organic compounds at laboratory scale as well as in industry, where not only fine chemicals but also large scale preparations are carried out catalytically. Very often, high value added chemicals are prepared with the aid of C—C bond forming (cross-coupling) reactions that allow for efficient "construction" of a range of simple and complex molecules by selective coupling of two building blocks via the newly formed C—C bond(s). One of the prominent examples of such processes is the Heck–Mizoroki reaction (or simply Heck reaction) discovered in the early 1970s [1]. Heck reaction is based on the coupling of olefins with organic halides (typically haloarenes) affording substituted alkenes suitable for further synthetic transformations [2]. The manifold industrial applications of Heck reaction, which have been reviewed several times [3], can be exemplified by the preparation of materials as diverse as monomer precursors of benzocyclobutene-based resins (Cyclotene™ by Dow Chemical), herbicide Prosulfuron, and the nonsteroidal anti-inflammatory drug Naproxene.

Typically, the Heck reactions make use of various palladium catalysts ranging from defined molecular compounds (i.e., various Pd salts and complexes) and "molecular" catalysts generated in situ from a Pd precursor and an appropriate modifier (typically a ligand), to various heterogeneous and heterogenized catalysts. Any immobilization of a palladium catalyst over a solid support is potentially attractive for industrial, large-scale applications because such catalysts can be relatively easily recovered and recycled. In addition, the stable and efficient heterogenized catalysts appear particularly suitable for the preparation of pharmaceutically active substances, in the case of which the contamination with residual metals is strictly controlled [4].

In our work, we have focused on palladium catalysts deposited on various siliceous supports modified with N-donor groups and their applications to the Heck coupling [5]. The results obtained with the catalysts derived from siliceous supports such as mesoporous molecular sieves MCM-41 [6] and SBA-15 [7] or much cheaper and hydrolytically stable silica gel have shown that the type (internal structure in particular) of the support affects the overall catalytic performance of the resulting immobilized catalysts less than the amount and the nature of the anchoring donor groups used to modify the parent support [5]. This is rather natural because the donor groups determine the mode of interaction between the deposited metal and the support, thereby controlling the activity, selectivity and stability of the catalyst, as well as a possible leaching of the active metal from the solid support.

Although a number of papers has been published on the applications of palladium catalysts deposited over siliceous supports

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* Corresponding author. Fax: +420 221 951 253.
E-mail address: stepnic@natur.cuni.cz (P. Štěpnička).

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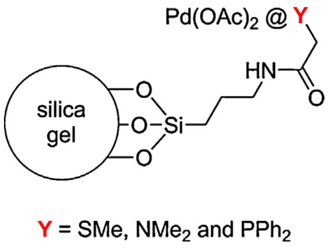
http://dx.doi.org/10.1016/j.cattod.2013.09.012



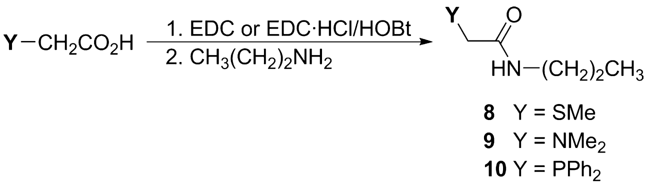
Scheme 1.

modified with aminopropyl [8], mercaptopropyl [9], phosphine [10] and carbene [11] donor groups in the Heck reactions, there is – up to the best of our knowledge – no literature report dealing with the direct comparison of catalysts possessing structurally similar modifying groups equipped with chemically different donor moieties. This prompted us to prepare a series of structurally analogous palladium catalysts from donor-modified, silica gel-based supports and to compare their catalytic properties in a model Heck reaction. To this end, we have synthesized palladium catalysts from silica gel functionalized with chemically similar amide donor pendant groups possessing different terminal donor moieties (Scheme 1). In the preparation of these materials, we used the readily accessible 3-aminopropyl modified silica gel, which was reacted with donor-functionalized acetic acids ($Me_2NCH_2CO_2H$, $Ph_2PCH_2CO_2H$, and $MeSCH_2CO_2H$) to afford the respective surface-bound amide pendants. This approach exploiting amide functional group as a defined linking moiety has been utilized only scarcely in the design of deposited palladium catalysts [12]. In this contribution, we report the preparation of deposited palladium catalysts from supports bearing three different donor-amide groups at the surface, and a comparison of their catalytic performance with simple catalysts obtained in situ by mixing a palladium source with the respective “molecular” donor-amide ligands.

2. Results and discussion

2.1. Preparation of the deposited catalysts and their molecular analogues

The deposited, donor-amide functionalized palladium catalysts were prepared as shown in Scheme 2 [13]. In the first step, dry chromatography-grade silica gel was reacted with an excess of (3-aminopropyl)trimethoxysilane in refluxing toluene to afford the aminopropylated support **1**. This material was in turn reacted with the respective substituted acetic acids in the presence of peptide coupling agents [14] to give the corresponding amide-functionalized supports **2**–**4**. As the last step, the supports were palladated via treatment with palladium(II) acetate in dichloromethane using 1 mmol of Pd(OAc)$_2$ per 1 g of the functionalized silica gel to afford catalysts **5**–**7**. Amides **8**–**10**, representing molecular analogues of the functional pendants present in the deposited catalysts **5**–**7**, were obtained by direct amidation of the respective substituted acetic acids with 1-aminopropane (Scheme 3).

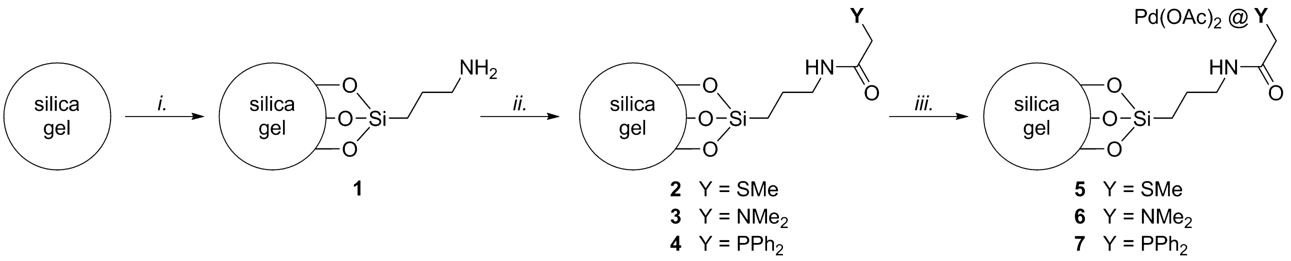


Scheme 3. Preparation of the molecular donors **8**–**10**. Legend: EDC, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide; HOBt, 1-hydroxybenzotriazole.

Materials **1**–**7** were characterized by IR spectroscopy and elemental analysis. Prior to the palladation, supports **2** and **4** showed the S/N and P/N molar ratios below unity while in the case of **3**, the amount of nitrogen was lower that the double of the amount of nitrogen in the parent material **1**. This suggests an incomplete conversion of the 3-aminopropyl pendants into the amide ones or, in other words, the presence of unreacted aminopropyl groups at the supports’ surface [15]. The palladation led to incorporation of ca. 0.5–0.6 mmol Pd per gram of the resulting solid catalyst. The Pd/donor molar ratios were 1.06 (Pd/S) for **5** and 1.30 (Pd/P) for **7**. The Pd/N ratio determined for **6** was only 0.88 owing to the presence of two nitrogen atoms in the functional pendant (in the ideal case).

The IR spectra of all materials were dominated by broad intense absorptions of the siliceous support at 3000–3500 (ν_{OH}), ca. 1100–1200 cm^{-1} (intense band due to asymmetric Si—O—Si stretching), 800 cm^{-1} (symmetric Si—O—Si stretching), and 460 cm^{-1} (Si—O—Si bending) [16]. Besides, the spectra of **2**–**4** displayed bands attributable to N—H vibrations, C—H valence bands (ca. 2750–3000 cm^{-1}) and, mainly, characteristic vibrations of the amide moieties (amide I at 1640–1660 cm^{-1}, and amide II at ca. 1535–1540 cm^{-1}). The positions of the amide bands corresponded well with those determined for the respective molecular amides **8**–**10** (see below). Upon palladation, however, these bands shifted to lower wavenumbers (amide I band typically by ca. 90 cm^{-1}), reflecting very likely coordination of the anchored Pd species by the donor pendant attached to the support surface. These features are demonstrated in Fig. 1 for materials obtained from *N*,*N*-dimethylglycine. Trends observed in the other series (i.e., **2**–**5**–**8** and **4**–**7**–**10**) were similar.

The molecular amides **8**–**10** were characterized by NMR and IR spectroscopy and by high-resolution mass spectrometry. The compounds displayed all expected signals in the NMR spectra as well as the characteristic amide bands at 1630–1650 (amide I) and 1530–1545 cm^{-1} (amide II) in their IR spectra. Notably, the energy of the amide I vibration (largely C=O stretching) was found to increase in the order **10** < **8** < **9** (P < S < N), thus following inversely the trend of the electronegativities of the pivotal atoms in the terminal group (N > S > P).



Scheme 2. Preparation of anchored Pd catalysts **5**–**7**. Legend: *i*, (3-aminopropyl)trimethoxysilane in toluene, refluxing; *ii*, amidation with the appropriate acid $\mathbf{Y}CH_2CO_2H$ in the presence of peptide coupling agents (1-hydroxybenzotriazole and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) or the corresponding hydrochloride (EDC·HCl)); *iii*, treatment with Pd(OAc)$_2$ in dichloromethane.

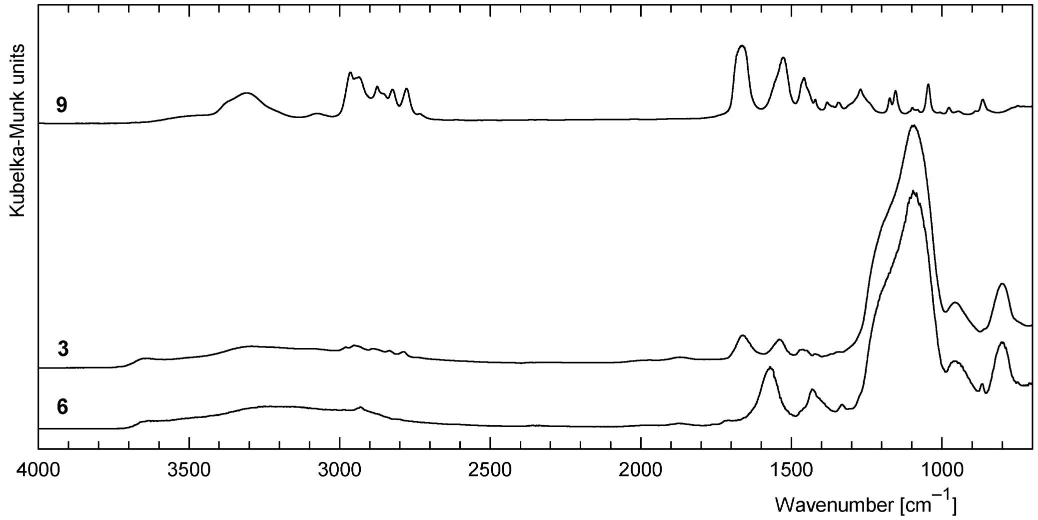


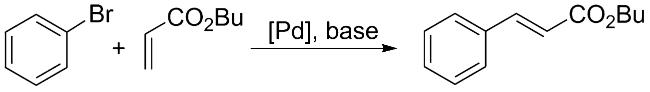
Fig. 1. IR spectra of materials **3** and **6**, and the molecular amide **9**.

2.2. Catalytic evaluation

The catalytic properties of the supported catalysts **5**–**7** were evaluated in the model Heck coupling of bromobenzene with *n*-butyl acrylate to give *n*-butyl cinnamate (Scheme 4). The reaction mixtures typically contained 1.5 equiv. of bromobenzene (bromobenzene is the most volatile component in the reaction mixture), an excess of base (sodium acetate) and the catalyst in an amount corresponding to 1.0 mol.% of palladium with respect to *n*-butyl acrylate. The initial reaction tests were aimed at finding the best reaction conditions in terms of the reaction solvent, amount of base and temperature. All these parameters were shown to have a pronounced effect on the performance of the newly prepared catalysts.

Kinetic profiles for the testing reactions performed with catalysts **5**–**7** (1 mol.%) in two different solvents at 150 °C and in the presence of anhydrous sodium acetate (1.5 equiv.) as the base are shown in Fig. 2. In *N*,*N*-dimethylacetamide (DMA), the best results were obtained with the S- and P-donor catalysts **5** and **7** (**5**: 87% yield after 4 h, ≈100% yield after 8 h; **7**: 86% yield after 4 h, 92% yield after 8 h). Catalyst **6** containing the N-donor groups performed slightly worse (59% yield after 4 h, 71% yield after 8 h). An even more pronounced discrimination was seen in 1-octanol, in which catalysts **5** and **6** turned practically inactive during the first 30 min (cf. the yields after 1 h/8 h; **5**: 8%/12%, **6**: 14%/26%) whereas the phosphine-containing catalyst **7** maintained its catalytic activity during the whole experiment and achieved 94% yield of the coupling products in 8 h. Reactions performed similarly in tri-*n*-butylamine as the third tested solvent ensued in considerably lower conversions (cf. conversions after 4/8 h; **5**: 14%/14%, **6**: 20%/17%, **7**: 17%/16%), presumably due to a higher donor ability and reducing properties of this solvent [17].

Influence of the reaction temperature was rather expected (see Fig. 3) as the yields of the coupling product obtained with 1 mol.% Pd catalyst after 2 h [18] increased exponentially with increasing temperature. In terms of activity (yields), the catalysts become more differentiated at higher temperatures. The best results were obtained with catalyst **6**, whose activity increased most rapidly upon raising the reaction temperature. The different catalytic performance of the catalysts and their temperature dependences suggest that the catalytic activity (in a particular solvent) is determined by the available donor atoms, which obviously determine the nature and strength of the interaction between palladium and the functionalized support, and also by an overall stability (presumably thermal and redox) of the deposited catalysts.



Scheme 4. Heck reaction of bromobenzene with *n*-butyl acrylate to give *n*-butyl cinnamate.

As for the base, we studied only the reactions performed in the presence of sodium acetate, which is the most effective for the particular testing reaction according to our previous experience [5]. However, in this study we focused on the influence of the nature of this salt, which is readily available in hydrated and anhydrous forms. Thus, the reactions were performed in the presence of fused anhydrous sodium acetate or sodium acetate trihydrate (1.5 equiv.) with 1 mol.% Pd at 140 °C for 2 h using either nitrogen-flushed vessels (inert conditions) or reaction tubes sealed in the air. The results summarized in Table 1 indicate that the best yields for all catalysts are consistently obtained in reactions carried out with the hydrated base and with the exclusion of the air.

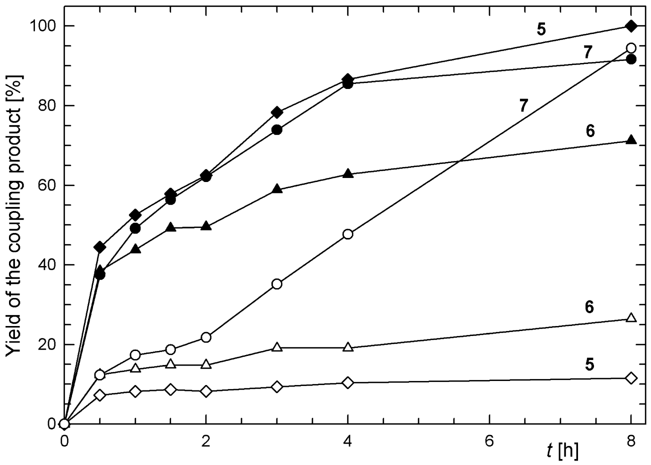


Fig. 2. Kinetic profiles for the model reaction carried out with catalyst **5** (diamonds), **6** (triangles) and **7** (circles) performed in *N*,*N*-dimethylacetamide (filled symbols) and 1-octanol (empty symbols). Conditions: 1.0 mmol of *n*-butyl acrylate, 1.5 mmol of bromobenzene and 1.5 mmol of anhydrous sodium acetate in 5 mL of the solvent; 1 mol.% Pd, reaction at 150 °C under nitrogen. The solid lines connecting the experimental points in this and the following figures serve only as a guide for an eye.

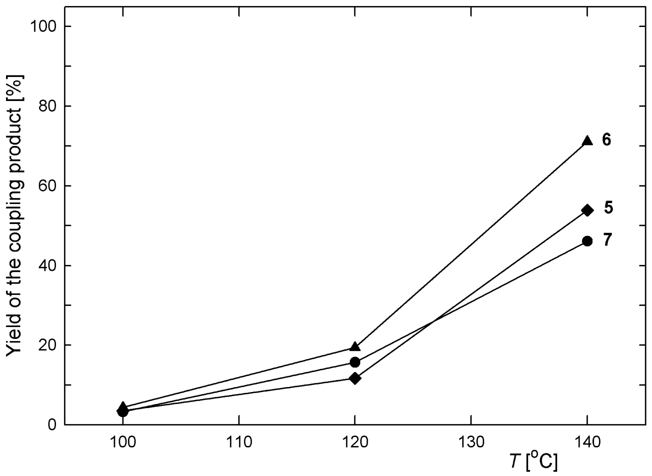


Fig. 3. Dependence of the yield of the coupling product upon the reaction temperature. Conditions: 1.0 mmol of *n*-butyl acrylate, 1.5 mmol of bromobenzene and $CH_3CO_2Na{\cdot}3H_2O$ in 5 mL of *N*,*N*-dimethylacetamide; 1 mol.% Pd, reaction under nitrogen for 2 h.

Table 1
The influence of the base and inert conditions on the yield of the coupling product.[a]

Conditions	Yield of the coupling product (%)		
	Catalyst **5**	Catalyst **6**	Catalyst **7**
Nitrogen/dry base	34	64	32
Nitrogen/hydrated base	64	**89**	46
Air/dry base	17	28	28
Air/hydrated base	18	49	42

[a] Conditions: 1.0 mmol of *n*-butyl acrylate, 1.5 mmol of bromobenzene, 1.5 mmol of CH_3CO_2Na or $CH_3CO_2Na{\cdot}3H_2O$ in 5 mL of *N*,*N*-dimethylacetamide; 1 mol.% Pd, reaction at 140 °C for 2 h.

Table 2
The influence of the amount of water present in the base on the yield of the coupling product.[a]

Equiv. of H_2O per 1 equiv of NaOAc	Yield of the coupling product (%)		
	Catalyst **5**	Catalyst **6**	Catalyst **7**
0	9	19	9
1	16	24	19
1.5	17	**30**	18
2	14	19	18
3	12	19	16

[a] Conditions: 1.0 mmol of *n*-butyl acrylate, 1.5 mmol of bromobenzene, mixtures of CH_3CO_2Na and $CH_3CO_2Na{\cdot}3H_2O$ in varying ratios (total amount of sodium acetate: 1.5 mmol), 5 mL of *N*,*N*-dimethylacetamide; 1 mol.% Pd, reaction at 120 °C under nitrogen.

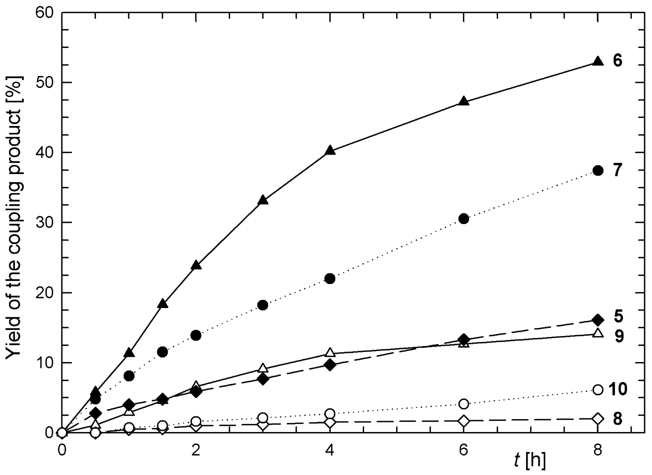


Fig. 4. Kinetic profiles for the model Heck reactions carried out in the presence of deposited catalysts **5**–**7** and their analogs based on the combination of $Pd(OAc)_2$ and ligands **8**–**10**. Conditions: 1.0 mmol of *n*-butyl acrylate, 1.5 mmol of bromobenzene, 0.75 mmol of CH_3CO_2Na and 0.75 mmol of $CH_3CO_2Na{\cdot}3H_2O$ in 5 mL of *N*,*N*-dimethylacetamide; 1 mol.% Pd, reaction at 120 °C under nitrogen. Catalysts based on **8**–**10** were obtained by adding the respective amide ligand (20 μmol) and $Pd(OAc)_2$ (10 μmol) to the reaction mixture.

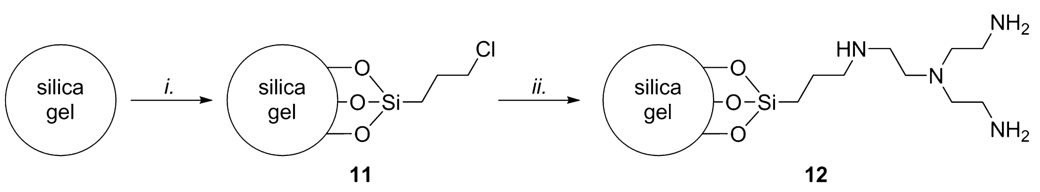
Next, we varied the amount of water in the reaction system by introducing a mixture of anhydrous sodium acetate and sodium acetate trihydrate in appropriate amounts (Table 2). In accordance with previous tests, the lowest yields were uniformly achieved in reactions with anhydrous base. In the case of catalyst **6**, increasing amount of water in the base gradually improved the yields up to 1.5 mole of water per one mole of sodium acetate represented by a 1:1 mixture of CH_3CO_2Na and $CH_3CO_2Na{\cdot}3H_2O$ (N.B. This amount corresponds to 2.25 equiv of water with respect to *n*-butyl acrylate and 1.5 equiv. with respect to bromobenzene). Quite surprisingly, any further increase in the amount of water available in the reaction mixture up to 4.5 equiv. (i.e., 1.5 equiv. of $CH_3CO_2Na{\cdot}3H_2O$ vs. *n*-butyl acrylate) caused a decrease in the yield of the coupling product. A similar but much less pronounced trend was seen also for catalyst **5** while catalyst **7** containing phosphine functional groups showed practically negligible variation in the yield over the range of 1–3 equiv. of water per one molecule of the base under identical conditions.

Using the optimized reaction conditions (1 mol.% Pd, AcONa + $AcONa{\cdot}3H_2O$ as the base) and relatively low reaction temperature (120 °C), the anchored Pd catalyst **5**–**7** were compared with catalysts generated in situ by mixing palladium(II) acetate with equimolar amount of the respective molecular donors **8**–**10**. Kinetic profiles shown in Fig. 4 clearly demonstrate a superior performance of the immobilized catalysts, whose activity decreased in the order **6** > **7** > **5**. Although the homogenous catalysts afforded much lower yields of the coupling product, they maintained the same trend (**9** > **10** > **8**, or N > P > S in terms of the terminal donor atoms). Consequently, the results obtained with the least active heterogenized catalyst **5** were very similar to the most active “molecular” catalyst **9**.

The differences in the catalytic properties of material possessing identical metal binding sites in free (molecular) or immobilized form can be accounted for by the role of the chemically inert siliceous support. The latter probably acts as a matrix, in which both the Pd(II) species and palladium(0) particles can be dispersed and to which they can return after leaving the catalytic cycle. Moreover, elimination of the metal from the solid support with covalently bound donor groups can be expected to afford metal species devoid of any firmly bound donors (probably stabilized only by coordination of the donor solvents) and thus highly prone to oxidative addition of the aryl halide, which is believed to open the catalytic cycle [2]. The heterogeneous catalysts thus produce active (naked) metal particles albeit in only a low concentration due to metal scavenging effect of the functionalized support.

The fact that the heterogenous catalysts act as a source of active metal particles for the reaction in the liquid phase was confirmed by a series of poisoning tests [19]. For instance, no coupling product was detected in the reaction mixture containing the most active catalyst **6** when the reaction was performed in the presence of mercury metal from the very beginning. Similarly, addition of mercury or N-donor metal scavenger **12** [20], which was prepared as shown in Scheme 5, to the reaction mixture containing the heterogeneous catalyst after 2 h of reaction immediately stopped the reaction as demonstrated by the kinetic profiles in Fig. 5.

Attempts to recycle the heterogeneous catalyst were not successful (Table 3). Catalysts **5** and **6** recovered after the first run



Scheme 5. Preparation of metal scavenger **12**. Legend: *i*, (3-chloropropyl)triethoxysilane in toluene, refluxing; *ii*, alkylation with $N(CH_2CH_2NH_2)_3$ followed by neutralization with ammonia in ethanol/water.

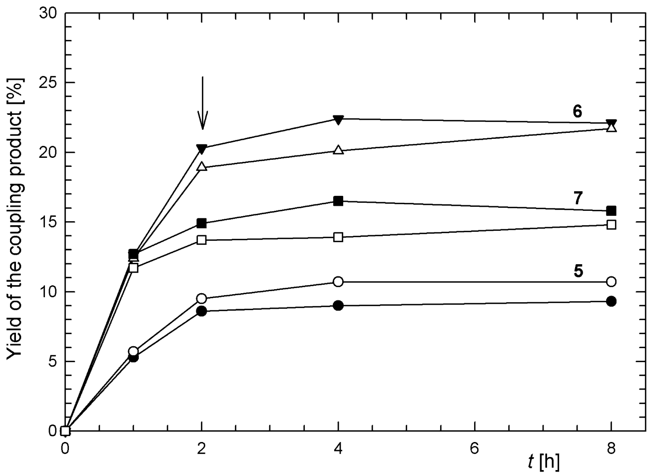


Fig. 5. Catalyst poisoning tests for **5**–**7**. The catalytic poisons – mercury (filled symbols) or material **12** (empty symbols) – were added after 2 h (indicated with an arrow). Conditions: 1.0 mmol of *n*-butyl acrylate, 1.5 mmol of bromobenzene, 0.75 mmol of CH_3CO_2Na and 0.75 mmol of $CH_3CO_2Na·3H_2O$ in 5 mL of *N*,*N*-dimethylacetamide; 1 mol.% Pd, reaction at 120 °C under nitrogen.

showed practically negligible activities whereas the phosphine based material **7** achieved ca. 13% conversion when used for the second time (cf. 29% in the first run). Analysis of the reaction mixtures revealed that yield of the coupling products increases linearly with the amount of palladium present in the liquid phase [21]. Although the amount of metal present in the liquid phase can be considerably higher during the reaction because the palladium content was determined in liquid phases withdrawn after cooling the reaction mixture to room temperature, the data corroborate that catalysts **5**–**7** behave as a source of active palladium species for the catalytic process occurring in the liquid phase. Furthermore, the data in Table 3 clearly demonstrate that the amount of leached-out metal is much higher in reactions performed in air than in those carried out under nitrogen, which in turn corresponds with the results summarized in Table 2 and discussed above (the role of solvate water and inert atmosphere). It appears likely that the inert atmosphere prevents decomposition of the Pd species and possible degradation of the donor support, thereby limiting the amount of palladium which is not re-deposited from the liquid phase.

Table 3
Amount of Pd in the liquid phase and yields of the coupling product for reactions mediated by fresh and recycled catalysts **5**–**7**.[a]

Catalyst	Pd content in the liquid phase [ppm][b]	Yield of the coupling product [%]
5 under N_2	19	15
6 under N_2	36	59
7 under N_2	23	29
5 recycled under N_2	2	2
6 recycled under N_2	1	2
7 recycled under N_2	5	13
5 in air	43	–
6 in air	92	–
7 in air	114	–

[a] Conditions: 1.0 mmol of *n*-butyl acrylate, 1.5 mmol of bromobenzene, 0.75 mmol of CH_3CO_2Na and 0.75 mmol of $CH_3CO_2Na·3H_2O$ in 5 mL of *N*,*N*-dimethylacetamide; 1 mol.% Pd, reaction at 120 °C, reaction time 8 h.

[b] The amount of palladium was determined in a sample withdrawn after cooling the reaction mixture.

3. Conclusion

Amidation of 3-aminopropylated silica gel with donor-functionalized acetic acid mediated by peptide coupling agents proceeds smoothly to give materials modified with multidonor amide groups (ca. 0.5–0.8 mmol of the donor pendants per 1 g of the support). Palladation of such functionalized supports with palladium(II) acetate affords deposited palladium catalysts that efficiently mediate Heck coupling of *n*-butyl acrylate with bromobenzene to afford *n*-butyl cinnamate. Catalytic efficiency varies greatly with the nature of the terminal donor groups and the reaction conditions. Apart from the rather expected influence of the reaction solvent and temperature, the reaction is affected also by the form of the base (namely by the amount of water of crystallization in sodium acetate) and inert/non-inert conditions. Since the catalyst poisoning and metal leaching tests suggest the catalysts to serve as a source of active metal species, the catalytic outcome is determined by the amount of metal available in the liquid phase and, hence, reflects the donor ability of the functional pendants and the solvent, chemical stability of the anchoring groups and other factors that can affect the metal leaching (e.g., the amount of water in the reaction mixture).

4. Experimental

4.1. Materials and methods

Unless stated otherwise, the syntheses were carried out under argon or nitrogen atmosphere using standard Schlenk techniques. (Diphenylphosphino)acetic acid was prepared according to the literature [22]. Toluene was dried over sodium metal and freshly distilled under argon. Dichloromethane was dried with potassium carbonate and distilled. All other chemicals were obtained from commercial sources (Sigma–Aldrich and Alfa-Aesar; solvents from Lachner) and were used as received.

IR spectra were recorded in diffuse reflectance mode (DRIFTS) on a Nicolet Magna 760 FTIR spectrometer in the range 400–4000 cm^{-1} (64 scans, resolution 4 cm^{-1}). The samples were diluted with KBr prior to the measurement. NMR measurements were performed with a Varian UNITY Inova 400 spectrometer at 25 °C. Chemical shifts are given relative to internal tetramethylsilane (^1H and ^{13}C) or to external 85% aqueous H_3PO_4 (^{31}P), all set to 0 ppm.

The content of C, H, N and Cl was determined by the conventional combustion method. Palladium loading in solid samples was determined by ICP-OES on an IRIS Interpid II (Thermo Electron) instrument using axial plasma and ultrasonic CETAC nebulizer U-5000AT+. The samples were dissolved in a mixture of concentrated HF and HNO_3 (3:2; both suprapure Merck) at 50 °C for 15 min, and the solutions were diluted with redistilled water. Spectral line at 324.240 nm was used for the measurement. The amount of palladium in liquid samples was determined by ICP-MS for the ^{105}Pd isotope. One milliliter of the sample was added to aqua regia (50 mL) and the mixture was evaporated. The solid residue was dissolved in redistilled water prior to the analysis.

*4.2. Preparation of aminopropylated silica (material **1**)*

Conventional chromatography-grade silica gel (Fluka, 0.063–0.2 mm; 25 g), which was dried in an oven prior to the use (room temp. → 550 °C at 1 °C min^{-1}, then at 550 °C for 5 h), was suspended in dry toluene (500 mL). Neat (3-aminopropyl)trimethoxysilane (12 mL, 74 mmol) was introduced and the resulting mixture was heated at reflux for 25 h. After cooling, the solid was filtered off, washed successively with toluene, acetone and pentane (200 mL each), and allowed to dry in the air. Yield: 31 g. IR DRIFTS (cm^{-1}): 3640 w, 3070 w br, 2938 w, 2964 w, 1866 w, 1632 w, 1558 w, 1490 w, 1092 s, 950 w, 799 m, 691 w, 460 s; elemental analysis (mmol g^{-1}): C 4.43, H 15.8, N 1.26.

*4.3. Preparation of materials **2–4***

1-Hydroxybenzotriazole hydrate (HOBt; 1.535 g, 10 mmol) and (methylthio)acetic acid (0.584 g, 5.5 mmol) were dissolved in dry dichloromethane (100 mL). The mixture was cooled in an ice bath and treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC·HCl; 1.917 g, 10 mmol). After stirring for 30 min, modified silica gel **1** (5.0 g), which was freshly activated by drying under vacuum at 130 °C for 2 h, was added and the resultant mixture was stirred at room temperature overnight (18 h). Then, the solid material was filtered off, washed carefully with methanol and dichloromethane, and dried in the air. Yield: 5.1 g. IR DRIFTS (cm^{-1}): 3652 w, 3292 mb, 2980 vw, 2929 w, 2872 vw, 1996 vw, 1868 vw, 1648 w, 1536 w, 1442 vw, 1092 s, 958 w, 800 m, 698 w, 464 s; elemental analysis (mmol g^{-1}): C 6.29, H 17.2, N 1.05, S 0.78.

Material **3** was prepared in exactly the same manner using *N*,*N*-dimethylglycine (0.567 g, 5.5 mmol) for the amidation. Yield: 4.9 g. IR DRIFTS (cm^{-1}): 3648 w, 3306 mb, 2978 vw, 2952 vw, 2886 vw, 2832 vw, 2788 vw, 1870 vw, 1664 w, 1540 w, 1464 vw, 1092 s, 958 w, 800 m, 462 s; elemental analysis (mmol g^{-1}): C 6.08, H 17.8, N 1.55. The phosphine-modified support **4** was prepared similarly starting from modified silica gel **1** (2.50 g) EDC·HCl (0.958 g, 5.0 mmol), HOBt (0.768 g, 5.0 mmol), (diphenylphosphino)acetic acid (0.672 g, 2.75 mmol) and triethylamine (0.75 mL, 5.0 mmol). Yield: 2.6 g. IR DRIFTS (cm^{-1}): 3640 w, 3288 m br, 3060 vw, 2938 vw, 2872 vw, 1640 w, 1534 w, 1432 vw, 1100 s, 958 w, 800 m, 736 w, 696 w, 468 s; elemental analysis (mmol g^{-1}): C 11.3, H 23.3, N 0.73, P 0.48.

*4.4. Palladation of materials **2–4***

A solution of palladium(II) acetate (0.448 g, 2.0 mmol) in dry dichloromethane (10 mL) was introduced to a stirring suspension of the respective support in the same solvent (2.0 g in 50 mL). The resulting mixture was stirred at room temperature for 2 h before being filtered. The solid product was washed carefully with dichloromethane and dried in the air.

Material **5**. IR DRIFTS (cm^{-1}): 3640 w, 3222 w br, 2930 vw, 1560 w, 1425 w, 1100 s, 954 vw, 798 w, 686 vw, 460 s. Elemental analysis (mmol g^{-1}): C 7.19, H 16.0, N 0.90, S 0.61, Pd 0.64. Material **6**. IR DRIFTS (cm^{-1}): 3642 w, 3246 wb, 2930 vw, 1872 vw, 1708 vw, 1570 w, 1432 w, 1330 vw, 1096 s, 956 w, 862 vw, 802 w, 682 w, 456 s. Elemental analysis (mmol g^{-1}): C 6.89, H 17.1, N 1.41, Pd 0.62. Material **7**. IR DRIFTS (cm^{-1}): 3648 w, 3254 w br, 3062 vw, 2930 vw, 1990 vw, 1870 vw, 1714 vw, 1560 w, 1438 w, 1092 s, 952 vw, 800 w, 742 vw, 692 vw, 466 s; elemental analysis (mmol g^{-1}): C 9.94, H 16.8, N 0.76, P 0.39, Pd 0.50.

*4.5. Preparation of amide **8***

(Methylthio)acetic acid (0.106 g, 1.0 mmol) and EDC·HCl (0.383 g, 2.0 mmol) were successively added to neat *n*-propylamine (2.0 mL, 24 mmol). The resulting mixture was stirred at room temperature for 2 h and then diluted with brine. The resulting mixture was extracted with dichloromethane (3× 10 mL). The organic washing were combined, dried over $MgSO_4$ and evaporated with silica gel. The crude pre-adsorbed product was transferred onto a top of a chromatographic column (silica gel, ethyl acetate) and the column was eluted with ethyl acetate. Following evaporation, amide **8** was isolated as a yellowish oil (60 mg, 41%). ^{1}H NMR ($CDCl_3$, 399.95 MHz, 25 °C): δ 0.95 (t, 3H, $^3J_{HH}$ = 7.37 Hz, $C\textit{H}_3CH_2$), 1.57 (m, 2H, $CH_3C\textit{H}_2$), 2.13 (s, 3 H, CH_3S), 3.20 (s, 2H, SCH_2), 3.27 (m, 2H, $NHC\textit{H}_2CH_2$), 6.92 (s, 1H CONH); ^{13}C{^{1}H} NMR ($CDCl_3$, 100.58 MHz, 25 °C): δ 11.3 ($NH(CH_2)_2CH_3$), 16.4 (CH_3S), 22.8 ($NHCH_2\textit{C}H_2$), 38.3 (SCH_2), 41.4 ($NHCH_2$), 168.2 (CONH); IR DRIFTS (cm^{-1}): 3292 m, 3078 w, 2964 m, 2932 m, 2874 w, 1648 s, 1552 m, 1460 w, 1438 w, 1382 vw, 1315 w, 1246 vw, 1222 vw, 1160 w, 1100 w, 1074 vw, 984 vw, 954 vw, 884 vw, 786 vw, 746 vw, 688 w, 612 vw, 576 w, 472 vw; HRMS calc. for. $C_6H_{14}NOS$: 148.0791, found 148.0790.

*4.6. Preparation of amide **9***

N,*N*-Dimethylglycine (0.206 g, 2.0 mmol) and 1-hydroxybenztriazole hydrate (0.461 g, 2.8 mmol) were dissolved in dry dichloromethane (10 mL). The solution was cooled in an ice bath and treated with EDC·HCl (0.575 g, 3.0 mmol) and triethylamine (0.75 mL, 5.0 mmol). After stirring for 30 min, neat *n*-propylamine (0.50 mL, 6.0 mmol) was introduced and the mixture was stirred at room temperature overnight (18 h). Then, anhydrous potassium carbonate (ca. 2 g) was added and the mixture was stirred for another 10 min and filtered. The filtrate was evaporated with chromatographic silica gel and the preadsorbed crude product was purified as described for **8** (silica gel; 1% triethylamine in dichloromethane-methanol 3:1) to give amide **9** as a colorless oil (0.103 g, 37%). ^{1}H NMR ($CDCl_3$, 399.95 MHz, 25 °C): δ 0.94 (t, 3H, $^3J_{HH}$ = 7.37 Hz, $C\textit{H}_3CH_2$), 1.55 (m, 2H, $CH_3C\textit{H}_2$), 2.30 (s, 6H, $N(CH_3)_2$), 2.95 (s, 2H, $NHC\textit{H}_2CO$), 3.25 (m, 2H, $NHC\textit{H}_2CH_2$), 7.17 (s, 1H, CONH); ^{13}C{^{1}H} NMR ($CDCl_3$, 100.58 MHz, 25 °C): δ 11.4 ($NH(CH_2)_2CH_3$), 22.9 ($NHCH_2\textit{C}H_2$), 40.6 ($NH\textit{C}H_2CH_2CH_3$), 46.0 ($N(CH_3)_2$), 63.2 (CH_2CO), 170.4 (CONH); IR DRIFTS (cm^{-1}): 3308 m, 3076 w, 2964 s, 2876 m, 2824 m, 2778 m, 1664 s, 1526 s, 1458 m, 1420 vw, 1382 w, 1344 w, 1270 w, 1174 w, 1154 w, 1098 w, 1046 m, 1002 vw, 978 vw, 942 vw, 864 w, 746 vw, 678 vw, 594 w, 506 vw; HR MS calc. for $C_7H_{17}N_2O$: 145.13354, found 145.13367.

*4.7. Preparation of amide **10***

(Diphenylphosphino)acetic acid (0.244 g, 1.0 mmol) and 1-hydroxybenztriazole hydrate (0.184 g, 1.1 mmol) were dissolved in dry dichloromethane (10 mL). The mixture was cooled in ice and treated with neat EDC (0.20 mL, 1.1 mmol). After stirring for another 30 min, neat *n*-propylamine (0.16 mL, 2.0 mmol) was introduced and the stirring was continued at room temperature overnight. The reaction mixture was quenched with 10% aqueous citric acid (10 mL). The organic layer was separated, washed with brine and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (silica gel; ethyl acetate) to afford amide **10** as yellowish solid (0.169 g, 59%). ^{1}H NMR ($CDCl_3$, 399.95 MHz, 25° C): δ 0.80 (t, 3H, $^3J_{HH}$ = 7.43 Hz, $C\textit{H}_3CH_2$), 1.37 (m, 2H, $CH_3C\textit{H}_2$), 3.02 (s, 2H, $PC\textit{H}_2CO$), 3.13 (m, 2H, NHCH_2), 5.61 (s, 1H, CONH), 7.32–7.37 (m, 6H, Ph), 7.41–7.46 (m, 4H, Ph); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100.58 MHz, 25 °C): 11.3 ($NH(CH_2)_2CH_3$), 22.7 ($NHCH_2CH_2$), 37.5 (d, $^{1}J_{PC}$ = 20 Hz, PCH_2), 41.5 (CH_2CO), 128.7 (d, $^{2}J_{PC}$ = 7 Hz, Ph *ortho*-CH), 129.1 (Ph *para*-CH), 132.6 (d, $^{3}J_{PC}$ = 19 Hz, Ph *meta*-CH), 137.2 (d, $^{1}J_{PC}$ = 12 Hz, Ph C_{ipso}), 169.1 (d, $^{2}J_{PC}$ = 9 Hz, CONH); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 161.90 MHz, 25 °C): −16.8 (s); IR DRIFTS (cm^{-1}): 3326 m, 3070 vw, 3052 w, 3002 vw, 2962 m, 2930 w, 2874 w, 1945 vw, 1872 vw, 1802 vw, 1634 s, 1528 s, 1482 w, 1460 w, 1432 m, 1398 m, 1344 vw, 1314 w, 1276 vw, 1246 w, 1188 w, 1150 m, 1098 w, 1068 w, 1028 w, 1000 w, 956 w, 910 vw, 884 vw, 856 w, 788 w, 736 s, 692 s, 618 vw, 582 w, 502 m, 476 m, 429 w; HR MS: calc. for $C_{17}H_{21}NOP$: 286.1355, found 286.1354.

*4.8. Preparation of metal scavenger **12***

Silica gel for column chromatography (Fluka, particle size 0.063–0.2 mm; 100 g) was dried by heating to 550 °C for 8 h, cooled under nitrogen and mixed with dry toluene (1000 mL). Neat (3-chloropropyl)triethoxysilane (42 mL, 0.17 mol) was added to the suspension and the resulting mixture was heated at reflux for 24 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was washed successively with toluene (1.5 L), acetone (1.0 L), methanol (2.0 L) and, finally, with dichloromethane (500 mL). The obtained solid was dried in the air to give chloropropylated silicagel **11** (95 g).

Elemental analysis (mmol g^{-1}): C 2.3, H 6.5, Cl 0.48; IR-DRIFTS (cm^{-1}): 3742 w, 3660 w, 3268 w br, 2980 w, 2956 vw, 2936 vw, 2900 vw, 2854 w, 1986 w sh, 1864 w br, 1618 w, 1446 vw, 1182 s sh, 1084 s, 970 w sh, 808 m, 456 s.

Material **11** (13.0 g), freshly dried at 130 °C under vacuum for 2 h, was mixed with dry toluene (200 mL) and tris(2-aminoethyl)amine (10.0 mL, 67 mmol). The resulting mixture was heated at reflux for 40 h and then cooled to room temperature. The solid was filtered off, washed with toluene and azeotropic ethanol (500 mL each) and then stirred with aqueous ammonia (300 mL of ethanol and 100 mL of 25% aqueous ammonia) for 3 h. The resulting material was filtered off, washed with ethanol until the washings were neutral and dried in air to afford material **12** as yellow solid (14.0 g).

Analytical data for **12**: Elemental analysis (mmol g^{-1}): C 4.1, H 13, N 1.4, Cl traces; IR-DRIFTS (cm^{-1}): 3630 vw, 3126 wb, 2980 vw, 2942 vw, 2896 vw, 1860 w, 1660 w, 1460 w, 1194 m sh, 1090 s, 970 w sh, 798 w, 456 s.

4.9. Catalytic tests

All catalytic experiments were performed in a parallel batch reactor Heidolph Synthesis I. In a typical run, *n*-butyl acrylate (0.127 g, 1.0 mmol), bromobenzene (0.236 g, 1.5 mmol), sodium acetate (1.5 mmol) and palladium catalyst (1 mol.% Pd) were mixed in the appropriate solvent (typically *N*,*N*-dimethylacetamide; 5 mL). The reaction vessels were sealed and heated at the appropriate temperature. Small aliquots were withdrawn and centrifuged at 4000 rpm for 5 min before analyzed by gas chromatography using an Agilent 6850 chromatograph equipped with a DB-5 column (internal diameter: 0.18 mm; film thickness: 0.18 μm; length: 20 m). Decaline or *n*-dodecane were used as internal standards. Experiments with homogenous catalysts were performed similarly except that the Pd/ligand catalyst was generated in situ by adding the appropriate ligand (20 μmol) and palladium acetate (10 μmol) directly to the reaction mixture.

Catalyst poisoning tests were carried out using the standard reaction mixture (butyl acrylate: 1.0 mmol; bromobenzene: 1.5 mmol; sodium acetate and sodium acetate trihydrate: 0.75 mmol each; 1 mol.% Pd and 5 mL of DMA, internal standard: *n*-dodecane). The reaction vessel was carefully flushed with nitrogen (three vacuum/nitrogen cycles) before the solvent was introduced to the solid components. The reaction was performed at 120 °C. The respective catalytic poison (0.1 mL of mercury or 200 mg of material **12**) was added either together with the solvent (i.e., at the very beginning) or after the reaction was allowed to proceed at 120 °C for 2 h.

Acknowledgements

Financial support from the Czech Science Foundation (project nos. 104/09/0561 and 13-08890S) and the Grant Agency of Charles University in Prague (project no. 639512) is gratefully acknowledged.

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